Comparison of brain vessel imaging from transtemporal and transcondylar approaches using contrast-enhanced transcranial color-coded duplex sonography and Virtual Navigator

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Aims. The transcondylar approach is a new and used for detection of chronic cerebro-spinal venous insufficiency (CCSVI) and intracranial venous reflux in patients with multiple sclerosis. The aim of this study was to assess the ability of native and contrast enhanced (CE-) transcranial color-coded duplex sonography (TCCS) to detect flow and reflux in deep cerebral veins and intracranial venous sinuses from transcondylar and transtemporal approaches.

Methods. Brain magnetic resonance imaging and TCCS from transtemporal and transcondylar approaches using the new technology – Fusion Imaging – in 8 volunteers and 5 patients with multiple sclerosis.

Results. Using TCCS and CE-TCCS, the arteries of the circle of Willis could be detected from the transtemporal approach in 13/13 subjects in both examinations, while detection of the venous system was possible in 7/13 and 9/13 subjects, respectively. However, the arteries of the circle of Willis and venous system were detected through the transcondylar approach in only 5/13 ($P=0.041$) and 1/13 ($P=0.031$) subjects using TCCS, and in 12/13 ($P=0.921$) and 7/13 ($P=0.687$) subjects using CE-TCCS, respectively.

Conclusions. The results reveal that the TCCS transcondylar approach has serious limitations for the standard detection of intracranial venous reflux.

Key words: ultrasound, magnetic resonance imaging, reflux, venous system, fusion imaging, Virtual Navigator

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INTRODUCTION

Chronic cerebro-spinal venous insufficiency (CCSVI) is a vascular syndrome first defined by Zamboni et al., who assumed its association with multiple sclerosis (MS) (ref.^{1,2}). This hypothesis however has been questioned in several studies and requires confirmation and further investigation³.

The CCSVI theory is based on the fact that deoxygenated blood flow from the brain and spinal veins is slowed down or blocked on its way back to the heart. This condition arises mainly from blockage in the internal jugular (IJV) and/or azygous veins¹. A reflux, i.e. venous blood flow to the brain, can occur during specific respiration phases, either in the IJVs, the vertebral veins (VVs) or in intracranial veins (deep cerebral veins – DCVs, sinuses and veins draining subcortical gray matter – VDSGM) (ref.¹).

The diagnosis and severity assessment of CCSVI are performed by sonographic examination of neck veins (IJVs and VVs) and intracranial veins (DCVs, sinuses and VDSGM), examined both in sitting and supine positions⁴.

CCSVI diagnosis is currently based on five ultrasound (US) criteria related to vein morphology and venous blood flow: 1) reflux constantly present in an outflow pathway (IJV and/or VV) with the patient's head at 0° (supine position) and 90° (sitting/standing position); 2) reflux present in the DCVs and/or sinuses; 3) high-resolution B-mode evidence of proximal IJV stenosis and/or other B-mode anomalies; 4) no flow detection in the IJVs and/or VVs despite deep inspirations in both positions (0° and 90°) or, alternatively, in one position, with reflux in the same vessel in the other position; and 5) negative difference between IJV cross-sectional areas (CSA) measured with the patient's head at 0° and 90°.

The assessment of a number of criteria, equal or superior to 2 yields a positive diagnosis for CCSVI (ref.²). The examination of the same veins and sinuses, plus the observation of the VDSGM, enables calculation of the venous hemodynamic insufficiency severity score (VHISS 0-16) for the assessment of the severity of the venous hemodynamic condition of the patient⁴.

The changes in blood flow in the intracranial veins are crucial for the CCSVI theory. The DCVs and sinuses

are imaged through the condylar US bone window (transcondylar approach) at the level of the condyloid process of the mandible⁵. Nevertheless, the main limitation of a transcranial sonographic examination is the insufficiency of the bone window. Although the detection of pathological flow in the intracranial veins is crucial for the CCSVI theory, the quality of the condylar US bone window and its affect on venous flow detection have not been studied yet.

The aim of the study was to assess the ability of the native and contrast-enhanced (CE) transcranial color-coded duplex sonography (TCCS) to detect flows and refluxes in deep cerebral veins and intracranial venous sinuses by transcondylar and transtemporal US approaches.

MATERIALS AND METHODS

Subjects

Eight healthy volunteers and five MS patients underwent brain magnetic resonance imaging (MRI) and sonographic examination of cervical and intracranial arteries, veins and sinuses after providing informed consent. Inclusion criteria were the subject's ability to perform a prolonged inspiration without moving the head and age 25-45 years. Exclusion criteria were any contra-indication to MRI and neurological diseases other than MS.

Magnetic resonance image acquisition

The Virtual Navigator registration procedure required for synchronization between US data and the MRI volume dataset consists of two phases: first an anatomical marker registration, considering a subject's external facial landmarks, then a fine tuning to refine the synchronization between the two imaging modalities using internal cerebral anatomical landmarks. For the first phase, the registration pen was used to point at eight anatomical landmarks on the subject's face, which were then matched with the same points targeted on the MRI volume rendering on the US system: four points at the sides of the eyes, one point in the middle of the eyes, one point on the tip of the nose and two points on the sides of the nose. The precision of this first part of the registration procedure resulted in an average craniocaudal error of 0.5 cm (range 0-0.7 cm) and an average lateral shift of 0.1 cm (range 0-0.5 cm). The second phase was based on selecting internal cerebral anatomical landmarks visible both on the second imaging modality dataset (MRI) and during the US real-time scanning. The internal anatomical markers consisted of the midbrain, the middle cerebral artery and the circle of Willis, acquired through the US temporal bone window. A suitable video overlap between the two imaging modalities was a valuable tool for an immediate visual check of the registration precision level.

For every subject, a proton density (PD) MRI brain volume was acquired using a 1.5 Tesla scanner (Siemens Magnetom Avanto, Erlangen, Germany), with a maximum gradient strength of 33 mT/m and a slew rate of 125 mT/m/ms, using a standard 12-channel matrix head coil. The following pulse sequences were acquired from

all subjects: 1) scout T1 sequence: three sagittal slices, three coronal slices and one axial slice with low resolution (voxel size = $2.2 \times 1.1 \times 6 \text{ mm}^3$) for positioning and orientation of the next sequences; 2) PD turbo spin echo, with the following parameters: TR = 3270 ms, TE = 32 ms; echo train length = 5; flip angle = 150° , 50 interleaved, 2.5-mm thick axial slices with a matrix size = 256×256 , interpolated to 512×512 , and a field of view (FOV) = $250 \times 250 \text{ mm}$. The acquisition time was approximately 7 min. The central slice of the slab was positioned to run parallel to a line that joins the most inferior-anterior and inferior-posterior parts of the corpus callosum⁶, visible on the sagittal scout T1. This standard guarantees the reproducibility of the acquisition protocol and the covering of all the brain, with particular attention paid to the inclusion of six fiducial markers inside the FOV.

Transcranial color-coded duplex sonography examination and navigation procedures

An Esaote MyLabTwice US system (Esaote S.p.A., Genova, Italy) and Esaote PA240 Phased Array Probe (Operating Bandwidth: 1-4 MHz; B-Modes Frequencies: 2.0-3.3 MHz; CFM-PW Frequencies: 1.6-2.5 MHz) were used for both the TCCS and CE-TCCS examinations. The US system was equipped with the Virtual Navigation (Esaote S.p.A., Genova, Italy - MedCom GmbH, Darmstadt, Germany) option⁷, which allows real-time image fusion of TCCS or CE-TCCS and PD-weighted MRI images, previously transferred to the US system. The US scanner with a 639-039 CIVCO Reusable Tracking Bracket (CIVCO, Kalona, IA, USA) with sensor mount, was used. The acoustic lens, which covers the borders of the probe, forms a soft envelop, in order to enhance the patient comfort during the transcranial examination, which may have a slightly longer duration for obtaining a correct and complete view of the cerebral hemodynamic situation. The Virtual Navigator procedures were implemented using an electromagnetic tracking system, composed of a transmitter and a small receiver, mounted on the US probe. The transmitter position, which is considered the origin of the reference system, was fixed through a support, and the receiver provided the position and orientation of the US probe in relation to the transmitter⁸.

Examinations were carried out by a well-trained sonographer (with 16 years of TCCS experience) for the venous intracranial evaluations with TCCS and CE-TCCS from transtemporal and transcondylar approaches. For both the TCCS and CE-TCCS examinations, a proper head support was also used in order to keep the subject's head as steady as possible. Each subject was examined in the supine position on a horizontal bed (i.e., 0° tilt) with the US system through both transcranial windows; the temporal periauricular window and condylar US bone window at the level of the condyloid process of the mandible.

MRI imaging was switched off on the US system during targeting and examining image fusion procedures of the intracranial arteries (siphon of the internal carotid artery, anterior cerebral artery, middle cerebral artery, posterior cerebral artery), veins (deep middle cerebral vein, basal vein of Rosenthal) and sinuses (superior

petrosal sinus, inferior petrosal sinus, cavernous sinus, transversal sinus, confluens sinuum). The B-mode with color Doppler modality was used to select the addressed vessels. Selected vessels, targeting quality, and view direction (Fig. 1) were checked by means of the image fusion between PD MRI and TCCS/CE-TCCS. A positive result was evaluated when at least one artery of the circle of Willis and one DCV or sinus were detected.

A 5-mm pulsed wave Doppler (PW) sample volume was then positioned into the imaged vessel for acquisition of the blood flow curve and the angle corrected peak systolic velocity (PSV), end-diastolic velocity (EDV), pulsatility index (PI) and resistive index (RI) were measured. The intracranial arteries, veins and sinuses were evaluated through the transtemporal US approach and afterwards through the transcondylar approach. A fine tuning procedure using internal anatomical reference points was performed periodically every 2 min to prevented loss of matching.

Application of the echocontrast agent

After the native TCCS examination of intracranial vessels was made, the echocontrast agent SonoVue® (Bracco, Milan, Italy) was used for the CE-TCCS examination. A total volume of 2.5 mL of SonoVue® was slowly infused to the cubital vein, and intracranial vessels from transcranial and transcondylar TCCS approaches were examined applying the same native TCCS examination protocol.

Duplex sonography of cervical arteries and veins

The Esaote MyLabTwice US system (Esaote S.p.A., Genova, Italy) and Esaote LA332 Linear Array Probe

(Operating Bandwidth: 3-11 MHz) were used for the duplex sonographic examination of cervical arteries (common carotid artery, internal carotid artery, external carotid artery, vertebral artery) and veins (internal jugular vein, vertebral vein) bilaterally in both longitudinal and transversal sections. The proximal IJV stenosis and other IJV anomalies and a negative difference between IJV CSA measured with the patient in supine (0°) and sitting (90°) positions were evaluated in B-mode. Blood flow including its direction was imaged in the color Doppler mode in all vessels during inspiration and expiration phases. Angle-corrected peak PSV, EDV, PI and RI were measured in all vessels in PW Doppler mode. The presence of a reflux in both supine (0°) and sitting (90°) positions was evaluated during inspiration and expiration phases.

Statistics

The normality of distribution was checked by the Shapiro-Wilk test. Data with a normal distribution are reported as means $\pm$ standard deviation. All parameters not fitting a normal distribution are presented as means, medians and interquartile range. The registration error obtained by the corresponding fiducial markers procedure using the root mean square error and the system accuracy measured with the registration pen was evaluated. The McNemar-Bowker test for paired data was used to compare vessel imaging acquisitions through the transcondylar and transtemporal approaches using TCCS and CE-TCCS. $P < 0.05$ was considered statistically significant. Data were analyzed using statistical software SPSS version 15.0 (SPSS Inc., Chicago, IL, USA).

Fig. 1. Fusion Imaging of brain MRI and TCCS images.

Ethical aspects

The entire study was conducted in accordance with the Helsinki Declaration of 1975 (as revised in 2004 and 2008). The study was approved by the local ethics committee. All subjects provided informed consent.

RESULTS

During two days of examinations, eight healthy volunteers (3 men, 5 women; age 26-42, mean 33.5 ± 5.1 years) and five MS patients (1 man, 4 women; age 28-41, mean 34.2 ± 4.6 years) were enrolled in the study (Table 1). All subjects underwent brain MRI and sonographic examinations of cervical and intracranial arteries, veins and sinuses from transtemporal and transcondylar approaches using the fusion imaging technique.

Measured using a registration pen, the root mean square error was < 0.5 cm and the accuracy of the system was < 1 mm for all subjects. The mean time for the complete sonographic examination including the fusion imaging procedure was 34.2 ± 5.3 min. The duration of

the separate TCCS examinations from the transtemporal and transcondylar approaches was 11.5 ± 2.1 min. The complete registration phase took an average of 4 min.

All 4 examined arteries of the circle of Willis were detected through the transtemporal TCCS approach in 13 out of the 13 subjects and, in all subjects, PSV, EDV, PI and RI were measured (Table 2). There were no significant differences between patients and healthy controls in PSV, EDV, PI, or RI ($P > 0.05$ in all cases). At least one DCV or sinus was detected from the transtemporal TCCS approach in 7 out of the 13 subjects. All intracranial DCVs and sinuses except cavernous sinus were detected in 4 subjects.

At least one artery of the circle of Willis and one DCV or sinus were detected from the transcondylar TCCS approach in only five out of the 13 subjects ($P = 0.041$) and one out of the 13 subjects ($P = 0.031$), respectively (Table 3). No intracranial arteries, DCVs or sinuses were detected in any subject. After the administration of the echocontrast agent, an increased number of imaged vessels was registered, significantly more frequently compared to the transcondylar US approach

Table 1. Demographic data of enrolled subjects.

	MS patients	Healthy volunteers
Number of subjects	5	8
Age, mean $\pm$ SD; years	34.2 ± 4.6	33.5 ± 5.1
Male gender; n (%)	1 (20.0 %)	3 (37.5 %)
Duration of the disease, mean $\pm$ SD; years	6.2 ± 1.6	NA
EDSS scale – median (min, max, IQR)	1 (0; 4.5; 1 – 1)	NA

EDSS – Expanded Disability Status Scale; IQR – interquartile range; MS – multiple sclerosis; NA – not applicable; SD – standard deviation

Table 2. Blood flow parameters measured from transtemporal approach using non-contrast enhanced TCCS.

	PSV; mean $\pm$ SD (cm/s)	EDV; mean $\pm$ SD (cm/s)	PI; mean $\pm$ SD	RI; mean $\pm$ SD
Siphon of ICA	101.2 ± 11.4	48.4 ± 4.7	0.81 ± 0.05	0.52 ± 0.02
Middle cerebral artery	131.2 ± 13.1	67.8 ± 5.1	0.83 ± 0.05	0.54 ± 0.02
Anterior cerebral artery	92.7 ± 6.3	44.6 ± 3.3	0.82 ± 0.04	0.53 ± 0.02
Posterior cerebral artery	55.5 ± 6.2	25.2 ± 2.7	0.81 ± 0.04	0.53 ± 0.02
Superior petrosal sinus	34.2 ± 2.6	24.7 ± 2.7	–	0.28 ± 0.04
Inferior petrosal sinus	31.8 ± 2.1	23.8 ± 2.4	–	0.35 ± 0.05
Transversal sinus	27.1 ± 2.9	17.1 ± 2.0	–	0.35 ± 0.05
Confluens sinuum	17.1 ± 2.4	11.8 ± 2.1	–	0.31 ± 0.04
Deep middle cerebral vein	12.7 ± 1.8	8.7 ± 1.3	–	0.29 ± 0.06
Basal vein of Rosenthal	13.8 ± 1.9	9.2 ± 1.2	–	0.33 ± 0.05

EDV – end-diastolic velocity, ICA – internal carotid artery, PI – pulsatility index, PSV – peak systolic velocity, RI – resistive index, TCCS – transcranial color-coded duplex sonography

Table 3. Comparison of intracranial vessels detection between transtemporal and transcranial ultrasound approaches.

	Transtemporal approach	Transcondylar approach	<i>P</i>
Detection of at least one intracranial artery using TCCS, n (%)	13 (100 %)	5 (38.5 %)	0.041
Detection of at least one intracranial vein or sinus using TCCS, n (%)	7 (53.8 %)	1 (7.7 %)	0.031

TCCS – transcranial color-coded duplex sonography

Table 4. Comparison of intracranial vessels detection between transcranial color-coded duplex sonography (TCCS) and contrast enhanced transcranial color-coded duplex sonography (CE-TCCS).

	TCCS	CE-TCCS	<i>P</i>
Detection of at least one intracranial artery using transtemporal approach, n (%)	13 (100 %)	13 (100 %)	1.000
Detection of at least one intracranial artery using transcondylar approach, n (%)	5 (38.5 %)	12 (92.3 %)	0.016
Detection of at least one intracranial vein or sinus using transtemporal approach, n (%)	7 (53.8 %)	9 (69.2 %)	0.500
Detection of at least one intracranial vein or sinus using transcondylar approach, n (%)	1 (7.7 %)	7 (53.8 %)	0.031

TCCS – transcranial color-coded duplex sonography; CE-TCCS – contrast enhanced transcranial color-coded duplex sonography

(Table 4). Administration of the echocontrast agent led to non-significant differences in the number of imaged arteries or veins and sinuses from the transtemporal and transcondylar approaches (Table 3). Intracranial venous reflux was not detected in any subject. The bidirectional Doppler signal from the region of the cavernous sinus detected in three subjects was evaluated as a breathing artifact (Fig. 2).

A reflux in IJV was detected in three MS patients but only unilaterally and only in the supine (0°) position with normalization of blood flow in the sitting (90°) position in all cases. No pathological blood flow in the IJV was detected in healthy volunteers. No reflux in VVs, DCVs or intracranial sinuses, negative difference between IJV CSA nor proximal IJV B-mode anomalies were detected in any subject.

DISCUSSION

The transcondylar TCCS approach was recently introduced for the assessment of the intracranial venous system, mainly for the detection of the blood flow reflux in MS patients⁵. It has gained particular attention within the scientific community due to its novelty and unconventionality⁹, compared to the conventional transtemporal and transoccipital US approaches¹⁰. Nevertheless, the quality of the bone window was its main limitation, similar to the transtemporal, transoccipital and transfrontal approaches.

The results of the present study demonstrated that an insufficient bone window was significantly more frequent in the transcondylar US approach, where the intracranial venous system was detected in only one out of the 13 (7.7%) middle-aged subjects, than in the transtemporal one. However, a detection of the reflux in DCVs and/or sinuses from the transcondylar approach is one of five

Fig. 2. Fusion Imaging technique: Breathing artifact in the region of cavernous sinus detected by transcranial color-coded duplex sonography from transcondylar approach using Doppler mode.

signs of CCSVI diagnosis and the most important one from the pathophysiological point of view.

Due to technical difficulties in the assessment of the morphology and flow characteristics of intracranial veins through the transcondylar bone window, fusion imaging technology using the Virtual Navigator tool was used in the study. The possibility of using of this technology was published recently^{11,12}. DCVs and sinuses are located at a depth of 6-8 cm from the US probe, their diameter is only 2-4 mm, and they run parallel to the skull (ref.¹⁰). The venous blood flow is slow (0.10-0.40 m/s) and it is affected by the respiratory phase⁸. Moreover, the cavernous sinus is located close to the nasal space, and the respiration air flow may imitate the venous blood flow. Fusion imaging technology is able to help with the correct detection of venous blood flow due to real-time fusion of MRI and TCCS images, where the venous system was imaged using brain MRI and venous blood flow was encoded to the MRI image using the color Doppler mode^{8,11,12}. The accuracy of the system measured using a registration pen was excellent (< 1 mm) with the root mean square error < 0.5 cm. These results are in accord with those of previous studies^{7,8,13}.

The improvement of the blood flow detection from intracranial arteries, veins and sinuses can be achieved by the echo-contrast agent application. The echo-contrast agent SonoVue[®] was used in the study. Slow intravenous administration of SonoVue[®] lead to a 10-20 dB increase in the Doppler signal obtained from intracranial vessels¹⁴. Using CE-TCCS, the number of patients with detected DCVs or intracranial sinuses increased by 29% via the transtemporal US approach and, even by seven times via the transcondylar US approach, compared to the native TCCS. These results show that CE-TCCS is more suitable for intracranial venous flow detection than native TCCS. Nevertheless, the ability of CE-TCCS to detect intracranial venous reflux has not been tested yet.

The limited number of examined subjects and inclusion of only middle-aged subjects could represent the main limitations of the study. Moreover, reflux in the IJV was detected in only three MS patients, only unilaterally and exclusively in the supine (0°) position with normalization of blood flow in the sitting (90°) position in all three cases.

CONCLUSION

The study results showed that the TCCS transcondylar approach had serious limitations for the standard US detection of intracranial venous reflux. Injection of echocontrast agent significantly improves the detection of the intracranial venous system through the transcondylar US bone window.

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Author contributions: DS: study design, manuscript drafting; MK, MR: performed sonographic examinations, data collection and interpretation; JH: performed brain magnetic resonance and data collection; KL: statistical analysis; RH: manuscript revision.

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