Prikaz premera ovojnice optičnega živca z ultrazvokom s kontrastnim sredstvom – dokaz zasnove raziskave

Contrast–enhanced ultrasound imaging of the optic nerve sheath diameter – a proof of concept study

Avtor / Author

Andrej Bergauer[1,4], Gregor Prosen[2,4] Nina Kobilica[1,4] Vojko Flis[1,4] Marko Jevšek[3,4] Tomaž Šeruga[3,4]

Ustanova / Institute

[1]Univerzitetni klinični center Maribor, Oddelek za vaskularno kirurgijo, Maribor, Slovenija; [2]Center za urgentno medicino Maribor, Slovenija; [3]Univerzitetni klinični center Maribor, Oddelek za radiologijo, Maribor, Slovenija; [4]Univerza v Mariboru, Medicinska fakulteta, Maribor, Slovenija

[1]University Clinical Center Maribor, Department of Vascular Surgery, Maribor, Slovenia; [2]Center for Emergency Medicine Maribor, Slovenia; [3]University Clinical Center Maribor, Department of radiology, Maribor, Slovenia; [4]Faculty of Medicine University of Maribor, Maribor, Slovenia

Ključne besede:
Oko, magnetna resonance, ovojnica optičnega živca, ultrazvok s kontrastom, anatomija ožilja

Key words:
Eye, magnetic resonance imaging, optic nerve sheath diameter, contrast-enhanced ultrasound, vascular anatomy

Članek prispel / Received
5. 4. 2017
Članek sprejet / Accepted
29. 6. 2017

Naslov za dopisovanje / Correspondence

Tomaž Šeruga, Univerzitetni klinični center Maribor, Radiološki oddelek, Ljubljanska 5, 2000 Maribor
Telefon +386 41674670
E–pošta: ttseruga@gmail.com

Izvleček

Namen: *Namen študije je bila primerjava dobljenih rezultatov meritev premera ovojnice vidnega živca med kontrastno ojačanim ultrazvokom (CEUS) in visoko resolucijsko magnetno resonanco (HRMR). Glavni cilj je bil oblikovanje nove metode merjenja premera ovojnice vidnega živca, ki je enostavnejša za izvajanje, enostavnejša za interpretacijo in lažje ponovljiva kot sedaj uporabljane metode.*

Metode: *Za izvedbo študije smo pridobili mnenje Državne komisije za medicinsko etiko Republike Slovenije; študija je registrirana pod št 30/03/12. Devet zdravih mladih odraslih oseb smo pregledali z MR visoke ločljivosti in z ultrazvokom z aplikacijo kontrastnega sredstva. Meritve premera ovojnice optičnega živca smo po obeh metodah opravljali 3 mm za zrklom. Podatkovne*

Abstract

Purpose: *The present proof of concept study was performed to evaluate the consistency between measurements of the optic nerve sheath taken using contrast–enhanced sonography and high–resolution magnetic resonance imaging (MRI). The main goal was to devise a novel candidate method to measure the optic nerve sheath diameter that is easy to perform, straightforward to interpret, and highly reproducible.*

Methods: *The approval of the National Medical Ethics Committee of the Republic of Slovenia was obtained; the study was registered under No. 30/03/12. Nine healthy young adults were examined with high–resolution MRI and contrast–enhanced ultrasound (CEUS). Measurements of the optic nerve sheath diameter were performed 3 mm behind the bulb, us-*

nize smo anonimizirali in neodvisnim ocenjevalcem zakrili. Statistična analiza je vključevala stopnjo ujemanja meritev z Bland–Altmanovo analizo in oceno stopnje ujemanja med ocenjevalci, ki smo jih izračunali z medrazrednim korelacijskim koeficientom.

Rezultati: *Bland–Altmanovi grafi kažejo na splošno dobro ujemanje obeh metod v klinično sprejemljivih mejah ujemanja oz. prekrivanja. Medrazredni korelacijski koeficient, izračunan za obe metodi, kaže oz. potrjuje, da je kontrastni UZ najmanj toliko ponovljiv kot magnetna resonanca visoke ločljivosti.*

Zaključek: *Opisana metoda z uporabo kontrastno ojačanega ultrazvoka za merjenje premera ovojnice optičnega živca zahteva dobro poznavanje relevantne anatomije. Uporaba kontrastno poudarjenega ultrazvoka omogoča relativno enostavno in zanesljivo nastavitev merilnih točk. Retrobulbarni artefakti so pri UZ manj zavajajoči kot pri MR. Izhajajoč iz majhnega vzorca je metoda primerljiva z visoko ločljivo magnetno resonanco. Za dokončno oceno uprabnosti metode je potrebno opraviti vrednotenje metode na večjem vzorcu zdravih oseb, prav tako pa tudi na vzorcu bolnikov s povišanim intrakranialnim tlakom.*

ing both methods. The datasets were anonymized and the readers, blinded. Statistical analysis included evaluation of agreement using Bland–Altman plots. The assessment of inter–rater reliability was achieved by calculation of the intra class correlation coefficient.

Results: *Bland–Altman plots showed favorable overall agreement between both methods, with clinically acceptable limits of agreement. The intra class correlation coefficient calculated for both methods suggests that the CEUS method was at least as reproducible as high–resolution MRI.*

Conclusion: *The described method, using CEUS to measure the optic nerve sheath diameter, facilitates the identification of the surrounding anatomy. When CEUS is employed, the measurement points can be easily and reliably set, and retro bulbar artifacts are less confounding. Based on results from a relatively small sample, this method seems to be comparable with high–resolution MRI. Evaluation of the method on a larger sample of healthy subjects and patients with increased intracranial pressure is needed.*

INTRODUCTION

The concept of the optic nerve sheath reacting to changes of intracranial pressure has been quite firmly established, and has been corroborated by experimental data and cadaver studies. The phenomenon of papilledema caused by the extension of elevated intracranial pressure into the subarachnoid space of the optic nerve was explained in the 1960s by Hayreh (1,2). In the 1990s, Helmke, Hansen, Liu, and Kahn produced substantial data on distensibility and pressure, and the related enlargement of the optic nerve sheath, based on cadaver studies with intrathecal infusion of Ringer's solution (1,3,4). Enlargement of the optic nerve sheath is evidently not a static indicator, but varies with changes in intracranial pressure within a matter of seconds (2). Transbulbar sonography has been shown to be well suited to imaging of the optic nerve sheath complex, and a correlation between the optic nerve sheath diameter (ONSD) as seen on transbulbar sonography, and invasive measures of intracranial pressure has been established. Previous studies have been conducted both on adult and pediatric populations (5). The etiology of elevated intracranial pressure (ICP) varies, ranging from trauma to the effects of acute mountain sickness (6–12).

Although most studies show a positive correlation between ONSD values and intracranial pressure, standard values for normal and abnormal sonographic measurements vary significantly. Similar studies done with magnetic resonance imaging (MRI) show much more consistency. The diameters that are consistent with normal ICP values on MRI are higher than previously published values for transbulbar sonography (1,13,14,15). The relative consistency of measurements reported in various studies using MRI is attributed to enhanced differentiation of various anatomical structures (1).

The variability of measured diameters in different studies using transbulbar sonography has been attributed to several factors (including parallel incidence of the ultrasound probe on the structure being investigated, sonographic artifacts of the retrobulbar region, etc.). All of these factors can be ultimately condensed to a problem of exact positioning of the measurement points, as the ONSD is relatively small. In a recent cadaveric study by Steinborn et al., in which high–resolution ultrasound was employed, greater variance in measurement values of the ONSD was observed, when the transbulbar (transverse) approach was used, in comparison to the sagittal and coronal approaches (1). In a study by Moretti et al., conducted on patients with spontaneous intracranial hemorrhage, a similar superiority of the sagittal orientation of the probe was evident, and this was attributed to the increased incidence of sonographic artifacts, when the probe was positioned horizontally (3). A call has been made for the standardization of image quality and interpretation. That goal is ultimately linked to the ability of the operator to establish anatomical landmarks that are considered as measurement points (1). The method should be simple, and its interpretation should be straightforward. Furthermore, measurements should be highly reproducible to be useful at the bedside, and effectively performed by an operator who is not specialized in ocular or transbulbar sonography.

Our main goal was therefore to devise a candidate method with those attributes. We used contrast–enhanced sonography to delimit the points for ONSD measurements. The retrobulbar space is occupied by various perfused structures. The pattern of the course of the main vessel branches, capillaries, and venules is highly specific in relation to the optic nerve. In the center of the nerve, there are arteria and vena centralis retinae; and on the outer boundary of the subarachnoid space, there is the vagina externa nervi optici (formed bythe dura mater), through which arterioles and venules pass in a highly directional fashion (Figure 1). The method should be capable of demonstrating the course of these small vessels reliably, as they can be considered as landmarks to conduct a measurement. The usual techniques of color coded Doppler is not sufficiently sensitive, and is prone to several operator–dependent artifacts. We hypothesized that the use of a second–generation ultrasonic contrast agent (SF6 in a lipid monolayer) would highlight those landmarks.

MATERIALS AND METHODS

The approval of the National Medical Ethics Committee of the Republic of Slovenia was obtained, and the study was registered under No. 30/03/12. Informed consent was obtained from all nine healthy young adults enrolled in the study. There were three female and six male volunteers, ranging between 21 to 33 years of age (mean 24 years). None of the subjects had any known preexistent systemic or ophthalmic conditions. Another healthy adult was enrolled as a method

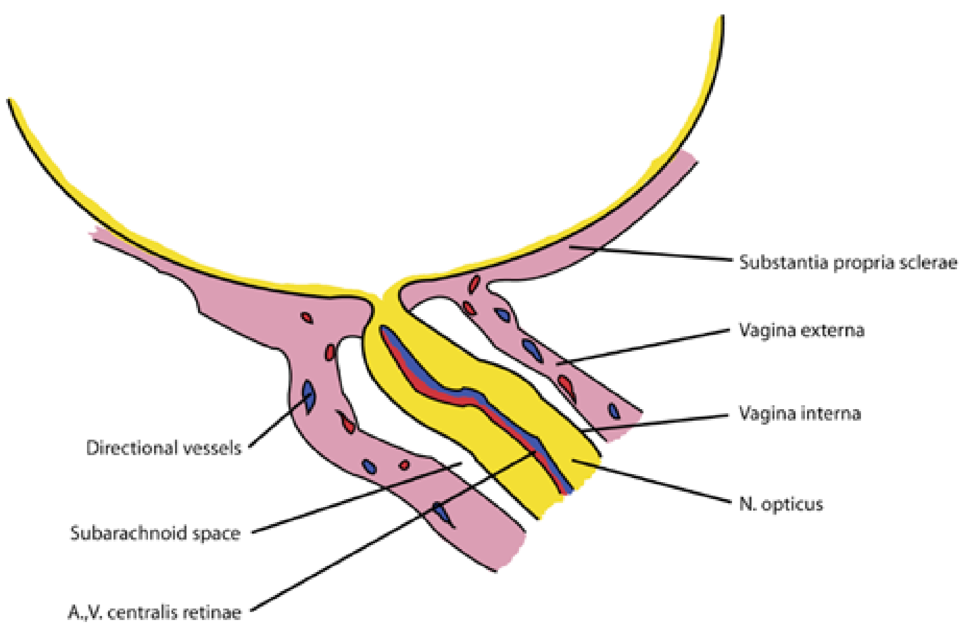

Figure 1. *Diagram of directional vessels in tunica externa of the optic nerve visualized by CEUS and used as an anatomical marker of the outer border of the subarachnoid space. (The structures are not drawn to scale.)*

demonstrator. The data obtained on that subject were not included in the analysis because the blinding procedure could not have been assured. Contrast–enhanced ultrasound (CEUS) and MRI of the ONSD were performed on the method demonstrator, for the purpose of training the readers. Contrast–enhanced ultrasound was performed on a high–end ultrasound system (Aplio XG, Toshiba Medical Systems, Otawara, Japan), using a linear transducer (PLT–704SBT, 4.8–11 MHz). The settings of the mechanical index (MI) were adjusted to a range that was consistent with the application of contrast (MI 0.04–0.07). A second–generation contrast agent was used (Sonovue™, Bracco Imaging S.p.A., Milano, Italy), of which5 mL from the commercially available kit was injected through a peripheral line. The scan was recorded on a picture archiving and communication system (PACS) (IMPAX Enterprise, Agfa Healthcare NV, Mortsel, Belgium) in a Digital Imaging and Communications in Medicine (DICOM) format as a clip. The imaging modalities used included low MI imaging without any superimposed technique, and with the use of dynamic flow imaging in the same scans. The scan was done in a transverse plain on the right eye only. Minimal, constant pressure was maintained on the bulb throughout the scan. No specific instructions were given to the subject about the gaze position. The only goal was to maintain the best possible image of the retrobulbar space including the optic nerve sheath complex for as long as possible. No analyses or measurements were performed online.

The MRI was performed on a 3T whole body system GE Signa HDxt (GE Healthcare, Little Chalfont, UK). The head of the subject was placed on an8–channelhigh–resolution brain coil. The 3D Fiesta – C sequence was used (TR 5.7 msec, TE 2.3 msec, slice thickness 0.6 mm with 0.3 mm overlap, Matrix 448X416, field of view 30×24 zip, number of averages 1.39, scan time 4:37 min, image acquisition in parasagittal plane). The data was reconstructed on a GE ADW 4.4 workstation (GE Healthcare) with 1 mm precision in the sagittal, coronal, and transverse plains. The images obtained were recorded on a PACS (IMPAX Enterprise, Agfa Healthcare NV, Mortsel, Belgium). Both datasets recorded in the DICOM format were transferred to a workstation, on which DICOM viewing software (Osirix ver. 5.0.1, 64 bit, Pixmeo SARL, Bernex, Switzerland)was running, for evaluation of the measurement tools.

The exact protocol was used for image acquisition in the nine remaining subjects. After collection of the datasets, the data for both CEUS and MRI was anonymized and labeled with randomly generated numbers. The labels from the CEUS dataset and those from the MRI dataset did not correspond. The key with which they could have been linked was not known to the evaluators during the analysis.

The exact measuring procedure was demonstrated on the method demonstrator dataset. The collected images were reviewed and three measurements were recorded for both CEUS and MRI datasets, thereby completing the demonstration of measurement procedure.

One senior experienced neuroradiologist, one senior radiology resident, and one senior surgery resident

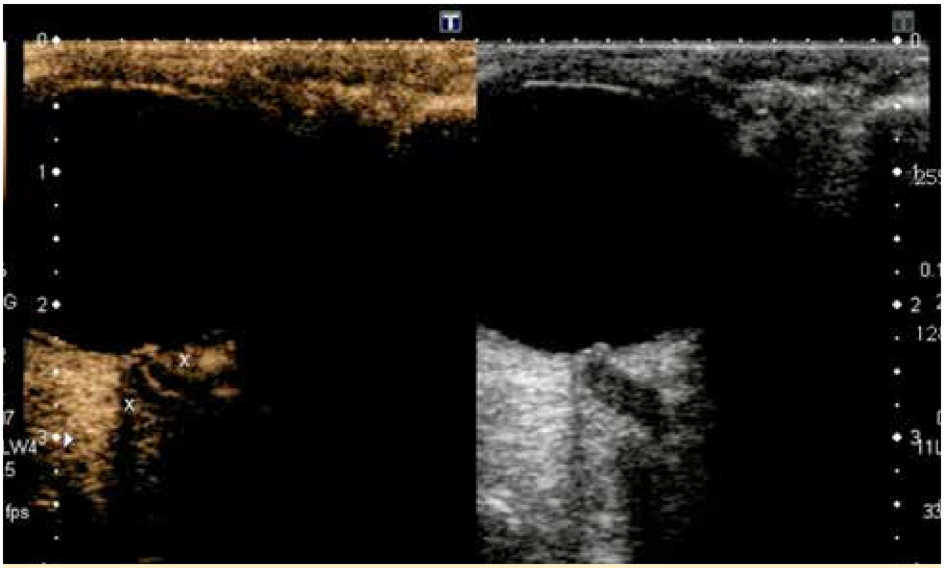

Figure 2. *Still image of the hyperechogenic ultrasonic contrast flowing in a.,v. centralis retinae and in directional vessels in the tunica externa (marked with x) of the optic nerve.*

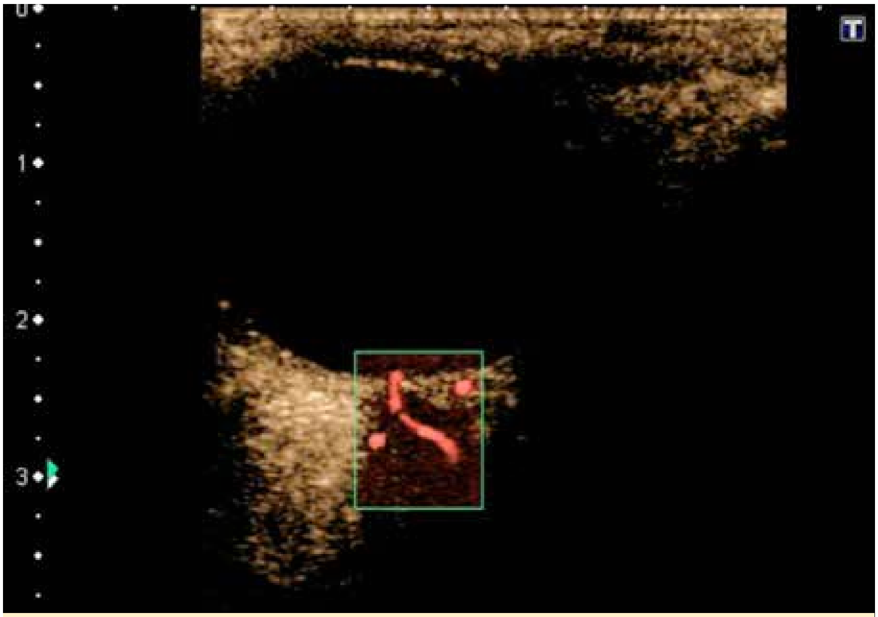

Figure 3. *Still image of the ultrasonic contrast flowing in a.,v. centralis retinae and in directional vessels in the tunica externa, visualization of ultrasonic contrast flow is augmented with dynamic flow imaging (red marks).*

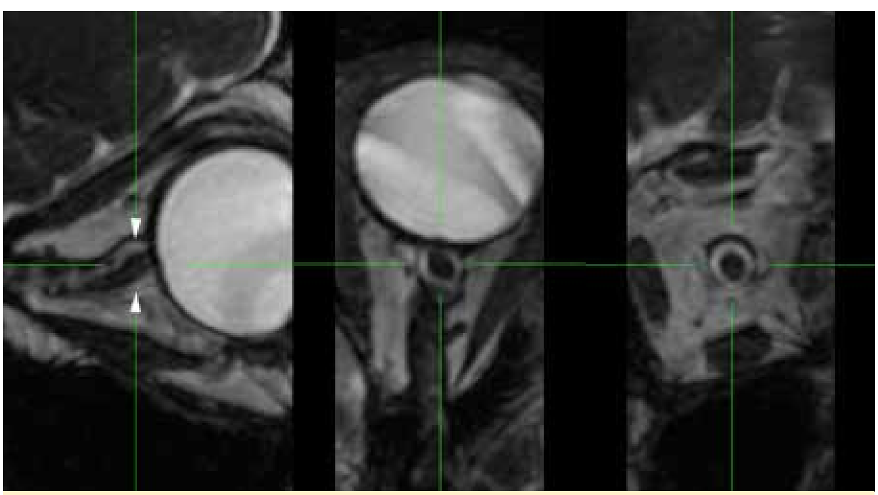

Figure 4. *Orthogonal multi planar reconstruction of the MRI of the optic nerve with subarachnoid space being clearly hyperintensive. Outer boundary of subarachnoid space 3 mm behind the bulb is marked with arrowheads in first projection.*

evaluated the anonymized CEUS and MRI datasets of the remaining nine subjects. The CEUS and MRI datasets of each subject were evaluated separately, in conformity with the procedure demonstrated on the method demonstrator dataset.

Measuring technique

The entire length of the recorded clip of the CEUS scan was examined. The visible flows of contrast through the a. and v. centralis retinae were identified, as well as that through a highly directional complex of vasculature in the tunica externa of the optic nerve (Figure 2). The same structures were identified and observed with the use of dynamic flow imaging. For definition of the measurement points, three images were selected, in which central and lateral signals were clearly visible on dynamic flow imaging. Measurements were taken using those three images, 3 mm posterior to the eye bulb, perpendicular to the direction of the a. and v. centralis retinae, and measurement points were defined as the inner borders of both lateral signals on dynamic flow imaging (Figure 3).

The MRI images were inspected in the sagittal, transverse, and coronal planes. The structure observed was the outer border of the hyperintensive area, surrounding the isointense to hypointense signal of the optic nerve. The measurement points were defined as the outer border of the hyperintensive area surrounding the optic nerve, 3 mm posterior to the eye bulb, and perpendicular to the course of the optic nerve (Figure 4). Three images were selected based on the best visibility of the defined measurement points, and three measurements were taken and recorded. No differentiation between the different planes was attempted. The only criterion considered was good visibility of the measurement points.

RESULTS

The mean values and standard deviations of the measurements of the ONSD for all nine subjects are given in Table 1. Bland–Altman plots were constructed to compare MRI and CEUS measurements from each of the three raters separately (Figs. 5–7); another plot was constructed for all three raters combined, using averages of the three measurements taken by each rater (Fig. 8); and another plot was constructed for all three raters combined, using non–averaged measurements of all three raters (Fig. 9). For the first rater, the limits of agreement were –0.34 mm to + 0.39 mm (SD 0.0187). For the second rater, the limits of agreement were –0.25 mm to + 0.32 mm (SD 0.0144). For the third rater, the limits of agreement were –0.25 mm to + 0.31 mm (SD 0.0142). The limits of agreement for the averages of the measurements of the three raters were –0.20 mm to + 0.25 mm (SD 0.0114). The limits of agreement using non–averaged measurements of the three raters were –0.29 mm to + 0.35 mm (SD 0.0162). The Bland–Altman plots show favorable

Table 1. *Mean values and standard deviations [mm] of optic nerve sheath diameter for contrast enhanced ultrasound (CEUS) and magnetic resonance imaging (MR).*

Subject	CEUS (SD) [mm]	MRI (SD) [mm]
1	5.45 (0.08)	5.54 (0.07)
2	4.68 (0.10)	4.81 (0.09)
3	4.26 (0.09)	4.16 (0.06)
4	5.20 (0.10)	5.20 (0.10)
5	5.50 (0.11)	5.63 (0.08)
6	5.40 (0.13)	5.29 (0.10)
7	5.74 (0.07)	5.92 (0.14)
8	5.93 (0.08)	5.88 (0.09)
9	5.03 (0.06)	5.03 (0.07)

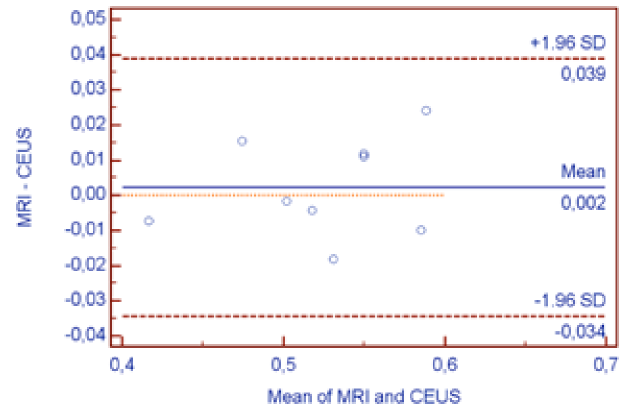

Figure 5. *Bland – Altman plot comparing measurements of the ONSD using the described CEUS and MRI method for the first rater.*

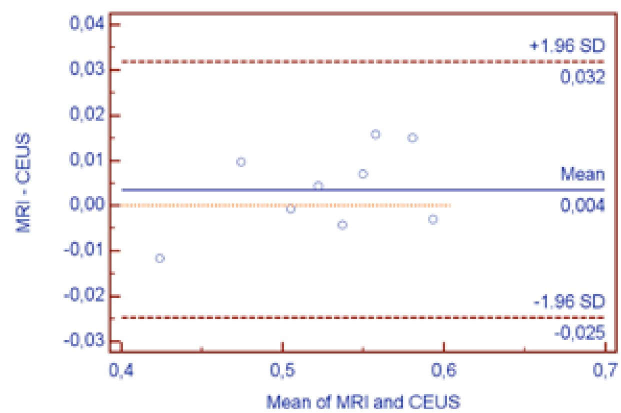

Figure 6. *Bland – Altman plot comparing measurements of the ONSD using the described CEUS and MRI method for the second rater.*

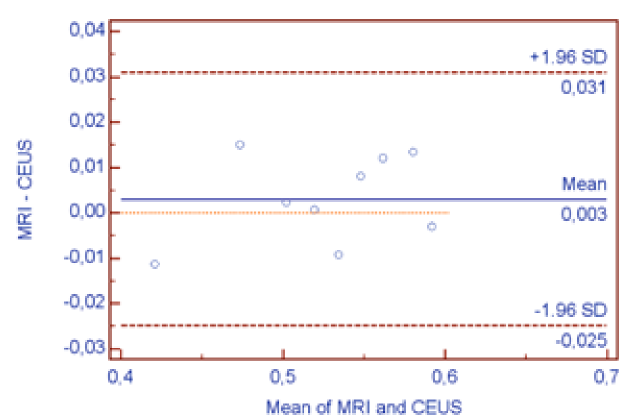

Figure 7. *Bland – Altman plot comparing measurements of the ONSD using the described CEUS and MRI method for the third rater.*

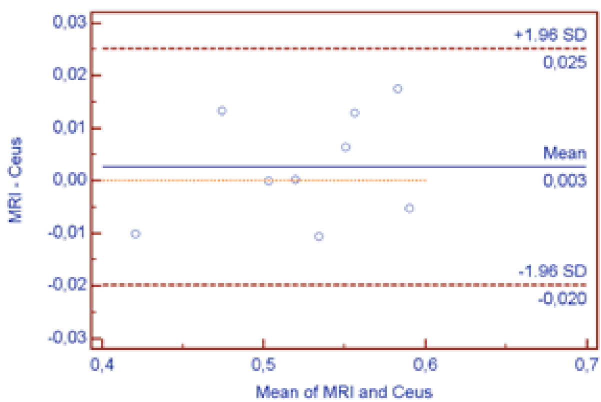

Figure 8. Bland – Altman plot comparing measurements of the ONSD using the described CEUS and MRI method for averages of measurements of all raters.

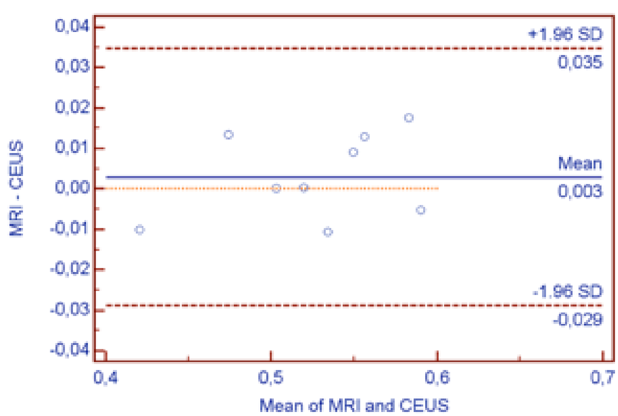

Figure 9. Bland – Altman plot comparing measurements of the ONSD using the described CEUS and MRI method for non–averaged measurements of all raters.

agreement between both methods, within clinically acceptable limits of agreement. To assess inter–rater reliability, the intra class correlation coefficient (ICC) was calculated, using the absolute agreement model. For CEUS single measures, the ICC was 0.9965 with a 95% confidence interval of 0.9891 to 0.9991. For MRI single measures, the ICC was 0.9923 with a 95% confidence interval of 0.9771 to 0.9981. The measurements recorded with the CEUS technique seemed to be just as reproducible as those recorded with high definition MRI.

For statistical analyses, statistical software was used (IBM SPSS Statistics ver. 20™, IBM Corp, MedCalc for Windows ver. 12.3.0.0, MedCalc Software, Mariakerke, Belgium).

No adverse reactions were recorded during the examinations, and none of the subjects reported any adverse reactions on a follow–up visit, 30 days after imaging was performed.

DISCUSSION

In sonographic terms, the ONSD is comparatively small. Therefore, the measurement of relatively small changes in its diameter can be a daunting task, especially within the setting of acute and emergency medicine. The paramount importance of the correct interpretation of ultrasound anatomy and possible artifacts has been emphasized in previous studies (1,3, 4,16,17). It has already been established that the occurrence of artifacts that affect the correct anatomical identification of measurement points is more frequent when the probe is positioned horizontally (1,3). However, the horizontal position of the probe is on many occasions, the preferred position in emergency situations, as it can be rapidly achieved and evaluation of the pupillary reflex can be simultaneously performed with only slight repositioning of the probe. Furthermore, minimal pressure is exerted on the eye bulb, thereby avoiding bulbar compressions and possible related complications. In emergency and acute medicine situations, the transducer cover or other spacer that can be discarded after use on a single patient, is warranted, thus generating another set of haphazard artifacts that affect the correct anatomical identification of the measurement points. Using the CEUS to delineate the measurement points exactly, we tried to demonstrate the possibility of facilitating the correct identification of anatomical landmarks, using the directional vascular structures in the vagina externa of the optic nerve. We tried to show that correct sonographic identification is quite straightforward and independent of the possible retrobulbar and other sonographic artifacts, because the measurement points are visualized as a visible flow of contrast through the marker vascular structures. This fact is reflected by favorable agreement of the results obtained using CEUS, with those obtained using high–resolution MRI, and by the reproducibility of measurements recorded by different raters using CEUS that was comparable with that achieved using high–resolution MRI. However, the sample in our study was small, reflecting the proof of concept nature of the study.

CONCLUSION

The use of ultrasonic contrast is safe and simple. The interpretation of sonographic anatomy, using ultrasonic contrast in marker vascular structures becomes much easier, as it is not prone to motion artifacts, in comparison to color Doppler or power Doppler alone. The other B–mode artifacts can also be easily recognized as such, because the actual flow of contrast through the marker vascular structures is visible in real time. The learning curve was not evaluated in this study; however, it is expected to be quite steep.
The described method has to be evaluated on a larger sample and a greater number of raters, to establish accuracy of the ONSD measurement in comparison to high–resolution MRI in a healthy population. Furthermore, the utility of the method has to be evaluated on patients with raised intracranial pressure who have an ICP monitoring device implanted, to establish the assumed correlation with raised ICP and establish a cut–off value for normal ICP.
Initial examinations of the ongoing clinical study on patients with raised ICP and an implanted ICP monitoring device in our surgical intensive care unit show promising initial results. In addition, the effects of mannitol can be observed in real time, using the described CEUS technique (unpublished data).

LIST OF ABBREVIATIONS

ONSD; optic nerve sheath diameter
ICP; intracranial pressure
MRI; magnetic resonance imaging
MI; mechanical index

COMPETING INTERESTS

The authors declare that they have no competing interests.

ACKNOWLEDGMENTS

Mirjana Brvar provided help with the contrast–enhanced ultrasound and invaluable knowledge on its scope and limitations that enabled us to conduct the study. Robert Pintarič conducted all the MRI scans and provided technical support concerning image acquisition and archiving on the PACS systems; he also oversaw the blinding procedure.

REFERENCES

1. Steinborn M, Fiegler J, Kraus V, Denne C, Hapfelmeier A, Wurzinger Let al. High resolution ultrasound and magnetic resonance imaging of the optic nerve and the optic nerve sheath: anatomic correlation and clinical importance.Ultraschall Med 2011, 32:608–13.
2. Soldatos T, Chatzimichail K, Papathanasiou M, Gouliamos A: Optic nerve sonography: a new window for the non-invasive evaluation of intracranial pressure in brain injury.Emerg Med J 2009, 26:630–4.
3. Moretti R, Pizzi B, Cassini F, Vivaldi N: Reliability of optic nerve ultrasound for the evaluation of patients with spontaneous intracranial hemorrhage. Neurocrit Care 2009, 11:406–10.
4. Newman WD, Hollman AS, Dutton GN, Carachi R: Measurement of optic nerve sheath diameter by ultrasound: a means of detecting acute raised intracranial pressure in hydrocephalus.Br J Ophthalmol 2002, 86:1109–13.
5. Dubourg J, Javouhey E, Geeraerts T, Messerer M, Kassai B: Ultrasonography of optic nerve sheath diameter for detection of raised intracranial pressure: a systematic review and meta-analysis. Intensive Care Med 2011:1–10.
6. Fagenholz PJ, Gutman JA, Murray AF, Noble VE, Camargo CA, Harris NS: Optic nerve sheath diameter correlates with the presence and severity of acute mountain sickness: evidence for increased intracranial pressure.J. Appl. Physiol. 2009, 106:1207–11.
7. McAuley D, Paterson A, Sweeney L: Optic nerve sheath ultrasound in the assessment of paediatric hydrocephalus.Childs Nerv Syst 2009, 25:87–90.
8. Le A, Hoehn ME, Smith ME, Spentzas T, Schlappy D, Pershad J. Bedside sonographic measument of optic nerve sheath diameter as a predictor of increased intracranial pressure in chuldren. Ann Emerg Med 2009,53:758-91.
9. Beare NAV, Kampondeni S, Glover SJ, Molyneux E, Taylor TE, Harding SP et al.: Detection of raised intracranial pressure by ultrasound measurement of optic nerve sheath diameter in African children. Trop. Med. Int. Health 2008, 13:1400–4.
10. Goel RS, Goyal NK, Dharap SB, Kumar M, Gore MA: Utility of optic nerve ultrasonography in head injury.Injury 2008, 39:519–24.
11. Sutherland AI, Morris DS, Owen CG, Bron AJ, Roach RC: Optic nerve sheath diameter, intracranial pressure and acute mountain sickness on Mount Everest: a longitudinal cohort study.Br J Sports Med 2008, 42:183–8.
12. Verzel D, Gračner T: Spectral domain optical coherence tomography for detecting glaucoma. Acta medico-biotechnica 2014, Vol. 7: 32-40.
13. Geeraerts T, Newcombe VFJ, Coles JP, Abate MG, Perkes IE, Hutchinson PJA et al.: Use of T2-weighted magnetic resonance imaging of the optic nerve sheath to detect raised intracranial pressure. Crit Care 2008, 12:R114.
14. Kimberly HH, Noble VE: Using MRI of the optic nerve sheath to detect elevated intracranial pressure.Crit Care 2008, 12:181.
15. Shirodkar CG, Rao SM, Mutkule DP, Harde YR, Venkategowda PM, Mahesh MU: Optic nerve sheath diameter as a marker for evaluation and prognostication of intracranial pressure in Indian patients: An observational study. Indian J Crit Care Med. 2014 Nov;18 (11):728-34.
16. Rajajee V, Vanaman M, Fletcher JJ, Jacobs TL: Optic nerve ultrasound for the detection of raised intracranial pressure.Neurocrit Care 2011, 15:506–15.
17. Rifenburg RP, Williams JJ: Optic nerve head drusen: a case of false-positive papilledema discovered by ocular ultrasound in the emergency department. Crit Ultrasound J 2010, 2:75–6.