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# Cerebral hemodynamic monitoring combined with infusion test in hydrocephalus

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ABSTRACT

*Introduction:* Disturbance in cerebrospinal fluid (CSF) circulation may overlap with abnormality of cerebral blood flow (CBF) in hydrocephalus. Transcranial Doppler (TCD) ultrasonography is a non-invasive technique able to assess CBF velocity (CBFv) dynamics in response to a controlled rise in ICP during CSF infusion tests.
*Research question:* Which TCD-derived cerebral hemodynamic parameters change during controlled rise of ICP, and in which direction?
*Material and methods:* Infusion tests combined with TCD monitoring and non-invasive monitoring of arterial blood pressure (ABP) were conducted in 65 hydrocephalic patients. TCD-based hemodynamic variables: spectral pulsatility index (sPI), compliance of CSF space (Ci), cerebral autoregulation index (Mx), critical closing pressure (CrCP), cerebrovascular wall tension (WT) and diastolic closing margin (DCM-distance between diastolic ABP and CrCP) were calculated retrospectively.
*Results:* During the test ICP increased on average to 25 mm Hg ($p < 0.0001$), with a parallel decrease in cerebral perfusion pressure (CPP, $p < 0.0003$). The CBFv waveform changed, showing a rise in sPI ($p < 0.0001$). Ci decreased inversely proportional to a rise in ICP, and correlated well with changes of compliance calculated from the Marmarou model. CrCP increased in response to rising ICP ($p < 0.001$) while WT decreased ($p < 0.002$). DCM correlated with cerebrospinal elasticity ($R = -0.31$; $p < 0.04$). Cerebral autoregulation was worse in patients with normal CSF circulation, measured as resistance to CSF outflow (Rout): Pearson correlation between Mx and Rout was $R = -0.41$; $p < 0.02$.
*Conclusion:* A controlled rise in ICP affects cerebral hemodynamics in a moderate manner. Parameters like cerebral autoregulation index or DCM correlate with CSF dynamics and may be considered as supplementary variables for the diagnosis of hydrocephalus.

## 1. Introduction

In patients suffering from hydrocephalus the assessment of cerebrospinal fluid (CSF) dynamics is an important part of the diagnostic process. We use a constant rate infusion study to test the system of CSF circulation. However, the main aim of management of hydrocephalus is to restore jointly disturbed CSF circulation and abnormal distribution of cerebral blood flow (Klinge et al., 1999; Momjian et al., 2004; Owler et al., 2004). Hence, the assessment of the interplay between CSF dynamics and cerebral blood circulation, as well as information concerning regulation of the vascular bed, can add value in the process of patient diagnostics. Transcranial Doppler (TCD) performed during infusion tests appears to be very useful in the investigation of different aspects of cerebral circulation (Kopniczky et al., 1995).

The Infusion study is a computerized procedure, based on the measurement of intracranial pressure (ICP). It enables a quick bedside assessment of CSF dynamics and the evaluation of essential parameters of the Marmarou model (Marmarou et al., 1975) of CSF circulation: resistance to CSF outflow, and elasticity. It is a unique clinical scenario, where the ICP is being increased in a controlled way by infusion of artificial CSF. Thus, it creates the possibility to observe what happens to cerebral blood flow when ICP rises. The most important role of an infusion study is to differentiate between the possible cause of the dilatation of ventricles and adverse clinical symptoms seen in patients. Two scenarios are possible: hydrocephalus (too much CSF) or atrophy (not enough brain tissue).

To perform an infusion test direct access to the CSF space is required

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**List of acronyms**

| | |
|---|---|
| ABP | arterial blood pressure |
| CaBV | cerebral arterial blood volume |
| CBF | cerebral blood flow |
| CBFv | cerebral blood flow velocity |
| CBV | cerebral blood volume |
| Ci | cerebrospinal compliance |
| CPP | cerebral perfusion pressure |
| CrCP | critical closing pressure |
| CSF | cerebrospinal fluid |
| DCM | diastolic closing margin |
| E | elasticity |
| FV | flow velocity |
| ICP | intracranial pressure |
| Mx | index of autoregulation |
| Routflow, Rcsf | resistance to CSF outflow |
| sPI | spectral pulsatility index |
| TCD | transcranial Doppler |
| WT | cerebral arterial wall tension |

(Borgesen et al., 1992), therefore an LP has to be performed. Alternatively, infusion can be carried out through a pre-implanted Ommaya reservoir or shunt pre-chamber (if patient has a shunt in-situ). Following this, the baseline ICP is monitored over a longer period of time (optimally greater or equal than 10 min). After the start of constant rate infusion of artificial CSF, ICP begins to increase gradually, from baseline to a new steady state called plateau pressure.

We considered selected hemodynamic parameters calculated from continuous monitoring of the TCD waveform:

- Magnitude of slow (0.005–0.05 Hz) vasogenic waves of ICP
- Spectral Pulsatility index (SPI)
- Cerebrospinal compliance (Ci)
- Critical Closing pressure (CrCP) and other associated indices
- Autoregulation of CBF

## 2. Material & methods

In our database we have 63 patients in whom parallel TCD recording was performed during infusion tests. This study was not powered to reveal association of clinical outcome after intervention (mainly shunting) and TCD-assessed vascular dynamics, but to illustrate influence of rising ICP during infusion test on selected TCD parameters. All patients had ventricular dilatation and suffered clinically from symptoms frequently seen, but not exclusively, in hydrocephalus (elements of Hakim's triad). The initial diagnosis was a mixture of hydrocephalus (78%), cerebrovascular disease (35%), Parkinson's disease (13%), Alzheimer disease (23%). They were all adults. Some of them had an MRI scan done before referral (32%) and in 43% of them, deep white matter lesions (associated with ischaemia) where found.

A plethysmographic blood pressure monitor (Ohmeda, Englewood, CO, USA) was used to monitor arterial blood pressure. A TCD ultrasonograph (Neuroguard; Medasonics, Fremont, CA, USA) was used to insonate middle cerebral artery. The probe was kept in place using a dedicated holder.

The infusion study is a standard clinical investigation for NPH patients, thus the approval from the local ethical committee was waived. Additional non-invasive TCD monitoring during the test was approved by the local Ethics Committee in Cambridge (08/H0306/103).

The measurement during infusion study is more precise and provides more information than a single lumbar puncture. Intracranial pressure is a complex signal with several vasogenic components. Their analysis can provide further, clinically useful, information. Most specific is pulsatile component. The amplitude of its first harmonic is commonly abbreviated AMP. The respiratory component is also visible. So called slow waves, related to regular changes in cerebral blood volume (CBV) are detected within the frequency range 0.005–0.05 Hz.

On the basis of the infusion test, we can calculate the values of parameters describing the CSF circulation and craniospinal compensation. Resistance to CSF outflow (units mmHg/(ml/min)) is considered a crucial parameter. It is calculated as observed pressure rise divided by infusion rate. Elasticity (units: 1/ml) is calculated by observing how fast cerebrospinal system compliance (increase in CSF volume divided by increase in ICP) decreases with the rise in ICP recorded during the infusion test.

Everything in the brain is pulsatile. Synchronous pulsations can be noticed in: arterial pressure, ICP, and cerebral blood flow velocity (CBFv).

An example of a recording from a full infusion test with simultaneous monitoring of intracranial pressure (ICP), arterial blood pressure (ABP) and transcranial Doppler flow velocity (FV) is presented Fig. 1. The total time of recording is from 20 to 35 min.

**Slow vasogenic waves of ICP** were first described in patients after head injury by Lundberg (Lunberg, 1960), who named them B waves.

Scientists studying hydrocephalus observed their presence later, and started to associate them with positive prognosis of shunting (Stephensen et al., 2005). Specific slow waves of ICP can be noted during infusion. They are probably related to poor pressure-volume compensation of the CSF space, and in some cases can help in differentiation between hydrocephalus and atrophic changes.

The vasogenic character of slow waves was also underlined. Synchronization of ICP B waves and transcranial Doppler fluctuations in blood flow velocity in the middle cerebral artery was additionally reported.

**Spectral Pulsatility index (sPI).** A rise of ICP greater than 20 mm Hg, commonly produces rise in TCD pulse waveform. Here we used the spectral pulsatility index, based on frequency analysis of TCD waveform:

sPI= First harmonic of FV pulsatile component/ mean FV

### 2.1. Cerebrospinal compliance (Ci)

We made an attempt to calculate the cerebrospinal compliance (Ci) and assessed its variability with increasing intracranial pressure during infusion test (Kim et al., 2010).

By definition, compliance is calculated as increase of volume added (ΔV) divided by increase in pressure (ΔP):

$$Ci = \Delta V / \Delta P,$$

Using TCD, changes in cerebral arterial blood volume (CBV) during a cardiac cycle can be evaluated.

Under the assumption that venous outflow from the brain is much less pulsatile than arterial inflow the fluctuation of CBV can be calculated as a time integral, (a sum of samples) of the difference between inflow and outflow; Where inflow is an instant value of flow velocity, outflow is equal to mean flow velocity.

$$CBV(n) = \sum_{i=m}^{n} [FV(i) - mean(FV)] \bullet S_a$$

In the formula above Sa is an unknown cross-sectional area of an insonated vessel, CBFV is cerebral blood flow velocity, I is an index of the sample within one heart period (from sample m to n).

In this way CBV forms a new digital signal, which can be plotted together with other signals – see Fig. 2.

The pulsatile component of cerebral arterial blood volume and amplitude of this signal divided by amplitude of ICP potentially

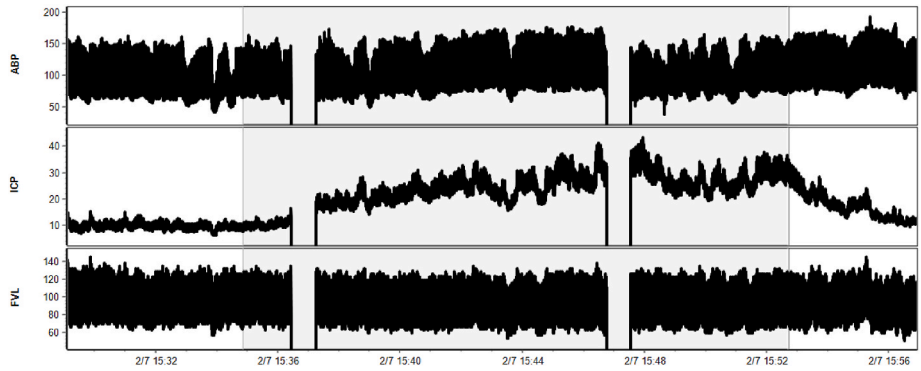


**Fig. 1.** Example of recording of original signals during infusion test: Blood pressure (ABP, units mmHg), intracranial pressure (ICP, units mmHg) and blood flow velocity in left middle cerebral artery (FVL, units cm/s). X-axis- time in hours:min. Infusion of mock CSF with a rate 1.5 ml/min started at 15:34 and finished just after 15:52 after ICP reached plateau at around 31 mm Hg. Gaps in recording are periods of artifacts in TCD signal, excluded from analysis.

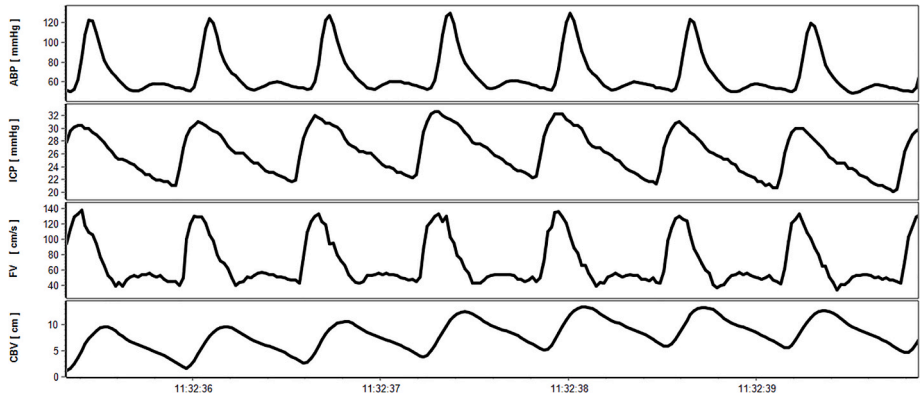


**Fig. 2.** Example of pulse waveform of ABP [mm Hg], ICP[mm Hg], FV [cm/s] and cerebral blood volume (CBV – units are volume per cross-sectional area of an insonated vessel [cm]). CBV is pulsatile, therefore its amplitude (first harmonic) can be calculated using spectral analysis along with amplitude of arterial blood pressure.

estimates compliance of cerebrospinal space:

$$Ci = AMP_{CBV}/AMP_{ICP}$$

Similarly, compliance of arterial walls can be calculated as

$$Ca = AMP_{CBV}/ AMP_{ABP}$$

### 2.2. Critical closing pressure

Critical closing pressure shows a threshold value of blood pressure below which brain arteries collapse.

Theoretically (Dewey et al., 1974), CrCP is a sum of ICP and active tension of arterial walls (WT).

The difference between diastolic ABP and CrCP is called Diastolic Closing margin (DCM). When DCM reaches zero, arterial blood ceases to flow during the diastolic part of the heart cycle (Rhee et al., 2016).

In traumatic brain injury the average CrCP is 43 mm Hg, wall tension 25 mm Hg and both are strongly dependent on PaCO2 (Varsos et al., 2014).

There are different methods available to calculate CrCP. The most popular one, although not most accurate, is regression between two 'clouds' of points- 20 or 30 values of systolic and diastolic flow velocity and blood pressure. The intersection point of a regression line with "Zero" flow velocity gives the value of CrCp.

### 2.3. Cerebral autoregulation

Based on the analysis of slow waves of cerebral perfusion pressure (CPP) and transcranial Doppler flow velocity FV, an assessment of cerebral autoregulation can be performed.

We looked at slow waves of ABP, ICP and FV. CPP was calculated as a difference ABP-ICP.

A moving time window correlation coefficient between slow waves of flow velocity and CPP is a dynamic index of autoregulation, Mx. It allows continuous monitoring of autoregulation (Czosnyka et al., 1996).

- If FV is pressure passive, Mx is positive. This indicates that autoregulation is impaired.
- Mx that is negative or zero signifies functional autoregulation.

All parameters were calculated retrospectively using ICM + software (Cambridge enterprise ltd., UK): https://icmplus.neurosurg.cam.ac.uk/.

## 3. Results

63 patients underwent infusion tests with TCD monitoring; 44% female and 56% percent male. The mean age was 61 years, IQR: 38–69. Calculated compensatory parameters were: resistance to CSF outflow 13.8 (IQR 9.2–20.4.3) mmHg/(ml/min), and elasticity 0.23 (IQR: 0.11 to 0.48) 1/ml.

79% of infusion tests were performed through pre-implanted Ommaya reservoir. 21% were performed through shunt prechamber. Tests performed only in patients with proven obstructed shunt were

included in this paper.

During infusions test ICP increased from 8.2 ± 5.1 mm Hg to 25.1 ±8.3 mm Hg ($p < 0.00001$). Mean arterial pressure increased slightly from 106.6 ± 29.7 mm Hg to 115.2 ±31 mm Hg ($p < 0.0001$). As a result, cerebral perfusion pressure decreased during the test from 98.4 ± 29.1 mm Hg to 90.1±30.7 mm Hg ($p < 0.001$). Mean blood flow velocity decreased slightly from 56.7 ± 17 cm/s to 51.1 ±18.3 cm/s ($p < 0.0001$). Those patients with Rout>13 mm Hg/(ml/min) had subsequently shunt inserted. Unfortunately, we did not access to uniform follow-up data.

Fig. 3 presents example of ICP, FV and ABP, plus basic hemodynamic variables changing during infusion test.

**B waves** in ICP are synchronized with the same slow waves seen in TCD recording of blood flow velocity in MCA – see Fig. 4. During a rise of ICP, the magnitude of TCD slow waves does not change significantly (2.19 ±0.56 vs 1.89±078 cm/s) while the magnitude of ICP slow waves increases (0.78 ± 0.34 vs 2.28 ± 1.11 mm Hg; $p < 0.0001$).

### 3.1. Pulsatility index

On average sPI increases during the test, although the magnitude of this increase is low (from 0.83 ±0.21 to 0.95 ± 0.26; $p < 0.0001$). This indicates that hemodynamic changes during the test are limited.

### 3.2. Compliance

During infusion tests, when mean ICP rises, pulse amplitude of ICP rises as well, but the amplitude of CBV stays more or less constant. As a result, estimator of compliance decreases with rising ICP. The magnitude of the decrease is by 45% ± 17.3 % ($p < 0.00001$) of baseline value.

In agreement with the Marmarou's model of CSF circulation, Ci is inverse function of ICP ($R = -0.76$; $p < 0.005$). It indicates that with increasing ICP, compliance of CSF space decreases.

### 3.3. Critical closing pressure

As ICP increased, CrCP increased and wall tension slightly decreased (see Table 1).

DCM decreased non-significantly and remained of good positive value. Baseline DCM was correlated with cerebrospinal elasticity ($R = -0.31$; $p < 0.04$).

**Autoregulation**. Interesting clinical information was provided by the assessment of autoregulation during the test and its correlation with resistance to CSF outflow (Rout).

In our group of patients diagnosed towards NPH we found that those with low and normal resistance to CSF outflow (who therefore do not suffer from hydrocephalus) more frequently suffer from cerebrovascular disease which manifests with depleted autoregulation. Those with increased resistance to CSF outflow usually improve after shunting. Their autoregulation is usually good. This finding appeared to be useful in selecting patients for shunt surgery, see Fig. 5.

No matter how high Resistance to CSF outflow is, with very much dominant vascular co-morbidity, outcome after shunting is poor. If Rout is low, the element of vascular impairment prevails almost always, and improvement after shunting cannot be expected.

Choice of management (shunting or not shunting) belonged to consultant neurosurgeon in charge. It was usually done on a basis of clinical/imaging picture and a value of Rout. None of TCD parameters correlated with this choice or further improvement noticed in follow-up. New studies concentrated on relationship between TCD finding and response to shunting are on they way.

## 4. Discussion

Testing of CSF dynamics is recommended in diagnosis of hydrocephalus as an auxiliary procedure (Marmarou et al., 2005). The results of the test, however, cannot predict improvement after shunting with 100% accuracy (Wikkelso et al., 2013). Therefore, additional methods of assessment, particularly non-invasive, are advised. They may add predictive power of resistance to CSF outflow and elasticity.

Links between CSF dynamics and cerebrovascular parameters have been indicated in the past as particularly useful, as improvement of clinical status after successful shunting is associated with improvement in CBF (Klinge et al., 1999).

TCD explains the nature of slow vasogenic waves of ICP. They are related to changes in cerebral blood volume and are synchronized with slow waves in TCD blood flow velocity (Droste and Krauss, 1993). The rise in magnitude of ICP slow waves during the test seems to be convincingly associated with the decrease in cerebrospinal compensatory reserve due to filling of the space with infused fluid. Pulsatility index decreases during infusion, due to a significant decrease in cerebral perfusion pressure (de Riva et al., 2012).

The compliance of the cerebrospinal space decreases during a controlled rise in ICP in accordance to the theory formulated by Marmarou in his model of cerebrospinal pressure-volume compensation (Marmarou et al., 1975). This is one of the reasons we can see such a

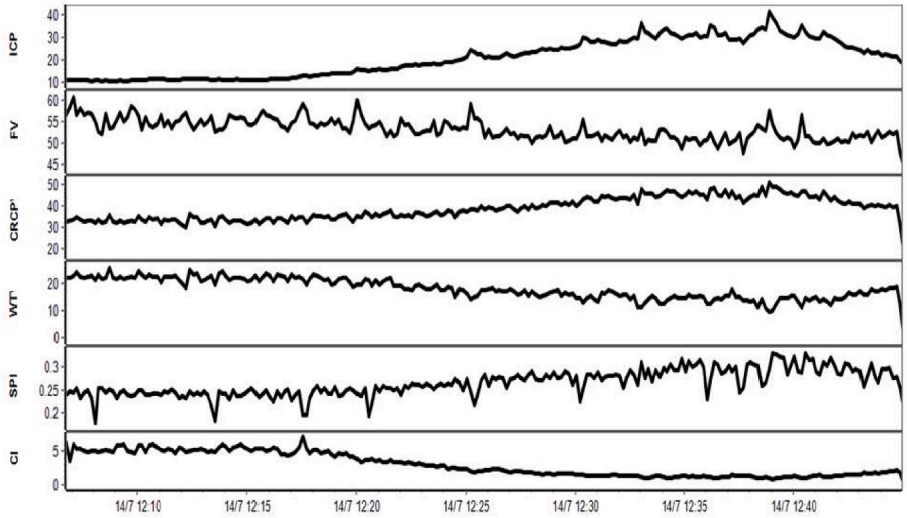


**Fig. 3.** Example of recorded variables (ICP, blood flow velocity [cm/s]), critical closing pressure (CrCP [mm Hg]), arterial wall tension (WT[mmHg]). Spectral pulsatility index (SPI) and compliance of cerebrospinal space (Ci [cm/mmHg]) during infusion test.

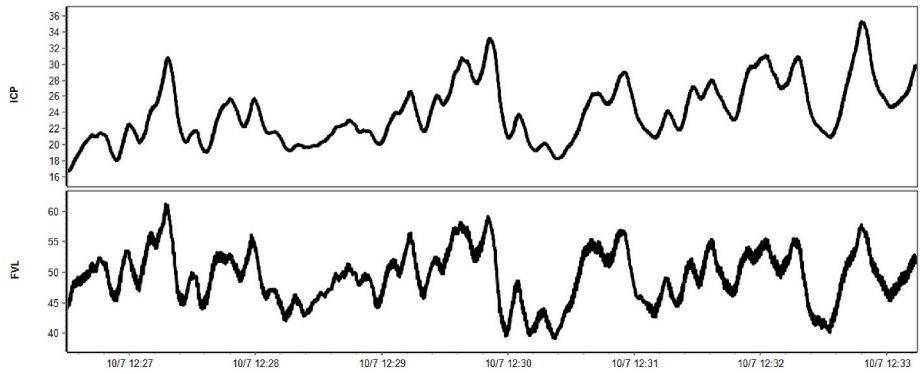


**Fig. 4.** Example of slow vasogenic waves of ICP [mm Hg] and TCD blood flow velocity in the left MCA (FVL-[cm/s]). There is a clear synchronization between slow waves in ICP and blood flow velocity.

**Table 1**
Parameters of Critical Closing Pressure (CrCP) recorded during infusion test. WT-wall tension, DCM-diastolic closing margin.

| Variable | Baseline | Plateau | p-value |
|---|---|---|---|
| **CrCP [mm Hg]** | 50.86 ± 23.46 | 62.52 ± 23.71 | P < 0.001 |
| **WT [mm Hg]** | 44.19 ± 22.63 | 37.54 ± 21.65 | P = 0.005 |
| **DCM [mm Hg]** | 49.31 ± 17.11 | 46.80 ± 18.22 | P = 0.070 |

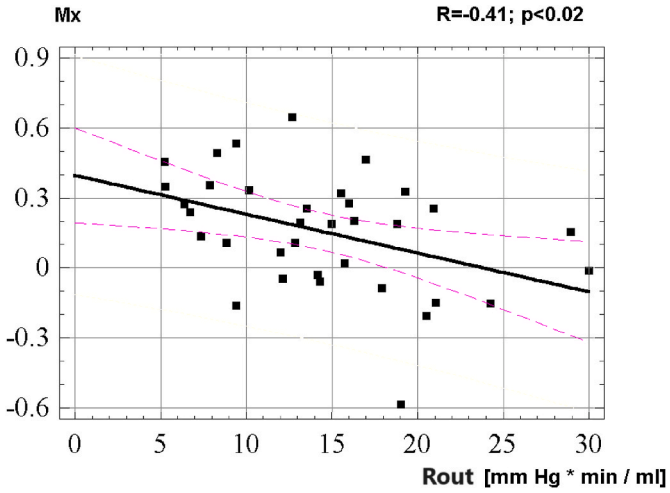


**Fig. 5.** Significant relationship between resistance to CSF outflow (**Rout**) and autoregulation index Mx.

characteristic increase in pulse amplitude of ICP during most infusion studies (except studies done in individuals with exceptionally large compensatory reserve-open fontanelle, after craniotomy, with CSF leak, or with advanced brain atrophy).

Critical closing pressure rises during the test as ICP decreases. However, CrCP has two components: ICP and arterial walls tension. As CPP decreases with raising ICP, wall tension decreases (in patients with efficient cerebrovascular reactivity). The diastolic closing margin decreases during the study, however in all cases it remained above 20 mm Hg, showing that the risk of cerebral ischaemia during infusion test is indeed negligible (Varsos et al., 2014).

Both cerebral autoregulation (assessed with Mx index) and DCM correlate with compensatory parameters estimated with infusion test: Routflow and Elasticity. Since error for estimation is substantial (for Routflow ± 3 mmHg/(ml/min) and for Elasticity 0.13 1/ml; Swallow et al., 2014), additional (and independent) confirmation with TCD measurement can be valuable.

Our study also emphasizes the role of supplementary vascular assessment in patients diagnosed with hydrocephalus. Substantial vascular co-morbidity may prevent improvement after shunting even in patients with significant impairment of CSF circulation (Czosnyka et al., 2002).

At present it is unclear how TCD may make decisions regarding shunting more precise. This requires further studies. Our preliminary report humbly answers the simple question of how rising ICP affects TCD hemodynamic parameters.

This study has several limitations. First of all, it is a retrospective analysis of data recorded previously. To some extent it repeats results reported previously. The cohort of included patients is too small to conduct analysis of improvement of clinical status after shunting.

## 5. Conclusions

Monitoring of cerebral hemodynamics with transcranial doppler ultrasonography is a feasible, non-invasive procedure, which helps in interpretation of CSF infusion test. Parameters like cerebral autoregulation index or DCM correlate with CSF dynamics variables and may be considered as supplementary variables for diagnosis of hydrocephalus.

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## Authors' contribution

**ZC** methodology (equal); data collection (equal); visualization (lead); writing – original draft (lead). **AL**: methodology (equal); formal analysis (equal); writing – review & editing (equal). **AP**: data analysis (equal); writing – review & editing (equal). **PS**: data collection, writing – review & editing (equal) **AJJ**: writing – review & editing (equal); **PMC**-data analysis, statistics, writing-draft and final editing **MC**: conceptualization (lead); methodology (supporting); supervision; formal analysis (supporting); writing – original draft (supporting).

## Declaration of competing interest

PS and MC has a financial interest in part of the licensing fee of ICM + software used for signal recording and analysis. The other authors have nothing to disclose.

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