Accuracy, Precision, Sensitivity, and Specificity of Noninvasive ICP Absolute Value Measurements

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Abstract An innovative absolute intracranial pressure (ICP) value measurement method has been validated by multicenter comparative clinical studies. The method is based on two-depth transcranial Doppler (TCD) technology and uses intracranial and extracranial segments of the ophthalmic artery as pressure sensors. The ophthalmic artery is used as a natural pair of "scales" that compares ICP with controlled pressure Pe, which is externally applied to the orbit. To balance the scales, ICP = Pe a special two-depth TCD device was used as a pressure balance indicator. The proposed method is the only noninvasive ICP measurement method that does not need patient-specific calibration.

Keywords Noninvasive ICP absolute value method • Two-depth transcranial Doppler meter • Bland–Altman analysis • Regression analysis • ROC analysis

Introduction

Intracranial arteries are natural pressure sensors. The ophthalmic artery (OA) is a unique vessel with almost the same anatomy of intracranial and extracranial segments. Thus, we proposed to use the OA as natural "scales" for intracranial pressure (ICP) measurement and to apply a specially developed two-depth transcranial Doppler meter as a balance indicator of such "scales". The noninvasive arterial blood pressure (ABP) measurement method is also based on the balancing of two pressures. It does not need patient-specific calibration and it measures absolute values of systolic and diastolic ABP. The proposed method for noninvasive ICP absolute value measurements is a "reinvention" of a noninvasive ABP measurement method for solving individual patient-specific calibration problems. All noninvasive ICP measurement approaches based on the correlation of something in the human head with ICP cannot measure an absolute ICP value because of the need for patient-specific calibration [1–10]. Such calibration is impossible because a "gold standard" noninvasive ICP meter does not exist.

The aim of this study was to assess the accuracy, precision, sensitivity, and specificity of the proposed method (Bland–Altman, regression, and receiver operator characteristics analysis) in large groups of neurological and intensive care patients. Furthermore, another purpose of the study was to validate the linearity of noninvasive ICP measurements by performing a head-up and head-down tilting study (HUT/HDT) in randomly chosen healthy volunteers.

Materials and Methods

The proposed apparatus for noninvasive ICP measurement can derive an indication of the absolute value of ICP in a noninvasive manner. This indication is obtained by using the ultrasound Doppler measuring technique that is applied through the closed eyelid to the ophthalmic artery of the patient in a safe manner [11–14]. The noninvasive ICP measurement device used in this study was developed in the Health Telematics Science Institute of Kaunas University of Technology, Lithuania.

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This noninvasive method is based on the two-depth TCD technique for simultaneous measurement of flow velocities in the intracranial and extracranial segments of the ophthalmic artery (OA). These measurements are performed before, during, and after applying a series of small external pressure (Pe) steps to the tissues surrounding the eyeball. The methodology employed is similar to that of measurement using a pair of scales. The intracranial segment of the OA is compressed by ICP and the extracranial segment of OA is compressed by externally applied pressure, Pe. The blood flow parameters in both of these OA segments are monitored and they are approximately equal when Pe = ICP. The two-depth TCD device is used as an accurate indicator of the balance point (Pe = ICP), when the measured parameters of blood flow velocity waveforms in the intracranial and extracranial segments of OA are identical. During the measurement cycle Pe can be increased in 4-mmHg, 3-mmHg, or 2-mmHg steps to obtain a balance point where ICP = Pe. The Pe step was equal to 4 mmHg in this clinical study to have as short as possible time for snapshot noninvasive ICP measurements.

The prospective randomized comparative clinical studies (including blinded studies) of simultaneous noninvasive ICP and "gold standard" invasive ICP measurements have been performed in different groups of neurological and ICU patients in a few centers:

- Turku Hospital: TBI patients, invasive "gold standard" ventricular or parenchymal pressure sensors (parenchymal pressure is not equal to ICP according to the definition of ICP), prospective study
- Republic Vilnius University Hospital: TBI patients, ventricular "gold standard" invasive ICP sensors, prospective study
- Lithuanian University of Health Sciences, Neurological Clinic: prospective neurological patient phase III study: noninvasive ICP compared with "gold standard" CSF pressure measured via lumbar puncture

Results

The study population of the multicenter prospective study consisted of 121 primarily nonselected adult patients with severe brain injury or neurological disease treated in an intensive care unit and monitored with the need for ICP measurement. The demographic and hemodynamic data of the patient group are presented in Table 1.

A comparative study of noninvasive and invasive ICP measurements on TBI and neurological patients was carried out in the University Hospital in Turku (Finland), in Neurological Clinics, Lithuanian University of Health Sciences (Kaunas), and in Vilnius University Hospital (Lithuania) between December 2011 and June 2013. The results of this study are shown in Fig. 1a as a Bland–Altman plot of 151 paired noninvasive and invasive ICP data points. The results of plotting invasive "gold standard" ICP vs noninvasive ICP show linear regression and high correlation ($r = 0.82$) between the data under comparison (Fig. 1b). Precision expressed by a standard deviation of the difference between invasive and noninvasive ICP measurements is SD = 2.44 mmHg (confidence level [CL] = 0.96). Accuracy expressed by the absolute systematic error is equal to 0.17 mmHg (CL = 0.96).

The randomly chosen healthy volunteers were included into the linearity study of noninvasive ICP measurements (20–52 years of age). ICP was increased artificially by using a head-down tilt (HDT). Six different body positions were used: vertical (HUT) body position, sitting, supine, and three HDT positions. Three fixed body tilting angles were identified for every single healthy volunteer and used in order to create additional hydrostatic pressure of 10 mmHg (HDT1), 20 mmHg (HDT2), and 30 mmHg (HDT3) compared with the reference point of ICP value measured in a supine body position.

The number of healthy volunteers, tilting table position intervals, mean ICP values, together with standard deviations in everybody position, are shown in Table 2. The noninvasive ICP measurement linearity test results are shown in Fig. 2a.

Table 1 Study population

City, country	Kaunas, LT	Vilnius, LT	Turku, FI	Total
Number of patients in three clinical centers in Lithuania and Finland	101 patients 111 data points	7 patients 28 data points	4 patients 12 data points	121 patients 151 data points
Pathological conditions:				
Multiple sclerosis	33			33
Idiopathic intracranial hypertension	56			56
Hydrocephalus	8			8
Guillain–Barré syndrome	2			2
Polyneuropathy	2			2
Traumatic brain injury		7	4	11

Data collected from 121 patients (151 independent paired data points)

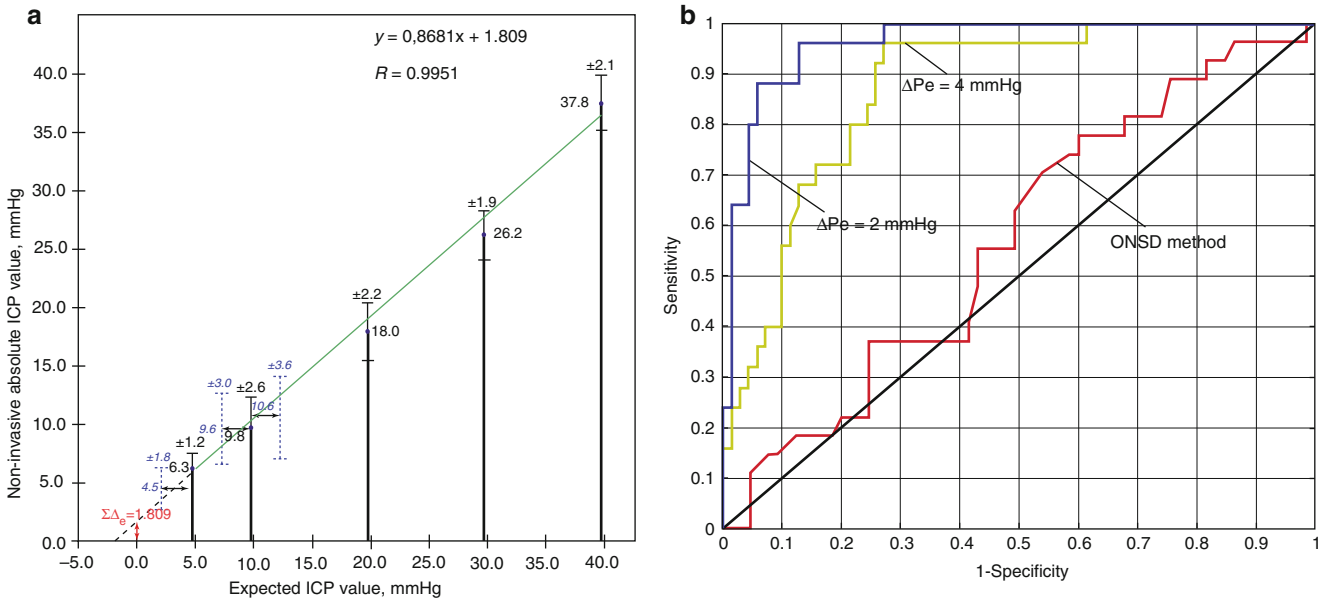

Fig. 1 (**a**) Bland and Altman plot and (**b**) regression line plot of independent paired data points of the simultaneous noninvasive absolute intracranial pressure (ICP) value measurements and the invasive "gold standard" ICP measurements (total 151 data points): *circle points* – Kaunas (Lithuania) study of 101 neurological patients, 111 independent paired data points ("gold standard" invasive ICP is measured via a lumbar puncture); *square points* – ongoing Vilnius (Lithuania) study 7 patients with traumatic brain injury (TBI), 28 independent paired data points (invasive ICP is measured by using the Codman microsensor parenchymal catheter with ICP sensor REF 82–6631); *diamond points* – ongoing Turku (Finland) study, 4 TBI patients, 12 independent paired data points (invasive ICP is measured by using the Codman microsensor ventricular catheter with ICP sensor REF 82–6653). Here: Δ – absolute difference (absolute error) of the paired noninvasive and invasive ICP data; mean ICP is a mean value of invasively and noninvasively measured absolute ICP values; *horizontal lines* – the absolute error Δ corridor (±4.0 mmHg) caused by the ΔPe sampling step of externally applied pressure, which was equal to 4.0 mmHg; the *vertical lines* show two clinically important ICP thresholds: the general critical ICP threshold of the neurological patients (14.7 mmHg) and the critical ICP threshold of the severe TBI patients (20.0 mmHg). A standard deviation of the random error (precision) SD = 2.44 mmHg (confidence level [CL] = 0.96)

Table 2 Results of the study of healthy volunteers in six body positions

Body position	Number of healthy volunteers	Tilting table position	Mean ICP, mmHg	±SD, mmHg
Standing	10	−90	4.2	2.5
Sitting	16	−90	4.3	3.1
Supine	41	0	9.8	2.6
HDT1	11	(21.6; 25.8)	18.2	2.2
HDT1	10	(32; 40.5)	26.2	1.9
HDT1	10	(42.31 50.7)	37.8	2.1

HDT head-down tilt

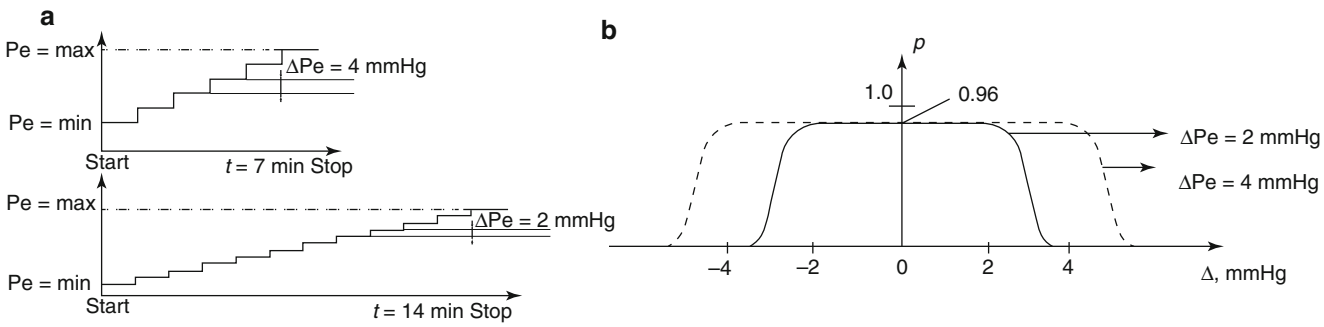

Fig. 2 (**a**) Study of healthy volunteers: 217 snapshot noninvasive ICP measurements in six body positions: the bars show the mean noninvasively measured ICP absolute values and SDs in mmHg; the *dashed bars* represent the phase-contrast MRI-measured absolute mean ICP values and SDs in sitting and supine body positions [15, 16]. Here, $\Sigma\Delta_S$ = the integrated systematic error of the head-up tilt/head-down tilt (HUT/HDT) experiment. (**b**) Empirical receiver operating characteristic (ROC) curves of two different noninvasive ICP measurement methods: for the optic nerve sheath diameter (ONSD) method, the area under the ROC curve (AUC) was 0.51; for the noninvasive ICP value method, ΔPe = 4.0 mmHg, AUC = 0.87; for the noninvasive ICP value method, ΔPe = 2.0 mmHg, AUC = 0.96

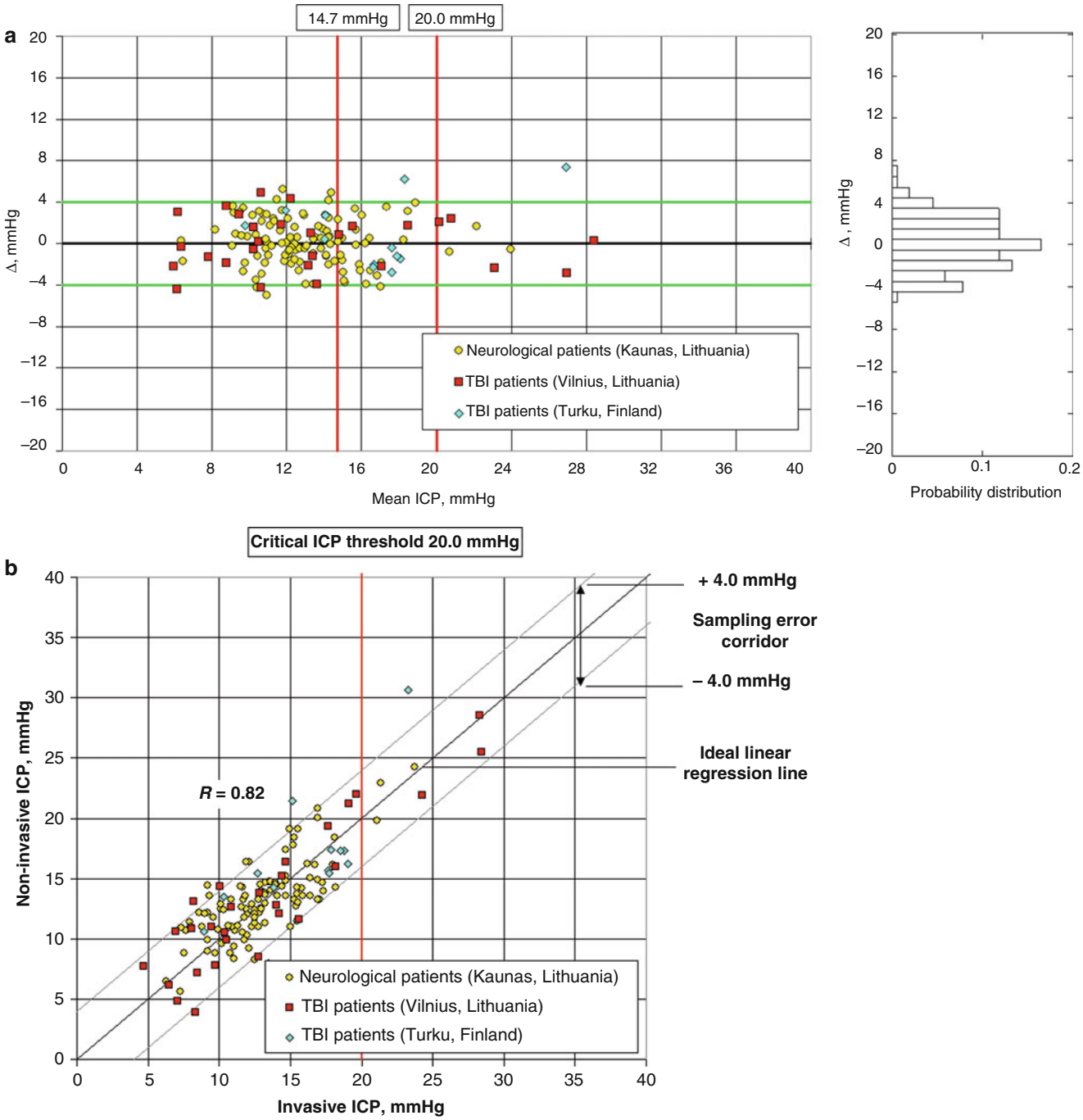

Fig. 3 (**a**) Noninvasive ICP measurement procedures using sampling steps ΔPe = 4.0 mmHg and ΔPe = 2 mmHg. (**b**) Noninvasive ICP measurement random errors' corridors $p(\Delta)$ as a superposition of uniform error distributions (caused by sampling steps ΔPe = 4 mmHg and ΔPe = 2 mmHg) together with Gaussian random error distributions (caused by instrumental and methodological errors of the noninvasive ICP meter). Here, p is the probability that paired noninvasive and invasive measurement data points (Fig. 1) will be within the error corridor $p(\Delta)$ when CL = 0.96

Discussion

Receiver operating characteristic (ROC) analysis showed that the best result for sensitivity and specificity of noninvasive ICP measurements with ΔPe = 4 mmHg was obtained at the cutoff point of 13.11 mmHg. Sensitivity at that point was 93.6 %; specificity at this value was 72.6 %. The achieved area under the ROC curve (AUC) was 0.87. The sensitivity and specificity of noninvasive ICP measurement may be increased when setting the ΔPe sampling step to 2.0 mmHg, as depicted in Fig. 2b. The achievable optimal sensitivity and specificity would then be 87.1 %, 91.8 % respectively and AUC = 0.96. The achieved AUC values of the proposed noninvasive ICP measurement method are much higher in com-

parison with other approaches to noninvasive ICP measurement, which rely on ICP correlation with another physiological parameter (Fig. 2b) [2–10, 14].

By reducing the sampling step from 4–2 mmHg it is possible to decrease the SD of random errors (Fig. 1). On the other hand, the time of noninvasive snapshot ICP measurement would double in this case, as shown in Fig. 3. Pe max, Pe min and the number of pressure steps (Fig. 3) can be selected interactively by the operator of the noninvasive ICP meter.

Conclusions

1. The Bland–Altman plot of 151 paired noninvasive and invasive ICP data points shows that the mean systematic error (accuracy) of noninvasive absolute ICP value measurement is equal to 0.17 mmHg and that the standard deviation of the random error (precision) SD = 2.44 mmHg (CL = 0.96).
2. The negligible mean systematic error (0.17 mmHg) is statistically significant evidence (CL = 0.96) that noninvasive absolute ICP value measurement technology does not need a patient-specific calibration, when $\Delta Pe = 2$ mmHg.
3. Receiver operating characteristic curve analysis confirms the high sensitivity (88 %), specificity (92 %), and area under the ROC curve (0.96) of the noninvasive ICP measurement method.
4. The study of healthy volunteers (217 snapshot ICP noninvasive measurements in six body positions) confirms the linearity ($R = 0.995$) of the noninvasive absolute ICP value measurement method in the clinically important absolute ICP range (6.3–37.8 mmHg), which is below and above the critical ICP thresholds: 14.7 mmHg (neurology) and 20.0 mmHg (neurosurgical intensive care).
5. The two-depth TCD-based method is the only noninvasive ICP value measurement method that does not need a patient-specific calibration.

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Conflict of Interest Professor Arminas Ragauskas is the inventor of the patented noninvasive absolute ICP measurement method.

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