Predicting secondary insults after severe traumatic brain injury

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BACKGROUND: Secondary insults such as hypotension, hypoxia, cerebral hypoperfusion, and intracranial hypertension are associated with poor outcome following severe traumatic brain injury (TBI). Preventing and minimizing the effect of secondary insults are essential in the management of severe TBI. At present, clinicians have no way to predict the development of these events, limiting their ability to plan appropriate timing of interventions. We hypothesized that processing continuous vital signs (VS) data using machine learning methods could predict the development of future intracranial hypertension.

METHODS: Continuous VS including intracranial pressure (ICP), heart rate, systolic blood pressure, and mean arterial pressure data were collected from adult patients admitted to a single Level I trauma center requiring an ICP monitor. We tested the ability of Nearest Neighbor Regression (NNR) to predict changes in ICP by algorithmically learning from the patients' past physiology.

RESULTS: Continuous VS were collected on 132 adult patients over a minimum of 3 hours per patient (5,466 hours total; 65,600 data points). Bland-Altman plots show that NNR provides good agreement in predicting actual ICP with a bias of 0.02 (±2 SD = 4 mm Hg) for the subsequent 5 minutes and −0.02 (±2 SD = 10 mm Hg) for the subsequent 2 hours.

CONCLUSION: We have demonstrated that with the use of physiologic data, it is possible to predict with reasonable accuracy future ICP levels following severe TBI. NNR predicts ICP changes in clinically useful time frames. This ability to predict events may allow clinicians to make better decisions about the timing of necessary interventions, and this method could support the future development of minimally invasive ICP monitoring systems, which may lead to better overall clinical outcomes after severe TBI. (*J Trauma Acute Care Surg*. 2015;79: 85–90. Copyright © 2015 Wolters Kluwer Health, Inc. All rights reserved.)

LEVEL OF EVIDENCE: Prognostic study, level III.

KEY WORDS: TBI; prediction; ICP.

Traumatic brain injury (TBI) is the most common cause of trauma-related deaths in the United States.[1] For patients with severe TBI, maintaining normal intracranial pressure (ICP) is of paramount importance. Even brief periods of elevated ICP are associated with adverse outcomes, and marked elevation of ICP or elevation unresponsive to medical or surgical management may lead to herniation and death.[2] Intracranial hypertension (ICH) is usually detected by nursing staff, and physicians then make treatment decisions often after the patient has had a period of elevated ICP. Despite vast advancements in the management of patients with TBI, clinical care remains generally reactive in nature. An algorithm that predicts the development of elevated ICP would provide clinicians with a means to potentially preemptively intervene and mitigate the negative effects of ICH. ICP management is a central focus of neurotrauma critical care[3–5]; thus, investigation has focused on the development of early-warning decision-assist systems both to predict and to provide early treatment of ICH.

Previous work has shown great progress but has also demonstrated several challenges in forecasting future fluctuations in ICP.[6–8] Analysis of continuous ICP wave forms may provide clues to the physiologic state of the patient and provide a mosaic framework for predicting future ICP. This led us to ask whether previous patterns in both ICP and peripheral continuous vital signs (VS) could predict future ICP values. We then hypothesized that processing continuously collected data would allow us to predict future values of ICP, direct care, and plan for future interventions.

PATIENTS AND METHODS

This retrospective study was performed at the R Adams Cowley Shock Trauma Center in Baltimore, Maryland, after approval by the University of Maryland School of Medicine Human Research Protections Office. Study subjects included all adult patients admitted with severe TBI (postresuscitation Glasgow Coma Scale [GCS] score < 9) who had an intraparenchymal continuous ICP monitor. p data collection for this project was initiated when an ICP monitoring device was placed either in the trauma resuscitation unit or in the intensive care unit between 2008 and 2010. Continuous, high-resolution, automated electronic VS data, including heart rate (HR),

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systolic blood pressure (SBP), shock index (SI), mean arterial pressure (MAP), pulse pressure (PP), and ICP, were collected from study subjects every 6 seconds during the course of hospitalization. The Camino intraparenchymal monitor (Integra LifeSciences Corp., Plainsboro, NJ) directly measures ICP in the brain parenchyma or the subarachnoid space after surgical implantation and provides continuous pressure measurements.[9] The 6-second high-resolution electronic monitoring data contain noise, outliers, and missing values. Using a 5-minute-long moving window, we smoothed the continuous VS wave form by averaging the values inside the window, thereby reducing the impact of noise and outliers.

The exact mechanism by which systemic VS effect ICP is not fully understood; however, it is reasonable to assume that human cerebral hemodynamics have common underlying mechanisms as several mathematical models have been proposed, which approximate such mechanisms.[10–14] We also assumed that ICP values are outputs of functions of these VS and that human cerebral hemodynamics have common underlying mechanisms between individuals, with individual variation. This assumption implies that two patients with similar responses to external stimuli and internal regulation should have similar trends of physiologic status after treatment.

Nearest Neighbor Regression (NNR) provides a method by which a patient can be compared with a historical data set based on similarities in physiologic VS to make predictions on future values given the known path of the historical data set. When matching patients with similar physiologic status, two important challenges emerge: (1) definition of a system state space and (2) definition of a distance metric to determine nearest neighbors of historical observation to the current conditions. After matching a set of nearest neighbors using similarities in short trends in HR, SBP, MAP, ICP, SI, and PP values, we selected a forecast generation method that captured the system characteristics for prediction of a short future horizon through "borrowing" training ICP values from a historical data set by means of similarity (Fig. 1).

VS are not completely independent of their previous values and may be correlated to their past values over short durations. Such "memory" of past ICP fluctuations can help to predict future values. We used autocorrelation and cross-correlation tools to measure the linear predictability of a time point, that is, if a sequence of observation is simply generated from a random process and if a linear model is sufficient to estimate and predict the variable being observed.[15]

System state similarity is measured by Euclidean distance between two system states. In this study, we selected HR, SBP, SI, MAP, PP, and ICP in the current and past 5, 10, 15, and 20 minutes. For a new patient with the previously mentioned VS measured in the past 20 minutes, we searched for other patients with similar VS characteristics to gather sufficient training points by measuring the distances between the new state and all other states. The top k nearest states (neighbors) and their next 5-minute to 2-hour ICPs were used as a training set to build regression models for different prediction horizons.

After finding similar system states and their corresponding future ICP records, we used regression methods to build prediction models. Because of our limited knowledge of the physiologic mechanisms by which past VS correlate with and/or influence ICP, we adopted the Gaussian process regression method to estimate the function values at each variable. This approach relaxes the parameter space into an infinite space. However, other regression methods can also fit into this framework, such as generalized linear regression, and so on. For comparison, we also applied the regression tree and simple shifting estimation method, adjusting for age, sex, and GCS score as extra features.[16]

RESULTS

We identified 132 adult patients with severe TBI during the course of this study for whom continuous, automated VS data were available. Mean (SD) age for the study group was 40.2 (18.09) years. Patients were predominantly male (104 of 132) and, overwhelmingly, had severe TBI caused by blunt force trauma (96.97%). While 64 patients (48.5%) had isolated head injuries, others often had significant injuries to the chest and abdomen. Full demographics are listed in Table 1. Continuously collected VS including ICP, HR, SBP, SI, MAP, and PP were available at 5-minute temporal resolution for more than 3 hours. This pool provided 65,600 data points, the equivalent of 5,466 hours and 40 minutes of VS monitoring. The prediction horizon ranged from 5 minutes to 2 hours. In training the NNR models, only past and present VS and ICP measurements were used. The predicted ICP values then were compared against the measured ICP value for evaluation (Fig. 2).

Bland-Altman plots show that NNR provides good agreement in predicting actual ICP with a bias of 0.02 (±1.96 SD = 4 mm Hg) for the subsequent 5 minutes and −0.02 (±1.96 SD = 10 mm Hg) for the subsequent 2 hours. These plots (Fig. 3) illustrate the agreement between measured and predicted ICP at 5-minute, 1-hour, and 2-hour prediction horizons in the Gaussian process regression. Figure 4 compares the 1.96 SD

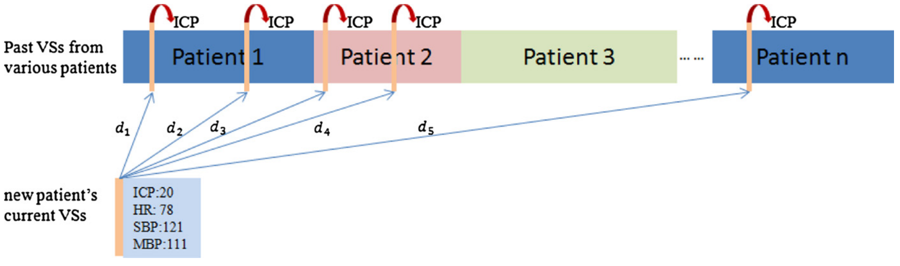

Figure 1. Illustration of searching nearest neighbors given the current system state of a new patient.

TABLE 1. Patient Demographics

n	132
Age, mean (SD), y	40.20 (18.09)
Sex	Male, 104; female 28
Mortality	18 (13.63%)
Injury Severity Score (ISS)	29 (25–38.75)
Postresuscitation GCS score	6 (4–9)
Marshall Score	2 (2–3)
Head Abbreviated Injury Scale (AIS) sore	4 (4–5)
Isolated head injury	64 (48.5%)
Chest AIS score > 2	61 (46.2%)
Abdomen AIS score > 2	14 (10.6)
Mechanism of injury	
Blunt	128 (96.97%)
Penetrating	4 (3.03%)

and mean of predicted values against the measurement from the Bland-Altman plots of the NNR (*red curves*) in comparison with two other commonly used statistical methods, the regression tree (*blue curves*) and simple shifting estimation method (*green curves*). NNR consistently outperformed these alternative methods in predicting future ICP.

DISCUSSION

Despite significant advancements in the specialized care of neurotrauma, TBI is still the most important cause of death and prolonged disability worldwide.[17,18] Primary injury to the brain occurs at the time of impact. Thus, for those who survive, care centers on prevention of secondary injuries by normalizing ICP to avoid the deleterious effects of ICH.[19,20] High-quality continuous electronic data garnered by modern physiologic monitoring systems have the potential to provide an unprecedented insight into the dynamic physiologic response to brain injury, illness, and intervention. In this study, we have shown that the nearest neighbor method provides reasonably accurate and clinically potentially useful predictions of future ICP values. The method is sufficiently flexible to incorporate newly incoming information into the calculation, such as a new VS that can better approximate the physiologic similarity. Given a short duration (20 minutes) of ICP measurement to calibrate the algorithm, it can be used to build patient-specific models that are adaptive to new physiologic changes as they occur.

Although our work shows promise in accurately predicting future ICP fluctuations based on past data, some ICP elevations remain elusive. Patients cough, have recurrent intracranial events, or experience random ICP disturbances that alter ICP trajectory and are difficult to predict. However, the likely effects on ICP of known stimulating events such as suctioning or patient positioning can be estimated if we understand how a patient has responded previously. Reactions to stimuli differ between patients, and in the event that the exact stimuli are known, the responsiveness to those stimuli or interventions can be learned and predicted through NNR. As more is known concerning the natural course and seemingly random fluctuations of ICP following TBI, we may realize the ability to predict these events as well.

While our results showed the utility of NNR, several important limitations exist. This work is a single-center study on a relatively small sample size, and thus, generalizing our

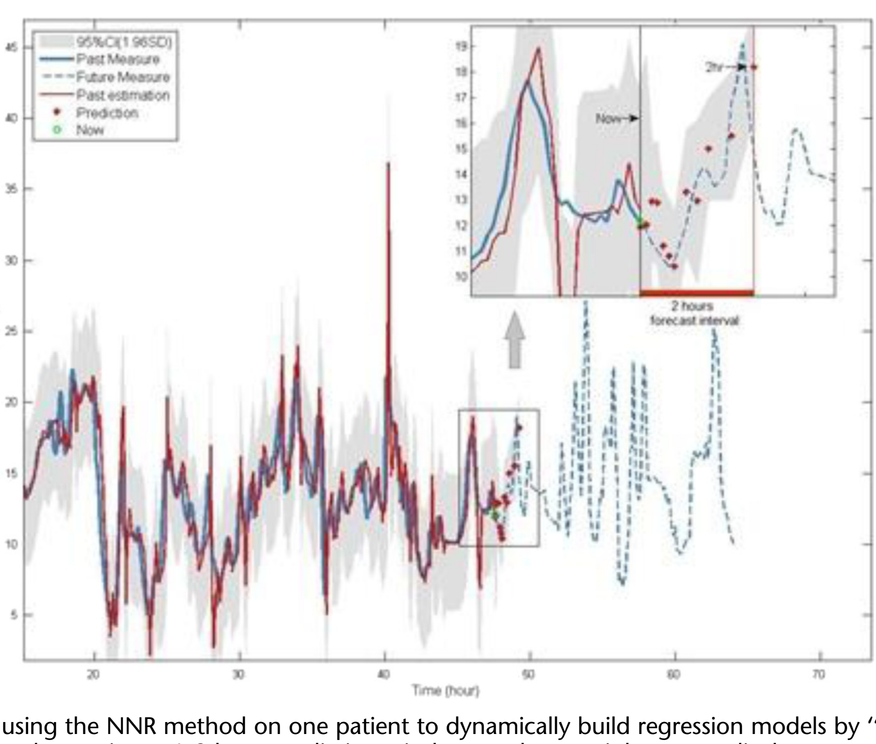

Figure 2. Illustration of using the NNR method on one patient to dynamically build regression models by "borrowing" data (especially the ICP) from other patients. A 2-hour prediction window on the top-right corner displays a trend for ICP, under the assumption that this patient will receive standard treatment.

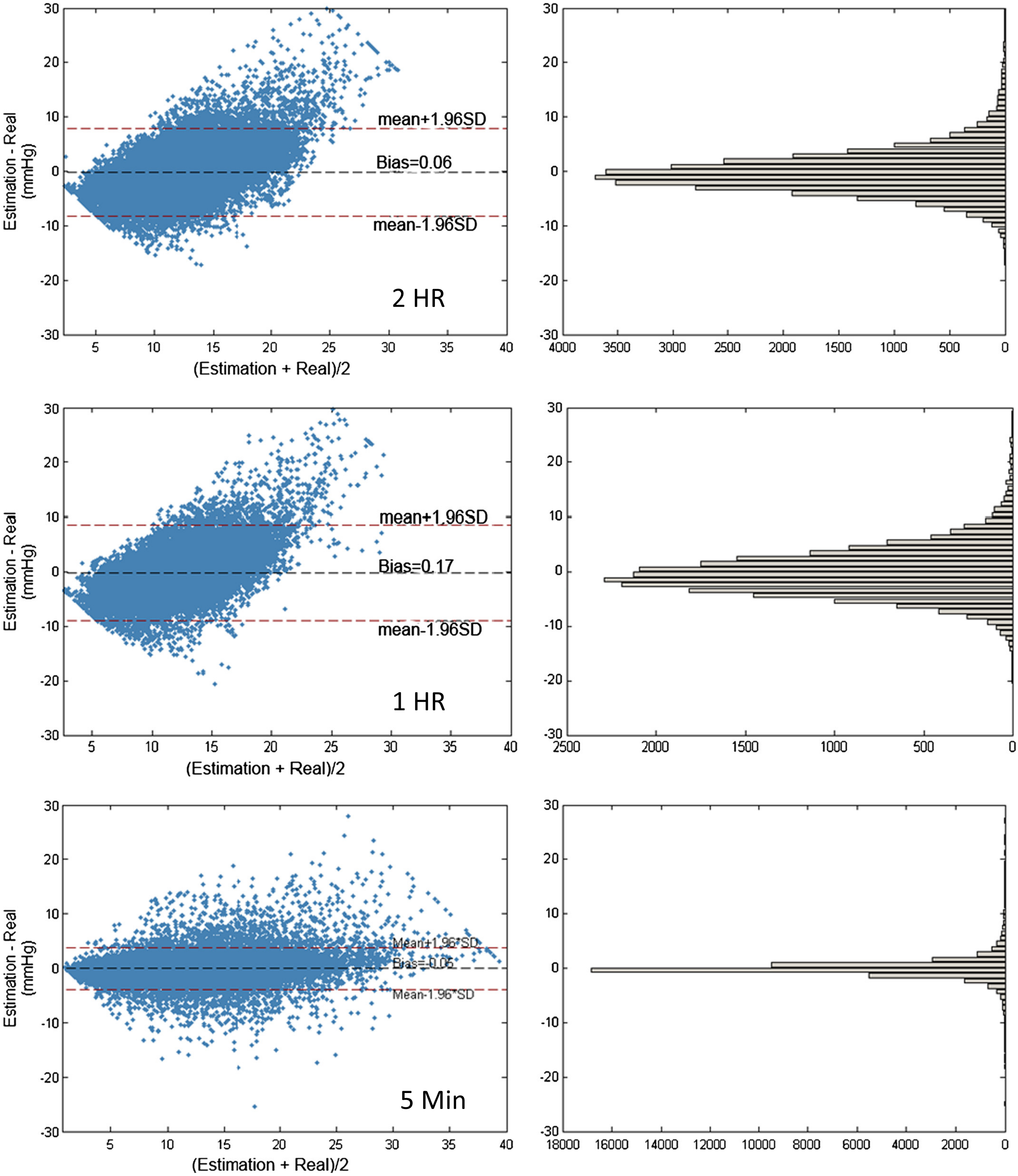

Figure 3. Performance of comparison of prediction for different prediction horizons (5 minutes, 1 hours, and 2 hours) of the NNR using past ICP.

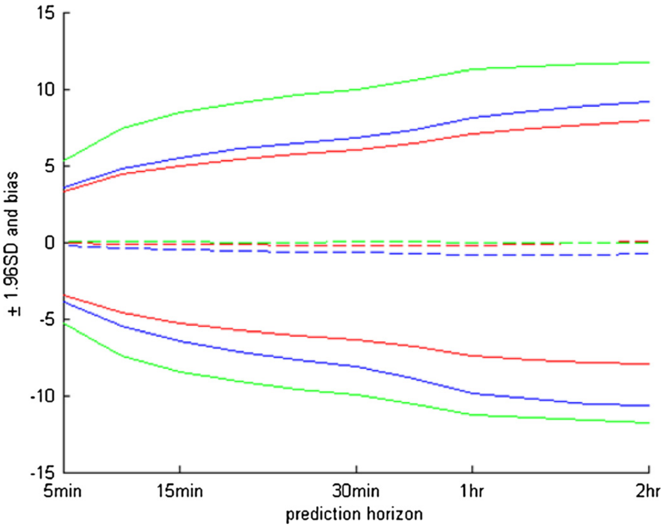

Figure 4. 1.96 SD and bias of ICP predictions of NNR (*red line*), regression tree (*blue line*), and simple shifting method (*green line*).

results to the population at large will require further study at multiple centers using larger, more diverse populations. Although this ICP monitoring framework is very flexible for estimation (current) or prediction (future), it depends on a historic data set, and the quality of data in that data set has significant impact on the estimation accuracy. In addition, finding a similar system state between a new patient and the data set relies on the selection of a set of relevant noninvasive VS. To improve accuracy, additional work is needed to optimize the combination of VS used in this model.

In addition, further work should focus on building a database on the effects of stimuli, systemic injuries, and interventions on ICP levels in patients with TBI. Systemic injuries and clinical interventions often have significant impact on VS or ICP trajectory. Our methodology does not yet incorporate the effect of interventions on predictions of future events. In some recently published work on the effect of medical interventions on ICP, we identified a set of drugs commonly used in ICP management, which have statistically significant effects in changing ICP for up to 4 hours after administration.[21] If our estimation model can incorporate drug treatment given a few hours previously, estimation of current ICP could be adjusted accordingly. In the near future, noninvasive measurement of ICP may replace current methods of measuring ICP.[22] Future work may incorporate these modalities to test the predictive value of noninvasive ICP measures on future ICP. We will also expand our work to focus on more clinically relevant intervals, such as ICP levels higher than 20 mm Hg or values with high instability.

Valid predictive algorithms have the potential to revolutionize the care of patients with TBI, not only to rapidly identify the necessity of interventions to preempt periods of looming ICH but also to identify patients who are recovering well and may not need further escalation of care. It would allow consulting teams to choose the proper timing of events known to raise ICP such as peripheral surgical procedures. In the military setting, it would give physicians, who often are tasked with operating in austere environments with finite resources, a useful triage tool and allow for more informed decisions on when a patient may best withstand the physiologic stressors of aeronautical evacuation to higher-level care facilities.

Our work shows that the statistical technique of NNR can be used to make potentially clinically useful estimates of future ICP values following severe TBI. The results obtained through the use of this machine learning technique add to the body of evidence that ICP provides an important metric for avoidance of secondary brain injury and may offer a physiologic pattern to forecast the course of the disease. This represents an incremental step toward the eventual validation of predictive models for use in decision-assist algorithms. Our results also show the utility of incorporating continuous VS data analysis into ICP prediction. While previous work has shown the ability to predict future episodes of ICH generally,[6–8] we now show that NNR can predict future ranges of ICP in clinically relevant time frames. This advanced notice has the potential with further refinement to impact virtually all aspects of neurointensive care by providing a means to proactively direct the need for escalation or deescalation of therapeutic interventions and possibly avoid the deleterious effects of ICH altogether.

AUTHORSHP

B.W.B., S.Y., P.F.H., and K.K. were primarily responsible for the study design, data collection/analysis/interpretation, and writing. L.G.S., T.M.S., and D.M.S. provided critical revisions and literature search for the manuscript.

DISCLOSURE

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REFERENCES

1. Dutton RP, Stansbury LG, Leone S, Kramer E, Hess JR, Scalea TM. Trauma mortality in mature trauma systems: are we doing better? An analysis of trauma mortality patterns, 1997–2008. *J Trauma*. 2010;69(3):620–626.
2. Stein DM, Hu PF, Brenner M, Sheth KN, Liu K-H, Xiong W, Aarabi B, Scalea TM. Brief episodes of intracranial hypertension and cerebral hypoperfusion are associated with poor functional outcome after severe traumatic brain injury. *J Trauma*. 2011;71(2):364–373.
3. Smith M. Monitoring intracranial pressure in traumatic brain injury. *Anesth Analg*. 2008;106(1):240–248.
4. Brain Trauma Foundation, American Association of Neurological Surgeons; Congress of Neurological Surgeons. Guidelines for the management of severe head injury. *J Neurotrauma*. 2007;24(Suppl 1):S1–S106.
5. Czosnyka M, Pickard JD. Monitoring and interpretation of intracranial pressure. *J Neurol Neurosurg Psychiatry*. 2004;75(6):813–821.
6. McNames J, Crespo C, Bassale J, Aboy M, Ellenby M, Lai S, Goldstein B. *Sensitive precursors to acute episodes of intracranial hypertension*. Como: Italy: 4th International Workshop Biosignal Interpretation; 2002:303–306.
7. Hamilton R, Xu P, Asgari S, Kasprowicz M, Vespa P, Bergsneider M, Hu X. Forecasting intracranial pressure elevation using pulse waveform morphology. *Conf Proc IEEE Eng Med Biol Soc*. 2009;2009:4331–4334.
8. Hu X, Xu P, Asgari S, Vespa P, Bergsneider M. Forecasting ICP elevation based on prescient changes of intracranial pressure waveform morphology. *IEEE Trans Biomed Eng*. 2010;57(5):1070–1078.
9. Pattinson K, Wynne-Jones G, Imray CH. Monitoring intracranial pressure, perfusion and metabolism. *Continuing Education in Anaesthesia, Critical Care and Pain*. 2005;5:130–133.

10. Weerakkody RA, Czosnyka M, Trivedi RA, Hutchinson PJ. Intracranial pressure monitoring in head injury. In: Peter C. Whitfield et al. (eds.) Head Injury. Cambridge: Cambridge University Press; 2009. pp. 87–102.
11. Czosnyka M, Smielewski P, Kirkpatrick P, Laing RJ, Menon D, Pickard JD. Continuous assessment of the cerebral vasomotor reactivity in head injury. *Neurosurgery.* 1997;41(1):11–19.
12. Czosnyka M, Smielewski P, Timofeev I, Lavinio A, Guazzo E, Hutchinson P, Pickard JD. Intracranial pressure: more than a number. *Neurosurg Focus*. 2007;22(5):1–7.
13. Ursino Mauro. A mathematical study of human intracranial hydrodynamics part 1—the cerebrospinal fluid pulse pressure. *Ann Biomed Eng*. 1988;16(4):379–401.
14. Kashif FM, Verghese GC, Novak V, Czosnyka M, Heldt T. Model-based noninvasive estimation of intracranial pressure from cerebral blood flow velocity and arterial pressure. *Sci Transl Med*. 2012;129(4):44.
15. Shumway RH, Stoffer DS. *Time Series Analysis and Its Applications: With R Examples*. 3rd ed. New York, NY: Springer; 2011:17–22.
16. Breiman L, Friedman JH, Olshen RA, Stone CJ. *Classification and Regression Trees*. Monterey, CA: Wadsworth & Brooks/Cole Advanced Books & Software; 1984.
17. Lu J, Marmarou A, Choi S, Maas A, Murray G, Steyerberg EW. Mortality from traumatic brain injury. *Acta Neurochir Suppl*. 2005;95:281–285.
18. Kramer AH, Zygun DA. Neurocritical care: why does it make a difference? *Curr Opin Crit Care*. 2014;20(2):174–181.
19. Sheth KN, Stein DM, Aarabi B, Hu P, Kufera JA, Scalea TM, Hanley DF. Intracranial pressure dose and outcome in traumatic brain injury. *Neurocrit Care*. 2013;18(1):26–32.
20. Jiang JY, Gao GY, Li WP, Yu MK, Zhu C. Early indicators of prognosis in 846 cases of severe traumatic brain injury. *J Neurotrauma*. 2002;19(7):869–874.
21. Colton K, Yang S, Hu PF, Chen HH, Bonds B, Scalea TM, Stein DM. Intracranial pressure response after pharmacologic treatment of intracranial hypertension. *J Trauma Acute Care Surg*. 2014;77(1):47–53.
22. Kristiansson H, Nissborg E, Bartek J Jr, Andresen M, Reinstrup P, Romner B. Measuring elevated intracranial pressure through noninvasive methods: a review of the literature. *J Neurosurg Anesthesiol*. 2013;25(4):372–385.

EDITORIAL CRITIQUE

Dr. Bonds and colleagues from the R Adams Cowley Shock Trauma Center in Baltimore have attempted to forecast values of intracranial pressure (ICP) based on prior patterns in both ICP and continuous peripheral vital signs, with the ultimate goal of minimizing the effect of secondary insults to the brain after injury. To do this, they have used a k-nearest neighbor regression model in which several parameters, including heart rate, systolic blood pressure, shock index, mean arterial pressure, and pulse pressure are used to predict changes in ICP. This group found excellent agreement between actual ICP values and a predictive model using the regression analysis described in this study. I have some concern that of the five covariates chosen, only three were independent of each other. The resulting multicollinearity of these predictor variables may lead to erratic changes in the estimate of the ICP parameter with only small changes in the data entered into the model.

Modern physiologic monitoring systems such as those employed for the purposes of this study have the potential to generate a large volume of continuous electronic data. In the future, we should expect that such data sets will become more commonly available. Analyses of these data sets will have important potential clinical applications, such as described in this study. Decisions regarding the continuation of sedating medications and of the need for ICP monitoring may potentially be made based on the understanding of the correlation between continuous vital signs and ICP. The recognition of such relationships promises to be extremely useful in clinical practice. I look forward to continued research on this topic and the further use of large data sets to generate predictive models in trauma care in a general sense.

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