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Objective duplex ultrasound evaluation of the extracranial circulation in multiple sclerosis patients undergoing venoplasty of internal jugular vein stenoses: A pilot study

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Abstract

Objective: Chronic cerebrospinal venous insufficiency (CCSVI) is a condition associated with multiple sclerosis (MS) and manifested by stenoses in the extracranial venous circulation. There is a need for an objective non-invasive assessment of CCSVI that is able to accurately identify the location of stenoses and quantify physiological changes in blood flows following treatment.

Method: A duplex ultrasound method, extracranial duplex ultrasound (ECDU), is described where the internal jugular veins (IJVs) and vertebral veins (VVs) were examined in the supine and sitting position before and after venoplasty in eight patients with clinically diagnosed MS. High-resolution B-mode imaging was used to detect obvious stenoses, intraluminal membranes, valve abnormalities and vein wall thickening. ECDU was then used to assess blood flow including reflux. To assess obstruction, venous blood volume flows (BVFs) were taken bilaterally from the proximal (J1), mid (J2) and distal (J3) segments of the IJVs and the mid cervical VVs. To assess cerebral perfusion, bilateral BVF measurements were taken, in the supine position only, from the proximal internal carotid arteries (ICA) and mid cervical vertebral arteries (VA). The global arterial cerebral blood flow (GACBF) was then calculated as the sum of the ICA and VA measurements.

Results: Pre-venography ECDU detected IJV stenoses or obstruction in all patients. Venography findings were consistent with those of the pre-treatment ECDU with the exception of the detection of bilateral IJV stenoses in two patients diagnosed with unilateral IJV stenosis by ECDU. A significant improvement in GACBF was evident following venoplasty ($p < 0.05$). A trend to improvement in the post-treatment BVFs of both the IJVs and the mid cervical VVs was also observed. This improvement was most marked in the left VVs ($p = 0.052$) and the J2 segment of right IJVs ($p < 0.05$).

Conclusion: The ECDU examination described provides a reliable objective assessment of IJV and VV stenoses and, with the use of BVFs, can quantify the degree of obstruction. These results support the use of ECDU as a non-invasive post-operative assessment of the success of venoplasty. The ability of ECDU to measure GACBF provides an additional parameter to monitor vascular pathophysiology in MS patients. The current findings support the view that the early symptomatic benefits observed after venoplasty for stenoses in the extracranial venous circulation may be the result of increased cerebral perfusion.

Keywords

Duplex ultrasound, multiple sclerosis, CCSVI

Introduction

Recent reports suggest that the chronic neurological disease, multiple sclerosis (MS), is associated with stenoses and obstructions of the internal jugular and azygos veins.[1–4] Zamboni et al.[5] postulate that these venous obstructions may contribute to the development and progression of MS and that venoplasty of the

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internal jugular and azygos obstructions may produce some clinical benefits. The term chronic cerebrospinal venous insufficiency (CCSVI) has been used to refer to the venous anomaly associated with MS.

The pathway for venous outflow of the intracranial blood has been described.[6,7] The internal jugular veins (IJVs) are considered to be a principal outflow pathway. An extra-jugular system consisting of the vertebral veins (VVs), deep cervical and intra-spinal veins, and the external jugular veins is also thought to be important. Research suggests that the distribution of cerebrovenous outflow across pathways depends on body position.[8,9] In the supine position, the IJVs are the primary pathway. Whereas in the erect position the jugular flow is reduced, and the extra-jugular system, in particular the VVs and intra-spinal veins, form the principle drainage route.

According to Zamboni et al.,[2] when obstruction in the IJVs occurs, a vicarious venous shunt develops through collaterals in order to bypass the obstruction. This shunt, in turn, produces reflux or reverse flow which can be detected at various sites in the extracranial venous circulation. Zamboni further argues that the obstructions in the IJVs and azygos veins can result in intracranial venous reflux and reversal of the normal postural control.[1]

Whilst venography is regarded as the gold standard for identification of venous stenoses, duplex ultrasound[10] is used as a non-invasive method for screening for venous stenoses and has the capability to monitor the progress of venous disease following treatment. Zamboni et al.[1] have used five parameters of duplex ultrasound to indicate the likely presence of CCSVI in MS patients:

1. Reflux in the IJVs and/or VVs in sitting and/or supine posture, assessed using duplex ultrasound methodology;
2. Reflux in the deep cerebral veins in sitting and/or supine position, assessed using transcranial Doppler;
3. High-resolution B-mode evidence of IJV stenoses;
4. Flow not Doppler detectable in the IJVs and/or VVs;
5. Reverted postural control of the main cerebral venous outflow pathways, as determined by cross-sectional area changes.

Based on the observation that none of the control subjects satisfied more than one of these criteria[1], Zamboni et al.[5] proposed that at least two of the five duplex/Doppler ultrasound indicators must be present to make the diagnosis of CCSVI. It may be argued, however, that this requirement has been made to support the specific construct of CCSVI in its proposed relationship to the development of MS[5] and that it impedes an open-minded evaluation of the extracranial venous system in MS patients. The criteria overly depend on the presence of reflux, which is known to increase in prevalence with age in normal subjects,[11] and cross-sectional area, which is highly variable in the normal population due to changes of position, intra-thoracic and central venous pressures, and pressure from surrounding structures such as the carotid artery.

As the primary pathology in CCSVI is an obstructive lesion, blood volume flow (BVF) measurements, calculated as a product of blood velocity and cross-sectional area, should provide objective quantification of flow disturbances and indicate the likely presence of stenoses and/or reverted postural control. High-resolution B-mode evidence of a stenosis then becomes secondary supportive evidence of obstruction, as a stenosis is only considered to be of clinical relevance if it has a detrimental effect on blood flow. BVF measurements can also be used after venoplasty to determine the success or otherwise of the procedure.

MRI studies[12,13] have demonstrated that cerebral white matter perfusion is reduced in MS and that this abnormality appears early in the disease process.[14] Zamboni et al.[15] have also shown that hypoperfusion of brain parenchyma is associated with the severity of CCSVI in patients with MS. If, as has been proposed, the simultaneous obstruction of principal and collateral venous outflow leads to elevated venous pressure and eventual insufficiency of cerebral blood flow (CBF),[16] it could be postulated that a significant obstruction of the extracranial venous outflow may result in a concomitant reduction of the cerebral arterial inflow. Doepp et al.[6,17] have described a duplex ultrasound method where cerebral arterial inflow, or global arterial cerebral blood flow (GACBF), is measured as the sum of blood flow volume in both internal carotid (ICAs) and vertebral arteries (VAs). Inclusion of this measurement in the extracranial duplex examination of MS patients could provide an index of cerebral perfusion.

The aim of the present study was to assess the usefulness of BVFs, as measured by duplex ultrasound, in first determining the presence of disturbances in venous extracranial blood flow in patients with MS and second in the post-operative assessment of the effectiveness of venoplasty performed for IJV stenoses.

Method

Eight patients with clinically diagnosed MS were examined. Following extracranial duplex ultrasound examination (ECDU), all eight patients were referred to either an interventional radiologist or an endovascular surgeon independent of our diagnostic clinic for selective venography and, where indicated, transluminal

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balloon venoplasty. The eight patients were then re-examined by the same vascular sonographer between six and 29 weeks following the procedure (mean ± SD, 13.9 ± 7.8 weeks) to assess any changes following treatment.

Colour flow duplex ultrasound scanning was performed using a 7.5 MHz linear array multi-frequency transducer (Xario XG PLT704SBT, Toshiba). The patients were first asked to remove clothing from the neck area and examined supine (0°) with the head in a neutral position. Gel was applied to both sides of the neck from the suprasternal notch to the jaw.

Each IJV was first visualised in a sagittal plane, lateral to the common carotid artery. The IJV was followed to its confluence with the subclavian and brachiocephalic veins at the base of the neck. At the confluence with the subclavian vein, the IJV was sometimes difficult to visualise due to overlying bone. Heel-toeing or steering the transducer assisted in imaging this segment. Visualisation was enhanced by using adequate gel as an acoustic stand-off. In B-mode, the proximal IJV was assessed for the presence of valves and whether they were mobile or inverted. The presence of vein wall thickening, intraluminal membranes, total or partial occlusion of the vein and obvious collaterals were also assessed using high-resolution B-mode. All anomalies were recorded. Colour Doppler was then employed to demonstrate flow in the vein, the direction of flow and turbulence. Stagnation of flow, defined as stationary blood that elicits no Doppler signal, was also noted. Cephalad flow (reflux) was assessed during normal respiration. Valsalva was not employed. If reversed flow was present on the pulsed or colour Doppler signals, the time duration of reflux was measured on the pulsed Doppler tracing. Reflux was considered to be present if the duration exceeded 0.88 s.[5,10] Colour Doppler also assisted in quickly locating stenoses utilising the artefact, aliasing. Post-stenotic turbulence was demonstrated as simultaneous blue and red signals. Importantly, at all times during ultrasound assessment of the IJV, the ultrasound transducer was lightly placed on the skin surface to avoid compression of the vein.

BVF measurements were obtained bilaterally from the proximal (J1), mid (J2) and distal (J3) IJV segments,[18] the mid cervical VAs and veins (VV) and the proximal internal carotid arteries (ICA) with the patient in the supine position (Figure 1(a) and 1(b)). The pulsed Doppler sample volume was placed in the centre of the longitudinally imaged IJV with a sample gate size the diameter of the vessel. Pulsed Doppler recordings were obtained over 4–6 cardiac cycles and angle correction was employed. With the Doppler spectrum frozen, calipers were used to trace the venous Doppler signal (Figure 2) for 3–5 cardiac cycles. The diameter of the vein was measured at the location of the sample volume (Figure 2) to obtain the cross-sectional area (CSA). The BVF in millilitres per minute was displayed (Figure 2) and recorded. Total GACBF was calculated as the sum of the ICA and VA BVF measurements.[17]

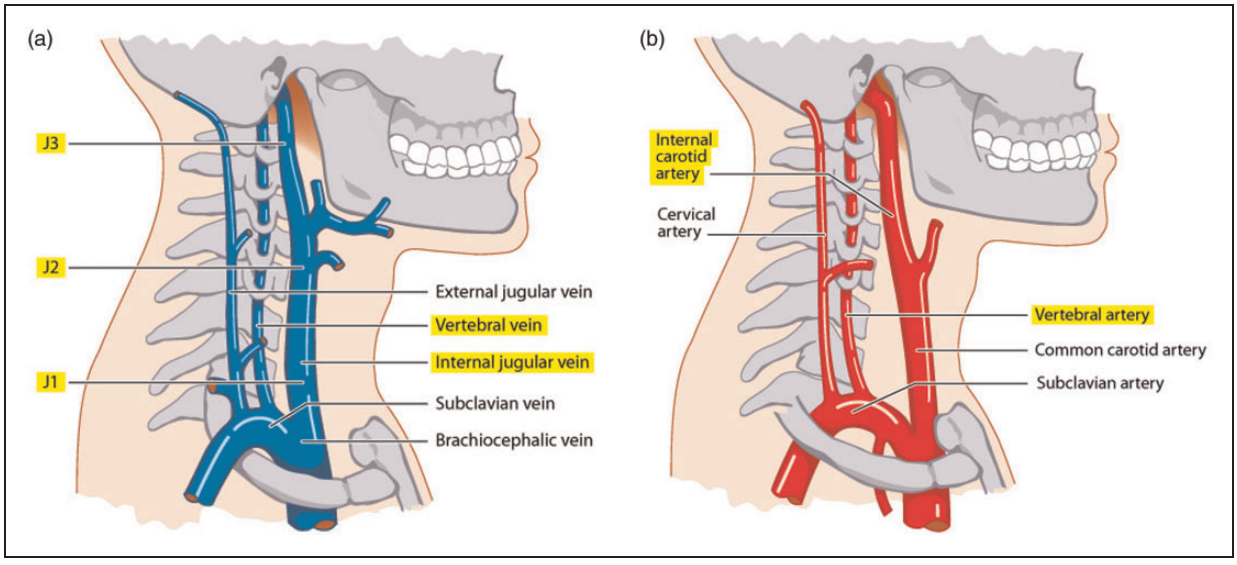

Figure 1. (a) Schematic diagram demonstrating blood volume flow (BVF) measurement sites J1, J2, J3 in the internal jugular vein (IJV) and vertebral vein (VV) and (b) Schematic diagram demonstrating BVF measurement sites in the internal carotid artery (ICA) and vertebral artery (VA).

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When both the right and left sides were completed in the supine position, the patient was positioned in an upright, seated position (90°) with the head in a neutral position looking straight ahead. The patient was asked to take several deep inspirations and expirations and to rest quietly for a 2-min period to allow for adaptation to the postural change before commencement of the erect examination.[18] The right and left IJV and VVs were re-assessed for valvular competence, reflux, stenosis or thrombosis, external compression and stagnation of flow. BVF measurements of the J1, J2 and J3 segments of the IJV and mid cervical VVs were repeated as described above. Care was taken to obtain sitting measurements in the same location as the supine measurements. A typical BVF worksheet is shown in Figure 3.

Differences in pre- and post-treatment GACBF and BVF for J1, J2 and J3 of the IJV were calculated and statistically evaluated using the Wilcoxon matched pairs test and a two-tailed probability test. Data were regarded as significant when $p < 0.05$.

Results

The eight MS patients were aged between 26 and 63 years with a (mean ± SD, 47.9 ± 11.6 years). The female to male ratio was 5:3, and disease duration was between one and 41 years (mean ± SD, 14.5 ± 13.6 years). At the time of examination, five patients were diagnosed as relapsing-remitting (RR) MS and three were diagnosed with secondary progressive (SP) MS.

All eight patients were diagnosed with IJV stenoses or obstruction, on the basis of reduced BVFs in the supine position, by pre-venography ECDU. Of these, three patients were diagnosed with bilateral stenoses. In all patients, at least one IJV had reduced BVF in the J2 segment when compared to the 'normal' J2 BVF reference range published by Valdueza et al.[8] Six patients had reversed postural control in one IJV. This was defined by an increased BVF in one or more of the IJV segments when changing from the supine to sitting position. High-resolution B-mode sonography detected abnormalities in only two patients.

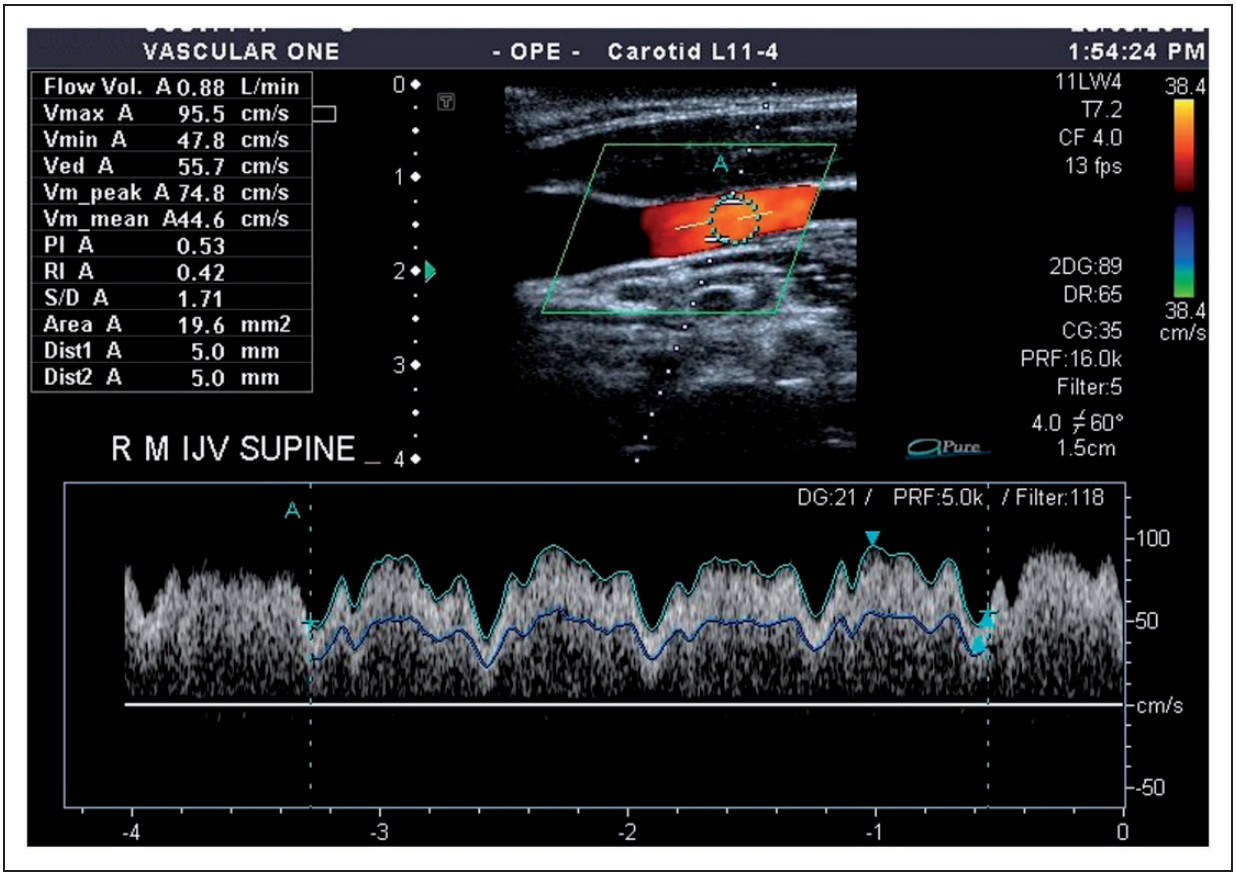

Figure 2. Duplex ultrasound image with colour Doppler demonstrating measurement of BVF in the J2 segment of an IJV by calculating the circular cross-sectional area of the vein with BVF averaged over 3–5 cardiac cycles in the supine position. The BVF measurement obtained from the J2 segment IJV shows an abnormally high flow rate of 880 ml/min.
IJV: internal jugular vein.

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Supine	Flow Volumes Right (ml/min)	Flow Volumes Left (ml/min)
IJV (J1)	**836**	**346**
IJV (J2)	**400**	**154**
IJV (J3)	**266**	**37**
Vertebral	**7**	**17**
Int. Carotid A.	**279**	**482**
Vertebral A.	**53**	**60**
Global Arterial Cerebral Blood Flow 874 mls/min		
Sitting		
IJV (J1)	**1317**	**46**
IJV (J2)	**249**	**41**
IJV (J3)	**349**	**0**
Vertebral	**82**	**61**

Figure 3. Typical worksheet detailing the BVF measurements obtained in the extracranial duplex ultrasound (ECDU) examination. This example indicates stenosis in the distal (J3) segment of the left IJV, moderate bilateral VV obstruction and reverted postural control in the right IJV.
IJV: internal jugular vein.

Table 1. Bilateral venous blood volume flows (ml/min) in the proximal (J1), mid (J2) and distal (J3) segments of the internal jugular veins (IJV) and the mid cervical vertebral veins (VVs), measured in the supine position before and after venoplasty.

				Before venoplasty		After venoplasty		
Measurement site			*N*	Mean	±SD	Mean	±SD	*P**
IJV	Left	J1	7	396.9	±272.2	375.7	±128.7	0.612
		J2	7	202.3	±106.7	248.6	±166.9	0.612
		J3	7	164.7	±146.7	147.1	±165.7	0.735
	Right	J1	6	652.8	±502.3	940.0	±557.4	0.116
		J2	6	278.8	±181.3	443.3	±361.0	0.046
		J3	6	202.2	±106.4	448.3	±451.1	0.249
VV	Left		7	12.3	±10.6	32.9	±20.6	0.052
	Right		6	19.7	±29.9	40.0	±28.3	0.116

*Wilcoxon matched pairs test

Reflux was detected in one patient, and abnormal turbulence was observed at both proximal valves in the second patient. Four of the five Zamboni criteria were assessed (criteria 2 was not assessed). One patient satisfied all four criteria, three patients satisfied two of the four assessed criteria, three satisfied one of the criteria and one did not satisfy any of the criteria assessed.

Venography and venoplasty were performed on all eight patients. Venography results correlated well with the pre-treatment ECDU with the exception that two patients diagnosed with uni-lateral IJV stenosis by the pre-treatment ECDU were found to have bilateral IJV stenoses on venography. Using venography as the gold-standard, the sensitivity and specificity of the ECDU technique for identification was calculated as 85% and 100%, respectively. The positive and negative predictive values were 100% and 60%.

Following venoplasty, there was a trend to improvement in the BVFs of both the IJVs and the mid cervical VVs. This finding was most marked in the left VVs ($p = 0.051$) and the J2 segment of right IJVs ($p < 0.05$, Table 1). In four patients, the results of the comparison of pre- and post-intervention venous BVFs showed that the venoplasty had not been clinically successful in at least one of their treated veins.

Before and after venoplasty, there was an increase in mean BVF from the distal J3 segment to the proximal J1 segment on both sides. This effect has been described previously and is thought to be due to contribution of flow from a number of tributaries (thyroid, lingual, pharyngeal) of the IJV.[19,20]

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Table 2. Global arterial cerebral blood volume flow (GACBF; ml/min) measured in the supine position before and after venoplasty and sub-grouped on symptom presentation into relapsing-remitting (RR) and secondary progressive (SP) multiple sclerosis (MS) subject groups.

		Before venoplasty		After venoplasty		
Subjects	*N*	Mean	±SD	Mean	±SD	*P**
All (RR MS + SP MS)	8	901.4	±232.8	1238.8	±199.9	0.036
RR MS	5	838.4	±180.7	1340.0	±168.5	0.043
SP MS	3	1006.3	±313.0	1070.0	±121.2	1.000

*Wilcoxon matched pairs test

There was also a significant improvement in GACBF following venoplasty (Table 2). This improvement was primarily related to a post-treatment increase in GACBF in the relapsing-remitting MS patients. The GACBF of patients with secondary progressive MS, while increased, was not significantly changed.

Discussion

The use of objective measurements of BVFs in the three segments (J1, J2, J3) of the IJVs was able to accurately predict 11 out of 13 stenoses in the IJVs in this group of eight MS patients. There were no false positives predicted. Follow-up ECDU examination revealed a trend to improvement in the BVF of the treated IJVs, especially the J2 segment of the right IJV and interestingly the left VV. The lack of post venography change in flow rates measured for a number of segments may reflect early restenosis. Restenosis is a frequent occurrence after venoplasty. Alternative therapy and repeat venoplasty may therefore be indicated in these situations. A surprise finding was the significant increase in GACBFs found in the relapsing-remitting patients. This finding supports the view that the early symptomatic benefits observed after venoplasty for stenoses in the extracranial venous circulation in MS patients may be a result of increased cerebral perfusion.

The described ECDU, by providing quantification of blood volume flows at specific segments of the extracranial venous outflow tracts, accurately predicts the location of stenoses and then is able to monitor progress of the condition over time. With those patients identified as having CCSVI and MS, this examination then becomes as significant as periodical MRI examination of the brain and spinal cord in the management of the condition. The ability of ECDU to measure GACBF provides an additional parameter to monitor vascular pathophysiology in MS patients.

Several points need to be made regarding technical aspects of volume flow measurements in veins. First, veins are elliptical due to their less muscular wall in comparison to arteries and their diameter and shape are variable due to cardiac output, central venous pressure, pulsatility and phasicity. Whilst the internal carotid and vertebral artery diameters are constant, the proximal and mid IJV diameters are often fluctuating and this will lead to considerable variability in the BVF measurement. We therefore advise the need for a large cross-sectional study of normal subjects of a range of age groups to be performed in order to obtain more reliable normal ranges for the BVF measurements.

Moreover, an IJV BVF is based on two factors. First, that venous velocity signals are measured over several cardiac cycles and the flow 'averaged'. Second, to calculate volume flow, a CSA of the vein is required. In our assessment, the CSA was calculated by measuring the AP diameter of the vein in the longitudinal plane which assumes the vein is circular, whereas in fact it is more elliptical in shape.[20] We have estimated that this may reduce the actual BVF measurement by up to a third. A more accurate measurement would be to image the vein in a transverse view and trace the wall of the vein. To perform this measurement as well as obtain pulsed Doppler waveforms from the IJV in a sagittal view at the same location from multiple sites of the IJV is not time efficient in normal practice but may be advisable for research and the calculation of a normal range for each segment of the IJV. The measurement that we have obtained by our method should therefore be regarded as an index of BVF and remains a valid method for assessing BVF with serial measurements over time in the ongoing management of a patient.

Conclusion

The ECDU examination described provides a reliable objective assessment of IJV and VV stenoses and, with the use of BVFs, can quantify the degree of obstruction. These results support the use of ECDU as a non-invasive post-operative assessment of the success of venoplasty. The ability of ECDU to measure GACBF provides an additional parameter to monitor vascular pathophysiology in MS patients. The current findings

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support the view that the early symptomatic benefits observed after venoplasty for stenoses in the extracranial venous circulation may be the result of increased cerebral perfusion.

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Conflict of interest

None declared.

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