CCSVI- Chronic Cerebrospinal Venous Insufficiency

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- President Paolo Zamboni
- Vice-President Robert Zivadinov
- Executive committee members: David Hubbard, Franz Schelling, Mark Godley,

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 and generally monitor lesions, flow and iron over time

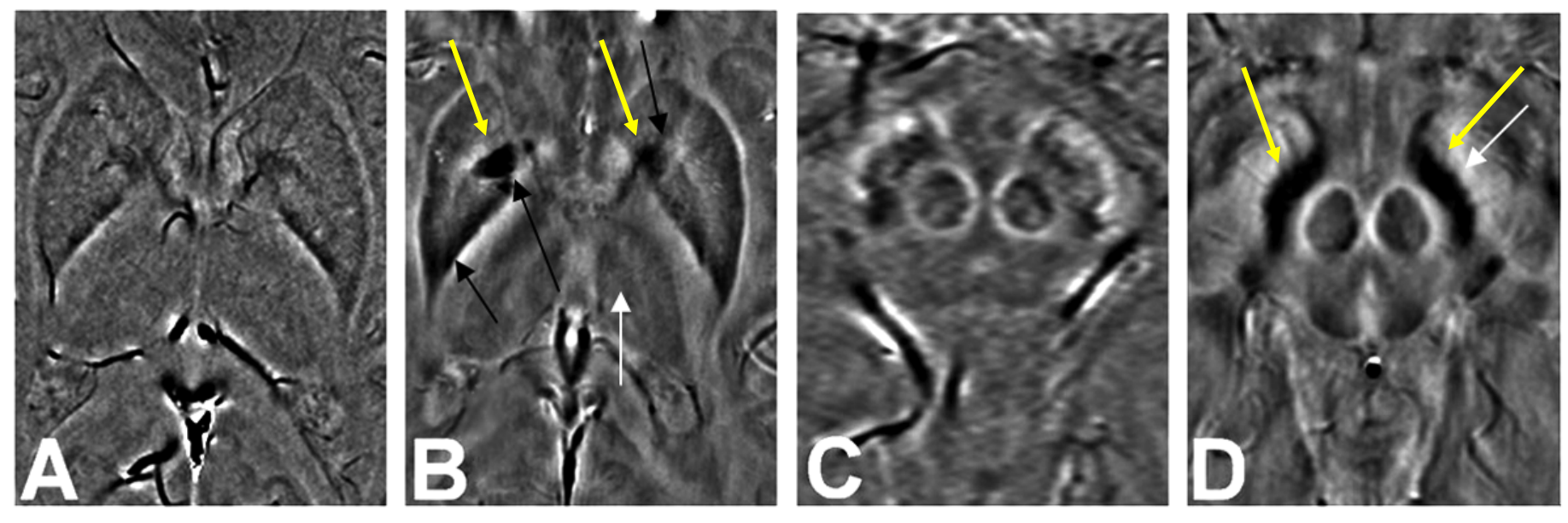
Susceptibility weighted imaging (SWI) serves as a means to monitor small veins in the brain. Susceptibility mapping (SWIM) may well serve as a means to monitor oxygen saturation in veins with diameters on the order of several pixels (i.e., diameters of 1 to 2mm or larger) in diameter.

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

Normal thalamostriate veins

Caudate veins and the thalamostriate venous drainage system as seen with SWI at 7T.

Iron build-up in the basal ganglia



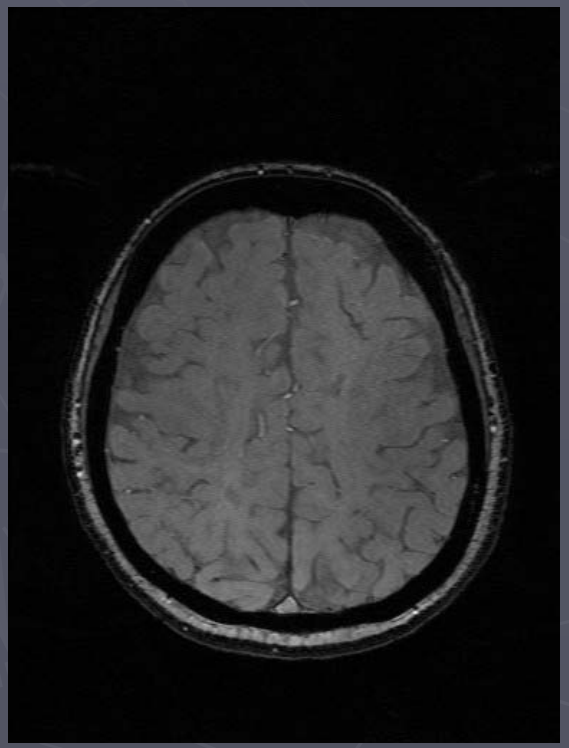
A,B show iron build up in the caudate and globus pallidus for an MS patient (B) compared with that from an age matched normal (A). C,D show iron build up in the substantia nigra for an MS patient (D) compared with that from an age matched normal (C).

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.

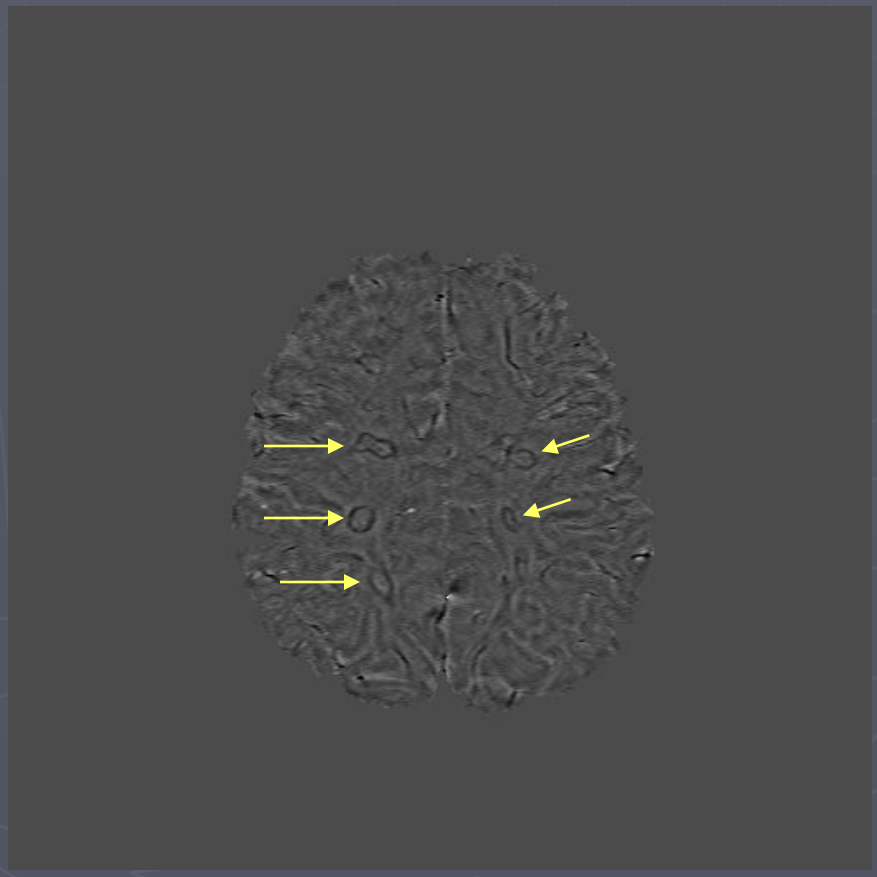
MULTIPLE SCLEROSIS LESIONS:

Iron as seen in SWI may correlate with a breakdown of the blood brain barrier in a more subtle fashion that the usual GdDTPA T1 enhanced lesions (data courtesy of Liu Jiangtao)

Magnitude GE image

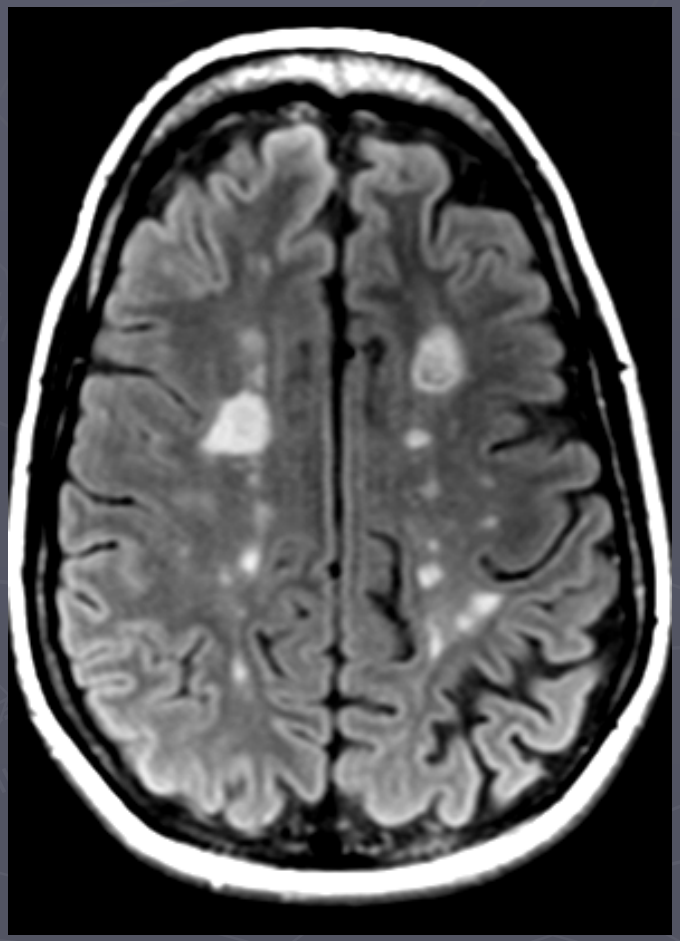


Phase SWI showing ring structures around MS lesions.

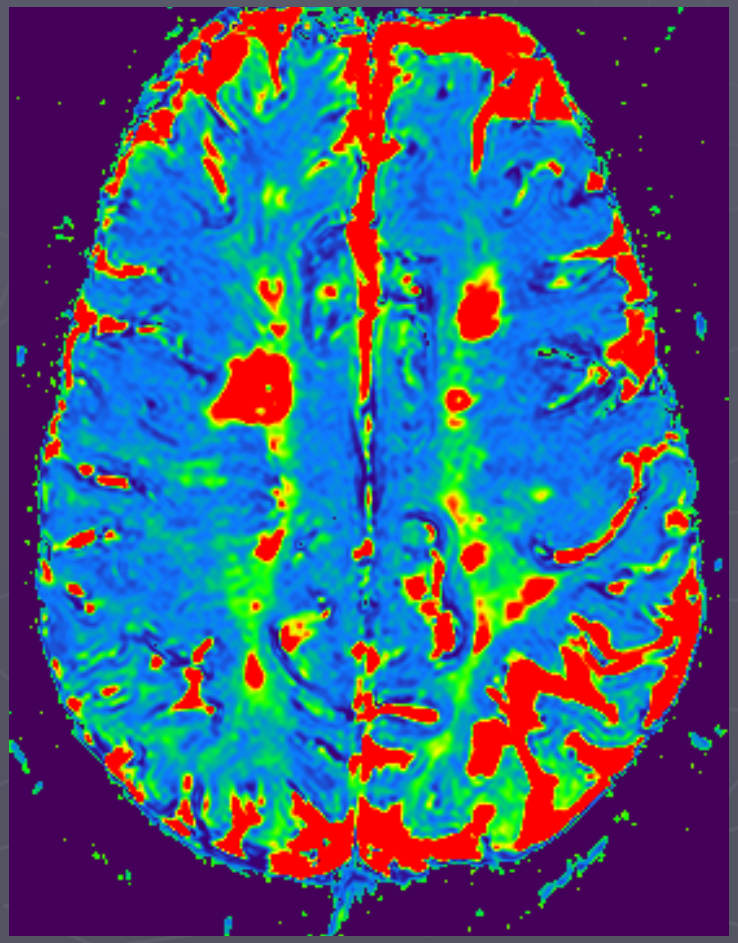


MULTIPLE SCLEROSIS LESIONS: FLAIR and Perfusion Weighted Imaging (PWI can be used to study the hemodynamics of the brain)

Anatomic evidence of lesions from FLAIR imaging

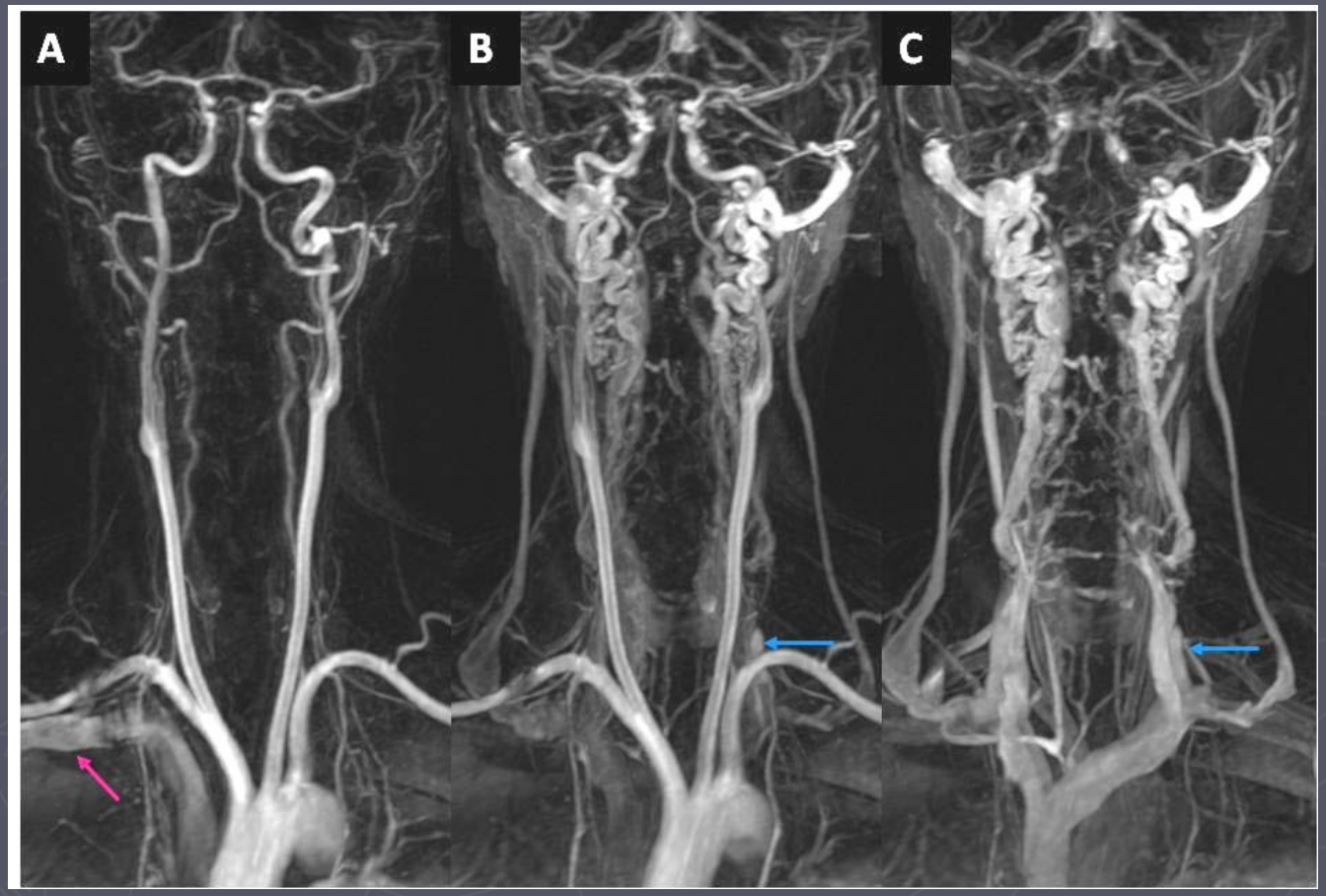


PWI shows all MS lesions have the same vascular characteristics



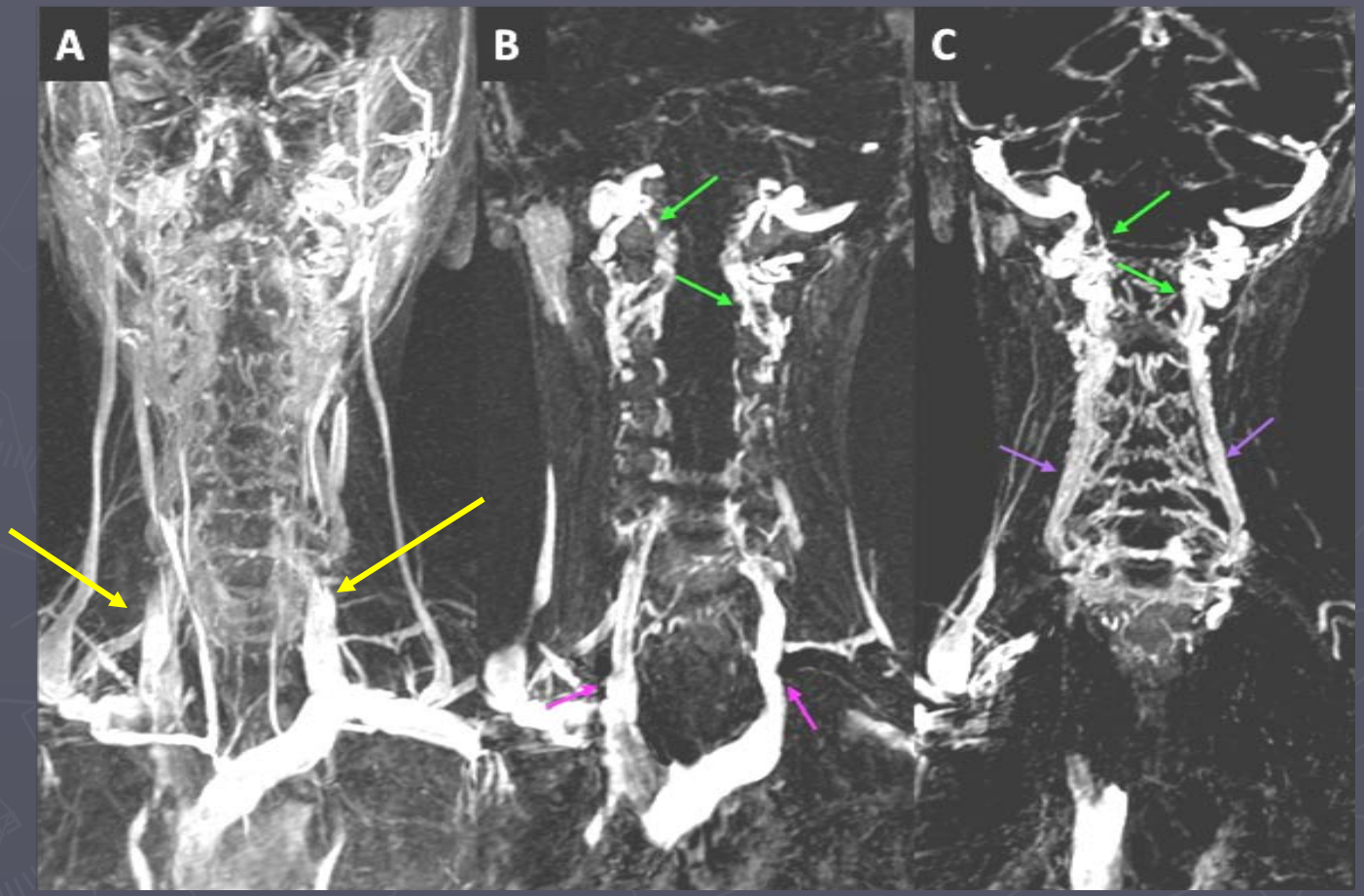
Left: Stenosis at the stump of the LIJV with collateral input from the vertebral system Right: String like jugular in the RIJV

Deep cervical veins and vertebral veins assume the role jugular veins

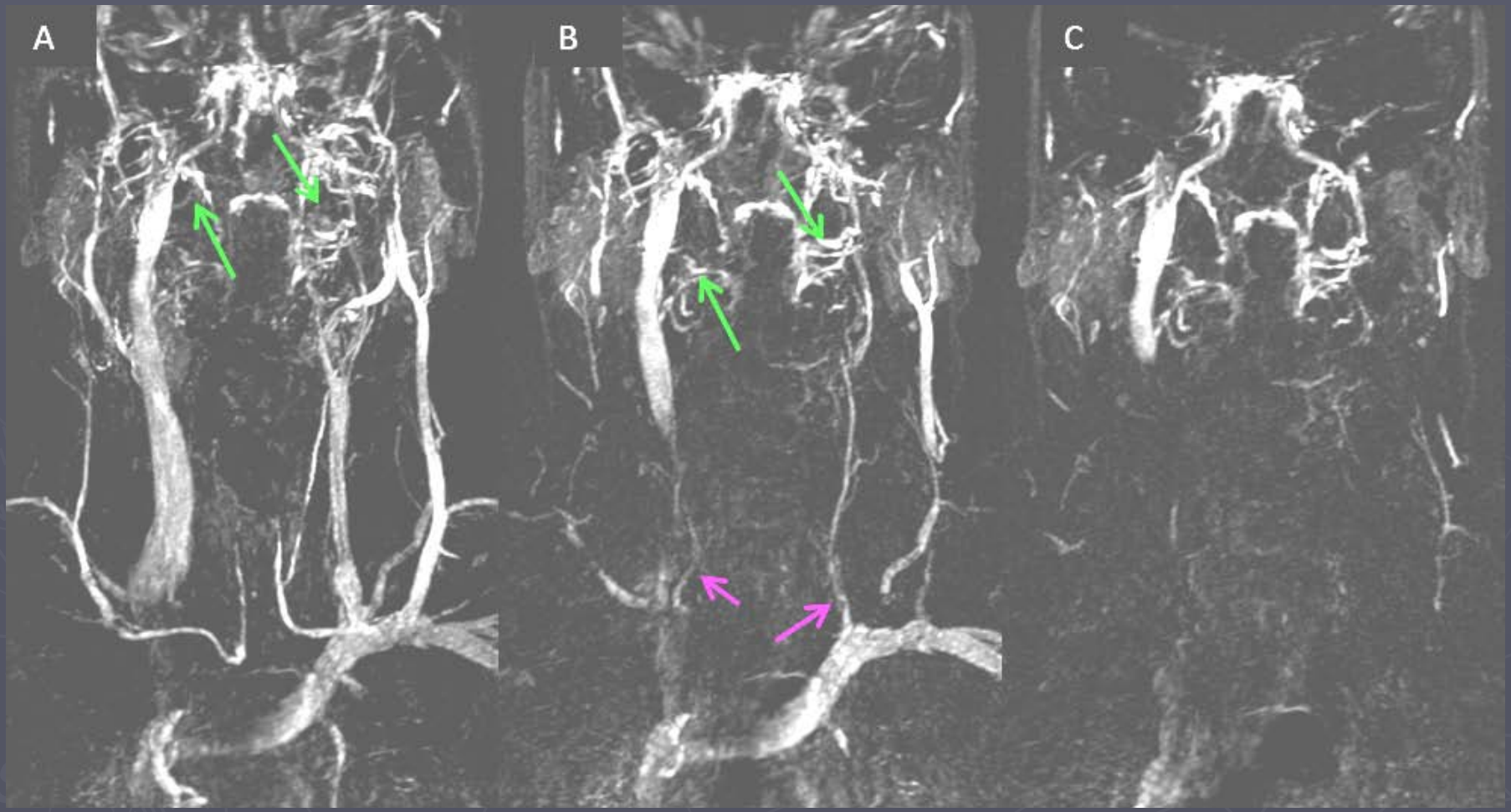


Note the irregularities in the lower right external jugular vein.

Ladder-like vertebral plexus for an individual with abnormal jugulars



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



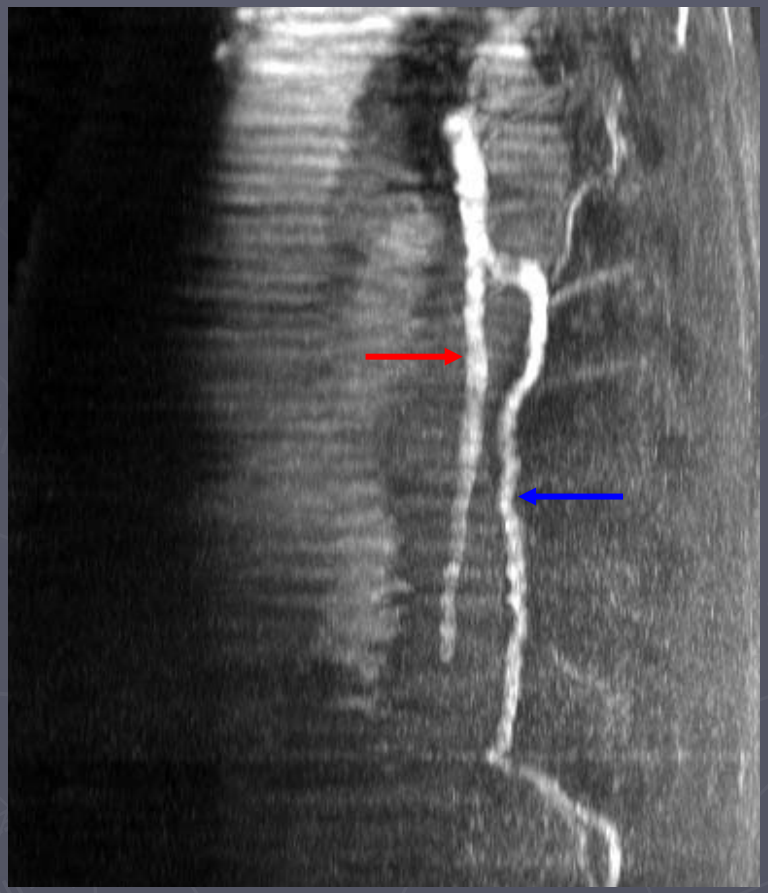
MR examples of CCSVI in MS patients where pre-treatment planning would reveal significant data that could affect how the veins are accessed.

Stenosed RIJV

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

Stenosed RIJV

Azygous and Hemi-azygous

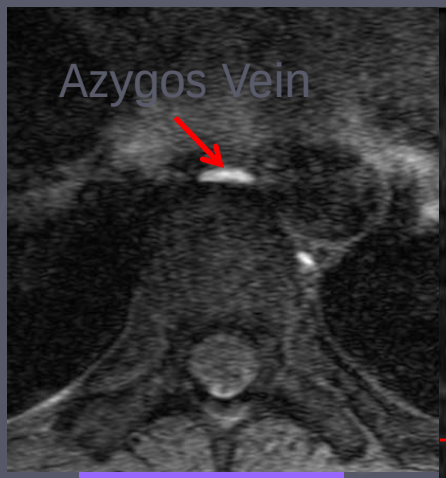


Example of azygous vein imaging not yet motion corrected. Potential is there to do better.

In this case, the azygous looks reasonably uniform.

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

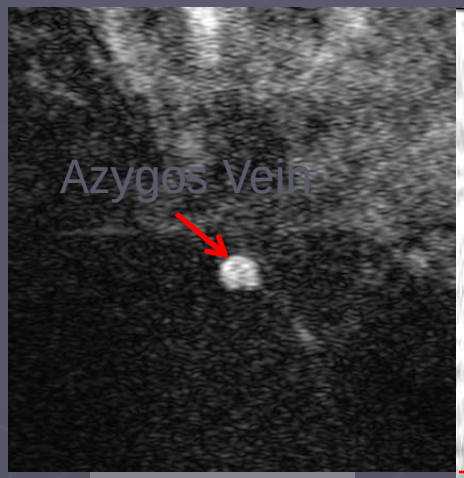
An Example Showing Azygos Vein in an MS Patient in Supine and Prone Position



Axial Image

MIPed Sagittal Image

Example for Supine Position

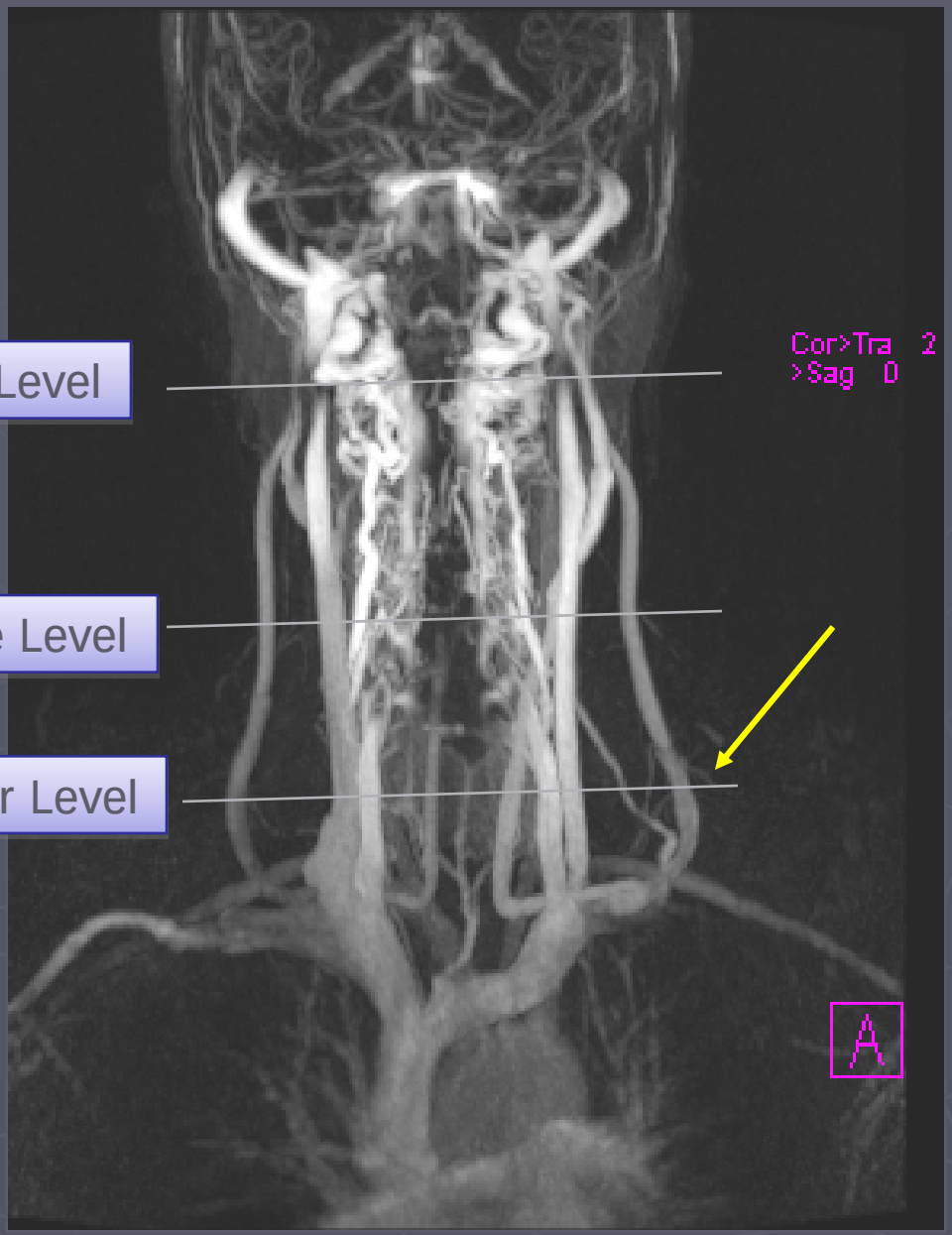


Axial Image

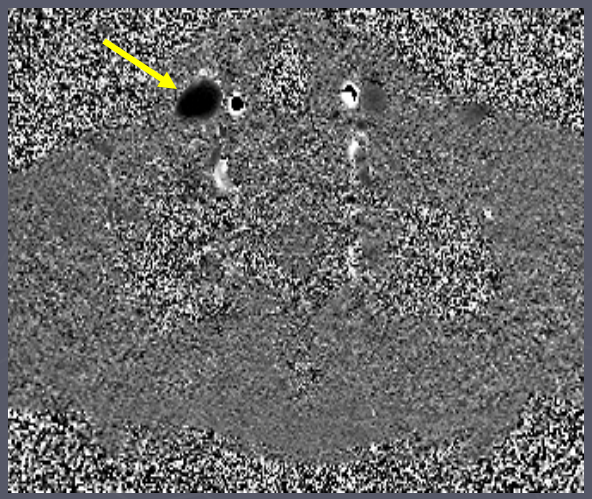
MIPed Sagittal Image

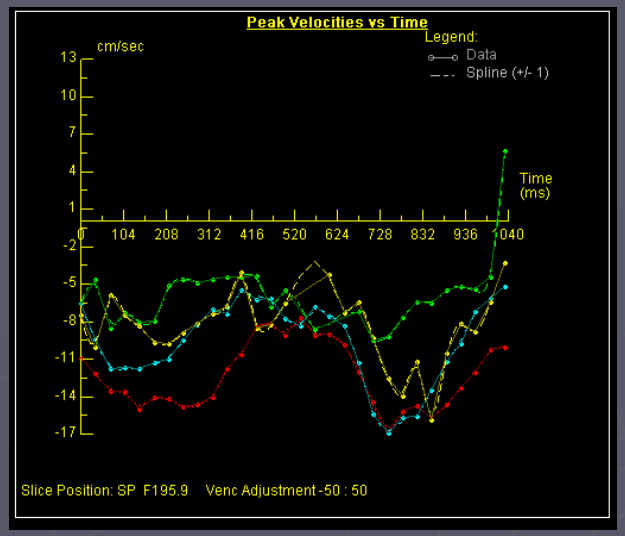
Example for Prone Position

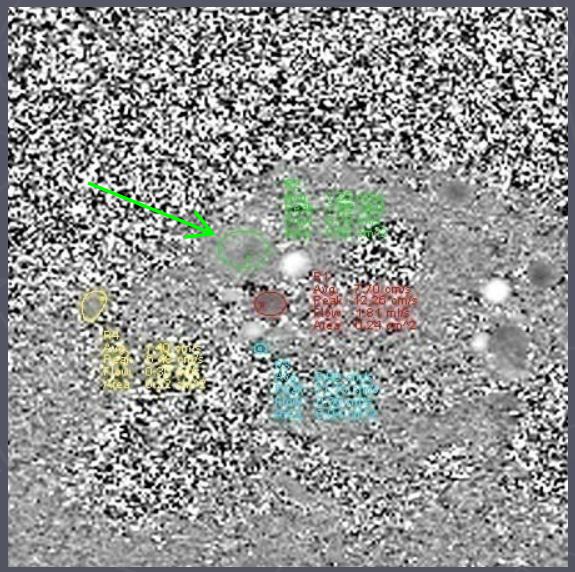
Choosing transverse planes for flow quantification

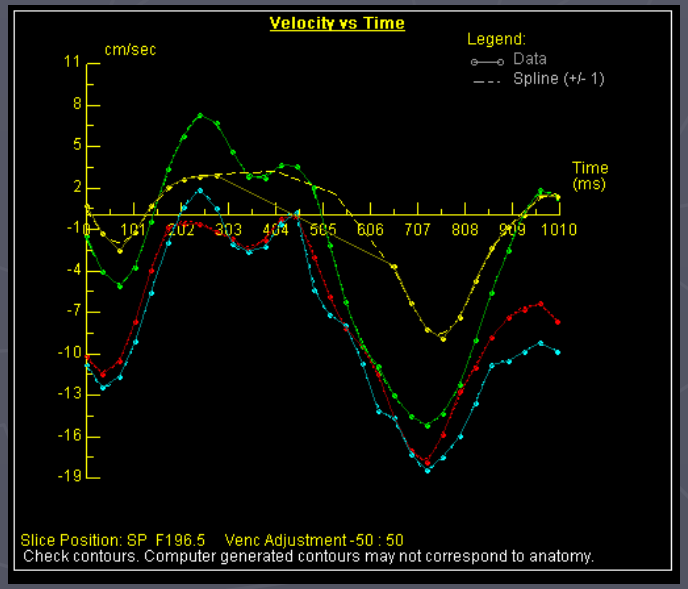


Flow Quantification

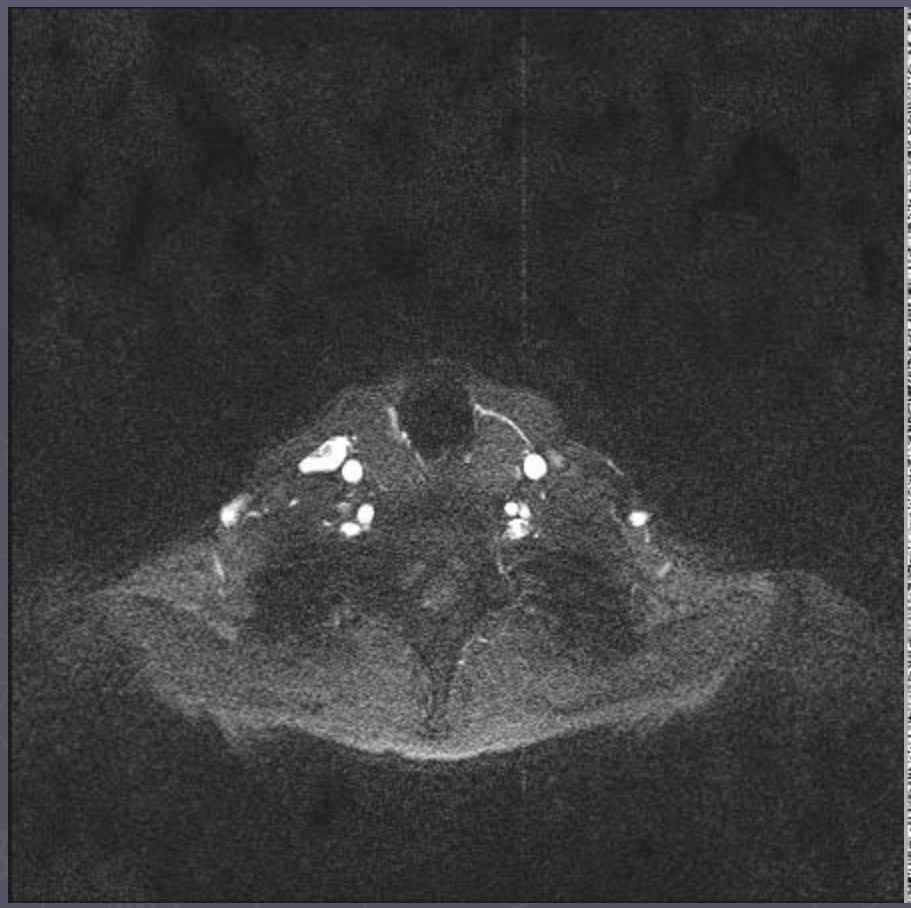


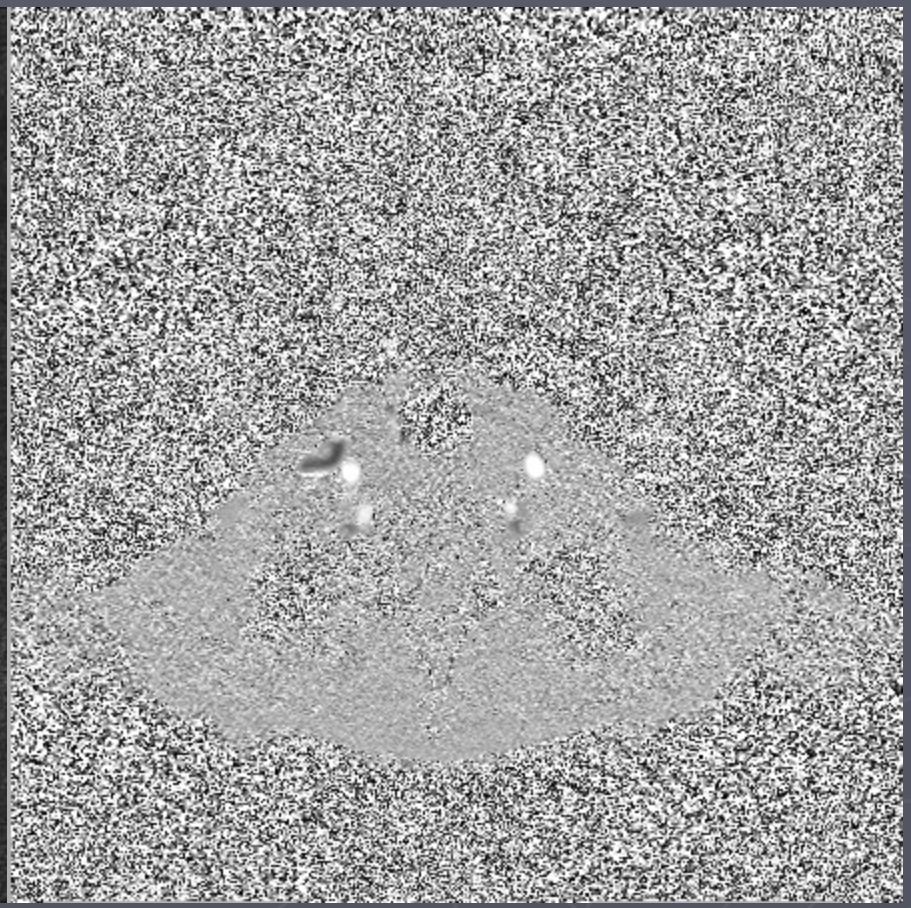




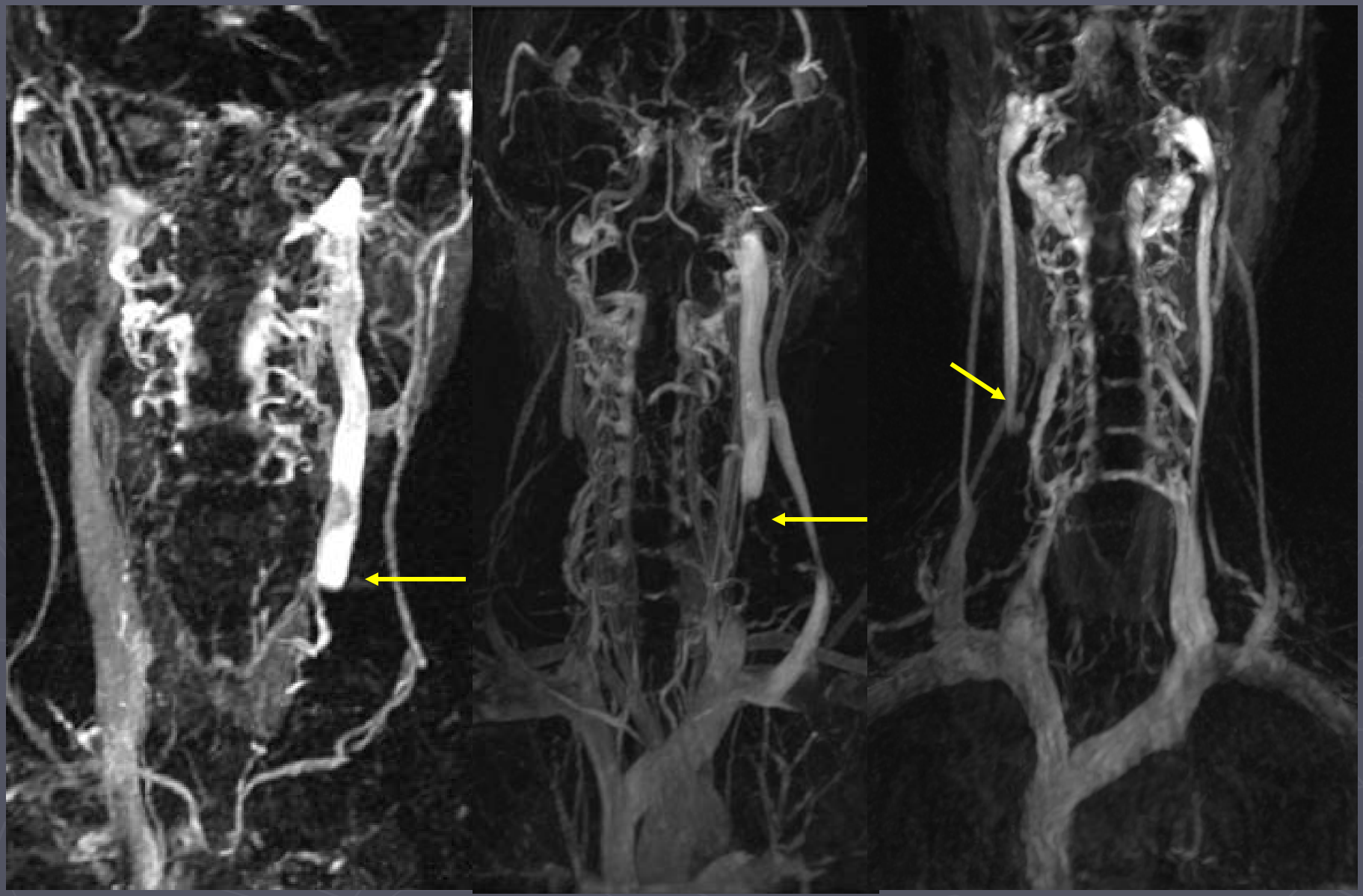


Flow in the neck as a function of the cardiac cycle.

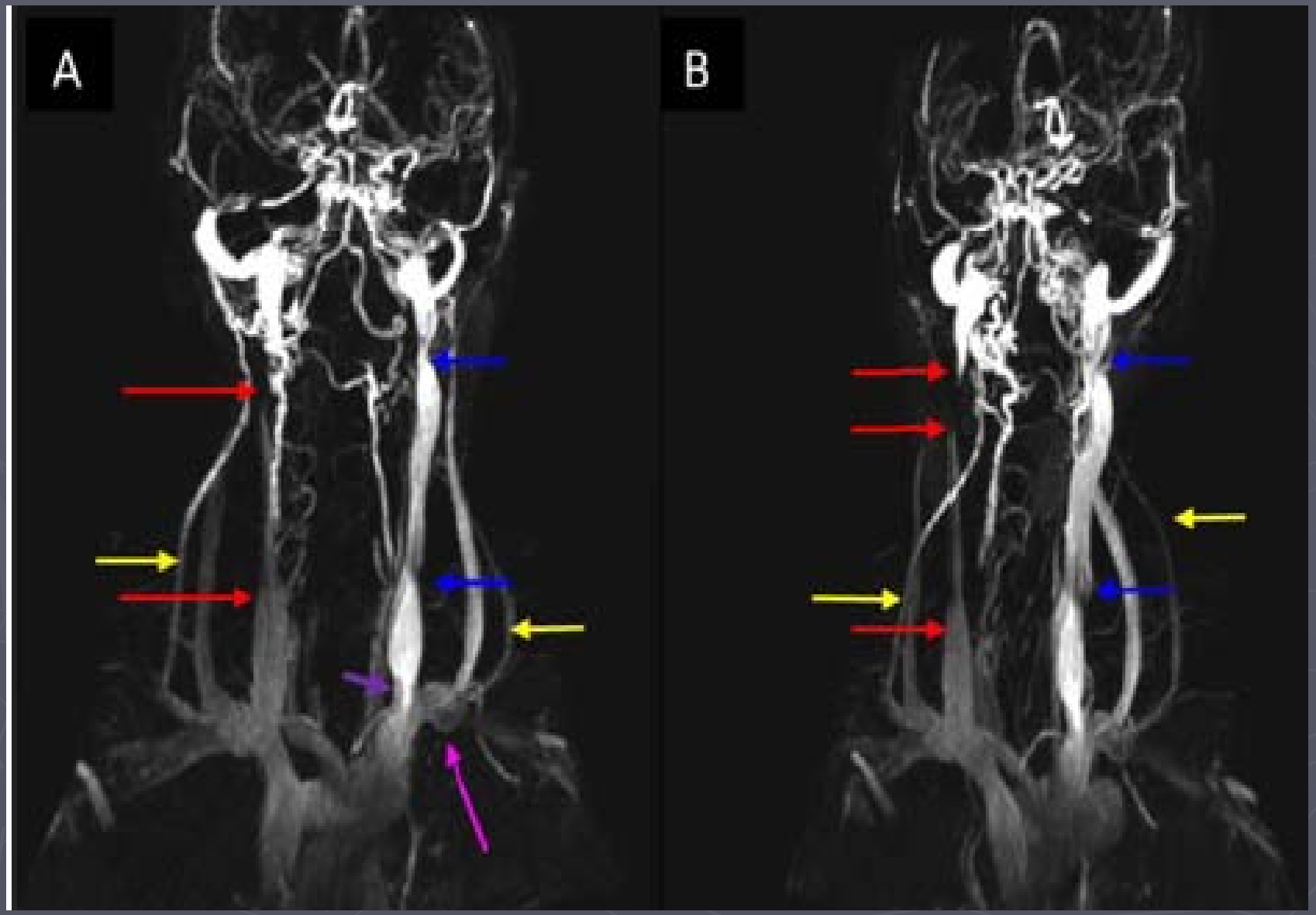




Truncular venous malformations (TVM)



Disconnect between the RIJV and the sigmoid sinus.



Classifying patient types

Key conditions, consider a patient with:

- Only one major vein with
  - Either excellent vertebral plexus flow
  - Or very poor collateral flow
- Will they have more lesions if they have
  - Either low flow or
  - Poor collateral flow
- Can they be treated if they have:
  - just a stenosis or
  - If they have poor 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

Characterization of venous abnormalities in CCSVI

Anatomical markers	***Possible Criteria Threshold***
Presence/Engorgement of Collaterals	*Present/Absent/Engorgement/Symmetry/Tortuous Shape*
External Jugular Vein	Absent/ Engorgement of CSA < 49mm²/ Symmetry/Tortuous shape
Anterior Jugular Vein	Absent/Engorgement of CSA < 25mm²/ Symmetry/Tortuous shape
Vertebral Vein	Absent/Engorgement of CSA < 25mm²/ Symmetry/Tortuous shape
Vertebral Plexus	Engorgement; Symmetry
Deep Cervical Vein	Absent/ Engorgement of CSA < 25mm²/ Symmetry/Tortuous shape
Stenosis in Neck	*Present/Absent*
IJV stenosis superior to C3 (UL)	CSA < 12.5mm²
IJV stenosis inferior to C3 (LL)	CSA < 25.0mm²
Truncular Venous Malformation	Present/Absent
Missing IJV (s)	One or Both IJVs missing including superior/inferior jugular bulbs
Missing Vertebral Veins	Present/Absent at the C6 level
Missing Deep Cervical Veins	Present/Absent
Stenosis in Thoracic Cavity	*Present/Absent*
Azygous stenosis	Stenosis of 75% of Azygous CSA
Azygous compression between heart and spine	Present/Absent
Missing Azygous	Present/Absent
Missing Hemi-azygous	Present/Absent
Missing both Azygous and Hemi-azygous	Present/Absent
Azygous engorgement	CSA>1cm²

Valves
Constrast Discontinuity at Confluence
Biphasic Flow
Jetting Effect
Developmental Anomalies
Narrowing at the Confluence
SWI Markers
Small veins
Visibility of veins
Iron content
Pulvinar Thalamus
Putamen
Globus Pallidus
Caudate Nucleus
Red Nucleus
Substantia Nigra
Dentate Nucleus
Micro-bleeds
Lesions

Quantitative Flow Markers	***Possible Criteria Threshold***
C6 level flow	*Present/Absent*
Dominant IJV: Sub-Dominant IJV	> 4:1
Dominant vein: Sub-Dominant vein	> 4:1
Total venous flow	< 8 ml/s
Total IJV flow	< 5 ml/s
Total percent of venous flow carried by IJV	< 32%
High velocity of flow through veins	> 25 cm/s
Low velocity of flow through veins	< 1 cm/s
C2 level flow	*Present/Absent*
Dominant IJV: Sub-Dominant IJV	> 5:1
Dominant vein: Sub-Dominant vein	> 5:1
Reflux	*Present/Absent*
Reflux of flow in IJV	> 10%
Percent of CDC that IJV demonstates low flow and reflux flow	> 30%
% of CDC Vertebral Vein shows reflux	> 30%
% of CDC Deep Cervical Vein shows reflux	> 30%
% of CDC External Jugular Vein shows reflux	> 30%

Qualitative Flow Markers	***Preferred MR Imaging Method***
Contrast Discontinuity through vessel	3D TRI
Loss of signal	2D TOF
Inhomogeneous signal at confluence	2D TOF

Anatomical Assessment

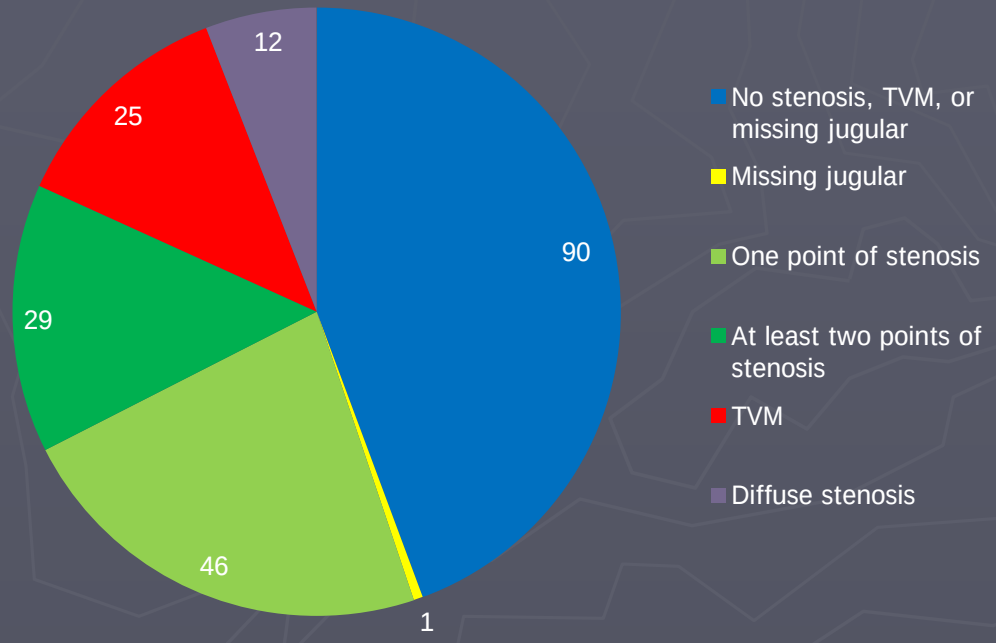
Stenosis: Narrowing or reduction of IJV caliber size to less than 25mm² at the lower neck level (inferior to C3) or less than 12.5mm² at the upper neck level (superior to C3).

TVM: Truncular Venous Malformation; 1. congenial truncation of the IJV in which there may or may not be a thin connection between superior and inferior segments, 2. the continuation of the IJV at the upper neck level by vessels other than the sigmoid sinus, and 2. apparent discontinuity between superior and inferior segments of the IJV where another vessel may reconstitute the inferior segment.

Diffuse Stenosis: Stenosis through the length of the IJV; shoestring stenosis.

Missing Jugular: IJV is not present in any form between the sigmoid sinus and the subclavian/brachiocephalic vein

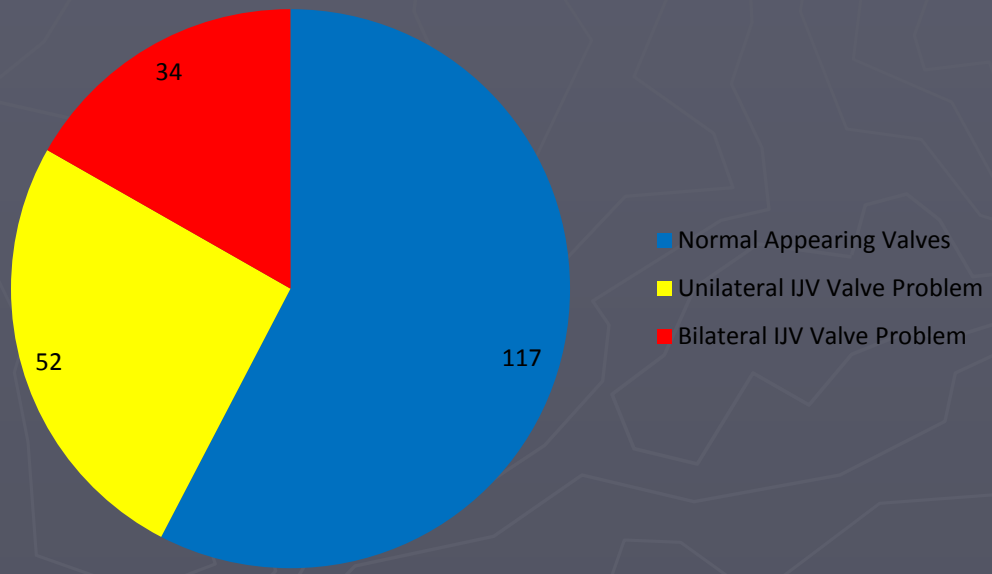
Anatomical Assessment of 203 MS Patients: Stenosis, TVM, and Missing Jugular



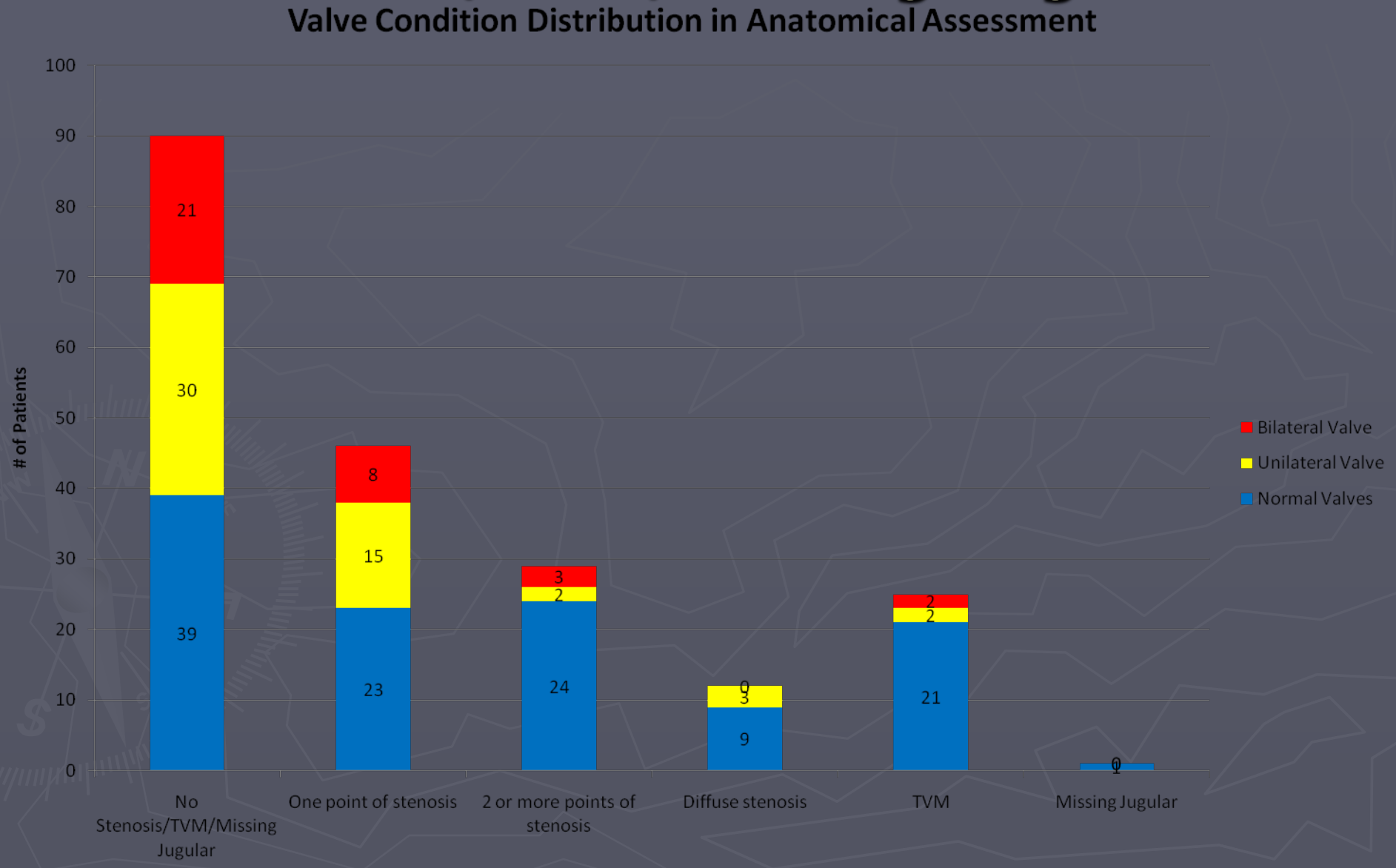
Anatomical Assessment

Possible IJV valve problems are identified on time resolved 3D CE MRAV data by; narrowing near the confluence where the inferior jugular bulb structure would normally be found, contrast jetting effect near the confluence, regurgitation of contrast into the IJV during or before the arterial phase (may also indicate lack of valve).

Anatomical Assessment of 203 MS Patients: Possible IJV Valvular Insufficiency/Incompetence

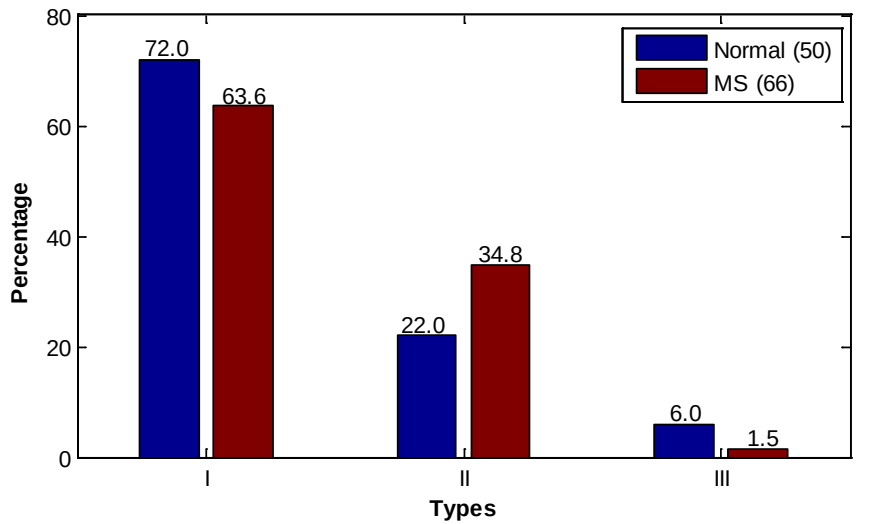


Anatomical Assessment Valves and Stenosis/TVM/Missing Jugular

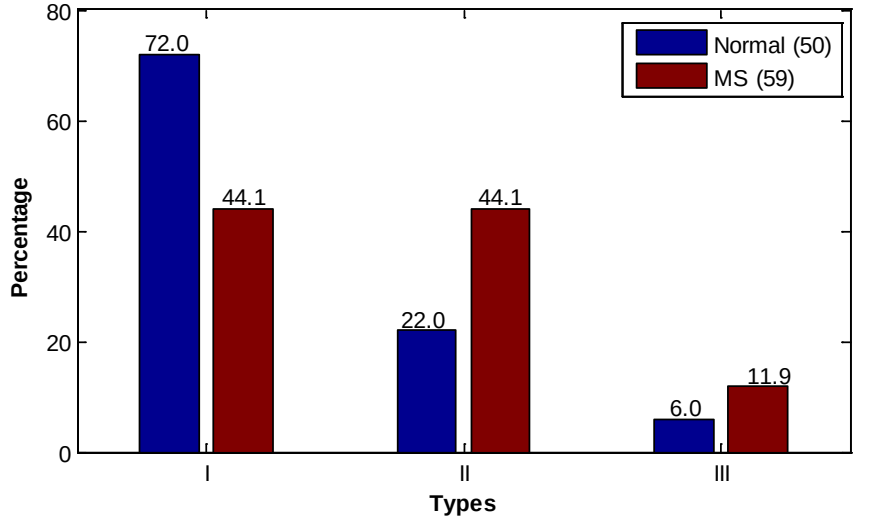


Numbers for Histogram

	Normal Valves	Unilateral Valve	Bilateral Valve	Total #
No Stenosis/TVM/Missing Jugular	39	30	21	90
One point of stenosis	23	15	8	46
2 or more points of stenosis	24	2	3	29
Diffuse stenosis	9	3	0	12
TVM	21	2	2	25
Missing Jugular	1	0	0	1
Total #	117	52	34	203

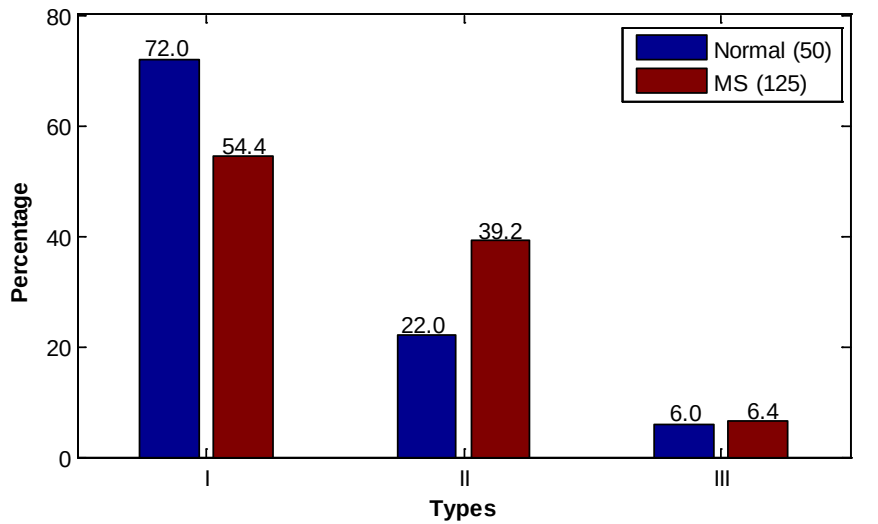


Non-Stenotic MS vs. Normal (Site 1)

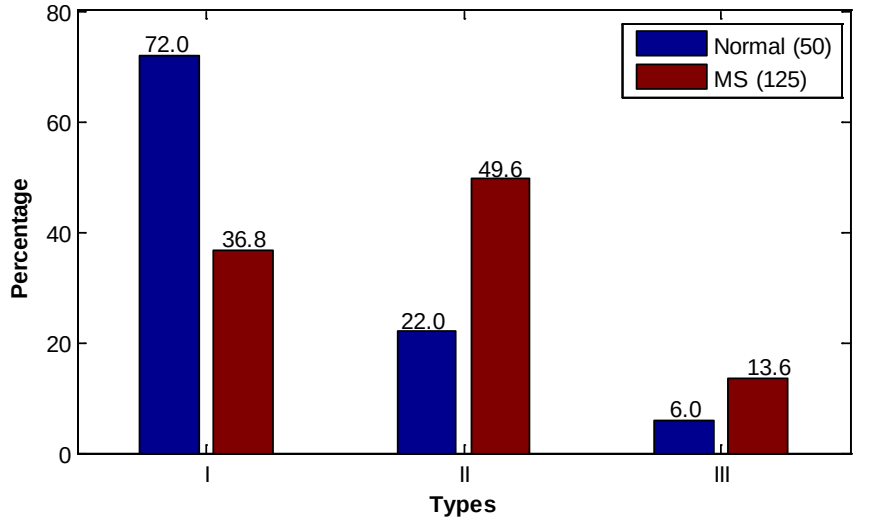


Stenotic MS vs. Normal (Site 1)

Comparison of non-stenotic and stenotic MS patients with normals using the ratio of IJV flow diivided by total arterial flow: F(IJV)/F(tA).
(Doepp et al., Neuroradiology, 2004)
(Type I: F(IJV)/F(tA)>=2/3; Type II: 2/3>F(IJV)/F(tA)>=1/3; Type III: F(IJV)/F(tA)<1/3)

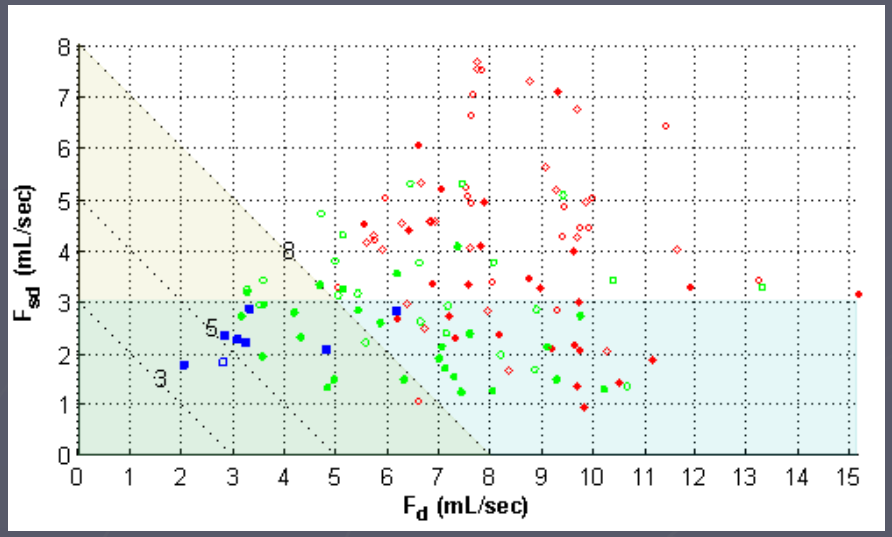


MS vs. Normal (Site 1)

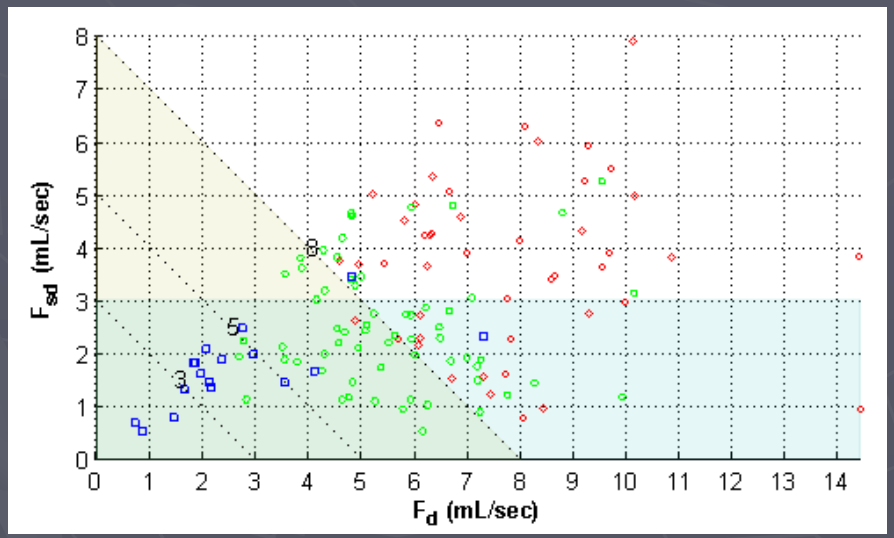


MS vs. Normal (Site 2)

Comparison of 125 MS patients at each site and 50 normals using the ratio of IJV flow diivided by total arterial flow: F(IJV)/F(tA).
(Doepp et al., Neuroradiology, 2004)
(Type I: F(IJV)/F(tA)>=2/3; Type II: 2/3>F(IJV)/F(tA)>=1/3; Type III: F(IJV)/F(tA)<1/3)

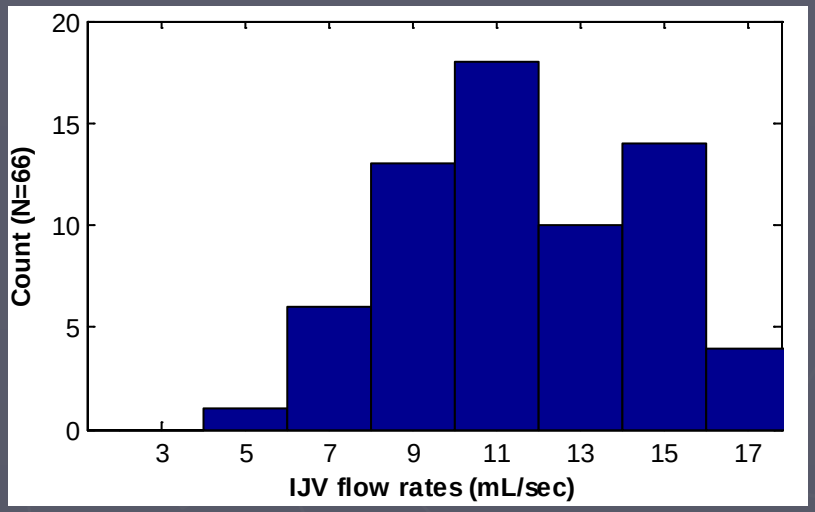


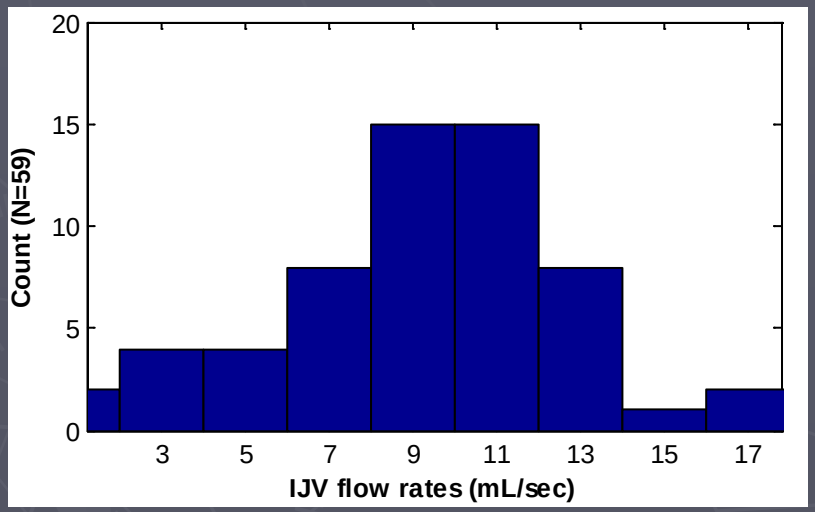
Dominant vs. Sub-dominant Venous flow (Site 1)



Dominant vs. Sub-dominant Venous flow (Site 2)

Flow rate scatter plots of sub-dominant vein vs. dominant vein for 125 MS patients each site color-coded by Doepp categorization criterion. Red, green and blue correspond to Types I, II and III. Solid symbols are stenotic MS cases (upper and lower level stenosis, bilateral stenosis, diffused stenosis and TVM).

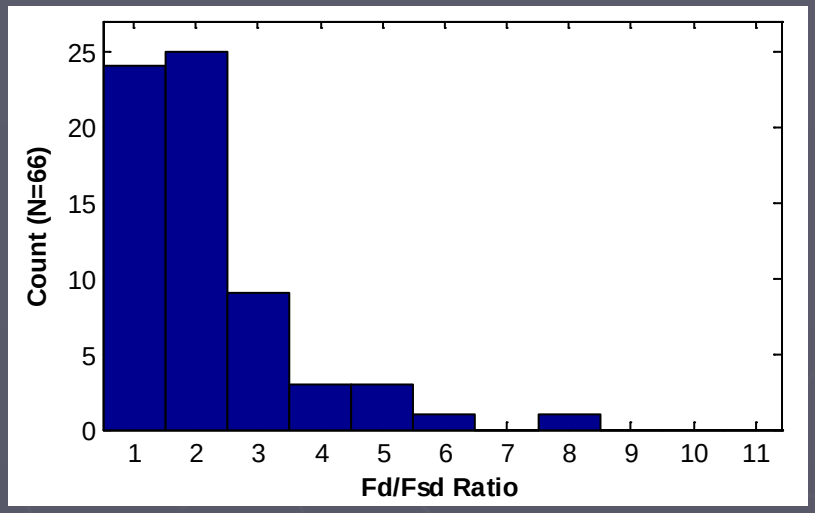




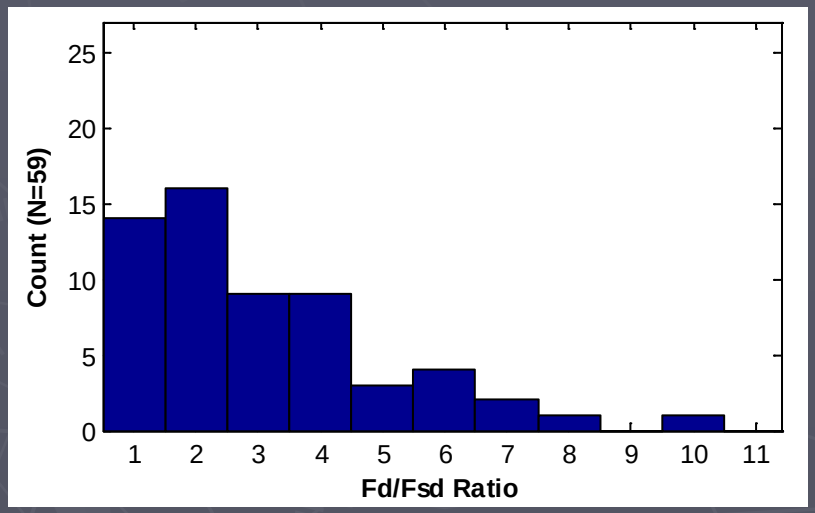
Non-Stenotic (11.6±2.9ml/sec) (Site 1)

Stenotic (9.05±3.47ml/sec) (Site 1)

Histograms of IJV flow rates for 66 non-stenotic MS patients (top) vs. 59 stenotic MS patients (bottom). *t*-test: h = 1, p = 0.00001

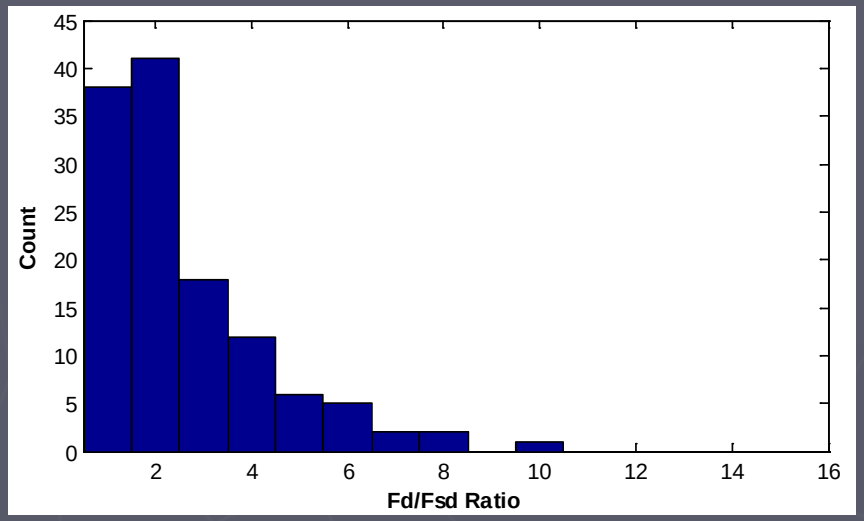


Non-Stenotic (2.19±1.34) (Site 1)

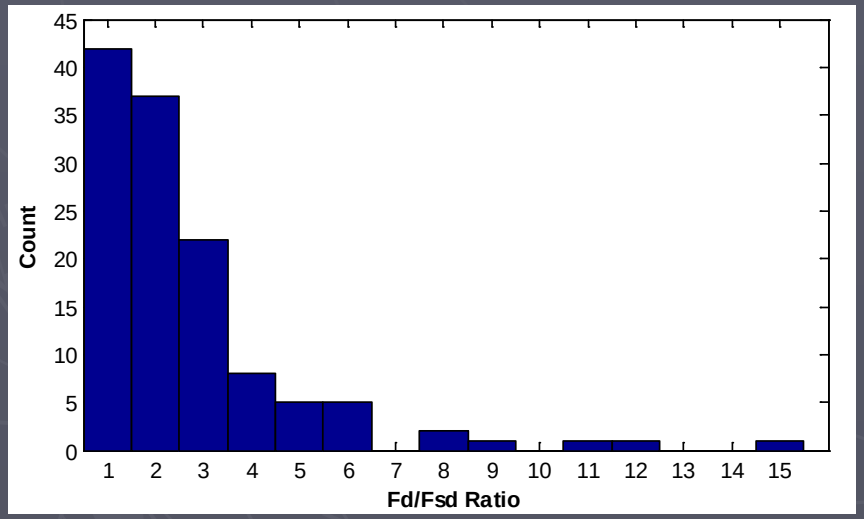


Stenotic (3.15±2.02) (Site 1)

Histograms of Fd/Fsd ratio for 66 non-stenotic MS patients (top) vs. 59 stenotic MS patients (bottom). *t*-test: h=1, p=0.002



Fd/Fsd Ratio (2.64±1.76) (Site 1)



Fd/Fsd Ratio (2.71±2.22) (Site 2)

Histograms of Fd/Fsd ratio for 125 MS patients each from Site 1 and Site 2.

Quantitative Flow Measurements Flow Rate (Site 1 vs. Site 2, N=125)

	Site 1		Site 2	
	Mean	Std	Mean	Std
Age (years)	47.50	10.04	49.08	10.42
HR (/sec)	70.41	9.93	70.70	12.65
Flow Rate (mL/sec)				
LCCA	6.29	1.36	-5.72	1.30
RCCA	6.40	1.36	-5.89	1.43
LVA	1.73	0.74	-1.37	0.71
RVA	1.48	0.61	-1.21	0.60
LIJV	-4.06	2.72	3.34	2.56
RIJV	-6.35	2.95	4.90	2.90
tIJV	-10.42	3.43	8.23	3.79
tLA	8.02	1.74	-7.10	1.58
tRA	7.89	1.49	-7.10	1.64
tA	15.90	2.87	-14.20	2.91
tLV	-5.98	2.60	5.15	2.64
tRV	-8.83	2.74	6.95	2.86
tV	-14.81	2.74	12.10	3.63

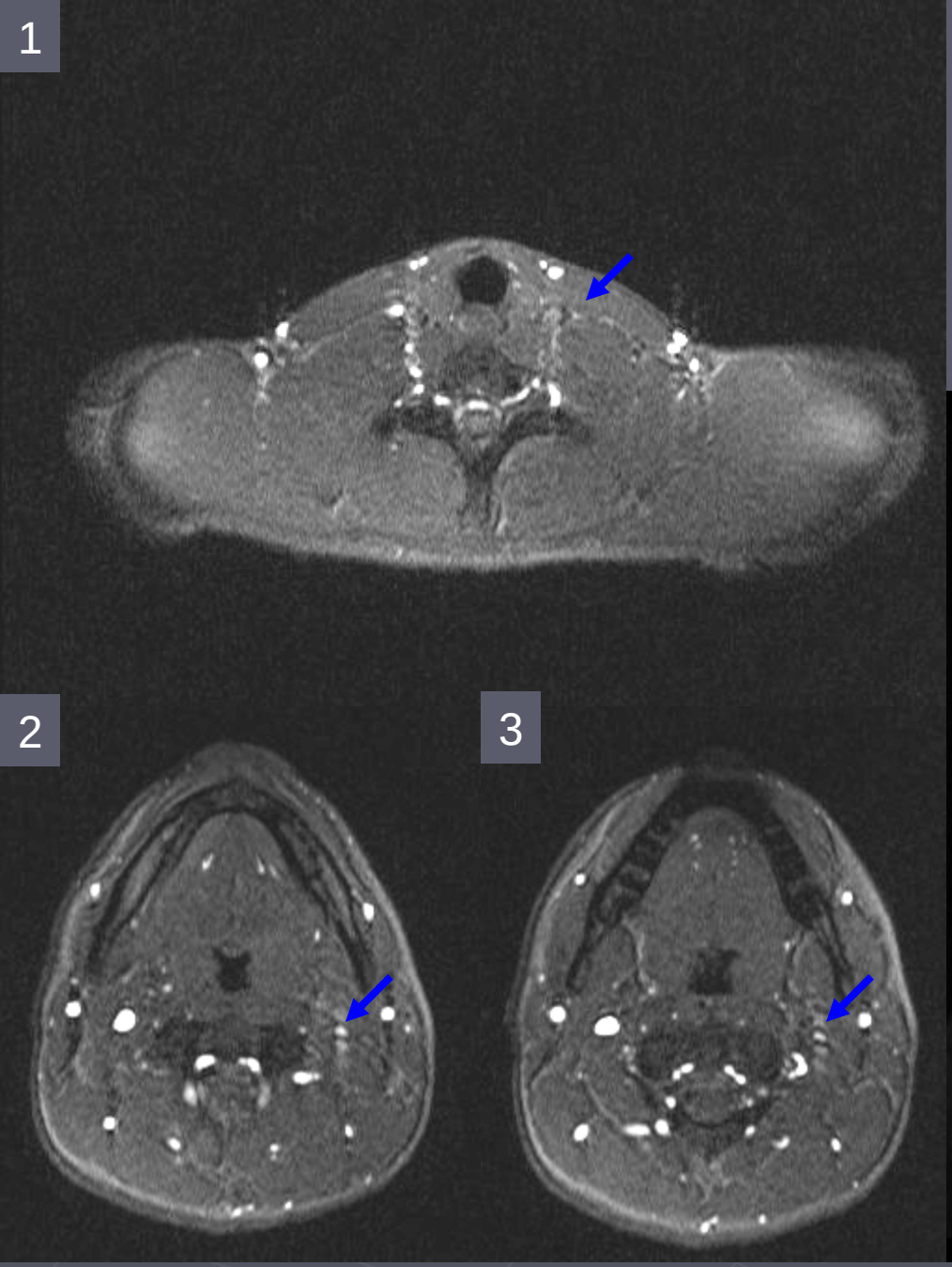
Flow Distributions (Site 1 vs. Site 2, N=125)

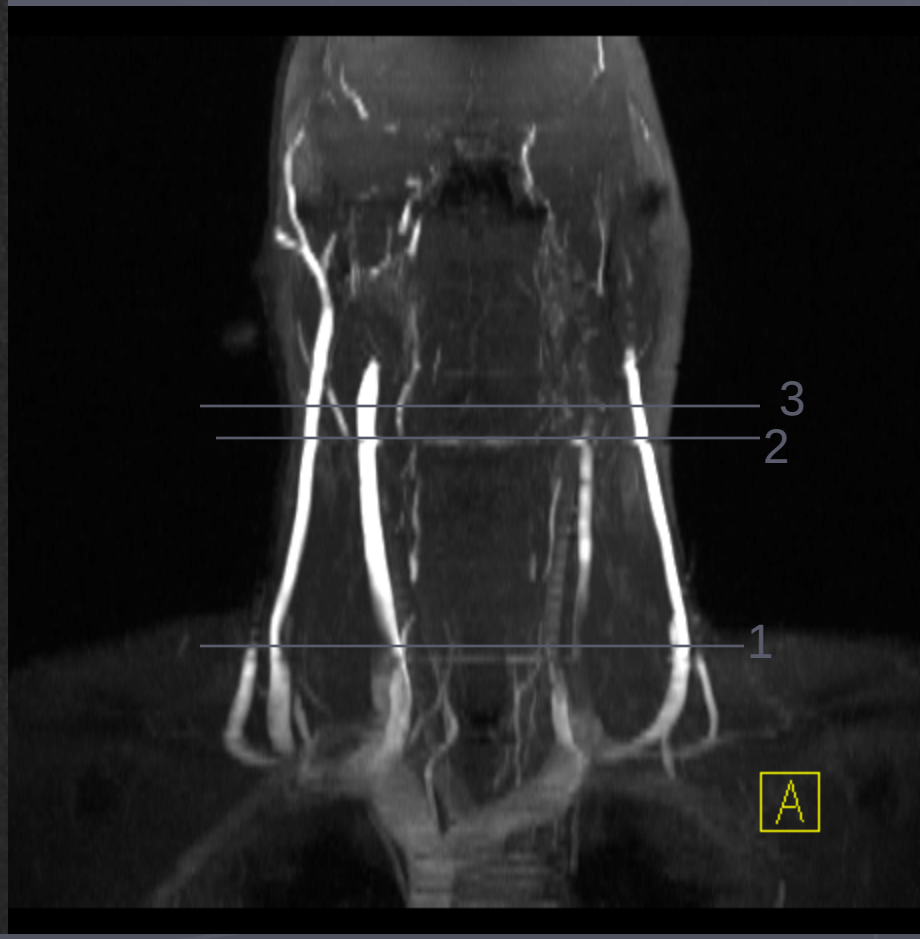
Flow Distribution (%)	Site 1		Site 2	
	Mean	Std	Mean	Std
LCCA/tA	39.43	3.72	40.38	4.56
RCCA/tA	40.20	4.24	41.43	4.35
LIJV/tV	27.42	17.13	27.11	18.60
RIJV/tV	42.83	18.28	39.38	20.73
tLA/tA	50.28	4.80	50.00	5.08
tRA/tA	49.72	4.80	50.00	5.08
IJV/tV	70.24	19.08	66.49	22.60
IJV/tA	-66.29	20.64	-58.64	27.47
A-V mismatch (%)	6.21	12.30	14.37	21.51
Fsd/Fd	0.51	0.25	0.52	0.25
Fd/Fsd	2.64	1.76	2.71	2.22

Vessel Cross-Sectional Area (Site 1 vs. Site 2, N=125)

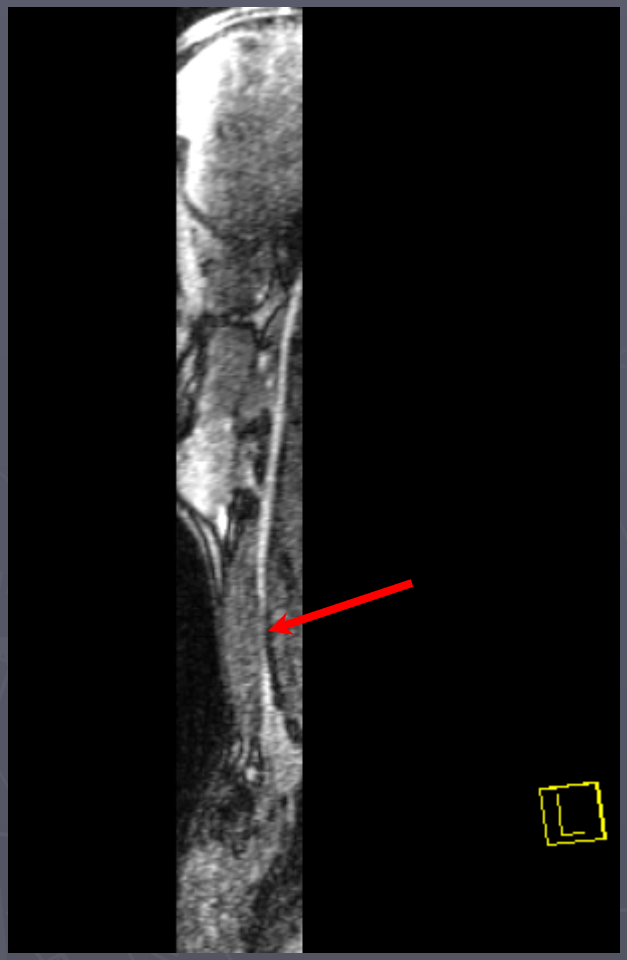
Vessel CS Area (mm^2)	Site 1		Site 2	
	Mean	Std	Mean	Std
LCCA	31.74	7.12	36.12	11.69
RCCA	33.72	7.36	35.41	10.17
LVA	13.23	4.58	13.55	5.75
RVA	12.30	4.34	12.89	5.42
LIJV	57.34	37.76	49.29	41.52
RIJV	75.40	45.63	60.68	56.32
tLA	45.00	9.73	49.76	13.86
tRA	46.05	9.10	48.46	12.68
tA	91.05	16.77	98.23	24.03
tLV	98.77	43.48	98.05	50.38
tRV	120.00	49.44	108.88	63.68
tV	218.78	79.12	206.93	102.51

2D TOF MRV



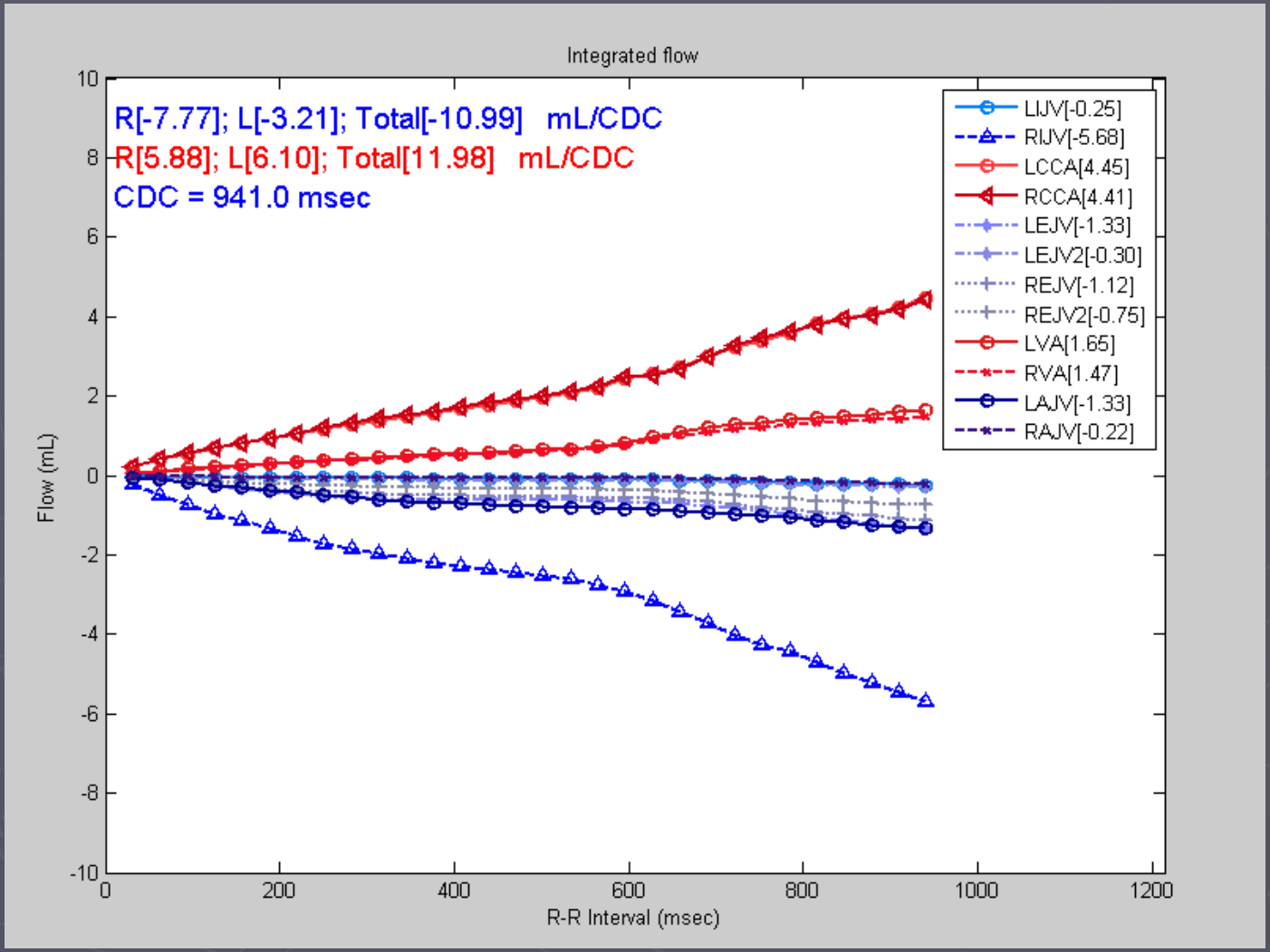


Transverse slices showing the pinching in the left IJV

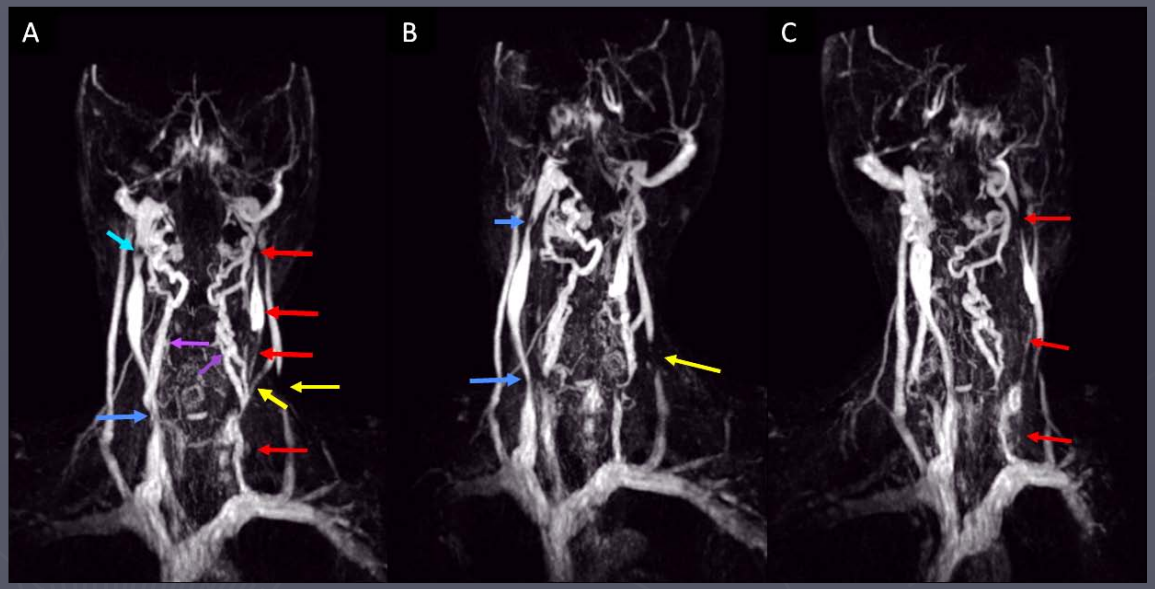


Sagittal 3D MRV showing narrowing and 3D sagittal FLAIR showing a lesion.

No flow of the LIJV into the subclavian vein



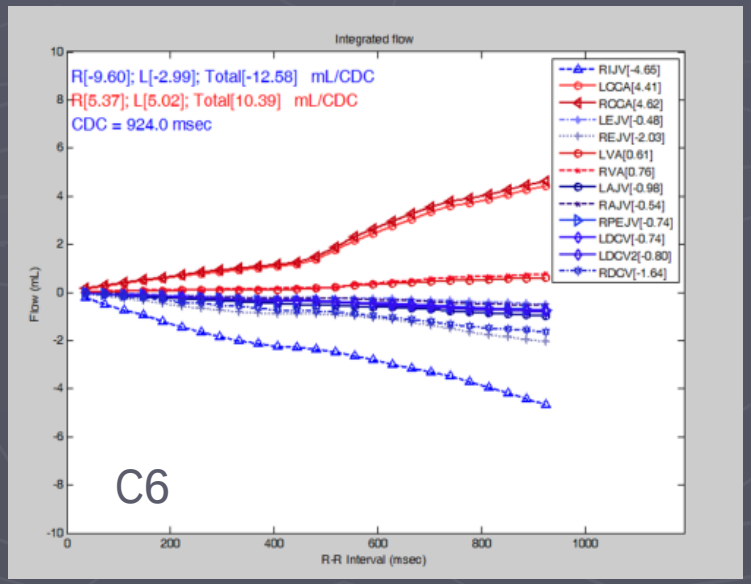
Parkinson's study: CCSVI look alike

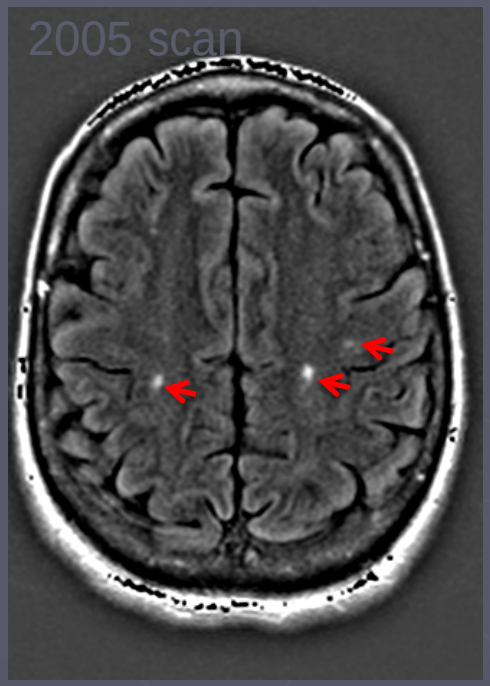


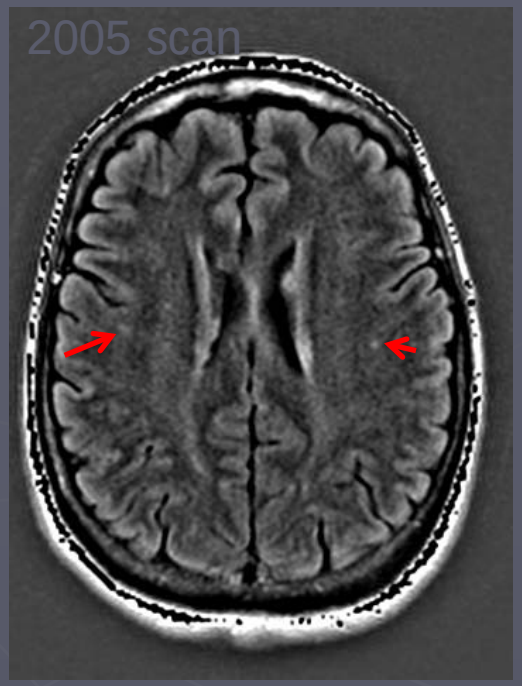
LIJV is stenosed at UL and truncated at LL

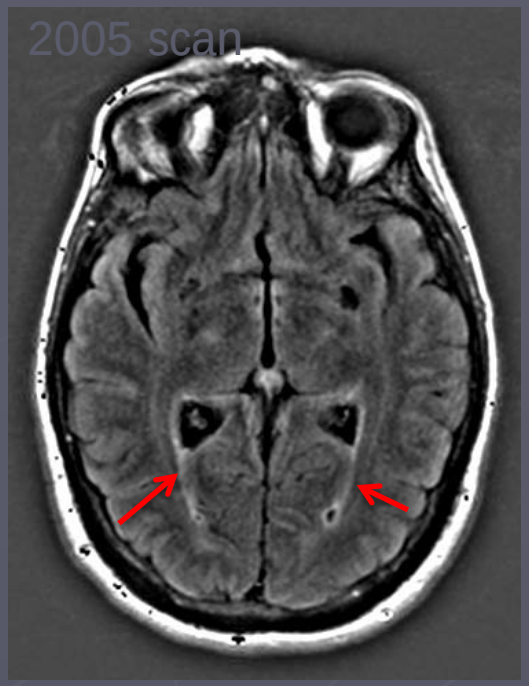
RIJV is stenosed at LL

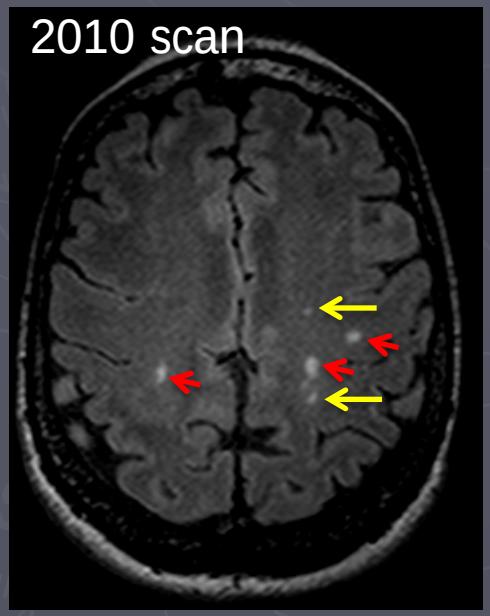
LEJV is stenosed at LL

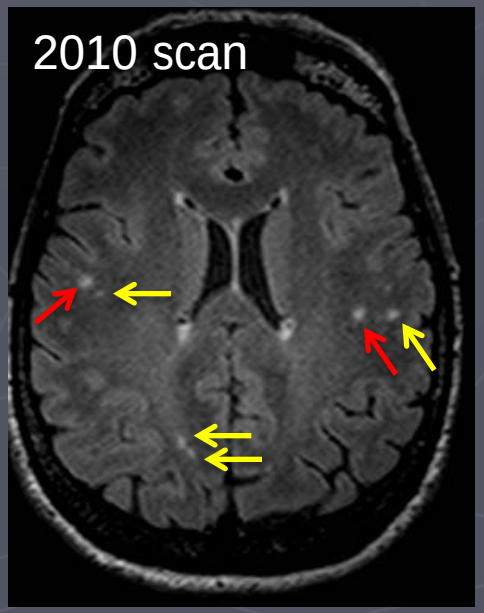


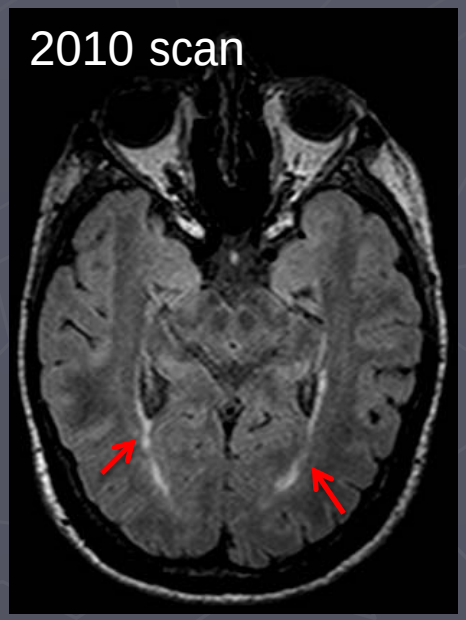












Lesions are seen in 2005 scans-red arrows; the lesions are at he same level as seen in the 2010 scans

The 2010 scans shows multiple new lesions formed-yellow arrows

Conclusions

- The MS population can be broken into two types:
  - Non-stenotic normal appearing structural variants
  - Stenotic or TVM abnormal structural variants
- The stenotic group can be broken into two types:
  - Those less than 8ml/s which dominate those cases seen below 8ml/s
  - Those greater than 8ml/s which have sufficient collateral flow
- Even large numbers of patients may have statistically significant differences in flow outcomes.
- Please visit www.ms-mri.com for updates and www.isnvd.com

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.
- Please visit www.ms-mri.com for updates and www.isnvd.com