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VIEWPOINT

A Proposal for a New Protocol for Sonographic Assessment of the Optic Nerve Sheath Diameter: The CLOSED Protocol

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Abstract
Measuring and monitoring of intracranial pressure is considered standard of care in patients with suspected intracranial hypertension. Sonographic assessment of the optic nerve sheath diameter (ONSD) has been promising and potentially useful for noninvasive intracranial hypertension screening. ONSD measurements are easy to perform, repeatable at bedside, fast, low cost, and radiation-free. However, they are still burdened by inter-rater variability, lack of ultrasound (US) setting standardization (e.g., US frequency, focus depth, etc.), and possible artifacts. To overcome this problem, we propose the CLOSED protocol associated with equipment specifications, as a guide to minimize the occurrence of such artifacts enabling a more reliable and accurate measurement. We suggest that color Doppler could be used as a new standard evaluation for the ONSD.

Keywords: CLOSED protocol, Optic nerve sheath diameter, Ultrasound color Doppler, Central retinal artery, Point-of-care ultrasound

Introduction

Intracranial pressure (ICP) measuring and monitoring is considered care standard for suspected intracranial hypertension patients. Invasive measurement techniques still have significant side effects and complications such as bleeding and infections [1–3]. ICP's basic principles are based on anatomical continuity of the optic nerve (ON) sheath with the intracranial dura mater and cerebrospinal fluid (CSF) movement according to pressure gradients. ICP variations are detectable by measuring the sheath diameter of the ON, due to the direct connection between ON sheath diameter (ONSD) compartment and cerebral ventricular system. Sonographic assessment of the ONSD can be considered promising and potentially useful for noninvasive intracranial hypertension screening [4, 5]. ONSD is easy to perform, repeatable at bedside, fast, cheap and radiation free. Previous studies reported a high intra- and interobserver reliability [6, 7]. Despite standardization of ultrasound (US) settings (e.g., US frequency, focus depth, etc.), a clear cutoff for intracranial hypertension, and guidelines/recommendations are yet not available. Furthermore, the measurement of artifacts could alter the real value [8]. We propose and describe a new simple and systematic protocol—the CLOSED protocol (Color Doppler–Low power examination–Optic disk clarity–Safety [short examination duration]–Elevate frequency–Dual measurements)—to perform the sonographic assessment of ONSD to obtain safe, reliable and comparable measurements. The CLOSED protocol is the result of a narrative review on this topic and results of several expert meetings.

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Methods and Technique

After a standard learning curve of 25 measurements [9], two different operators of a single-center refined US settings supported by an experienced sonographer. All patients with suspected high ICP or normal pressure hydrocephalus were submitted to ONSD measurements according to the research protocol approved by the local Ethical Committee. US examinations and measurements of the ONSD were performed in B-mode and color Doppler mode on a MyLab™Twice US system (Esaote, Italy), using an 11–3 MHz linear array probe.

Correct identification of the margins, ON course, and its sheath is of paramount importance for the sonographic ONSD assessment. ONSD should be measured 3 mm behind the optic disc, because at this distance the sheath is subject to maximum diameter fluctuations due to ICP [10–12]. Color Doppler visualizes the central retinal artery (CRA) and vein (CRV) (Fig. 1), which run in the middle of the distal segment of the ON [13, 14]. CRA and CRV visualization helps to correctly identify the ON course, which can be difficult due to artifacts, wrong angulation of the probe, and nerve tortuosity [15–17]. Furthermore, identifying the ophthalmic artery (OA) with color Doppler, which runs parallel to the ON, increases accurate identification of ONSD margins (Fig. 2).

ONSD Assessment with the CLOSED Protocol

CLOSED is our proposed acronym to recall the key elements for an accurate ONSD measurement. A brief description of each element is provided:

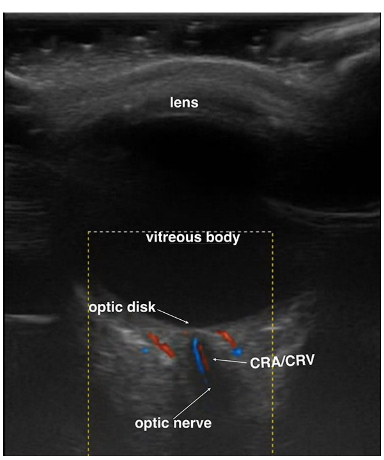

Fig. 1 US color image of the eye with lens, vitreous body, optic disk, and ON which is externally delimited by vessels with the CRA and CRV running to the center of the ON (Color figure online)

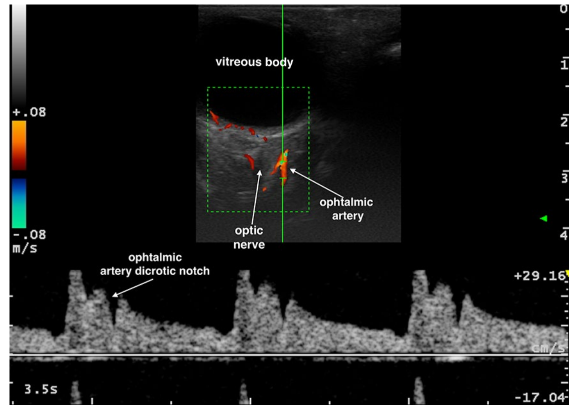

Fig. 2 US color Doppler image of the OA delimiting the median border of the ONSD. Doppler waves of the OA with its characteristic dicrotic notch (Color figure online)

- *Color Doppler* used to identify CRA, CRV, and OA in order to better detect the nerve course;
- *Low power output* a sensitive organ, such as the retina, requires the lowest possible output power for a safe use of diagnostic US;
- *Optic disk clarity* the clearance of the optic disk is a minimum requirement for a correct landmark 3 mm behind the papilla.
- *Safety (short examination duration)* minimize image information loss recording an US video clip to reduce the examination duration for the safety of the patient (ALARA principle [as low as reasonable achievable]);
- *Elevate frequency* for a better quality of US images.
- *Dual measurements* two measurements should be taken for each eye: horizontal and vertical.

Device Setting

- Optimal frequency for US ONSD measurements should be balanced to avoid any potential damage to the ocular structure [18]. Although the high US frequencies produce a better spatial resolution [19, 20], the ALARA principle must always be considered [21]. Despite the availability of very high frequency probes, we suggest using a conventional 10 MHz probe to safeguard the patient's eye from possible damage. Potential biological damage caused by thermal and mechanical effects was noticed in experimental US conditions [21]. The mechanical index (MI) and thermal index (TI) should be below a cutoff value where harmful effects are possible [29]. According to the Food and Drug Administration recommendations for ophthalmic use, the following upper limit parameters should be observed: TI = Max (TIS_as, TIC) should be ≤ 1 °C; spatial-peak temporal-average intensity ($I_{SPTA.3}$) ≤ 50 mW/cm^2; and MI ≤ 0.23 [22].

- According to our protocol, the procedure must be stopped immediately if the patient reports any discomfort. Actually, no cases have been reported. No safety concerns for the duration of the insonation are reported. The standard procedure usually requires 1 min for each eye [18].
- It is important to reduce the power output of the US, usually expressed as a percentage. Authors obtained good images with 20% power and even 25% can be used in compliance with MI and TI limits.
- The depth should be set at 40–45 mm to obtain a sufficiently large image of the eyeball (which should be kept in the center of the screen) to visualize the anatomical structures in proximity of the nerve.
- The focus should be kept at a depth of about 25–30 mm—the depth of focus must be positioned where the ON is usually displayed and where the measurement is to be performed. However, adjustments should be taken into consideration according to the anatomy of each patient.
- The frequency of the probe should be kept at around 10 MHz to obtain the best balance between wave penetration and resolution.
- The gain compensates signal attenuation (a reduction in sound amplitude), as the waves propagate through tissues. In our experience, gain at 55–60% produces adequate brightness. An excessive gain could lead to excessive contrast and less clear images.
- The Doppler value of the pulse repetition frequency gives sufficiently clear images when set to 1.0 kHz.
- Power Doppler can be used to assess the OA waveform to distinguish it from veins based on the classical incisural notch.
- Authors consider a pediatric linear probe on some patients for anatomical conformation useful. As reported by other authors, the probe is crucial in the ONSD US and only measurements obtained with the same probe-type should be compared [22].

Patient Positioning

- The technique and safety measures (even though side effects are very low) should be explained to the patient whenever possible [23, 24].
- The patient should be supine, in neutral head position, with an chest elevation of about 15°–25° to facilitate venous drainage, even though position-related side effects are still debated and controversial [25]. The performer should sit behind the patient's head. The probe-cable should not be in tension or suspension, in order to minimize tension, which limits fine movements.
- The lens of the eye is, by definition, a refractive lens and might deflect the angle of US wave incidence. Patients should keep a stable gaze, looking straight ahead, because even with closed eye, pupils could be pointed upward and outward (Bell's phenomenon)—a natural orientation of gaze—leading to a tortuous ON image similar to a situation of increased ICP [15]. Therefore, keeping the gaze centered, in longitudinal and transverse measurements, reduces the likelihood of error. The Doppler image can help confirming the correct trajectory of the nerve to obtain accurate measurements of the ONSD.

Probe Positioning

- US gel should be used to avoid air between probe and skin. Eyelashes can present a challenge. Some authors proposed the use of Tegaderm on the closed eyelid to prevent possible direct contact between the eye and the gel [26]. It is important to minimize the pressure with the probe on the eyeball, because it is a sensitive organ and a deformed US image is unreliable.
- The probe marker should always be oriented in the same way. Conventionally, the authors recommend keeping the probe laterally in the horizontal measurement and superiorly in the vertical measurement.
- During horizontal measurement, the probe should be placed at an approximate angle of 15°–20° on the patient's closed upper eyelid. For the vertical measurement, the probe should be placed on the center of the patient's closed eye, slightly toward the corner of the nose (latero-to-medial direction), trying to intercept the nerve direction (Fig. 3).

Imaging and Measurements

- An accurate image of the eye and the posterior orbital structures, including the ON and its sheath, should appear on the US screen after checking correct device settings, patient, and probe positioning. The sheath diameter must be measured 3 mm behind

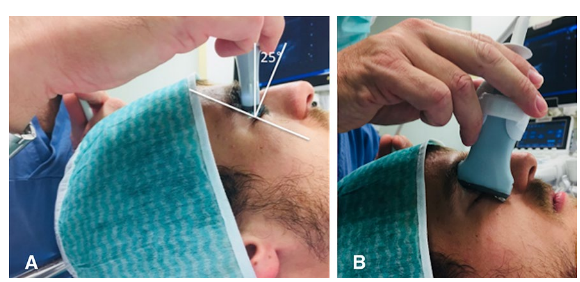

Fig. 3 **a** Lateral view of the probe in a horizontal position on the patient's upper eyelid, at an angle of about 25°; **b** lateral view of the probe in a vertical position on the upper and lower eyelids of the patient, with a slight latero-medial inclination (Color figure online)

the merging point of the nerve from the papilla, which is considered the point of greatest distensibility [10–12]. The nerve appears in B-mode, the CSF surrounding the nerve appears black and, externally, the nerve sheath appears as two hyperechoic binaries; furthermore, the papilla of the retina must appear free from false images, clean, and usually hyperechoic. We recommend to take measurements on images in which nerve and sheath are completely visible from the eye to the 3 mm landmark into consideration.

- The quality of B-mode is often inadequate and the diameter measurement may be unsatisfactory because of unclear margins. To minimize errors induced by acoustic shadow cones and false images, the use of color Doppler is mandatory. The authors suggest to visualize the CRA and/or CRV and to use these vessels as landmarks to identify the correct anatomical plane for reliable ONSD measurements (Fig. 4).
- The OA is another useful landmark provided by the color Doppler, which is not always visible on the same plane as that of CRA and CRV. The OA runs parallel to the ON [13] and is easy to distinguish from other small arteries for its typical power Doppler curve (Fig. 1). This further anatomical marker may allow the sonographer to be more confident about the margins of the ONSD. However, possible color Doppler artifacts (like the blooming effect) should be kept in mind [27].
- To reduce the examination time, we recommend capturing a short video clip, from which the performer can then extract the best frame for measurement.
- Two measurements (dual measurements) should be taken for each eye: horizontal and vertical. The best-captured frame should be used for measurements to minimize any operator-dependent error. In case of doubt or clear discrepancies between the horizontal and vertical measurements, the horizontal measure should be considered as most reliable [22]. At least during the learning stages, we recommend that two operators should select the frame to agree on the four measurement points.
- Once measurements have been completed, the frame is named and saved, and additional notes are added if necessary (e.g., idiopathic normal pressure hydrocephalus, subarachnoid hemorrhage, idiopathic intracranial hypertension, etc.). The authors suggest using the conventional sequence for measurements (e.g., left eye horizontal; left eye vertical; right eye horizontal; right eye vertical).

Novelty in US Assessment

The novelty of this paper consists of two main points, in terms of US technique: (1) the definition of the recommended setting for the US; and (2) the use of arteriovenous color Doppler to better define the anatomy of the nerve, sheath, and course to obtain a reliable and objective measurement.

The CLOSED protocol includes two important elements allowing a safe and accurate ON sheath evaluation. First, appropriate US settings are essential to keep the procedure safe. In fact, ocular structures, containing a large amount of collagen, like the cornea and eye lens, are US absorbers, which heat up during US exposure. US exposure, especially if prolonged, may cause transient chemosis, conjunctival injection, corneal clouding, lens opacities, reduction in intraocular tension, or permanent destruction of the ciliary body [28, 29]. The CLOSED protocol allows the operator to perform a safe and fast examination adjusting settings to obtain proper and fast image acquisition. In this regard, as recently described by Rasulo and Bertuetti, the use of color Doppler to visualize retinal vessels may play an important role. In fact, visualization of retinal artery allows the operator to reduce the likelihood of artifacts and to better identify borders of the ON sheath [30]. This will increase safety, effectiveness, and accuracy of the examination, reducing US exposure of the ocular structures.

Limitations

Our protocol is based on the results of a narrative review and several expert meetings without strict methodological approach. Furthermore, multiple US systems and machines are currently available and a standard setting may not be achieved. Our purpose was to provide a broad vision to suggest some basic settings rather than a rigid and dogmatic standard. Finally, US measurements are dependent on the operator's experience and skills. In case of clinical uncertainty, a more objective diagnostic investigation (e.g., computed tomography if rapid/urgent assessment is needed or magnetic resonance imaging in more stable cases) should be performed.

Conclusion

The noninvasive measurement of ICP remains an important element of scientific debate and the role of ONSD in this field is more and more promising. However, ONSD measurements are often not accurate, as a number of artifacts can affect them. We propose the CLOSED protocol as a guide to minimize the occurrence of such artifacts enabling safer, more reliable, and accurate measurements. Color Doppler use could be proposed as a new

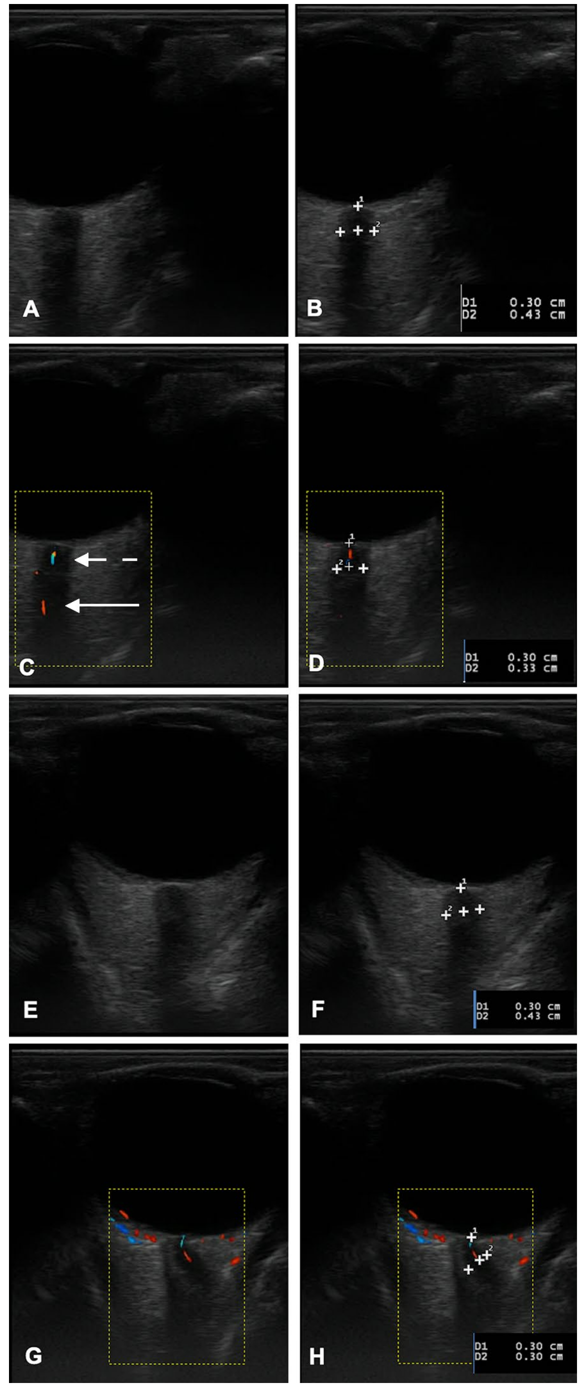

Fig. 4 The color US usefulness in the CLOSED protocol. **a** US B-mode image showing an acoustic shadow that could be interpreted as the ON with its sheath and **b** ONSD measurement (4.3 mm) **c** Color US of the same section. The CRA and CRV (arrow) are visualized in the center of the ON. The proximal segment of the CRA (dotted arrow) is also shown. The visualization of this portion of the CRA within the shadow cone proves that the B-mode visualized ON is nothing but an artifactual acoustic shadow. In fact, this part of the CRA is externally located to the ON sheath. **d** Color US correct measurement of ONSD (3.3 mm). Analyzing in detail the image, a darker central portion, in which the CRA and CRV run, is clearly visualized, while two greyish portions are recognizable at the lateral margins. The central darker portion has to be intended as the real ON. In fact, the greyish portions are artifactual images, not recognizable in the classic B-mode as shown in Panel B. Once the direction of the ON is confirmed by the direction of the aforementioned vessels, the ONSD value could be determined by a measurement, perpendicular to the ON, 3 mm behind the optic disc. **e**–**h** Another example of the usefulness of the color US in the ONSD measurement. US B-mode image (**e**), showing an ON that seems to run straight and centrally and **f** its measurement (4.3 mm). **g** Color US image of the same section (**g**) revealing a tortuous ON. **h** Color US image with the real ONSD measurement (3 mm). Even in this case a simple B-mode image would not have been able to recognize a twisty ON and would have led to an erroneous ONSD measurement. In fact, the ON is the darker portion inside which the CRA and CRV run; the two greyish lateral portions are artifactual images given by an acoustic shadow. In addition, in this case, the measurements of the artifact would have produced an overestimation of the ON diameter. The standard procedure, once the authentic anatomical margins have been defined, allows a definition of real ONSD diameter values (Color figure online)

standard of care for ONSD evaluation. Of course, clinical studies are needed to prove feasibility, applicability, and safety of the CLOSED protocol to test sensitivity, specificity, and overall accuracy compared with a standard technique not including color Doppler visualization of the CRA.

Abbreviations
ALARA: As low as reasonably achievable; CRA: Central retinal artery; CRV: Central retinal vein; ICP: Intracranial pressure; ICU: Intensive care unit; IIH: Idiopathic intracranial hypertension; iNPH: Idiopathic normal pressure hydrocephalus; $I_{SPTA.3}$: Spatial-peak temporal-average intensity; MI: Mechanical index; ms: Millisecond; ON: Optic nerve; ONSD: Optic nerve sheath diameter; PRF: Pulse repetition frequency; SAH: Subarachnoid hemorrhage; TI: Thermal index; TIC: Thermal index cranium; TIS_as: Soft tissue thermal index at surface; US: Ultrasound.

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Authors contribution
Aspide, Bertolini was involved in conception and design. Aspide, Bertolini, Albini was involved in acquisition of data. Aspide, Bertolini, Biasucci contributed in drafting the article. All authors critically revised the article and reviewed the submitted version of manuscript. Albini was also involved in Technical/material support. Mazzatenta, Palandri, and Biasucci contributed in study supervision.

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Conflicts of Interest
The authors declare that the article content was composed in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Ethical approval
The local Institutional Review Board approved the present study. CLOSED protocol adhered to ethical standards and Helsinki Declaration.

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