

# The role of magnetic resonance imaging in assessing venous vascular abnormalities in the head and neck: a demonstration of cerebrospinal venous insufficiency in a subset of multiple sclerosis patients

E. Mark Haacke,<sup>1,2</sup> Sean K. Sethi,<sup>1</sup>  
Jing Jiang,<sup>1</sup> Ying Wang,<sup>1</sup>  
David T. Utriainen<sup>1</sup>

<sup>1</sup>Magnetic Resonance Innovations, Inc.;

<sup>2</sup>Department of Radiology, Wayne State University, Detroit, MI, USA

## Abstract

The study of chronic cerebrospinal venous insufficiency (CCSVI) and its impact on the development and progression of multiple sclerosis (MS) remains controversial. Although the initial thrust in evaluating CCSVI was with ultrasound, other modalities including magnetic resonance imaging (MRI) have been used to study venous vascular abnormalities. This review focuses on the findings of a number of past MRI studies including a look at a combined study of four previous works with a cohort of 559 MS patients regarding structure and function of the extra-cranial vasculature. Strengths and limitations of each paper are discussed which give insight into conflicting reports of venous abnormalities in MS patients and healthy controls. Guidelines for data acquisition and analysis for future studies related to extra-cranial structure and flow, both arterial and venous, are discussed. This includes the grading of stenosis of the internal jugular veins (IJVs) as well as normalized flows through major veins of the neck. The lack of agreement between most studies is likely due to inconsistent data acquisition and incomplete data analysis. Our own work over four independent sites shows good agreement, indicating that there is a high incidence of stenosis and structural venous abnormalities in the MS population and that this change results in reduced outflow of the IJVs and increased collateralization of venous return to the heart compared to healthy controls.

## Introduction

From the onset of the description of multiple sclerosis (MS) to the more current autoimmune descriptions, there has been a belief that the venous system is involved in the

pathogenesis of MS. Few argue that MS lesions are venocentric, but the implications of this finding are unclear. Some believe that, from a mechanical point of view, venous hypertension should lead to venocentric lesions.<sup>1</sup> A more modern view invokes a venous involvement of the small veins or venules in the pathophysiology of the disease in an attempt to explain how it might be auto-immune in nature. It has also been suggested that blood flow plays a critical role in the ability of the brain to maintain neuronal myelination.<sup>2</sup> The use of contrast agents in magnetic resonance imaging (MRI) has proven useful in the study of MS. It is apparent from the observed contrast leakage into the cerebral parenchyma for some lesions that there is disruption of the blood brain barrier, but many auto-immune models do not take into account the potential endothelial dysfunction or potential mechanical damage to these veins. From an MR imaging standpoint, a number of studies have observed a reduction in cerebral blood flow in the lesions of relapsing remitting MS patients.<sup>3</sup> Understanding the role, which cerebral blood flow plays, especially the venous involvement, is now at a critical divide. Many questions have arisen which require further assessment, such as: *What is the source of the venous involvement?* and *Is it related to the pathogenesis of the disease?* or *Is the presence of abnormal venous flow just a comorbidity with an autoimmune source of the disease?* Still, it is important to consider that there are many vascular situations with abnormal venous flow that can lead to neurological effects.<sup>2,4,5</sup>

Although groups in the past have demonstrated major involvement of the venous system with MS,<sup>6,7</sup> the first clinical attempt to deal with the abnormal vasculature specifically for MS came from the work of Paolo Zamboni.<sup>8</sup> He recognized that there were extra-cranial venous structural and flow abnormalities that, in themselves, created a highly resistive secondary network of collateral flow that might explain upstream effects on the venous system in the brain. This extra-cranial effect had been noticed previously in patients with paraplegia and quadriplegia by Aboulker *et al.* in the early 1970s.<sup>9</sup> Over the first half of that decade, they treated many patients who had stenoses of the jugular, azygous, subclavian and iliac veins as well as the vena cava. Both groups found that treating the veins could have a significant affect in relieving symptoms of their patients, but only for a fraction their patients. Still, in some cases the benefit was clear.

The initial investigative work of Zamboni *et al.* was based on the use of ultrasound (US) as an imaging tool to probe the venous flow. From this work, he determined a set of five criteria that he believed could be related to abnormal structure and function (flow) of the extra-cra-

Correspondence: E. Mark Haacke, Magnetic Resonance Innovations, Inc., 440 East Ferry Street, Detroit, MI 48202, USA.  
Tel.: +1.313.758.0065 - Fax: +1.313.758.0068.  
E-mail: Nmrimging@aol.com

Key words: Multiple sclerosis; flow quantification; chronic cerebrospinal venous insufficiency; magnetic resonance imaging.

Acknowledgements: the authors would like to thank MR Innovations India; Dr. Naftali Raz, Dr. Ana Daugherty and Dr. Phil Levy from Wayne State University for usage of some of their healthy control data; and Giacomo Gadda from the University of Ferrara, for his assistance in preparing some of the figures and their statistics.

Contributions: the authors contributed equally.

Conflict of interests: the authors declare no potential conflict of interests.

Funding: research reported in this publication was supported in part by the National Heart, Lung, and Blood Institute of the National Institutes of Health under Award Number R42HL112580; as well as National Institutes of Health Award Number 5R01MD005849. The content of this paper is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

Received for publication: 31 January 2015.

Revision received: 27 March 2015

Accepted for publication: 30 March 2015.

This work is licensed under a Creative Commons Attribution 3.0 License (by-nc 3.0).

©Copyright E.M. Haacke *et al.*, 2015  
Licensee PAGEPress, Italy  
*Veins and Lymphatics* 2015; 4:5012  
doi:10.4081/vl.2015.5012

nia and intra-cranial venous system.<sup>8</sup> Unfortunately, over the last few years, different groups have been unable to replicate his work or each other's work with the results representing a broad range of patients and normal controls who may meet these criteria.<sup>10-18</sup> This has resulted in a controversial scientific debate between different groups research findings.<sup>19</sup> Currently, there is no consensus as to whether these criteria are valid or not. This may be, in part, due to the fact that US is highly operator-dependent. The importance for MS patients is not whether US works or not, but rather: *Are there venous vascular abnormalities in patients with MS?*

In this review, we will address an alternate approach to US by means of analyzing the vasculature of the head and neck quantitatively using MRI. A major advantage of MRI is that it allows evaluation of the structural patency and

dimensions of the head and neck vasculature and brain parenchyma as well as imaging flow data in minutes. For the flow data, the in-plane resolution is collected around 0.5 mm<sup>2</sup> so a clearly defined cross sectional area (CSA) can be found easily for all major vessels (arteries and veins) and the blood flow into the brain and out of the head-neck system into the heart can be quantified. This can be accomplished at both 1.5 T and 3.0 T for all manufacturers and, once a given protocol has been established, the results will be operator-independent.

A number of groups have tried using MRI to study the anatomy and/or flow of the vessels in the neck with varying degrees of success.<sup>10,12-15,20-31</sup> Again, as in US, the results between studies are not consistent. Part of the problem here is not the methodology; rather it is either the incompleteness of the studies and/or the associated processing of the data. The purpose of this review is to understand, if possible, why that might be the case by evaluating not only how the data were collected by each group but also how they were analyzed. In the end, we recommend a user-friendly, widely available MRI protocol that, with a fairly complete analysis of the data, may offer the ability for both healthy controls and MS patients to be carefully and consistently studied across different sites.

## Materials and Methods

### Recommended imaging protocol

To study venous abnormalities in MS patients, both the anatomy and flow of the vessels must be investigated with the patient in the supine position. The evaluation of the vascular anatomy of the head and neck can be done using either coronal 3D time-resolved contrast-enhanced (CE) MR arteriovenography (MRV) with coverage of the carotid arteries and internal jugular veins (IJVs), or by using transverse 2D time-of-flight (TOF) venography. Both should provide coverage from at least the level of the aortic arch to the sigmoid sinuses. The 3D CE MRV requires the timed use of a contrast agent. The time resolution for this 3D coverage should be only a few seconds (less than 10 s and preferably less than 5 s to capture the arterial phase clearly) per slab. Acquiring many time points will take between one and two minutes if the late phase venous information is desired. The 2D TOF MRV of the neck does not require the use of a contrast agent, however, the signal is dependent on the velocity of blood flow exceeding a threshold (the slice thickness/echo time) and takes longer to acquire.

MR flow quantification is finding a new life using 4D flow quantification which provides a 3D representation of flow dynamics throughout

the cardiac cycle.<sup>32</sup> The resulting data makes it possible to estimate pressure gradients along the vessels. The 4D flow measurements have also been shown to have accuracy and precision for both arterial and venous flows at varying velocity encodings which is promising for future applications studying venous stenosis and abnormal flow patterns.<sup>33</sup> The technique has also been used in combination with computational fluid dynamics to validate 3D printed phantoms of vascular structures.<sup>34</sup> However, this technique requires substantial time to collect and process. Still, for now, in the best interests of a clinically oriented research protocol, simplicity and speed are of great concern. The data which are collected should be easy to interpret and any post-processing which is needed, whether it is 3D modeling or functional quantitative measurements, should require minimal user input and minimal time. Therefore, our recommendation is to use 2D phase-contrast (PC) flow quantification (FQ) bearing in mind that as MR technology becomes faster, 4D methods will eventually become viable. Generally, 2D FQ is readily available from all MR manufacturers. The acquisition time is usually only 2 or 3 min depending on resolution and cardiac period. Flow throughout the cardiac cycle can be obtained roughly every 30 to 40 ms. In order to provide an adequate mapping of blood flow, data from at least two levels should be collected. The first slice should be set perpendicular to the flow of the IJVs and carotid arteries at the level cranial to the IJV valve and caudal to the carotid bifurcation (preferably at the C5/C6 level). The second slice should be set perpendicular to the flow of the IJV and carotid arteries at the level caudal to the vertebral arteries exiting of the vertebral column and cranial to the carotid bifurcation by over a few centimeters (preferably at the C2/C3 level).<sup>35,36</sup> The velocity encoding (VENC) should be set to 50 cm/s; this is to ensure sufficient signal-to-noise ratio in slower flowing veins. Any aliasing that occurs from the faster carotid artery flow during peak systole can be unwrapped using simple algorithms. This sequence does not require the administration of a contrast agent. Putting all components of a standard (conventional) neuro-imaging protocol together with the suggested flow protocol discussed above can be done in stages. A versatile protocol containing sequences which can be acquired on nearly any magnet is ideal, and the required core sequences and admitted variations both with and without contrast are discussed in the recent paper by Zivadinov *et al.*<sup>37</sup>

### Recommended analysis of the data

Ideally, data should be processed by individuals trained in using an acceptable software package for processing flow data. This software should be capable of reliable measures of cross sectional area and flow in both positive and negative directions. If both 2D and 3D

MRV data are collected, the coronal 3D contrast enhanced data can be reformatted to match the 2D TOF MRV data.<sup>25</sup> Usually available software packages detect the vessel boundaries automatically and provide a means to modify the boundary if the user so chooses. Some definition of stenosis is required and we recommend that vessels with a CSA less than 25 mm<sup>2</sup> at or caudal to the C3 level and less than 12.5 mm<sup>2</sup> cranial to the C3 level be denoted as stenotic.<sup>20-22,25,35,36,38</sup> Lack of visibility of the IJVs in all imaging modalities with clear visualization of surrounding vasculature in a segment should be referred to as atresia, and lack of visibility observed throughout the entire vessel length as aplasia. If a VENC of 50 cm/sec is used and aliasing occurs in either the arteries or veins, a phase unwrapping algorithm must be available or used when the flow velocity exceeds 50 cm/s.

In order to create an across system and across sequence robust result, we recommend normalizing the IJV flow to the arterial sum (tA) of the common carotid and vertebral (VA) arteries at the C5/C6 level and the internal carotid and VA at the C2/C3 level. This normalization will also account for variations in total flow into and out of the brain among subjects. The ratio between the IJV carrying the higher flow, considered the dominant jugular (dJ), and the lower flow, considered the subdominant jugular (sdJ) should then be calculated. All such measurements should be evaluated by each processor. A processor can be considered reliable if the intra-class correlation statistic [ICC(2)] for an individual vessel measurement is greater than 0.85. Finally, we recommend evaluating two populations: stenotic and non-stenotic for both the MS and healthy control (HC) groups. Differences that might not otherwise be apparent can become evident such as the number of stenotic (ST) and non-stenotic (NST) cases in each group and the flow associated with ST and NST individuals.

### Our experience over four independent studies covering 559 multiple sclerosis cases

In our own work in this area, we used SPIN (signal processing in nuclear MR; MR Innovations, Inc., Detroit, MI, USA) software and had six processors trained so that their data analysis had an ICC of 0.85 or better for all quoted flow measures. SPIN has a built in anti-aliasing algorithm. Vessel boundaries are calculated using a full width at half maximum algorithm.<sup>39</sup> We analyzed the following flow indices: total IJV flow normalized to total arterial flow (tIJV/tA), sub-dominant IJV normalized to dominant IJV (sdJ/dJ), and sub-dominant IJV normalized to total arterial (sdJ/tA) at both the C2/C3 and C5/C6 neck levels. A general linear model (GLM) was used to differentiate normalized IJV

flow between groups (ST, NST, and HC), controlling for age and sex and a univariate GLM was used to allow paired t-tests to study group differences. To determine the discrimination of these measures between disease states, a receiver operating characteristic (ROC) curve analysis was performed. Optimum ROC sensitivity and specificity was determined as the point with the least distance from the coordinate (0,1) with sensitivity as the y-axis and 1-specificity as the x-axis. Statistical significance for both the Student's *t*-test and the area under the curve evaluation was determined using  $P < 0.05$ . A chi-square test for proportion was used to test the number of ST cases between the groups with significance of  $P < 0.05$ .

## Results

Our recent work<sup>25</sup> using the MR protocol introduced above to assess IJV structure and function showed lower tIJV/tA blood flow in the MS group (138 subjects) compared to a group of healthy controls (67 subjects). More specifically, this MS group was divided into stenotic (72 subjects) and non-stenotic (66 subjects) giving three groups of roughly equal size ST MS, NST MS, and HC. Significant flow differences were found in the IJVs between the MS and HC groups. This research showed significant differences between the ST-MS group and the HC group, between the ST-MS and the NST-MS groups, and no differences in flow between the NST-MS group and the HC group. The largest difference in tIJV/tA flow between the ST-MS and HC groups was observed below the cut-off of 0.66 for C2/C3 and 0.62 for C5/C6. That is, the percentage of ST-MS patients below these cutoff values was much larger than that of the NST-MS or HC populations. When applying these thresholds to the HC and MS groups, 4/67 (6%) of the HC group and 51/138 (37%) of the MS group fall below those two boundaries. Of the MS group, 44/72 (61%) ST-MS and 7/68 (11%) NST-MS subjects fell under the cut-offs indicating a disparate flow behavior between the two groups.

The first flow related study on MS from our group found that 136 (68%) out of 200 MS patients showed the presence of anatomic abnormalities, including stenosis or atresia, in the IJVs.<sup>22</sup> In this study the flow measurements were reported for C5/C6 neck level only and were normalized as tIJV/tA. The result was compared to the normalized IJV flows reported by Doepp *et al.*<sup>40</sup> for 50 healthy controls. The NST-MS behaved similar to the HC, however, the ST-MS had significantly reduced IJV flow. The sdJ/dJ index was calculated, and it was found that 67% had flow in the subdominant IJV less than 3 mL/s and a sdJ/dJ ratio less than 1/3. The next study found 79% of the stenotic

group had a sdJ/tA flow of less than 20%, a tIJV/tA of less than 50% and/or a sdJ/dJ flow ratio of less than 1/3.<sup>21</sup> Similar findings were seen in a fourth study where out of 323 MS patients, 223 (69%) had a stenosis.<sup>20</sup> The tIJV/tA was significantly lower at both C2/C3 and C5/C6 neck levels in the ST-MS group compared to the NST-MS group, with 56+/-26% and 51+/-23% compared to 85+/-13% and 73+/-12% respectively.

In order to better demonstrate the validation of cross-site studies employing the same protocol and processing, a meta-analysis was done on the data from the four previously mentioned studies<sup>20-22,25</sup> plus our available database yielding a total of 559 MS cases and 95 HC. The flow data were reprocessed using SPIN software rather than FLOW-Q software. In this large group analysis, it is clear from the MRV and flow data that there are venous structural abnormalities in both the HC and MS populations, and that primary outflow obstruction will lead to collateralization of flow to the heart. A summary of each type of stenosis, atresia, and aplasia is given in Table 1. More than half (61.8%, 346/559) of the MS group showed abnormal vasculature using both the 2D TOF MRV and 3D CE MRAV data, whereas, only 11 of 49 HC (22.4%, 46 subjects did not have venographic imaging to review) showed abnormal vasculature. A goal in this meta-analysis was to determine if these structural and functional changes could still separate the HC and MS groups. Examples of the appearance of venous abnormalities with a description of the collateralization of flow are shown in Figure 1 for both MS and HC. To better understand how the structural changes have affected the venous drainage, an ROC analysis was performed to compare the MS and HC groups, as well as the

ST-MS and HC groups, to determine if a significant separation in flow patterns could be observed. All cases were plotted comparing the normalized IJV flows at C2/C3 vs C5/C6 levels and are shown in Figure 2A and B. Based on the distribution of flows between groups, the optimum cutoff for tIJV/tA for categorizing the most ST-MS subjects while categorizing the least HC for the C5/C6 level was 61% yielding a sensitivity of 0.80 and specificity of 0.62 and for the C2/C3 level the optimum cutoff was 73% yielding a sensitivity of 0.74 and specificity of 0.71. The MS subjects tend to show a larger variety of compensation which involves reflux of flow through the common facial vein out of the IJV and into superficial collaterals, bypassing any stenosis in the IJV through neighboring collaterals, and other large shifts of outflow into and out of the IJVs. The number of ST-MS, NST-MS, HC, and total MS cases that fall below both thresholds is 192/346 (55.5%), 23/213 (10.8%), 12/95 (12.6%), and 215/559 (38.5%). Of the ST-HC cases, 6/11 (54%) fall below both thresholds; it is noteworthy that these cutoffs are similar to Sethi *et al.*<sup>25</sup> Lastly, none of the HC showed any tIJV/tA below 25% for both C5/C6 and C2/C3 neck levels. In Figure 2C and D, the MS patients are broken into two groups (upper or lower level stenosis) for each of the left and right jugular veins. It can be seen that the healthy controls tend to sit in the middle of the plots while many of the MS patients are bunched toward or along the axes due to their slower flow in one vein. To better understand the role of stenosis, we evaluated the flow data as a function of stenosis location. For example, if there is an upper neck level stenosis of the left IJV (LIJV), how is flow redirected and is there a change in the paired non-stenotic right IJV (RIJV)? The stenosis level was considered

**Table 1. Stenosis type by group.**

	MS (559)	(MS %)	HC (49)	HC (%)
Stenosis type	346	61.8%	11	22.4%
LL RIJV stenosis	133	23.8%	4	8.2%
UL RIJV stenosis	93	16.6%	1	2.0%
LL LIJV stenosis	158	28.3%	7	14.3%
UL LIJV stenosis	115	20.6%	4	8.2%
LL RIJV atresia	6	1.1%	0	0.0%
UL RIJV atresia	17	3.0%	1	2.0%
LL LIJV atresia	13	2.3%	0	0.0%
UL LIJV atresia	33	5.9%	0	0.0%
RIJV diffuse stenosis	8	1.4%	0	0.0%
LIJV diffuse stenosis	21	3.7%	0	0.0%
RIJV aplasia	1	0.2%	0	0.0%
LIJV aplasia	2	0.4%	0	0.0%

MS, multiple sclerosis; HC, healthy control; LL, lower level; RIJV, right internal jugular vein; UL, upper level; LIJV, left internal jugular vein. For the HC, 46 subjects were part of a different study which did not include venography. Note in the last 8 narrowing or stenotic categories, there are 101 MS cases or 18% while in the HC there is only 1 case or 2%.



either a single point in the upper or lower neck and if it was in the RIJV or LIJV. Figure 2C and D show the distribution of each type of stenosis and the affect it has on C2/C3 and C5/C6 flows in both IJVs. It is reported in the literature and generally known that the RIJV is dominant to the LIJV in over half the population, a smaller group has co-dominant IJVs, and an even smaller group shows LIJV dominance. Figures 2C and 2D demonstrate this trend as seen in the HC NST as showing the RIJV with higher flow (about 1/3 of that in the LIJV). If we have an upper or lower LIJV stenosis this will reduce the flow in the LIJV, we only see a slight increase, if any, through the RIJV. This indicates there may be collateralization on the left side. However, when there is a RIJV upper neck level stenosis it reduces the outflow through the IJV and increases it through the LIJV dramatically, clearly separating this group from the HC. The same is seen in a lower RIJV stenosis but to a lesser extent. Therefore, it appears that a stenosis in one jugular vein only will redirect flow to the other, or *vice versa*.

## Discussion

One of the key issues in this review is to consider why results from many groups using MRI are so disparate. Many of the studies thus far are not an exact recapitulation of the original US methods proposed by Zamboni,<sup>8</sup> but generally look for the hallmarks of chronic cerebrospinal venous insufficiency (CCSVI) which are venous structural and flow abnormalities using several different methods of data collection and analysis. We wish to promote a more uniform data collection and analysis so that groups around the world can easily compare their results and hopefully draw more consistent conclusions. Many investigators have spent a lot of time on their studies but do not collect all relevant data or do not process the data they have collected consistently. Some examples from the recent literature are presented below.

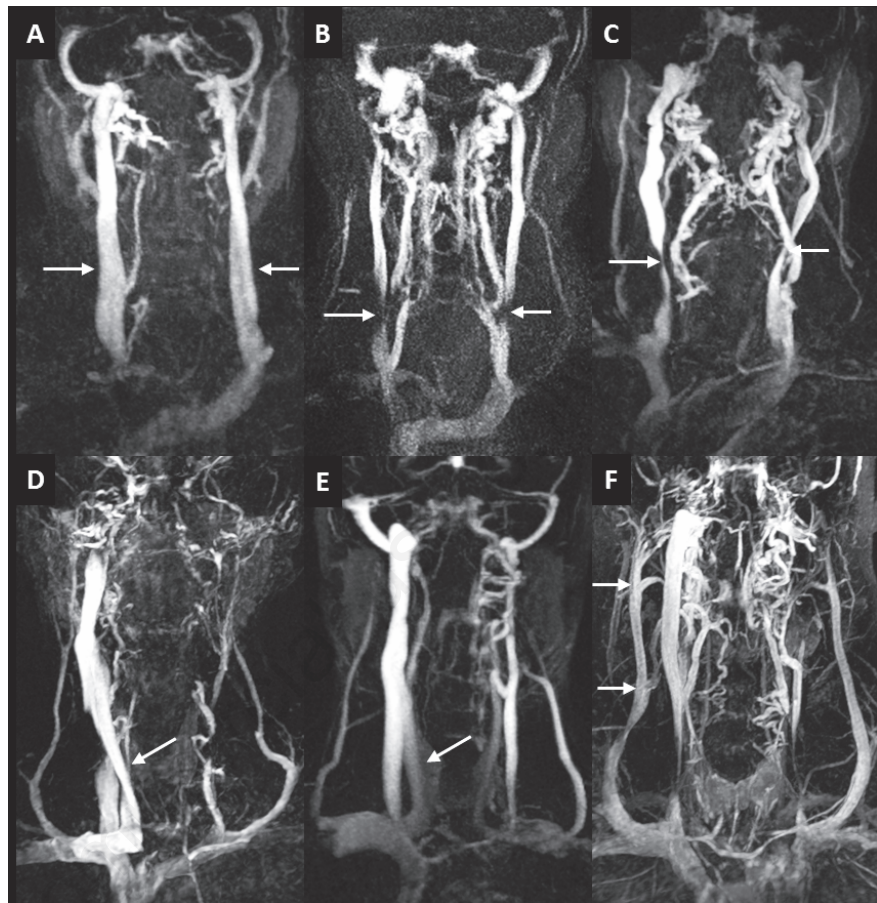
### Studies from Buffalo neuroimaging and Stanford using ordinal internal jugular vein assessments

After the original CCSVI study, Zivadinov and colleagues published five studies using 2D TOF MR venography and 3D TRICKS sequences on a 3T scanner.<sup>13,27,28,31,41</sup> In all of their studies, the morphology of the IJVs was classified using an ordinal scale: absent, pinpoint, flattened, crescentic, and ellipsoidal in which absent and pinpoint were considered abnormal. When evaluating the IJV, the narrowest point along the inferior and superior part of the segments was considered.

Asymmetries were also assessed in the IJVs and vertebral veins; prominent venous collaterals were noted. Any collaterals that were >5 mm in diameter (or 7 mm for the segment of the inferior segment of the external jugular

vein) were noted as prominent.

In the first pilot study by Hojnacki *et al.*<sup>41</sup> with 10 MS and HC, US and selective venography were used and compared to the MRI modalities with respect to sensitivity and



**Figure 1.** Examples of 3D contrast-enhanced (CE) magnetic resonance arteriovenography (MRV) of multiple sclerosis (MS) patients and healthy controls (HC). A) HC with normal appearing internal jugular vein (IJV) (arrows) with some collateral enhancement. The IJVs in this HC carry the dominant outflow towards the heart. B) HC with abnormal appearing IJVs with bilateral lower level stenosis (arrows). The IJV flows normalized to the total arterial input at the C2/C3 and C5/C6 levels are 27% and 24%, respectively, a trend which is seen in many HC where flows are consistent between levels. Compensation appears to divert venous flow to the para-spinal and deep cervical veins through the anterior condylar confluence. C) MS patient with bilateral lower level stenosis (arrows) of the IJV. It closely resembles the HC in B with 32% of flow through the IJV and 44% through the para-spinal and deep cervical veins at the C5/C6 level. D) MS patient with diffuse stenosis of the left IJV and a tight stenosis of the right IJV at the lower neck level. The outflow at the C2/C3 level through the right IJV is 70% of total arterial inflow, while at the C5/C6 neck level it is reduced to 9%. The right anterior jugular vein (AJV, white arrow) carries 52%, indicating that the outflow through the IJV at the upper neck was redirected through the common facial vein as an anastomosis to the AJV. This type of primary compensation due to structural anomalies can be seen when there is high flow at the upper neck level and low flow at the lower neck, or when an upper level stenosis prevents inflow from the sigmoid sinus and the common facial vein reconstitutes high flow into the IJV at the lower neck level. E) MS patient without stenosis in the right IJV, however, as in D, the flow is redirected to the AJV (white arrow) via the common facial vein connection near the C4 vertebrae level. This indicates that there may be other structural or functional abnormalities which are not clearly evident in the CE MRV which result in quantitative changes in flow. F) MS patient with a tight stenosis at the lower neck level. The flow is redirected to the external jugular vein (EJV) via multiple anastomoses at different levels of the neck (white arrows). At the C2/C3 level the right IJV carries 42% of total arterial input; however at the C6 level it carries a negligible amount. At the C2/C3 level the right EJV carries 16% and by the C5/C6 level this increases to 52%.

specificity of diagnosing CCSVI. The sensitivity and specificity for detecting IJV abnormalities for 3D TRICKS were 31% and 100%, and 25% and 100% 2D TOF respectively. MRV methods were shown to have lower sensitivity and specificity compared to US and selective venography; thus, MRV methods were concluded to have limited value when studying CCSVI. Lack of experience and evaluation standards using MRV were cited as drawbacks to the study. Further, the methods were noted to not have the resolution to depict intraluminal and vessel wall anomalies such as septa, webs, annulus, *etc.* No saturation pulse was used in the 2D TOF imaging, which may miss bidirectional or reflux flow.

The second study by Zivadinov *et al.*<sup>31</sup> was a longitudinal study among 10 MS and 6 HC subjects. Catheter venography (as gold standard) and US were performed for comparison. For detecting IJV anomalies, low specificity was noted between two MRV techniques (30-40%) and catheter venography, while high specificity (99%) was noted; this contrasts with the work of the previous study. This protocol did not screen for any secondary venous collateralization. Zivadinov's third study involving 57 MS patients and 21 HC found no differences between the two groups in using the MRV methods, thus not supporting the results of Zamboni who was able to distinguish MS from HC with certainty using US. No differences in venous collateral prominence or IJV asymmetries were found between MS and HC subjects.<sup>13</sup>

Two additional studies by Dolic *et al.*<sup>27,28</sup> were done: one using a multimodal approach to evaluating CCSVI (MRV and US), and one using the same methods to evaluate the frequency of venous intraluminal and extraluminal abnormalities. The first study showed no differences in flow morphology using TOF and TRICKS imaging between MS and HC, even though differences were found in US.<sup>28</sup> In the latter study, no differences in IJV appearance were found between MS and HC using the MRV methods; in the MS group alone, however, progressive MS subjects showed more IJV abnormalities in MRV compared to non-progressive MS subjects.<sup>27</sup> Combining modalities increased the specificity for screening for MS, but the sensitivity remained low indicating only a subset of the MS patients may present with vascular pathology. While all five of these studies did not find any differences in IJVs between the two groups, this study was strictly an anatomical one and did not include phase-contrast flow quantification or CSA using MRI. Some of the pitfalls of the analyses are detailed in work by Rahman *et al.*<sup>38</sup> and Sethi *et al.*<sup>25</sup>

Two additional MR venography studies were from the Stanford group. The first study by Zaharchuk and colleagues<sup>42</sup> compared 2D TOF MRV and 3D TRICKS with contrast venography

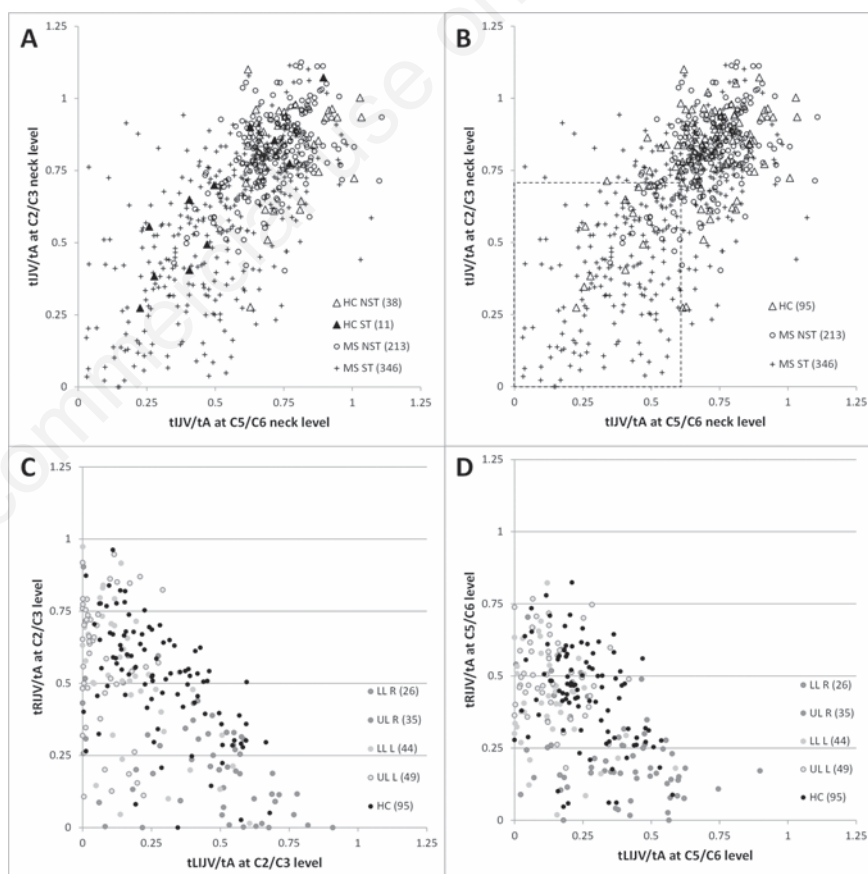
in MS patients (no controls were used). IJV calibers were assessed with 2D TOF at three different neck levels and scored ordinally as follows: 0 for normal round or ovoid, 1 for mild flattening, 2 for moderate flattening, and 3 for severe flattening or lack of visualization. The presence of collateral veins was assessed using a similar ordinal method with a score of 0 being none or minimal and 3 being most prominent. Contrast venography was used as a standard to compare with the MRI images. They found that the most common stenoses were in the upper (C1-C2) and lower (C6-T2) segment of the IJV. Though good agreement was seen in the upper and mid-portions of the neck between 2D TOF MRV and contrast venography, poor agreement was noted in the lower neck level (C6-T2). They also concluded that this may be due to turbulent or slow flow which may underestimate the IJV area in 2D

TOF MRV. Collaterals were best visualized in TRICKS as their slow flow may not generate signal in 2D TOF MRV.

The second study by McTaggart *et al.*<sup>43</sup> used similar MR venographic methods to assess IJV stenosis and venous collaterals in 19 patients with MS and 20 healthy controls. It proved to be one of the first studies that noted differences in the IJVs with respect to MRV; more specifically, the MS group showed greater flattening compared to the healthy control group, however, they did not show differences in the presence of venous collaterals in 3D TRICKS. Both the Stanford studies and the Zivadinov studies did not use quantitative CSA measurements for comparing jugular veins, nor did they use flow quantification for comparison.

### Structural-focused studies

Rahman *et al.*<sup>38</sup> assessed 170 MS and 40 HC



**Figure 2.** A) Internal jugular vein (IJV) flow normalized to arterial flow for the C5/C6 neck level plotted against the C2/C3 neck level for cases with venography only. B) IJV flow normalized to arterial flow for the C5/C6 neck level plotted against the C2/C3 neck level for all cases. Threshold lines of total IJV flow normalized to total arterial flow (tIJV/tA) at C6 < 0.61 and tIJV/tA at C2 < 0.73 are drawn (dotted lines). C-D) Left (LIJV) vs right (RIJV) distribution of the normalized internal jugular veins flow at the lower level (C5/C6) and upper level (C2/C3) in subjects with different types of obstruction and in healthy controls (HC). Normalization for the C5/C6 flow is referred to the sum of common carotid artery and vertebral artery measured at the same level. NST, non-stenotic; ST, stenotic; MS, multiple sclerosis; LL, lower level; UL, upper level.



subjects using 2D TOF MRV and 3D TRICKS using a quantitative measure of CSA for the IJVs.<sup>22</sup> A larger CSA was observed in the 3D TRICKS data compared to the 2D TOF MRV data. A number of anomalies were noted in the MS group such as atresia, aplasia, diffuse or tight stenosis, and ectasia caused by compression from the carotid arteries. Generally the anatomy was depicted more completely using 3D TRICKS compared to 2D TOF MRV. This is because if the vessel is patent the contrast agent will show signal even if there is slow flow, whereas in 2D TOF little signal is generated for slow flow. Cases in which flow may jet down the side of the vessel may present with a smaller area size or pinpoint in 2D TOF MRV compared to 3D TRICKS, in which the entire lumen may be seen (this may be the cause of the larger CSA in 3D TRICKS). While this study neither proved nor refuted the CCSVI hypothesis, it did bring interesting dimension on how to use both the 2D and 3D methods in a complimentary way.

One of the first papers using MR anatomic and flow data was presented by Sundström *et al.*<sup>26</sup> who looked at flow at the C2/C3 level for 21 MS patients and 20 healthy controls at 3T. They found a trend toward lower total cerebral blood flow in the MS cases. However, upon normalization of the total IJV flow to the total CBF they found both groups had an average of 70% although the spread in these normalized flows ranged from 0.12 to 0.97 for the MS group and 0.32 to 0.87 in the control group. It is important to note that they reported separately left and right IJV normalized flows, which makes it comparable to previous studies looking at dominance patterns of IJV flow. However, the limited size of the group makes it impossible to draw any conclusions as to whether having normalized total IJV flow less than 60% is abnormal or not. They also showed several cases with reflux and stenosis (3 MS patients no HC).

Wattjes *et al.*<sup>14</sup> studied 20 MS patients and 20 HC at 3 T and found no cases with reflux. However, no quantitative flow data is given in this paper. They note that 50% of MS patients had stenosis and 40% of HC using a 50% stenosis rule. There is no surprise in this finding given that they did not use an absolute measure of cross sectional area (see the discussion under Rodger *et al.*<sup>12</sup> as to why this choice of 50% is inappropriate for veins).

Doepf *et al.*<sup>15</sup> presents a more balanced view by reporting the level of stenoses. They studied 40 patients at 1.5 T using MRV to assess IJV stenosis, and found 12 had narrowing greater than 50% (relative to maximal CSA), 19 between 50 and 80% and 9 greater than 80%. Flow, however, was measured using Doppler between intervertebral segments C4/C5 or C5/C6. They showed that there is a significant difference in total IJV flow between those with

no stenosis and those with a stenosis greater than 80% (but not between those with no stenosis and those with 50 to 80% narrowing). Specifically, they quote total IJV flow for the non stenotic group as 616 +/- 40 mL/min for standard error of the mean (P=0.02) and, for the greater than 80% group, they quote IJV flow as 381 +/- 75 mL/min for standard error of the mean (P=0.01). Clearly, there is a significant difference for total IJV flow between the non-stenotic and high-grade stenotic groups, even though their method of stenosis assessment is different from ours. Their conclusion then is very similar to ours although our stenosis cutoff was based on a 25 mm<sup>2</sup> CSA.

Macgowan *et al.*<sup>30</sup> measured arterial and venous blood flow for 26 MS adolescent patients and 26 age-matched normal controls. They found there was a trend for reduced flow in the left internal jugular vein but that the difference was not significant. However, they did not classify patients as stenotic or non-stenotic. The measured average arterial flow was 754 mL/min (including the common carotid and vertebral arteries). They did not compare total jugular flow between groups.

Rodger *et al.*<sup>12</sup> measured venous blood flow in 100 MS patients and 100 normal controls. They quote left and right jugular flow but do not quote arterial flow. They did not compare total jugular flow between groups, they did not normalize the flow and they did not sub-categorize patients into stenotic or non-stenotic groups.

Since CCSVI is about abnormal total jugular flow, both the previous two papers failed to quote the most critical piece of information. Further, the variation in total IJV flow may well be much less than either jugular alone and hence may lead to a clear difference in their two populations. In fact, both found a trend to lower LJJV flow in the MS population but they did not normalize their data to arterial flow. Further sub-categorizing the data into stenotic and non-stenotic types has the potential to separate that sub-population of MS patients with abnormal flow more clearly. If the data were to be re-analyzed, both these studies may well validate the findings discussed in our meta-study in this paper, that ST-MS patients have significantly reduced total IJV flow.

Another recent paper by Trabousee *et al.* compares MR with catheter venography.<sup>11</sup> They use a percentage definition of stenosis for veins similar to that used in evaluating carotid arteries (which have geometrically consistent CSA from the subclavian to the bifurcation). This is not appropriate for veins because they can flare out at the base near the subclavian vein and are quite variable in size throughout their course. Several other groups have used the more realistic definition of stenosis as a vessel CSA falling below a fixed threshold of either 25 mm<sup>2</sup><sup>22</sup> or 30 mm<sup>2</sup><sup>8</sup> at or below C3/C4

and 12.5 mm<sup>2</sup> at or above C2/C3.<sup>22</sup> Trabousee *et al.* make the claim that there is no difference in stenosis rates between HC and MS patients, with a stenosis rate of 74% in MS patients and 70% in HC.<sup>11</sup> Their study defined IJV stenosis as a narrowing of more than 50% of the widest vessel segment below the mandible. In a recent abstract, we showed that if our data were re-analyzed using this percentage approach, we would have found 83% of MS patients and 44% of HC were stenotic suggesting that the percentage definition of stenosis for veins is unrealistic.<sup>25</sup>

Costello *et al.* did a large study of 120 MS patients and 60 HC with US and MR.<sup>10</sup> They found no evidence of CCSVI for either group. They also found no differences in measured narrowings using CE MRAV between the groups. However, they included the criteria greater than 50% stenosis rather than the absolute 25 mm<sup>2</sup> or 30 mm<sup>2</sup> suggested in recent years since, as discussed earlier, greater than 50% stenosis is not appropriate for veins. No MR flow measurements were done in this study. Likewise, Jurkiewicz *et al.* found no differences in stenosis or CSA between 21 MS patients and 19 HC in children.<sup>23</sup> No flow measurements were done in this study.

To demonstrate this problem, we re-analyzed our own data from the four previous studies<sup>20-22,25</sup> to show the number of cases from each group as a function of percentage stenosis. Figure 3 shows a percentage of the MS and HC groups that are stenotic using a variable CSA at the C5/C6 neck level. At a CSA ≤25 mm<sup>2</sup>, none of the HC classify as stenotic for the RIJV, while 4% of the HCs meet this criteria for the LIJV. Of the MS group, 24% of them classify as stenotic for the RIJV, and 38% of them meet this criterion for the LIJV. In general, more MS patients are classified as stenotic even as the CSA cutoff value increases. The strongest separation between MS and HC occurs for narrowing less than 25 mm<sup>2</sup>. Clearly the choice of an absolute cutoff makes more sense in studying stenoses in veins.

Kramer *et al.*, compared catheter venography (CV) and CE MRA in 99 subjects.<sup>44</sup> No significant pressure gradients were seen (but they used greater than 3 mm Hg as their criteria for significant changes). A subset of 39 patients received both CE-MRA and CV. Stenosis measurements between MR and CV were in good agreement. As far as expected pressure changes are concerned, a recent computational fluid dynamics paper showed that the presence of stenosis can lead to pressure increases of up to 2.5 mmHg which for veins represents a major increase in pressure across a stenosis.<sup>45</sup> Changes also occur in the superior sagittal sinus and straight sinus and, therefore, may affect the venous pressure changes in the basal ganglia and midbrain, areas where

increases in iron deposition are seen for MS patients. The real question is: *What constitutes a major change in pressure for the venous system?*

The work by El-Sankari and colleagues was more flow-orientated rather than anatomical.<sup>29</sup> Their group studied primary and secondary venous flow, arterial flow, and cerebrospinal fluid (CSF) flow using MRI flow quantification. They did not note any flow reductions in the IJV, nor did they find any differences in the oscillating properties of the venous flow curves. However, they did note reduced arterial perfusion in MS patients, as well as decreased CSF dynamic oscillations in MS.

In summary, apart from the work of Feng, Utriainen, Sethi and Haacke,<sup>20-22,25,35</sup> none of these other papers has a complete set of anatomic and quantitative flow data at C2/C3 and C5/C6. Many of the papers do not discuss total jugular flow or normalized jugular flow, or they use an incorrect assessment of the cross sectional area for stenosis as being 50% of maximum jugular area. In Sethi *et al.*, the sensitivity and specificity of the ability to use an anatomic assessment to predict abnormal flow were 0.78 and 0.76 at the C5/C6 neck level; at C2/C3 it was 0.84 and 0.68, respectively.<sup>25</sup> What this means is that we can predict with at least 78% certainty that an MS patient that we classify as stenotic will have a normalized jugular flow lower than 62% at the C5/C6 neck level. We have established similar cut-offs for sensitivity and specificity with our group meta-analysis presented in the results section.

As for the anatomical information seen with MRI, there appears to be a variety of stenosis types for MS patients as shown in Table 1. Notably, the atresias, diffuse stenoses, and aplasia cases are only seen in the MS group.

There are other considerations that relate to the vascular system. These include evidence of iron in the basal ganglia and midbrain,<sup>46</sup> veno-centric MS lesions,<sup>6</sup> abnormal cerebrospinal flows,<sup>47,48</sup> abnormal perfusion,<sup>3</sup> and more recently evidence for significant reductions in cerebrovascular reserve in MS patients suggesting that there is a change in the brain's ability for MS patients to respond to challenges that alter blood flow.<sup>49</sup>

Several other relevant studies considered the effects of inspiration on flow measurements. Kudo *et al.*<sup>50</sup> studied the use of 2D PC MR venography and 2D PC flow images to measure flow changes in the IJV in 107 subjects with lacunar infarction. They found that during deep inspiration that 57 (36) subjects had decreased signal on the right (left) sigmoid sinus while 12 (33) had increases on the right (left). They found a decrease in flow velocity in 92 (70) subjects in the right (left) sigmoid sinus and an increase in the remaining subjects. Mehta *et al.*<sup>51</sup> studied 15 volunteers, they also showed that during deep inspi-

ration there is a reduction in dural sinus flow. In the MR studies discussed above, breath-hold or Valsalva maneuvers were not part of the protocol during imaging.

Using 3D contrast enhanced MRAV and specially placed saturation bands, Paksoy *et al.*<sup>52</sup> demonstrated in three cases that flow reversal in the inferior petrosal sinus is due to a compression of the brachiocephalic vein preventing proper outflow in the LIJV.

Impaired venous flow may not be limited to MS. In a recent study from our group by Liu *et al.*<sup>24</sup> looking at idiopathic Parkinson's disease (IPD), the appearance of veins using TOF MRV, PC MRI flow at the C2 neck level, and lesion loads in T2 FLAIR were compared between 23 IPD patients and 23 age matched HC. The result differs from what was observed with the large group analysis of MS subjects in that the major flow abnormalities seemed to be a lack of flow in the left transverse sinus and left IJV. This abnormal venous outflow correlated with the T2 lesion loads. Although the criteria differed from the analysis done on MS subjects, it does imply that venous vascular abnormalities may be found within sub-populations of other neurological and neurodegenerative diseases. Jang *et al.*<sup>53</sup> recently reviewed 2D TOF MRA data for 3475 patients from a general radiological database. In their assessment, they assessed the IJVs and the dural sinuses for venous reflux defined as tubular high-intensity signal in the presence of in-slab saturated arteries. They found 1.6% of the sample showed venous reflux flow, and all instances were on the patients' left side. Generally, the reflux finding was more prevalent in females,

and in older patients. It is notable that in the cohort with reflux, the following symptoms were presented: ischemia (39.3%), intracranial arterial stenosis (14.3%), headache (10.7%) and dizziness (8.9%). TOF is very useful in qualitatively detecting smaller vessels that are hard to measure quantitatively with phase-contrast flow MRI, however, in cases where the reflux may be too slow in which a velocity does not meet a certain threshold, no signal will be present in TOF.

Some of the limitations in many of these studies include the drawbacks of using MRV methods.<sup>13,31,41</sup> Most notably, the low resolution prohibits it from viewing intraluminal abnormalities such as valves, septa, flaps, and annuli. The venous appearance can also depend on hydration status, head and neck coil positioning, transmural pressure, and respiratory phase.

Another limitation of the proposed MRI protocol is its inability to directly visualize many intraluminal obstacles, such as membranous webs, septum, and malfunctioning valves, which have been observed as being prevalent in the MS population. While the resulting flow changes can be measured using 2D flow quantification, the implementation of 4D flow quantification will provide a more comprehensive assessment of pressure and flow changes directly at these points of obstruction. It is also pertinent to note that while imaging modalities have their unique strengths and weaknesses, a strong protocol may be derived from their combination or fusion, such as US and MRI. Lastly, the division of subjects into stenotic and non-stenotic subgroups may

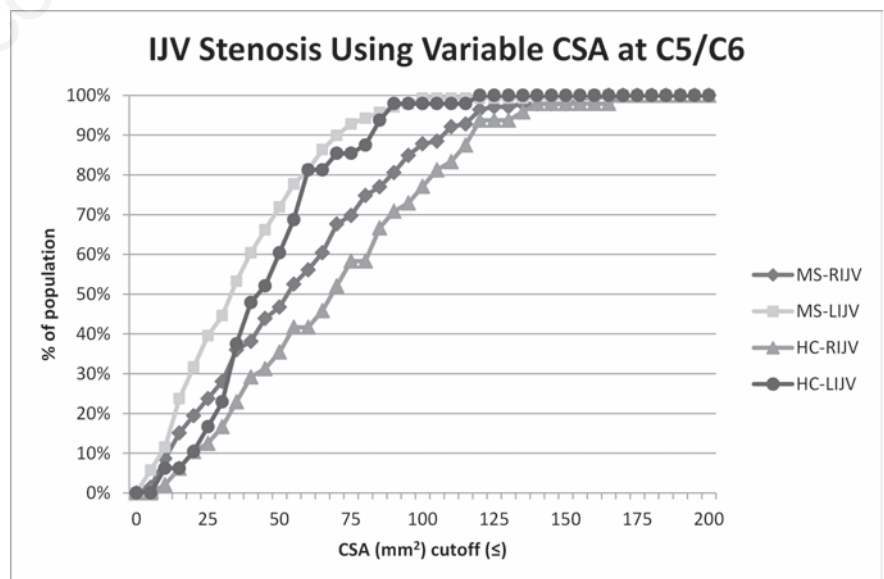


Figure 3. The percentage of the multiple sclerosis (MS) and healthy control (HC) groups (data from Sethi *et al.*<sup>25</sup>) which are stenotic when using a variable cross sectional area (CSA) rather than a fixed CSA to measure lower level stenosis. RIJV, right internal jugular vein; LIJV, left internal jugular vein.

invoke criticism by those directly comparing MS and healthy controls. The rationale behind dividing the group, is that the flow distribution in the MS population is very large, but we recognized that the spread of healthy controls and non-stenotic MS is a tight group, therefore we reiterate that the abnormalities we are finding in both flow and anatomy are in a subset of the MS group, and not representative of the entire spectrum of the disease.

## Conclusions

Despite the fact that there are many papers published on venous effects in MS patients in MRI, the only consistent data appears to come from breaking the MS population into stenotic and non-stenotic groups and then performing specialized flow processing in each group. The basic findings are that far more MS patients show anatomical abnormalities for the jugular veins and that the total jugular flow in the stenotic MS patients is significantly less than that in the non-stenotic and healthy control group. We recommend that all MR-related investigations collect high resolution MR venographic anatomic and flow data for the dural sinuses and jugular veins and that not just individual jugular flow but total jugular venous flow and normalized jugular flow be evaluated at both the C2/C3 and C5/C6 levels.

## References

- Schelling F. Damaging venous reflux into the skull or spine: relevance to multiple sclerosis. *Med Hypotheses* 1986;21:141-8.
- Haacke EM, Beggs CB, Habib C. The role of venous abnormalities in neurological disease. *Rev Recent Clin Trials* 2012;7:100-16.
- Law M, Saindane AM, Ge Y, et al. Microvascular abnormality in relapsing-remitting multiple sclerosis: perfusion MR imaging findings in normal-appearing white matter. *Radiology* 2004;231:645-52.
- Haacke EM. Chronic cerebral spinal venous insufficiency in multiple sclerosis. *Expert Rev Neurother* 2011;11:5-9.
- Dake MD, Zivadinov R, Haacke EM. Chronic cerebrospinal venous insufficiency in multiple sclerosis: a historical perspective. *Funct Neurol* 2011;26:181-95.
- Tan IL, van Schijndel RA, Pouwels PJ, et al. MR venography of multiple sclerosis. *AJNR Am J Neuroradiol* 2000;21:1039-42.
- Adams CW. Perivascular iron deposition and other vascular damage in multiple sclerosis. *J Neurol Neurosurg Psychiatry* 1988;51:260-5.
- Zamboni P, Galeotti R, Menegatti E, et al. Chronic cerebrospinal venous insufficiency in patients with multiple sclerosis. *J Neurol Neurosurg Psychiatry* 2009;80:392-9.
- Aboulker J, Bar D, Marsault C, et al. [Intraspinal venous hypertension caused by multiple abnormalities of the caval system: a major cause of spinal cord problems]. *Chirurgie* 1977;103:1003-15.
- Costello F, Modi J, Lautner D, et al. Validity of the diagnostic criteria for chronic cerebrospinal venous insufficiency and association with multiple sclerosis. *CMAJ* 2014;186:E418-26.
- Trabousee AL, Knox KB, Machan L, et al. Prevalence of extracranial venous narrowing on catheter venography in people with multiple sclerosis, their siblings, and unrelated healthy controls: a blinded, case-control study. *Lancet* 2013;383:138-45.
- Rodger IW, Dilar D, Dwyer J, et al. Evidence against the involvement of chronic cerebrospinal venous abnormalities in multiple sclerosis. A case-control study. *PLoS One*. 2013;8:e72495.
- Zivadinov R, Lopez-Soriano A, Weinstock-Guttman B, et al. Use of MR venography for characterization of the extracranial venous system in patients with multiple sclerosis and healthy control subjects. *Radiology* 2011;258:562-70.
- Wattjes MP, van Oosten BW, de Graaf WL, et al. No association of abnormal cranial venous drainage with multiple sclerosis: a magnetic resonance venography and flow-quantification study. *J Neurol Neurosurg Psychiatry* 2011;82:429-35.
- Doepf F, Wurfel JT, Pfueller CF, et al. Venous drainage in multiple sclerosis: a combined MRI and ultrasound study. *Neurology* 2011;77:1745-51.
- Doepf F, Paul F, Valdueza JM, et al. No cerebrocervical venous congestion in patients with multiple sclerosis. *Ann Neurol* 2010;68:173-83.
- Monti L, Menci E, Piu P, et al. A sonographic quantitative cutoff value of cerebral venous outflow in neurologic diseases: a blinded study of 115 subjects. *AJNR Am J Neuroradiol* 2014;35:1381-6.
- Baracchini C, Perini P, Calabrese M, et al. No evidence of chronic cerebrospinal venous insufficiency at multiple sclerosis onset. *Ann Neurol* 2011;69:90-9.
- Zamboni P, Menegatti E, Occhionorelli S, Salvi F. The controversy on chronic cerebrospinal venous insufficiency. *Veins and Lymphatics* 2013;2:e14.
- Feng W, Utriainen D, Trifan G, et al. Characteristics of flow through the internal jugular veins at cervical C2/C3 and C5/C6 levels for multiple sclerosis patients using MR phase contrast imaging. *Neurol Res* 2012;34:802-9.
- Feng W, Utriainen D, Trifan G, et al. Quantitative flow measurements in the internal jugular veins of multiple sclerosis patients using magnetic resonance imaging. *Rev Recent Clin Trials* 2012;7:117-26.
- Haacke EM, Feng W, Utriainen D, et al. Patients with multiple sclerosis with structural venous abnormalities on MR imaging exhibit an abnormal flow distribution of the internal jugular veins. *J Vasc Interv Radiol* 2012;23:60-8 e1-3.
- Jurkiewicz E, Kotulska K, Nowak K, et al. MR venography in children and adolescents with multiple sclerosis does not show increased prevalence of extracranial veins anomalies. *Eur J Paediatr Neurol* 2014;18:218-22.
- Liu M, Xu H, Wang Y, et al. Patterns of chronic venous insufficiency in the dural sinuses and extracranial draining veins and their relationship with white matter hyperintensities for patients with Parkinson's disease. *J Vasc Surg* 2015;61:1511-20.e1.
- Sethi SK, Utriainen DT, Daugherty AM, et al. Jugular venous flow abnormalities in multiple sclerosis patients compared to normal controls. *J Neuroimaging* 2014 [Epub ahead of print].
- Sundström P, Wählin A, Ambarki K, et al. Venous and cerebrospinal fluid flow in multiple sclerosis: a case control study. *Ann Neurol* 2010;68:255-9.
- Dolic K, Marr K, Valnarov V, et al. Sensitivity and specificity for screening of chronic cerebrospinal venous insufficiency using a multimodal non-invasive imaging approach in patients with multiple sclerosis. *Funct Neurol* 2011;26:205-14.
- Dolic K, Marr K, Valnarov V, et al. Intra- and extraluminal structural and functional venous anomalies in multiple sclerosis, as evidenced by 2 noninvasive imaging techniques. *AJNR Am J Neuroradiol* 2012;33:16-23.
- ElSankari S, Baledent O, van Pesch V, et al. Concomitant analysis of arterial, venous, and CSF flows using phase-contrast MRI: a quantitative comparison between MS patients and healthy controls. *J Cereb Blood Flow Metab* 2013;33:1314-21.
- Macgowan CK, Chan KY, Laughlin S, et al. Cerebral arterial and venous blood flow in adolescent multiple sclerosis patients and age-matched controls using phase contrast MRI. *J Magn Reson Imaging* 2014;40:341-7.
- Zivadinov R, Galeotti R, Hojnacki D, et al. Value of MR venography for detection of internal jugular vein anomalies in multiple sclerosis: a pilot longitudinal study. *AJNR Am J Neuroradiol* 2011;32:938-46.
- Stankovic Z, Allen BD, Garcia J, et al. 4D flow imaging with MRI. *Cardiovasc Diagn Ther* 2014;4:173-92.



33. Tariq U, Hsiao A, Alley M, et al. Venous and arterial flow quantification are equally accurate and precise with parallel imaging compressed sensing 4D phase contrast MRI. *J Magn Reson Imaging* 2013;37:1419-26.
34. Anderson JR, Diaz O, Klucznik R, et al. Validation of computational fluid dynamics methods with anatomically exact, 3D printed MRI phantoms and 4D pcMRI. *Conf Proc IEEE Eng Med Biol Soc* 2014;2014:6699-701.
35. Utriainen D, Feng W, Elias S, et al. Using magnetic resonance imaging as a means to study chronic cerebral spinal venous insufficiency in multiple sclerosis patients. *Tech Vasc Interv Radiol* 2012;15:101-12.
36. Utriainen D, Trifan G, Sethi S, et al. Magnetic resonance imaging signatures of vascular pathology in multiple sclerosis. *Neurol Res* 2012;34:780-92.
37. Zivadinov R, Bastianello S, Dake MD, et al. Recommendations for multimodal noninvasive and invasive screening for detection of extracranial venous abnormalities indicative of chronic cerebrospinal venous insufficiency: a position statement of the international society for neurovascular disease. *J Vasc Interv Radiol* 2014;25:1785-94 e17.
38. Rahman MT, Sethi SK, Utriainen DT, et al. A comparative study of magnetic resonance venography techniques for the evaluation of the internal jugular veins in multiple sclerosis patients. *Magn Reson Imaging* 2013;31:1668-76.
39. Jiang J, Kokeny P, Ying W, et al. Quantifying errors in flow measurement using phase contrast magnetic resonance imaging: comparison of several boundary detection methods. *Magn Reson Imaging* 2015;33:185-93.
40. Doepp F, Schreiber SJ, von Munster T, et al. How does the blood leave the brain? A systematic ultrasound analysis of cerebral venous drainage patterns. *Neuroradiology* 2004;46:565-70.
41. Hojnacki D, Zamboni P, Lopez-Soriano A, et al. Use of neck magnetic resonance venography, Doppler sonography and selective venography for diagnosis of chronic cerebrospinal venous insufficiency: a pilot study in multiple sclerosis patients and healthy controls. *Int Angiol* 2010;29:127-39.
42. Zaharchuk G, Fischbein NJ, Rosenberg J, et al. Comparison of MR and contrast venography of the cervical venous system in multiple sclerosis. *AJNR Am J Neuroradiol* 2011;32:1482-9.
43. McTaggart RA, Fischbein NJ, Elkins CJ, et al. Extracranial venous drainage patterns in patients with multiple sclerosis and healthy controls. *AJNR Am J Neuroradiol* 2012;33:1615-20.
44. Kramer LA, Cohen AM, Hasan KM, et al. Contrast enhanced MR venography with gadofosveset trisodium: evaluation of the intracranial and extracranial venous system. *J Magn Reson Imaging* 2014;40:630-40.
45. Caiazzo A, Montecinos G, Muller LO, et al. Computational haemodynamics in stenotic internal jugular veins. *J Math Biol* 2015;70:745-72.
46. Habib CA, Liu M, Bawany N, et al. Assessing abnormal iron content in the deep gray matter of patients with multiple sclerosis versus healthy controls. *AJNR Am J Neuroradiol* 2012;33:252-8.
47. Beggs CB, Magnano C, Shepherd SJ, et al. Aqueductal cerebrospinal fluid pulsatility in healthy individuals is affected by impaired cerebral venous outflow. *J Magn Reson Imaging* 2014;40:1215-22.
48. Lagana MM, Chaudhary A, Balagurunathan D, et al. Cerebrospinal fluid flow dynamics in multiple sclerosis patients through phase contrast magnetic resonance imaging. *Curr Neurovasc Res* 2014;11:349-58.
49. Marshall O, Lu H, Brisset JC, et al. Impaired cerebrovascular reactivity in multiple sclerosis. *JAMA Neurol* 2014;71:1275-81.
50. Kudo K, Terae S, Ishii A, et al. Physiologic change in flow velocity and direction of dural venous sinuses with respiration: MR venography and flow analysis. *AJNR Am J Neuroradiol* 2004;25:551-7.
51. Mehta NR, Jones L, Kraut MA, Melhem ER. Physiologic variations in dural venous sinus flow on phase-contrast MR imaging. *AJR Am J Roentgenol* 2000;175:221-5.
52. Paksoy Y, Genc BO, Genc E. Retrograde flow in the left inferior petrosal sinus and blood steal of the cavernous sinus associated with central vein stenosis: MR angiographic findings. *AJNR Am J Neuroradiol* 2003;24:1364-8.
53. Jang J, Kim BS, Kim BY, et al. Reflux venous flow in dural sinus and internal jugular vein on 3D time-of-flight MR angiography. *Neuroradiology* 2013;55:1205-11.