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# Assessment of Cerebral Blood Flow During Infusion Test in the Diagnosis of Normal Pressure Hydrocephalus

## Ocena mózgowego przepływu krwi podczas testu infuzyjnego w diagnostyce wodogłowia normotensyjnego

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#### **Abstract**

**Background.** Many studies indicate that the increase in intracranial pressure (ICP) leads to cerebral blood flow velocity (CBFV) changes. This relationship was accurately determined in patients with traumatic brain injury. **Objectives.** The aim of this study was to determine how the changes in intracranial pressure induced during an infusion test influence cerebral blood flow.

**Material and Methods.** 40 patients with enlarged ventricular systems (Evan's ratio > 30%) who underwent a diagnostic lumbar infusion test (LIT) were included. Tests were performed at the Department of Neurosurgery, Wroclaw Medical University. CBFV in the middle cerebral artery was measured using transcranial Doppler (TCD) simultaneously during the standard lumbar infusion test. TCD measurements were continued with simultaneous recording of CSF pressure with a frequency of 100Hz. A total number of 5800 measurements (10-second periods) performed during the three phases of the infusion test (stable, infusion and decrease) was obtained.

**Results.** In the stable phase of LIT, a weak positive correlation between ICP and mean CBFV (R = 0.193, p < 0.01) was observed. There was no statistically significant correlation between ICP and the pulsatility index (PI, Gosling Index). During the increased-ICP phase of LIT (infusion, decrease), we observed significant changes in CBFV expressed by a decrease of diastolic velocity and an increase of systolic velocity. A simultaneous increase of pulsation correlated with an increase in ICP (R = 0.371, p < 0.01). There were no significant changes in mean CBFV.

Conclusions. In patients with ventriculomegaly, the mean cerebral blood flow is maintained despite a significant increase in ICP, within the limits of the infusion test. It is noted the relative increase of the pulsatility indices of CBF may indicate preserved cerebrovascular reactivity (Adv Clin Exp Med 2012, 21, 1, 55–61).

Key words: normal pressure hydrocephalus, cerebral blood flow, transcranial Doppler.

#### Streszczenie

**Wprowadzenie.** Obserwacja kliniczna potwierdzona badaniami wskazuje, że w przypadku wzrostu ciśnienia wewnątrzczaszkowego dochodzi również do zmian mózgowego przepływu krwi. Zjawiska te zostały szczegółowo zbadane u chorych po ciężkich urazach czaszkowo-mózgowych. Istnieje uzasadnione podejrzenie, że zmiany mózgowego przepływu krwi mogą występować również podczas indukowanego nadciśnienia wewnątrzczaszkowego podczas testu infuzyjnego w diagnostyce wodogłowia normotensyjnego.

**Cel pracy.** Określenie, w jaki sposób zmiany ciśnienia wewnątrzczaszkowego (ICP), które występują w czasie wykonywania testu infuzyjnego, wpływają na mózgowy przepływ krwi.

Materiał i metody. Badaniami objęto 40 pacjentów z poszerzonym układem komorowym, u których wykonano test infuzyjny podczas diagnostyki wodogłowia normotensyjnego. Badania prowadzono w Klinice Neurochirurgii Akademii Medycznej we Wrocławiu. Podczas standardowej procedury testu infuzyjnego lędźwiowego monitorowano prędkość przepływu krwi w tętnicy środkowej mózgu z użyciem ultrasonografii przezczaszkowej (TCD). Zapis TCD odbywał się w sposób ciągły z częstotliwością 100 Hz i był rejestrowany symultanicznie z zapisem ciśnienia płynu mózgowo-rdzeniowego (PMR) w kanale kręgowym. Analizę przeprowadzono we wszystkich trzech okresach testu infuzyjnego, tj. spoczynek, infuzja i swobodny spadek ciśnienia.

**Wyniki.** W badanej grupie pacjentów w początkowym, stabilnym okresie testu infuzyjnego wykazano słabą pozytywną korelację między ICP a średnią prędkością przepływu krwi (R = 0,193). W tym okresie nie było istotnej korelacji ICP z pulsacją przepływu oznaczaną z użyciem współczynnika PI (*Gosling Pulsatility Index*). Podczas

T.A. Szczepański et al.

indukowanych zmian ciśnienia w okresach infuzji oraz swobodnego spadku zmiana zapisu prędkości przepływu wyrażała się spadkiem końcowo rozkurczowej prędkości oraz wzrostem prędkości skurczowej. Jednoczesny wzrost pulsacji przepływu dodatnio korelował ze zmianą ICP (R = 0,371). Nie wykazano istotnych zmian średniej prędkości przepływu krwi.

Wnioski. W grupie pacjentów z poszerzonym układem komorowym średni przepływ mózgowy krwi jest stały pomimo istotnego wzrostu ciśnienia PMR w granicach wyznaczonych przez test infuzyjny. Stwierdza się natomiast względny wzrost pulsacji i współczynników oporowych przepływu mózgowego, co może świadczyć o zachowanej reaktywności naczyń mózgowych (Adv Clin Exp Med 2012, 21, 1, 55–61).

Słowa kluczowe: wodogłowie normotensyjne, przepływ mózgowy, Doppler przezczaszkowy.

Transcranial Doppler (TCD) is a completely non-invasive method of testing cerebral blood flow velocity, is easy to use and allows for continuous monitoring in high resolution. The listed advantages make it a basic diagnostic tool used for measurements of cerebral blood flow [1]. Tests employing TCD are used in patients with various intracranial pathologies. One large group tested with TCD is patients who have suffered subarachnoid hemorrhages from a ruptured aneurysm [2, 3]. Other groups are patients with intracranial hemorrhage [4, 5], idiopathic intracranial hypertension [6] and active hydrocephalus [7]. Moreover, many of the authors analyze blood flow velocity changes in patients following severe traumatic brain injuries [8-11] in whom determining blood flow velocity is one of the obligatorily monitored parameters [12].

A strong correlation between changes in the cerebral blood flow velocity in the middle cerebral artery and cerebral blood flow (CBF) has been proven experimentally in animal models [13, 14]. A positive correlation was also confirmed in healthy individuals [15, 16]. It is therefore assumed that changes of blood flow velocity measured with TCD mirror changes of CBF [17–19].

In 1988, Giulioni et al. analyzed the literature about intracranial hemodynamics [20]. They indicate that cerebral blood flow shows significant changes with a large increase in ICP (above 60 mm Hg). As later studies showed, the results from 1988 were not confirmed.

The aim of the present study was to determine how the changes in intracranial pressure affect cerebral blood flow during an infusion test.

#### **Material and Methods**

The study included 40 patients, hospitalized in the Department of Neurosurgery of Wroclaw Medical University, in whom an infusion test with simultaneous recording of blood flow velocity in the middle cerebral artery was done due to suspected normal pressure hydrocephalus (NPH). The purpose of hospitalizing the patients in this department was to carry out diagnos-

tic tests for NPH and to identify indications for surgical treatment (implantation of a ventriculoperitoneal shunt).

The age of the patients was from 20 to 88 years  $(61\pm16.02\,\mathrm{years})$ . The study group included 14 women from 20 to 88 years old  $(58\pm20.13\,\mathrm{years})$  and 26 men from 26 to 83 years old  $(63\pm13.38\,\mathrm{years})$ . In the study group, an enlargement of the ventricular system was evaluated on the basis of CT or MRI. The value of the Evans ratio was between 0.30 and 0.66  $(0.41\pm0.073)$ . In the radiological images there were no signs of acute hydrocephalus. Another inclusion criterion was the presence of Hakim's triad or incomplete Hakim's triad with a history of coexistent symptoms of elevated intracranial pressure like headaches, visual disturbances and papilledema.

During the infusion test, isotonic fluid was administered into the subarachnoid space of the spinal canal via lumbar puncture. During this test, intracranial pressure (ICP) increases until it reaches a plateau state. ICP measurement was also done via lumbar puncture because ICP can also be determined in the spinal canal when the path of cerebro-spinal fluid (CSF) circulation is maintained [21]. A lumbar infusion test with fluid supply fixed at 2 ml/min with the use of a volumetric infusion pump was carried out in all patients. The protocol we use is commonly used in many centers [22–24]. During a strictly monitored pressure elevation, the value of ICP was between 5 and 50 mm Hg. The testing procedure consisted of three basic periods. The first one is a ca. 10-minute-long measurement while stable, during which natural fluctuations of CSF and blood flow velocity were recorded. The second period is the beginning of the infusion with an induced increase of ICP value. The infusion of fluid was carried out until a new state of balance (plateau phase) was determined or until ICP reached 40 mm Hg (for over 60 s), which is regarded as the safety limit and requires the infusion to be interrupted. The third period is the time of free decrease in CSF pressure after the infusion (Fig. 1).

In the present study, the authors included Transcranial Doppler examination of blood flow velocity in the middle cerebral artery with a DOP-

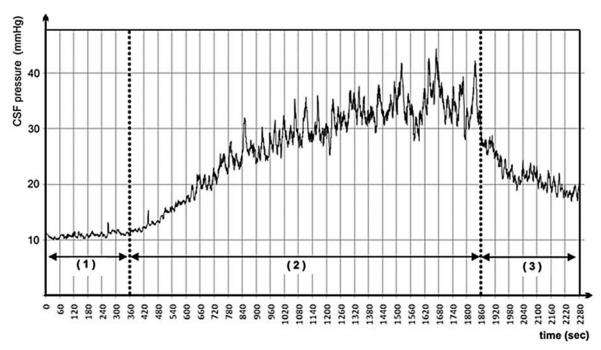


Fig. 1. Continuous recording of sample infusion test with marked investigated periods: 1 – stable, 2 – infusion, and 3 – decrease

Ryc. 1. Zapis ciągły przykładowego testu infuzyjnego z oznaczonymi okresami 1 – spoczynek, 2 – infuzja, 3 – spadek

PLER BOX device. A 2 MHz Doppler probe was fastened in the temporal region with a special helmet. The TCD recording was constant and simultaneous with the recording of CSF pressure in the spinal canal at a frequency of 100 Hz. The following analyzed values described blood flow velocity: Vps (peak systolic velocity, cm/s), Vmean (mean velocity, cm/s), Ved (end diastolic velocity, cm/s) and AMP value (amplitude, the difference between systolic and diastolic velocity, cm/s). Blood flow pulsatility was described with a PI index (Gosling's pulsatility index, calculated as:

10-second periods (one measurement) were used for analysis. The value of a single measurement was calculated by determining the median of 10 1-second segments for all the variables tested. The measurements were gathered in a Microsoft Excel file according to a homogenous

scheme. This way, 5800 measurements were obtained (Table 1).

The study received approval on Dec. 5, 2009 from the Bioethics Committee of Wroclaw Medical University (KB-346/2009).

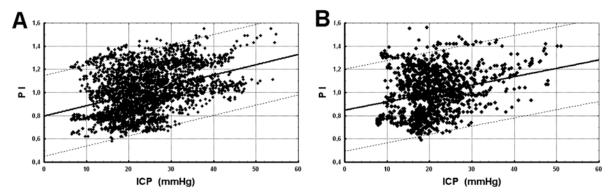
#### **Statistical Analysis**

Further statistical analysis was carried out with the Statistica 9.0PL package. The significance level ( $\alpha$ ) assumed was 0.05. The choice of an appropriate method depended on the statistical features of data analyzed and on the fulfillment of the assumptions of the statistical test chosen for verifying the study hypothesis. Mean values, median, maximum and minimum, and standard deviation (SD) were determined. Friedman's ANOVA analysis and Kendall's coefficient of concordance, as well as Kruskal-Wallis ANOVA on ranks and multiple comparisons of mean ranks for all tests were used for statistical evaluation.

**Table 1.** Average number of measurements taken per patient by period: 1 – stable, 2 – infusion, and 3 – decrease (n = 40) **Tabela 1.** Średnia liczba pomiarów wykonanych u jednego pacjenta z podziałem na okresy spoczynku, infuzji oraz spadku (n = 40)

Number	Period 1 – stable	Period 2 – infusion	Period 3 – decrease	Total
(Liczba)	(Okres 1 – spoczynku)	(Okres 2 – infuzji)	(Okres 3 – spadku)	(Suma)
Mean ± SD	34 ± 12	78 ± 28	32 ± 9	145 ± 37
(Min; max)	(13;73)	(43; 174)	(15; 52)	(91; 254)

T.A. Szczepański et al.



**Fig. 2.** A graph of the correlation of PI and ICP during the period 2 – infusion (A) and during the period 3 – decrease (B). In both periods there is a positive correlation at the significance level of p < 0.01 (number of observations: A = 3130, B = 1298)

**Ryc. 2.** Wykres korelacji dla zmiennych PI i ICP w okresie 2 – infuzja (A) oraz w okresie 3 (B). W obu okresach występuje dodatnia korelacja na poziomie istotności statystycznej p < 0,01 (liczba obserwacji: A = 3130, B = 1298)

#### Results

An analysis of 5800 measurements was carried out separately for every period of the infusion test, i.e. period 1 – stable, period 2 – infusion, and period 3 – decrease.

In the stable period, in which a fluctuation of normal ICP values was observed, a very poor positive correlation only was found between ICP and Vmean (R = 0.193). No correlations were shown in this period between changes in ICP and changes in the flow pulsation expressed by PI changes.

During artificially induced ICP changes (i.e. infusion and decrease periods), increased flow pulsatility was observed. A positive correlation of ICP and PI changes were observed during infusion (R=0.369) and in the decrease period (R=0.242). A positive correlation between ICP and PI variables was confirmed by an separate analysis for each patient (the mean correlation coefficient during the infusion period was 0.666 while in the decrease period it was 0.528). Contrary to the stable period, the period of induced changes showed no significant correlation of changes in ICP and Vmean (Fig. 2).

For a more thorough analysis of flow pulsatility changes, the values of CSF pressure from the entire study group were divided into 5 sections every 10 mm Hg. The statistical analysis of Vps and Ved variables demonstrated that systolic flow velocity increases with the increase of ICP pressure (differences of means up to 5.5 cm/s). Moreover, the value of diastolic blood flow velocity decreases (differences of means up to 7.4 cm/s) (Fig. 3).

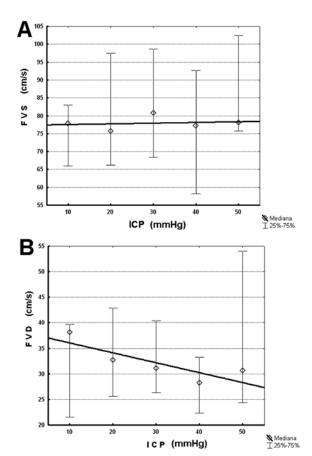
In the specified sections, we also carried out an analysis of Vmean changes. Statistical analysis did not demonstrate any differences between sections 10-20-30. Differences at the level of 2.2 cm/s in the 40 section are lower than the demonstrated natural Vmean fluctuations at rest (median =  $5.95 \pm 4.74$ ), which proves that blood flow velocity at ICP up to 50 mm Hg shows no clinically significant differences (Fig. 4).

In summary, in patients with ventriculomegaly, the mean cerebral blood flow is maintained despite a significant increase in ICP within the limits of the infusion test. A relative increase in the pulsatility indices of CBF was noted, which may indicate preserved cerebrovascular reactivity.

#### Discussion

Present study included a group of 40 patients (a total of 5800 measurements). In the available literature, there are results of studies regarding cerebral blood flow with the use of TCD during an infusion test in adults. Present study is the only one to include a description of all blood flow parameters, i.e. Vps, Vmean, Ved and PI, while authors of other studies presented only the measurement results for FVM and PI. Moreover, available studies include smaller groups, i.e. from 8 patients in Behrens' et al. study [24] to the maximum of 35 patients in Czosnyka's et al. study [22].

The first report to use TCD during an infusion test can be found in the 2000 study of Schmidt et al. [26]. They did 19 lumbar infusion tests during diagnostic tests preceding the implantation of a ventriculo-peritoneal shunt. The study group included 9 patients with idiopathic normal pressure hydrocephalus and 10 patients with secondary normal pressure hydrocephalus. On this small group of patients, they confirmed the usefulness of the developed mathematical model for calculating ICP in an non-invasive manner (based on arte-

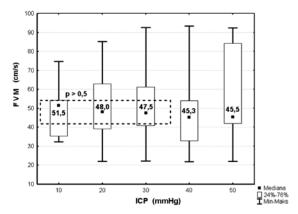


**Fig. 3.** Graphs of mean values and median quartile ranges for observations of ICP and FVS (A), ICP and FVD (B). Systolic flow velocity increases with the increase of ICP pressure and the value of diastolic blood flow velocity decreases

**Ryc. 3.** Wykresy median oraz rozstępu kwartylowego dla obserwacji w przedziałach ICP i FVS (A) oraz FVD (B). Wraz ze wzrostem ICP dochodzi do spadku prędkości końcowo rozkurczowej oraz w mniejszym stopniu wzrostem prędkości skurczowej

rial blood pressure and blood flow velocity in the middle cerebral artery). They did not describe the relations between values characterizing cerebral blood flow and intracranial pressure.

On a group of 10 patients, Jarus-Dziedzic et al. carried out an analysis of changes in the diastolic value of blood flow velocity and PI index in the consecutive minutes of the infusion test [23]. The analysis showed no significant relationship between blood flow velocity and ICP. Researchers also observed no correlation between the value of absorption resistance rate and the change of blood flow velocity value assessed prior to the beginning of the infusion and at infusion peak. There is no description of the methodology of the analysis carried out, therefore the published results cannot be used as a reference. Based on available literature, it must be assumed that there are correlations between the ICP and blood flow velocities that were not observed in the study group.



**Fig. 4.** Comparison of mean values of FVM in the intervals of ICP. For values 10; 20; 30, the medians show no significance differences

**Ryc. 4.** Porównanie średnich wartości FVM w przedziałach ICP. Dla wartości 10; 20; 30 różnice median nie wykazują istotności statystycznej

Haubrich et al. also proved no statistically significant analysis for FVM value and pulsatility changes presented as changes of the PI index [27]. They carried out a ventricular infusion test on a group of 20 patients 21–78 years (9 with NPH, 6 with NPH after a traumatic brain injury and 5 with idiopathic intracranial hypertension). It must be noted, though, that the group was not homogenous and recording was not continuous, and only 5-minute fragments at rest and during the plateau stage were analyzed. In present study, continuous recording and the analysis of the entire infusion test, including the decrease stage, have concluded that PI correlates positively with ICP values.

The study of Zofia Czosnyka et al. published in 2002 was very interesting and reliable [22]. In the study group of 35 patients, they demonstrated a change in blood flow velocity in the middle cerebral artery during the infusion test. The observation resulted in a decrease in the mean blood flow velocity by 4 cm/s, which did not correlate with CSF pressure. In present study, the authors achieved results similar to those of Czosnyka et al. and the decrease of the mean blood flow value was 2.2 cm/s. It must be noted, though, that this value is lower than the natural fluctuations of mean blood flow velocity that we observed in the rest phase, which were  $5.95 \pm 4.74$  cm/s. Therefore, it should be doubted whether the velocity decrease by 2.2 cm/s proven with statistical methods signifies a real decrease of flow velocity. During the test, there was a statistically significant increase of the PI index which correlated with the increase of ICP (r = 0.480; p < 0.01). This conclusion was confirmed in present observations: there is no correlation between ICP and the PI index at rest. The author has also proven that, in the period of CSF pressure changes (infusion and

T.A. Szczepański et al.

decrease phase), there is a correlation between ICP and IP (R = 0.369; p < 0.01).

The latest report regarding the PI index is a study published in June 2010 by Behrens et al. [27]. On 8 patients, they carried out a lumbar infusion test with ICP measurement, using an interstitial sensor. During the test, they did an infusion of fluid into the spinal canal to the maximum value of 50 mmHg. During infusion, several thresholds of CSF were maintained, when blood flow in the middle cerebral artery was measured for 30 to 90 seconds. A total of 35 measurements were gathered in a group of 8 patients. In connection with the demonstrated high diversity between the eight patients, simulations of ICP and IP were also carried out based on a mathematical model. The authors presented an analysis of the cerebral blood flow, vessel diameter and PI index, which was the basis for the conclusion that PI index is not a reliable prognostic of intracranial pressure. In their opinion, PI changes are caused by changes of physiological parameters (arterial blood pressure and its amplitude, the state of autoregulation, susceptibility of the middle cerebral artery and age). It must be noted, though, that Behrens et al. studied a group of only 8 patients, and TCD measurements were done only on the chosen ICP values in the range between

0 and 50 mmHg. Considering the above factors, we cannot exclude the possibility that the result of the study is falsely negative, which is emphasized by Mayer in his commentary to the article.

Based on present analysis of 5800 measurements in a group of 40 patients with an enlarged ventricular system and who are suspected of NPH, the author must confirm the proper functioning of vascular regulation mechanisms anticipated in the methodology of the infusion test. As a result of their effect during increased ICP, thanks to changes of resistance in the area of the vascular bed, the mean cerebral blood flow is unchanged. Increasing the value of flow pulsatility, should be interpreted as a compensatory response related to the maintaining of cerebral blood flow after a decrease of perfusion pressure [28]. A PI change is caused by changes of intracranial pressure [29]. With few physiological changes of ICP, the mean blood flow velocity and the amplitude of flow velocity are congruent with changes of ICP. In the stable period, there were no statistically significant correlations of ICP with blood flow pulsatility (PI). The lack of changes of blood flow pulsatility in relation to ICP may signify a lack of active vascular autoregulation, which may result from normal values of intracranial pressure.

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