A Method for Estimating Zero-Flow Pressure and Intracranial Pressure

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Background: It has been hypothesized that the critical closing pressure of cerebral circulation, or zero-flow pressure (ZFP), can estimate intracranial pressure (ICP). One ZFP estimation method used extrapolation of arterial blood pressure as against blood-flow velocity. The aim of this study was to improve ICP predictions.

Methods: Two revisions have been considered: (1) the linear model used for extrapolation is extended to a nonlinear equation; and (2) the parameters of the model are estimated by an alternative criterion (not least squares). The method is applied to data on transcranial Doppler measurements of blood-flow velocity, arterial blood pressure, and ICP from 104 patients suffering from closed traumatic brain injury, sampled across the United States and England.

Results: The revisions lead to qualitative (eg, precluding negative ICP) and quantitative improvements in ICP prediction. While moving from the original to the revised method, the ± 2 SD of the error is reduced from 33 to 24 mm Hg, and the root-mean-squared error is reduced from 11 to 8.2 mm Hg. The distribution of root-mean-squared error is tighter as well; for the revised method the 25th and 75th percentiles are 4.1 and 13.7 mm Hg, respectively, as compared with 5.1 and 18.8 mm Hg for the original method.

Conclusions: Proposed alterations to a procedure for estimating ZFP lead to more accurate and more precise estimates of ICP, thereby offering improved means of estimating it noninvasively. The quality of the estimates is inadequate for many applications, but further work is proposed, which may lead to clinically useful results.

Key Words: blood flow, brain, head injury, intracranial pressure, noninvasive

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Monitoring and manipulation of intracranial pressure (ICP) aids patient management and may improve clinical outcome after trauma and other conditions.[1–12] Increased ICP impairs neural function by reducing blood flow (causing ischemia) and by direct mechanical compression or herniation of brain tissue. Measurements of ICP require placement of a pressure sensor within the cranium. The invasiveness of this procedure has led to the development of a variety of noninvasive approaches. One class of approaches uses transcranial Doppler (TCD) and arterial blood pressure (ABP) measurements.[13–15] Another class is based on imaging and analysis of various compartments of the eye—in particular, the ophthalmic artery or the optic nerve sheath diameter.[16–22] In the present study, blood-flow velocity (FV) in the middle cerebral artery, derived from TCD, and ABP are used to develop an alternative approach for the estimation of ICP.

Burton[23] conducted an analysis showing that arterial critical closing pressure (CCP) may approximate both ICP and a force resulting from the tension of the smooth muscles of the arterial walls. Aaslid and colleagues[24,25] examined several methods for estimating CCP, comparing the results with a "gold standard," measured during induced ventricular fibrillation. Michel et al[26] and Kottenberg-Assenmacher et al[27] used physics-based models to address CCP measurements and have reported how it may aid in estimating ICP noninvasively. Another study, more focused on the hemodynamics in pregnancy,[28] has examined the connection between CCP and ICP. The role played by the cerebrovascular wall tension in the CCP-ICP connection has been examined as well.[29]

A simple method for estimating CCP involves fitting a least-squares line through ABP versus FV. Specifically, one first considers the scatterplot of ABP versus FV when the 2 have been aligned to have a comparable phase (ie, maximum correlation). If the scatterplot displays a linear relationship between ABP and FV, the y-intercept of a line fitting the scatterplot defines an estimate of CCP. This method is simple because the alternatives generally consider smoothing or filtering based on Fourier analysis of the various time series, as carried out in the study by Aaslid et al.[25] Preprocessing of this type adds complexity to the analysis, and, for this reason, the CCP estimation method considered here is a variation of the simple, extrapolation method. The main goal of the study here is not to improve on the estimation of CCP itself but rather

to develop alternative models of CCP estimation that better correlate with ICP.

Czosnyka et al[30] examined several methods for estimating CCP and also studied the correlation between CCP and ICP. Using a data set involving 98 patients, they reported a correlation coefficient of 0.41 between ICP and CCP. They also reported that ICP can be predicted from CCP to within ± 27 mm Hg (95% confidence level). Thees et al[31] found a correlation of 0.91, based on 70 patients (no predictive error bar has been reported). On a data set involving 20 patients, Buhre et al[32] used a method developed by Weyland et al[33] and reported a correlation coefficient of 0.93 and a 2 SD (ie, approximately 95.5% confidence interval) of ± 15.2 mm Hg. In the work carried out by these authors, CCP was often referred to as the zero-flow pressure (ZFP), and so we define the "ZFP hypothesis" as the hypothesis that ICP can be estimated from some estimate of ZFP (or CCP).

In the current paper, 2 revisions to the extrapolation method have been examined, both aimed at improving the estimation of ICP. The revisions involve: (1) relaxing the linearity of the equation/model used for extrapolation; and (2) using an alternative criterion (not least squares) for estimating the parameters of the model. The first revision ensures that the ICP predictions are physical (ie, non-negative), and the second revision eliminates the need to align FV and ABP—a necessary step in the original extrapolation method. In addition to these qualitative improvements, the revised method also leads to more accurate and precise estimates of ICP.

MATERIAL AND METHODS

Patients

Patient data for this preclinical study were collected from a variety of hospitals in the United States, after a study at the University of Washington led by Dr. Mourad, as well as from Addenbrooke's Hospital, Cambridge, England, led by Dr. Czosnyka.

The core contributing hospitals within the United States were Harborview Medical Center (Seattle, WA), Columbia University Medical College (New York City, NY), and the University of Texas Medical School at Houston, TX. Data from 59 patients (49 male, 10 female) with a mean age of 34 years (range, 13 to 81) and a mean Glasgow Coma Score of 5 (range, 3 to 11) were collected. Studies there met the following inclusion criteria: (1) all patients experienced closed head injury; (2) no patient received neurosurgical intervention other than placement of an invasive ICP monitor; (3) all patients had an ABP catheter in place at the time of the study; (4) all patients could tolerate a TCD examination; (5) all patients were 8 years old or older; and (6) informed consent was obtained from all patients or their families. These criteria were also followed at Addenbrooke's Hospital, except that patients regardless of age could consent to participate in the study and, in addition, all patients were intubated. Finally, for both centers, all patients were monitored and treated following the specifications of the Brain Trauma Foundation.[9,10]

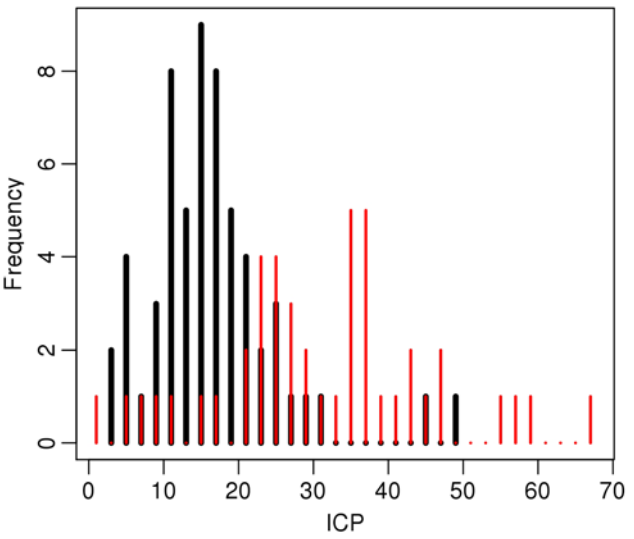

FIGURE 1. Distribution of intracranial pressure (ICP) for the University of Washington patients (black) and the Cambridge patients (red).

Figure 1 shows the distribution of the mean invasive ICP (in black) of 59 patients collected by the team at the University of Washington. In addition, 45 patients from Cambridge, England, were chosen from over 300 anonymous cases collected by that institution to "fill in" the gaps in the ICP distribution of data collected at the University of Washington. These gaps are on the high-ICP side of the distribution. However, to avoid a situation in which all high-ICP patients are from Cambridge, low-ICP patients from Cambridge were also included in the analysis. The distribution of ICP for the Cambridge patients is shown in red in Figure 1. Schmidt et al[13] described the circumstances under which these data were collected, including the fact that TCD recording was a part of routine daily examination of cerebral hemodynamics, and anonymous use of these recordings for further retrospective methodological studies was approved by the local Neurocitical Care Users Committee.

Data

For each patient, ABP, ICP, and maximum blood-FV within the middle cerebral artery (or FV) Doppler time series were acquired through clinically approved TCD units and processed using custom software so as to provide synchronized ABP, ICP, and FV data. Data acquisition lengths varied from 5 to 30 minutes and were obtained anywhere from 0 to 11 days after placement of an ICP sensor. ICP was monitored using a ventricular catheter (Integra Lifesciences Corporation or Camino Laboratories), by which cerebral spinal fluid drains were closed and supervised during data capture. ICP was also monitored with a Camino parenchymal catheter (Integra Lifesciences Corporation) or a Codman parenchymal ICP microsensor (Codman Neuroscience). Blood pressure was

acquired invasively from an arterial line placed in the radial, femoral, brachial, or ulnar artery. All patients from Cambridge were sedated, paralyzed, and ventilated to maintain adequate oxygenation and mild hypocapnia. All patients from the University of Washington cohort underwent the same treatment, except for 1 patient who was no longer under ventilation when this study was performed.

All retrospective data processing and analysis was conducted at the Applied Physics Laboratory (APL), University of Washington. Data collected through the APL hospital cohort were digitized at 125 Hz, whereas data collected in Cambridge were digitized at 40 Hz. To place the data sets on the same footing, the APL data sets were downsampled to 40 Hz. A fixed duration (5 min) was selected from each of the 104 patients for statistical analysis.

Data Processing and Statistical Analysis

In this study, the methodology of Weyland et al[33] and Buhre et al[32] (WB method) has been revised. The revised method involves 2 specific alterations: (1) the linear model/equation in the WB method is replaced with a nonlinear equation; and (2) the least-squares criterion for estimating the parameters of the model is replaced with an alternative criterion that does not have a common name; we shall refer to it as the *SD criterion*. These revisions are further described in the Appendix. The main purpose of the first revision is to prevent negative ICP predictions that arise in the WB method. The primary benefit of the second revision is to preclude the preprocessing step of aligning the FV and ABP time series. This alignment is necessary for the least-squares criterion method, and requires the specification of quantities that add to its complexity. For example, given that the alignment procedure is an optimization problem, one must specify the quantity being optimized; the correlation or the covariance between the 2 series are common choices but can lead to different results. The duration of the 2 time series over which the alignment is performed is another quantity that can affect the results. In addition to these benefits, the revised methodology (involving both revisions) leads to higher-quality ICP predictions as compared with those of the WB method. The goodness of the ICP estimates is assessed in terms of the bias, SD, and root-mean-square of the errors (RMSE).

To demonstrate the ingredients of the WB method, consider the data from a single patient. Figure 2A shows the time series for FV (solid curve) and ABP (dashed line) for 1 patient for a duration of 2.5 seconds (ie, 100 data points displayed at 40 Hz). Figure 2B displays the scatterplot of ABP versus FV (circles) after they have been aligned. The 2 lines are based on the least-squares criterion (dotted) and the SD criterion (solid); their equations are $y = 14.1 + 0.70x$ and $y = 13.0 + 0.73x$, respectively. The ZFP hypothesis asserts that the y-intercept of the least-squares line approximates the mean ICP. The mean of the observed ICP for this patient is 13.5 mm Hg, marked with an arrow along the y-axis. Evidently, the y-intercept of the least-squares line agrees with this

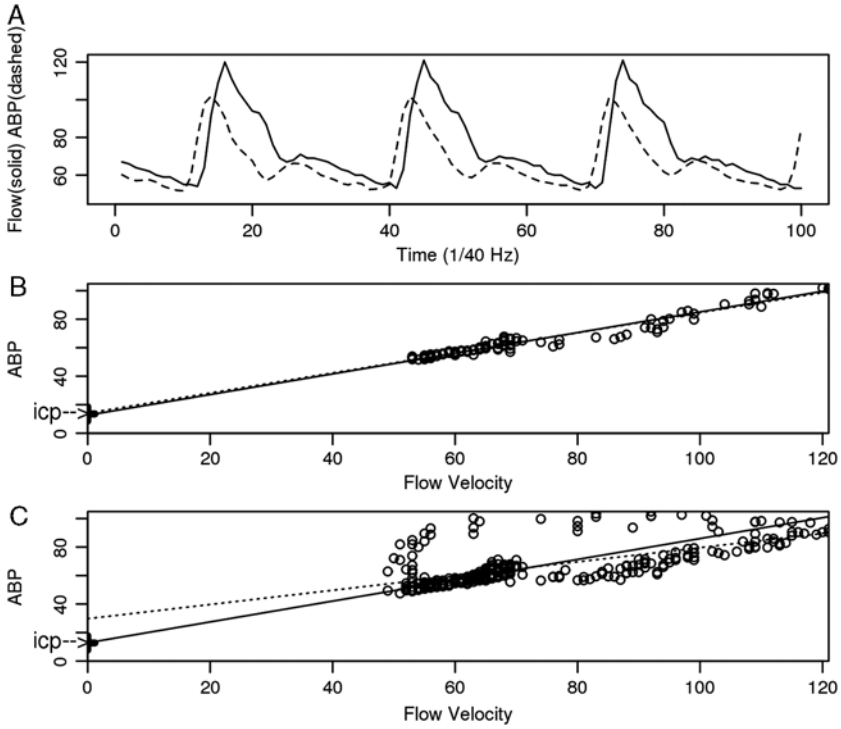

FIGURE 2. A, The time series of flow velocity (FV) (solid line) and arterial blood pressure (ABP) (dashed line) for 1 patient. B, Scatterplot of ABP versus FV (circles), the least-squares fit (dotted line), and the SD line (solid line). The mean ICP for this patient is labeled along the *y*-axis with an arrow. C, Same as B, but before alignment of the 2 time series.

patient's mean ICP, supporting the ZFP hypothesis for this patient. In this case, the lines according to the 2 criteria are nearly identical, and so they lead to approximately equal estimates of mean ICP.

As mentioned above, a utility of the SD criterion is that it does not require an alignment of the ABP and FV time series. This is demonstrated in Figure 2C, where the scatterplot of ABP versus FV is shown without any alignment. Also shown are the lines corresponding to the least-squares and the SD criteria; their equations are $y = 29.7 + 0.50x$ and $y = 13.0 + 0.73x$, respectively. Whereas the y-intercept of the former deviates considerably from the mean ICP of 13.5 mm Hg, that of the latter does not. Indeed, the SD line for the nonaligned data is identical to that of the aligned data. This feature is not a coincidence and is explained in the Appendix. The SD line is unaffected by any phase difference between the ABP and FV time series. Therefore, use of the SD line simplifies the WB method by eliminating the alignment procedure.

Our paper compares the WB method with the revised method developed here. Each method is applied to a segment of the ABP and FV time series of 7.5 seconds (ie, 300 data points). This duration was selected because it is sufficiently long to cover several respiratory cycles (2 to 4, depending on the patient) at the same time being sufficiently short to be unaffected by slow waves in ICP. Although the results are relatively insensitive to the length of the time series, very short time segments do not produce sufficient cases for an adequate estimation of the fit. In contrast, recall that the ZFP as estimated from the ABP and FV observed over a time segment is expected to approximate the mean of ICP over that same time segment. As such, results obtained from very long time segments are likely to be confounded by slow changes in ICP.

To utilize the information in the time series more fully (ie, beyond only one time segment of 7.5 s in duration), 200 different segments of the time series are sampled randomly. Each of these 200 trials yields an estimate of mean ICP. This sampling of the time series is important because any given time segment may, or may not, confirm the ZFP hypothesis. Only the aggregate of all the 200 estimates legitimately assesses the validity of the hypothesis and its statistical significance.

All analyses were performed using a statistical analysis software called R.[34]

RESULTS

Figure 3 shows the scatterplot of the observed ICP versus ZFP (ie, the estimated ICP) for all 104 patients for the WB method (Fig. 3A) and the revised method (Fig. 3B). Each cluster/color in the figures corresponds to a patient, and so each cluster contains 200 points associated with the aforementioned 200 trials. The vertical and horizontal lines denote the grand mean of the observed ICP across all patients. The diagonal line has a slope of 1 and a 0 y-intercept. If the estimates were perfect, all the points in the scatterplot would reside on this diagonal line. In contrast, if the ZFP hypothesis did not hold at all, the points would be randomly distributed (at best, about the vertical line). Without performing any quantitative analysis, it is quite evident from these scatterplots that the ZFP hypothesis does hold in the WB method (Fig. 3A) because that procedure produces negative (unphysical) ZFP values. In contrast, the revised method (Fig. 3B) does not. The revised method also produces a "tighter" scatterplot, suggesting higher-quality predictions, further discussed below.

Instead of a scatterplot of ICP versus ZFP, many studies consider the Bland-Altman plot, that is, the plot of the errors (ICP-ZFP) versus the average of ICP and ZFP. Figure 4A shows such a plot for the WB method. The 3 dashed lines show the average of the errors (ie, bias) $\pm$ 2 SDs; in this case, they are at -4 ± 33 mm Hg. The fact that the average of the errors is below 0 indicates that the estimates are (positively) biased; that is, ZFP is generally larger than the observed ICP. Furthermore, the averages of ICP and ZFP take on negative values as a consequence of ZFP itself taking negative values. To eliminate these negative values, it may be tempting to simply shift all ZFP by some positive amount; however, this increases the bias further. Similarly, shifting ZFP by some negative amount decreases the bias, but only at the cost of increasing the incidents of negative ZFP.

The results from the revised method are shown in Figure 4B. The average $\pm$ 2 SD of the errors is now at 0 ± 24 mm Hg. The $\pm$ 2 SD of the errors is reduced, from 33 to 24 mm Hg. In short, the revised method leads

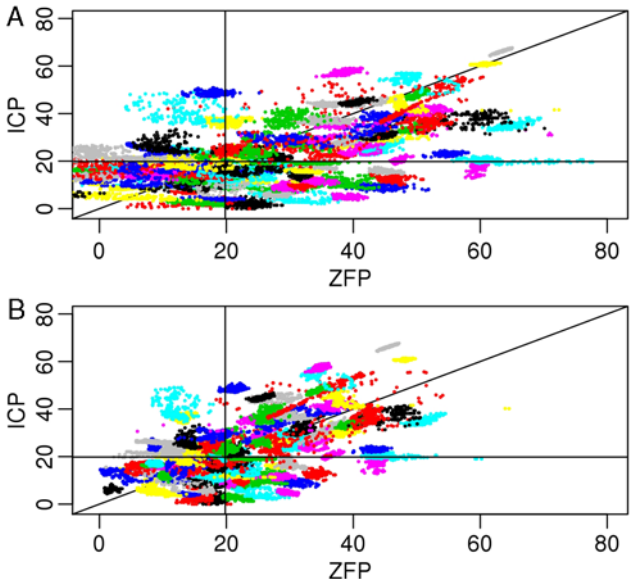

FIGURE 3. The scatterplot of the observed intracranial pressure (ICP) versus zero-flow pressure (ZFP) (ie, estimated ICP) for all 104 patients (clusters in different colors) according to the Weyland et al and Buhre et al (WB) method (A) and the revised method (B). Each cluster contains 200 points corresponding to 200 different time segments of the time series for that patient. The vertical and horizontal lines denote the grand mean of the observed ICP across all patients. The diagonal line is a line with slope equal to 1 and y-intercept equal to 0.

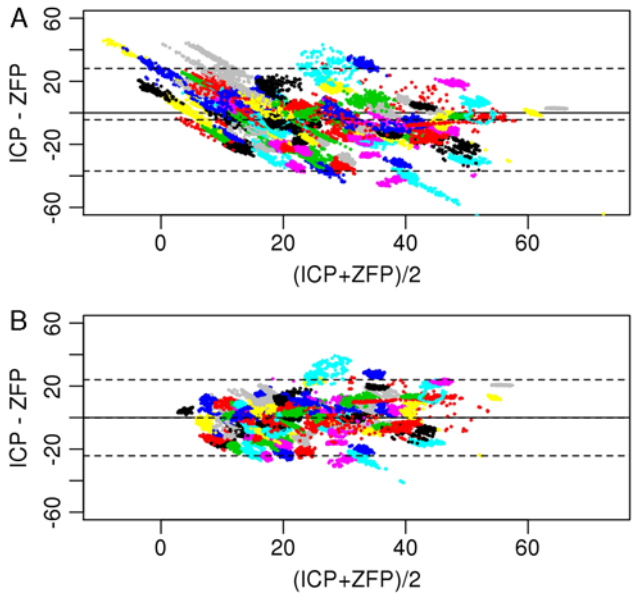

FIGURE 4. Comparison of intracranial pressure (ICP) and zero-flow pressure (ZFP) for the Weyland et al and Buhre et al (WB) method (A) and the revised method (B). The dashed horizontal lines denote the mean and mean ± 2 SD. They are −4 ± 33 and 0 ± 24 mm Hg, respectively.

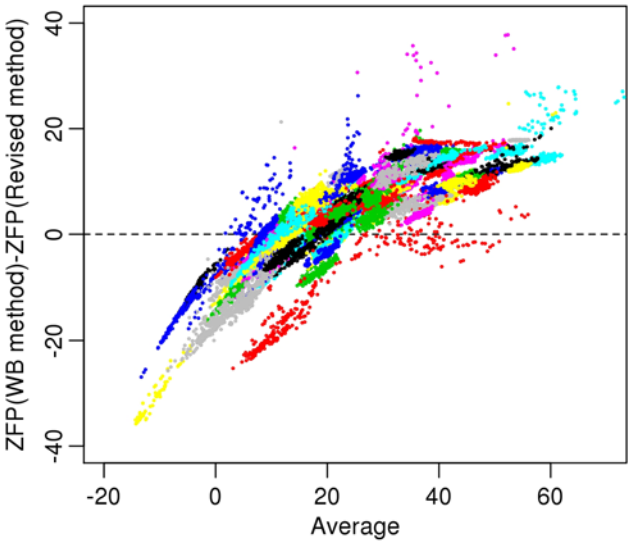

FIGURE 5. A Bland-Altman plot showing the difference between the zero-flow pressure (ZFP) estimated by the 2 methods [Weyland et al and Buhre et al (WB) method and revised] as a function of their average. The 2 estimates appear to have a nonlinear and complex relationship that varies across patients.

to estimates that are non-negative (ie, physical) and more precise than those for the WB method. The average error in the revised method is nearly 0, as a consequence of setting γ in Eq.(4) to 17.5 mm Hg. The reason for this choice is discussed in the next section.

Table 1 shows quantiles of the distribution of errors for the 2 methods. It is evident that the revised method is superior to the WB method in terms of both the median (50th percentile) and the spread of the distribution of errors. The distribution of RMSE values is also shown. The median RMSE values for the 2 methods are 11.1 and 8.2 mm Hg, respectively; the revised method has the narrower of the 2 distributions, thereby leading to more precise estimates of ICP.

A direct comparison of the WB method with the revised method is presented in the form of a Bland-Altman plot, showing the difference between the 2 estimates of ZFP as a function of their average (Fig. 5). Evidently, the 2 estimates can differ significantly, depending on the patient. For some patients, the difference between the 2 estimates is small (± 5 mm Hg) and centered around 0. For other patients, the 2 estimates can differ as much as ± 20 mm Hg. For some patients, the revised estimates of ZFP are consistently higher than the WB estimates, whereas for other patients that comparison is reversed. Moreover, the nonlinear pattern (across patients) shown in Figure 5 implies that the 2 estimates are nonlinearly related; this nonlinearity is a direct consequence of the nonlinearity of Eq. (4). In short, the relationship between the 2 estimates is complex and varies between patients.

DISCUSSION

The "ZFP hypothesis" asserts that the ZFP approximates ICP. Although many groups have contributed to testing this hypothesis, one of the simplest methods estimates ZFP by extrapolation using a least squares, straight line fit of ABP versus FV after the 2 time series have been aligned. Here several revisions to that method (called the "WB method") are proposed: first, instead of a straight line fit, a nonlinear equation is used. Second, instead of the least-squares criterion for estimating the parameters of the fit, the SD criterion is used. These revisions preclude negative ICP predictions and eliminate the least-squares requirement of maximally correlating the FV and ABP data. Moreover, it is shown that these revisions improve the estimates of ICP in terms of their bias (accuracy) and SD

TABLE 1. The Percentiles of the Distribution of Errors and of RMSE for the 2 Methods

	Percentiles of Error					Percentiles of RMSE				
	0th	25th	50th	75th	100th	0th	25th	50th	75th	100th
WB method	−67.4	−14.9	−4.8	5.5	46.6	0.0	5.1	11.1	18.8	67.4
Revised method	−41.2	−8.4	0.1	8.1	39.2	0.0	4.1	8.2	13.7	41.2

RMSE indicates root-mean-squared error; WB method, Weyland et al and Buhre et al method.

(precision), as well as their RMSE. The mean ± 2 SD of the errors for the revised model is about 0 ± 24 mm Hg, in contrast to −4 ± 33 mm Hg as obtained by applying the WB method to our data set. The median RMSE for the revised model is 8.2 mm Hg, compared with 11.1 mm Hg using the WB method.

Buhre et al[32] reported a value of 15.2 mm Hg for the ± 2 SD of errors when they applied the WB method to their data set, nearly half of the value found here (33 mm Hg) when the WB method is applied to the current data set. A few explanations for the discrepancy are as follows. One difference between the 2 studies is in the mean ICP across all patients; Buhre and colleagues reported a mean ICP of 34.7 mm Hg for their data set, as opposed to 20 mm Hg for the current data set. Thus, their patients have generally higher ICP than those analyzed here. Therefore, it may be that the ZFP hypothesis works better at higher ICP values. Another difference is in the size of the sample; the data set analyzed by Buhre and colleagues consists of 20 patients, much smaller than the 104 patients in the data set analyzed here. Furthermore, they reported that the median number of measurements taken from each patient was about 7, resulting in a total of 180 measurements. The number of measurements taken from each patient in the current data set is 200, resulting in a total of 20,800 measurements. The larger number of patients and the larger number of measurements per patient together are likely to lead to the larger errors found on the current data set.

It is important to explain why the mean of the errors from the revised method is nearly 0 mm Hg. The revised method is based on a model [Eq. (4)] that, in addition to the intercept and slope parameters (α, β), also has another parameter (γ) that effectively controls the mean of the errors (ie, the bias of the ICP predictions). Whereas the former parameters vary between patients, the latter is a constant for all patients. Given that it controls bias, it can be set to a value that in turn renders the predictions bias free. For the current data set, that value is 17.5 mm Hg. Assuming the 104 patients in the data set are a random sample from the population of interest, γ = 17.5 mm Hg should give bias-free predictions for all "future" patients not included in the current data. To test that expectation, a resampling method[35] was used for the purpose of estimating the sampling variability of bias when γ = 17.5 mm Hg (only bias was considered because it is the facet of performance most affected by γ). Specifically, the proposed model (with γ = 17.5 mm Hg) was applied to half of the 104 patients, randomly selected, and the bias of the predictions was recorded. This resampling procedure was repeated 10 times, each time taking a different random sample of 52 patients and computing the bias of the predictions. The mean ± 2 SD across the 10 trials was found to be 0.9 ± 2.0 mm Hg, well within the bounds of observational and instrumental error. In other words, the bias-free nature of the predictions on the current data set (as assured by γ = 17.5 mm Hg) is likely to be insensitive to sampling variations.

Also, note that *only the mean* of the observed values of ICP is used in determining this value of γ because bias is simply the difference between the mean of the observed and predicted ICP. This observation offers another explanation for why the choice of γ = 17.5 mm Hg is likely to be generalizable to the population at large. It is also possible to set γ = 0, in which case the observed mean of ICP is not used at all at any stage in the development of the revised model. The result (not shown here) is that the revised method still outperforms the WB method in terms of the percentiles of the errors and the RMSE, although the bias of the errors is no longer 0.

A visual examination of Figure 3 suggests that, although there is a correlation between ICP and ZFP "between patients," the correlation "within patient" is less clear. For some patients, the 200 points are tightly clustered around a line (implying a strong within-patient correlation), but for other patients no such correlation is evident. We are currently investigating the characteristics of the patients (eg, the location of the ABP gauge) that may distinguish between these types of patients. The decomposition of variance (into between-patients and within-patient) may also improve the estimates of ICP through the development of mixed-effects models.[36]

In all of the analyses performed here, the quantity called ZFP has served only as a predictor of ICP; it has been assumed that this ZFP is an accurate measure of the "true" ZFP. Indeed, even the quantity called ABP has been assumed to be an accurate estimate of the true ABP. The first assumption has been addressed by Aaslid et al,[25] wherein it appears that examining the first harmonics of the time series for ABP and FV may lead to more accurate estimates of the true ZFP. Kalmar et al[37] have also considered alternative measures of ZFP. Hsu et al[38] examined the effects of more accurate measures of the true ABP in assessing the true ZFP. It is, therefore, possible that the ICP predictions from our method can be improved further by invoking more accurate measures of the true ZFP and ABP.

An important limitation of our study centers on our use of ABP data. Specifically, the height difference between the point of ABP measurement and point of TCD measurement was not reported with the data collected at Addenbrooke's Hospital. We therefore did not reduce the peripherally measured ABP by an amount proportional to this height difference to create a proxy for cerebral ABP at the middle cerebral artery. This may have introduced a systematic overestimation of cerebral ABP and therefore a shift in the scatterplots to the right with systematical errors of ZFP and consequently of γ. This potential source of error would, however, contribute equally to both the WB method and the SD method, leaving the conclusion of this paper intact—namely, the advantage of the SD method relative to the WB method. Future work will consider correction to the measured ABP on the basis of the potential height difference between the point of measurements of ABP and blood flow in the brain, which may improve the results further.

CONCLUSIONS

Proposed revisions to a methodology for estimating ICP from ZFP, through FV and ABP, have been shown

to lead to improved predictions of invasively measured values of ICP. Although the ± 2 SD of errors is reduced from 33 to 24 mm Hg, the quality of the predictions remains mostly unacceptable, at least clinically, because most applications would require a prediction error of ≤10 mm Hg. Further work, including those suggested here, is necessary before this approach can yield a clinically useful predictor for ICP.

APPENDIX

For data on (x, y), the WB method calls for a straight line fit.

$$y=\alpha+\beta x, \quad (1)$$

where the parameters α, β are estimated via the least-squares criterion from data on x = FV and y = ABP, that is,

$$\alpha=\text{mean(ABP)}-\text{mean(FV)}\times\beta, \qquad \beta=\frac{r\times\text{SD(ABP)}}{\text{SD(FV)}}, \quad (2)$$

and r is Pearson correlation coefficient between ABP and FV. The ZFP hypothesis asserts that the least-squares estimate of α (ie, the y-intercept) approximates ICP. The *SD criterion* is based on the SD of x and y (hence the "SD" in the name). The line according to the SD criterion is defined as the line that goes through the point defined by the mean of x and mean of y, with a slope given by the ratio SD(y)/SD(x), where SD denotes standard deviation.[39] In short, the equation of an SD line for ABP versus FV is that given in Eq. (1), but with

$$\alpha=\text{mean(ABP)}-\text{mean(FV)}\times\beta, \qquad \beta=\frac{\text{SD(ABP)}}{\text{SD(FV)}}. \quad (3)$$

Note that the only difference is that the correlation coefficient does not enter into the latter. This is the reason why the SD line is unaffected by the alignment of x and y. The geometry underlying the SD criterion is in many ways more intuitive than that of the least-squares criterion, despite the popularity of the latter. For example, if a scatterplot displays a cigar-shaped or elliptical pattern, then the SD line coincides with the major axis of the ellipse, while the least-squares line has a slope generally smaller than that of the SD line.[39] Note that, in Eq. (2), as r approaches 1, then the estimates of α and β according to the least-squares criterion coincide with the estimates given by the SD criterion in Eq. (3). Said differently, the SD line and the least-squares line coincide when x and y are aligned.

The structure of the fit in Eq. (1) does not preclude negative values of the y-intercept. To disallow such unphysical values of ICP, we propose the following fit

$$(y-\gamma)^{1/2}=\alpha+\beta x \quad (4)$$

where γ is a fixed non-negative constant. Then, the ZFP is given by $\gamma+\alpha^2$, and so cannot be negative. Structures involving the exponential have also been tested, but with no noticeable difference.

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