Acta Neurochirurgica (2020) 162: 1011–1017
https://doi.org/10.1007/s00701-019-04168-w

ORIGINAL ARTICLE - CSF CIRCULATION

Timing of intraventricular infusion test for diagnosing idiopathic normal pressure hydrocephalus

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Received: 25 August 2019 / Accepted: 5 December 2019 /Published online: 7 January 2020

Abstract

Background Infusion tests, which measure resistance to outflow (R_{out}), are used in selecting patients suspected for idiopathic normal pressure hydrocephalus (iNPH) for shunt surgery. Infusion tests can be performed through an external ventricular drain (EVD). A 24-hour time gap from EVD insertion to an infusion test is a routine practice at our department due to concerns that the surgical procedure might influence the test results in the immediate postoperative period. The objective of the study was to investigate if timing of an intraventricular infusion test influences the results of the test in patients suspected for iNPH.

Methods Ten patients scheduled for an intraventricular infusion test were included. Measurements of baseline intracranial pressure (ICP) and plateau ICP were obtained during constant rate intraventricular infusion test performed at two time points (1 and 24 h after EVD insertion) and R_{out} was calculated from these measures and compared within patients.

Results Eight patients completed both infusion tests. In one of the 18 infusion tests performed, it was not possible to define an ICP plateau and this infusion test was excluded, leaving 7 paired infusion tests. Median R_{out} was 12.9 mmHg/ml/min (range 7.0–22.0) 1 h after EVD insertion and 11.3 mmHg/ml/min (range 7.8–18.1) after 24 h. Overall, there were no statistically significant differences in R_{out} ($P = 0.83$), baseline ICP ($P = 0.70$), or plateau ICP ($P = 0.81$) between the recordings performed 1 h and 24 h after EVD insertion. For two of the seven patients with paired infusion tests, there was poor agreement between R_{out} values at 1 and 24 h.

Conclusion Overall, R_{out} estimates do not change significantly between 1 and 24 h after EVD insertion. We therefore propose that infusion tests can be performed shortly after surgery to reduce the period of indwelling EVD and duration of hospitalization.

Keywords Normal pressure hydrocephalus · Infusion test · CSF outflow · Intracranial pressure monitoring

Abbreviations

CSF	Cerebrospinal fluid
ETV	Endoscopic third ventriculostomy
EVD	External ventricular drain
ICP	Intracranial pressure
ΔICP	Differences between post and pre infusion resting ICP
iNPH	Idiopathic normal pressure hydrocephalus
R_{out}	Resistance to outflow
VP-shunt	Ventriculoperitoneal shunt

This article is part of the Topical Collection on *CSF Circulation*

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Introduction

Patients with idiopathic normal pressure hydrocephalus (iNPH) often present with gait disturbance, dementia, and urinary incontinence, and have ventriculomegaly on CT and MR imaging [14]. A ventriculoperitoneal (VP) shunt can be inserted to relieve these symptoms [5, 13]. Infusion tests are performed to improve selection of patients who will benefit from shunt surgery [8, 9, 25]. Based on the infusion test, it is possible to estimate the absorption of cerebrospinal fluid (CSF) measured as CSF resistance to outflow (R_{out}), as deficit in the absorption of CSF is assumed to be part of the pathology

of iNPH [7]. Because of a positive predictive value as high as 86% for R_{out} > 12 mmHg/ml/min regarding effect of VP shunt treatment [25], infusion tests are widely accepted in the diagnosis of iNPH [6, 16, 19]. There are different methods for performing infusion tests; the most reliable being outflow resistance obtained with steady state, e.g., constant rate infusion [24]. Infusion test can be performed both via lumbar puncture and via an intraventricular drain [4]. In contrast to the lumbar test, which is performed within minutes after needle insertion, an intraventricular infusion test can be performed sooner or later after drain insertion. This raises the question if timing of the infusion test influences the measurement.

The present study was conducted to investigate if infusion tests performed shortly after surgery provide the same R_{out} as tests performed after 24 h in the same patient.

Methods

The study was approved by the Danish Data Protection Agency (ID 2012-58-0004) and the National Committee on Health Research Ethics for the Capital Region of Denmark (ID H-15016032). Written informed consent was obtained from all patients included in the study.

Study population

We included 10 patients scheduled for an intraventricular infusion test at the Department of Neurosurgery, Rigshospitalet, between January 2016 and September 2017. All patients had hydrocephalus on CT/MRI, symptoms of normal pressure hydrocephalus (NPH), and were scheduled for intraventricular infusion test at our department as part of their clinical evaluation. Patients were not included if the hydrocephalus nurse was not available for both infusion tests. Our hydrocephalus service includes a clinical nurse specialist allocated specifically to patients with hydrocephalus and other CSF disorders.

Infusion test protocol

Practical aspects of infusion tests are center-specific with no published guideline for the timing of the infusion test after external ventricular drain (EVD) insertion. In our center, we have routinely used a 24-hour time gap between EVD placement and the infusion test due to a concern that intracranial pressure (ICP) is affected by surgery in the immediate postoperative period, and that CSF may egress along the drain until brain tissue glues to the drain yielding falsely low R_{out} values.

Infusion tests were performed with constant rate of 60 ml/hour intraventricular infusion of artificial cerebrospinal fluid (Ringer Lactate) through an EVD while measuring ICP with the patient in a supine position. The Raumedic Neurovent was inserted as EVD. The device has a tip transducer integrated into the drain and can be used both to measure ICP and perform CSF drainage. The first infusion test was performed 1 h after insertion of the EVD, and repeated with the same set-up 24 h after EVD insertion.

Baseline ICP was measured for 10 min before the infusion was started. When ICP reached a plateau (determined visually by the hydrocephalus nurse), infusion was stopped [10, 12]. After the test was completed, ICP monitoring was continued until it reached baseline level. Infusion was discontinued if the patient experienced headache or nausea, or if ICP increased above 40 mmHg.

ICP was monitored and analyzed with the software package ICM+ (Cambridge Enterprises Ltd, Cambridge, UK) [21].

The resistance to CSF outflow (R_{out}) was calculated by the formula:

$$\mathrm{Rout} = \frac{\text{plateau ICP–baseline ICP}}{\text{infusion rate}}$$

All infusion tests were performed by a specialized hydrocephalus nurse (authors DC and SDJ), which ensured consistency in practical procedure routine.

Study variables

For all patients, we collected baseline data on age, sex, symptomology (gait disturbance, incontinence, and signs of dementia), and duration of symptoms. Results extracted from infusion tests were: R_{out}, plateau ICP, baseline ICP, duration of test, and discomfort during test. Baseline and plateau ICP was assessed through blinded evaluation of ICP curves (by consensus among authors THA, ALC, AVH, and MJ) (Fig. 1). We also noted treatment consequences of the infusion test as well as clinical status at 3-month follow-up. As the predictive value of R_{out} is not the focus of this investigation, clinical outcome after surgical treatment was assessed retrospectively by reviewing medical records for the 3-month follow-up with self-reported clinical status.

Statistics

The main study endpoint was the reproducibility of R_{out} and R_{out} values from infusion tests after 1 and 24 h and was compared using Wilcoxon signed rank test and a Bland-Altman plot. A P value < 0.05 was considered the statistical level of significance. The statistical software package "R" version 3.2.0 (The R Foundation for Statistical Computing, Vienna, Austria) was used for analyzing data and visualization of the collected data. Sample size calculation was performed for paired sample significance testing with power 0.9 and alpha 0.05, and the results from a previous publication by Tans et al. [24] reporting a standard deviation of 1.2 mmHg/ml/min between repeated measurements of R_{out}.

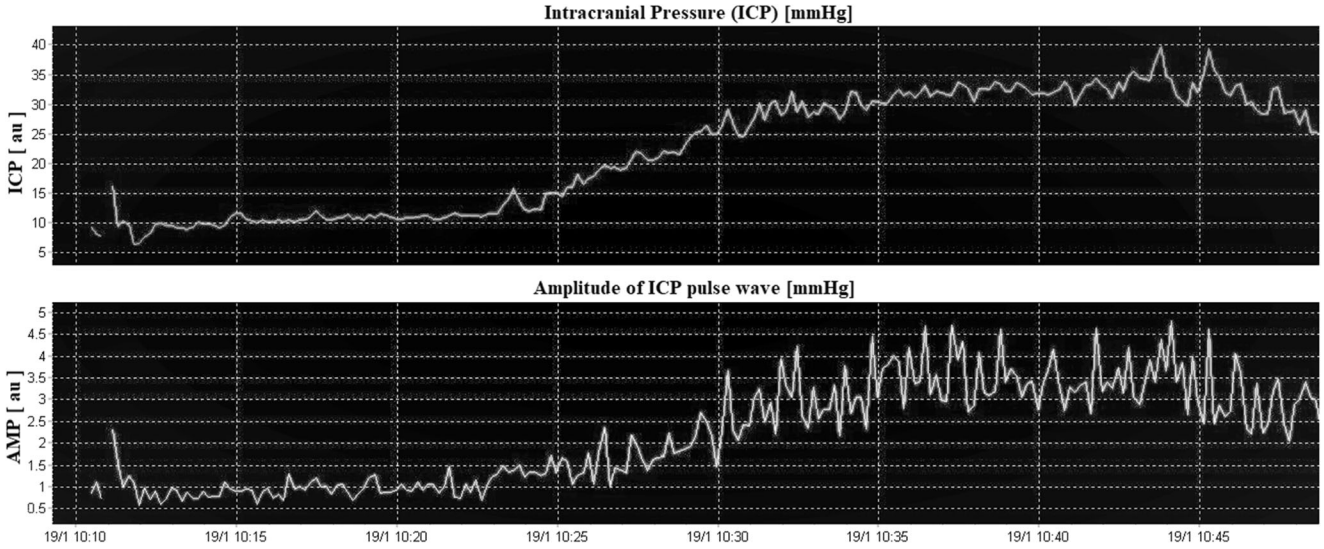

Fig. 1 Example of an intracranial pressure (ICP) curve from infusion test (patient 4, 1 h after external ventricular drain insertion). ICP intracranial pressure, AMP pulse wave amplitude of ICP signal

Results

Patients

Ten patients (6 men and 4 women) scheduled for an intraventricular infusion test at the Department of Neurosurgery at Copenhagen University Hospital, Rigshospitalet, were included in this study. Median and mean age was 75 years (range 64–81). All patients had signs of communicating hydrocephalus on head CT scan, and had symptoms consistent with NPH (Table 1). Eight of the ten patients had memory difficulties, all ten patients had gait and/or balance disturbance, and all ten patients had urinary incontinence. Of the 10 patients included in the investigation, 8 patients completed both infusion tests. Patients 4 and 5 were the two patients not completing the infusion test planned 24 h after EVD insertion (Table 1). One patient was excluded as an ICP plateau was not clearly visible during the infusion test performed 1 h after EVD placement. The final study population thus comprised 7 patients.

Infusion tests

Median R_{out} one hour after EVD insertion was 12.9 mmHg/ml/min (range 7.0–22.0), and after 24 h median R_{out} was 11.3 mmHg/ml/min (range 7.8–18.1). This difference in R_{out} was not statistically significant ($P = 0.83$). In 4 out of the 7 patients, the difference in R_{out} was < 1 mmHg/ml/min. The remaining three patients had the following difference in R_{out} values between the test after 1 and 24 h + 2.4, − 4.7, and + 5.2 mmHg/ml/min (Table 2). Differences in R_{out} between repeated infusion tests can be illustrated by a Bland-Altman plot (Fig. 2).

Median baseline ICP one hour after surgery was 11.0 mmHg (range 3.7–16.6), and 24 h after surgery it was

Table 1 Patient characteristics of the 10 patients suspected for normal pressure hydrocephalus (NPH)

Patient	Age	Sex	NPH symptoms*			Duration of symptoms (years)	Treatment after infusion test
			G	M	I		
1	76	F	yes	yes	yes	2	VP-shunt
2	78	M	yes	yes	yes	4–5	VP-shunt
3	78	M	yes	yes	yes	1	None
4	73	M	yes	yes	yes	5–7	VP-shunt
5	74	M	yes	yes	yes	2–3	ETV
6	81	F	yes	yes	yes	10	None
7	80	M	yes	yes	yes	2	None
8	73	F	yes	no	yes	6–7	VP-shunt
9	73	M	yes	yes	yes	1	None
10	64	F	yes	no	yes	1.5–2	None

* NPH symptoms: *G* gait disturbance, *M* memory deficiency (subjectively), *I* urinary incontinence

Table 2 Resistance to CSF outflow (R_{out}) 1 vs. 24 h after external ventricular drain (EVD) insertion (mmHg/ml/min)

Patient nr.	R_{out} after 1 h	R_{out} after 24 h	Difference
1	12.9	18.1	+ 5.2
2	19.4	14.7	− 4.7
3	9.0	11.4	+ 2.4
4	19.0	NA*	NA
5	22.0	NA*	NA
6	7.0	7.8	+ 0.8
7	9.2	8.7	− 0.5
8	16.4	16.4	0
9	12.0	11.1	− 0.9
10	NA	8.1	NA

*Patient 5 had an elevated baseline ICP of 20 mmHg why the test was not performed, and patient 4 had his infusion test stopped due to a rapid increase of ICP to 50 mmHg soon after the infusion was started.

12.6 mmHg (range 4.2–29.8) mmHg ($P = 0.70$). Baseline ICP changed considerably between the two tests in three patients (patient 4, 5, and 7, see Table 3). In patient 7, this change in baseline ICP from 9.5 to 16.0 mmHg did not translate to a large difference in R_{out} values, since the plateau ICP changed in parallel from 18.7 to 24.7 mmHg. Patients 4 and 5 had higher baseline ICP during the test performed after 24 h, and subsequent infusion tests were not performed.

The median plateau ICP 1 h after surgery was 25.7 mmHg (range 17.2–36.1), and 24 h after surgery the median plateau ICP was 23.5 mmHg (range 12.3–31.1, $P = 0.81$, Table 4).

Clinical consequences of infusion tests

Using a cutoff at $R_{out} > 12$ mmHg/ml/min as the threshold for pathological R_{out}, five patients had increased R_{out} in both their infusion tests and were selected for surgical treatment. Four patients underwent shunt surgery and one patient with an infusion test indicating obstructive hydrocephalus and symptoms of NPH underwent ETV (endoscopic third ventriculostomy). The remaining five patients were not considered eligible for surgery due to R_{out} below the threshold.

Three patients reported clinical improvement at the 3-month follow-up visit after shunt surgery. One of these reported possible effect on memory but no effect on urinary incontinence or gait, and two reported effect on memory and cognition. The fourth patient with a VP-shunt had no clinical effect after shunt insertion and head CT indicated overdrainage through the shunt system. The patient had no

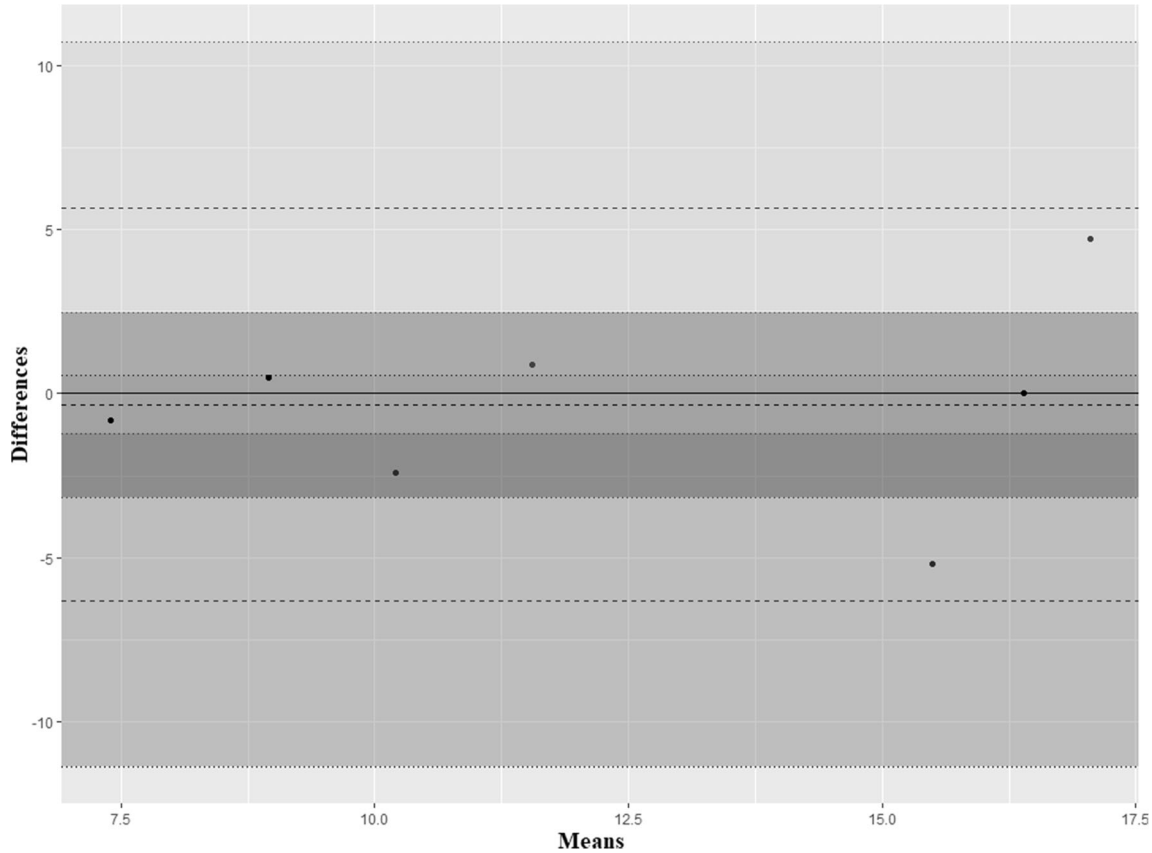

Fig. 2 Bland-Altman plot for comparison of R_{out} from infusion tests performed 1 and 24 h after EVD insertion. The mean values of R_{out} are plotted on the *x*-axis. Differences between R_{out} values are plotted on the *y*-axis

Table 3 Baseline intracranial pressure (ICP) 1 vs. 24 h after external ventricular drain (EVD) insertion (mmHg)

Patient nr.	Baseline ICP after 1 h	Baseline ICP after 24 h	Difference
1	12.8	12.9	+ 0.1
2	16.6	16.4	− 0.2
3	11.4	10.8	− 0.6
4	10.6	16.6	+ 6.0
5	14.1	19.8	+ 5.7
6	10.2	9.0	− 1.2
7	9.5	16.0	+ 6.5
8	15.8	12.3	− 3.5
9	9.2	9.0	− 0.2
10	3.7	4.2	+ 0.5

symptoms of overdrainage, and a subsequent head CT showed regression of overdrainage. The patient who underwent ETV experienced short-term effect on gait, and the patient was seen again after 6 months and reported effect on all NPH symptoms (gait, memory, and urinary incontinence). One patient had a complication of ventriculitis and was treated with intrathecal antibiotics.

Discussion

The diagnosis of iNPH relies on clinical presentation, head CT/MRI scans, and additional invasive diagnostic tests, e.g., infusion tests and tap tests [12]. In the present investigation, we tested the hypothesis that R_{out} differs according to time after EVD insertion and found no significant difference in R_{out} calculated from ICP measurements during infusion tests performed 1 and 24 h after EVD insertion. For 4 out of 7 patients, the difference in R_{out} was < 1 mmHg/ml/min between infusion tests performed 1 and 24 h after EVD insertion.

Table 4 Plateau intracranial pressure (ICP) 1 vs. 24 h after external ventricular drain (EVD) insertion (mmHg)

Patient nr.	Plateau ICP after 1 h	Plateau ICP after 24 h	Difference
1	25.7	31.0	+ 5.3
2	36.0	31.1	− 4.9
3	20.4	22.2	+ 1.8
4	29.6	NA	NA
5	36.1	NA	NA
6	17.2	16.8	− 0.4
7	18.7	24.7	+ 6.0
8	32.2	28.7	− 3.5
9	21.2	20.1	− 1.1
10	NA	12.3	NA

The remaining 3 patients had a difference in R_{out} of more than 2 mmHg/ml/min.

Reproducibility of R_{out}

We routinely do not perform intraventricular infusion tests earlier than 24 h after EVD insertion due to concerns that surgery might affect testing by introducing biological changes to the CSF system. Theoretically, a CSF spill during the EVD insertion, CSF leakage along the catheter, or ICP changes induced by recent surgery might affect testing. In our experience, the CSF spill is minimal, since the surgeon plugs the EVD as soon as the ventricular system has been reached. In lumbar infusion tests, a falsely high increase in pressure can be measured if there is blockage of tissue at the orifice of the needle [12]. Our study does not support these theoretical concerns. With a reliable result 1 h after EVD insertion, the infusion test can be performed earlier than we do in our current clinical practice. The EVD can then be explanted a few hours after surgery and the patient discharged on the same day. This will shorten length of stay for each patient and reduce infection risk. This study therefore offers a faster expedition of diagnosis, and presumably a shorter waiting period until shunt surgery, which improves the result of shunt surgery for patients with iNPH [3].

Other investigations of repeated infusion tests have also found a high reproducibility of R_{out} [1, 2, 22–24]. Studies are mainly on lumbar infusion tests or test both lumbar and intraventricular but does not perform subanalysis regarding location [23, 24]. Reproducibility of R_{out} was high in studies repeating infusion tests only 5 min apart [2] and up to 102 days between repeated tests [23]. Tans et al. [24] performed both intraventricular and lumbar infusion tests and performed repeated test in 10 patients. They found a mean difference in R_{out} of 1.7 ± 1.2 mmHg/ml/min, but the location (intraventricular or lumbar) for the 10 patients and the time gap between repeated infusion tests were not provided. Juniewich et al. [15] support the notion that the infusion test introduces changes to the CSF system. They measured resting ICP before and after infusion, performing both lumbar and intraventricular constant rate infusions tests, and found the differences between post and pre infusion resting ICP (ΔICP) higher than 1 mmHg in 20 infusion tests out of 27. This was considered significant. The mean ΔICP for the 20 infusion tests was 3.0 ± 0.7 mmHg. However, decreasing ICP was only recorded for about 10 min after infusion and not necessarily until ICP returned to resting ICP. In our study, 3 patients exhibited an increase in baseline ICP before the second infusion test, and 2 exhibited decrease in baseline ICP, but the difference in baseline ICP for the entire group was not statistically significant. We also found no significant difference for plateau ICP between infusions tests. We can however not exclude the possibility that the infusion tests performed 24 h after EVD insertion are affected by the

previous infusion test. Therefore, we assessed the agreement between replicate measurements by a Bland-Altman plot (Fig. 2). For patients 1 and 2, the agreement between paired infusion tests was poor, though the plot illustrates good agreement for most of the patients. Our data thus support that the infusion test does not need to be delayed beyond 1 h after drain insertion.

Treatment and pathological R_{out}

The diagnosis of iNPH can be a difficult, making infusion tests an important tool in selecting patients who would benefit from shunt surgery. Malm et al. [18] performed lumbar infusion tests in normal individuals aged 60–82 years, and found a mean R_{out} of 11 mmHg/ml/min. In a study with intraventricular infusion tests, a R_{out} below 10 mmHg min/ml was considered physiological, R_{out} 10–13 mmHg min/ml borderline and R_{out} above 13 mmHg/min/ml pathological [20].

Eide et al. [11] performed constant rate lumbar infusion tests while measuring ICP in both the lumbar cerebrospinal space and in the brain parenchyma. They reported a higher lumbar R_{out} than ventricular R_{out} with a mean difference of 2.7 mmHg/ml/min. This might be explained by differences in compliance of the two compartments. However, it suggests that differentiated thresholds for abnormal R_{out} should be adapted for intraventricular and lumbar infusion tests.

There is no complete consensus regarding the treatment threshold of R_{out}. Previous publications have concluded that shunt surgery based on R_{out} values above 18 mmHg/ml/min improves outcome [6, 7]. However, other investigators recommend a lower threshold at 12 or 13 mmHg/ml/min [11, 15, 17, 20]. Setting the limit at 18 mmHg/ml/min yields a lower sensitivity, possibly excluding patients who would benefit from a shunt [17]. The infusion tests for patients 1 and 2 had a difference in R_{out} of + 5.7 and − 4.7 mmHg/ml/min, respectively. This difference seems large enough to potentially change the clinical consequence drawn from the tests.

We performed power analysis to detect a difference of 2 mmHg/ml/min, as we believe a significant difference should be of at least 2–3 mmHg/ml/min. We have not chosen a specific value for a significant difference since a difference in R_{out} matters more when in the area of 15–18 mmHg/ml/min where a pathological R_{out} is unsure. A difference in R_{out} above 18 mmHg/ml/min or below 12–15 mmHg/ml/min is less essential since the clinical conclusion on pathological or not does change. For the patients with a large difference in R_{out} , it can certainly be debated that though the statistical value is not influenced, the clinical value might be. Swallow et al. [23] commented that the parameters estimated with infusion testing have to be considered as a range in which the actual value of the patient lies rather than as a fixed value. We concur with this statement, since analysis of the ICP curve partly depends on clinical assessment, and the plateau is not always easily identified. The risk of finding different results seems to be related to technical variability and inter-observer differences in analyzing the ICP curves.

Limitations

It was not possible to repeat infusion tests in all patients. Two patients had infusion tests with a pattern of obstructive hydrocephalus with a steep increase in ICP, and no ICP plateau. This study was intended for patients with normal pressure hydrocephalus only.

We believe that inter-observer variation was an important limitation in the analysis of ICP curves.

Conclusion

We compared R_{out} estimated through infusion tests performed 1 and 24 h after EVD insertion. For two of the seven patients, there was poor agreement between paired infusion tests, though overall there was no significant difference in R_{out} between paired tests. We therefore propose that infusion tests can be performed shortly after EVD insertion, though further studies seem needed to confirm this.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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Comments

LP infusion test may be performed in all cases. It is unsafe when on MRI lack of communication between cranial and lumbar CSF space is seen. Otherwise LP infusion test is safe (no serious complications in our hospital, where around 3000 LP infusion tests were performed, infection rate <1%). It gives information on whole CSF dynamics, including Rout, elasticity, baseline pressure, compensatory reserve at baseline, slope of amplitude-pressure line, etc. LP test is much less invasive than the test through EVD and much cheaper- information is almost the same.

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