Doppler Haemodynamics of Cerebral Venous Return

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Abstract: Physiologic functioning of the cerebrovenous system is indispensable for maintaining normal brain function. However, in contrast to the cerebroarterial system, the cerebral venous return is not routinely investigated. Combined high-resolution echo-colour-Doppler (ECD) and transcranial colour coded Doppler sonography (TCCS) represents an ideal method to investigate the haemodynamics of cerebral venous return. TCCS-ECD is noninvasive, repeatable, cost-effective and permits to investigate the cerebral venous outflow in its dependence upon changes in posture and the alternating pressure gradients of the thoracic pump. Several authors reported normal parameters concerning related aspects of cerebral venous return. However, there is no ECD-TCCS standardization of what can be considered a normal venous return. The authors have summarized the current knowledge of the Doppler haemodynamics of the cerebrovenous system and propose a list of reproducible clinical parameters for its sonographic evaluation. In future, the development of this diagnostic technique could be of singular interest in iron-related inflammatory and neurodegenerative disorders like multiple sclerosis.

INTRODUCTION

Posture and respiratory movements play a fundamental role in ensuring the correct cerebrospinal venous outflow. At the time of expiration, intrathoracic pressure is approximately -5 cm H_2O and forced inspiration generates even lower intrathoracic pressures of about -8 cm H_2O (Schaller, 2004; Zamboni *et al*., 2007). The pressure gradients favour venous return to the right heart, which fact can be easily assessed with high-resolution ECD and TCCS, which thus constitute an ideal method for investigating the haemodynamics of cerebral venous return (Schaller, 2004; Valdueza *et al*., 2000; Gisolf *et al.*, 2004; Schreiber *et al*., 2003; Doepp *et al*., 2004).

In addition, ECD showed a postural control of the extracranial outflow pathways, as follows: (Valdueza *et al*., 2000) the IJV is the predominant venous pathway in the supine position, as confirmed by an increased blood flow in that posture; redirection of venous flow to the VVs occurs in the upright position, with concomitant reduction of blood flow in the IJVs.

To the contrary, MR and selective injection venography are limited to evaluating cerebral venous haemodynamics under different postural and respiratory circumstances. Thereby, especially the latter provides excellent morphological but though exclusively static findings.

Several authors reported normal parameters after investigating different aspects of cerebral venous Doppler haemodynamics in the last decade. However, there is no ECD-TCCS standardisation of what can be considered a normal venous return. The authors have summarized the current knowledge of the Doppler haemodynamics of the cerebrovenous system and propose a list of parameters and a clinical methodology for reproducibly assessing them, that allow to tell whether cerebral venous outflow runs normally, or not.

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ECD-TCCS EQUIPMENT AND PATIENT POSITION DURING THE INVESTIGATION

Nowadays the investigation of the cerebral venous haemodynamics can envisage the contemporaneous analysis of both the intracranial and extracranial pathways, by combining with the same ultrasound machine respectively the examination of the DCVs and main dural sinuses, by means of the TCCS probe (Baumgartner *et al*., 1997; Stoltz *et al*., 1999; Zamboni *et al*., 2007), with that of the IJVs-VVs by means of the ECD probe (Schaller, 2004; Valdueza *et al*., 2000; Gisolf *et a.l*, 2004; Schreiber *et al*., 2003; Doepp *et al*., 2004). The transducer used at the intracranial level is at low frequency, usually 2.5 Mhz, whereas at the cervical level it is at high frequency, 7.5-10 Mhz or more, according to the different depth of the veins respective to the body surface where the transducer is placed.

The posture of the subject under examination obtains, as indicated above, a crucial part determining the main route of cerebral outflow. For this reason the subject should be investigated at least in both supine and sitting position (0°and 90°), but it has further been proposed to assess venous flow from the brain with the body positioned at 0°, +15°, +30°, +45°, +90° in both the IJVs and VVs. (Valdueza *et al*., 2000). This objective can be realized with the subjects being positioned on a tilt bed.

TCCS VENOUS INVESTIGATION

The main parameters of the TCCS investigation of the intracranial veins are the diameter of the third ventricle (III V), and flow parameters which include direction, velocity and resistance index.

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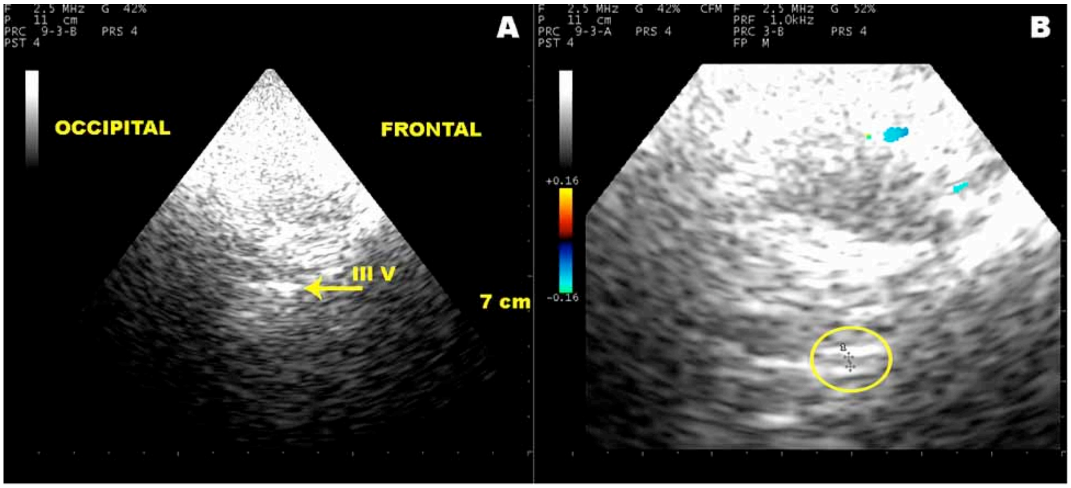

Fig. (1). A: TCCS through the ventricular plane of the trans-temporal window, axial section. At an insonation depth of about 7 cm the echo-lucent third ventricle is seen (IIIV), limited by two echogenic bright margins; **B**: by using the zoom function is easier to measure the III V diameter in the magnification of the image.

Assessment of Third Ventricle Diameter

According to the Monro-Kellie law, the sum of brain volume plus cerebro-spinal fluid (CSF), plus cerebral blood volume (CBV) always remains constant (Schaller, 2004). Therefore, an increase in venous pressure/volume determines a volume compensation achieved by changes in both extra- and intracellular cerebral fluid volume (Carmelo *et al*., 2002; Wey and Kontos, 1982). From this point of view, the assessment of the diameter of the III V is an important parameter, easy and rapid to assess by B-mode TCCS, for its being, interestingly, related to both CBV and CSF volume. In addition, III V measured by B-mode TCCS closely and significantly correlates with MRI assessment (Kallmann *et al*., 2004).

The transducer is placed at the level of the trans-temporal bone window, and the depth of the insonation is adjusted to 10 cm. At an insonation depth of about 7 cm it is possible to consistently identify the echo-lucent III V, limited by two echogenic bright margins, as well as the two comma-shaped frontal horns of the lateral ventricles (Kallmann *et al*., 2004; Zamboni *et al*., 2007). In normal subjects III V diameter is about 4 mm in the supine position (Kallmann *et al*., 2004), (Fig. **1**).

Interestingly in multiple sclerosis it is significantly wider, and an increased diameter corresponds to an increased disability score. This finding is of course related to the tissue loss and a compliant reduced brain volume (Kallmann *et al*., 2004). However, it suggests, according to the Monro-Kellie hypothesis, also a relationship with modifications of CBV, which was found in multiple sclerosis (Wuerfel *et al.,* 2004; Rashid *et al.,* 2004).

Intracranial Venous Flow Direction

Physiological intracranial venous flow is mono-directional, and characterized by low velocity and low resistance index. It can be recorded again through the *trans*-temporal approach, but the *trans*-occipital or the *trans*-ophthalmic windows can be used as well (Baumgartner *et al*., 1997; Stoltz *et al*., 1999; Zamboni *et al*., 2007; Zipper and Stoltz, 2002; Valdueza *et al.,* 1996). Subjects can be examined in both sitting and supine positions and the venous flow is enhanced by inviting the subject to breathe (Zamboni *et al*., 2007). Using the trans-temporal acoustic bone window, it is highly probable to insonate at least one of the DCVs, including basal veins of Rosenthal, great vein of Galen, and internal cerebral veins, according to criteria previously described (Valdueza *et al*., 1996; Stolz *et al.* 1999; Zipper *et al.,* 2002).

In a study, patients affected by multiple sclerosis were examined in both sitting and supine positions, demonstrating reflux flow. The reflux in the intracranial veins is defined as a flow recorded in a direction opposite to the physiologic one for a duration > 0.5 sec., a finding significantly different from the mono-directionality registered on normal volunteers.

In about 50% of multiple sclerosis patients TCCS demonstrated pathological venous reflux within DCVs and transverse sinuses during the activity of the thoracic pump. Such refluxes were absent in the DCVs in healthy subjects and while only 7% of healthy individuals exhibited venous refluxes in the transverse sinus (Zamboni *et al*., 2007).

EXTRACRANIAL DOPPLER VENOUS INVESTIGATION

Examination is performed with high frequency transducers as above reported. Subjects should be examined at least in sitting and supine positions, or better on a tilting bed with the body positioned at 0°, +15°, +30°, +45°, +90°(Valdueza *et al*., 2000). Either the IJVs and the VVs can be examined by using both the transversal and/or the longitudinal cervical access. The operator uses minimal pressure over the skin in order to prevent compressing the vein and thereby affecting the measurement, as previously reported (San Millan Ruiz *et al*., 2002; Valdueza *et al*., 2000; Gisolf *et al*., 2004; Schreiber *et al*., 2003; Doepp *et al*., 2004).

The operator can assess the following: flow direction, flow velocity, competence of the IJV valve, cross sectional area in relation to change in posture, duplex derived flowmetry, and anomalous morphology.

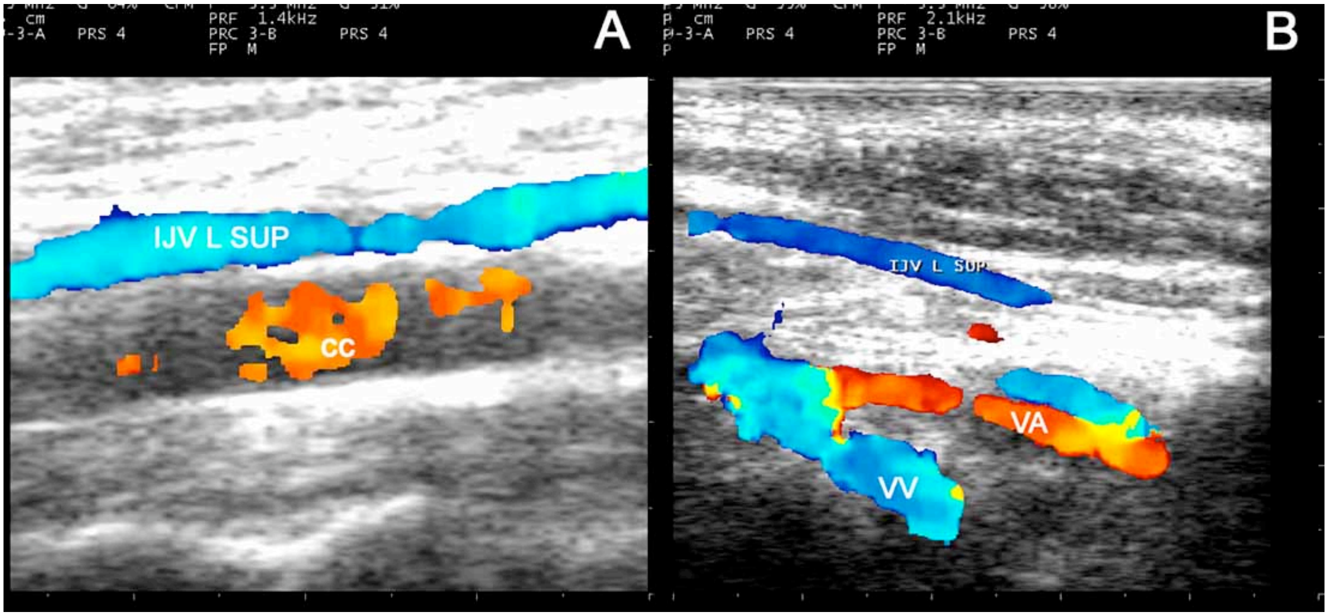

Fig. (2). The longitudinal cervical access in supine position (SUP), left side (L) **A**: red flow directed toward the brain depicts the common carotid (CC), whereas blue colour depicts the outflow in the IJV; **B**: with transducer placed just above the supraclavicular fossa, through a more posterior longitudinal access, the left IJV together with respectively the vertebral artery in red (VA) and the vertebral vein in blue (VV) are insonated.

Assessment of Flow Direction and Doppler Flow Parameters

The flow direction, in either the IJVs or the VVs, can be measured during inspiration and/or expiration, but it is recommended to measure it in the respiratory pause (Valdueza *et al*., 2000); flow direction can be measured also with Valsalva for testing the competence of the jugular valve but this will be treated separately. The direction of flow can be analyzed either with the pulsed wave sample placed in the vessel, at a 60° angle, or with the Colour Coded Mode, by comparing the colour of the flow in the IJVs/VVs with that of the satellite carotid and/or vertebral artery, respectively (Fig. **2A**,**B**).

According to consensus statements on peripheral vein ECD investigations, we define as monodirectional a flow always directed toward the heart. Flow is considered bidirectional when, in at least one of such conditions, we detect a flow reversal from its physiological direction for a duration < 0.5 sec. When the phase of reverse flow is > 0.5 sec, it is defined as venous reflux (Nicolaides *et al*., 2000; Coleridge-Smith *et al*., 2006).

Assessment of Doppler flowmetry in ml/min by using the softwares included in the package of the ultrasound equipment, is performed at the level of the thyroid gland for the IJVs and at the level of C5-C6 for VVs (Valdueza *et al*., 2000). Therefore, it has been suggested to record flow measurement beginning two minutes after the change in posture and after several deep breaths in order to permit blood redistribution in the venous system.

It is well apparent in Table **2** that predominance of the IJV in cerebrovenous drainage is limited to the supine position. In the erect position, the vertebral venous system represents the major outflow pathway. Moreover, in the supine position, a duplex derived-flowmetry of 700±270 ml/m was measured in normal volunteers. This was found to change completely, however, when the subject changed to the upright position, as the IJV flow fell to 70±100 ml/m, whereas in the VV it rose from 40±20 to 210±120 ml/m (Valdueza *et al*., 2000).

Table 1. Duplex Derived Flowmetry and CSA Recorded in Normal Subjects (Data Derived from (Valdueza *et al*., 2000))

	IJVs Flow ml/min	VVs Flow ml/min	IJVs CSA mm^2	VVs CSA mm^2
Supine position (mean ± SD)	700±270	40±20	106±37	10.6±2.8
Sitting position (mean ± SD)	70±100	210±120	17±8	11.9±3.6

The apparent unexplained rest of about 450 ml/min in the standing posture represents the gravitational effect of the hydrostatic pressure, which causes the displacement of 70% of the total volume of blood below the heart level (Folkow and Neil, 1973).

From this point of view, the higher hydrostatic column in the valveless vertebral-azygos system in the erect position favours venous drainage through this route, rather than through the IJV.

Competence of the Jugular Valve

Although the presence of valves in the distal portion of the IJVs has been widely described by anatomists and pathologists, they can be even absent. IJVs valves were found in 93 % of the post-mortem studies, and in 87 % of patients by means of high resolution B-mode ultrasounds; the majority of unilateral valve were found on the right side (Lepori *et al*., 1998).

As far as the competence of the venous valve is concerned, it is well established in Doppler haemo-dynamics to test it by means of the Valsalva manoeuvre. According to a recent study on reflux time cut-off values, we can consider reflux a flow reversal from its physiological direction for a duration > 0.88 sec across the IJVs valve (Nedelmann *et al.,* 2005). It has been reported that 33% of healthy individuals showed unilateral or bilateral IJVs valve incompetence. However, reflux recorded in accordance to this condition of measurement is strongly associated with transient global amnesia, in 68% of cases, with significantly higher prevalence as compared to controls (Sander and Sander, 2005; Schreiber *et al*., 2005).

B-Mode Detection of Anomalous IJVs Morphology

It has been reported that it is possible to observe IJVs stenosis and, in contrast, also IJVs aneurysms. An asymmetry, defined as a cross sectional area (CSA) at least twice that of the contralateral IJV was noted in 62.5% of cases. In addition, stenosis of the IJVs with a CSA of 0.4 cm^2 or less was measured in 23% of cases (Lichtenstein *et al*., 2001).

To the contrary, in Sardinia frequently, IJVs aneurysms in the absence of trauma, AV fistula and thoracic malformation have been described.

The abnormal dilatation was related to a fibrotic wall with absence or reduction of smooth muscle cells suggesting a congenital/developmental malformation (Zamboni *et al.,* 1990).

Flow not Doppler Detectable in the IJVs and/or VVs

It has been described that there occurs the absence of a Doppler detectable venous flow in the IJVs and/or VVs despite numerous deep inspirations. In normal subjects this finding was never observed with the head in any position but the supine, in 6 % of cases (Doepp *et al*., 2004).

CSA Variation According to the Predominant Pathway of Cerebral Venous Drainage

Δ CSA in the IJVs, obtained by subtracting the CSA measured in the supine from that in the sitting position, is a positive value in normal subjects, as clearly shown in Table **1** (Schaller, 2004; Valdueza *et al*., 2000; Gisolf *et al*., 2004; Schreiber *et al*., 2003).

In Fig. (**3**) the change in CSA in response to the change in posture, and the corresponding ΔCSA, are apparent: CSA is wider in the supine position and reduced in the sitting. It can be considered a pressure/volume relationship, in practice a

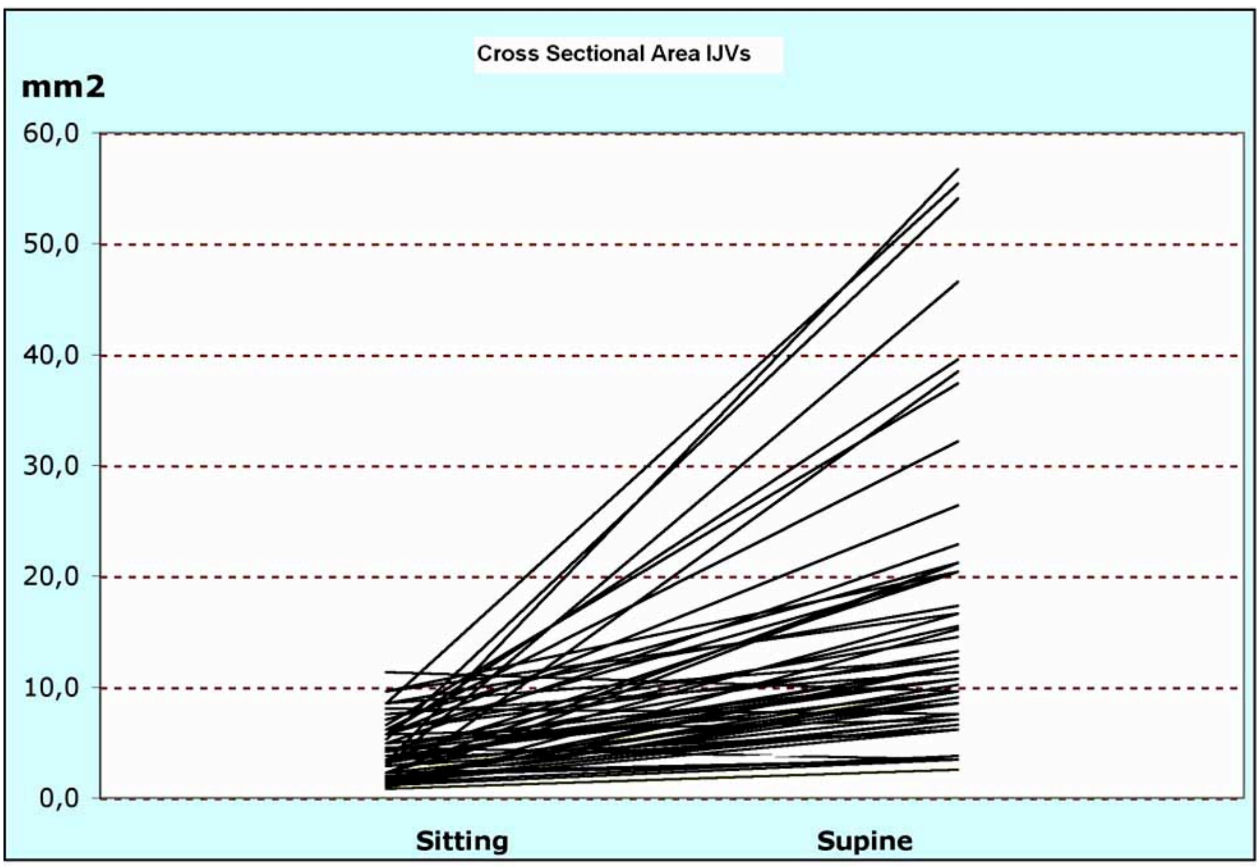

Fig. (3). The increase of CSA observed while passing from sitting to supine position in the IJV reflects the variation of blood volume; the latter is maximum when the subject lying down and the hydrostatic pressure is around zero. In contrast, in up-right position it has been there resulted a proportional reduction in volume with a negative hydrostatic pressure. From this point of view such a curve represents a rough estimation of the compliance of the given jugular system, representing a pressure/volume relationship. (Data derived from a personal observation on 60 healthy subjects).

non-invasive compliance curve of the jugular system. In fact, CSA variation reflects the variation of blood volume which flows in the IJV (Table **1**) in response to changes in hydrostatic pressure determined by the different bodily positions (Zamboni *et al*., 1997; Zamboni *et al*., 1998).

CONCLUSIONS AND PERSPECTIVES

The adequate functioning of the cerebrovenous system may be one of the most important factors indispensable for the maintenance of a normal brain function (Schaller, 2004). Still, in contrast to the cerebroarterial system, the cerebral venous return is not routinely investigated. This review marks the combination of ECD and TCCS as the ideal method for tracing individual variations and anomalies in the haemodynamics of cerebral venous return.

As yet TCCS-ECD has only been taken advantage of in the assessment of transient global amnesia and in multiple sclerosis, but this imaging technique might as well be used for elucidating further clinical conditions.

In multiple sclerosis, TCCS-ECD recommends itself for monitoring the progression of the disease through a faster and cheaper assessment of the diameter of the III V as compared to MRI. In perspective, it seems also promising to study the topographic relationship between the cerebral veins exhibiting reflux at TCCS together with the location of plaques found at MRI; particularly, MR susceptibility weighted imaging, which allows contemporaneous imaging of veins and plaques, offers even greater promise (Koopmans *et al.,* 2008). Finally, in view of the increased iron deposits forming a constant feature of either chronic venous disorders or multiple sclerosis (Zamboni, 2006; Zivadinov and Bakshi, 2004), it should be interesting to measure, by means of MR susceptibility weighted imaging (Haacke *et al*., 2007), the amount of iron in plaques of multiple sclerosis, evaluating the plaques' topographic correspondence with the refluxing cerebral veins.

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GLOSSARY AND ABBREVIATIONS

ECD	=	EchoColor-Doppler
TCCS	=	Transcranial color-coded Doppler sonography
IJV	=	Internal Jugular Vein
VV	=	Vertebral Vein
DCVs	=	Deep cerebral veins, including internal cerebral vein, basal vein, Galen vein
CSA	=	Cross sectional area of the IJV
ΔCSA	=	Difference in CSA assessed in supine and sitting posture in the IJV
Basic requirement of venous haemodynamics	=	To permit, by a mono-directional flow, a drainage of a volume of blood per unit of time adequate to a certain territory. This assumption has to be valid in all conditions.
Reflux	=	Venous flow reversal to the physiologic direction for a duration > 0.88 sec in the extracranial pathways, and > 0.50 sec in the DCVs.

REFERENCES

Baumgartner, RW, Nirkko, A C, Müri, RM, Gönner, F. (1997) Transoccipital power-based color-coded duplex sonography of cerebral sinuses and veins. *Stroke* **28**: 1319-1323.

Carmelo, A, Ficola, A, Fravolini, ML, La, Cava, M, Maira, G, Mangiola, A. (2002) ICP and CBF regulation: a new hypothesis to explain the "windkessel" phenomenon. *Acta Neurochir Suppl* **81**: 112-6.

Coleridge-Smith, P, Labropoulos, N, Partsch, H, Myers, K, Nicolaides, A, Cavezzi, A. (2006) Duplex ultrasound investigation of the veins in chronic venous disease of the lower limbs--UIP consensus document. Part I. Basic principles. *Eur J Vasc Endovasc Surg* **31**: 83-92.

Doepp, F, Schreiber, SJ, von Münster, T, Rademacher, J, Klingebiel, R, Valdueza, JM. (2004) How does the blood leave the brain? A systematic ultrasound analysis of cerebral venous drainage patterns. *Neuroradiology* **46**: 565-70.

Folkow, B, Neil, E. (1973) Circulation. Oxford University Press, New York pp. 10-11.

Gisolf, J, van Lieshout, JJ, van Heusden, K, Pott, F, Stok, WJ, Karemaker, JM. (2004) Human cerebral venous outflow pathway depends on posture and central venous pressure. *J Physiol* **560**: 317-27.

Haacke, EM, Ayaz, M, Khan, A, Manova, ES, Krishnamurthy, B, Gollapalli, L, Ciulla, C, Kim I, Petersen, F, Kirsch, W. (2007) Establishing a baseline phase behavior in magnetic resonance imaging to determine normal vs. abnormal iron content in the brain. *J Magn Reson Imaging* **26**: 256-64.

Kallmann, BA, Sauer, J, Schliesser, M, Warmuth-Metz, M, Flachenecker, P, Becker, Dagger, G, Rieckmann, P, Mäurer, M. (2004) Determination of ventricular diameters in multiple sclerosis patients with transcranial sonography (TCS)--a two year follow-up study. *M J Neurol* **251**: 30-4.

Koopmans, PJ, Manniesing, R, Niessen, WJ, Viergever, MA, Barth, M. (2008) MR venography of the human brain using susceptibility weighted imaging at very high field strength. *MAGMA* **21**: 149-58.

Lepori, D, Capasso, P, Fournier, D, Genton, CY, Schnyder, P. (1999) High-resolution ultrasound evaluation of internal jugular venous valves. *Eur Radiol* **9**: 1222-6.

Lichtenstein, D, Saïfi, R, Augarde, R, Prin, S, Schmitt, JM, Page, B, Pipien, I, Jardin, F. (2001) The internal jugular veins are asymmetric. Usefulness of ultrasound before catheterization. *Intensive Care Med* **27**: 301-5.

Nedelmann, M, Eicke, BM, Dieterich, M. (2005) Functional and morphological criteria of internal jugular valve insufficiency as assessed by ultrasound. *J Neuroimaging* **15**: 70-5.

Nicolaides, AN, and the International Consensus Group. (2000) "The investigation of chronic venous insufficiency. A Consensus Statement". *Circulation* **102**: 126-163.

Rashid, W, Parkes, LM, Ingle, GT, Chard, DT, Toosy, AT, Altmann, DR, Symms, MR, Tofts, PS, Thompson, AJ, Miller, DH. (2004) Abnormalities of cerebral perfusion in multiple sclerosis. *J Neurol Neurosurg Psychiatry* **75**: 1288-93.

San Millan Ruiz, D, Gailloud, P, Rufenacht, DA, Delavelle, J, Henry, F, Fasel, JH., (2002) The craniocervical venous system in relation to cerebral venous drainage. *Am J Neuroradiol* **23**: 1500-8.

Sander, K, Sander, D. (2005) New insights into transient global amnesia: recent imaging and clinical findings. *Lancet Neurol* **4**: 437-44.

Schaller, B, (2004) Physiology of cerebral venous blood flow: from experimental data in animals to normal function in humans. *Brain Res Rev* **46**: 243-260.

Schreiber, SJ, Doepp, F, Klingebiel, R, Valdueza, JM. (2005) Internal jugular vein valve incompetence and intracranial venous anatomy in transient global amnesia. *J Neurol Neurosurg Psychiatry* **76**: 509-513.

Schreiber, SJ, Lurtzing, F, Gotze, R, Doepp, F, Klingebiel, R, Valdueza, JM. (2003) Extrajugular pathways of human cerebral venous blood drainage assessed by duplex ultrasound. *J Appl Physiol* **94**: 1802-1805.

Stolz, DE, Kaps, M, Kern, A, Babacan, SS. (1999) Reference data from 130 volunteers transcranial color-coded duplex sonography of Intracranial veins and sinuses. *Stroke* **30**: 1070-1075.

Valdueza, JM, Schmierer, K, Mehraein, S, Einhaupl, KM. (1996) Assessment of normal flow velocity in basal cerebral veins: a transcranial Doppler ultrasound study. *Stroke* **27**: 1221-1225.

Valdueza, JM, von Munster, T, Hoffman, O, Schreiber, S, Einhaupl, KM. (2000) Postural dependency of the cerebral venous outflow. *Lancet* **355**: 200-201.

Wei, EP, Kontos, HA. (1982) Responses of cerebral arterioles to increased venous pressure. *Am J Physiol* **243**: H442-H447.

Wuerfel, J, Bellmann-Strobl, J, Brunecker, P, Aktas, O, McFarland, H, Villringer, A, Zipp F. (2004) Changes in cerebral perfusion precede plaque formation in multiple sclerosis: a longitudinal perfusion MRI study. *Brain* **127**: 111-9.

Zamboni, P, Cossu, A, Carpanese, L, Simonetti, G, Massarelli, G, Liboni, A. (1990) The so-called venous aneurysms. *Phlebology* **5**: 45-50.

Zamboni, P, Menegatti, E, Bartolomei, I, Galeotti, R, Malagoni, AM, Tacconi, G, Salvi, F. (2007) Intracranial venous haemodynamics in multiple sclerosis. *Curr Neurovasc Res* **4**: 252-258.

Zamboni, P, Portaluppi, F, Marcellino, M.G, Quaglio, D, Manfredini, R, Liboni, A, Stoney, RJ. (1998): *In vitro* > *in vivo* assessment of vein wall properties. *Ann Vasc Surg* **12**: 324-329.

Zamboni, P, Portaluppi, F, Marcellino, M.G, Pisano, L, Manfredini, R, Liboni A. (1997) Ultrasonographic assessment of ambulatory venous pressure in superficial venous incompetence. *J Vasc Surg* **26**: 796-780.

Zamboni, P. (2006) The big idea: iron-dependent inflammation in venous disease and proposed parallels in multiple sclerosis. *J R Soc Med* **99**: 589-593.

Zipper, SG, Stolz, E. (2002) Clinical application of transcranial colour-coded duplex sonography--a review. *Eur J Neurol* **9**: 1-8.

Zivadinov, R, Bakshi, R. (2004) Role of MRI in multiple sclerosis II: brain and spinal cord atrophy. *Front Biosci* **9**: 647-64.