

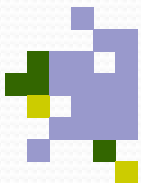
# Further Evidence for Venous Structural and Flow Abnormalities in Patients with Multiple Sclerosis

Sean Sethi

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# Acknowledgements

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# Overview

- Purpose
- Materials and Methods
- Anatomical and Flow results
- Latest study refuting CCSVI
- Flow and Parkinson's Disease
- Conclusion



# Putnam's 1935 work on venous obstruction in a dog model



Tracey Putnam developed an experimental dog model of venous obstruction to study MS. His work supports the recent rediscovery of this concept by Dr. Paolo Zamboni of Italy.

He stated:

*“The similarity between such lesions and many of those seen in cases of multiple sclerosis in man is so striking that the conclusion appears almost inevitable that venular obstruction is the essential immediate antecedent to the formation of typical sclerotic plaques.”*



# Purpose

- To measure blood flow and structural venous anatomy using MRI

**For the fourth time**, our group will be able to show that a subset of the MS population has an abnormal flow distribution

**But most importantly—we now have a large cohort of healthy controls to compare MS data to, which has not been done in any group using MRI**

# References

- 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: 802-809.
- Feng W, Utriainen D, Trifan G, Sethi, S. Hubbard, D., Haacke, E.M. Quantitative flow measurements in the internal jugular veins of multiple sclerosis patients using magnetic resonance imaging. *Rev Recent Clin Trials* 2012;7:117-126.
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# 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 an intervention
- use as a baseline to study the anatomy and flow after treatment if complications develop



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

Sequence	Time (approx.)
3 plane scout of the brain	1:00
Axial T2/PD Head	6:30
Axial T1 Head 3D	6:30
Axial T2 fast FLAIR	4:30
3 plane scout of the C-spine	1:00
Sagittal T2/PD C-spine	5:00
Sagittal T1 C-spine	3:40
Select Axial T2 C-spine through lesions	4:00* (optional)
Inject Gadolinium (no wait time)	0:00
3D CE MRAV Neck	2:30
Flow Quantification at C2/C3 and C6/C7 with Venc = 50cm/s	3:00
Axial T1 Head post Gad	4:30
C-spine T1 FS post Gad	3:40
Select Axial T1 C-spine post Gad through lesions	4:00* (optional)
Total Time	41:50 (49:50*)

Source: [www.ms-mri.com](http://www.ms-mri.com)



# Subject information

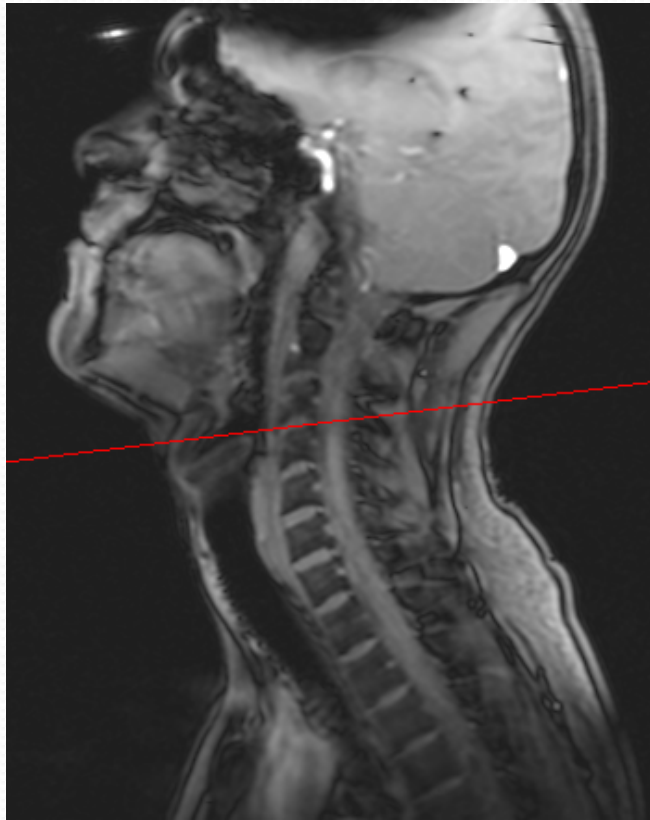
A comprehensive MR protocol was run on 139 MS patients and 69 healthy controls (HC)

- Ages
  - MS: 48.6 +/- 11.6 years
  - HC: 41.8 +/- 13.5 years
- Female: Male
  - MS: 2.3: 1
  - HC: 2.4: 1
- Disease duration
  - 12.3 +/- 9.1 years

# Materials and Methods

- Internal jugular vein (IJV) stenosis was assessed using MR venography
- MS subjects classified as stenotic (ST) or non-stenotic (NST)
- Two dimensional phase contrast flow quantification (PC-FQ) was collected at the C2 and C6 neck levels perpendicular to the IJV flow.
- Unpaired student t-test done between all three groups to measure differences in IJV flow

# Stenosis Thresholds



$IJV \leq 12.5 \text{ mm}^2$

C3

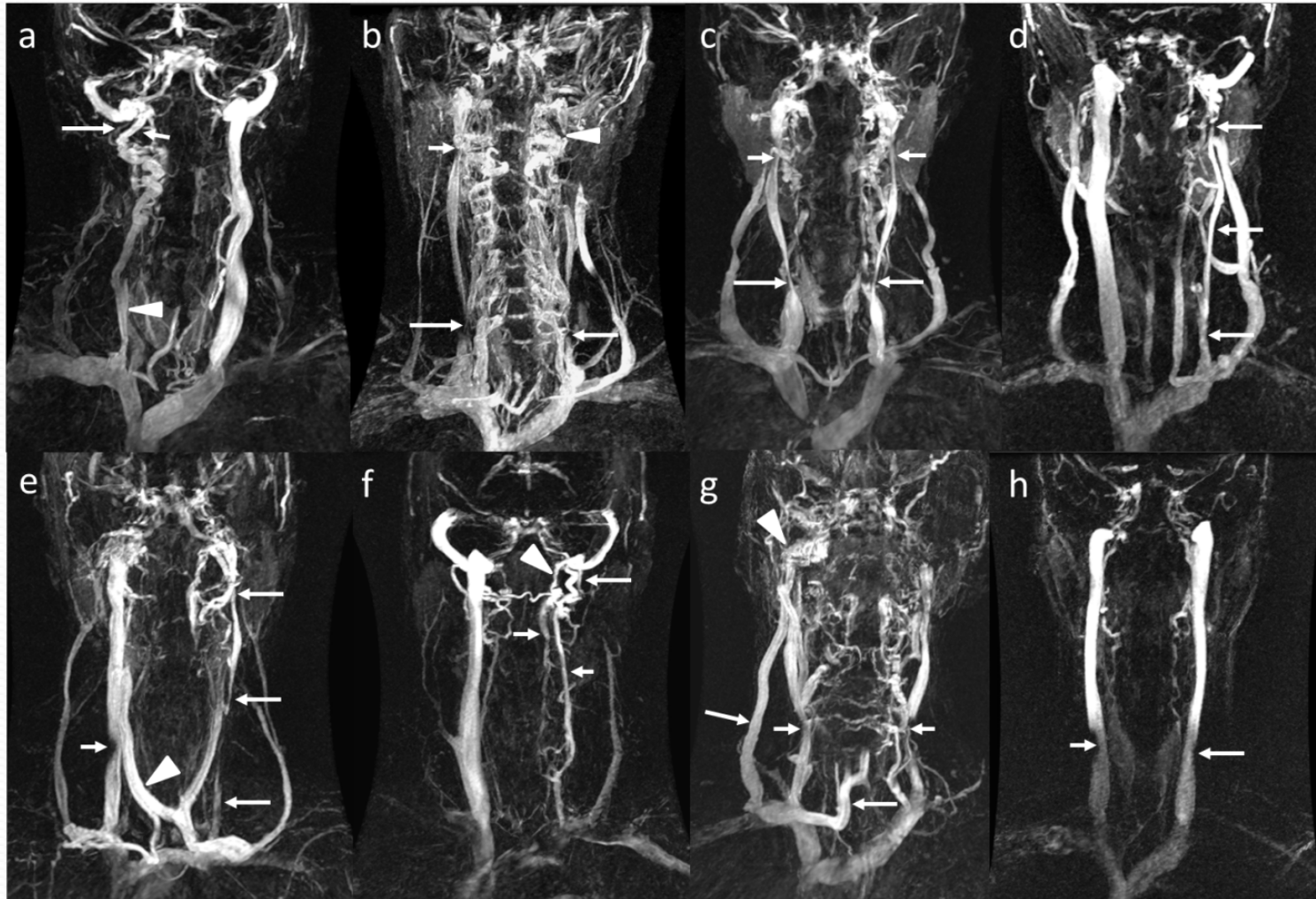
$IJV \leq 25 \text{ mm}^2$



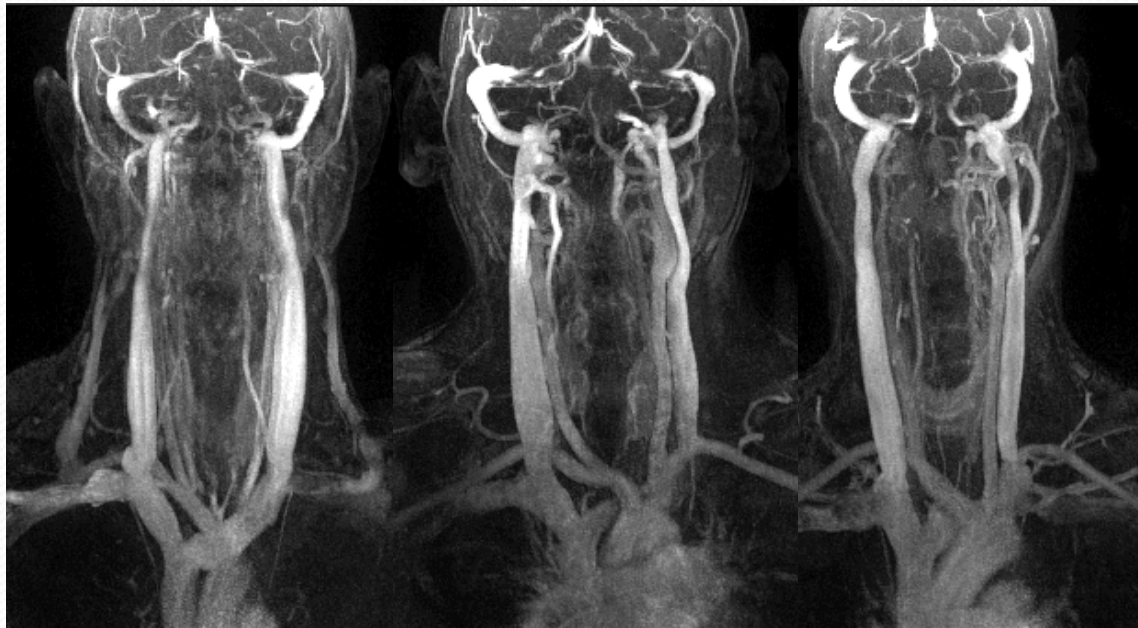
C3

Cases where IJV shows atresia or aplasia also categorized as stenotic

# Examples of Jugular Pathology in MS



# IJVs in healthy control cases



IJVs present consistent caliber at all neck levels

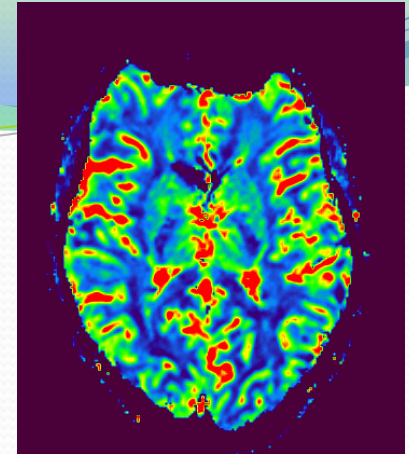


# SPIN Software

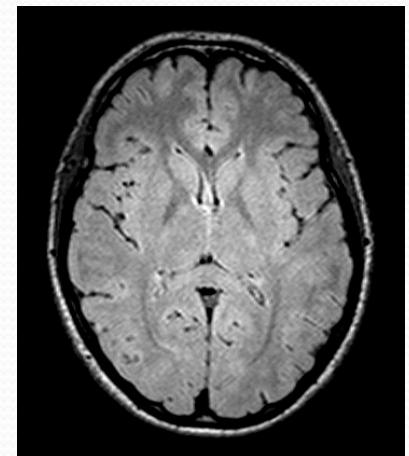
- Using in-house software SPIN, we are able to process multiple types of data
  - Image-viewing
  - Perfusion
  - Iron quantification
  - Flow quantification
  - DTI analysis
  - White matter lesion volume and quantities in FLAIR

For more information go to  
[www.mrinnovations.com](http://www.mrinnovations.com)

PWI



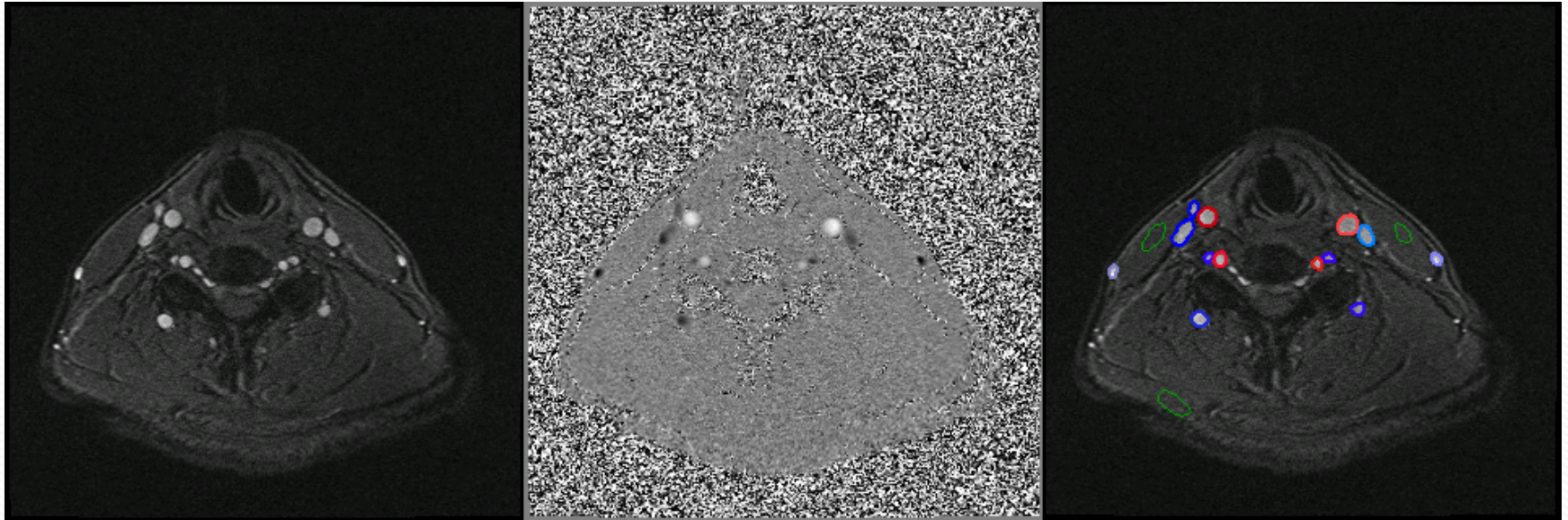
FLAIR



SWI



## Flow Quantification using PC-MRI



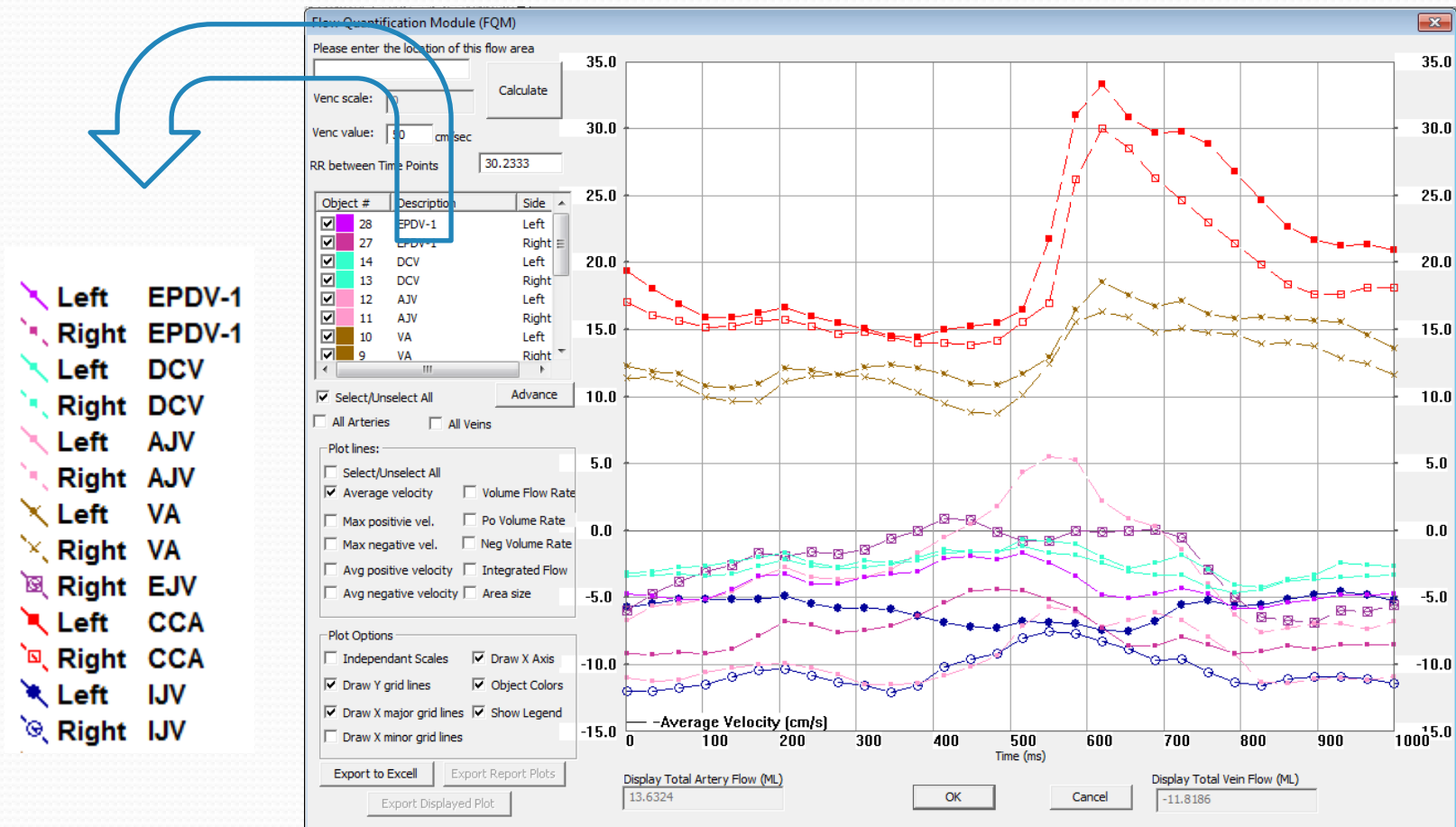
Magnitude Image

Phase Image

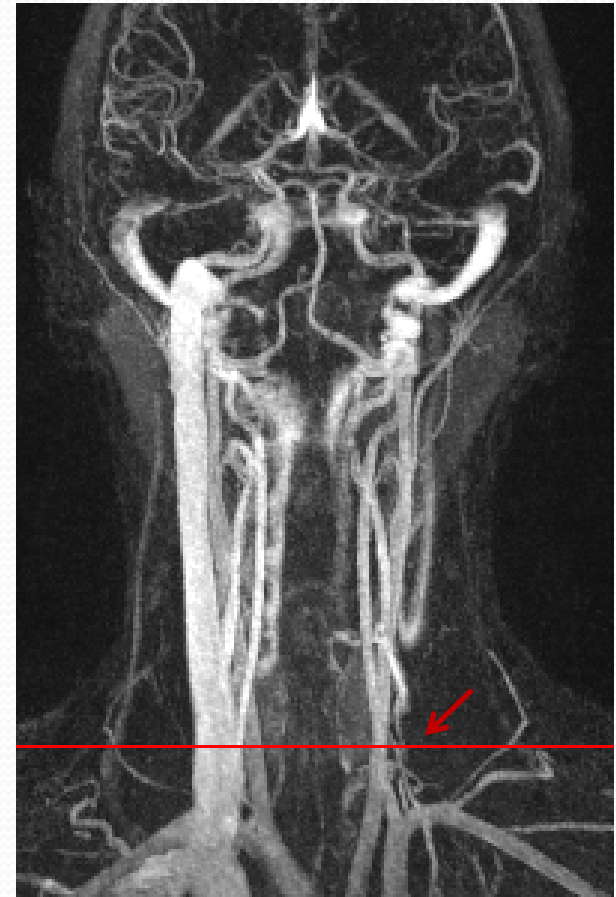
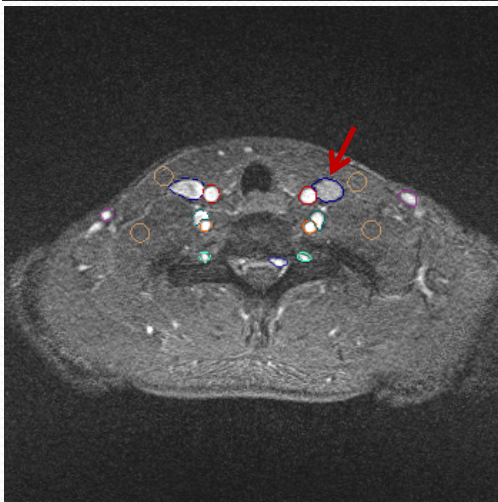
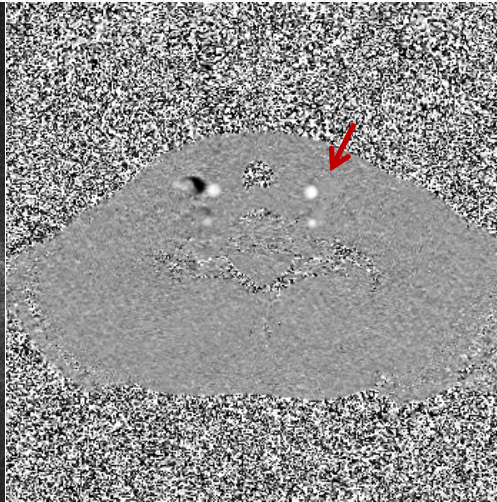
Magnitude image  
with contours and  
non-flow regions



# Flow as a function of the cardiac cycle



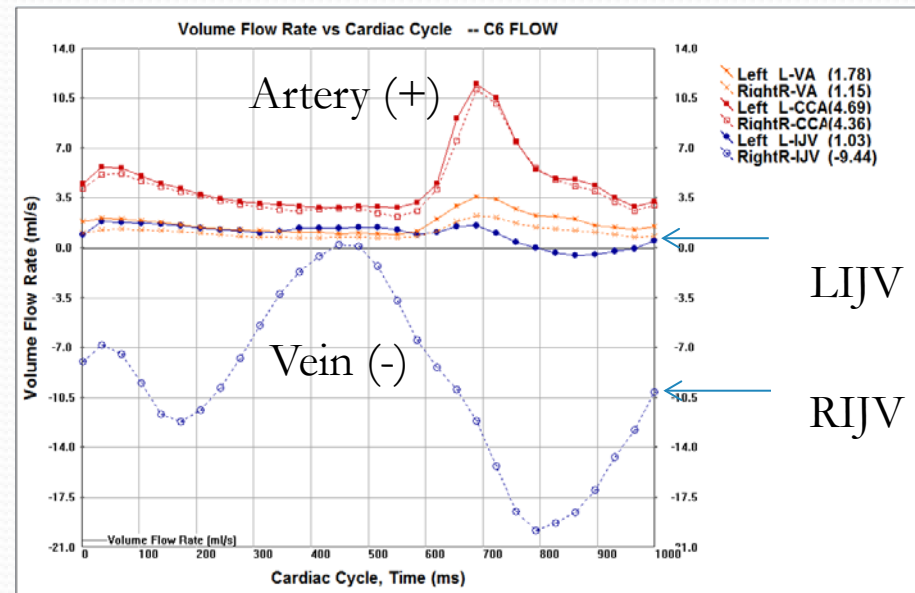
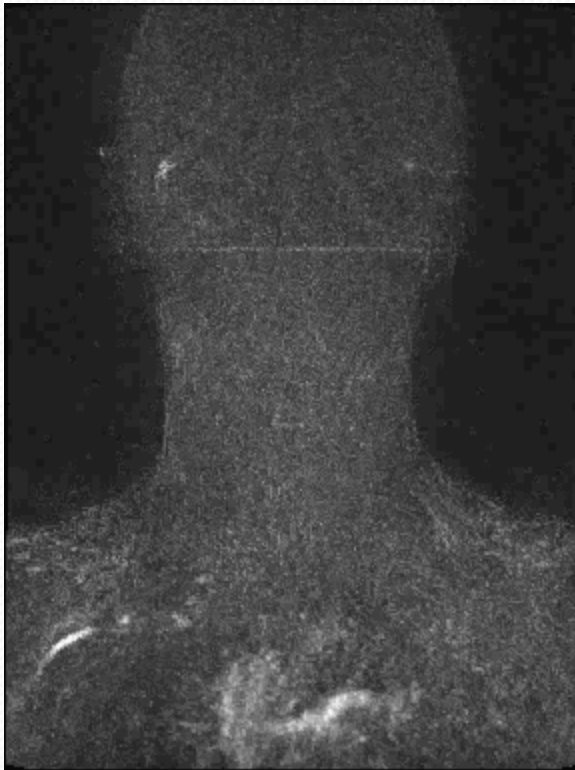
## Example of retrograde flow in left IJV at C6



Contrast-enhanced 3D  
MRV

# Example of retrograde flow in left IJV at C6

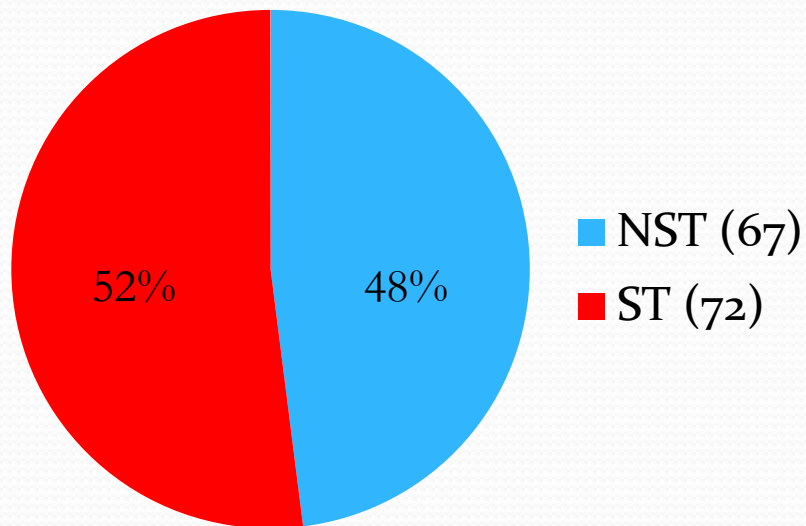
Volume Flow Rate Plot (mL/s)



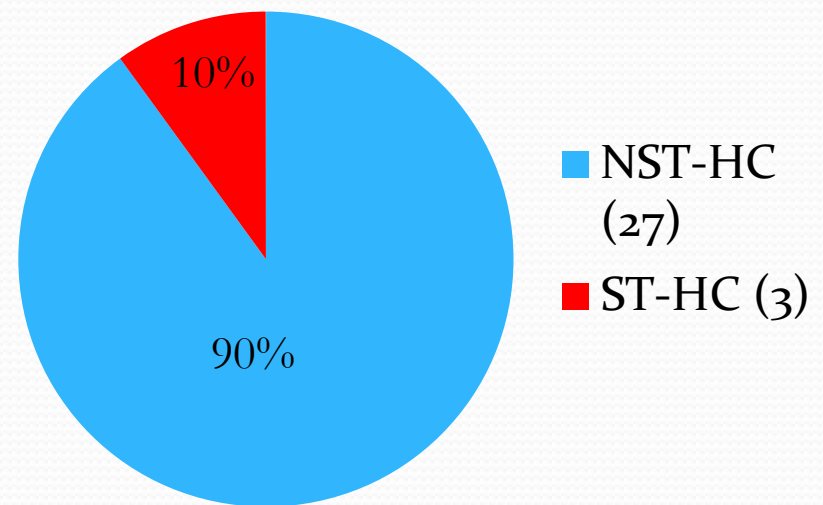
LIJV flow rate = 1.03  
mL/sec

# Results - Anatomic

**Stenosis Evaluation in  
MS Group (139)**



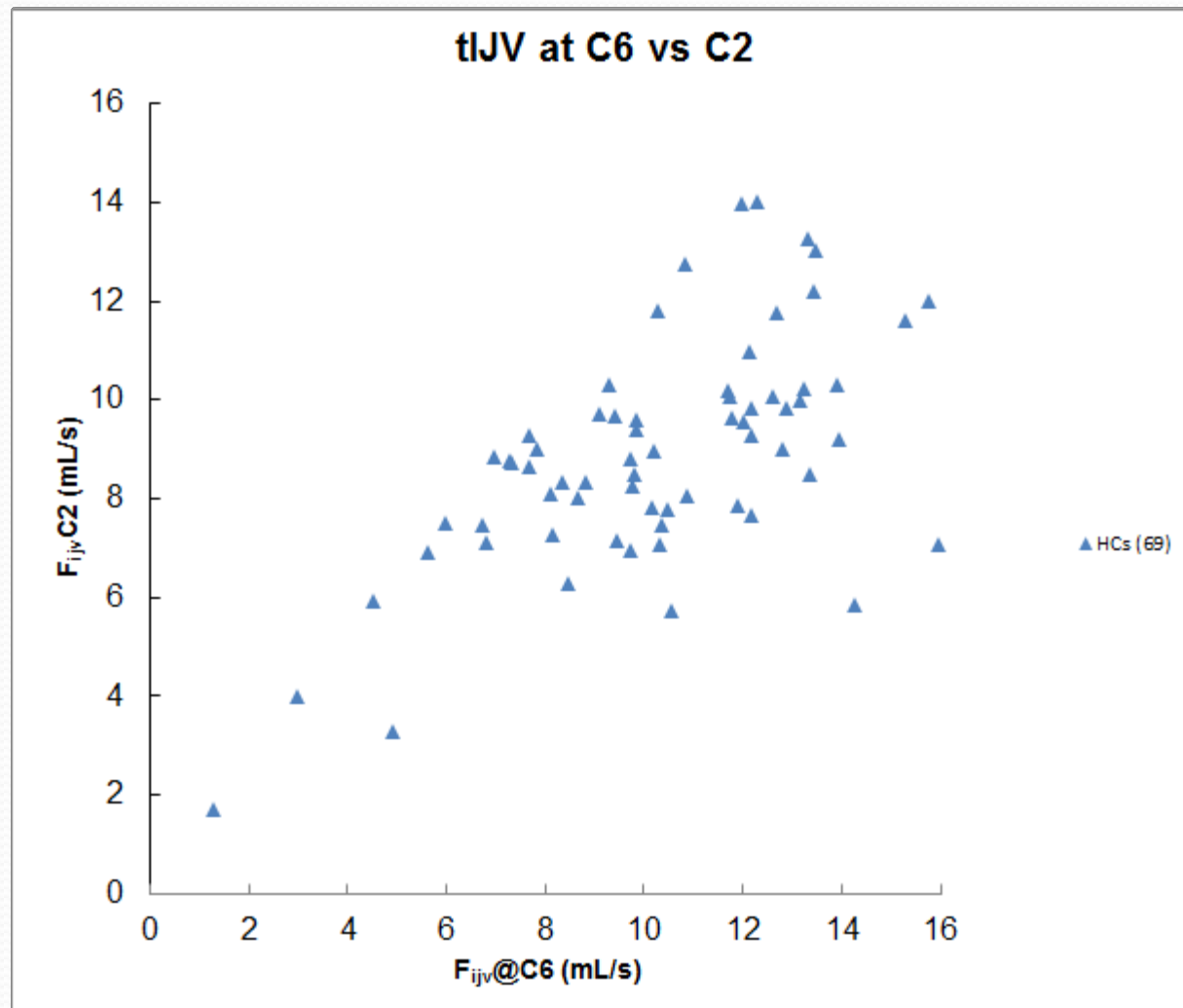
**Stenosis Evaluation in  
HC Group (30)**



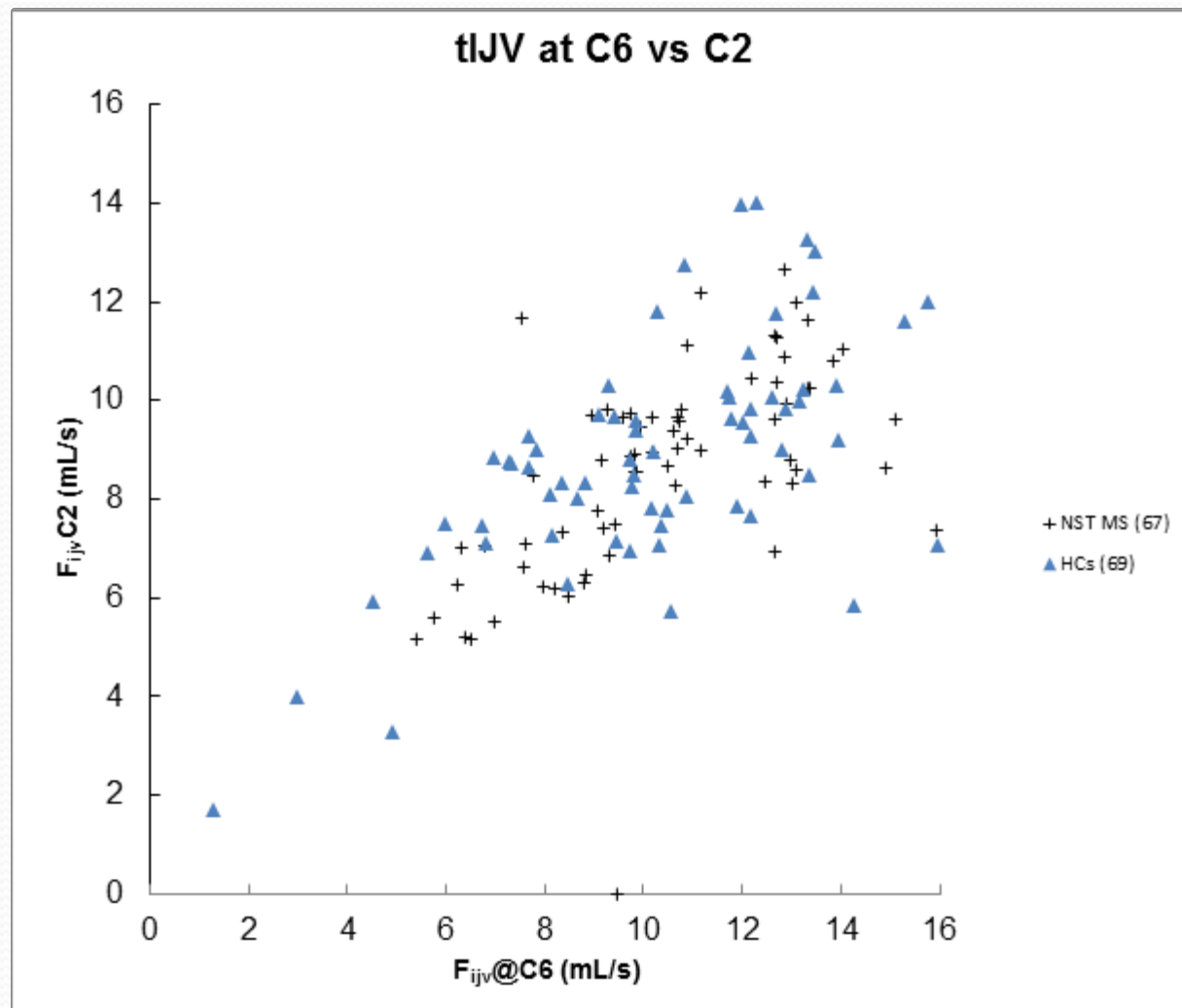
# Results - Flow

- Significant differences were found in **normalized** IJV flow in HC vs. ST, and NST vs. ST.
- No significant difference seen in **normalized** IJV flow between HC and NST
- Findings pertain to both vessels and neck levels

## Total IJV flows for C6 versus C2 neck levels

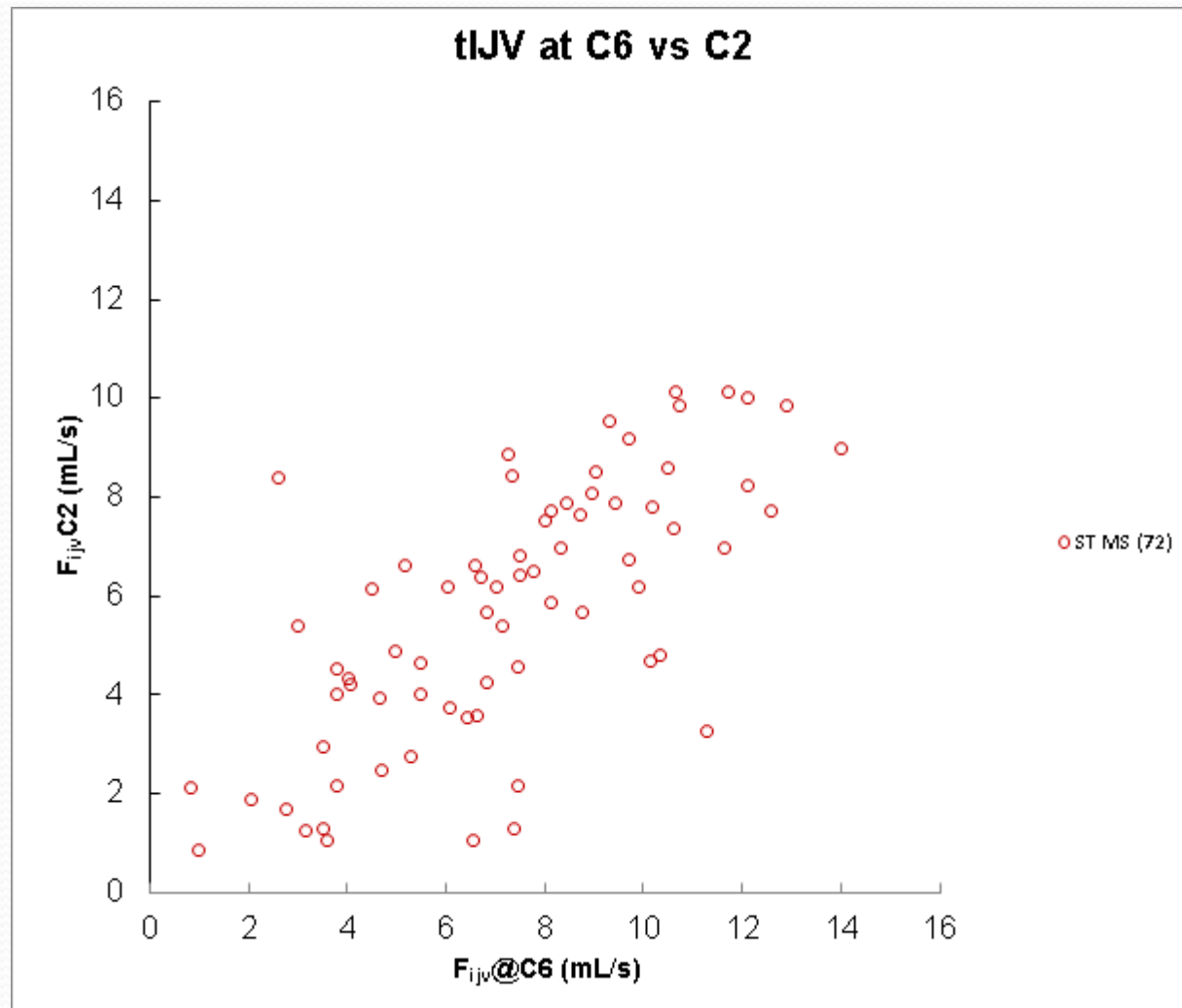


## Total IJV flows for C6 versus C2 neck levels





## Total IJV flows for C6 versus C2 neck levels



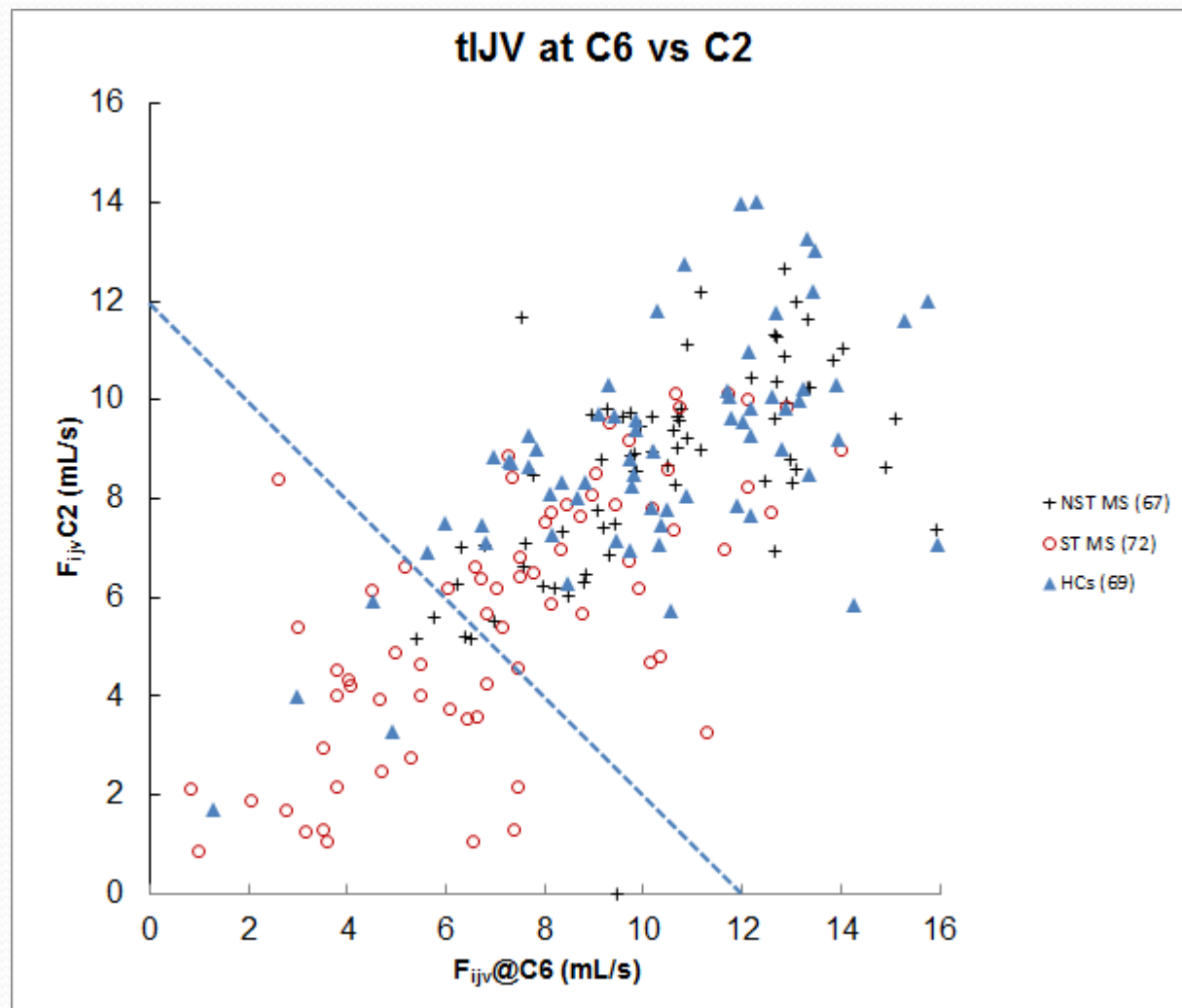
# Total IJV flows for C6 versus C2 neck levels

<12 mL/s

HC: 4 (6%)

NST: 4 (6%)

ST: 30 (42%)



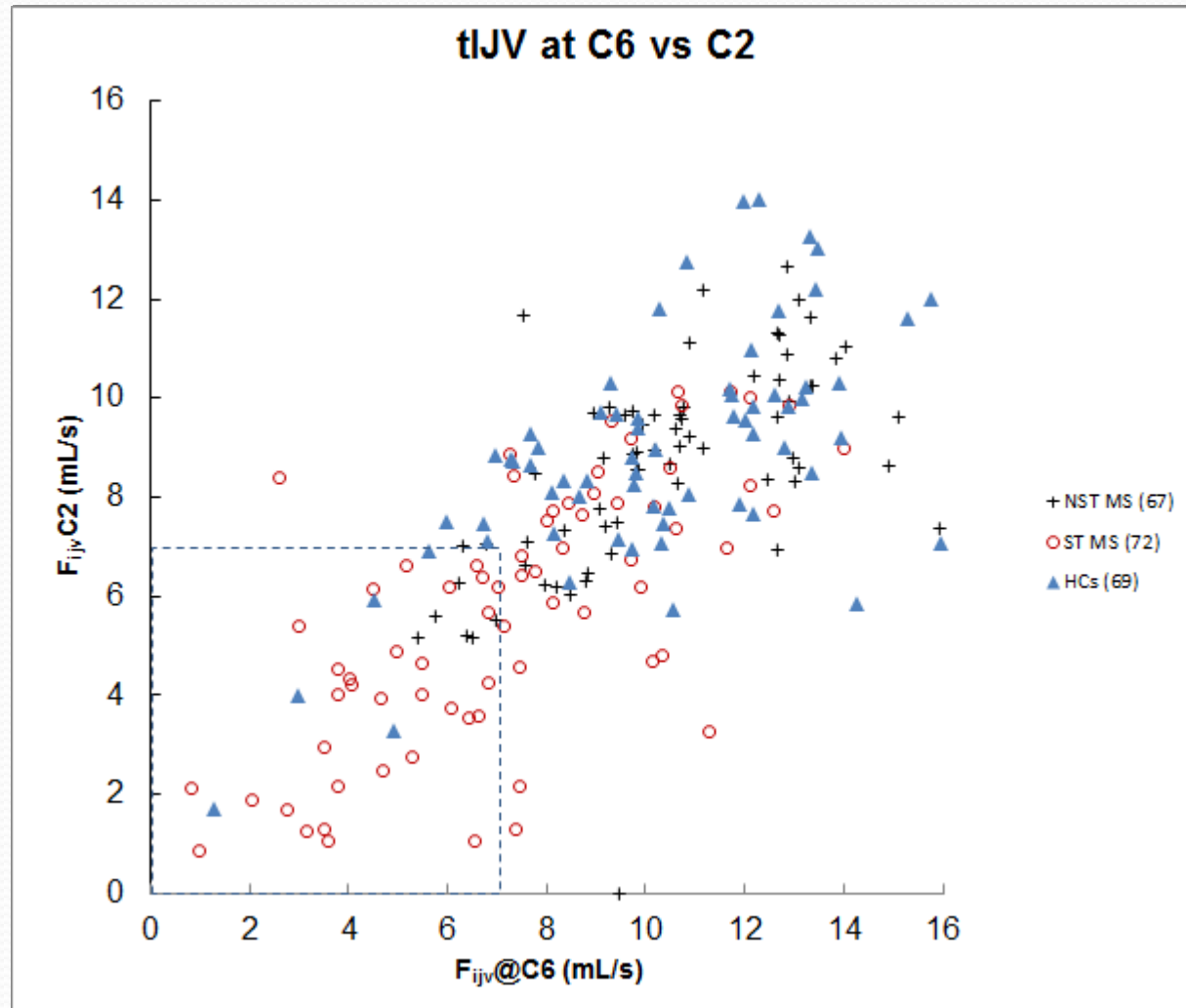
# Total IJV flows for C6 versus C2 neck levels

<7mL/s:

HC: 5 (7%)

NST: 5 (7%)

ST: 33 (46%)



# Normalized IJV flow calculation

IJV flow was normalized to the arterial flow to account for physiological differences between people

- For C6: Normalized IJV flow = 
$$\frac{\text{total IJV flow}}{\text{CCA} + \text{VA flow}}$$
- For C2: Normalized IJV flow = 
$$\frac{\text{total IJV flow}}{\text{ICA} + \text{VA flow}}$$

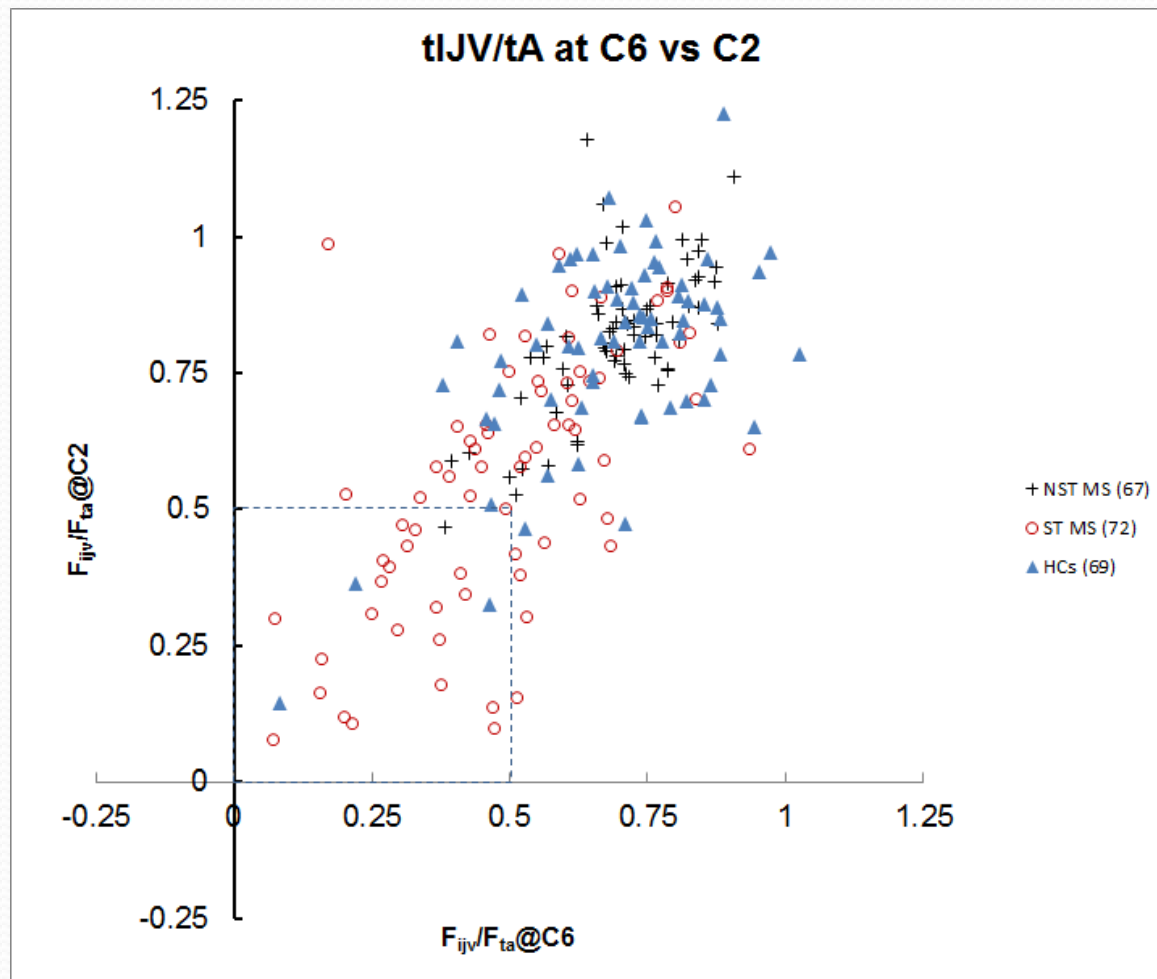
# C6 versus C2 total IJV flows normalized to their arterial flows

Total cases in  
each group  
where IJV Flow  
<0.5 at both C6  
and C2 levels:

ST MS: 22 (31%)

NST MS: 1 (1%)

HC: 3 (4%)



# Recent study against CCSVI

- Study done with 100 age-matched MS patients and 100 healthy controls
- Ultrasound and MRI performed on them
- Results showed no evidence of reflux, stenosis, blockage in internal jugular veins (IJV), or vertebral veins, as well as no differences in venous architecture between MS and normals
- **This case-control study provides “compelling evidence against the involvement of CCSVI in multiple sclerosis.”**

# Our Evidence of Flow Abnormalities

There are five levels of analysis:

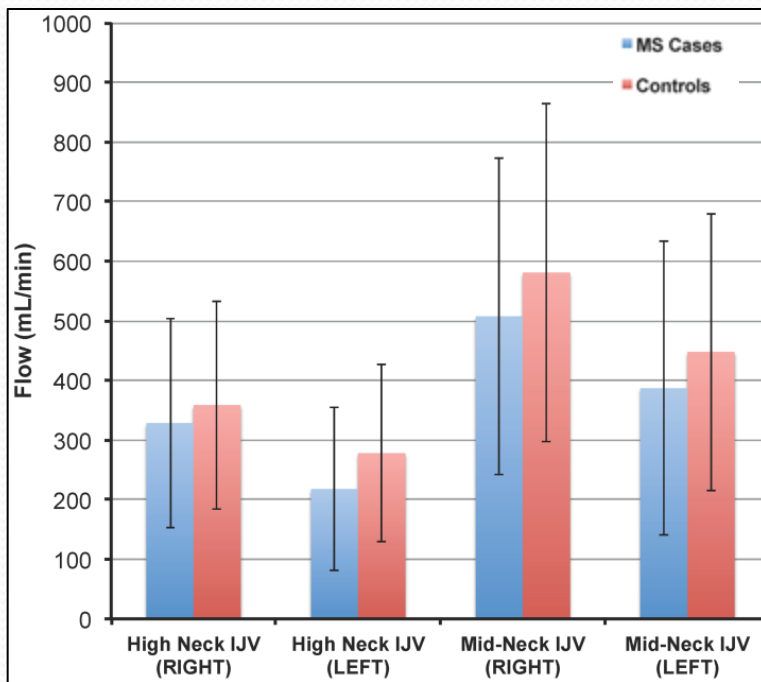
1. Evaluate ST vs. NST patients
2. Compare individual IJV flows at C2 & C6
3. Evaluate total IJV flow at both C2 & C6
4. Evaluate normalized IJV flow at both C2 & C6
5. Establish a quantitative threshold that separates HCs from stenotic MS patients

In the material presented so far, we have presented the flow information for every patient in a 2D quantitative plot.

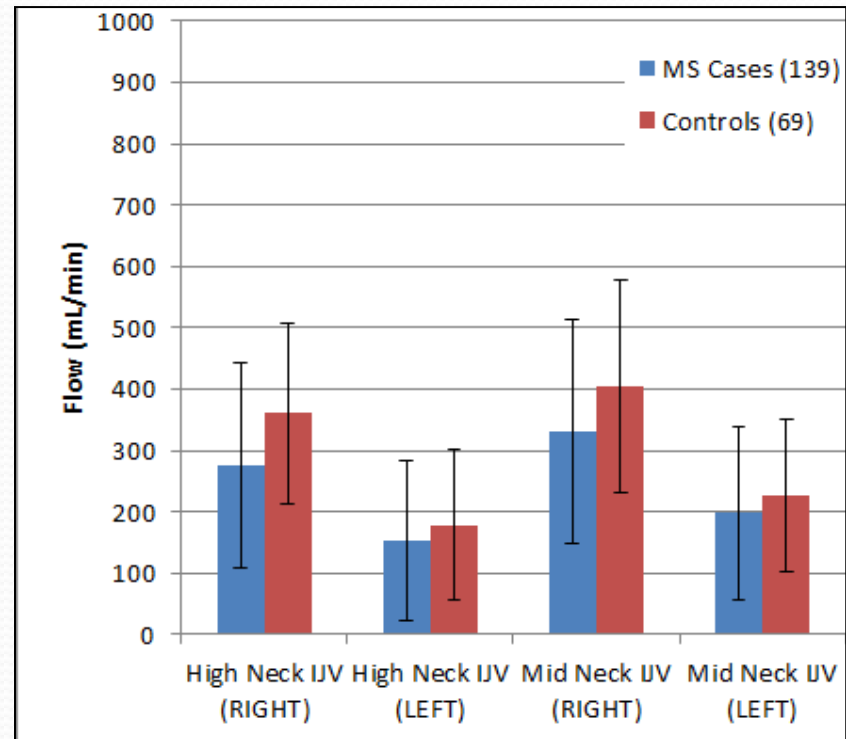
*If one were to evaluate only point number two by merging all the patient information into a simple histogram it is unlikely that we would find any difference between MS and HC.*



# This is exactly what was done in the paper by Rodger et. al.



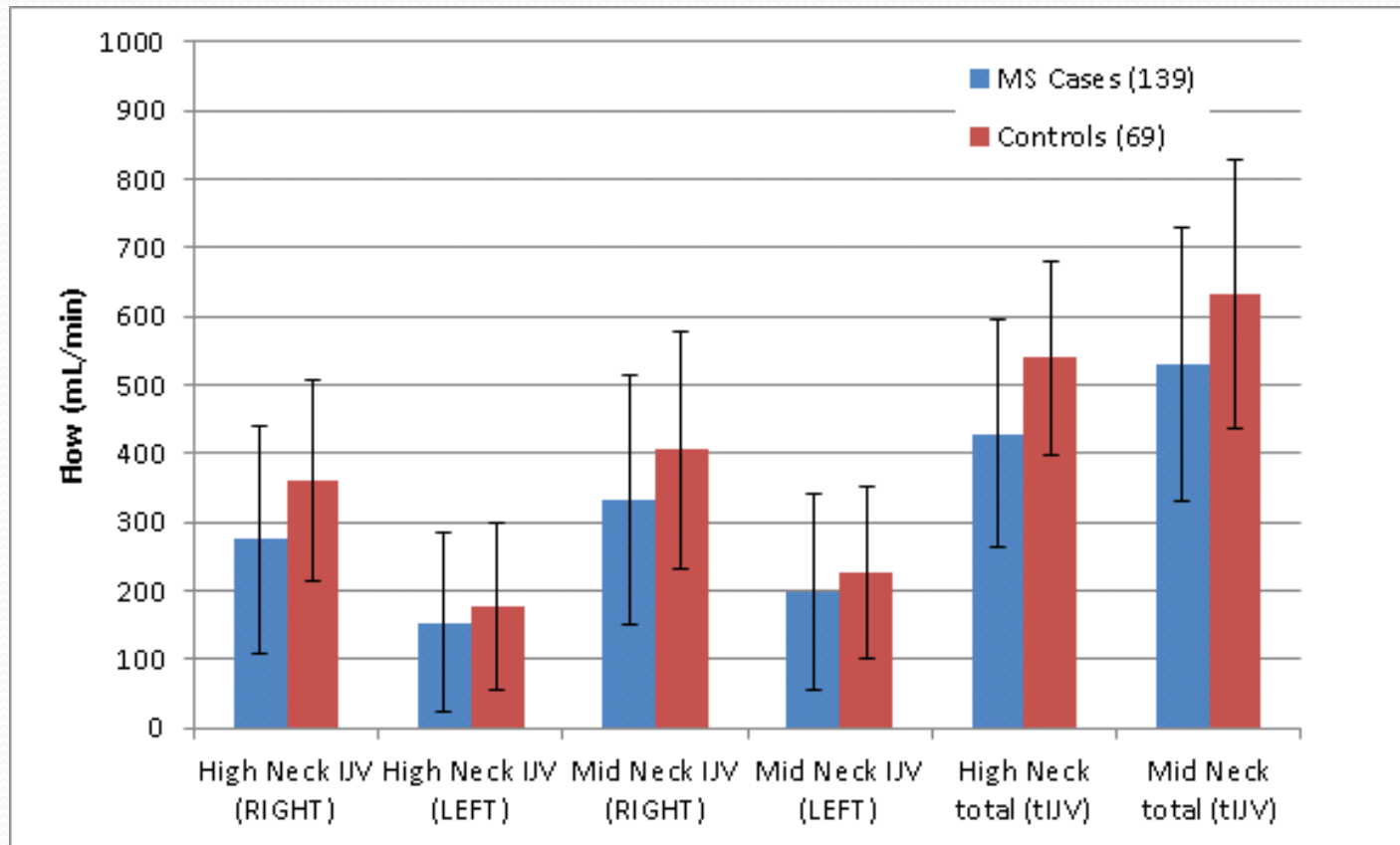
Rodger et. al



Our group

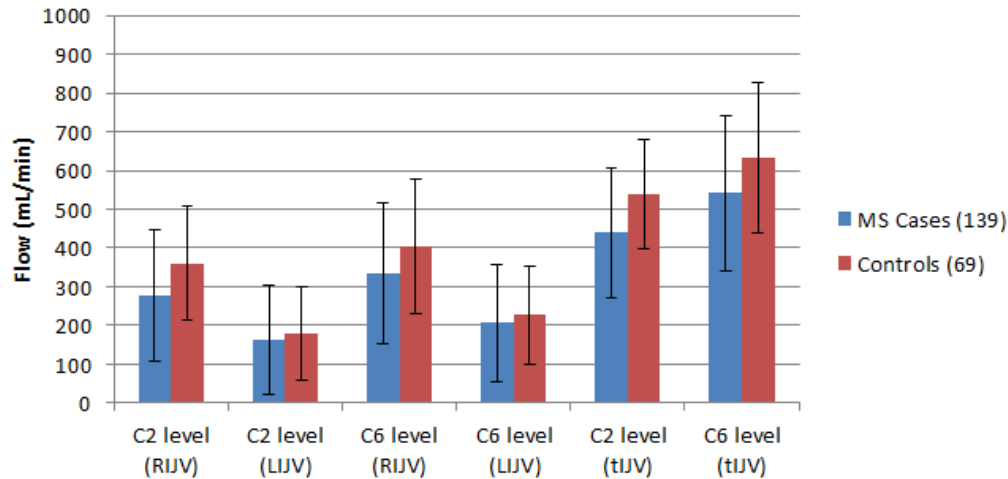
Mean flow plots with 1 standard deviation bars comparing the Rodger's paper vs. our flow data.

# Mean flow plots now with total IJV flow



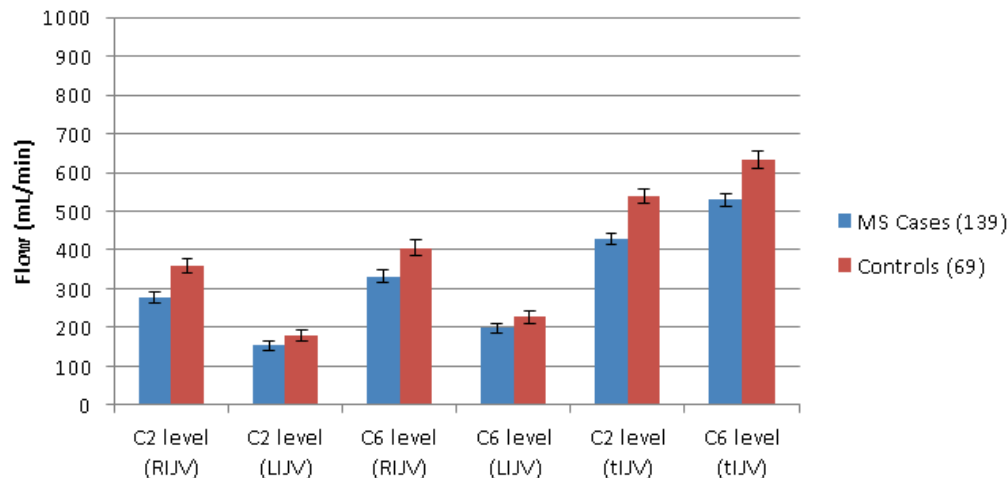
Our analysis

### Comparison of mean flow values between MS and HC groups



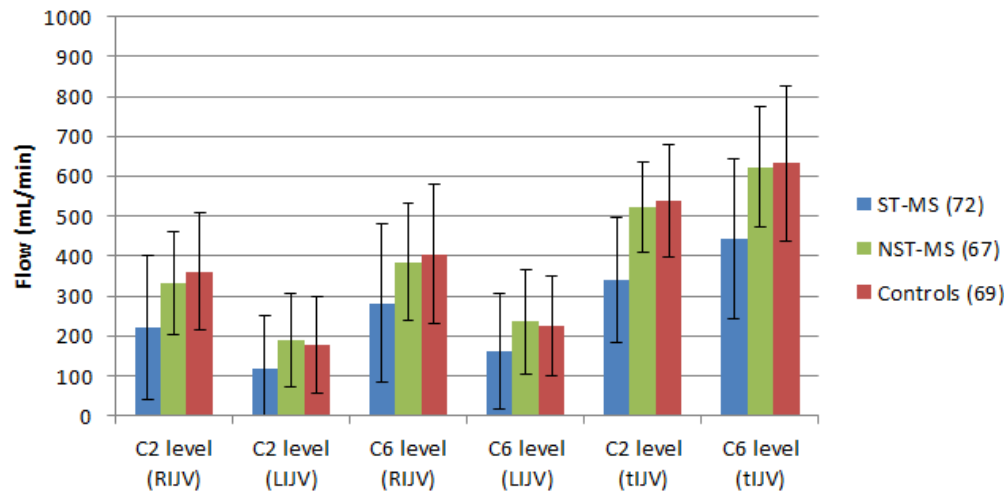
Our data with one standard deviation (upper) and standard error of the mean (lower histogram).

### Comparison of mean flow values between MS and HC groups



Note that although the individual veins may not be significantly different in their flow that the total flow in the veins is in fact significantly different.

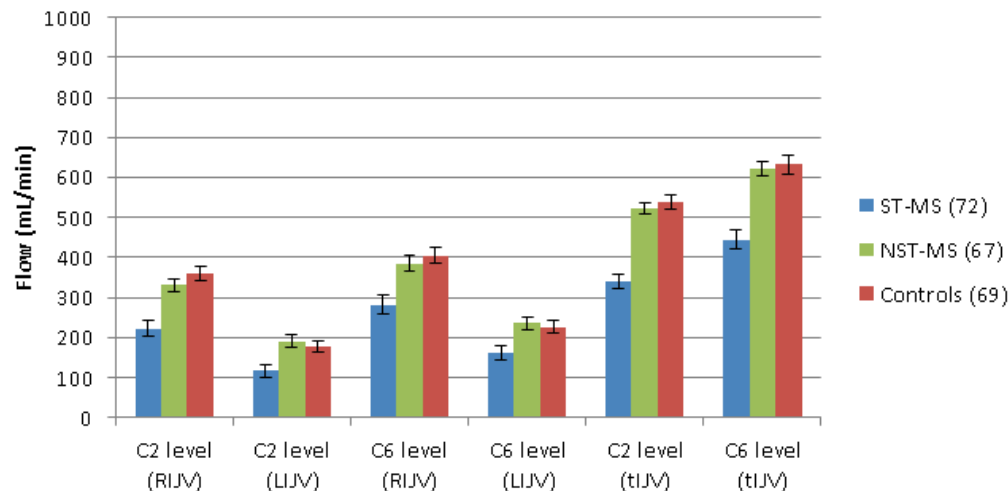
### Comparison of mean flow values between Stenotic MS group, Non-stenotic MS groups, and HC groups



Same data, but separated into ST and NST

Note that the normals and NST MS cases look almost identical. Clearly this is very encouraging and these results agree with Doepp from 2004.

### Comparison of mean flow values between Stenotic MS group, Non-stenotic MS groups, and HC groups



# Key Points

- RIJV and LIJV may not show flow differences, but when summed show differences between MS and HC.
- Separating MS data into ST and NST groups improves the separation.
- Rodger et. al. do not show total flows and, therefore, it is not surprising that they don't find a difference.
- However, we would not be surprised if Rodger et. al. took their data and calculated total IJV flow, they indeed may find the same results as us.



# Limitations and Future Directions

- Different sites have different scanners, however, their sequences use the same principles and we are in the process of evaluating one subject who was scanned on the different systems to test consistency with anatomy and flow.
- Evaluate the optimal cut-offs to separate ST from HC and NST.
- Continue to collect more normal controls.

# Conclusions

- CCSVI is a condition that may lead to or exacerbate many diseases such as: headache, idiopathic intracranial hypertension, multiple sclerosis and Parkinson's disease.
- Total flow and normalized flow may be used as potential biomarkers for developing neurodegenerative disease, and developing better treatment options.
- **In over 650 MS cases that we have analyzed, we see stenotic and anomalous IJVs in at least 50% of the cases.**
- Combining these flow measurements with PWI and SWI to study the brain's hemodynamics in these diseases may provide a further understanding of the role of abnormal venous flow in neurodegenerative disease.





# Informational Websites and Contact

For more information on the role of abnormal venous flow in neurodegenerative diseases see

[www.ms-mri.com](http://www.ms-mri.com)

For more information on MR research at Wayne State University please visit

[www.mrc.wayne.edu](http://www.mrc.wayne.edu)

For more information on SPIN software please visit

[www.mrinnovations.com](http://www.mrinnovations.com) or email  
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# References

- 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: 802-809.
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