

Arterial blood pressure vs intracranial pressure in normal pressure hydrocephalus

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Objective – To characterize the association between arterial blood pressure (ABP) and intracranial pressure (ICP) in idiopathic normal pressure hydrocephalus (iNPH) patients, and its impact on outcome of shunt surgery. **Materials and methods** – We analyzed all 35 iNPH patients whose ABP and ICP were recorded simultaneously during 6 years (2002–2007). The static and pulsatile pressures were averaged over consecutive 6-s intervals; the moving correlations between ICP and ABP (static and pulsatile) were determined during consecutive 4-min periods to explore time-related variations. **Results** – Neither static nor pulsatile ABP were altered in iNPH shunt responders. Elevated pulsatile ICP, but normal static ICP, was seen in responders. The time-varying correlations of static and of pulsatile pressures were generally low, and did not differ between shunt responders/non-responders. **Conclusions** – In iNPH shunt responders, static or pulsatile ABP were not altered and only pulsatile ICP was elevated.

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Introduction

The clinical condition normal pressure hydrocephalus (NPH) consisting of gait disturbance, urinary incontinence and dementia, was described more than 40 years ago (1). However, the pathophysiology of this condition remains poorly understood (2).

Based on previous studies, elevated intracranial pressure (ICP) wave amplitude (the pulsatile component of ICP) is typical for those patients with idiopathic NPH (iNPH) who respond to shunt surgery (3–5). In particular, ICP wave amplitude was highly predictive of the degree of shunt response (3). At present, it has not been clarified why ICP wave amplitudes are high (> 4–5 mmHg) in the iNPH shunt responders. A number of studies have also pointed to the high frequency of vascular co-morbidity in NPH (6–12) and the high frequency of arterial hypertension (8–10). However, whether arterial blood pressure (ABP) impacts shunt response in NPH remains to be determined.

In general, the intracranial pulsatility relates to both the ICP–volume reserve capacity (i.e., intracranial compliance; 13–18) and the vascular compliance (18–20). The blood volume ejected during

each cardiac contraction produces an ABP pulse wave that is transferred into an ICP pulse wave. Past investigators have explored characteristics of how the vascular wave transfers into the intracranial wave (20–29).

In this study, we investigate how ABP associates with ICP (both the static and pulsatile components) and the clinical response to shunting in iNPH patients. The static pressure was characterized by the mean ABP and mean ICP; the pulsatile pressure was characterized by the ABP and ICP wave amplitudes.

Materials and methods

Patients

The patient material summarizes all 35 individuals evaluated from 2002 to 2007 for clinical iNPH at the Department of Neurosurgery, Rikshospitalet University Hospital, in whom continuous ABP/ICP monitoring was performed. The patients were referred from local neurological departments based on their symptoms of gait disturbance, incontinence and dementia, combined with radiological ventriculomegaly. The patients' diagnostic work-up was

administered during a 3-day hospitalization. Following clinical and radiologic assessment on day 1 (day of admittance), ABP/ICP monitoring was performed from days 2 to 3. After discharge from the department on day 3 the patient returned 1–3 weeks later for surgical treatment if indicated. The study was approved by the hospital authority of Rikshospitalet University Hospital, Oslo (07/5868).

Clinical and radiologic assessment

Based on neurological examination findings the severity of clinical iNPH was graded using our NPH grading scale (15 scores ranging from 3 to 15, which measures the combined severity of gait disturbance, urinary incontinence and dementia; 3). Information about co-morbidity such as documented history or treatment for cerebrovascular disease (transient ischemic attacks, stenosis of extracranial cerebral arteries, ischemic stroke), cardiovascular disease (myocardial infarction, valvular disease, cardiac insufficiency, heart arrhythmia), arterial hypertension and diabetes mellitus was derived from referral notes and from the history of the patients and their families. Patients underwent computer tomography or magnetic resonance imaging on day 1 if these diagnostic tests had not been performed recently. Evans index and ventricular score were also estimated following the same method as previously described (3).

Surgical treatment

The criteria for surgical treatment were based on a combination of clinical iNPH (gait disturbance, incontinence and dementia), increased ventricular size (Evans' index > 0.3), and findings from the diagnostic ICP monitoring.

Twenty-six patients received a HAKIMTM Programmable Valve Shunt System (Codman & Shurtleff, Inc., Le Locle, Switzerland). The median opening pressure at shunt implantation was 12 cm H₂O (range 10–14 cm H₂O). One patient received a programmable gravitational shunt (proGAV-Shunt System; Aesculap Miethke, Tutlingen, Germany) positioned at 6/25 (i.e., opening pressure of 6 cm H₂O in the horizontal position and of 25 cm H₂O in the vertical position).

Follow-up and outcome assessment

Follow-up was performed in our out-patient clinic at regular time intervals with the first visit at 3 months, and then after 6 and 12 months. All patients were examined clinically by a doctor; if a patient was unable to attend the clinic at one of the

follow-up controls he or she was interviewed by phone. We have defined an increase of ≥ 2 points on our NPH scale as representative of clinical improvement which generally correlates with patients' and families' perception. The surgically shunt-treated patients were categorized either as responders (change in NPH score ≥ 2) or non-responders (change in NPH score < 2).

ABP and ICP monitoring

ABP was measured continuously in the right radial artery using the Truwave PX-600F Pressure Monitoring Set (Edwards Life sciences LLC, Irvine, CA, USA). The ABP sensor was placed at the level of the heart. Patients were kept in their bed during the entire pressure recording.

ICP was monitored continuously using a solid sensor (Codman MicroSensorTM; Johnson & Johnson, Raynham, MA, USA), introduced 1–2 cm into the frontal brain parenchyma through a small burr hole and a minimal opening in the dura, as previously described (3, 30).

Analysis of ABP and ICP

The continuous ABP and ICP waveforms were sampled at 200 Hz and stored on a hospital server. For ABP/ICP analysis (30), the automatic algorithm established in the Sensometrics software (dPCom AS, Oslo, Norway) identified the cardiac beat-induced single pressure waves within the continuous ICP (Fig. 1A) and ABP (Fig. 1B) waveform. Each ICP and ABP wave was characterized by the amplitude ('pulse amplitude', dP), rise time (dT) and rise time coefficient (dP/dT; Fig. 1A,B). Metrics that the software computes in 6-s time windows include mean ABP, mean ICP, mean ABP wave amplitude, mean ICP wave amplitude and cerebral perfusion pressure (CPP) (i.e., difference between mean ABP and mean ICP). In addition, the ICP–ABP phase difference represents the average time difference between the occurrences of ICP and ABP single-pressure waves during a 6-s time window. A negative ICP–ABP phase difference thus implies that the ICP waves occur before the ABP single waves.

The 6-s time windows containing less than four accepted cardiac beat-induced waves were rejected. Among the 35 patient recordings the median percentage of accepted 6-s time windows was 83% (ranges 19–99%), suggesting a high quality of ICP recording.

The software computes the time-related correlations between ABP and ICP during consecutive 4-min periods (i.e., 40 consecutive 6-s time windows):

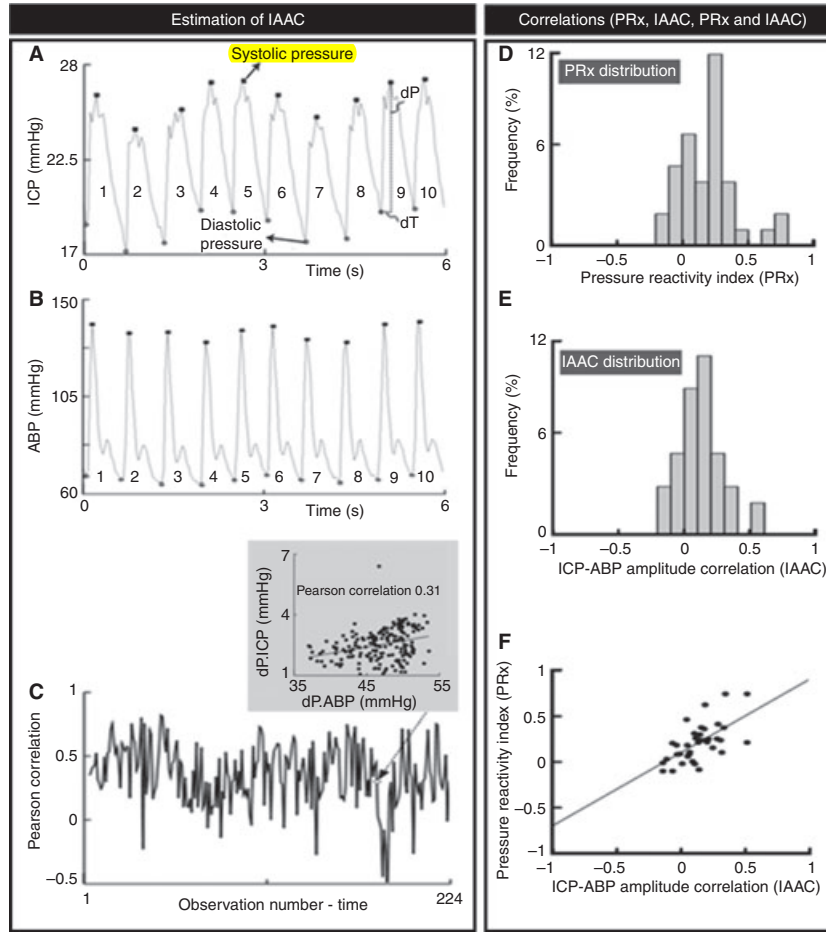


Figure 1. For one 6-s time window the intracranial pressure (ICP; A) and arterial blood pressure (ABP) signals (B) with identical time reference are shown. For every 40 consecutive 6-s time windows (i.e., 4-min period) (C) the Pearson correlations (ICP–ABP amplitude correlation or IAAC) evaluated for each 4-min interval were plotted against time. In this plot, a pressure recording of 224 consecutive IAAC values (i.e., 224 4-min periods) is shown and IAAC was greater than 0.4 in 49.6% of the observations. The gray-shaded inset shows the estimation of the Pearson correlation between single-wave amplitudes (dP) of the corresponding ICP and ABP waves for one 4-min interval. For the entire set of 35 patient recordings, the distribution of (D) the pressure reactivity index (PRx; mean 0.20) and (E) IAAC (mean 0.13) are provided. The linear relationship between PRx and IAAC can be seen in (F) the scatter plot of PRx against IAAC for the 35 patient recordings.

(i) the pressure reactivity index (PRx) estimated by the Pearson correlation coefficient between series of 40 samples of mean ICP and mean ABP, as previously described (31); (ii) the ICP–ABP amplitude correlation (IAAC) estimated by the moving Pearson correlation between pulse pressure amplitudes of the corresponding ICP and ABP waves, as previously described (32). This latter aspect is illustrated in Fig. 1C, showing a scatter plot consisting of the amplitudes of the corresponding ICP and ABP single waves during a 4-min period. During a patient recording a new IAAC value is determined for every new 4-min period and plotted against time (Fig. 1C). The method compares simultaneous ICP and ABP waves, and excludes artifacts caused by noise in the signal (e.g., patient movement, manipulation of cables and catheters, etc.) for this comparison.

The Pearson correlation is a measure of the strength of the relationship between two variables and ranges from -1 to $+1$. Thus, positive correlation indicates that both variables increase or decrease together, whereas negative correlation indicates that one variable increases as the other decreases, and vice versa. Based on previous observations, the assumptions for using Pearson correlations were fulfilled: both ICP and ABP wave amplitudes are continuous and independent variables that were normally distributed. For 4-min intervals, the correlation between these two variables reflects a linear relationship. For each of the 35 patients, the recordings determined the following: (i) average value of PRx and IAAC for the 4-min periods; (ii) percentage of 4-min time periods with $PRx \geq 0.5$ and $PRx \geq 0.6$; $IAAC \geq 0.5$ and $IAAC \geq 0.6$.

Statistical method

Statistical analysis was performed with SPSS, version 12.0 (SPSS Inc., Chicago, IL, USA). Differences between two groups were determined by Mann–Whitney *U*-test for continuous data, Pearson chi-square for categorical data and by one-way ANOVA with Bonferroni-corrected *post-hoc* tests for multiple groups. Correlations between patient groups were determined using Spearman correlations. Significance was accepted at the 0.05 level.

Results

The demographic, clinical and radiologic information about the 35 iNPH patients is presented in Table 1. Twenty-seven of the 35 patients received shunt surgery, in whom 21 (78%) were shunt responders and 6 (22%) were shunt non-responders. No complications were seen after monitoring. The success rate of this subgroup (shunted iNPH patients) compares with our entire data of iNPH patients followed after surgery during the years 2002–2007. Thus, in our total data collected from 130 patients, 103 (79%) were responders. Shunt surgery caused chronic subdural hematoma in one patient (4%), infection in one (4%) and shunt valve failure requiring a revision in four patients (15%). Twenty-three of the 35 (66%) patients presented with evidence of vascular co-morbidity, which was more common in responders than in non-responders (Table 1).

While mean ABP, ABP wave amplitude, mean ICP, CPP, and heart rate did not show any significant difference between shunt responders and non-responders, ICP wave amplitude was significantly elevated in shunt responders. Additionally, the ICP-ABP phase difference was also able to discriminate shunt responders from non-responders since the phase difference was significantly shorter in the shunt responders (see Table 2).

Fig. 1D,E show the distribution of the PRx (representing the moving Pearson correlation between mean ABP and mean ICP) and the distribution of IAAC (representing the moving Pearson correlation between ICP and ABP pulsatile amplitudes) among the 35 patient recordings. For both the static (PRx) and pulsatile (IAAC) components of each pressure recording, a low correlation was observed between ABP and ICP variables, whereas a significantly high correlation was found between PRx and IAAC (Spearman's correlation 0.63; $P < 0.001$; Fig. 1F). However, neither PRx nor IAAC significantly differed

Table 1 Demographic, clinical and radiologic data

	Shunt treatment		Conservative treatment
	Responders	Non-responders	
Number	21	6	8
Age (years)	76 (59–82)	66 (46–79)	70 (38–81)
Sex (F/M)	13/8	6/0	3/5
Vascular co-morbidity	17 (81%)**	1 (17%)	5 (63%)
Clinical state			
Duration of symptoms (years)	3 (0.5–10)	2.5 (1–10)	2 (0.5–5)
NPH score (15–3)	9 (5–11)**	11 (10–13)	11 (8–13)
Radiology			
Evan's index	0.4 (0.3–0.5)	0.4 (0.3–0.5)	0.3 (0.3–0.4)
Ventricular score	104 (81–136)	103 (93–130)	98 (88–119)

Significant differences between shunt responders and non-responders: * $P < 0.05$, ** $P < 0.01$ and *** $P < 0.001$ (Mann–Whitney *U*-test for continuous data; Pearson chi-square test for categorized data).

NPH, normal pressure hydrocephalus.

between shunt responders and non-responders (see Table 2).

Regardless of the presence ($n = 23$) or the absence ($n = 12$) of vascular co-morbidity there were no significant differences between patients in terms of ABP and ICP parameters, CPP or the time-varying ABP–ICP correlations (for both static and pulsatile components; data not shown).

Fig. 2 shows a relationship between post-shunt operation response and the ABP and ICP parameters. Although no differences in mean ICP (Fig. 2A), mean ABP (Fig. 2B), PRx (Fig. 2C), mean ABP wave amplitude (Fig. 2E) and IAAC (Fig. 2F) were observed for both shunt responders and non-responders, mean ICP wave amplitude was significantly increased in shunt responders compared with non-responders (Fig. 2D; $P < 0.001$; one-way ANOVA and Bonferroni-corrected *post-hoc* tests). Unlike other parameters, mean ICP wave amplitude was shown to be highly predictive (see Table 3).

Discussion

The patient material is comprised of 35 iNPH patients, 27 of whom underwent shunt surgery (21 responders, 6 non-responders). Our findings of a high proportion of vascular co-morbidity in this cohort (Table 1) compares with the established association between iNPH and vascular co-morbidity such as arterial hypertension, ischemic heart disease and diabetes (6–12). Although vascular co-morbidity was found to be more frequent in responders compared with non-responders (Table 1), no evidence in the results showed that mean ABP and ABP wave amplitude were

Table 2 The arterial blood pressure (ABP), intracranial pressure (ICP) and ICP/ABP correlation (IAAC) parameters^a

	Shunt treatment (<i>n</i> = 27)		Conservative treatment (<i>n</i> = 8)
	Responders (<i>n</i> = 21)	Non-responders (<i>n</i> = 6)	
Mean ABP			
Average (mmHg)	90 (68–115)	94 (75–104)	70 (60–94)
Percentage ≥80 mmHg/30 s	16 (1–20)	17 (3–20)	9 (1–18)
Mean ABP wave amplitude			
Average (mmHg/s)	77 (37.1–113.9)	68 (56.8–85.5)	63.1 (33.8–77)
Percentage ≥70 mmHg	87 (3–100)	46 (1–82)	60 (0–85)
Mean ICP			
Average (mmHg)	6.9 (2.6–15.5)	6.1 (2.2–11.7)	5.3 (–4.8–12.5)
Percentage ≥15 mmHg/30 s	1 (0–41)	0 (0–92)	0 (0–13)
Mean ICP wave amplitude			
Average (mmHg)	5.8 (4.8–7.9)***	3.0 (1.7–3.6)	4.0 (2.5–6.1)
Percentage ≥5 mmHg	70 (32–97)***	2 (0–10)	7.6 (1–90)
CPP			
Average	84.3 (55.8–110.8)	84.3 (71.1–105.5)	67 (49.2–89.4)
Percentage ≤50 mmHg/30 s	2 (0–24)	–	34 (13–55)
ICP–ABP phase difference			
Average (s)	–0.07 (–0.10 to –0.05)	–0.08 (–0.13 to –0.07)	–0.08 (–0.13 to –0.05)
Percentage ≥–0.10 s	98 (50–100)*	81 (27–97)	96 (2–99)
Heart rate	65 (49–90)	61 (55–74)	72 (47–92)
Pressure reactivity index			
Average	0.24 (–0.11–0.73)	0.19 (–0.02–0.22)	0.09 (–0.03–0.40)
Percentage ≥0.5	21 (3–90)	20 (6–29)	13 (4–39)
Percentage ≥0.6	10 (0–83)	8 (3–16)	4 (0–28)
IAAC			
Average	0.14 (–0.07–0.33)	0.11 (–0.15–0.50)	0.07 (–0.07–0.28)
Percentage ≥0.5	4 (0–26)	3 (0–60)	4 (0–17)
Percentage ≥0.6	2 (0–14)	0 (0–42)	3 (0–12)

^aRecording from 11 p.m. to 7 a.m. Significant differences between responders and non-responders: **P* < 0.05, ***P* < 0.01, ****P* < 0.001 (Mann–Whitney *U*-test).

altered in responders compared with non-responders (Table 2). Mean ICP was also similar in both responders and non-responders as previously seen (3, 4). Conversely, the ICP wave amplitude was significantly more elevated in responders than non-responders (Table 2), which is consistent with previous observations (3–5).

The high positive and negative predictive values of 100 for these thresholds of ICP wave amplitude (4 mmHg; Table 3) are related to the small size of this patient material. During this same period, in our 130 shunted iNPH patients the positive and negative predictive values for a significant shunt response were 93 and 91, respectively, when using the same threshold of ICP wave amplitude (unpublished observations).

The results also showed low values of PRx (Fig. 1D) and low values of IAAC (Fig. 1E), which suggest a weak correlation between the ABP and ICP parameters. Nevertheless, the correlation between PRx and IAAC was significant (Fig. 1F). This result is consistent with the previous findings of a weak yet significant relationship between PRx

and IAAC in head injury patients (32). When comparing shunt responders with non-responders there was no difference in PRx or IAAC (see Table 2). This implies that the time-related correlations between ABP and ICP variables were neither stronger nor weaker in those responding to shunt implantation.

The theoretical rational for using time-related Pearson correlation to explore characteristics of ABP-to-ICP transfer functions is that each cardiac contraction creates the ABP wave (input signal) that is transferred to the ICP wave (output signal). A high positive Pearson correlation (toward +1) suggests a strong relationship between the ABP and ICP measures indicating that the ABP waves are transformed more passively to the ICP waves. Based on earlier transfer function studies (22, 25–28), it can be speculated that such a high correlation indicates impaired cerebral autoregulation which refers to an ability to maintain constant cerebral blood flow during varying ABP.

The present data showed that all patients with elevated pulsatile ICP were shunt responders

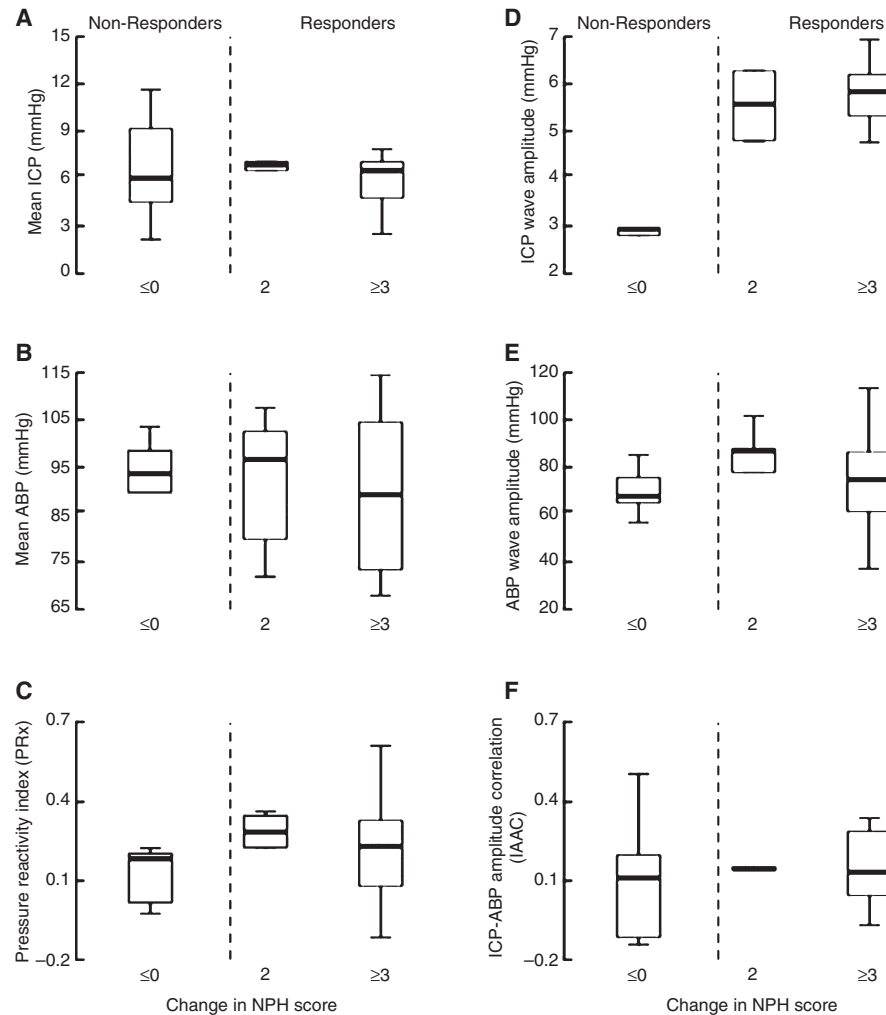


Figure 2. The categorized changes in normal pressure hydrocephalus score 1 year after shunt surgery are shown for the static component of pressure measurements, (A) mean intracranial pressure (ICP), (B) mean arterial blood pressure (ABP) and (C) pressure reactivity index, and for the pulsatile component of pressure measurements, (D) ICP wave amplitude, (E) ABP wave amplitude and (F) ICP–ABP amplitude correlation.

whereas none with low pulsatile ICP were shunt responders (Table 3). The results compare with our previous observations of elevated pulsatile ICP in those iNPH patients responding to shunting (3, 4). In NPH patients with elevated pulsatile ICP shunt placement leads to normalization of pulsatile ICP and clinical improvement (5). This dataset indicated, however, that the static or pulsatile ABP was not predictive of shunt response (Table 3). Thus, neither high mean ABP nor high ABP wave amplitude was indicative of shunt response.

Considered inclusively, this material provides evidence of elevated intracranial pulsatility in iNPH responders whereas the other measurements of ABP and ICP, including correlations between them, were comparable between responders and non-responders.

It has been reported that reduced intracranial compliance causes the small changes in intracranial

Table 3 Predictive values of different intracranial pressure (ICP) and arterial blood pressure (ABP) parameter thresholds

ICP and ABP thresholds	Treatment group (n = 27)		Predictive value
	Responders (n = 21)	Non-responders (n = 6)	
Mean ABP			
<80 mmHg	6	1	PPV 75
≥80 mmHg	15	5	NPV 14
Mean ABP wave amplitude			
<70 mmHg	8	3	PPV 81
≥70 mmHg	13	3	NPV 27
Mean ICP			
<8 mmHg	17	4	PPV 67
≥8 mmHg	4	2	NPV 19
Mean ICP wave amplitude			
<4 mmHg	0	6	PPV 100
≥4 mmHg	21	0	NPV 100

PPV, positive predictive value; NPV, negative predictive value.

volume induced by cardiac pulsations (about 0.5–1 ml, see Ref. 33) to generate large ICP wave amplitudes. In patients with cerebral bleeds (34) and in hydrocephalic dogs (35), pulsatile ICP and intracranial compliance were also inversely related to each other. In line with this reasoning, the hydrodynamic concept of communicating hydrocephalus considers communicating hydrocephalus such as NPH to be caused by reduced intracranial compliance (for review, see Refs 18, 36). It was argued that the reduced intracranial compliance is associated with restricted arterial pulsations, which in turn increase capillary pulsations and reduce capillary absorption of cerebrospinal fluid (18, 36). The author postulated that all vascular diseases that reduce arterial compliance can be causal for developing communicating hydrocephalus. Other possible mechanisms contributing to elevated - pulsatile ICP are reduced venous compliance (19), and impaired pulsation absorber mechanisms (29).

Conclusions

This cohort of iNPH patients gave no evidence of altered static or pulsatile ABP in those iNPH patients responding to shunt surgery. Conversely, in those responding to the shunt the pulsatile ICP is elevated despite normal static ICP. When exploring both the time-related correlation of static ABP and static ICP (PRx) as well as the time-related IAAC, we found only a weak correlation. Thus, the elevated pulsatile ICP in iNPH patients cannot be explained by altered static or pulsatile ABP. Rather, the elevated pulsatile ICP may be caused by intracranial alterations such as reduced intracranial compliance (18).

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Disclosure

The software used for analysis of the ICP recordings (Sensometrics Software) is licensed by Department of Neurosurgery, Rikshospitalet University Hospital, and manufactured by a software company (dPCom AS, Oslo) wherein Per Kristian Eide (MD PhD) has a financial interest.

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