

# Adaptive Noninvasive Assessment of Intracranial Pressure and Cerebral Autoregulation

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**Background and Purpose**—A mathematical model has previously been introduced to estimate noninvasively intracranial pressure (nICP). In the present multicenter study, we investigated the ability of model to adapt to the state of cerebral autoregulation (SCA). This modification was intended to improve the quality of nICP estimation and noninvasive assessment of pressure reactivity of the cerebrovascular system.

**Methods**—We studied 145 patients after severe head injuries or stroke. All patients had direct ICP, arterial blood pressure (ABP), and transcranial Doppler middle cerebral artery blood flow velocity (FV) monitored. The SCA was assessed by moving correlation (Mx index) of cerebral perfusion pressure (CPP=ABP–ICP) and cerebral blood flow velocity and correlation of ABP and ICP (PRx index). nICP was calculated from ABP and FV waveforms. When nICP was used instead of ICP, the SCA was continuously estimated, and the model was dynamically adapted to the SCA.

**Results**—High and moderate correlations between invasively (Mx, PRx) and noninvasively (nMx, nPRx) estimated autoregulation indexes were observed (Mx:  $R=0.90$ ,  $P<0.001$ ; PRx:  $R=0.62$ ,  $P<0.001$ ). Values of Mx and nMx indicated contradictory SCA in 4 of 167 evaluated recordings; values of PRx and nPRx were contradictory in 27 recordings. When the model was adapted to the SCA, the mean error of ICP estimation decreased significantly ( $P<0.005$ ).

**Conclusions**—Continuous adaptation of the model to SCA improves the accuracy of noninvasive estimation of ICP and ICP dynamics. The same model provides a noninvasive and continuous assessment of SCA. (*Stroke*. 2003;34:84-89.)

**Key Words:** autoregulation ■ cerebral blood flow ■ intracranial pressure ■ ultrasonography, Doppler, transcranial

In patients with severe brain injuries, cerebral autoregulation<sup>1,2</sup> (CA) may be affected for the long term, or it may fluctuate over time. Monitoring of CA can be important for decision making regarding the patient's critical care.<sup>3</sup> Various methods have been introduced recently to assess the state of CA (SCA) either by clinical testing such as the leg-cuff test<sup>4–6</sup> or by analysis of physiological signals.<sup>7–11</sup> Clinical tests, however, do not provide continuous monitoring. Methods suitable for continuous analysis of CA necessitated invasive intracranial pressure (ICP) measurements.<sup>9</sup> Moreover, methods that relate arterial blood pressure (ABP) to cerebral blood flow velocity (FV), ignoring the contribution of ICP to cerebral perfusion pressure (CPP),<sup>7,8,12</sup> are not suitable for use in patients with intracranial hypertension.

Earlier, we presented a procedure for a noninvasive assessment of ICP (nICP) that used FV and ABP signals.<sup>13–16</sup> This procedure previously was shown to depend on the patient's SCA. The objective of the present multicenter study was to combine the methods of continuous estimation of autoregu-

lation<sup>9,10</sup> with nICP assessment to achieve a continuous, minimally invasive assessment of SCA. The second aim was to check whether adaptation to a fluctuating SCA could improve the accuracy of nICP monitoring. Finally, the reliability of the noninvasive assessment of autoregulation was compared with the reliability of a method that avoided invasive ICP measurement by using ABP instead of CPP.<sup>5</sup>

## Materials and Methods

### Patient Population

We included 145 patients (mean age,  $35\pm 18$  years; range, 3 to 76 years; 111 male, 34 female). They suffered from either head injury ( $n=135$ ) or hemorrhagic stroke ( $n=10$ ). The patients were treated in Addenbrooke's Hospital, Cambridge, UK ( $n=113$ ; mean age,  $31\pm 16$  years; range, 3 to 76 years; 90 male, 3 female; traumatic brain injury [TBI] only; this material was used to construct the nICP procedure), and in various German medical centers ( $n=32$  in total; Munich-Bogenhausen,  $n=11$ ; Munich-Schwabing,  $n=13$ ; Chemnitz,  $n=5$ ; Frankfurt,  $n=3$ ; mean age,  $51\pm 15$  years; range, 20 to 75 years; 21 male, 11 female). At the time of data recording, all patients were sedated, paralyzed, and mechanically ventilated. Their arterial partial

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pressure of CO<sub>2</sub> ranged from 30 to 40 mm Hg. No patient showed vasospasm (exclusion criteria was middle cerebral artery [MCA] FV >100 cm/s) or evidence of stenosis of the intracranial or extracranial arteries. Subdural hematomas were found in 39, intracerebral hematomas in 35, and brain edema in 68 TBI patients. The hemorrhagic stroke group included patients with intracerebral (n=5), subarachnoid (n=4), and cerebellar (n=1) hemorrhages.

## Monitoring

Transcranial Doppler (TCD) measurements were taken by various 2-MHz pulsed Doppler devices (TC 2-64B, EME, in Munich-Bogenhausen and Chemnitz; Multidop-P, DWL, in Munich-Schwabing; Multiflow, DWL, in Frankfurt; and PC Dop842, Scimed, or Neuroguard, Medasonics, in Cambridge). Flow patterns of the MCA were continuously recorded in the hemisphere ipsilateral to the ICP measurements. The ultrasound probe was fixed mechanically with a holder frame or an elastic band. Blood pressure was measured with a standard manometer line inserted into the radial, femoral, or dorsalis pedis artery.

ICP was measured with either implanted intraparenchymal or intraventricular microsensors (Camino Laboratories in Cambridge and Munich-Bogenhausen; Codman Group Inc in Munich; Rehaug AG in Munich-Schwabing and Chemnitz), a sensor with air pouch probes (Spiegelberg Plc/Ltd/Co in Munich and Frankfurt), or an external ventricular drainage (in Chemnitz, Munich-Schwabing, and Frankfurt; only periods with closed drainage were evaluated.)

The study was approved by the ethics committee of the Technical University of Munich. In other centers, such a method of monitoring was routine clinical practice and did not require separate local ethics committee approval.

## Computer-Assisted Recording

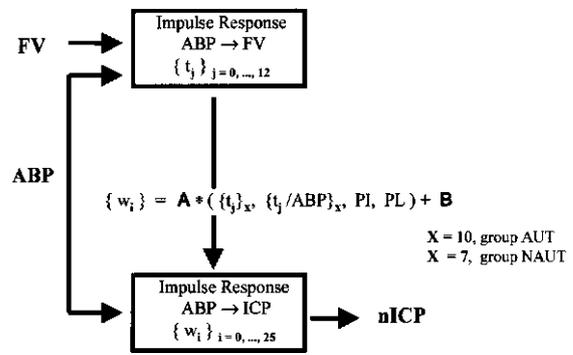
Personal computers were used for recording and analyzing FV, ABP, and ICP signals. The computers for signal recording were fitted with data acquisition systems (in Munich and Chemnitz, Daq 112B, Iotech, Inc; in Frankfurt, DTA300, Data Translation; in Cambridge, DTA2814, Data Translation). The sampling frequencies used ranged from 25 to 50 Hz. Signals were recorded daily for 20 to 120 minutes. Home-written data recording software was used in Munich and Chemnitz,<sup>13</sup> as well as in Cambridge and Frankfurt.<sup>17</sup>

## Assessment of SCA

Time-averaged values of ICP, ABP, CPP (CPP=ABP-ICP), and FV were calculated from time integration for 10-second intervals. An autoregulation index (M<sub>x</sub>) was calculated as a Pearson correlation coefficient of 36 consecutive samples of CPP and FV mean values, ie, every 6 minutes. Positive association between CPP and FV (M<sub>x</sub> >0) indicates passive dependence of blood flow on CPP. A zero or negative value of M<sub>x</sub> indicates that cerebral blood flow was independent of CPP, ie, intact (or even overregulating) CA. Index M<sub>x</sub> therefore describes autoregulation using its definition as a vascular reflex allowing maintenance of constant cerebral blood flow regardless of varying ABP or CPP.

Similarly, the pressure-reactivity index (PR<sub>x</sub>) was calculated as a Pearson correlation coefficient of 36 consecutive samples of ABP and ICP. PR<sub>x</sub> is similar to M<sub>x</sub> but takes into account active regulation in cerebral blood volume.<sup>18,19</sup> If CA works, a decrease in ABP provokes compensatory vasodilatation, an increase in cerebral blood volume, and hence an increase in ICP. Therefore, with intact autoregulation, PR<sub>x</sub> is negative. If CA fails, a rise in ABP produces no active vascular response but passive vascular distension, an increase in blood volume, and a rise in ICP. Therefore, in this state, changes in ICP and ABP will take place in the same direction, rendering PR<sub>x</sub> positive. M<sub>x</sub> and PR<sub>x</sub> are correlation coefficients, not ratios of signal changes, and thus are standardized in value (1 to -1).

In previous studies, M<sub>x</sub> was significantly correlated with the leg-cuff test<sup>8</sup> and the transient hyperemic response test.<sup>6</sup> However, grading of CA by monitoring the association between slow waves of FV and CPP has more in common with the classic definition of autoregulation<sup>1</sup> than with the concept of dynamic autoregulation.<sup>4</sup>



**Figure 1.** nICP assessment procedure. From FV and ABP signals, 28 TCD characteristics consisting of an ABP→FV IRF and its coefficients divided by ABP and additionally of PI and PL are computed. Linear transformation on the TCD characteristics by the nICP procedure matrix AB estimates the ABP→ICP IRF, which transfers ABP into the nICP signal. PI indicates pulsatility index; PL, pulse length.

The index M<sub>x</sub> has been shown to correlate with PR<sub>x</sub>, and both indexes<sup>9,10</sup> are strong predictors of outcome.<sup>3,10</sup> Autoregulation indexes were calculated if dynamics of slow waves in either ABP or FV signals (measured as relative SD of 10-second signal averages) exceeded definite thresholds: >0.03 for FV and 0.015 for ABP.

## Noninvasive ICP Assessment

The procedure uses parameters derived from FV and ABP waveforms. They are called TCD characteristics and essentially consist of coefficients of a linear ABP→FV transformation. The TCD characteristics are used to calculate a dynamic transformation formula connecting ICP and ABP (ABP→ICP).

The model assumes a linear relationship between TCD characteristics and the coefficients of the ABP→ICP transformation. This linear function (nICP matrix) constitutes the kernel of the nICP assessment procedure and may be constructed using the reference data consisting of FV, ABP, and direct ICP recordings from a well-defined group of patients. Figure 1 is a flow chart of the nICP assessment.

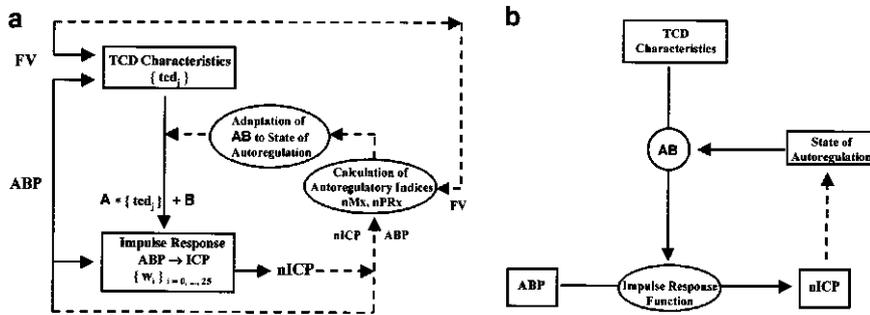
## Noninvasive ICP Assessment With Feedback-Controlled Adaptation to SCA

Previously, we used data from Cambridge from 113 reference TBI patients with either intact (AUT group, n=56) or disturbed (NAUT group, n=69) CA to generate 2 nICP procedures specifically suitable for nICP assessment in patients with corresponding SCA. We observed a clear benefit in the accuracy of assessment of nICP and its dynamics (A and B waves, ICP trends) if specific nICP procedures were used.

These results encouraged the following construction. For calculation of nICP, we used a linear combination of 2 CA-specific nICP procedures. During analysis, the state of autoregulation was regularly estimated by correlation between FV and nCPP (nM<sub>x</sub>) and between ABP and nICP (nPR<sub>x</sub>). These indexes were used as feedback to fit the nICP procedure to the current SCA. A linear combination of both above-mentioned CA-specific nICP assessment procedures was computed each time from the currently estimated SCA to create the best fitting procedure and to calculate final nICP values (Figure 2 and the Appendix).

The simultaneous use of Cambridge patients for construction of nICP procedure and for nICP assessment was avoided by excluding each tested patient from the construction of procedure; ie, each time, the remaining 112 patients were used to calculate the reference transformation that was used to calculate nICP in the 113th patient.

For evaluation of the accuracy of noninvasive SCA assessment, noninvasive autoregulation indexes nM<sub>x</sub> and nPR<sub>x</sub>, corresponding to M<sub>x</sub> and PR<sub>x</sub>, were calculated for each patient. Furthermore, M<sub>x,ABP</sub>



**Figure 2.** a, nICP assessment procedure with continuous control matrix adaptation to SCA. As in Figure 1, TCD characteristics and the nICP matrix AB are used to assess the nICP signal. In addition, Mx- and PRx-related autoregulatory indexes are calculated from nICP, ABP, and FV signals, and results are fed back to the procedure and used to modify AB suitably. Dotted lines show the information flow of feedback control. b, Three-level control structure of nICP assessment model. In level 1, nICP is controlled by the ABP signal via IRF, a function of

temporary ( $\approx 10$  seconds) validity. In level 2, control of IRF by TCD characteristics via nICP matrix facilitates a theoretically time-unlimited validity of the model but requires defined state of the patient's CA. In level 3, control of nICP matrix by SCA ensures broad applicability, independent of current SCA.

was calculated as the correlation coefficient between FV and ABP (instead of CPP in Mx).<sup>8</sup>

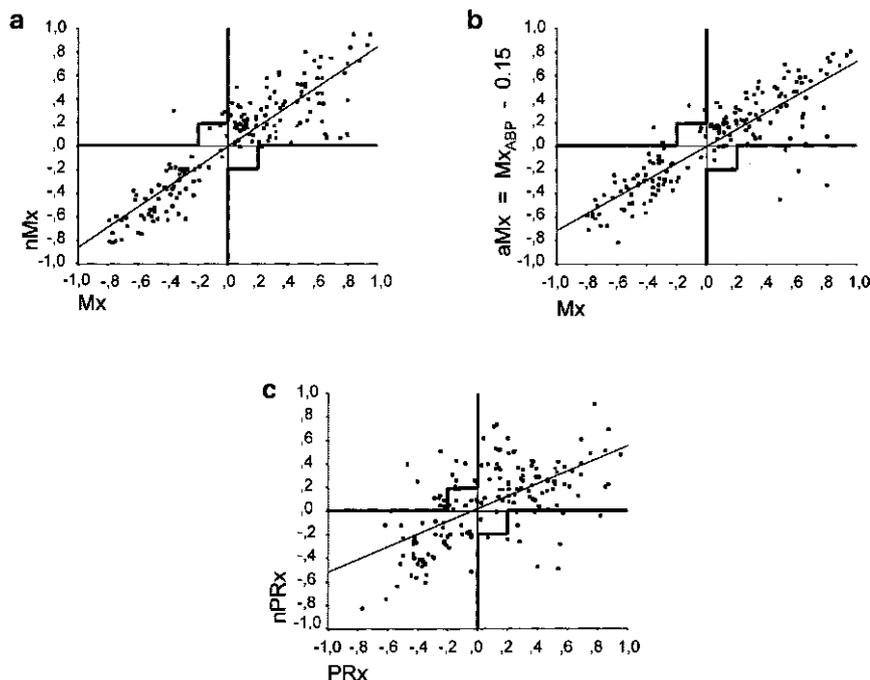
Although Mx, PRx  $>0.0$  indicated impaired CA and Mx, PRx  $<0.0$  indicated intact CA, it is clear from general properties of physiological systems that the value 0.0 (or any other value) does not constitute a sharp threshold between intact and impaired CA. It seems appropriate to assume an area (surrounding 0.0) of continuous transition from intact to impaired CA, indicating nondefinite states somewhere in between. These considerations motivated the following definitions. An autoregulatory index was defined to indicate a definite SCA if its value was either  $<-0.2$  or  $>0.2$  and a weak definite SCA if its value was  $>-0.1$  or  $>0.1$ . Two indexes were classified as contradictory if 1 indicated a definite SCA and the other was signed differently (eg, with this terminology, Mx=0.25 and nMx=-0.1 were contradictory, whereas PRx=-0.6 and nPRx=-0.01 were not). Cases of agreement and contradiction between noninvasive and invasive indexes were counted, and the sensitivity (ratio of invasively and noninvasively concurring definite impaired CA to definite impaired CA) and specificity (ratio of invasively and noninvasively concurring definite intact CA to definite intact CA) of such an estimation were calculated. Fuzzy sensitivity and fuzzy specificity were defined accordingly using weakly definite noninvasive indexes.

nICP was quantitatively compared with ICP using mean absolute errors ( $\Delta$ ICP) defined as the absolute value of 10-second averaged differences of ICP-nICP.

## Results

nICP was calculated from data collected in 197 different recordings of 145 patients. In 167 recordings, the dynamics of FV or ABP ( $FV_{DYN}$ ,  $ABP_{DYN}$ ) met the inclusion criteria for the evaluation of SCA. In these recordings, the autoregulation indexes Mx and PRx were calculated from FV, ABP, and measured ICP; nMx and nPRx were calculated with nICP instead of ICP; and  $Mx_{ABP}$  was calculated by correlating FV and ABP rather than FV and CPP. For comparisons with Mx and nMx (Figure 3a and 3b), a constantly shifted index,  $aMx = Mx_{ABP}$ , minus the mean value of the Mx-Mx<sub>ABP</sub> difference (0.15) was used.

Significant correlations ( $P < 0.001$ ) with coefficients  $R = 0.90$  between Mx and nMx,  $R = 0.62$  between PRx and nPRx, and  $R = 0.86$  between Mx and aMx were attained (Figure 3 and Table 1). In 125 recordings of 106 patients, Mx was definite ( $>0.2$  or  $<-0.2$ ). In 2 of these recordings, the value of nMx was contradictory to Mx; ie, nMx and Mx had different signs. aMx and Mx were contradictory in 6 recordings; in 4 of these, ICP was increasing  $>40$  mm Hg. The sensitivity of both nMx and aMx for detection of impaired



**Figure 3.** Scatterplots of 167 pairs of noninvasively and invasively assessed autoregulation indexes in 131 patients, together with the reference lines  $x=0$  and  $y=0$  and regression lines. Area of contradictory index pairs, according to its definition in Methods, lies outside the boundary lines. a, Scatterplot of nMx vs Mx. b, Scatterplot of aMx vs Mx. In this diagram, Mx<sub>ABP</sub> values were shifted down by 0.15 to let the regression line go through the origin and best fit aMx values into the area of correct estimation of SCA. Therefore, aMx was a better predictor of Mx than Mx<sub>ABP</sub>. c, Scatterplot of nPRx vs PRx (Mx<sub>ABP</sub> correlation ABP and FV:  $aMx = Mx_{ABP} - 0.15$ ).

**TABLE 1. Comparison of Noninvasively and Invasively Assessed Autoregulation Indices**

	Noninvasive Autoregulatory Indices and Their Invasive References					
	nMx	Mx	aMx	Mx	nPRx	PRx
Correlation coefficient	0.90		0.86		0.62	
Mean error of estimation	0.14		0.22*		0.24*	
Recordings with definite autoregulatory index	121	125	110	125	112	119
No. of which are contradictory to corresponding index	3	2	5	6	15	19
Sensitivity	0.73		0.73		0.61	
Specificity	0.92		0.79		0.67	
Fuzzy sensitivity	0.84		0.83		0.77	
Fuzzy specificity	0.97		0.92		0.78	

The indices nMx, aMx and nPRx were compared to the corresponding invasively assessed reference indices Mx and PRx. The number of cases was counted where either noninvasive or invasive estimators indicated definite SCA (row 3) in contradiction to its counterpart (row 4). Sensitivity and specificity of noninvasive assessment of SCA are presented in rows 5 to 8.

\*Significantly different ( $P < 0.001$ ) to nMx assessment error.

CA was 0.73, and the fuzzy sensitivity of nMx and aMx was 0.84 and 0.83. Subsequently, nMx indicated definite SCA in 121 recordings of 104 patients. nMx was contradictory to Mx in 3 cases, and aMx was contradictory to Mx in 5 cases. The specificity of nMx for Mx estimation was 0.92, the specificity of aMx was 0.79, and the fuzzy values were 0.97 and 0.92. The sensitivity of the nPRx index for predicting definite PRx values was 0.61, and its specificity was 0.67. The corresponding fuzzy values were 0.77 and 0.78 (Table 1).

The median  $\Delta$ ICP was 6.0 mm Hg. In 75% of the evaluated recordings,  $\Delta$ ICP was  $< 9.1$  mm Hg (Table 2). A paired  $t$  test comparison to nICP assessments with a fixed nICP procedure showed significantly lower ICP estimation errors if the nICP procedure was adapted to SCA (mean errors, 7.6 and 6.9 mm Hg;  $P < 0.005$ ). Restricted to TBI patients, the mean  $\Delta$ ICP was 7.1 mm Hg; it was 4.3 mm Hg in patients with stroke. Examples of nICP assessments during ICP A and B waves<sup>20,21</sup> are shown in Figure 4.

## Discussion

The model used to calculate nICP provides a method to monitor SCA. Noninvasive ICP was used to calculate the parameters nMx and nPRx to approximate the autoregulatory indexes Mx and PRx. Both sensitivity and specificity of nMx for the detection of Mx-valued SCA were  $> 0.7$ . Fuzzy values, which appeared to be more appropriate for a continuous-valued diagnostic test, were clearly higher. The values of nMx and Mx were contradictory in only 4 recordings. Regarding sensitivity and specificity values of 0.7 as critical thresholds for the validity of a diagnostic method, both indexes nMx and aMx appeared to be suitable for the estimation of SCA. However, aMx and Mx contradicted each other in 8 cases, clearly more often than nMx and Mx. The results of nPRx were least convincing because only the fuzzy values of sensitivity and specificity exceeded the critical threshold.

If arguing with the sensitivity and specificity of SCA detection, the reader should keep in mind that we identify “real” SCA with certain values of its indicative parameters Mx and PRx. Although a strong relationship between Mx and other methods for CA assessment, demonstrated by earlier studies,<sup>6,8</sup> appears to be obvious, an exact relationship between Mx, PRx, and CA may yet be unknown. In particular, this became evident in cases when the values of Mx and PRx indicated different SCA. A complete parameterized assessment of SCA might not be possible because of the complexity and variety of autoregulatory mechanisms. It is probable that CA after head injury and stroke is regionally disturbed; therefore, its assessment with MCA FV may be weighted by the volumes of brain tissue with preserved and disturbed autoregulation supplied by MCA.

Although our model was constructed from data of TBI patients, we additionally tested 10 stroke patients to check its broader applicability. Despite the small number of tested stroke patients, the results encourage further attempts to validate this method in stroke patients with intracerebral, subarachnoid, and cerebellar hemorrhages, whereas subarachnoid hemorrhages with manifestations of vasospasm and patients with infarcts are expected to be problematic because of their vessel abnormalities. Especially in stroke patients, the danger of intracranial hypertension is frequently underestimated. In many cases, ICP is not monitored, and it may cause severe secondary insults by unrecognized ICP elevation. Therefore, nICP assessment could be a helpful tool, particularly in these patients.

It was shown that the shifted correlation coefficient between ABP and FV (aMx) was a reasonable estimator of Mx. Although in most cases the contribution of ICP to CPP dynamics was low, in some patients when ICP was strongly increased or of high dynamics, CPP could not be replaced by ABP for SCA assessment.<sup>7,8</sup> nMx was a reliable estimator of Mx even in patients with increased ICP, in which case monitoring of SCA was of particular importance.<sup>22–24</sup>

**TABLE 2. Distributions of  $\Delta$ ICP in 197 Recordings**

nICP Assessment Method	Absolute Errors of nICP: Percentiles and 95% CI			
	25th [mm Hg]	50th [mm Hg]	75th [mm Hg]	90th [mm Hg]
Autoregulation controlled	2.7/(2.2, 3.4)	6.0/(4.9, 6.9)	9.1/(8.1, 10.5)	14.4/(12.5, 18.1)
Constant	2.8/(2.2, 3.7)	6.2/(5.3, 6.9)	10.6/(8.6, 11.6)	15.2/(14.1, 19.5)

Expressed in terms of 25th, 50th (median), 75th, and 90th percentiles together with the 95% CIs. The autoregulation-controlled nICP assessment method was compared to the constant method.

The study of SCA-specific nICP estimation was motivated by the observation that interactions of FV, ABP, and ICP signals are affected by CA. Improved accuracy of these procedures led to the idea of a dynamic adaptation to current SCA. In our model, SCA was assessed with nICP, which was calculated from FV and ABP signals. SCA in turn was used to control the nICP calculation rules. This closed control loop is in accordance with the physiological situation: ABP and FV signals cannot completely assess nICP dynamics, which additionally are influenced by such autoregulatory system changes as dilatation or constriction of cerebral vessels causing intracranial volume changes. The SCA-controlled nICP assessment procedure showed higher accuracy in ICP estimation than the corresponding constant procedure. It generally predicted ICP dynamics more accurately, ie, less dampened, than the constant method did (Figure 4a and 4b). Furthermore, it allowed reliable computation of nICP in patients with highly dynamic changes in autoregulatory behavior, eg, in patients with ICP plateau waves (Figure 4c and 4d)<sup>20</sup> in whom on the top plateau level of the patient's autoregulatory reserve was exhausted and the plateau wave generation was initiated by an autoregulatory response.<sup>18</sup>

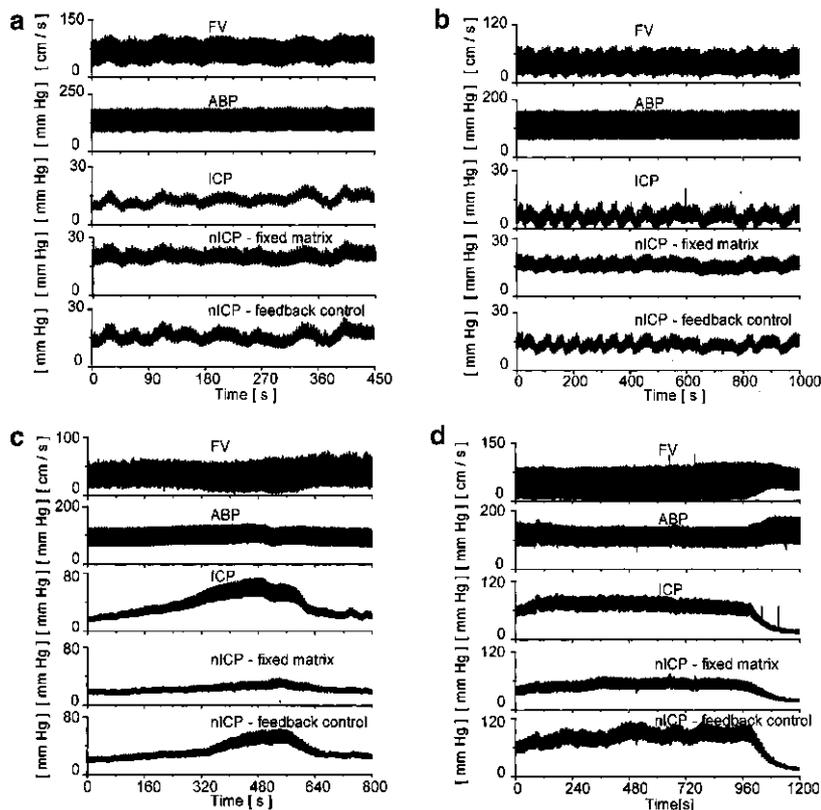
The SCA-controlled nICP assessment may be used without additional tests and is therefore easy to handle. Moreover, it provides continuous monitoring of SCA without clinical intervention. For a first approximation, SCA may be estimated by the correlation between ABP and FV signals. Use of nICP assessment improves the reliability of Mx estimation in cases of increased ICP dynamics and provides the additional index nPRx.

### Appendix

#### Structure of the nICP Assessment Procedure

The basic concept of the nICP assessment procedure (Figure 1) was to use certain parameters calculated from FV and ABP signals (TCD characteristics) for the estimation of a linear transformation function that computed the nICP signal from an ABP signal input (ABP→ICP). This linear transformation is familiarly called impulse response function (IRF). If input and output signals are known, the corresponding IRF may be calculated by standard methods of system analysis.<sup>25,26</sup> In our model, the ABP→ICP IRF was represented by 26 coefficients. The computational rules for nICP were given by

$$nICP_k = \sum_{i=0}^n w_i \cdot ABP_{k-i}$$



**Figure 4.** Curves of FV, ABP, measured ICP, nICP assessed by fixed matrix method, and nICP assessed by autoregulatory feedback control. Fixed matrix method showed reduced nICP dynamics compared with both ICP and feedback-controlled nICP. The feedback control method showed nICP dynamics similar to ICP dynamics in a and b, slightly reduced in c, and increased in d. a, b, ICP B-wave fluctuations and B-wave equivalents in FV could be observed, whereas ABP remained almost unchanged. Mx/PRx parameters indicated preserved CA. c, d, Examples of plateau wave manifestations. c, ICP increase was hard to assess by FV-ABP analysis because of weak decreases in diastolic FV and increases in PI during plateau wave. d, Opposite extreme in which a decrease in FV diastoles and an increase in pulsatility were strongly pronounced. Feedback-controlled method slightly overestimated the ICP changes and peak values. Increased dynamics led to erroneous ICP fluctuation at the top nICP level.

where  $n=25$ ,  $w_i$  was a 26-coefficient ABP→ICP IRF, and the consecutive samples  $ABP_i$ ,  $i=0\dots25$ , were equally spread over a time period of 3 cardiac cycles. For TCD characteristics ( $tcd_j$ ), we used a 13-coefficient ABP→FV IRF ( $t_j$ ), 13 ratios of  $t_j/ABP$ , pulsatility index (systolic FV minus end-diastolic FV divided by mean FV), and pulse length. The benefit for nICP assessment of this certain combination was validated by extending the preceding tests of different sets of TCD characteristics.

ABP→ICP IRF ( $w_i$ ) was calculated from  $tcd_j$  by multiplying a  $26 \times 28$  matrix A and adding a 26-dimensional vector B, expressed by the formula ( $w_i$ )= $A \times (tcd_j) + B$ .

The compound of A and B, the  $26 \times 29$  matrix AB, determined the properties of the nICP assessment procedure and was called the nICP matrix. AB was computed by a multiple regression analysis of data recordings from a patient reference group consisting of FV, ABP, and (measured) ICP curves. The multiple regression process related the TCD characteristics to the time-corresponding ABP→ICP IRF coefficients.

### Adaptation of the nICP Matrix to SCA

The improved nICP assessment procedure in this study (Figure 2a and 2b) consisted of a dynamically modified nICP matrix  $AB_{CUR}$ , which was a linear combination of 2 specific nICP matrices,  $AB_{AUT}$  and  $AB_{NAUT}$ . Both were previously calculated from reference groups of patients with preserved CA ( $AB_{AUT}$ ) and disturbed CA ( $AB_{NAUT}$ ). The nICP procedure started with a "neutral" nICP matrix,  $AB_{START}$  ( $AB_{START} = 0.4 \times AB_{AUT} + 0.6 \times AB_{NAUT}$ ), where 0.4 was found to be best for our purposes. The autoregulation indexes nMx and nPRx were computed every 50 seconds from FV, ABP, and nICP signals, and the control matrix  $AB_{CUR}$  was adapted to the current SCA by  $AB_{CUR} = (0.5 - MPR) \times AB_{AUT} + (0.5 + MPR) \times AB_{NAUT}$ , where  $MPR = (nMx + nPRx) / 2$ .

It is easily verified that  $AB_{CUR} = AB_{AUT}$ , if  $MPR = -0.5$ , indicating preserved CA;  $AB_{CUR} = AB_{NAUT}$ , if  $MPR = 0.5$ , indicating impaired CA; and  $AB_{CUR}$  lies between  $AB_{CUR}$  and  $AB_{AUT}$ , if  $MPR$  lies between  $-0.5$  and  $0.5$ .

Coefficients of  $AB_{CUR}$  and  $AB_{AUT}$  might also take on negative values. In this case, the properties of the opposite nICP matrix were boosted.

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