International Society for Neurovascular Disease (ISNVD) position on imaging modalities for detection of chronic cerebrospinal venous insufficiency (CCSVI)

Magnetic Resonance Imaging Protocol

Quantitative imaging of CCSVI using magnetic resonance imaging (MRI) provides an opportunity to study not just anatomical abnormalities such as stenosis of a major vein[1-7]but also the ability to quantify the flow[2,3,6,8]. These two pieces of information may provide new biomarkers over and above those originally introduced by Zamboni using ultrasound. Specifically, recent MRI findings suggest that the total internal jugular venous flow normalized to the arterial inflow as measured from the carotids and vertebral arteries and the dominance of flow on one side of the neck may represent risk factors for developing MS[2,3]. This would put them in the category of CCSVI biomarkers.

There are a number of sites currently running extensive MRI research protocols to study: angiography; diffusion; iron content; oxygen saturation and perfusion, for example. The complexity and length of these studies make them largely impractical for use in a standard clinical setting. As a complement to the standard clinical neuroimaging protocol to assess MS used by neurologists and neuroradiologists alike, we suggest a simple, rapid set of additional sequences to allow the extracranial vasculature to be assessed for anatomical and flow abnormalities. These measures will then provide both validation of and a complement to ultrasound measures.

A standard protocol is shown in appendix I to study MS patients (Tier I MS protocol). This protocol is based on neurologists' consensus for MR studies[9] This first pass protocol uses a contrast agent. Patients returning for another MR scan may or may not have a contrast agent used. To match both of these standard clinical imaging protocols, we have suggested two different CCSVI protocols that will provide anatomy and flow quickly for ease of clinical use. The first is a Tier II protocol (Tier IIa) that does not use a contrast agent and the second one (Tier IIb) that does use a contrast agent. Both protocols are very rapid, adding only a few minutes onto the conventional imaging times. As such, we believe that these could be easily adopted into a clinical setting.

A major benefit of using MRI is that it provides: the neurologist with what he needs for assessing MS (from a conventional MS protocol); the interventionalist with a 3D MR venography planning toolkit; and all other parties with critical flow information which may become a key marker for deciding whether to treat a patient. MRI is also operator independent for the most part and the same protocols can be run on most manufacturers' systems. The data are also easily reproduced when run on the same equipment from site to site. Potential biomarkers for CCSVI and MS can be identified from the data. MRI can longitudinally track the progress of the disease over time via lesion counts and type, physiologic changes like blood flow and cerebrospinal fluid (CSF) dynamics, and provide a baseline for future scans.

There are practical concerns regarding the implementation of this protocol. Both neuroradiologists and neurologists must be adequately trained to interpret the images. As with any imaging protocol, the reader must understand the technical limitations of the methodology and must have knowledge of the appropriate metrics to be analyzed from the quantitative data created from the exam.

In summary, MRI offers an important set of measures for both neurologists and interventionalists to use in the detection and treatment of CCSVI. Diagnosticians must be facile with the appropriate protocols and metrics and should be familiar with the benefits and limitations of each protocol.

Appendix I: Description of collecting data for an MRI CCSVI Protocol

The MRI CCSVI Protocol: In addition to the conventional sequences described in Tier I, additional specialized sequences are added to study the vasculature in the neck. On the vascular side, both anatomic and flow information are collected.

The following imaging protocol is presented for a 3T scanner but can be extended easily to other field strengths such as 1.5T or 7T. The scans proposed are: 2D time of flight MR venography (TOF MRV), time-resolved contrast enhanced 3D MR angiography and venography (MRAV), phase-contrast flow data at different levels in the neck, as well as the conventional T2 weighted imaging (WI), T2 fluid attenuated inversion recovery (FLAIR), and pre and post contrast T1 weighted imaging (WI) or magnetization prepared rapid gradient echo (MPRAGE) imaging.

2D TOF MRV scans are used to detect blood flow in arteries and veins. Using a saturation band, any flow toward the head (arterial flow) will be saturated, and the flow towards the heart (venous flow) will be highlighted in a velocity-dependent manner. From this sequence, veins are well visualized and it can be determined if they are patent, occluded, or stenosed. Since the data are collected with high resolution, vessel cross-section can also be calculated to evaluate the degree of stenosis.

3D CE MRAV can also be used to evaluate vascular abnormalities. The scan uses a T1 reducing contrast agent which passes through all vessels and leads to increased signal for vessels in T1 weighted scans. From the data, 3D anatomical assessments can be done to evaluate vessel patency. Atresias, aplasias, truncular malformations, valve issues, and stenoses can be detected.

2D PC-MRI images are used to assess flow dynamics in the head and neck veins and arteries. This information is valuable because it can corroborate and complement the information in the 2D TOF MRV and 3D contrast enhanced MRAV. It is not uncommon to visualize the major veins only later to find that many of the veins have compromised blood flow.

For more conventional imaging, T2WI is used to show tissue with long T2 components such as edema, CSF, tumors, and MS lesions. 3D T2 FLAIR is used because the images have suppressed CSF signal. FLAIR shows periventricular lesions well without the interference from CSF. Lesion quantity and volume can also be assessed with FLAIR. Eventually, it may be possible to compare lesion volume with blood flow or patient's physiological changes over time. T1WI is used at two parts of the scanning protocol to image the head: initially before contrast agent injection, and after contrast agent injection. Lesions that enhance post-contrast are considered as acute.

Scanning Procedure

- Initially, register the patient along with his/her height and weight. This plays an important role in flow quantification (FQ). (Tiers I and II)
- Activate appropriate (head, neck and spine) coils for imaging the region of interest. (Tiers I and II)
- Make sure to put the pulse trigger on the subject's (left/right) index finger or for a better flow quantification, cardiac gating can be used. (Tiers I and II)
- Initially, start imaging the head using T2, MPRAGE, FLAIR, and T1 weighted imaging sequences. Make sure to use the head and neck coils. (Tiers I and II)
- Next, move the table to center at the neck and acquire T2, 3D CE MRAV, and flow quantification (FQ) sequences. Make sure to use the head neck coils. Inject the contrast agent on the 3^{rd} or 4^{th} measurement of the 3D CE MRAV. (Tier IIb)
- The FQ plane will be set perpendicular to the internal jugular veins (IJV's) at both the C2/C3 and C6/C7 neck levels with a venc of 50cm/sec. (Tier II)
- Next, move the table center back to the head and acquire the data using the post gadolinium MPRAGE sequence. (Tier IIb)

Reporting the data

Over and above the standard clinical diagnostic data review by the neuroradiologist, one must also consider the 2D TOF and/or the 3D contrast enhanced MR angiographic data and the flow data. For the former, one can consider anatomical and vascular abnormalities in the various vessels including: the carotid arteries, vertebral arteries, jugular veins, external jugular veins, anterior jugular veins, vertebral veins, deep cervical veins, vertebral plexus, facial veins and thyroid veins. The cross sectional areas of these vessels can be evaluated at C2/C3 and C5/C6 using either the 3D CE MRAV and the 2D TOF MRV data. Further considerations include: the presence of stenoses, truncular venous malformations and malfunctioning valves. In evaluating the CSA, some criteria must be set. One criterion that has been used in the recent literature includes using a CSA of less than $25mm^2$ (1/3 of the CSA for an average IJV diameter of 1cm assuming a circular shape) at the lower half of the IJV body below C2/C3 to call the vein stenotic and a CSA of less than $12.5mm^2$ at the C2/C3 level as stenotic. The flow can also be reported from both the C2/C3 and C6/C7 levels for both arteries and veins. This can include the percentage of internal jugular venous flow compared to the arterial flow in that region, the ratio of dominant to sub-dominant jugular venous flow and the presence of no flow, reflux and circulatory flow. Users should be aware of aliasing and use anti-aliasing software to process the flow data. The flow data can be presented in terms of integrated flow in ml/sec, speed in cm/sec, positive flow in ml/sec (to show flow toward the brain and better visualize reflux or circulatory flow), negative flow in ml/sec, all throughout the cardiac cycle. Blood flow in the IJVs can be normalized to the total arterial flow at a given location as follows: at the C6/C7 level, total arterial flow included blood through the common carotid arteries and the vertebral arteries combined; while at the C2/C3 level total arterial flow included blood through the internal carotid arteries and the vertebral arteries combined. One such software that is available for use is SPIN (signal processing in NMR (nuclear magnetic resonance), Detroit, Michigan).

References

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Tier I standard neurological MR imaging protocol for MS patients

Sequence	Time (approx.)	
	3T MRI	**1.5T MRI**
3 plane scout of the brain - localizer	0:15	0:10
Axial T2/PD Head	2:50	4:30
Axial T2 fast FLAIR	2:30	4:30
Axial T1 Head 3D pre Gd	4:00	4:20
Inject Gadolinium (no wait time)	0:00	0:00
Axial T1 Head 3D post Gd	4:00	4:20
3 plane scout of the C-spine - localizer	0:20	0:15
Sagittal T2/PD C-spine	2:10	3:50
Sagittal T1 C-spine post Gad	2:40	5:00
Select Axial T2 C-spine through lesions	1:50* (optional)	2:20* (optional)
Select Axial T1 C-spine post Gad through lesions	1:50* (optional)	2:40* (optional)
Total Time	**20:45 (24:25*)**	**26:55 (31:55*)**

Tier IIa protocol for studying CCSVI in MS patients without contrast administration

Sequence	Time (approx.)	
	3T MRI	**1.5T MRI**
3 plane scout of the brain - localizer	0:15	0:10
Axial T2/PD Head	2:50	4:30
Axial T1 Head 3D	4:00	4:20
Axial T2 fast FLAIR	2:30	4:30
3 plane scout of the C-spine - localizer	0:20	0:15
Sagittal T2/PD C-spine	2:10	3:50
Sagittal T1 C-spine	2:40	5:00
Select Axial T2 C-spine through lesions	1:50* (optional)	2:20* (optional)
2D TOF MRV Neck	7:00	5:10
Flow Quantification at C2/C3 and C6/C7 with Venc = 50cm/s	1:45 x 2 = 3:30	1:25 x 2 = 2:50
Total Time	**25:15 (27:05*)**	**30:35 (32:55*)**

Tier IIb protocol for studying CCSVI in MS patients with contrast administration

Sequence	Time (approx.)	
	3T MRI	**1.5T MRI**
3 plane scout of the brain - localizer	0:15	0:10
Axial T2/PD Head	2:50	4:30
Axial T1 Head 3D	4:00	4:20
Axial T2 fast FLAIR	2:30	4:30
3 plane scout of the C-spine - localizer	0:20	0:15
Sagittal T2/PD C-spine	2:10	3:50
Sagittal T1 C-spine	2:40	5:00
Select Axial T2 C-spine through lesions	1:50* (optional)	2:20* (optional)
Inject Gadolinium (no wait time)	0:00	0:00
TWIST 3D MRAV Neck	3:10	2:30
Flow Quantification at C2/C3 and C6/C7 with Venc = 50cm/s	1:45 x 2 = 3:30	1:25 x 2 = 2:50
Axial T1 Head 3D post Gad	4:00	4:20
Sagittal C-spine T1 FS post Gad	2:40	5:00
Select Axial T1 C-spine post Gad through lesions	1:50* (optional)	2:40* (optional)
Total Time	**28:05 (31:45*)**	**37:15 (42:15*)**

Figure 1: *Conventional MRI scans showing the appearance of MS lesions in the brain*. (A) Axial T2WI and (B) T2 FLAIR show hyper-intense lesions within the white matter. The CSF signal appears bright in T2WI (pink arrow in A) however in T2 FLAIR the CSF signal intensity is greatly reduced allowing for the clear visualization of periventricular lesions (pink arrow in B). (C) Pre-contrast T1WI is another modality in which MS lesions are observed (yellow arrows in C) and a major benefit of having a T1 reducing contrast agent allows for (D) post contrast T1WI in which some MS lesions may become enhanced (yellow arrows in D). This enhancement indicates that the blood mixed with contrast agent is able to enter the parenchyma, meaning that the blood brain barrier is disrupted.

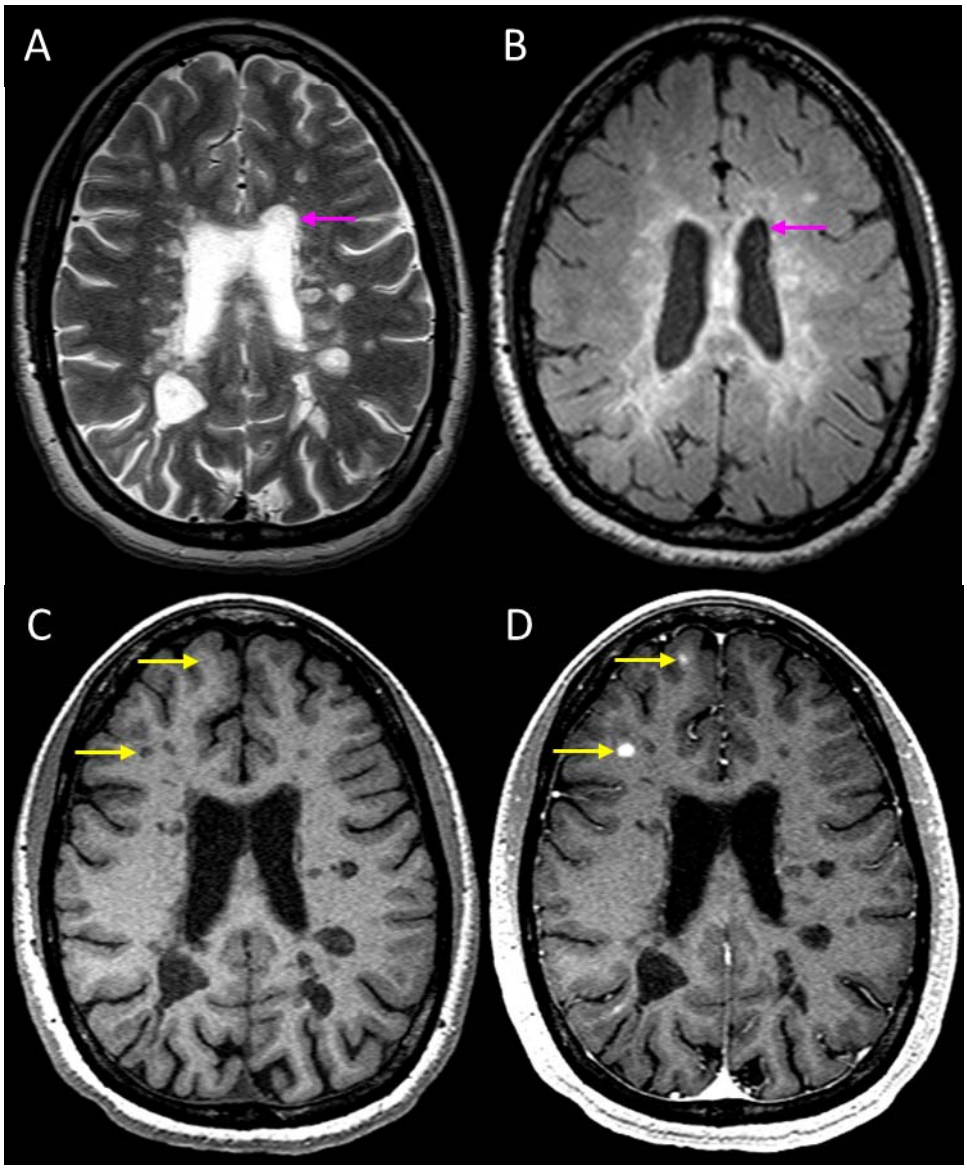


Figure 2: *Spine imaging.* T2WI covering the cervical spinal cord of a healthy control (A,B) and an MS patient (C,D) with spinal lesions. A sagittal T2WI slice (A) shows healthy white matter with uniform signal through the cervical spinal cord and a separate axial T2WI slice (B) confirms this appearance. In the MS patient, hyper-intense lesions are noticeable (yellow arrows in C,D) in both the sagittal (C) and axial (D) images.

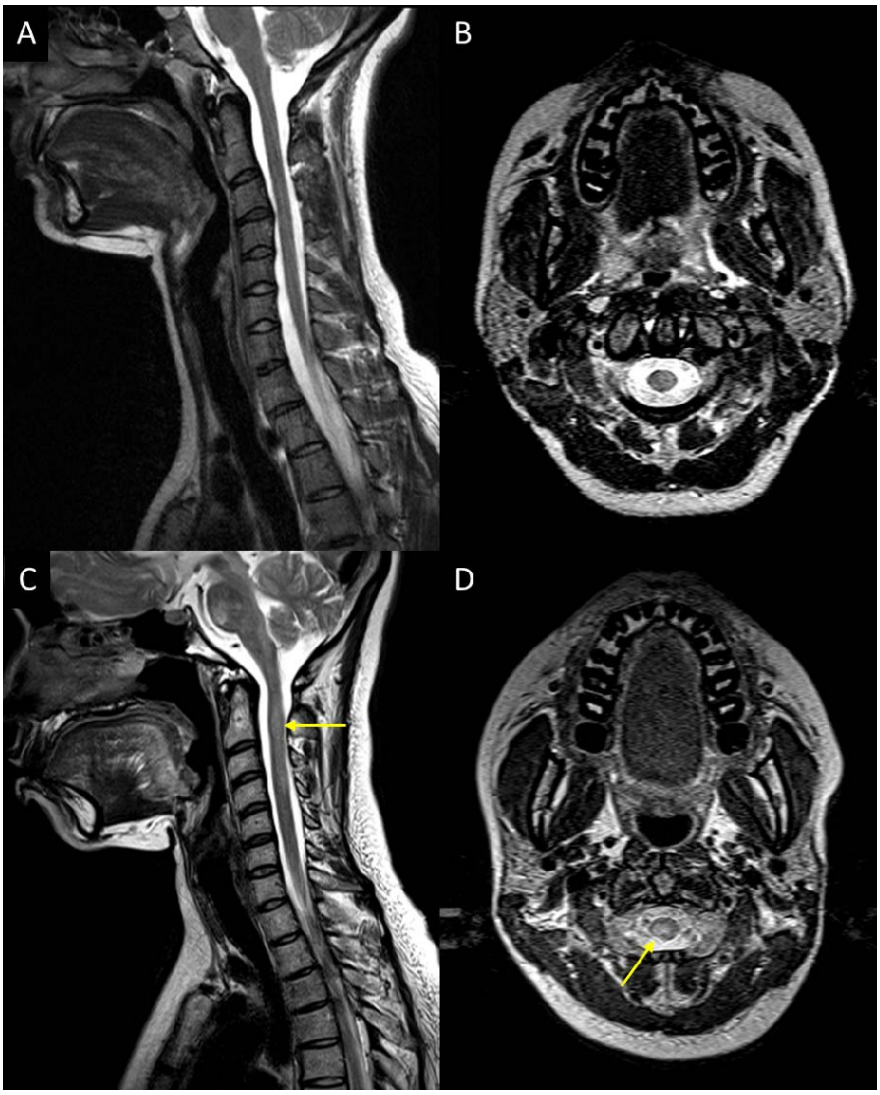


Figure 3: *The vasculature of the head and neck.* Both arteries and veins can be visualized with and without the use of an exogenous contrast agent as represented here in coronal projections of two modalities. (A-C) Dynamic, contrast enhanced MR angiography has temporal resolution capable of imaging arterial (A), early venous (B) and late venous (C) phases. This allows for the clear visualization of the arterial system including the common carotid arteries (orange arrows in A) as well as the venous system including the internal jugular veins (yellow arrows in B) and late enhancing collaterals (pink arrows in C). (D) With a tracking caudal saturation band suppressing signal within the arterial system, 2D time of flight MR venography allows for the visualization of the venous system as a whole, including the internal jugular veins (yellow arrows in D).

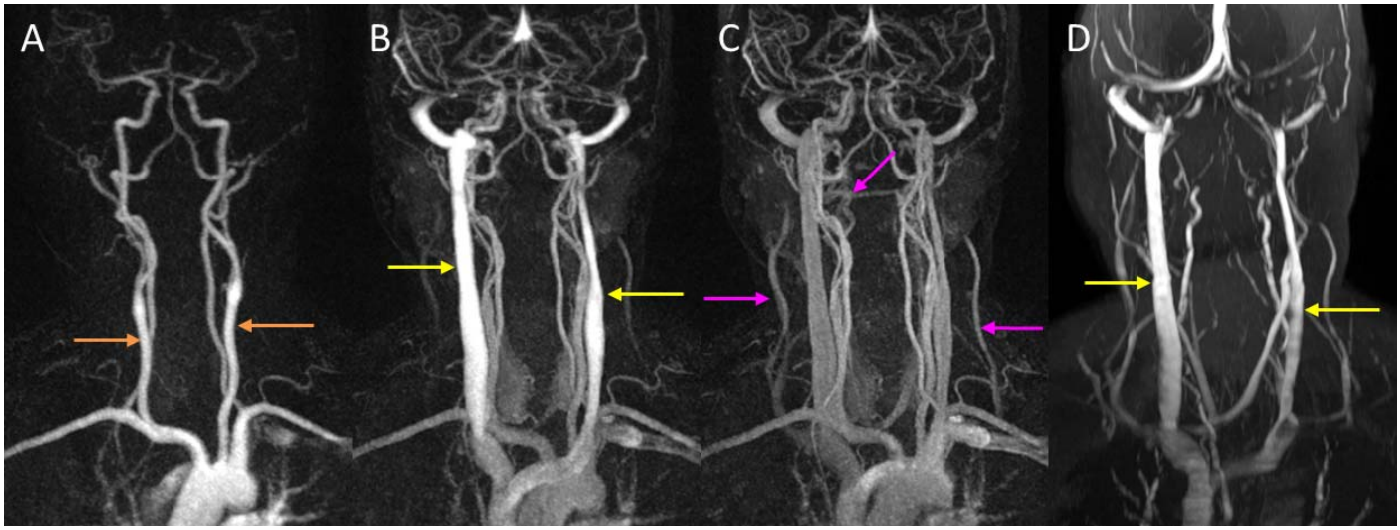
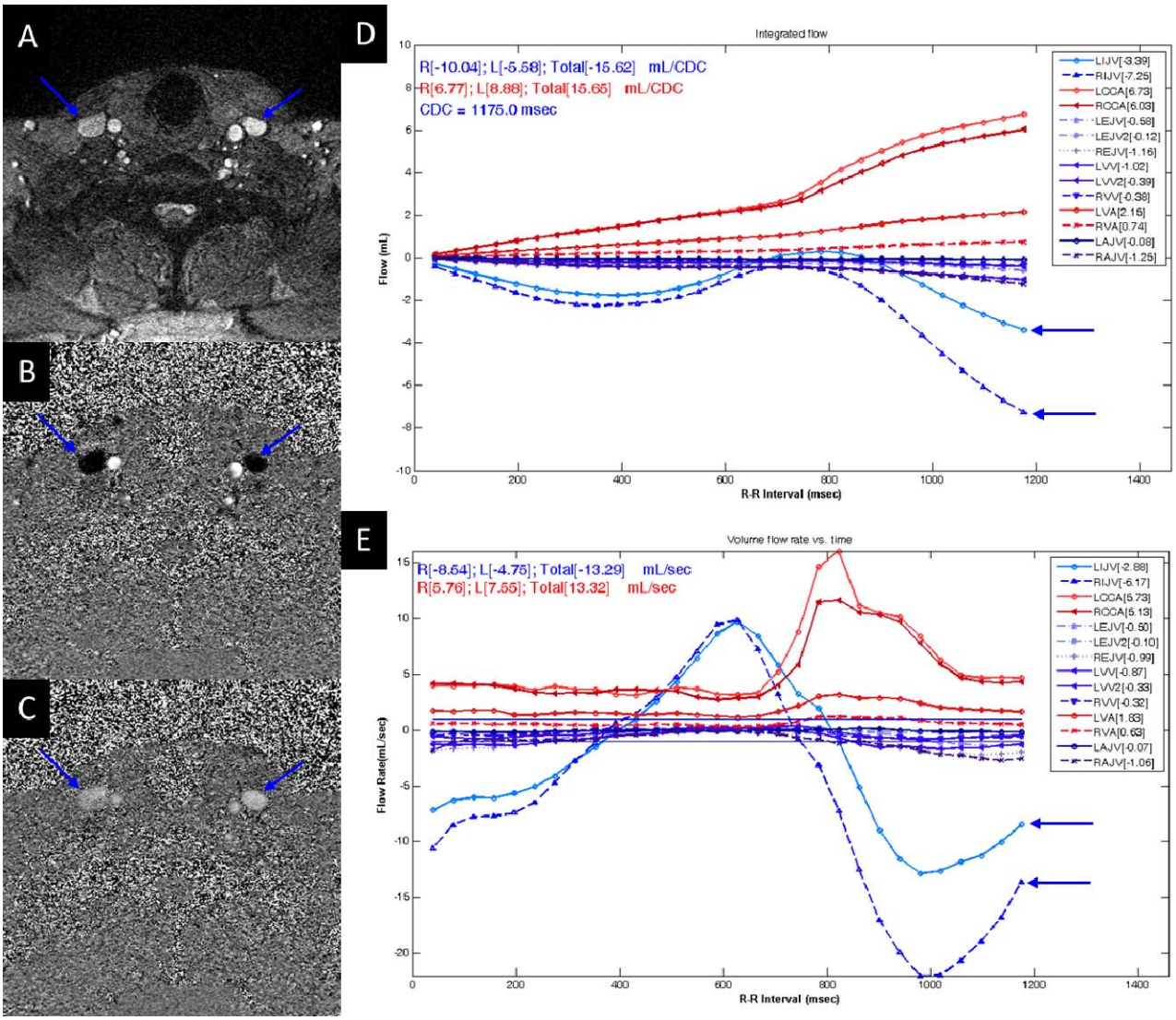


Figure 4: *Quantifying blood flow.* Two dimensional phase contrast MRI (2D PC-MRI) is a method which quantifies velocity passing through the acquisition slice as shown here at a slice positioned perpendicular to the major vessels of the neck between the sixth and seventh cervical vertebrae. (A) An axial magnitude image shows clear visualization of the vessels with blood flow in the neck, for example, the internal jugular veins (blue arrows in A). (B,C) Axial phase images show signal intensity which is directly proportional to the velocity of flow through the slice. A reversal of flow is shown in the internal jugular veins when the signal intensity changes from dark (blue arrows in B), meaning blood flow towards the heart, to bright (blue arrows in C) which indicates blood flow towards the brain. (D,E) When a region of interest is defined containing a vessel, the average velocity can be calculated from the phase image and then multiplied by the area giving flow volume (D) and rate (E). Typically on the order of 20 to 30 time points are collected throughout the cardiac cycle which are then plotted as a function of time. Consider for instance the internal jugular veins (blue arrows in D,E). From the phase images, a bright signal indicates positive plotted values and dark signal indicates negative plotted values. Notice that the IJV flow volume begins to show a positive acceleration in the integrated flow plot and the flow rate values change from negative to positive between approximately 400 and 800ms indicating reflux of both these jugular veins.



TIER IIa Protocol for CCSVI in MS patients (without contrast)

(NOTE: *Please follow the sequence order***)**

	Head (Center at the orbital ridge)			**Neck** (Center at the chin)				
Sequence Order	**#1**	**#2/#9**	**#3**	**#4**	**#5/#10**	**#6**	**#7**	**#8**
	T2/PD	**T1 MPRAGE**	**3D FLAIR**	**T2/PD C-spine**	**T1 C-spine**	**T2 C-spine through lesions (optional)***	**2D TOF MRV (neck)**	**Flow Quantification (Jugulars)**
Sequence	tse	tfl	tse_vfl	tse	tse	tse	fl_tof	fl_fq_retro
Orientation	Axial	Axial	Sagittal	Sagittal	Sagittal	Axial	Axial	Axial
TR (ms)	3000	1750	6000	3200	2140	4160	29	95.25
TE (ms)	12, 105	2.98	397	22, 100	10	94	5.02	10
TI (ms)	-	900	2200	-	899	-	-	-
FA (degree)	150	9	-	150	160	130	60	20
FOV (mm^2)	256x192	256x256	256x256	256x192	256x256	256x256	320x256	256x256
Matrix size	256x256	512x256	256x256	256x256	256x256	256x256	512x256	448x448
Nz/TH (mm)	46/3	192/1	160/1	17/3	17/3	19/3	128/3	1/2.5
Voxel size (mm^3)	1x1x3	0.5x1x1	1x1x1	1x1x3	1x1x3	1x1x3	0.6x1.3x3	0.6x0.6x2.5
Ave./Meas.	1	1	1	2/1	1/1	3/1	1	1
Concatenations	4	1	1	1	2	1		
Phase oversmpl	0%	0%	0%	0%	100%	0%	-	0%
Dist. factor	0%	0%	0%	0%	0%	0%	-25.0%	20%
Phase Enc. Dir	R>>L	R>>L	A>>P	A>>P	H>>F	A>>P	A>>P	A>>P
iPAT	2/31	2/24	2/24	2/32	2/27	2/32	2/24	2/24
BW (Hz/pixel)	181	180	781	142	230	250	217	192
Flow Comp	Slice	No	No	Read	No	Slice	Yes	No
Phase partial Fourier	Off	Off	Allowed	Off	Off	Off	Off	Off
Slice partial Fourier	Off	Off	7/8	Off	Off	Off	Off	Off
Flow Mode/Direction								Single Dir./ Through Plane
Venc. (cm/s)								50
1^{st} Signal/Mode								Pulse/Retro
Special Sat.							Tracking F	
Pre Saturation							Gap10mm; TH 40mm	
Echo spacing (ms)	11.7	7.6	3.32	11.1	9.94	11.8	-	-
Turbo factor	7	-	141	**5**	9	15	-	-
Echo trains per slice	16	-	1	20	30	9	-	-
Coils	Head	Head	Head+Neck	Head+Neck +SP1,2	Head+Neck +SP1,2	Head+Neck +SP1,2	Head+Neck +SP1,2	Head+Neck +SP1,2
Time	**03:26**	**04:03**	**05:20**	**02:13**	**02:14**	**1:58***	**06:57**	**01:42(x2)**
Total Time								**27:37 (29:35)***

Note:

- Please put a pulse trigger on the patient's index finger.
- Flow quantification will be done perpendicular to the internal jugular veins (IJV's) at the C2/C3 and C6/C7 neck levels with a venc of 50cm/sec.

TIER IIb Protocol for CCSVI in MS patients (with contrast)

(NOTE: *Please follow the sequence order***)**

	Head (Center at the orbital ridge)			**Neck** (Center at the chin)					
Sequence Order	**#1**	**#2/#9**	**#3**	**#4**	**#5/#10**	**#6**	**#7**	**#8**	**#11**
	T2/PD	**T1 MPRAGE Pre/Post Contrast**	**3D FLAIR**	**T2/PD C-spine**	**T1 C-spine Pre/Post Contrast**	**T2 C-spine through lesions (optional)***	**3D TWIST *Inject Contrast at the start of 5th measurement***	**Flow Quantification (Jugulars)**	**T1 C-spine through lesions (optional)***
Sequence	tse	tfl	tse_vfl	tse	tse	tse	twist	fl_fq_retro	tse
Orientation	Axial	Axial	Sagittal	Sagittal	Sagittal	Axial	Coronal	Axial	Axial
TR (ms)	3000	1750	6000	3200	2140	4160	3.31	95.25	2000
TE (ms)	12, 105	2.98	397	22, 100	10	94	1.25	10	9.9
TI (ms)	-	900	2200	-	899	-			
FA (degree)	150	9		150	160	130	18	20	160
FOV (mm^2)	256x192	256x256	256x256	256x192	256x256	256x256	340x255	256x256	256x256
Matrix size	256x256	512x256	256x256	256x256	256x256	256x256	384x384	448x448	256x256
Nz/TH (mm)	46/3	192/1	160/1	17/3	17/3	19/3	96/0.9	1/2.5	19/3
Voxel size (mm^3)	1x1x3	0.5x1x1	1x1x1	1x1x3	1x1x3	1x1x3	0.9x0.9x0.9	0.6x0.6x2.5	1x1x3
Ave./Meas.	1	1	1	2/1	1/1	3/1	1/20	1	2/1
Concatenations	4	1	1	1	2	1	-		3
Phase oversmpl	0%	0%	0%	0%	100%	0%	0%	0%	0%
Dist. factor	0%	0%	0%	0%	0%	0%	-	20%	0%
Phase Enc. Dir	R>>L	R>>L	A>>P	A>>P	H>>F	A>>P	R>>L	A>>P	A>>P
iPAT	2/31	2/24	2/24	2/32	2/27	2/32	2/24	2/24	2/32
BW (Hz/pixel)	181	180	781	142	230	250	650	192	230
Flow Comp	Slice	No	No	Read	No	Slice	-	No	No
Phase partial Fourier	Off	Off	Allowed	Off	Off	Off	6/8	Off	Off
Slice partial Fourier	Off	Off	7/8	Off	Off	Off	6/8	Off	Off
Flow Mode/Direction								Single Dir./ Through Plane	
Venc. (cm/s)								50	
1st Signal/Mode								Pulse/Retro	
Echo spacing (ms)	11.7	7.6	3.32	11.1	9.94	11.8	-	-	9.94
Turbo factor	7		141	**5**	9	15	-	-	**9**
Echo trains per slice	16		1	20	30	9	**-**	-	15
Coils	Head	Head	Head+Neck	Head+Neck +SP1,2	Head+Neck +SP1,2	Head+Neck +SP1,2	Head+Neck +SP1,2	Head+Neck +SP1,2	Head+Neck +SP1,2
Time	**03:26**	**04:03(x2)**	**05:20**	**02:13**	**02:14(x2)**	**1:58***	**02:26**	**01:42(x2)**	**3:08***
Total Time									**29:21 (34:27)***

Note: Please put a pulse trigger on the patient's index finger.

- 3D MRV - Inject remaining dose of contrast at the 5th measurement.
- Flow quantification will be done perpendicular to the internal jugular veins (IJV's) at the C2/C3 and C6/C7 neck levels with a venc of 50cm/sec.