Critical Closing Pressure during Controlled Increase in Intracranial Pressure – comparison of three methods

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Abstract

Objectives: Critical closing pressure (CrCP) is the arterial blood pressure (ABP) threshold, below which small arterial vessels collapse and cerebral blood flow ceases. Here we aim to compare three methods for CrCP estimation in scenario of a controlled increase in intracranial pressure (ICP) induced by infusion test performed in patients with suspected normal pressure hydrocephalus (NPH).

Methods: Computer recordings of directly measured intracranial pressure (ICP), ABP and Transcranial Doppler cerebral blood flow velocity (CBFV), from 37 NPH patients who underwent infusion tests, were retrospectively analyzed. The CrCP was calculated with three methods. With first harmonics ratio of the pulse waveforms of ABP and CBFV ($CrCP_A$) and two methods based on a model of cerebrovascular impedance, as a function of cerebral perfusion pressure ($CrCP_{inv}$), and as a function of ABP ($CrCP_{ninv}$) d.

Results: During controlled rise of ICP all three estimators of CrCP increased significantly ($p < 0.05$). During infusion tests the strongest correlation between ICP and CrCP was found for $CrCP_{inv}$ (median R was 0.41). For the other methods, the median of the correlation coefficient was less than 0.24. There is good agreement between three methods of CrCP calculation with mutual correlation coefficients being greater than 0.8 ($p << 0.05$). For $CrCP_A$ method, negative values can be encountered for about 20% of all results. Negative values of CrCP were not observed in estimators based on cerebrovascular impedance.

Conclusion: Invasive critical closing pressure is most sensitive to variations in ICP and CPP and can be used as an indicator of the cerebrospinal and cerebrovascular system status during infusion tests. All methods give similar results in response to ICP changes. In case of individual CrCP measurement for each patient, $CrCP_A$, may provide negative, non-physiological values.

Key words: critical closing pressure, wall tension, intracranial pressure, cerebral autoregulation, infusion test.

Introduction

Critical closing pressure (CrCP) is the arterial blood pressure (ABP) threshold, below which small arterial vessels collapse and blood flow ceases. It was first described by Burton [1]. Theoretically, cerebral CrCP is the sum of intracranial pressure (ICP) and vascular wall tension (WT) [2]. With the introduction of transcranial Doppler ultrasonography it became possible to assess CrCP noninvasively by comparing the waveforms of cerebral blood flow velocity (CBFV) and ABP [3, 4, 5]. One of the methods, proposed by Aaslid [6] is based on linear regression analysis between single pulse of CBFV and ABP as an intercept point of the regression line with the X axis (ABP) [7]. Alternatively, the fundamental harmonics of the pulse waveforms of ABP and CBFV can be used [8]. These methods however may provide an inaccurate estimation of CrCP as they can produce negative values of CrCP that cannot be interpreted physiologically [9]. Recently Varsos et al. [10] proposed a new methodology for CrCP estimation based on a cerebrovascular impedance model [11] as a function of cerebral perfusion pressure (CPP), ABP, cerebrovascular resistance (CVR), arterial compliance (C_a), and heart rate (HR). This multiparameter descriptor of CrCP has been extensively explored in patients with different cerebrovascular derangements such as: vasospasm after subarachnoid hemorrhage [12], traumatic brain injury [13] or in patients suffering from hydrocephalus [14]. Important advantage of this method of CrCP calculation is the fact that it is not providing the non–physiological negative values of pressure, as was in the case of Aaslid's method.

In this study we aim to compare three methods for CrCP estimation in scenario of a controlled increase of ICP induced by the infusion test performed in patients with suspected normal pressure hydrocephalus (NPH). It was previously showed that an increase in CrCP is related to increase in ICP [3]. However, it is unknown whether and to what extent the noninvasive and invasive methods of CrCP estimation can be used interchangeably in scenario of controlled rise in ICP.

Material and Method

Patients

Thirty seven patients with entry diagnosis of normal pressure hydrocephalus were studied. The median age of the patients was 57.0 years (quartile range: 37.0–64.0 years). On the basis of imaging examination (median width of third cerebral ventricle was 13.64 mm, quartile range: 10.15–17.22 mm) and clinical symptoms they have been admitted to the Hydrocephalus Clinic, Addenbrooke's Hospital, Cambridge, UK in order to undergo the

infusion test. The evidence of white matter ischemia on cranial imaging occurred in seven patients. Tests are performed as a standard clinical procedure. Patients are individually consented and anonymized digital recordings of monitored variables were post–processed as a part of clinical audit.

Infusion test procedure

The CSF space was accesed by a lumbar puncture. Spinal needle was inserted between the third and fourth lumbar vertebrae and used for both ICP measurements and saline fluid infusion. The needle was connected to an infusion pump and to the pressure transducer, from which the signal was transferred to the standard invasive pressure inputof bed–side monitor.. After about 10 minutes of the baseline pressure measurement the infusion was started. The test was performed with a constant–rate infusion, 1.5 ml min^{-1} or 1.0 ml min^{-1} if the baseline pressure was greater than 13 mmHg. The infusion was continued until a new steady state of ICP (plateau) reached, or until ICP safety limit of 40 mmHg was achieved.

Data acquisition and analysis

Cerebral blood flow velocity (CBFV) was measured from the middle cerebral artery (MCA) with a 2 MHz probe and monitored with the Transcranial Doppler (Neuroguard, Medasonics, Fremont, CA). Arterial blood pressure was measured non–invasively by Finapress finger cuff (Ohmeda, Englewood, CO). Raw signals were digitized using an analog–digital converter (DT2814, Data Translation, Marlboro, CA) sampled at a frequency of 50 Hz, recorded by WREC software (Wojciech Zabolotny, Warsaw University of Technology) and re–analysed using ICM+ software (Cambridge Enterprise, Cambridge, UK, http://www.neurosurg.cam.ac.uk/icmplus/). The amplitudes of the fundamental harmonics of ABP, CBFV and ICP were derived using 10 seconds discrete Fourier transformations. Heart rate (HR) was assessed as frequency associated with the first harmonic of ABP. All the calculations were performed over a 10 s window.

Calculation of Critical Closing Pressure

Method 1 ($CrCP_A$)

CrCP was determined using first harmonics ratio of the pulse waveforms of ABP and CBFV according to following formula [8]:

$$CrCP_A = ABP_{mean} - \frac{Amp_{ABP}}{Amp_{CBFV}} \cdot CBFV_{mean} \quad (1)$$

Where: ABP_{mean} – mean value of ABP; Amp_{ABP} and Amp_{CBFV} – amplitudes of the fundamental harmonics of ABP and CBFV, respectively.

Model-based estimation of CrCP:

To calculate multiparameter model of CrCP [10] it is necessary to estimate cerebrovascular resistance (CVR) and compliance (C_a). CVR represents the resistance of small cerebral arteries and it can be estimated using TCD mean blood flow velocity (CBFV), and mean cerebral perfusion pressure (CPP = meanABP – meanICP):

$$CVR = \frac{meanCPP}{meanCBFV \cdot S_a} \tag{2}$$

The arterial compliance (C_a) represents the change of arterial blood volume in response to change in arterial pressure and can be estimated as:

$$C_a = \frac{Amp_{CaBV} \cdot S_a}{Amp_{ABP}} \tag{3}$$

In equations 2 and 3, S_a represents the cross–sectional area of the insonated vessel. Obtaining of amplitude of the fundamental harmonic of cerebral arterial blood volume (CaBV) is described in detail in work [12] and presented in appendix.

Method 2 ($CrCP_{inv}$)

$CrCP_{inv}$ is calculated based on mathematical model of cerebrovascular impedance [10] and expressed by equation 4. Details of the mathematical analysis are given in appendix:

$$CrCP_{inv} = ABP - \frac{CPP}{\sqrt{(CVR \cdot C_a \cdot HR \cdot 2\pi)^2 + 1}} \tag{4}$$

Method 3 ($CrCP_{ninv}$)

In some clinical scenarios, when there is no need or possibility to monitor ICP, CrCP can be calculated from equation 5 with CPP approximated by ABP:

$$CrCP_{ninv} = ABP \cdot \left(1 - \frac{1}{\sqrt{(CVR_{ninv} \cdot C_a \cdot HR \cdot 2\pi)^2 + 1}}\right) \tag{5}$$

Where CVR_{ninv} is cerebrovascular resistance calculated from equation 2 with CPP approximated by ABP. This a simple modification of formula 4, taking ICP = 0.

Wall Tension

According to Burton's idea [1, 2] vascular wall tension can be expressed as the difference between CrCP and intracranial pressure and represent active vasomotor tone:

$$WT = CrCP - ICP \quad (6)$$

WT was calculated using two methods, the Aaslid's CrCP conception (WT_A) and cerebrovascular impedance methodology (WT_{inv}). Having available CrCP and WT, the ratio of these parameters was determined.

Statistical analysis

To determine whether the data is normally distributed the Shapiro–Wilk test was used. Nonparametric Wilcoxon test was utilized to examine the significance of a difference in analysed parameters between baseline and plateau phase of the test. The significance level of all tests was set at 0.05. Results are presented as median value ± quartile range (QR). Bland–Altman method was used to determine the agreement between three methods of CrCP calculation.

Results

The changes in ICP, ABP, CPP, CBFV between baseline and plateau phase of the test and calculated variables: $CrCP_A$, $CrCP_{inv}$, $CrCP_{ninv}$, WT_A, WT_{inv} along with ratios of WT and CrCP are presented in table 1.

During lumbar infusion mean ICP increased significantly ($p < 0.0001$) by 12.29 ± 6.31 mmHg from baseline to plateau level. ABP was significantly higher during infusion when compared with baseline, whereas the CPP and CBFV were significantly lower. Difference between baseline and plateau level for CPP and CBFV is 7.90 ± 10.16, $p = 0.001$ and 2.67 ± 2.49, $p < 0.0001$, respectively.

Table 1 - Median and quartile range (median ± QR) of measured and calculated variables from baseline and plateau level

N=34	Baseline	Plateau	p-value
ICP [mm Hg]	6.81 ± 7.27	19.76 ± 11.16	< 0.0001
ABP [mm Hg]	95.12 ± 36.36	100.40 ± 33.74	0.0085
CPP [mm Hg]	86.98 ± 26.59	81.87 ± 32.54	0.0010
CBFV [cm/s]	87.02 ± 28.81	50.34 ± 17.58	< 0.0001
$CrCP_{inv}$ [mm Hg]	44.99 ± 16.11	52.72 ± 20.74	< 0.0001
$CrCP_{ninv}$ [mm Hg]	44.73 ± 22.12	48.90 ± 24.29	0.0001

$CrCP_A$ [mm Hg]	33.39 ± 27.86	38.03 ± 33.68	0.0003
WT_{inv} [mmHg]	38.15 ± 17.98	31.48 ± 21.58	0.0002
WT_A [mmHg]	28.76 ± 28.22	15.24 ± 33.59	0.0105
$(WT/CrCP)_{inv}$ [mmHg]	0.87 ± 0.12	0.65 ± 0.19	< 0.0001
$(WT/CrCP)_A$ [mmHg]	0.87 ± 0.17	0.48 ± 0.39	< 0.0001

Critical Closing Pressure calculated using three methods

Following the rise in ICP, median CrCP obtained with all three methods significantly increased by 7.78 ± 6.00, $p < 0.0001$, for $CrCP_{inv}$, 5.89 ± 4.66, $p < 0.0001$ for $CrCP_{ninv}$ and by 9.38 ± 9.87, $p = 0.0001$, in case of $CrCP_A$. However, the values of Aaslid's estimator were lower than impedance methods by 10.80 ± 20.56, $p < 0.0001$, in baseline and by 12.45 ± 16.99, $p < 0.0001$, in plateau.

Results obtained with all 3 methods of CrCP calculation were strongly correlated with each other. The strongest correlation was found between $CrCP_{inv}$ and $CrCP_{ninv}$ ($R = 0.9675$, $p < 0.0001$). The associations between $CrCP_A$ and either $CrCP_{inv}$ or $CrCP_{ninv}$ were also significant but correlation coefficients were weaker ($CrCP_{inv}$ vs. $CrCP_A$, $R = 0.8398$, $p < 0.0001$ and $CrCPn_{inv}$ vs. $CrCP_A$, $R = 0.8295$, $p < 0.0001$). The Bland–Altman plots obtained for pooled data from both phases of the test (baseline and infusion) demonstrate a moderately good agreement between the Aaslid's method and both model–based methods (invasive and non–invasive ones) for CrCP calculation (figures 2a and 2b). The biggest discrepancies were seen when the $CrCP_A$ demonstrated negative values. On the other hand a very good agreement was found between invasive and non–invasive model–based methods (figure 2c). The mean difference between the CrCP values obtained with the two (invasive and non–invasive) methods was about 4.5 mmHg.

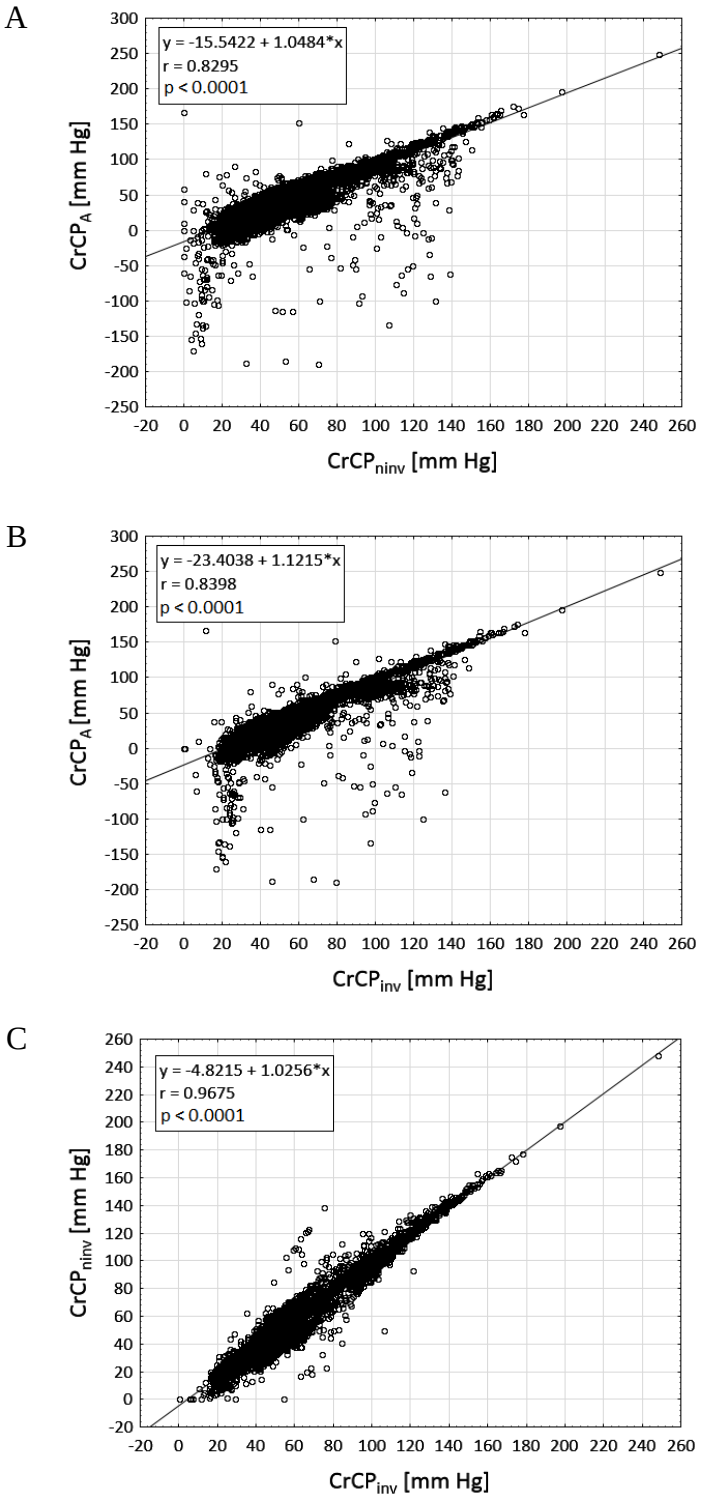


Figure 1 - Scatterplots of relationship between critical closing pressure calculated by A) non–invasive model–based method ($CrCP_{ninv}$) vs. Aaslid's method ($CrCP_A$), B) invasive model–based method ($CrCP_{inv}$) vs. Aaslid's method ($CrCP_A$) C) invasive vs. non–invasive model–based method ($CrCP_{inv}$ vs. $CrCP_{ninv}$).

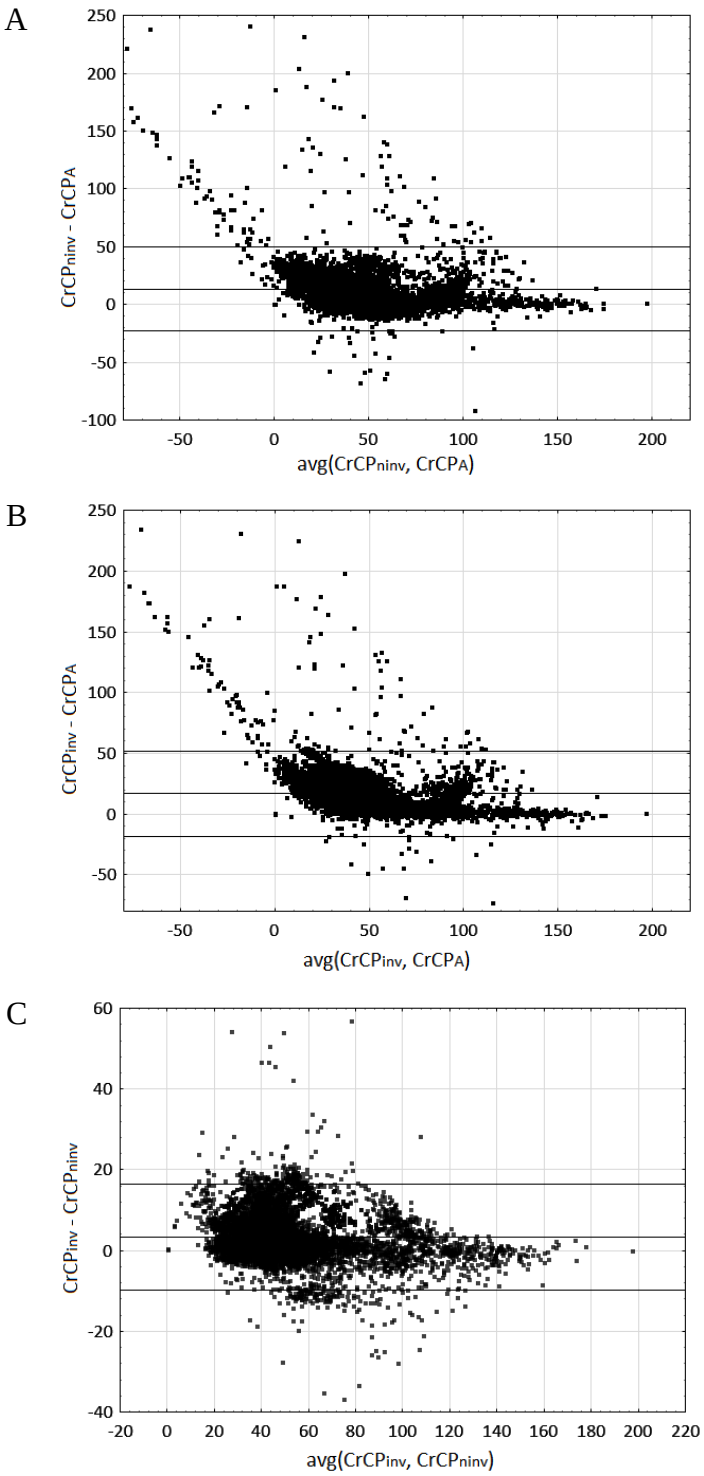


Figure 2 – The Bland–Altman plots for comparing difference between A) $CrCP_{ninv}$ and $CrCP_{A}$ B) $CrCP_{inv}$ and $CrCP_{A}$ C) $CrCP_{inv}$ and $CrCP_{ninv}$ for all measurement points. Horizontal lines are drawn at the mean difference and ± 2 times standard deviation (SD) of the differences.

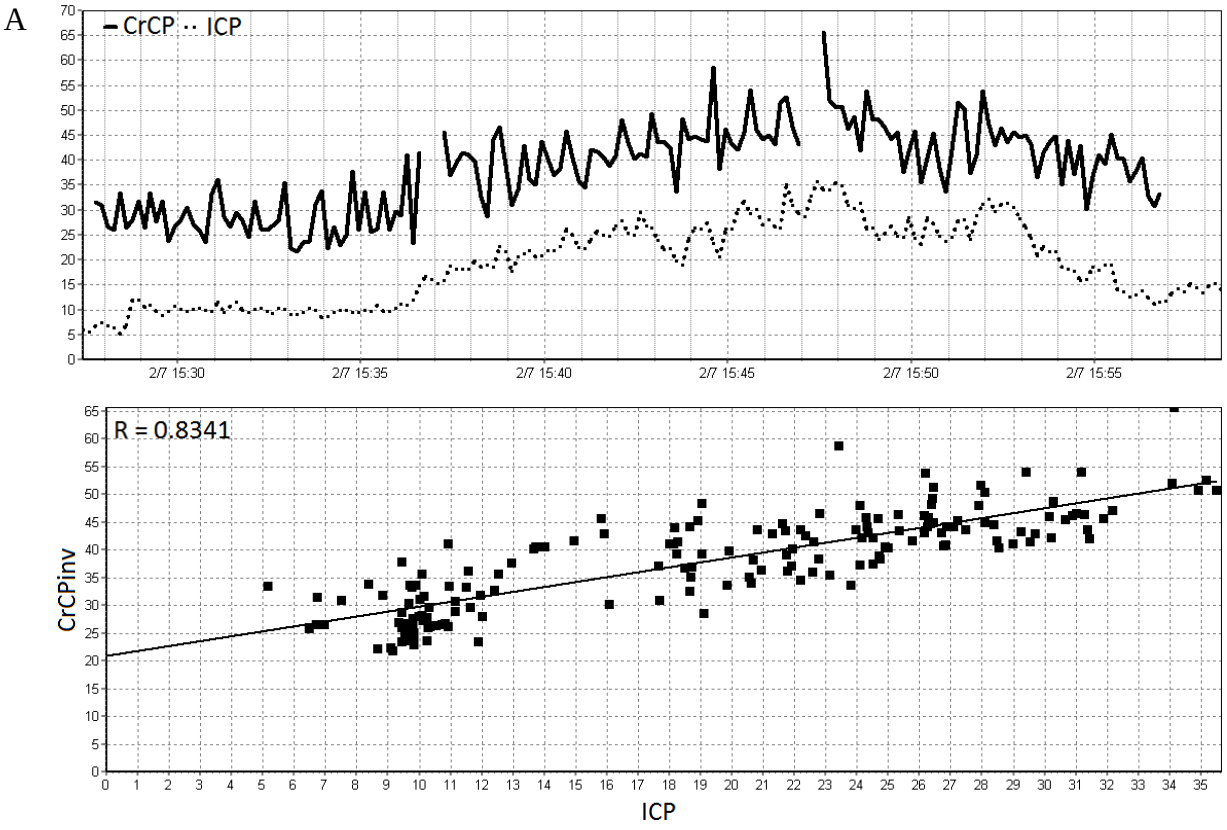
Correlation analysis between CrCP obtained with three methods and ICP was also performed based on data recorded in each individual patient. The results were highly variable (see table 2). Examples of a good and bad correlation are shown on figure 3.

Table 2 - Median, minimum, maximum and quartile range of correlation coefficients between ICP and CrCP calculated based on three methods.

	Median	Minimum	Maximum	Inter – Quartile Range
R between $CrCP_{inv}$ and ICP	0,4055	-0,5269	0,8310	0,4444
R between $CrCP_{ninv}$ and ICP	0,2384	-0,5170	0,6844	0,3337
R between $CrCP_{A}$ and ICP	0,2355	-0,2380	0,7054	0,4667

In 7 patients (20.58 %) correlation coefficient between ICP and CrCP had a negative values. Negative values occurred most often in case of $CrCP_{ninv}$. In 4 patients correlation coefficient between ICP and three estimators of CrCP had negative values.

A



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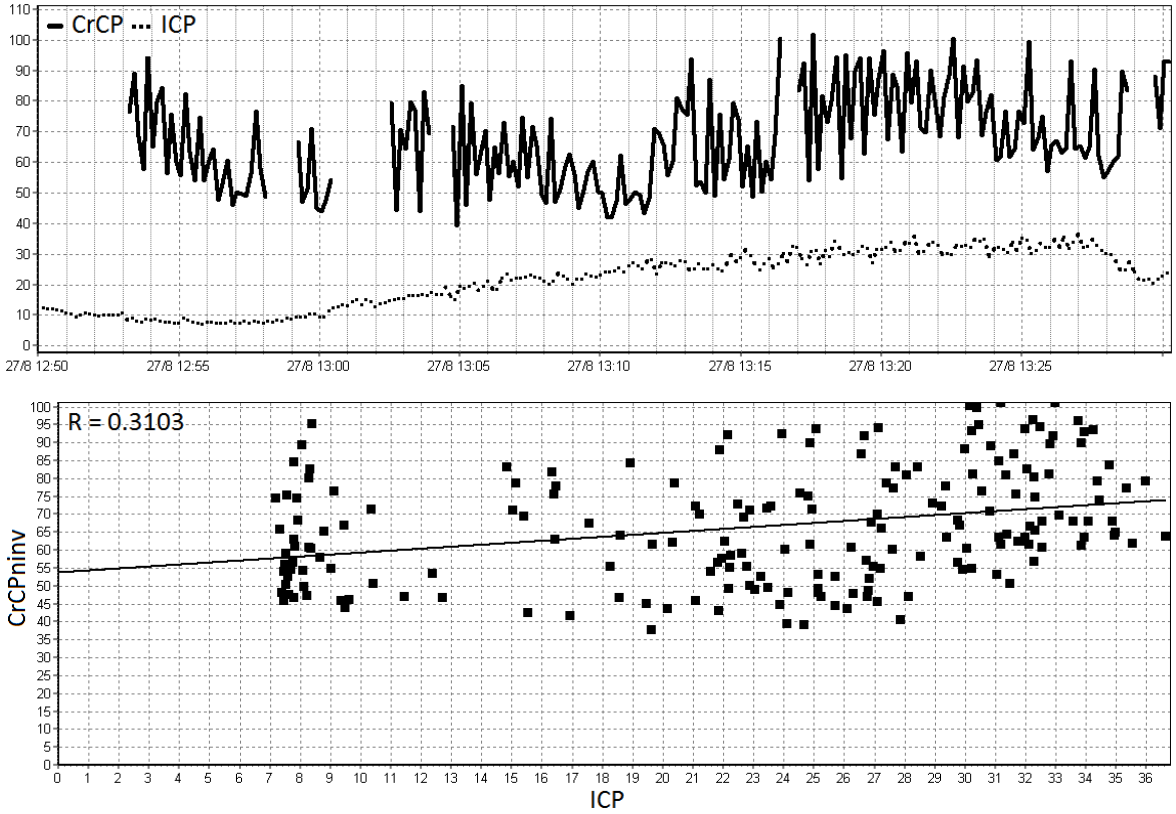

Figure 3 - Example of good (A) and bad (B) correlation between ICP and CrCP with the corresponding time plots.

As a result, the highest correlation coefficient for ICP and $CrCP_{inv}$ was found.

It was also observed that changes in CrCP from baseline to plateau ICP (ΔCrCP) were significantly correlated to changes in ICP (ΔICP), as demonstrated an example in figure 4. Correlations were observed in all three methods: ΔICP and $\Delta CrCP_A$, R = 0.4451; p = 0.0075, ΔICP and $\Delta CrCP_{ninv}$, R = 0.3901, p = 0.0205, ΔICP and $\Delta CrCP_{inv}$, R = 0.4349, p = 0.0090.

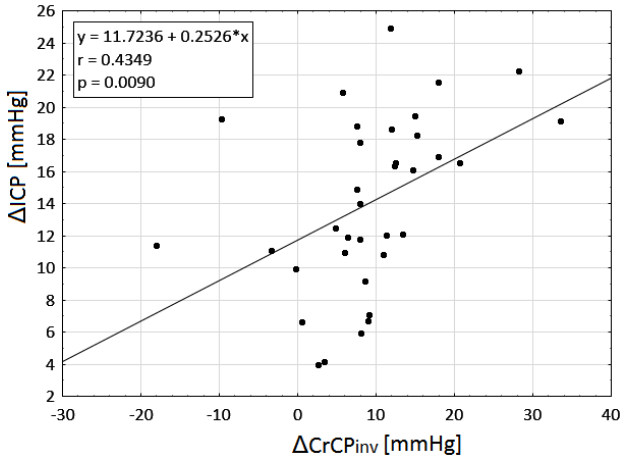

Figure 4 – Correlation between changes in invasive estimator of critical closing pressure ($\Delta CrCP_{inv}$) and changes in intracranial pressure (ΔICP).

Wall Tension calculated using two methods

WT showed a tendency to decrease due to compensating vasodilatation. The values of WT_A were lower than impedance–model based estimator ($p < 0.0001$). Correlation analysis between WT and cerebrovascular resistance (Figure 5) demonstrated that impedance–model based WT was positively correlated to CVR ($R = 0.6761$, $p < 0.0001$). We found weaker but significant correlation between CVR and WT_A ($R = 0.2445$, $p = 0.0358$). The ratio of WT and CrCP significantly decreased for both methods. WT/CrCP ratios were almost identical for two methods. During the test WT/CrCP ratio tends to decrease. Difference between plateau level and baseline for ratio of $(WT/CrCP)_{inv}$ was 0.2025 ± 0.1280 ($p < 0.0001$) and for ratio of $(WT/CrCP)_A$ was 0.3159 ± 0.2677 ($p < 0.0001$).

Changes in in cerebrovascular resistance (ΔCVR) is strongly correlated with changes in wall tension calculated by invasive model–based method ΔWT_{inv} $R = 0.7564$, $p < 0.0001$. However, the observed correlation between the changes in CVR and Aaslid's estimator of wall tension, although significant, were only moderate.

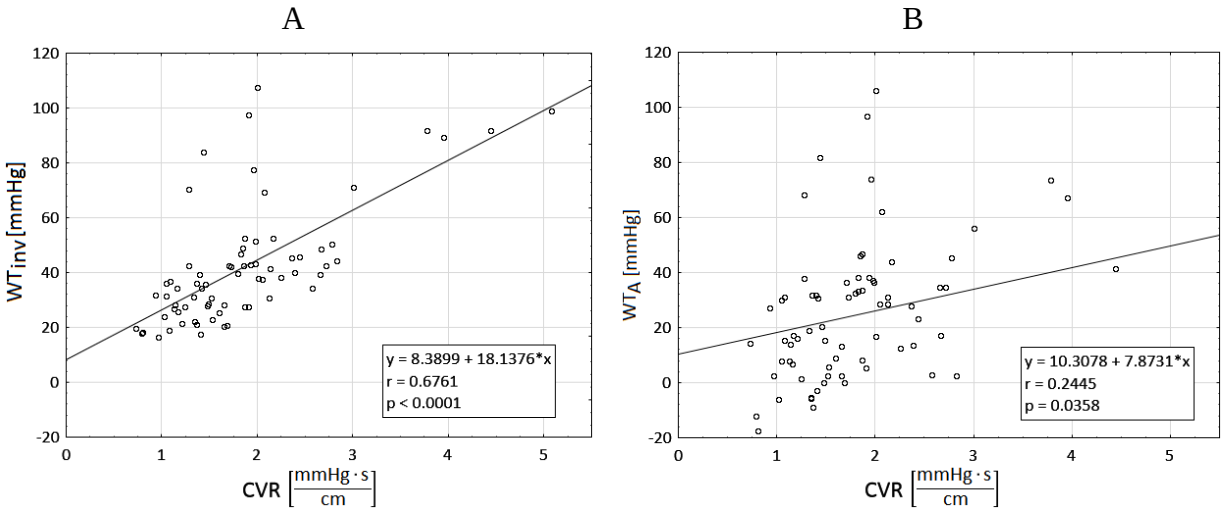

Figure 5 – Scatterplots of relationship between A) cerebrovascular resistance (CVR) and invasive model–based wall tension (WT_{inv}) B) CVR and Aaslid's estimator of wall tension (WT_A).

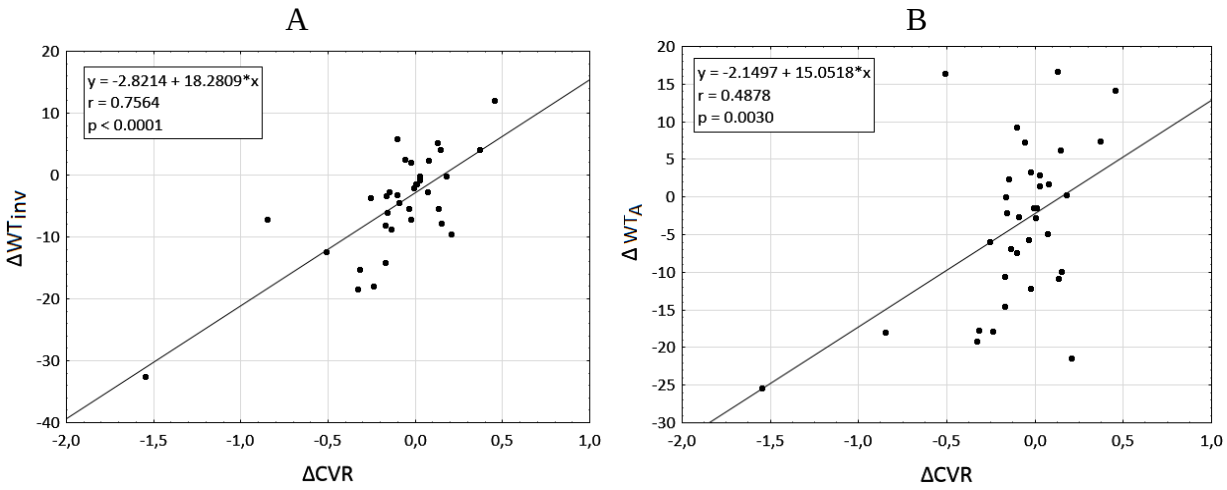

Figure 6 – Correlation between changes in A) cerebrovascular resistance (ΔCVR) and invasive model–based wall tension (ΔWT_{inv}) and B) CVR and Aaslid's estimator of wall tension (ΔWT_A).

Discussion

The aim of this study was to compare three methods of CrCP calculation. It is difficult to decide which method is better. We have shown a close relationship between the values of CrCP obtained using impedance model–based methods (invasive and non–invasive one) and based on Aaslid's equation. The mean difference between the CrCP values obtained with impedance–model based methods (invasive and non–invasive) was about 4.5 mmHg. CrCP calculation methods are relatively well correlated, although non–invasive CrCP expresses changes in ICP in weaker degree. Moreover in individual patients the absolute difference between these estimators was the smallest in case $CrCP_{inv}$ and $CrcP_{ninv}$ (Bland–Altman plots). Correlation between CrCP from Aaslid's equation and invasive/non–invasive CrCP was undoubtedly lower. The existence of negative $CrCP_A$ values caused discrepancies between the methods. $CrCP_A$ was lower than impedance model–based estimators. This is caused by methodological limitations of Aaslid formula. During controlled increase in ICP, $CrCP_A$ rendered negative values in situations of changes in amplitude and mean values of CBFV and/or ABP. The issue of low and negative values of $CrCP_A$ has been a known drawback in cases such as hyperemia or vasospasm [9, 13]. Therefore physiological interpretation of $CrCP_A$ is sometimes difficult.

Changes in critical closing pressure (ΔCrCP) are shown to be positively correlated to changes in intracranial pressure (ΔICP). During infusion tests, rising ICP leads to a significant increase in CrCP. We can observe contrasting effect of ICP on CrCP and wall tension (WT). Rising

ICP causes CrCP and WT to change in opposite directions (CrCP increasing and WT decreasing due to compensatory to decreasing CPP vasodilatation). Past studies performed under various conditions [15, 16] have demonstrated that both changes in ICP and WT cause changes in estimated CrCP. Changes in CrCP related to rise in ICP are partially damped by vasodilation (decrease in WT). This is first reason why CrCP is not the best estimator of ICP. Changes in cerebrovascular resistance, which is one of the most important mechanisms of cerebral homeostasis, are shown to be positively correlated to changes in WT_{inv}.

Relationship between CrCP, WT and ICP could also be demonstrated through the WT/CrCP ratio, which was shown to be significantly associated with changes in ICP. During infusion the ratio of WT and CrCP decreases, which suggests that the CrCP in intracranial hypertension becomes more active estimator of ICP. On the other hand, the ratio WT/CrCP can be used as measure of vasodilatation. WT decreased significantly when CPP decreased, which may be interpreted as an effect of cerebral vasodilatation.

Conclusions

There was a significant correlation between the analyzed methods of CrCP determining. All three indices were in agreement, although the best agreement between impedance model–based methods (invasive and non–invasive) was performed. The strongest correlation between ICP and CrCP occurs in case of application invasive impedance model–based method, which can be explained due to the use of ICP in the $CrCP_{inv}$ calculation formula. Rising ICP lead to increases in all three estimators od CrCP with vascular wall tension (WT) decreasing, signifying vasodilatation. Correlation between CrCP and ICP may be disturbed by decrease in WT during infusion.

Appendix

In impedance – based methods, impedance spectrum across the frequencies of cardiac cycle (ω) is given by parallel set of cerebrovascular resistance (CVR) and arterial compliance (C_a). Therefore, modulus of impedance could be expressed as:

$$|Z(\omega)| = \frac{CVR}{\sqrt{CVR^2 \cdot {C_a}^2 \cdot \omega^2 + 1}} \quad (1)$$

where ω symbolizes circular frequency (2Π*frequency).

In used model, the amplitude of fundamental harmonic of cerebral blood flow velocity could be expressed as a function of cerebrovascular impedance:

$$Amp_{CBFV} = \frac{Amp_{ABP}}{|Z(f_{HR})|} \quad (2)$$

where $|Z(f_{HR})|$ represents modulus of cerebrovascular impedance at the heart rate frequency (f_{HR}). Amp_{CBFV} and Amp_{ABP} symbolize first harmonics amplitudes of cerebral blood flow velocity and arterial blood pressure, respectively.

One can apply the same model to evaluate the mean value of fundamental cerebral blood flow velocity (CBFV) at the theoretical heart rate of zero. CBFV simulates a direct current, arterial compliance is saturated, and impedance ($|Z(0)|$) is a function of cerebrovascular resistance (CVR):

$$CBFV = \frac{CPP}{|Z(0)|} = \frac{CPP}{CVR} \quad (3)$$

where CPP is cerebral perfusion pressure and it is equal to difference between ABP and intracranial pressure (ICP).

Critical closing pressure (CrCP) could be evaluated based on equations (1), (2), (3) and Aaslid's formula [8], and could be expressed as:

$$CrCP_{inv} = ABP - \frac{CPP}{\sqrt{(CVR \cdot C_a \cdot HR \cdot 2\pi)^2 + 1}} \quad (4)$$

In above formula, pulsation of CPP may be approximated by pulsation of ABP, in case of there is no need or possibility to monitor ICP.

To calculate model–based CrCP [10], estimation of CVR and C_a is required. CVR represents the resistance of small cerebral arteries and it can be estimated using TCD mean blood flow velocity (CBFV), and mean cerebral perfusion pressure (CPP):

$$CVR = \frac{CPP}{CBFV \cdot S_a} \tag{5}$$

The C_a represents the change of arterial blood volume in response to change in arterial pressure and can be estimated as:

$$C_a = \frac{Amp_{CaBV} \cdot S_a}{Amp_{ABP}} \tag{6}$$

In equations 5 and 6, S_a represents the cross–sectional area of the insonated vessel. Obtaining the amplitude of the fundamental harmonic of cerebral arterial blood volume (CaBV) [12] could be evaluated based on pulsatile changes of CBFV. Therefore, it could be derived by using a 10 – second discrete Fourier transformation of CaBV time series.

CaBV can be approximated by sampling instant and average values of cerebral blood flow velocity:

$$C_aBV(n) = S_a \cdot \sum_{i=m}^{n} \big(CBFV_a(i) - meanCBFV_a(i)\big)\Delta t(i) \tag{7}$$

where n is the number of the samples, CBFVa(i) – sampled cerebral blood flow velocity, and Δt(i) is the time interval between the consecutive samples.

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