Validation of the optic nerve sheath response to changing cerebrospinal fluid pressure: ultrasound findings during intrathecal infusion tests

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Increased intracranial pressure leads to increased pressure around the optic nerve (ON), which underlies the formation of papilledema and the enlargement of the dural optic nerve sheath (ONS). In clinical practice, the presence of widened ONSs is demonstrable on neuroimaging, but their relationship to cerebrospinal fluid (CSF) pressure remains unknown. The authors investigated the ONS response to pressure during CSF absorption studies in 12 patients undergoing neurological testing. The ONS diameter was evaluated by serial B-mode ultrasound scans of the anterior ON near its entry into the globe.

All patients tested showed ONS diameter changes that exhibited covariance with the alteration of lumbar CSF pressure and were completely reversible during the infusion tests. The maximum difference in ONS diameter between baseline and peak pressure conditions was 1.8 mm on average (range 0.7–3.1 mm), corresponding to an average ONS diameter variation of 45% (range 15–89%). Regression analysis yielded a linear covariance between ONS diameter and CSF pressure with different slopes across subjects (0.019–0.071 mm/mm Hg, mean r = 0.78). However, this linear relationship was only present within a CSF pressure interval. This interval differed between patients: ONS dilation commenced at pressure thresholds between 15 mm Hg and 30 mm Hg and in some patients saturation of the response (constant ONS diameter) occurred between 30 mm Hg and 40 mm Hg. With a single exception, definitely enlarged ONS diameters (> 5 mm) were present when CSF pressure exceeded levels of 30 mm Hg. Retrospectively, discrimination between normal and elevated outflow resistance was possible on the basis of the ONS response to intrathecal infusion alone.

It is concluded that the human ONS has sufficient elasticity to allow a detectable dilation in response to intracranial hypertension. Because of a variable pressure–diameter relationship, the subarachnoid pressure cannot be predicted exactly by single scans. Therefore, the clinical relevance of this method relies on the demonstration of pathologically enlarged sheaths or ongoing enlargement on serial ultrasonography studies.

Key Words • intracranial pressure • cerebrospinal fluid pressure • outflow resistance • optic nerve sheath • ultrasound • noninvasive monitoring

Enlargement of the dural optic nerve sheath (ONS) can be demonstrated by means of magnetic resonance imaging and ultrasonography in patients with prolonged elevation of intracranial pressure (ICP) like that seen in idiopathic intracranial hypertension. Ultrasound techniques now allow us to determine the ONS diameter in B mode with a resolution of less than 0.4 mm and can be performed at bedside. Normative data have been published by various authors who agree on an upper normal ONS diameter of between 4.5 mm and 5 mm in adults. In agreement with postmortem findings of expanded ONS in fatal head injury cases, we recently reported the presence of pathologically enlarged nerve sheaths in critically ill patients suffering from severe head trauma and intracerebral hemorrhage.

These findings raise the possibility that ONS enlargement operates in vivo as a fast response to intracranial hypertension, thereby serving as one of its indicators. The relationship between ONS diameter and ICP in terms of absolute changes, reversibility, and response linearity (threshold and saturation effects) remains to be investigated. To answer these questions, we performed serial ultrasound measurements of the ONS in patients who were exposed to pressure changes during cerebrospinal fluid (CSF) infusion tests.

Clinical Material and Methods

Twelve patients (mean age 59.8 years, range 33–80 years) were examined by means of repetitive ON ultrasound B-mode scans during routinely performed intrathecal infusion tests (mean scans per patient, 52; range 26–71). All patients had been referred to the Neurological Department because of suspected CSF absorption disorder (communicating hydrocephalus or optic disc elevation of unknown origin, six patients each) and all gave written informed consent for the additional ultrasound studies.

The sonographic examination and the CSF absorption study were performed by two independent examiners. During the procedure, B-mode findings were numbered...
and their numbers registered online on the continuous paper registration of the absorption study (CSF pressure over time). All data analysis including linear correlations was performed offline.

**Lumbolumbar Spinal Infusion Testing Procedure**

After insertion of two 0.9-mm intrathecal needles in the lower lumbar intervertebral segments, the patient was placed in the left lateral supine position. One needle was connected to an infusion pump that delivered Ringer’s solution at adjustable constant flow rates ranging between 0.5 ml/minute and 4 ml/minute. The other needle was connected to a pressure transducer (Statham type 4-327-1; Transamerica Delaval, Pasadena, CA) for which the signal was displayed on a monitor and recorded on paper (speed 1 mm/second). Before and after infusion testing, the pulsatile pressure output signal was checked for: 1) its physiological relation to heart and respiratory rates; 2) its sensitivity to hyperventilation; and 3) sensitivity to jugular vein compression. All further pressure readings refer to the electronically determined mean CSF pressure. After signal calibration and 5-minute recording of baseline conditions, intermittent intrathecal infusions with constant flow rates were started at 0.5 ml/minute. These infusions were continued until a steady-state pressure was reached (variation of mean CSF pressure < 2 mm Hg within 2 minutes). After cessation of the infusion and recovery of the individual baseline CSF pressure, the infusion was restarted with a higher flow rate (in steps of 0.5 or 1 ml/minute). This cycle was repeated three to five times provided that the patient remained free of headache, nausea, visual complaints, or mental changes and plateau waves or pressure elevations greater than 60 mm Hg were absent (total test duration 150–210 minutes). The steady-state pressures and the corresponding flow rates were used to calculate the outflow resistance \( (R_o) \) in mm Hg/millilitre/minute.\(^{4,11,25}\) For further analysis, patients were divided into two subgroups of six according to \( R_o \) (\(< 12.5 \text{ mm Hg/ml/minute}, \text{ Group A}; > 12.5 \text{ mm Hg/ml/minute}, \text{ Group B} \)).

**Ultrasound Display of the ON**

Ultrasound B-mode images of the right anterior ON were obtained at regular intervals (every 2–4 minutes) during the infusion test. A 7.5-MHz probe (model 128; Acuson Co., Mountain View, CA) was placed on the temporal upper eyelid and adjusted to a suitable angle for display of the ON entry into the globe. Output intensity of the sound source and gain of the ultrasound detector were individually adjusted to produce optimum contrast between the retrobulbar echogenic fatty tissue and the low-reflection band representing nerve and perineural space (subarachnoid space). We used electronically placed cursors to mark the ONS diameter on this boundary, which is equivalent to the width of the perineural space.\(^{12}\) To improve ultrasound sensitivity, resolution, and reproducibility, we obtained these measurements in a zoom mode at a constant position located 3 mm behind the globe.\(^{14,20,21}\) We define the B-mode ultrasound resolution for the ONS diameter as the minimum detectable change in ONS diameter (0.4 mm).

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**Optic nerve sheath response**

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**TABLE 1**

*Optic nerve sheath response to intrathecal infusion tests in 12 patients with intracranial hypertension*

<table>
<thead>
<tr>
<th>Case No.†</th>
<th>PE</th>
<th>ONSD (mm)</th>
<th>CSFP (mm Hg)</th>
<th>ONSD (mm)</th>
<th>CSFP (mm Hg)</th>
<th>ONSD (mm)</th>
<th>CSFP (mm Hg)</th>
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<td></td>
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<td></td>
<td></td>
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<td>58</td>
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<td>12</td>
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<tr>
<td>2</td>
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<td>–</td>
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<td>4.6</td>
<td>38</td>
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<td>–</td>
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<td>31</td>
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<td>12</td>
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<tr>
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* Raw data are presented from the following test conditions: baseline = before infusion; peak = steady-state conditions at maximum flow rate; decompression = after return to baseline pressure. Note full reversibility and different peaks of the ONS response. Abbreviations: CSFP = CSF pressure; ONSD = ONS diameter; PE = papilledema; + = present; – = absent.

† Patients are listed by subgroups according to \( R_o \) (Group A = normal \( R_o \), Group B = elevated \( R_o \)).

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**Data Evaluation**

The ONS diameter and CSF pressure findings were evaluated under standard CSF infusion test conditions (at baseline, at various steady-state levels, and after decompression) and during the course of the infusion tests. Further analysis was performed by linear regression of raw and \( z \)-transformed ONS diameter and CSF pressure data. The first method generated the individual ONS diameter/CSF pressure ratio, which was used for subgroup and cross-subject analysis. The general relationship between ONS diameter and CSF pressure was evaluated from the pooled data after elimination of individual factors by \( z \) transformation (calculated according to the formula \( z = [−\text{mean}/\text{standard deviation}] \)). By this method, all measurements are treated as relative deviations from the individually observed mean value and become transposed into an interval between \(-3 \) and \(+3 \). Statistical testing was performed on a personal computer using commercially available software (SPSS +; SPSS Inc., Chicago, IL).

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**Results**

Clear changes of the ONS diameter were recorded during the infusion tests in all patients (Table 1). The observed maximum ONS dilation was found at the peak CSF pressure and varied between 0.7 mm and 3.1 mm among subjects (mean 1.8 mm). This corresponded to an average change of 45% in the individual baseline diameter (range 15–89%).

**Ultrasound Findings Under Constant CSF Pressure**

**Before Infusion.** The highest ONS diameters were ob-
served in patients with baseline CSF pressure greater than 12 mm Hg (range 3.5–6.1 mm). Patients with lower CSF pressure exhibited somewhat smaller ONS diameters (range 3.3–5.4 mm), but because of considerable overlap there was no significant difference in the nerve sheath findings between the two groups.

Hence, identification of patients with high and low CSF pressure on the basis of the nerve sheath findings was impossible. Interestingly, both patients with baseline ONS diameters above the usual normal upper limit (5 mm) belonged to Group B and had experienced either abnormally high baseline CSF pressure (Group B, Case 1) and/or an abnormal R$_o$ (Group B, Cases 1 and 3).

After Infusion. The spontaneous return of the CSF pressure to baseline levels was always accompanied by a reduction of ONS diameter. Preinfusion ONS diameters were subsequently regained in all patients (Table 1).

Illustrative Case

A typical response of the ONS is plotted in Fig. 1, which illustrates ONS sensitivity to both increasing and decreasing CSF pressure. In this example (Group A, Case 1), the ONS enlarged by 3.1 mm (from 3.5 to 6.6 mm) and the CSF pressure increased by 44 mm Hg (from 14 to 58 mm Hg). Minimum significant ONS diameter changes (≥0.4 mm) were observed when CSF pressure exceeded levels of 22 mm Hg. After decompression at the end of the infusion test, the ONS diameter normalized and reached the baseline value. Linear regression analysis of 67 measurements yielded a correlation coefficient of 0.867. The CSF pressure/flow-rate ratio (8 mm Hg/ml/minute) indicated unimpaired CSF absorption and thus did not support the hypothesis of malresorptive hydrocephalus. The overall ONS diameter/CSF pressure ratio (slope of the linear regression) was 0.05 mm/mm Hg in this case.

Ultrasound Findings Under Varying CSF Pressure

In all subjects, the changes in the ONS diameter during the infusion tests closely followed the recorded trace of the lumbar CSF pressure. Thus, intervals with increasing and decreasing CSF pressure could be identified on the basis of ONS diameter findings. In some patients, even

![Graph showing ONSD vs. CSFP](image-url)

**Fig. 1.** Graph (upper) and ultrasonography scans (lower) showing original data from a 74-year-old patient with headache and papilledema after sinus venous thrombosis who underwent lumbolumbar perfusion testing (Group A, Case 1; R$_o$ 8 mm Hg/ml/minute). Scans of the right ON were obtained during constant- and zero-flow conditions. Scans 2 to 7 refer to a flow rate of 1 ml/minute; 11 to 19, 2 ml/minute; 24 to 39, 3 ml/minute; and 42 to 55, 4 ml/minute. The remaining scans correspond to test intervals with zero flow rates. The graph shows the course of CSF pressure (CSFP, closed circles) and ONS diameter (ONSD, open circles) for 66 consecutive scans. Note the consistent change in ONS diameter above a CSF pressure of 20 mm Hg and its close relation to CSF pressure variations up to 50 mm Hg. In the typical examples of ONS ultrasonography scans (lower), the echolucent band represents the ON together with its sheath. The measurements of ONS diameter were obtained by placing cursors 3 mm behind the posterior orbital wall. Note the clear display of papilledema in most of the projections and reversible expansion of the ONS in correlation to the CSF pressure.
Optic nerve sheath pressure response

**TABLE 2**
Descriptive parameters of the ONS response to intrathecal volume loading*

<table>
<thead>
<tr>
<th>Case No.</th>
<th>R_{on} (mm Hg/ml/min)</th>
<th>ONSD/CSFP (mm/mm)</th>
<th>r</th>
<th>CSFP-T (mm Hg)</th>
<th>CSFP-S (mm Hg)</th>
<th>ONSD/Flow Rate (mm/ml/min)</th>
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<td>16.0</td>
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<td>0.18</td>
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<tr>
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<td>40.53</td>
<td>0.813</td>
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<tr>
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<td>32.9</td>
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<td>0.913</td>
<td>15.0</td>
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<tr>
<td>mean</td>
<td>23.4†</td>
<td>48.77§</td>
<td>0.917§</td>
<td>22.17§</td>
<td>NA</td>
<td>1.22‡</td>
</tr>
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</table>

* The ONSD change per pressure unit (ONSD/CSFP ratio), its correlation coefficient (r) and the upper and lower critical pressures (at threshold [CSFP-T], and at saturation [CSFP-S]) of the ONS response are given separately for each patient. Statistical comparison between group means confirms a significant difference in both R_{on} and ONSD/flow-rate ratio (‡ p < 0.02 and § p < 0.01, respectively). Abbreviation: NA = not applicable; for other abbreviations see Table 1.

§ Not significant.

small CSF pressure increments of 5 to 10 mm Hg were reflected in changes in ONS diameter (range 0.2–0.6 mm; see Fig. 1).

Dilations of the ONS with diameters clearly larger than the upper normal limit of 5 mm were induced in most cases by the infusion tests. With one exception (Group B, Case 3), ONS diameters larger than 5 mm coincided with mean CSF pressure readings of 30 mm Hg or more, that is, elevated pressure. In the patient who had idiopathic intracranial hypertension and bilateral papilledema (Group B, Case 3), the ONS diameter was already enlarged (5.4 mm) at the baseline pressure (11 mm Hg).

**Intrasubject Analysis.** A very close correlation between CSF pressure and ONS diameter was revealed by intra-subject analysis (Table 2). In 10 of 12 cases, linear regression yielded correlation coefficients (r) greater than 0.83 (median 0.87). Hence, most of the variability in ONS diameter (r^2) is determined by the subarachnoid pressure. Selective analysis of test intervals with ascending and descending CSF pressures (that is, in the presence and absence of infusion) did not produce significantly different r values.

At the upper and lower end of the pressure range this correlation was somehow violated. A significant change in ONS diameter (≥ 0.4 mm) did not occur before a certain level of CSF pressure was exceeded. This threshold effect at the lower CSF pressure end was present in all patients, but it commenced at different levels in each individual (18–30 mm Hg; see Table 2).

In three patients (Group A, Cases 4 and 5; Group B, Case 1) the ONS diameter remained constant while the CSF pressure rose at maximum infusion to peak levels, which resembled a saturation effect. In the remaining cases, however, we were not able to detect this phenomenon within the pressure range studied. Taken together, these findings indicate the presence of a CSF pressure interval that defines the range of operation of the ONS and that is not uniform among patients. Within this interval, no temporal delay of the ONS response was noted.

**Cross-Subject Analysis.** For this analysis we normalized the ONS response. First we compared the relative change in ONS diameter per pressure unit, which is equivalent to the slope computed by the linear regression analysis (ONS diameter/CSFP pressure ratio in millimeters per millimeter of mercury). These ratios varied considerably among patients (range 0.019–0.071, mean 0.047 mm/mm Hg; see Table 2), thus making an individual prediction of the CSF pressure impossible. There was no systematic relationship between baseline ONS diameter and ONS diameter/CSFP pressure ratio.

Second, response linearity was investigated after z transformation of all data (regression analysis r^2 = 0.752). The resulting plot of 655 transformed data points (Fig. 2) illustrates the close linear relationship between ONS diameter (ONS) and CSF pressure ([CSFP], r = 0.752). Outer lines correspond to the 95% confidence bounds.
in the ONS response. Group B patients (elevated $R_{\text{out}}$) exhibited an early rise in the ONS diameter (that is, at lower flow rates). For example, at flow rates of 2 ml/minute, all Group A patients had ONS diameters of less than 5 mm, whereas patients from Group B displayed ONS diameters between 5 mm and 7 mm at the same or lower flow rates.

**Statistical Analysis**

Statistical comparisons using Student's t-test showed a marked difference between subgroups ($D$) in the ONS diameter/flow-rate ratio ($D = 0.76 \text{ mm Hg/ml/minute}, p = 0.003$) similar to $R_{\text{out}}$ ($D = 15 \text{ mm Hg/ml/minute}, p = 0.019$).

**Discussion**

This study demonstrates the in vivo response of the anterior dural ONS to alterations in CSF pressure. Enlargements of up to 90% of the baseline ONS diameter were easily detectable on B-mode ultrasound. Comparison of the pressure response in 12 patients showed that changes in ONS diameter are predictable within the same patient but vary interindividually with respect to gain (diameter/pressure ratio) and the range of operation (threshold and saturation).

Optic nerve sheath dilation, a secondary phenomenon of CSF pressure equilibration between orbital and cranial cavities, has no clinical correlate by itself. However, when dilation is severe, it may lead to dural nerve sheath hemorrhage caused by rupture of dural bridging vessels and to intraocular bleeding, presumably caused by obstruction of the venous retinochoroidal communication by retrobulbar mechanical compression.$^{27}$ Nerve sheath dilation depends on the communication between the perineural CSF compartment around the ONs and the craniospinal subarachnoid space. Despite numerous fibrous adhesions within the subarachnoid space of the optic canal,$^{18,22}$ there is sufficient patency to allow a transfer of CSF. Since the first description of CSF flow,$^{30}$ numerous researchers have reproduced this finding in animal models by means of dye injection experiments (for a review see Hayreh$^{17}$), tracer studies,$^{2,5,31}$ and simultaneous pressure recordings.$^{6,19}$ Important evidence for the presence of this CSF route in humans came from a recent study on human postmortem preparations that found proportional increases of the perineural pressure after elevation of the intraventricular pressure by direct infusion.$^{23}$ Because preenucleation measurements of perineural pressure yielded readings within the range of ICP, the optic canal most likely imposes negligible resistance to CSF equilibration.$^{24}$ Regarding the function of cranioorbital CSF exchange, specific tasks have been proposed besides the homeostatic regulation of the neural environment.$^{7}$ These include supplementary routes for CSF drainage$^{2,5,26,32}$ and transport of immunocompetent leukocytes to the cervical lymph nodes.$^{16,28}$ Although its precise function remains speculative, our study strongly supports the notion that CSF exchange between the craniospinal subarachnoid space and its ON extension takes place regularly in vivo without temporal delays relevant for clinical diagnosis.

Earlier reports about ONS enlargement concentrated on morphological features rather than giving detailed information about ICP levels. However, two A-mode ultrasound studies merit further consideration. In a preoperative series of patients undergoing neurosurgery, the largest
diameters were observed in the subgroup with the highest ICP readings (6.5 mm ONS diameter equivalent to 30–55 mm Hg ICP). Pressure effects on the ONS were described in a patient with pseudotumor cerebri before and after lumbar decompression. The authors observed a rapid decrease of the enlarged ONS diameter by 1.5 mm, which is in good agreement with our decompression results following infusion testing and also indicates absence of dilation-induced ONS hemorrhage.

Progress in ultrasound technology and image processing allows display of the ON via B-mode scan with a resolution below 0.5 mm. Because of the two-dimensional display in B mode, a reproducible location along the nerve can be selected for measurement of ONS diameter. This is of major importance for quantification because the sheath has a nonuniform shape (bulbous near the globe) and distensibility (more flexible near the globe). Further advantages of B-mode imaging compared to the unidimensional A-mode echo display are the comprehensible output of results, which make it easier to learn and perform the procedure and the more widespread availability of B-mode ultrasound machines.

Our study shows that the ONS response operates within a limited CSF pressure interval. At the low-pressure end, a certain threshold CSF pressure needs to be exceeded (average 22 mm Hg in all patients). Below this level, no or only very small changes in ONS diameter may be expected (possibly below ultrasound resolution, which was 0.4 mm in this study). Thus, changes in the ICP would remain undetected by ONS diameter testing if the ICP was too low. However, above this threshold the ONS diameter is directly related to the CSF pressure, and its changes are reversible and predictable within the same patient. Therefore we conclude that elastic structures determine the sheath’s pressure response. Simple all-or-none responses in the ONS diameter were not encountered in our unsellected series. At higher CSF pressure levels, the ONS may lose its ability for further dilation, which corresponds to a depleted capacity for further expansion. Findings above the upper limit of ONS diameter nearly always corresponded to CSF pressure levels at or above 30 mm Hg.

These response characteristics are well explained by anatomical findings. The elastic properties refer to a specialized collagen fibril texture of the ONS. In contrast to ordinary dura mater, which contains densely packed fibrils arranged in parallel, the ONS consists of surprisingly flexible dural tissue. According to Raspanti and coworkers, the sheath ultrastructure closely resembles the flexible perineurium of peripheral nerves. The sheath saturation effect may relate to radially oriented trabecular fibers that traverse the subarachnoid space and connect pia mater of the nerve with the innermost arachnoid layer of the sheath. These are relatively rare in the anterior segment, in which the ONS possesses maximum capacity to distend and are more common in posterior parts that remain unchanged after experimental exposure to pressure. The pressure threshold for sheath dilation was above the range of normal ICP (18–30 mm Hg). Both trabecular fibers and sheath collagen structure may determine this aspect of the sheath response.

For clinical purposes, noninvasive estimation of ICP is of interest during the initial evaluation of patients with suspected intracranial complications or when the results of invasive ICP monitoring need to be checked for plausibility. Today, most centers perform transcranial Doppler ultrasonography to generate flow velocity indices that correlate to cerebral perfusion pressure and ICP. Recently, the transcranial Doppler response to CSF pressure alterations was investigated using the same paradigm as in our study. These authors reported significant changes in the pulsatility index in response to infusion and, when comparing patients with normal and elevated R, they found a significant difference in the infusion-related change in pulsatility index. Analysis of our data showed that the changes in ONS diameter in relation to infusion flow rate can also predict elevated R (critical ONS diameter/flow-rate ratio, 0.9 mm/ml/minute; equivalent to critical R of 12.5 mm Hg/ml/minute). The determination of the steady-state ONS diameter at a 2-ml/minute flow rate seems even more simple. According to our data, this may serve as another diagnostic criterion (> or < 5 mm). Indeed, this procedure allowed us to separate patients with elevated and normal R. Thus, similar to the transcranial Doppler study, we may speculate that direct ICP measurements during infusion tests can possibly be replaced by noninvasive ICP evaluation with ON ultrasound. However, a prospective study will be needed to ascertain the above-mentioned criterion for diagnostic purposes.

Conclusions

Although the nerve sheath is generally sensitive to ICP changes, conclusions drawn from ON ultrasound studies must be subject to the following limitations. First, an exact estimate of ICP cannot be provided because the relationship between ONS diameter and CSF pressure is unknown in the individual case. Second, a normal variability of the ONS diameter exists (for a review see Hansen, et al.) and the ONS diameter under baseline conditions is usually unknown. For the time being, diagnostic conclusions are therefore limited to qualitative statements about the presence of marked intracranial hypertension (most likely > 30 mm Hg) when abnormally wide ONSs are detected (larger than the upper normal limit of 5 mm). However, this procedure carries a risk that patients with low pre-morbid ONS diameters or low sheath elasticity may be missed as false negatives. Third, restriction of CSF exchange via the optic canal may interfere with the ONS response. Bilateral examinations are therefore mandatory, but in patients with orbitofacial trauma, even bilaterally normal ONS diameters do not exclude ICP dysregulation. We believe that monitoring with serial ON examinations offers an additional opportunity to estimate the level of CSF pressure in a fast and noninvasive way.

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