The Role of MR Imaging in the Diagnosis of CCSVI and in Pre-Treatment Planning and Monitoring Patient Outcomes

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The CCSVI MR Imaging Protocol: MRI offers a number of critical measures for MS patients

- ✓ ***Conventional MRI: FLAIR, T2, T1 pre/post contrast***
- ✓ ***Post contrast time resolved MRA/V: to find the stenoses***
- ✓ ***Flow quantification: to find the abnormal fluid dynamics (this can include veins, arteries and CSF)***
- ✓ ***SWI: to find the iron and venous damage in the brain***
- ✓ ***Quantify these effects before/after balloon angioplasty***

Please visit www.ms-mri.com for more information.

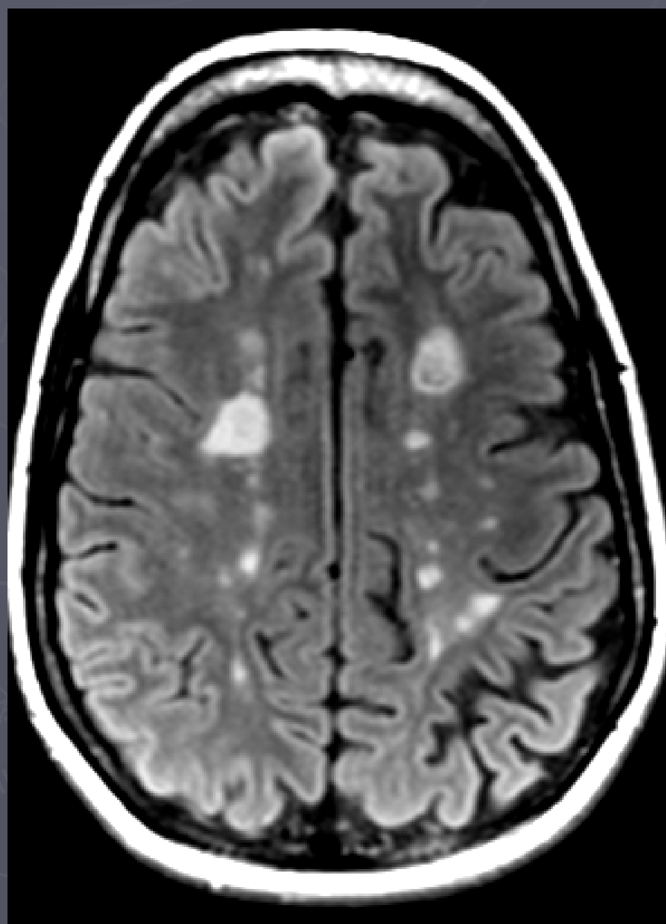
Why perform MR imaging before and after treatment?

We need to:

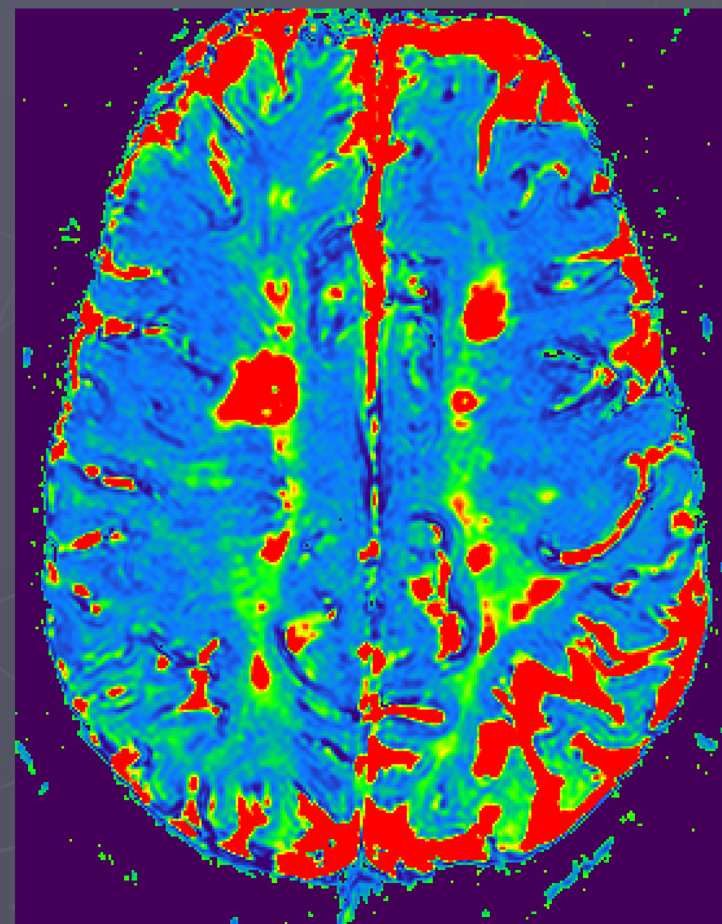
- monitor lesions and iron content
- monitor arterial, venous and CSF flow changes
- use the 3D data to help plan the intervention
- serve as a baseline to study the anatomy and flow after treatment if complications develop

MULTIPLE SCLEROSIS LESIONS: FLAIR and Perfusion Weighted Imaging (PWI can be used to study the hemodynamics of the brain)

Anatomic evidence of lesions from FLAIR imaging



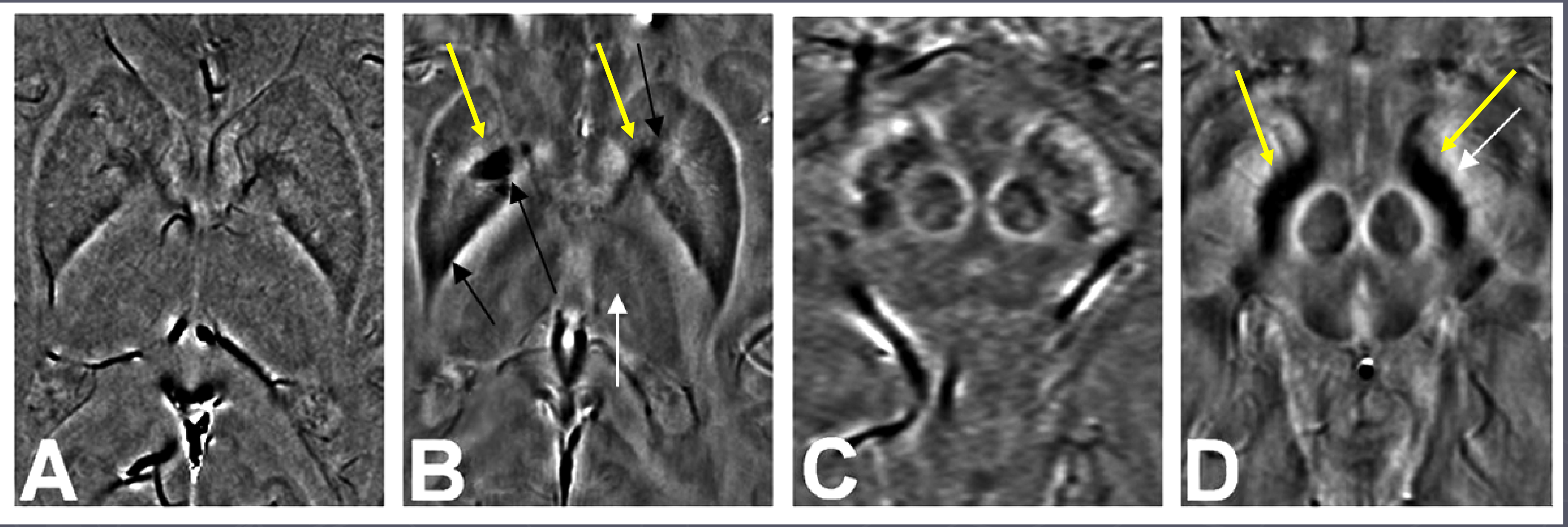
PWI shows all MS lesions have the same vascular characteristics



Susceptibility weighted imaging (SWI) serves as a means to monitor small veins in the brain. Susceptibility mapping (SWIM) may well serve as a means to monitor oxygen saturation in veins with diameters on the order of several pixels (i.e., diameters of 1 to 2mm or larger) in diameter.

Haacke EM et al. Susceptibility mapping as a means to visualize veins and quantify oxygen saturation. JMRI 2010;32:663-76.

Iron build-up in the basal ganglia



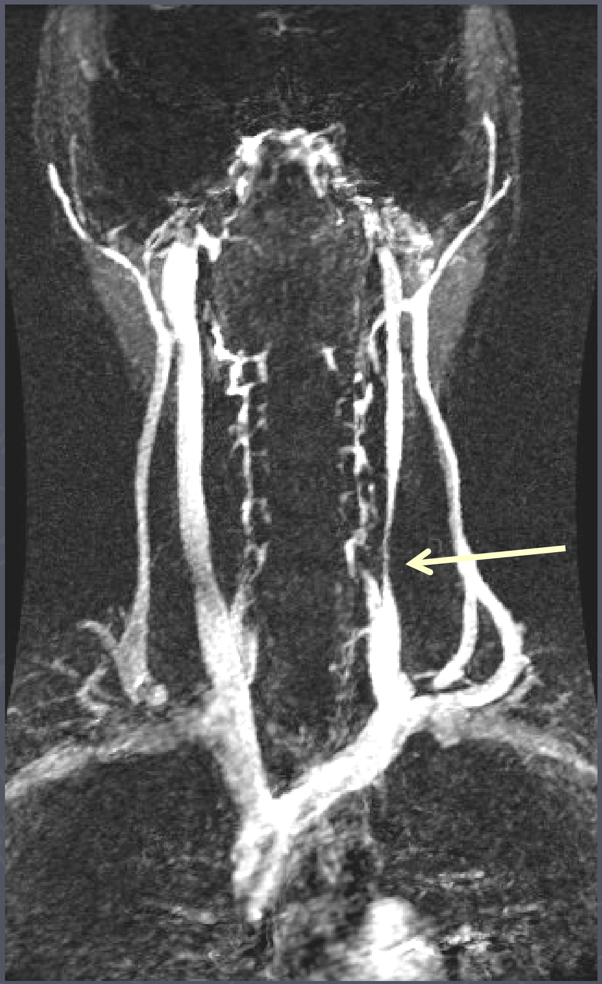
A,B show iron build up in the caudate and globus pallidus for an MS patient (B) compared with that from an age matched normal (A). C,D show iron build up in the substantia nigra for an MS patient (D) compared with that from an age matched normal (C).

Haacke EM et al. Iron stores and Cerebral Veins in MS Studied by Susceptibility Weighted Imaging (SWI); International Angiology 2010 Apr;29(2):149-57.

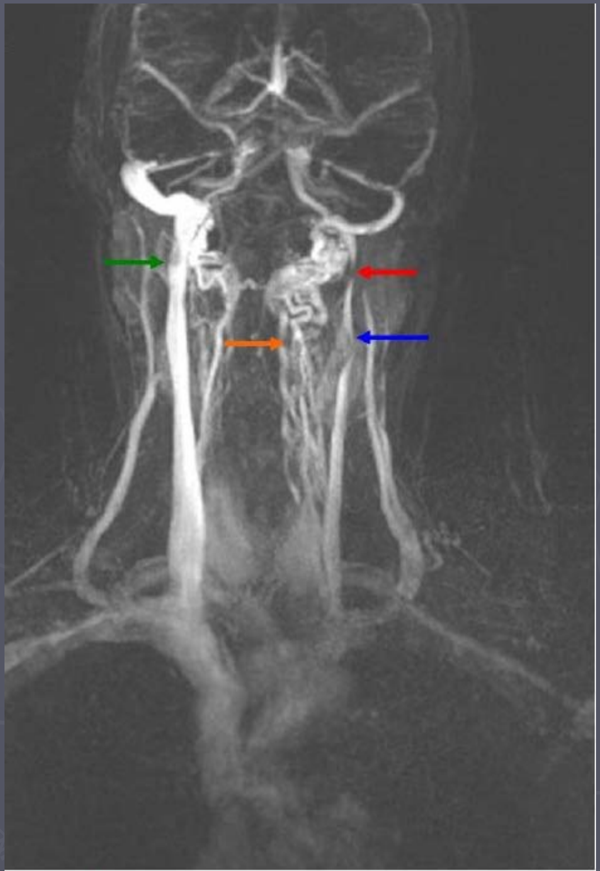
Paolo Zamboni and his team demonstrated that there were major venous abnormalities in MS patients both anatomically and functionally using angiograms as the gold standard.

Zamboni P et al. Chronic cerebrospinal venous insufficiency in patients with multiple sclerosis. *J Neurol Neurosurg Psychiatry* 2009;80:392-399.

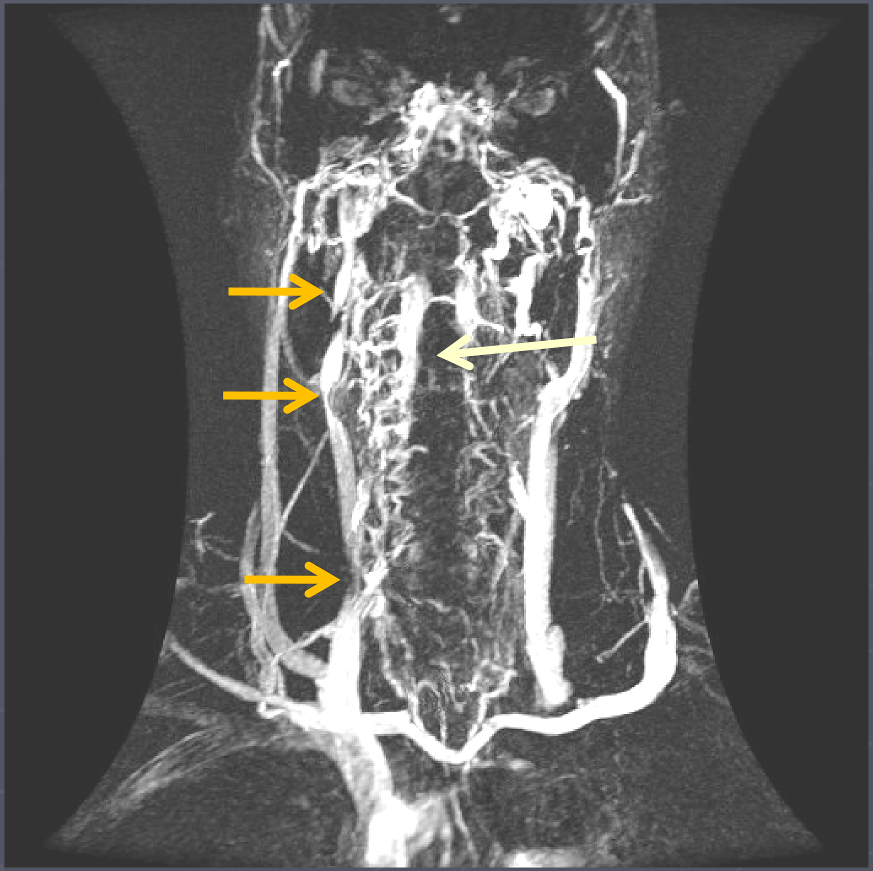
Left: Stenosis at the stump of the LIJV with collateral input from the vertebral system
Right: String like jugular in the RIJV



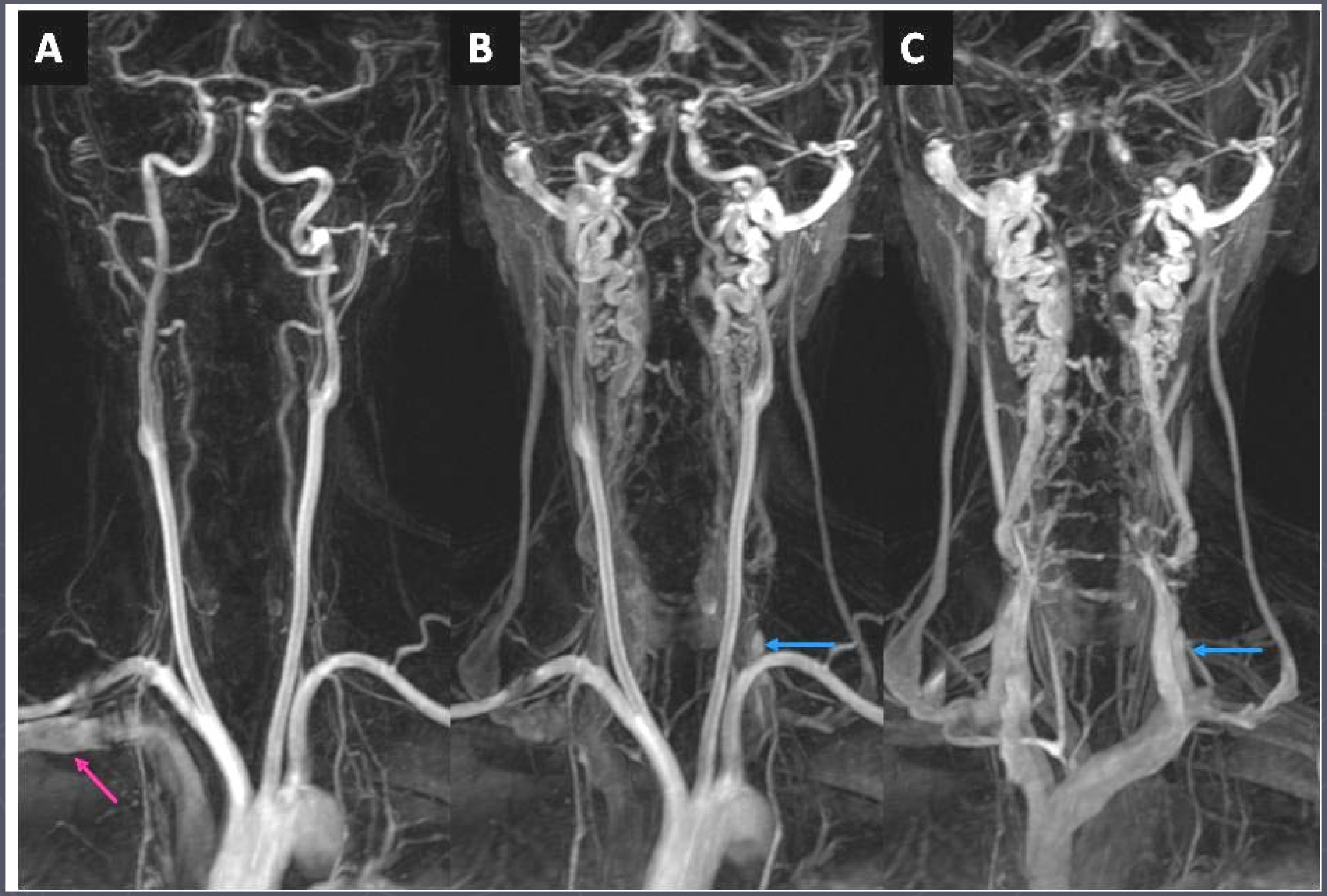
Collateral development on the same side as the stenosis



Stenosis of the left internal jugular vein at upper (red arrow) and middle neck level (blue arrow); green arrow=right internal jugular vein; orange arrow=deep cervical plexuses

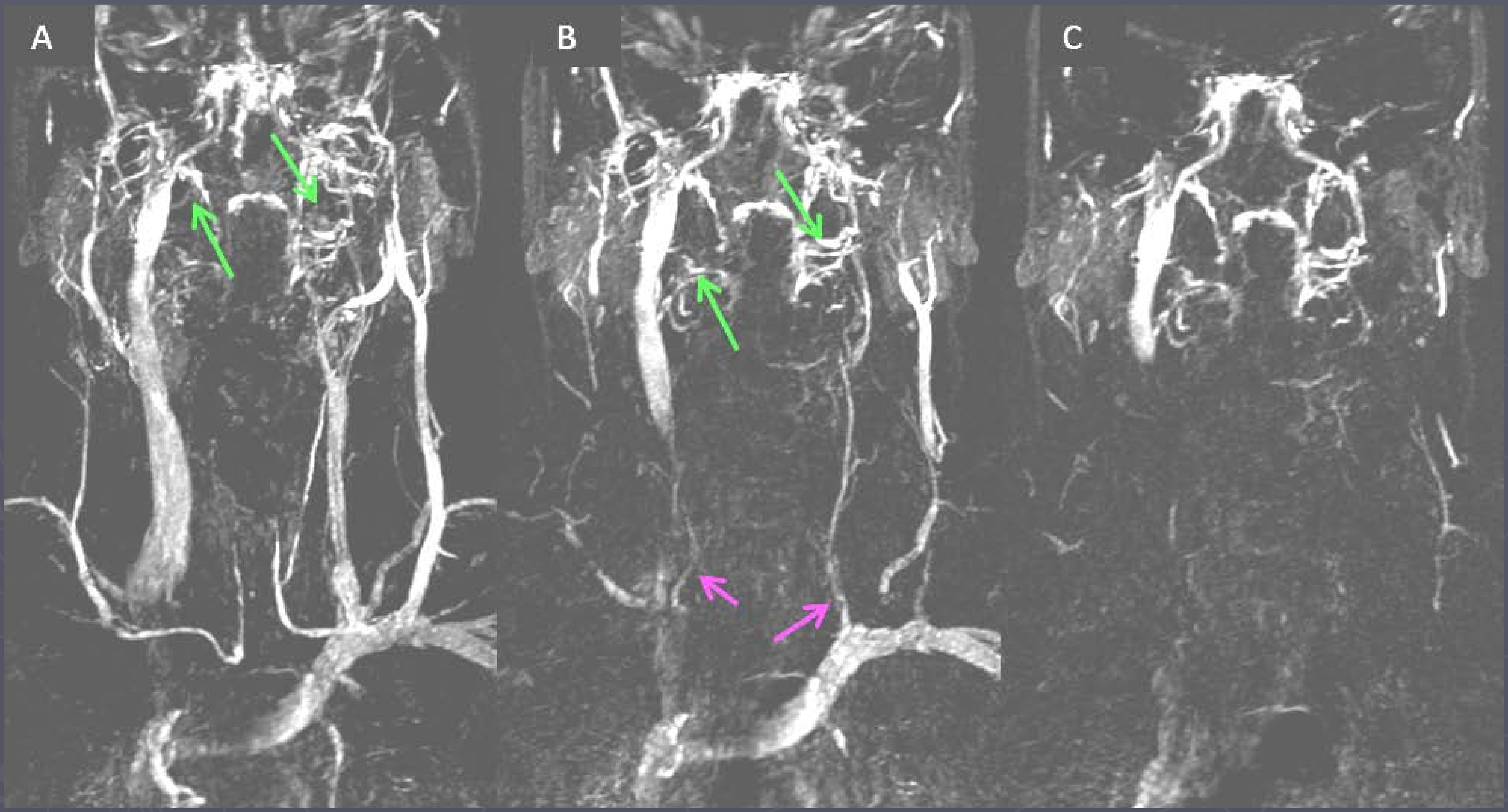


Deep cervical veins assume the role jugular veins

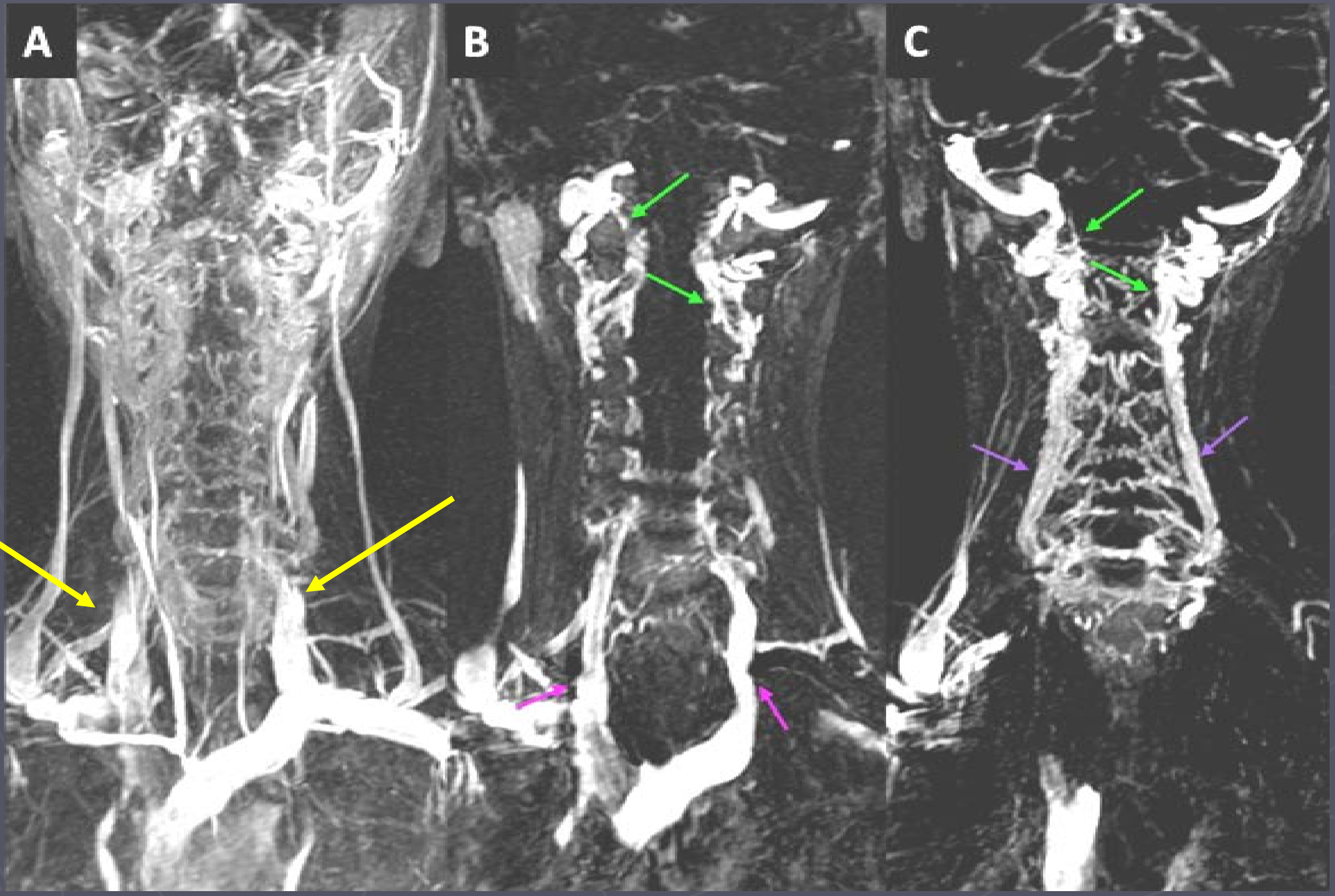


Note the irregularities in the lower right external jugular vein.

In some cases we find that the vertebral veins and deep cervical veins are almost under developed.



Ladder-like vertebral plexus for an individual with abnormal jugulars



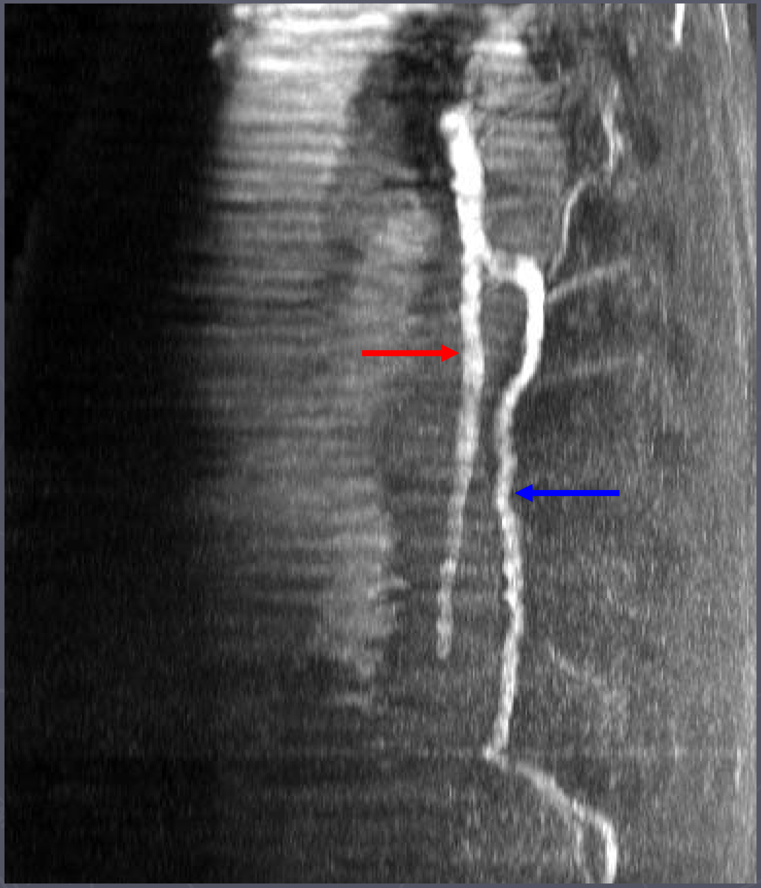
MR examples of CCSVI in MS patients where pre-treatment planning would reveal significant data that could affect how the veins are accessed.

Stenosed RIJV

Stenosis of the right internal jugular vein (red arrows); yellow arrow=external jugular vein

Stenosed RIJV

Azygous and Hemi-azygous

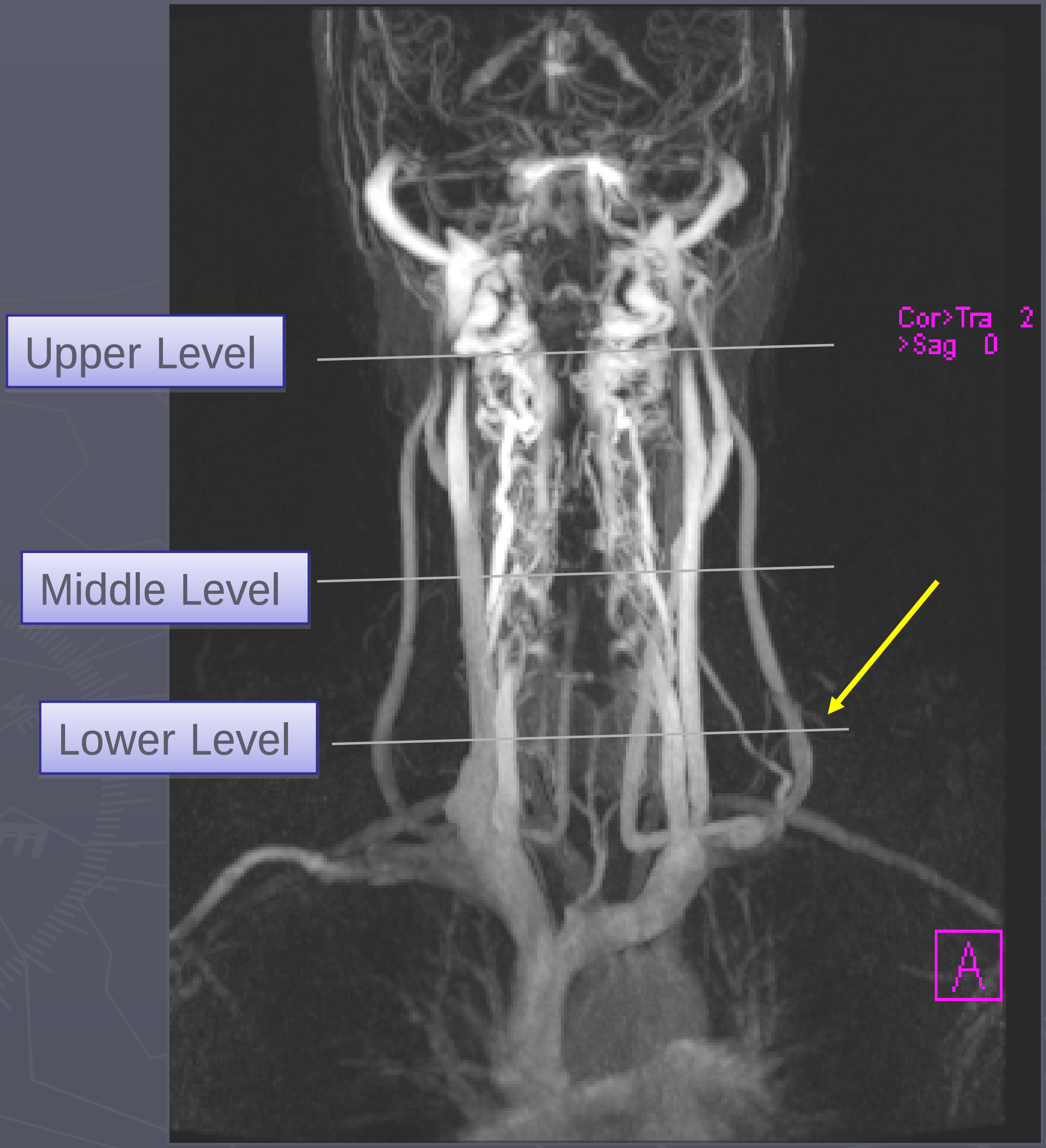


Example of azygous vein imaging not yet motion corrected. Potential is there to do better.

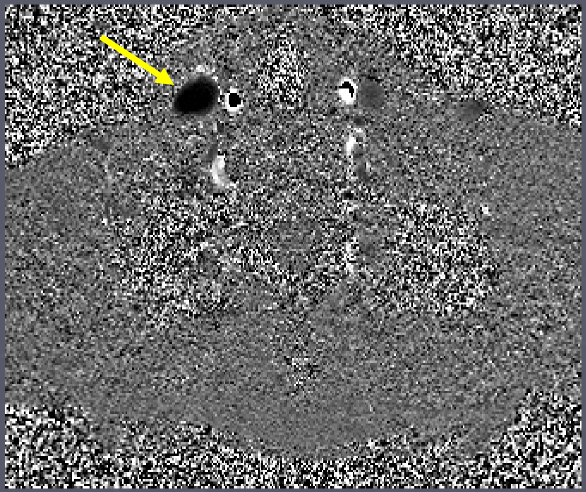
In this case, the azygous looks reasonably uniform.

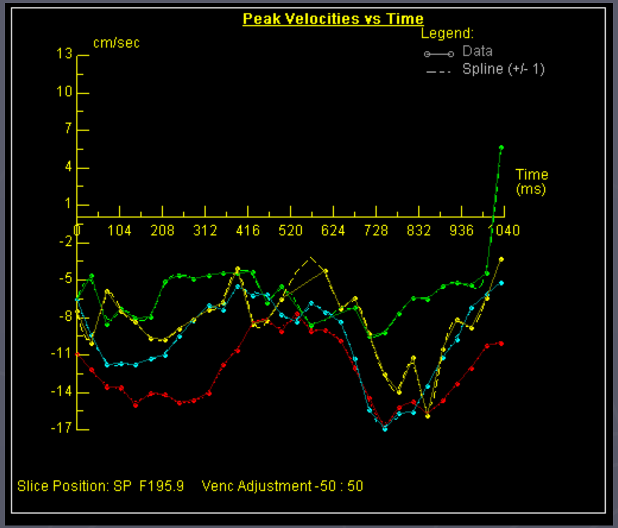
Data can be viewed in 3D and flow is also acquired for these vessels.

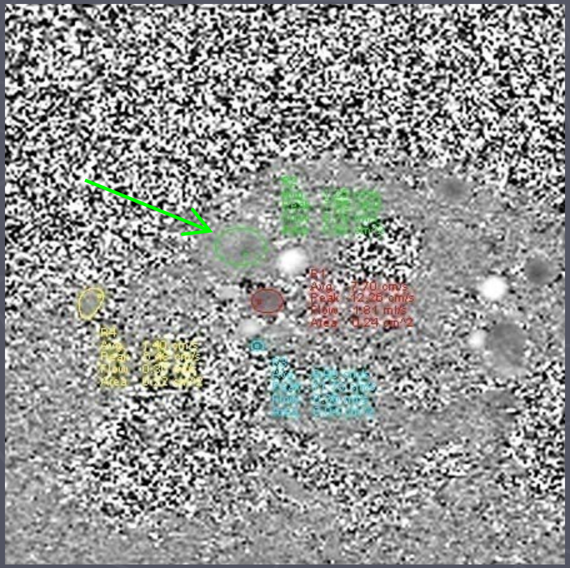
Choosing transverse planes for flow quantification

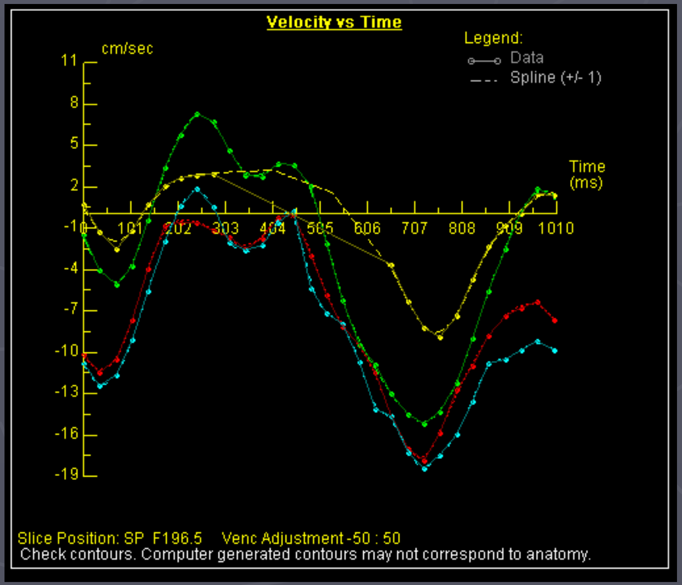


Flow Quantification

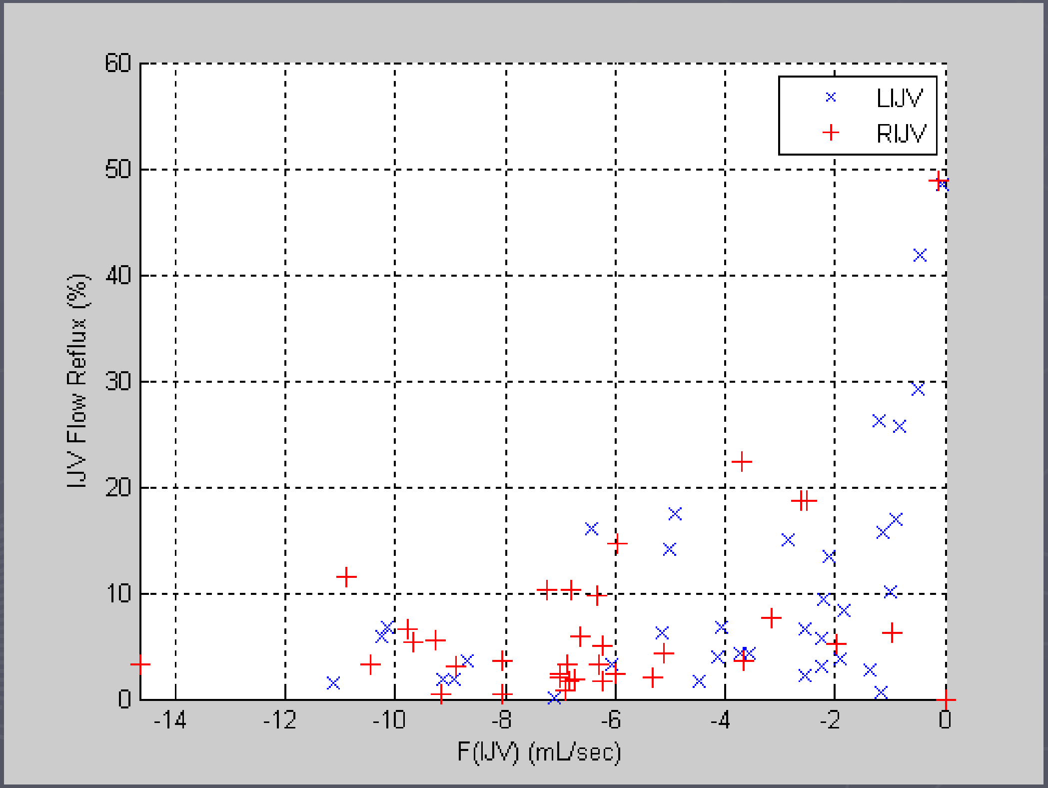








IJV Flow Reflux: The lower the flow the higher the reflux in percent of the cardiac cycle
From the first 35 cases of Dr. Hubbard's study.



F(IJV) = reflux flow/(total positive and negative flow)

Summary of first 50 cases analyzed from the Hubbard Study

- Truncular venous malformations: 10
- One or more stenoses: 12
- Bulging at the lower jugular level: 3
- Abrupt contrast change: 3
- Jetting and then filling in to normal: 1
- Missing jugulars: 1
- Pinching: 8
- Normal anatomy: circulatory flow 7, reflux 3, stasis 1,
  - no abnormal flow 1

	Vessel type	Area 1 (stenosed area)	Avg.area 2,3（above and below stenosis）	% stenosis	L	R	Lower level	Middle	Top	L (cm)	Figure
TVM											
- Thin strip											
- Ends											
- Alt feeds											
Stenosis											
- Round											
- Pinched											
- Pencil											
Bulging											
Line of CA											
- Above bulge											
- Below bulge											
Jet then widens											
Valves											
No jugulars											
Collaterals											

There are a minimum of 12 rows and 4 independent columns making the number of variables 48. With 50 cases per bin this would require a study of 2400 people. Counting all 12 x 7 bins would require 4200 MS patients required as minimum number for this multi-variable analysis.

Flow tables can be made as follows for each plane studied (lower, middle, upper):

Lower level	Right		Left		Total post angio	Total pre angio	% post angio
Flow Volume (ml/cardiac cycle)							
Flow rate (ml/s)							

If we add flow as another variable quantifiable with absolute flow, reflux and circulatory flow that adds three more variables giving 10 columns and 12 x 10 bins requiring 6000 MS patients as a minimum for good statistics.

Iron quantification table:

Parameters	CN	GP	PUT	PT	RN	SN	THA
TR-AI							
RII-TI							
RII-AI							
RII-NA							

Table 1: Abnormal iron content was found in each selected structure for different parameters (checked box). Note: TR-AI: Total Region - Average Iron per voxel; RII-TI: Region II - Total Iron; RII-AI: Region II - Average Iron per voxel; RII-NA: Region II Normalized Area; CN: Caudate Nucleus; GP: Globus Pallidus; PUT: Putamen; PT: Pulvinar Thalamus;RN: Red Nucleus; SN: Substantia Nigra; THA: Thalamus.

Adding iron as yet another series of variables would require a minimum of 7 x 50 or 250 and up to 28 x 50 or 1400 MS patients. And adding the different iron structures to the number of variables would require 12 x 17 bins and a total of 10,200 MS patients to pull apart all the different dependencies.

Imaging MS patients with ultrasound

Zamboni's ultrasound conditions

- Reflux constantly present in the IJV
- Reflux in the deep cerebral veins
- High resolution evidence of stenoses
- Flow not detectable in IJV or VV
- Decreases in IJV cross section when changing from sitting to supine

Simka conditions for grading CCSVI

- grade 1: venous outflow slowed, no reflux
- grade 2: venous outflow slowed, mild reflux and/or pre-stenotic dilation of the vein
- grade 3: venous outflow slowed, with reflux and outflow through collaterals
- grade 4: no outflow through the vein and the presence of significant collateral flow

Other MR Imaging Considerations

- The presence of truncular venous malformations
- Dilated IJV near the confluence with the brachiocephalic and subclavian veins
- Stuck or malfunctioning valves (seen as jetting/refilling)
- The presence of circulatory flow
- Very high flow rates to accommodate slow or reflux flow
- Normal vessels but reduced vertebral flow
- Abnormal jugular anatomy/flow and reduced flow in either or both vertebral veins and deep cervical veins

Future directions: Marrying interests in PTA and MRI

- combine ultrasound and MR imaging
- obtain pressure measurements above and below stenoses
- obtain PCO2 and hematocrit changes pre and post PTA
- compare information from both intravascular ultrasound and MRI on vessel lumen and vessel wall
- compare information from angiographic projections and MRI anatomical and flow information

Conclusions

- Patients must be imaged before and after treatment.
- Creating a database with this type of detailed imaging information coupled with appropriate neurological measures of patient's health will help better diagnose CCSVI, treat patients and follow patient's recovery.
- Such a database will allow for datamining and provide a means to better understand the vascular system and its role in neurological diseases such as multiple sclerosis.
- New procedures may be required as some cases are very complicated.
- A consensus or white paper on how to do the PTA should be prepared.

- We need to image as many normals as possible. Currently the number of patients being imaged and/or treated is in the 1000s, and we need age matched normals to go with this patient population.