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Model-Based Noninvasive Estimation of Intracranial Pressure from Cerebral Blood Flow Velocity and Arterial Pressure

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Intracranial pressure (ICP) is affected in many neurological conditions. Clinical measurement of pressure on the brain currently requires placing a probe in the cerebrospinal fluid compartment, the brain tissue, or other intracranial space. This invasiveness limits the measurement to critically ill patients. Because ICP is also clinically important in conditions ranging from brain tumors and hydrocephalus to concussions, noninvasive determination of ICP would be desirable. Our model-based approach to continuous estimation and tracking of ICP uses routinely obtainable time-synchronized, noninvasive (or minimally invasive) measurements of peripheral arterial blood pressure and blood flow velocity in the middle cerebral artery (MCA), both at intra-heartbeat resolution. A physiological model of cerebrovascular dynamics provides mathematical constraints that relate the measured waveforms to ICP. Our algorithm produces patient-specific ICP estimates with no calibration or training. Using 35 hours of data from 37 patients with traumatic brain injury, we generated ICP estimates on 2665 nonoverlapping 60-beat data windows. Referenced against concurrently recorded invasive parenchymal ICP that varied over 100 millimeters of mercury (mmHg) across all records, our estimates achieved a mean error (bias) of 1.6 mmHg and SD of error (SDE) of 7.6 mmHg. For the 1673 data windows over 22 hours in which blood flow velocity recordings were available from both the left and the right MCA, averaging the resulting bilateral ICP estimates reduced the bias to 1.5 mmHg and SDE to 5.9 mmHg. This accuracy is already comparable to that of some invasive ICP measurement methods in current clinical use.

INTRODUCTION

Intracranial pressure (ICP) is the hydrostatic pressure of the cerebrospinal fluid (CSF) that surrounds the neural tissue and cerebral vasculature in the cranial cavity. Mean ICP for adults in the supine posture is normally 5 to 15 mmHg (*1*). However, ICP can rise markedly in a variety of space-occupying intracranial pathologies, such as cerebral edema, intracranial hemorrhage, brain tumor, or acute hydrocephalus. The flow of oxygenated blood to the brain is driven by cerebral perfusion pressure (CPP), which is the difference between mean arterial pressure and ICP. An increase in ICP accordingly causes a decrease in cerebral blood flow (CBF) when compensatory mechanisms of cerebral autoregulation fail. Given the brain's sensitivity to even short disruptions in oxygen supply, it is not surprising that elevated ICP correlates with worsening of symptoms in patients with cerebrovascular injury and can lead to serious consequences, including brain ischemia, neural damage, and brain death (*2*–*4*). Medical guidelines for traumatic brain injury (TBI), for example, require maintaining ICP below 20 to 25 mmHg and CPP above 60 to 70 mmHg (*4*–*6*).

The standard methods currently used for clinical monitoring of ICP to the desired tolerances are all invasive, requiring a hole to be drilled in the skull to advance a pressure probe or catheter into the brain parenchyma, or through the brain tissue into the ventricular space. With some sacrifice in measurement accuracy, ICP can also be monitored in the subarachnoid or subdural spaces, without entering the brain tissue, although still entailing penetration of the skull. All these approaches thus require neurosurgical expertise and carry the risk of infection and tissue damage. Assessment of spinal fluid pressure by lumbar puncture can also provide a spot estimate of ICP; however, this is not recommended when ICP is suspected to be high because of the risk of brain herniation. Furthermore, a spot assessment cannot capture dynamic trends in ICP, which can by themselves be indicators of pathology.

The invasive nature of ICP measurement methods in current clinical practice has prevented more extensive availability of this neurological vital sign. Monitoring of ICP is mandated in patients with severe TBI and certain other serious conditions. However, if not for its invasiveness and risks, ICP measurements could benefit a much larger patient population because assessment of ICP should ideally be indicated for diagnosis and monitoring in a wide range of neuropathologies. Candidate groups include patients with hemorrhagic or ischemic stroke, mild or moderate TBI (from sports, falls, or car accidents), altered mental status or cognitive/psychological disorders, hydrocephalus and implanted shunts, and brain tumors (*7*–*9*). Knowledge of ICP may also aid in establishing differential diagnoses in more benign conditions in which ICP measurements are not generally deemed necessary, such as headache, migraine, or visual problems. The development of a noninvasive ICP (nICP) monitoring system with clinically acceptable accuracy is therefore warranted.

A variety of modalities has been explored for nICP estimation (*10*) through measurement of related physiological variables, for instance, using ultrasound signals to measure CBF velocity (CBFV) indices (*11*), skull vibrations (*12*), brain tissue resonance (*13*), or transcranial time of flight (*14*); venous ophthalmodynamometry (*15*); optic nerve sheath diameter assessment (*16*); sensing tympanic membrane displacement (*17*); analyzing otoacoustic emissions (*18*); magnetic resonance imaging to estimate incremental intracranial compliance, and thereby ICP (*19*); and recordings of visual evoked potentials

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(*20*). The approach described by Ragauskas *et al.* (*21*) applied external pressure on the eyeball to balance the flow characteristics in the intra- and extracranial segments of the ophthalmic artery. The balance condition was then detected by a two-depth transcranial Doppler (TCD) ultrasound, and the corresponding external pressure was taken as the estimate of ICP.

Some nICP estimation methods feed simultaneous measurements of peripheral arterial blood pressure (ABP) along with TCD measurements of CBFV into multiparameter mappings to generate the ICP estimate. Examples are mappings involving nested regressions (*22*), neural networks (*23*), or support-vector machines (*24*). The recording of ABP and CBFV waveforms in the clinical setting is quite routine; ABP measurement is already necessitated in a wide spectrum of critical care patients, and CBFV is the standard of care in patients with certain neurovascular pathologies. However, the large number of parameters and the lack of an underlying mechanistic model mean that such "black box" mappings can fail to adequately and robustly capture the relevant physiology.

Almost all the above noninvasive methods require calibration or tuning of parameters that relate the measured quantities to the ICP estimates. Such calibration or tuning typically involves the use of ICP measurements obtained invasively on the patient or from some reference population. Furthermore, training on a reference population causes the accuracy of the ICP estimates to depend on how well a particular patient is represented in the training set. As noted by Popovic and coauthors (*10*), after surveying nearly 30 nICP methods patented over the last 25 years, none of the methods is sufficiently accurate to allow for routine clinical use. An additional factor in the way of clinical adoption for some of the proposed approaches is the difficulty or expense (hardware, computation, human resources) of the involved measurements. None of the previously proposed approaches to nICP estimation has transitioned from the research setting to accepted clinical practice, although commercial products based on the methods in (*17*), (*21*), and (*22*) are available.

Here, we present a model-based approach to obtaining estimates of ICP on a beat-by-beat time scale from noninvasive waveform measurements of CBFV and ABP. Our approach does not require patient-specific calibration or training on a reference population. The associated computational burden is negligible, thereby allowing near–real-time estimation of ICP.

nisms that couple these variables at the seconds-to-minutes time scale. The much slower processes of CSF production and absorption were neglected. The model also captures the fact that ICP, rather than systemic venous pressure, establishes the downstream pressure for cerebral perfusion. This is a consequence of the Starling resistor effect, resulting from the collapse of the cerebral veins owing to ICP being greater than venous pressure (*27*); it is also the reason that CPP is defined as the difference between mean ABP and ICP, rather than between mean ABP and systemic venous pressure.

Our model is conveniently specified by its electrical circuit analog (Fig. 1C), where pressures are represented by voltages, and flows by currents. The instantaneous ABP and CBF at time t are represented by the voltage $p_a(t)$ and the current $q(t)$, respectively. The effective resistance of the cerebral vasculature supplied by the middle cerebral artery (MCA) is represented by the resistor R, and the effective compliance of this cerebral vasculature and surrounding brain tissue is represented by the capacitor C. Our algorithm for estimation of ICP—with simultaneous estimation of R and C—resulted from requiring the model constraints to be satisfied as closely as possible by the obtained measurements, over an estimation window comprising the data associated with several consecutive beats, and under the assumption that ICP, R, and C are constant over that window.

For each estimation window, the algorithm generated one nICP estimate, which can be considered an estimate of the mean ICP over the estimation window. The estimation window had to be long enough (more than five beats) to allow some averaging of the data over multiple beats, with a corresponding attenuation of the effects of measurement noise, respiratory artifacts, and other such perturbations. However, the window also needed be short (≤60 beats) compared to the time scales of significant transients in the underlying ICP.

The ABP in our model was arterial pressure at the MCA, whereas our ABP measurement was made at the radial artery. These two arterial pressure waveforms undoubtedly differ in transit time from the heart and in pulse morphology; their mean values are close, however, provided measurements are taken with respect to a common reference. Although there is no straightforward way to correct for morphological differences, our algorithm determines and applies an appropriate time shift to the measured radial artery ABP on the estimation window to obtain a waveform that can serve as a plausible proxy for ABP at the MCA.

RESULTS

Dynamic model and estimation algorithm

Detailed dynamic models of the cerebrovascular space (Fig. 1A) have been developed in the literature (*25*–*27*). We obtained a highly simplified model that focuses on the major intracranial compartments—brain tissue, cerebral vasculature, and CSF space—and the associated variables (Fig. 1B). The variables involved in the model are ABP at the level of the cerebral vasculature, CBF at the inlet of a major cerebral artery, and ICP. Our lumped model represents the relevant physiological mecha-

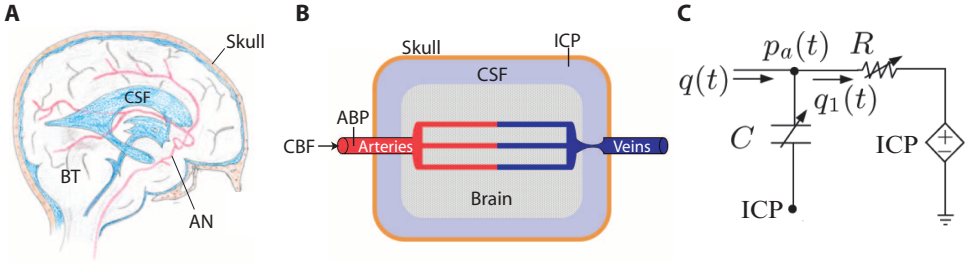

Fig. 1. Progressive abstraction of cerebrovascular physiology. (**A**) Relevant cerebrovascular anatomy: brain tissue (BT), cerebrospinal fluid (CSF), and cerebral arterial network (AN). (**B**) Schematic representation of the main cerebrovascular compartments and associated physiological variables: cerebral blood flow (CBF), arterial blood pressure (ABP), and intracranial pressure (ICP); the collapsed venous segment is also shown. (**C**) Lumped circuit-model representation of cerebrovascular physiology: CBF $q(t)$, cerebral arteriovenous flow $q_1(t)$, and ABP $p_a(t)$. ICP denotes both extraluminal pressure and the effective downstream pressure for cerebral perfusion.

Similarly, our measurements actually obtained CBFV rather than CBF. To the extent that the relationship between these two can be approximated by just a scale factor, our method can use CBFV instead of CBF. This is because the particular structure of the model constraints causes the ICP estimate to be insensitive to any scaling of CBF, as long as this scaling remains constant over each estimation window. The ICP estimate is therefore expected to be relatively insensitive to the cross-sectional area of the artery, the blood velocity profile across the vessel, and deviations of the insonation angle from its optimum, provided the combined effect of all these can indeed be captured (within each estimation window) by a single scale factor. When bilateral CBFV recordings are available, the ICP estimates can be obtained from the left and right sides separately, though using a common ABP waveform.

Method validation in patients with TBI

Validation of our method required a data set comprising simultaneous recordings of ABP, CBFV, and invasive ICP waveforms, all referenced to a common clock. Such carefully synchronized data are quite rare but were available to us from comatose patients with severe closed-head injury admitted to neurological intensive care at Addenbrooke's Hospital, University of Cambridge, UK, between 1992 and 1997. Data acquisition was part of routine clinical care for daily assessment of cerebral autoregulation after TBI. In total, we used 45 records from 37 patients (some patients were examined more than once during their hospital stay) (table S1). These records for our blinded analysis were picked from the data archive to represent a wide range of ICP variations (0 to 100 mmHg) as well as substantial transients within a record (a change of up to 50 mmHg over the course of a few minutes).

The invasive ICP waveform was recorded from an indwelling parenchymal probe (Fig. 2A). Each patient record also contained simultaneously captured continuous waveforms of ABP from radial-artery catheterization and CBFV from TCD ultrasonography of the MCA, with bilateral recordings available for 30 of those records from 25 patients (Fig. 2B). The record lengths ran from 10 to 240 min. After excluding data segments in which either the ABP or the CBFV waveform was dominated by significant noise or artifact, we were left with a total of about 35 hours of usable recorded data, which equaled more than 150,000 heartbeats. The patient population comprised 26 males and 11 females, with a median age of 25 years and a median Glasgow Coma Scale (GCS) score of 5 (on a scale of 3 to 14), indicating severe TBI on admission. Further patient information, including the Glasgow Outcome Score (GOS) at 6 months after hospitalization, is provided in table S1.

In the blinded first stage of our protocol, the ABP and CBFV waveforms alone were used to construct our ICP estimates. The estimates were then compared against the invasively obtained ICP measurements in the second stage.

ICP estimation performance

In the results presented below, our ABP time-shift correction has been limited to picking a single time shift for each record (rather than for each estimation window), computed as optimal overall for the entire record. Furthermore, for uniformity, the results are presented for 60-beat estimation windows. Using nonoverlapping windows of this size, we generated ICP estimates faster than once per minute, on average. The choice of a 60-beat window allowed averaging over several respiratory cycles. It is also possible to generate an estimate at each beat, even with a window comprising several beats, by "sliding" the estimation window one beat at a time. This corresponds to beat-by-beat estimation of ICP that has been averaged over the corresponding window. Before summarizing our estimation results across all the data in the 45 patient records (table S2), we present the results for four specific patients (Fig. 3). The results provide some orientation on the data and on the quality of the estimation results and also illustrate the range of dynamic variations represented. The reported ICP is the beat-averaged ICP waveform, computed for every beat.

Among the more demanding tests of estimation performance is when the underlying ICP goes through substantial changes, as in the case of a "plateau wave," in which ICP can spontaneously rise quite sharply to a level that is held for some time before returning to its previous baseline (*28*, *29*). One example (Fig. 3A) was recorded from a 23-year-old male (GCS = 7; patient record "AQ"). Our nICP estimates, computed in this instance on a sliding 60-beat window, closely tracked the transients in invasively measured, beat-averaged ICP. The root mean squared error (RMSE) over all beats was 5.1 mmHg, the mean error (bias) was 3.9 mmHg, and the SD of error (SDE) was 3.2 mmHg. The RMSE, bias, and SDE are interrelated: the mean squared error (RMSE squared) is essentially the sum of the squared

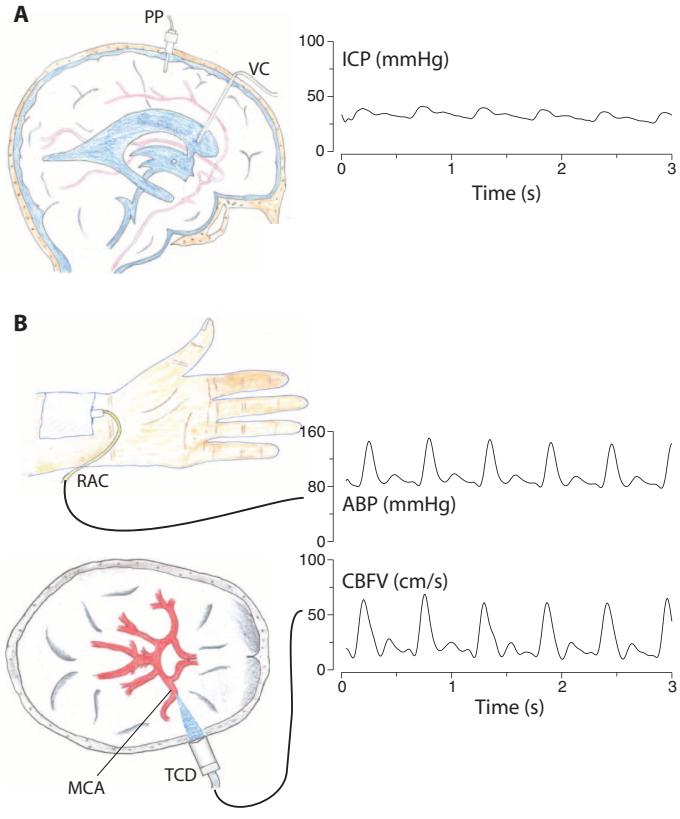

Fig. 2. Schematic representation of data acquisition, showing representative ICP, ABP, and CBF velocity (CBFV) waveforms. (**A**) Possible direct, invasive recordings of ICP over time through a parenchymal probe (PP) or ventricular catheter (VC). (**B**) Invasive recording of ABP waveform through radial artery catheterization (RAC) and noninvasive recording of middle cerebral artery (MCA) blood flow velocity waveform by transcranial Doppler (TCD) ultrasonography, used together for noninvasive estimation of ICP.

bias and the squared SDE. The RMSE is thus a useful aggregate measure of accuracy, whereas the SDE is a measure of precision or repeatability.

For all remaining results, the nICP estimates were computed on nonoverlapping (rather than sliding) 60-beat windows. In computing the corresponding error statistics, these estimates were referenced against ICP averaged over the associated window.

Another patient, a 30-year-old male (GCS = 3; patient record "AK"), exhibited severe progressive intracranial hypertension (Fig. 3B). The nICP estimates closely tracked measured ICP, both during the initial 15 min when ICP held steady and during the subsequent rise in ICP. The RMSE here was 6.0 mmHg, with a bias of −3.5 mmHg and an SDE of 5.0 mmHg.

A case in which our estimation algorithm fared less well involved two successive plateau waves in a 17-year-old male (GCS = 5; patient record "AO") (Fig. 3C). The RMSE in this record was 10.2 mmHg, the bias was 3.9 mmHg, with an SDE of 9.4 mmHg. Although nICP closely tracked measured ICP in the initial part (<50 min) of this 4-hour recording, it deviated substantially from the measured ICP in portions of the remaining time. Nevertheless, the estimated ICP still captured the duration and amplitude of the second plateau wave as well.

It is also of interest to know how the estimation algorithm performs when ICP is closer to its normal range of 5 to 15 mmHg. In a 15-min recording from a 32-year-old female (GCS = 7; patient record "AR"), the nICP estimate tracked the measured ICP (Fig. 3D), with an RMSE of 5.4 mmHg, a bias of −4.8 mmHg, and an SDE of 2.5 mmHg.

We summarize the estimation performance across all subjects in the form of Bland-Altman plots (*30*) of the estimation error, nICP − ICP, plotted against (nICP + ICP)/2 (Fig. 4). Here (as in Fig. 3, B to D), nICP is the estimate computed over nonoverlapping 60-beat windows and ICP denotes the average measured over the corresponding windows. Each plot was augmented by the corresponding error histogram, on which the plot of a Gaussian distribution of the same bias and SDE is superimposed for visual comparison.

In the 30 patient records in which bilateral CBFV recordings were available, we estimated ICP for each 60-beat window from the right- and left-sided CBFV signals independently and then averaged the resultant estimates to obtain nICP for that window. In the remaining 15 patient records in which only unilateral CBFV recordings were available, no such bilateral averaging could be performed.

The error between nICP and measured ICP for all nonoverlapping, 60-beat windows across all patients (a total of 2665 estimates from nonoverlapping data segments) showed a bias of 1.6 mmHg and SDE of 7.6 mmHg (Fig. 4A). Averaging these estimation results over 10 consecutive 60-beat windows in each patient resulted in 287 comparisons of nICP with ICP, again using disjoint data segments. The bias remained at 1.6 mmHg, but the SDE dropped to 6.9 mmHg.

When we confined our analysis to only those 30 patient records for which we had bilateral CBFV recordings and obtained nICP by averaging the ICP estimates from the right and left side, our results improved. Using 60-beat windows (1673 total estimates), the bias and SDE were then 1.5 and 5.9 mmHg, respectively (Fig. 4B). Again averaging these estimation results over 10 consecutive 60-beat windows (180 total comparisons), the bias remained at 1.5 mmHg, but the SDE dropped to 4.9 mmHg.

We also evaluated our estimates on a patient-record basis rather than data-window basis, comparing the average ICP and nICP values for each of the 45 patient records. The bias and SDE for this case were 0.9 and 6.5 mmHg, respectively (Fig. 4C).

The correlation coefficient between nICP and ICP, which is a measure of how well ICP can be predicted by an affine function of nICP, is often quoted in the literature on nICP estimation. This correlation coefficient was determined to be 0.90 for the data obtained on the 2665 nonoverlapping estimation windows (Fig. 4A). The analysis by Bland and Altman (*30*) shows that a high correlation coefficient is indeed to be expected for such a case, because the underlying ICP in our case varies over a range of 100 mmHg,

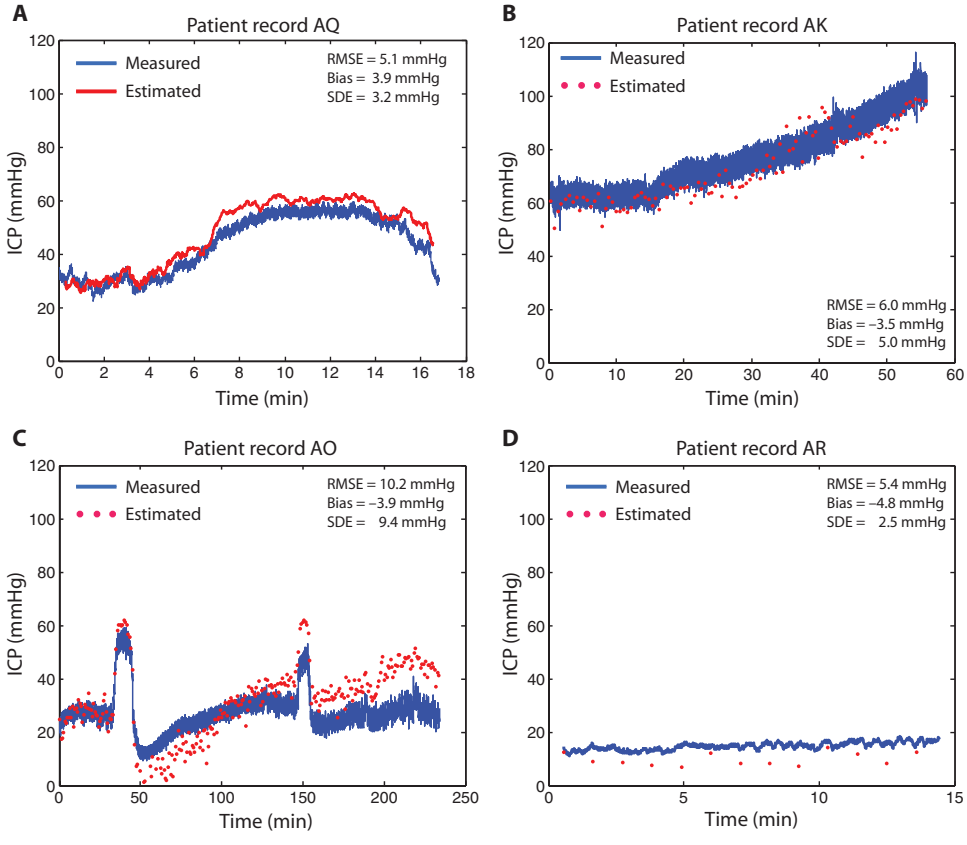

Fig. 3. Comparison of measured and estimated ICP in four brain-injured patients. In (A), ICP was estimated on a sliding 60-beat data window. In (B) to (D), the estimates were obtained on 60-beat nonoverlapping data windows. (**A**) Single plateau wave. (**B**) Severe progressive intracranial hypertension. (**C**) Two consecutive plateau waves. (**D**) Borderline normal ICP. All patient data are summarized in table S2.

whereas nICP tracks it with a notably smaller SDE of 7.6 mmHg. Performing the same computation for the bilateral data set comprising 1673 windows (Fig. 4B), the correlation coefficient dropped to 0.76 despite the smaller SDE of 5.9 mmHg, owing to the smaller range of underlying ICP variation (with only a few data points above 40 mmHg). A similar computation for the 45 estimates obtained on a patient-record basis (Fig. 4C) yielded a correlation coefficient of 0.92, reflecting the fact that the average ICP covers a range of about 75 mmHg across these records, whereas the corresponding SDE is under 6 mmHg.

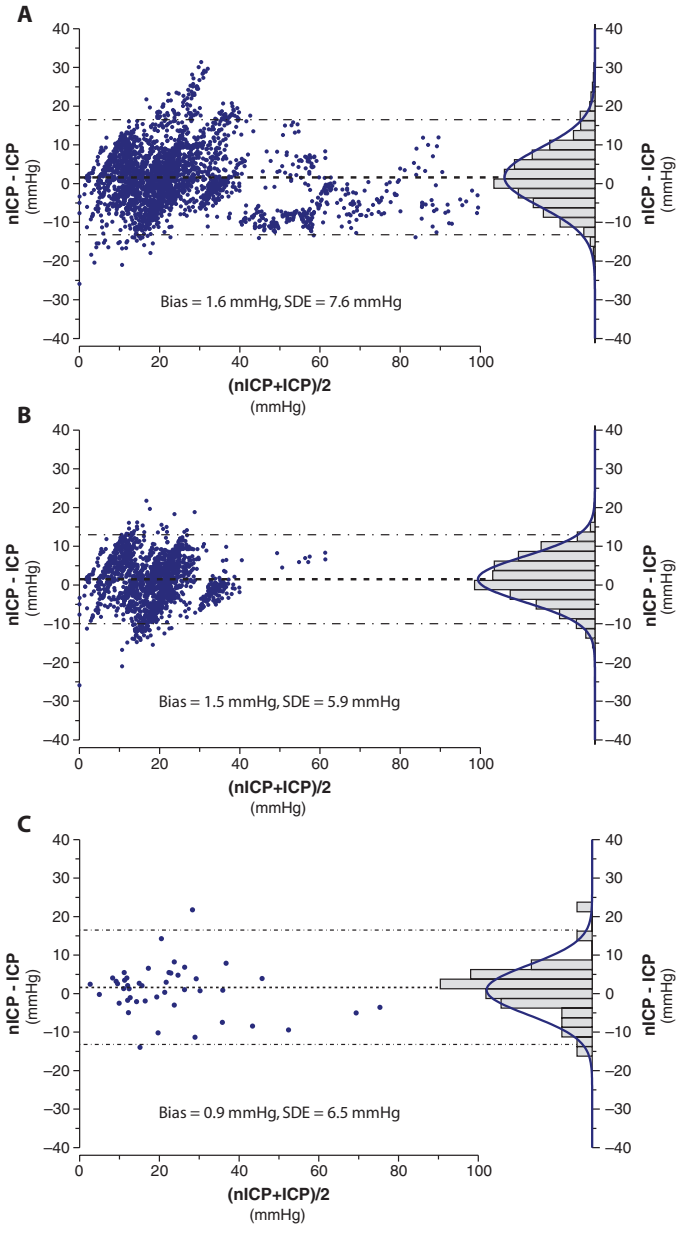

Fig. 4. Bland-Altman plots of overall estimation performance. ICP is mean measured ICP and nICP is the noninvasive estimate, each computed on a 60-beat estimation window. (**A**) ICP and nICP on 2665 nonoverlapping windows from 45 patient records. (**B**) ICP and nICP on 1673 nonoverlapping windows from 30 records with bilateral CBFV recordings, where averaging of left and right estimates reduced the bias and SDE from (A). (**C**) ICP and nICP averaged across all windows in each of 45 patient records. For all three plots, the bias is shown as the dashed line, and dash-dotted lines indicate the limits of agreement, computed as bias ± 2 SDE.

Additional perspective on our results comes from examining the ability of the nICP estimates to correctly identify elevated ICP within our data set. A common threshold for treatment in TBI is an ICP of 20 mmHg (*5*), so we took ICP >20 mmHg as our definition of elevated ICP. For the 2665 data pairs (Fig. 4A) and using an nICP of 20 mmHg as the threshold, we obtained a sensitivity of 83% and a specificity of 70% for detection of elevated ICP. A full receiver operating characteristic (ROC) was obtained by varying the nICP threshold from 0 to 100 mmHg (Fig. 5), with the definition of elevated ICP still being ICP >20 mmHg. This resulted in an area under the curve (AUC) of 0.83 for the ROC. We repeated this procedure on a patient-record basis. Using the earlier nICP threshold of 20 mmHg, the sensitivity and specificity were 90 and 80%, respectively. The ROC in this case (Fig. 5), again obtained by varying the nICP threshold, had an AUC of 0.88.

Referencing against ventricular ICP

Ideally, our nICP validation should have been against ventricular ICP measurements, because these are regarded as the clinical standard. However, only intraparenchymal ICP measurements were available to us. Because parenchymal probes themselves show error against the ventricular standard, we derived what the errors in our validation results would be if nICP was compared against ventricular measurements.

If I_p is the parenchymal measurement and I_v is the ventricular measurement, then our validation error referenced against the parenchymal probe can be expressed as follows:

$$\mathrm{nICP} - I_p = (\mathrm{nICP} - I_v) - (I_p - I_v) \quad (1)$$

where $(\mathrm{nICP} - I_v)$ is the estimation error our method would have if referenced to the ventricular standard, and $(I_p - I_v)$ represents the error of the parenchymal probe relative to the ventricular measurement. Taking expected values and rearranging yields

$$\mathrm{bias}(\mathrm{nICP} - I_v) = \mathrm{bias}(\mathrm{nICP} - I_p) + \mathrm{bias}(I_p - I_v) \quad (2)$$

Turning to variances, if the two error terms in parentheses in Eq. 1 are uncorrelated (see Discussion), then the error variances are related by

$$\mathrm{var}(\mathrm{nICP} - I_p) = \mathrm{var}(\mathrm{nICP} - I_v) + \mathrm{var}(I_p - I_v) \quad (3)$$

which can be rearranged as

$$\mathrm{var}(\mathrm{nICP} - I_v) = \mathrm{var}(\mathrm{nICP} - I_p) - \mathrm{var}(I_p - I_v) \quad (4)$$

DISCUSSION

Performance analysis and benchmarks

The accuracy measures for our nICP estimation approach are competitive with all other noninvasive methods for ICP estimation reported in the literature to date (*10*), even when these others have to be calibrated or trained on invasive ICP measurements from the

same patient or a collection of patients [for example, (*22*–*24*)]. A good benchmark for noninvasive, calibration-free, patient-specific estimation of absolute ICP is the previously mentioned approach that applied external pressure on the eyeball while monitoring ophthalmic artery flow (*21*). Referenced to lumbar puncture with pressure covering a range of 3 to 37 mmHg, the method achieved a bias of 0.9 mmHg and SDE of 6.2 mmHg in a total of 57 comparisons. However, limiting factors were the data acquisition time of 5 to 10 min per estimate and the intrusiveness of such an ocular procedure, both of which make the approach unsuited for continuous monitoring. Furthermore, the ability of this approach to estimate ICP levels higher than around 40 mmHg has yet to be established. In contrast, our approach can produce an estimate with just 5 to 60 beats of data (less than a minute), uses data obtainable through standard clinical modalities, allows continuous monitoring, and has demonstrated good performance for ICP as high as 100 mmHg.

In establishing targets for the desired accuracy of noninvasive estimation methods, one should keep in mind that intra-beat and respiration-induced fluctuations of ICP are normally in the range of 2 to 3 mmHg, so it is unlikely that an RMSE smaller than 3 mmHg is required for ICP monitoring. It is also helpful to examine the accuracy of current invasive methods and their mutual concordance. Ventricular and parenchymal pressure measurements are the primary approaches to invasive monitoring of ICP in clinical settings. The pressure as measured by a fluid-filled catheter located in a lateral ventricle remains the clinical gold standard against which other ICP measurement modalities ought to be evaluated; however, parenchymal and epidural probes are also often compared to one another.

Simultaneous measurement of ICP by a parenchymal probe and ventriculostomy showed a bias of −1.2 mmHg and an SDE of 3.4 mmHg in one study (*31*), although parenchymal probes have exhibited larger errors and drift over time in other studies (*32*–*34*). Simultaneous measurements of ICP by a parenchymal probe and an epidural probe have shown a bias of 4.3 mmHg, with an associated SDE of 8.5 mmHg (*35*). Subdural screws are deemed unreliable because of their relatively poor accuracy and tendency to underestimate high ICP, with median differences greater than 10 mmHg in 40 to 60% of comparisons against the ventricular catheter (*36*).

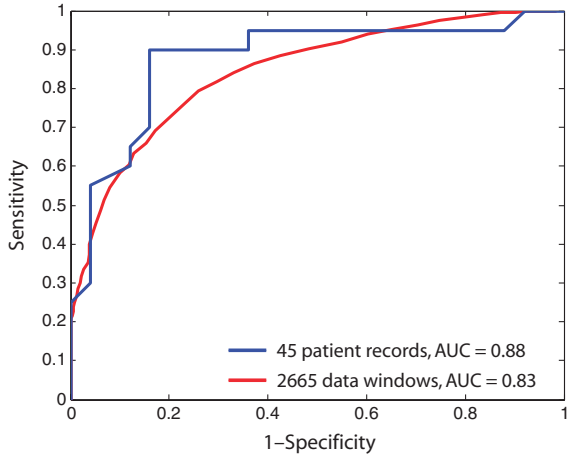

Fig. 5. Receiver operating characteristic (ROC) for detection of intracranial hypertension, defined as ICP > 20 mmHg. One ROC was computed for all 2665 nICP/ICP data pairs (red), and a second one for nICP/ICP data averaged across each of the 45 patient records (blue).

Given the above performance characteristics, our nICP estimation—with a bias under 2 mmHg and SDE under 6 mmHg—performs better than the invasive epidural and subdural measurements that are still used in current clinical practice. Furthermore, if intermittent ICP estimation suffices, temporal averaging of our nICP estimates reduces the RMSE. This was evident in the results presented for 10-window averaging, which preserved the bias at 1.5 mmHg and reduced the SDE from 5.9 to 4.9 mmHg in the case of 30 records with bilateral measurements.

As shown in Eq. 2, the bias of our nICP relative to ventricular measurements will be the sum of its bias relative to parenchymal measurements and the bias of the parenchymal measurements relative to the ventricular standard. Thus, the bias in our method relative to the ventricular standard might be greater or less than the bias obtained in our validation results, depending on the bias of the parenchymal probe. Similarly, Eq. 4 shows that the precision of our estimates referenced to the ventricular standard could improve over the precision obtained in our validation results. The derivation of Eq. 4 assumed that the errors between parenchymal and ventricular measurements are uncorrelated to the errors between our nICP and the same ventricular measurements. This assumption that the two errors are uncorrelated is plausible because very different measurement modalities are involved. Our approach uses ABP and CBFV measurements along with a model, whereas the parenchymal probe involves a solid-state sensor in the brain parenchyma.

An expected use of an nICP estimate would be for detection of elevated ICP. The potential of this approach is illustrated by our ROC analysis (Fig. 5), whose results are comparable with those reported, for example, in the setting of optic nerve sheath diameter measurement for detection of elevated ICP (*37*). However, our patient population here was selected to display a large range of ICPs and is therefore not necessarily representative of the population in which such a test would primarily be applied. The performance on a population displaying a smaller range of ICP variation might not be as good.

Although the accuracy of a measurement method is certainly one of its most important performance characteristics, accuracy by itself may not be the primary performance measure in every clinical situation. For example, in particular pathologies, it might be adequate to track changes and trends in ICP, rather than track its absolute value; in this case, a bias may be of less concern, as long as it is relatively constant. Our nICP tracks plateau-wave changes as large as 50 mmHg over the course of 5 min (Fig. 3C), and in fact does so with low bias and SDE.

Features of our approach

Our approach uses routinely acquired signals, provides beat-by-beat and patient-specific estimates of ICP, does not require any training on population data, does not need calibration, and is applicable across a large range of ICP variations. Rather than relying on statistical associations, we leverage the underlying dynamic physiological relationships to generate patient-specific estimates of ICP.

The simple dynamic model of cerebrovascular dynamics in our framework is similar to the Windkessel model of systemic vascular dynamics (*38*). This model is widely used in the cardiovascular domain because it contains a small number of physiologically interpretable

aggregate parameters that can be robustly estimated from the experimental data. Similar models have been used to some extent in the cerebrovascular setting (*39*, *40*). A key difference of our model from these other cases is in pegging downstream pressure for CBF as ICP rather than systemic venous pressure; this is crucial for estimating ICP from ABP and CBFV (*41*). More detailed models can be constructed (*27*), but it becomes fundamentally difficult to identify the more numerous parameters of such models from routine clinical measurements.

Simple static models relating available measurements to the physiological variables of interest underlie some commonly used clinical measurement modalities, such as pulse oximetry. The use of multivariable dynamic physiological models for similar purposes in clinical monitoring is still quite rare. However, extracting clinically meaningful information in real time from multiple channels of high-resolution data virtually mandates the use of such physiologically based computational models. Our approach to nICP estimation differs most fundamentally from previous attempts in its use of the salient dynamic physiological relationships among ABP, CBFV, and ICP.

Current limitations and future work

We have so far implemented our estimation algorithm in batch mode. However, the computations involved can be carried out in real time. Apart from the preprocessing steps—such as noise filtering, beat-onset detection, and time-shift estimation—the computation of our ICP estimate entailed only the least square error solution of two linear systems of equations, each with one unknown (the compliance in one case, and the resistance in the other). These are relatively trivial computations whose complexity varies linearly with the size of the estimation window. For example, our Matlab (The MathWorks) implementation took 0.13 s on a laptop (dual-core, 1.8 GHz) to compute continuous estimates for the 13-min patient record shown in Fig. 3D, producing 13 nICP estimates in total. Additionally, because our algorithm provides one ICP estimate for each estimation window—without reference to data outside that window—it can be used for spot assessment or intermittent monitoring.

Further reductions in bias and SDE will be necessary to match the accuracy of parenchymal probes referenced against ventricular catheters. Because we extract detailed features of the ABP and CBFV waveform morphology on a beat-by-beat basis, the estimation performance directly depends on the signal quality (time and amplitude resolution, noise, and artifact) of the acquired waveforms. Our validation tests were run on archived data collected over a multiyear period from 1992 to 1997, using varying equipment, personnel, and conditions. We anticipate that data collected on state-of-the-art instruments—and specifically with the requirements of our nICP estimation algorithm in mind—will likely improve the accuracy of our method. For example, the sampling frequency of our validation data ranged from 20 to 70 Hz, whereas modern instrumentation provides samples at 125 Hz or higher.

The performance of our estimation routine critically depends on accurate time alignment of the ABP and CBFV waveform features. We performed a carefully chosen time shift of the peripherally measured ABP waveform to better approximate the required ABP at the location of the CBFV waveform. We have thus far only applied a single time shift to each entire patient record, although our method allows for estimation of a new time shift for each estimation window. It is possible that adaptive determination of the optimal time shift on a window-by-window basis will improve results. Also, a higher sampling frequency would allow finer determination of the time shift, because the offset is currently restricted to multiples of the sampling interval.

Our method should be tested on larger patient pools, with more diverse pathological characteristics than the group presented here, which comprises cases of severe closed-head injury. This validation can be pursued in patients with subarachnoid hemorrhage, hydrocephalus, or idiopathic intracranial hypertension, because the standard of care permits invasive measurement of ICP for these conditions. An additional task will be to validate the use of a strictly noninvasively obtained ABP waveform (*42*) in place of a measurement at the radial artery. Although the latter measurement is commonly available in the critical care setting, catheterization of a major artery will not be an option in many situations in which ICP estimates are desirable. We have not made any use in this paper of the (arbitrarily scaled) estimates of cerebrovascular resistance and compliance, as seen from the MCA. These parameter estimates are obtained as adjuncts to our ICP estimates and associated CPP estimates, and determine the impedance of the local vascular bed. The dynamic response of the resistance and compliance estimates to changes in CPP may reflect the state of cerebrovascular autoregulation (*43*–*45*).

Overall, our results suggest that noninvasive, continuous, calibration-free, and patient-specific estimation of ICP with clinically acceptable accuracy is feasible. Such technology has the potential to markedly improve neuromonitoring in a variety of conditions in which ICP cannot be assessed currently.

METHODS

Data preprocessing

Analysis of the anonymized data used in this study was approved by the Neurocritical Care Users' Committee at Addenbrooke's Hospital and by the Massachusetts Institute of Technology (MIT) Institutional Review Board.

In cases in which the input waveforms were contaminated with high-frequency noise, we applied a low-pass filter with a cutoff frequency at 16 Hz (chosen appropriately for the noise observed in our data). We up-sampled all data records to 125 Hz from their native sampling frequencies of 20 to 70 Hz. We subsequently applied a beat-onset detection algorithm (*46*) to mark the onset of each individual blood pressure wavelet. Finally, we reviewed the beat-onset annotations to delete double detections, insert missed detections, and exclude beats of low signal quality.

Estimation algorithm

The instantaneous CPP, $p_a(t) - \mathrm{ICP}$, in our circuit model (Fig. 1C) drives two components of flow, which together constitute the instantaneous CBF, $q(t)$. One component represents the main unidirectional flow through the cerebrovascular resistance, whereas the other component corresponds to the transient distention and contraction of the compliance. Thus,

$$q(t) = \frac{p_a(t) - \mathrm{ICP}}{R} + C\frac{d(p_a(t) - \mathrm{ICP})}{dt} \quad (5)$$

We assumed that ICP in each estimation window was essentially constant at its mean value within that window. This assumption corresponds to neglecting the effects of the intra-beat pulsations of ICP relative to those of pulsations in ABP, and neglecting the effects

of slower variations in beat-averaged ICP over this estimation window, such as those induced by respiration. Similarly, despite the variations under autoregulation that are expected in R and C, we assumed that the effects of these variations were negligible over a short estimation window. These assumptions allowed us to set the derivative (or rate of change) of ICP to 0 in the estimation window, so the equation simplified to

$$q(t) = \frac{p_a(t) - \mathrm{ICP}}{R} + C\frac{dp_a(t)}{dt} \quad (6)$$

Note that a scaled version of $q(t)$, say $\alpha q(t)$, satisfies

$$\alpha q(t) = \frac{p_a(t) - \mathrm{ICP}}{R/\alpha} + \alpha C\frac{dp_a(t)}{dt} \quad (7)$$

which is identical to Eq. 6, except that R and C have been scaled, with ICP and $p_a(t)$ left unchanged. This justifies our using CBFV instead of CBF, under the assumption that the two are related just by a scale factor that is constant over each estimation window. In our algorithm, we set $\alpha = 1$, that is, used CBFV as though it was CBF, with the result that our estimated R and C are in arbitrary units.

We used Eq. 6 to develop a two-step estimation algorithm. Step I exploited the fact that the sharp transition in $p_a(t)$ during arterial systole induces a flow in the compliance that is large compared to that through the resistor, so the input flow $q(t)$ can be attributed primarily to the compliance branch in the model:

$$q(t) \approx C\frac{dp_a(t)}{dt} \quad (8)$$

Letting t_b and t_e indicate the beginning and end, respectively, of the systolic upstroke in $p_a(t)$, we can compute our estimate $\hat{C}$ of C by integrating Eq. 8 over the transition period, and solving the resulting equation below for $\hat{C}$:

$$(p_a(t_e) - p_a(t_b))\hat{C} = \int_{t_b}^{t_e} q(t)dt \quad (9)$$

However, to mitigate the effects of noise, we obtained the least square error solution $\hat{C}$ of the system of equations that resulted from writing Eq. 9 for each beat in the estimation window.

Step II used the result of step I to estimate the flow through the resistance according to

$$\hat{q}_1(t) = q(t) - \hat{C}\frac{dp_a(t)}{dt} \quad (10)$$

Finite differencing was used to approximate the derivative.

Expressing ICP in terms of $\hat{q}_1(t)$ using the relation

$$\mathrm{ICP} = p_a(t) - R\hat{q}_1(t) \quad (11)$$

allowed us to construct our estimate $\hat{R}$ of R using $\hat{q}_1(t)$ and $p_a(t)$ evaluated for two time instants t_1 and t_2 within a beat, again invoking our assumption that ICP is essentially constant during this beat (and throughout the estimation window). With this, $\hat{R}$ can be obtained by solving

$$(\hat{q}_1(t_2) - \hat{q}_1(t_1))\hat{R} = p_a(t_2) - p_a(t_1) \quad (12)$$

To reduce the sensitivity of this computation to the noise in $\hat{q}_1(t)$, we picked t_1 and t_2 to lie near the local minimum and maximum of the ABP pulse, respectively, and thereby maximize $\hat{q}_1(t_2) - \hat{q}_1(t_1)$. As with the compliance estimate, we then found the least square error solution $\hat{R}$ of the system of equations that resulted from writing Eq. 12 for each beat of the estimation window.

Finally, rewriting Eq. 11 in terms of beat-to-beat averages then gave the desired ICP estimate:

$$\widehat{\mathrm{ICP}} = \overline{p_a(t)} - \hat{R}\overline{\hat{q}_1(t)} \quad (13)$$

where the overbars denote time averages computed over the duration of one estimation window.

Time-shift correction of measured ABP

To estimate the time shift between radial ABP ($\mathrm{ABP_{rad}}$) and ABP at the MCA ($\mathrm{ABP_{mca}}$), we developed and applied two approaches motivated by the model in Eq. 6. The first approach exploited the fact that near the inflection point of the ABP pulse during the systolic upstroke, the term $\frac{dp_a(t)}{dt}$ attains its maximum value. The value of the derivative rolls off to zero at the peak of systole or the end of diastole. Thus, within a given beat period, the maximum value of $q(t)$ must occur close to the time corresponding to the systolic inflection point of $p_a(t)$. The desired time shift is then taken to be the shift required to align the inflection point of the $\mathrm{ABP_{rad}}$ pulse with the maximum of the CBFV pulse.

The second approach was based on the observation that in the vicinity of the local extrema of the ABP pulse, the compliance-related term in Eq. 6 can be ignored. The relationship between CBF and $\mathrm{ABP_{mca}}$ then becomes largely resistive and is determined by R and ICP only. Exploiting this insight, we developed a procedure to identify the local maxima and minima of ABP within each cardiac cycle and determine through regression an affine relationship between CBFV and $\mathrm{ABP_{rad}}$ at a candidate time shift. The regression was repeated for various time shifts to find the one that yielded the smallest residual error, at which point the relationship between CBFV and ABP was closest to being resistive.

To mitigate the effects of noise and sampling, we performed each time-shift calculation over a window of several consecutive beats. The median of the time shifts associated with all the windows in a record was used as the ABP time shift for the entire record. If the two time-shift estimation approaches yielded different values, we generated the corresponding nICP estimate for each and reported the average of the two estimates.

SUPPLEMENTARY MATERIALS

www.sciencetranslationalmedicine.org/cgi/content/full/4/129/129ra44/DC1
Table S1. Summary of information for each patient record (n = 45).
Table S2. Summary of estimation performance by patient record.

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Model-Based Noninvasive Estimation of Intracranial Pressure from Cerebral Blood Flow Velocity and Arterial Pressure

Faisal M. Kashif, George C. Verghese, Vera Novak, Marek Czosnyka and Thomas Heldt (April 11, 2012)

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Editor's Summary

Under Pressure

Measuring the pressure inside your head is no trivial task. It currently requires an invasive probe or catheter, inserted through a hole in the skull, directly into the brain or surrounding space. Monitoring intracranial pressure (ICP) is important for patients with severe neurological trauma, but because the process is so invasive, ICP measurements are avoided in routine assessment of other neuropathologies that could benefit from knowing this vital sign. To make ICP monitoring available to a larger patient population, Kashif *et al.* have developed a noninvasive method of estimating the pressure using tools already available in the clinic.

The authors created a simplified model of what's inside our heads: brain tissue, blood vessels, and cerebrospinal fluid. The variables involved in this model included arterial blood pressure (ABP), cerebral blood flow (CBF), and ICP. Using an electrical circuit as an analog, Kashif and colleagues were able to describe ABP and CBF as the respective voltage and current, the cerebral vasculature as the resistor, and the compliance of the vasculature and brain tissue as the capacitor. Hospital records of 37 patients with traumatic brain injury contained data for ABP (taken from the radial artery) and CBF velocity (from transcranial ultrasound), which were then plugged into the authors' model to estimate ICP. These estimated values were compared to the patient's actual invasive ICP waveforms, correctly identifying elevated ICP (>20 mmHg) with high sensitivity and specificity.

The beauty of the model described by Kashif *et al.*––other than its ability to estimate ICP noninvasively––is that it does not require calibration or training before application. This feature makes it amenable to use in the clinic, immediately upon examining a patient. Such a model-based approach will find use in many clinical situations where real-time estimation of ICP could spare patients the pain of and recovery from more invasive methods of measurement.

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