Defining Normative Cerebral Hemodynamics in Cognitively Healthy Older Adults with 4D Flow MRI

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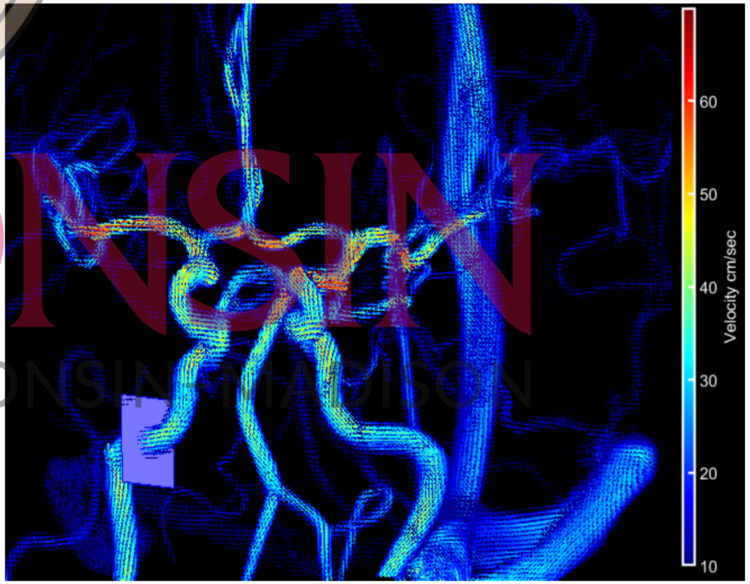
WISCONSIN ALZHEIMER'S DISEASE RESEARCH CENTER



Declaration of Financial Interests or Relationships

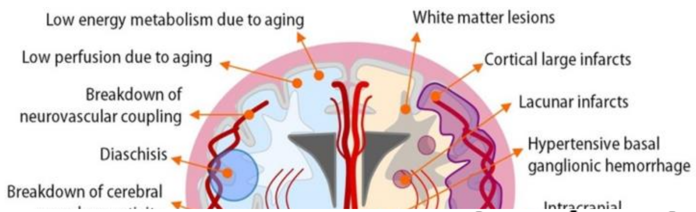
Speaker Name: Grant S. Roberts

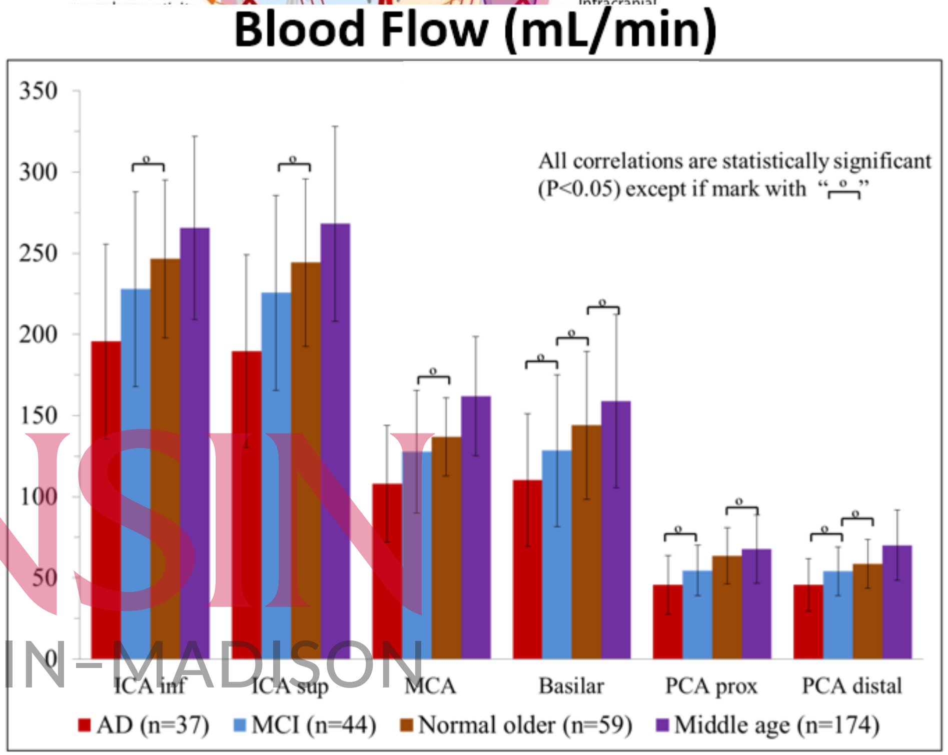
I have the following financial interest or relationship to disclose with regard to the subject matter of this presentation:

Company Name: GE Healthcare
Type of Relationship: Institutional Research Support (UW-Madison)

Background

- Adequate cerebral blood flow is important
- As we age, neurovascular changes begin to occur
  - Arterial stiffening[1]
  - Breakdown of neurovascular unit[2]
  - Affect cerebral hemodynamics and cognition
- Relationship with Alzheimer's disease (AD)
  - Macrovascular changes[3-5]
  - Microvascular (perfusion) changes[6]
  - Normative data is still lacking
- <u>Important to establish normal cerebrovascular hemodynamics in older adults</u>





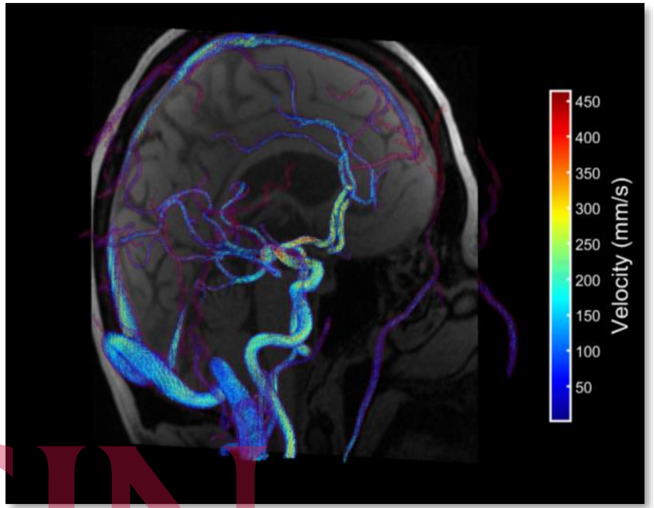
Courtesy: Leonardo Rivera-Rivera, PhD

[1]Mitchell GF, et al (2011). *Brain* 134(11).
[2]Tarantini S, et al (2017). *Exp Gerontol* 94.
[3]Rivera-Rivera LA, et al (2016). *JCBFM* 36(10).
[4]Rivera-Rivera LA, et al (2017). *JCBFM* 37(6).
[5]Rivera-Rivera LA, et al (2020). *NeuroImage Clin* 28.
[6]Clark LR, et al (2017). *Alzheimers Dement* 7.

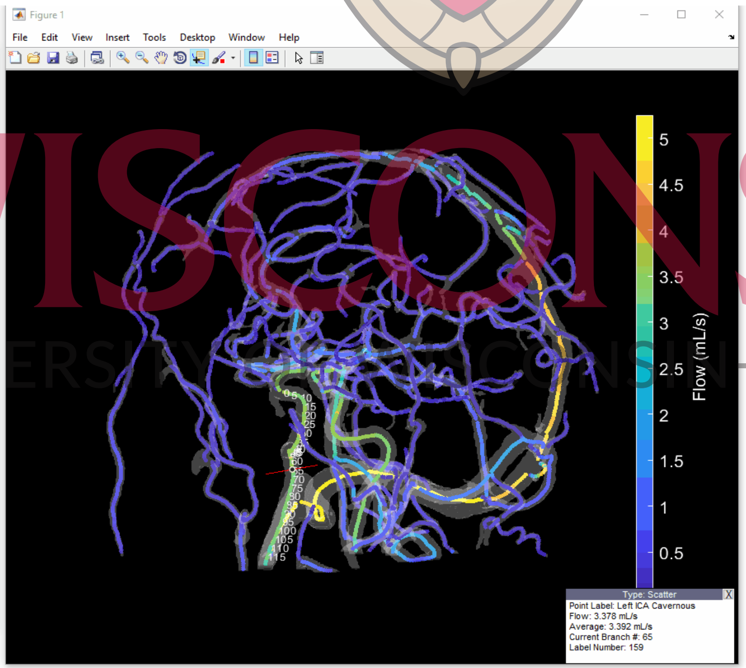
Background

- 4D flow MRI is a comprehensive vascular imaging technique
  - Post-processing is still a challenge
- We developed a cranial 4D flow analysis tool[1,2]
  - Open Source: https://github.com/uwmri/QVT
  - Added visualization tools
  - Interactive vessel selection

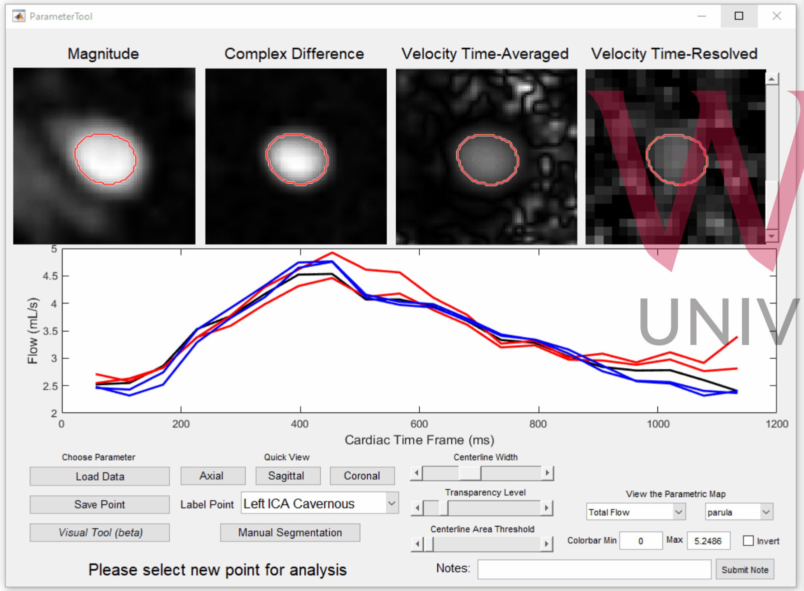
4D Flow Visualization Tool



Interactive Vessel Selection



Control Window



[1]Schrauben E, et al (2015). *JMRI* 42(5)
[2]Hoffman CA, et al (2019). *SMRA* p80

Purpose

- This tool will then be used to analyze 4D flow data from 759 older adults:
  - Aim 1: **Obtain reference values for (1) blood flow and (2) pulsatility in 13 major cerebral arteries and 4 major sinuses**
  - Aim 2: **Assess the relationship between age, sex, and ASCVD vascular risk scores on blood flow and pulsatility**

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Methods – Subjects

- Subjects retrospectively obtained from:
  - Wisconsin Alzheimer's Disease Research Center (ADRC)
  - Wisconsin Registry for Alzheimer's Prevention (WRAP)
  - Between March 2010 – March 2020
- Exclusion criteria:
  - Abnormal cognitive status
  - PiB index > 1.19[1]
  - Image quality and cardiac gating quality
- Take only most recent 4D flow MRI
- **759 subjects (mean age 65 years)**
  - Some measures deviate from "normal"
    - Sex (67% females)
    - APOE4 carriers
    - Parental history of dementia

Subject demographics			
	Count (n)	Percent (%)	N*
Sex			759
Female	506	66.7	
Male	253	33.3	
Race			757
White	645	85.3	
Black or African American	82	10.7	
American Indian	24	3.2	
Asian	2	0.3	
Other	4	0.5	
Diabetes	63	9.1	689
Smoker	29	4.2	689
On Anti-hypertensive Meds	240	34.8	689
Parental history of dementia	500	67.6	740
APOE ε4 carrier**	247	35.6	694
	Mean	**SD**	**N***
Age (years)	64.7	7.7	759
Systolic Blood Press. (mmHg)	125.1	16.4	751
Diastolic Blood Press. (mmHg)	76.9	8.3	751
Total Cholesterol (mg/dL)	199.0	39.4	744
Triglycerides (mg/dL)	106.4	56.7	744

***Total number of measured data points over all subjects (759 total).**
****APOE ε4 carrier defined as presence of at least one APOE ε4 allele.**

[1]Tudorascu DL, et al (2018). *Alzheimers Dement* 10.

Methods – Acquisition

- Subjects scanned at 3.0T
  - 3 different GE scanners
- Radially-undersampled acquisition
  - PCVIPR[1,2]
- Data reconstructed into 20 cardiac frames
- Reconstruction
  - Temporal view sharing
  - Parallel imaging with localized sensitivities
  - Maxwell term phase correction
  - 3rd order background phase correction

MRI Scanners and Coils

	Discovery MR750 (N=611)	Signa PET/MR (N=8)	Signa Premier (N=140)
MRI Coil Type			
48 channel	-	-	140
32 channel	565	-	-
8 channel	46	8	-

MRI Acquisition Parameters

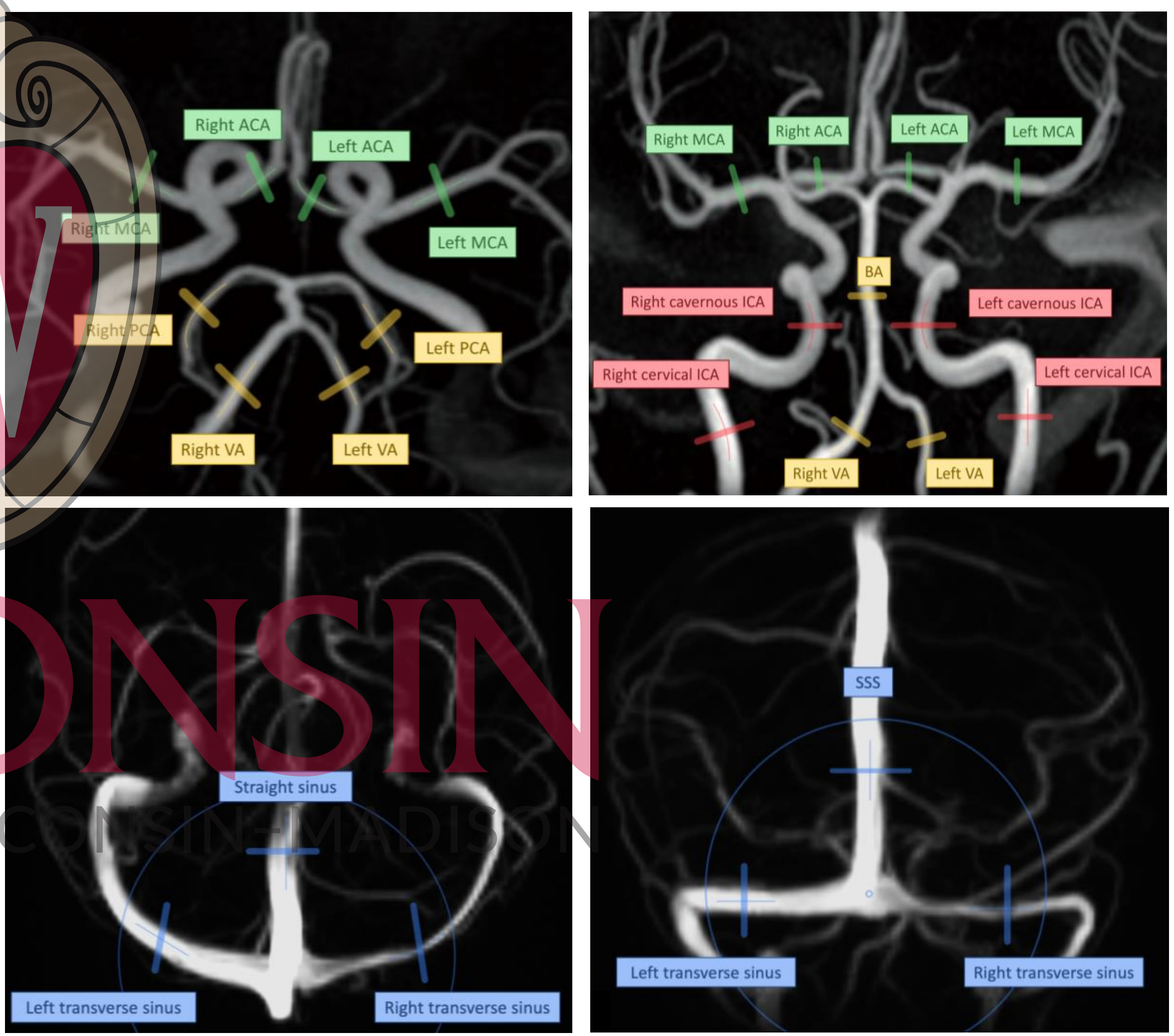
Characteristic	Value
TR (ms)	7.71
TE (ms)	2.63
Flip Angle (degrees)	8
Matrix Size	320
Resolution Size (mm)	0.69
Radial Projections	11000
VENC (cm/s)	80
Encoding Scheme	4-point (58%)
	5-point (42%)
Scan Time (min)	5.6 (58%)
	7.1 (42%)

[1]Gu T, et al (2005). *AJNR* 26(4).
[2]Johnson KM, et al (2008). *MRM* 60(6).

Methods – Post-Processing

- Hemodynamic Measures
  - **Volumetric flow rates** (mL/min)
  - **Pulsatility indices** (a.u.)
    - $PI = (v_{max} - v_{min})/v_{mean}$
- Vessel Segment Locations
  - 13 arteries + 4 veins

Vessel	Measurement Criteria
Total Cerebral Blood Flow (TCBF)	LICA + RICA + BA
Cervical ICA (x2)	C1 segment (1-10 CL points from end of vertical portion)
Cavernous ICA (x2)	C3 segment (1-10 CL points from end of vertical portion)
Middle Cerebral Artery (x2)	Middle M1 ± 5 CL points
Anterior Cerebral Artery (x2)	Middle A1 ± 5 CL points
Basilar Artery	10 ± 5 CL points superior from BA-VA junction
Vertebral Artery (x2)	10 ± 5 CL points inferior from BA-VA junction
Posterior Cerebral Artery (x2)	5-10 CL points before P1-P2 junction
Superior Sagittal Sinus	15 ± 5 CL points from SSS-TS-SS junction
Straight Sinus	15 ± 5 CL points from SSS-TS-SS junction
Transverse Sinus (x2)	15 ± 5 CL points from SSS-TS-SS junction



Results – Analysis

- All 759 cases were successfully analyzed
  - Observer 1 = 302 cases (40%)
  - Observer 2 = 457 cases (60%)
  - Approximately 5 minutes per case
- Aliasing? → Laplacian unwrapping[1]
- Poor Segmentation? → manual segmentation

	Observed			Unresolved		
Vessel	**ALI**	**SEG**	**NV**	**ALI**	**SEG**	**NV**
ICA_C1	0	1	2	0	0	-
ICA_C3	1	4	1	0	0	-
MCA	212	1	21	51	0	-
ACA	116	34	72	22	0	-
BA	4	3	2	0	0	-
VA	6	17	125	0	1	-
PCA	7	7	15	0	6	-
SSS	2	1	7	0	0	-
STR	5	1	6	0	0	-
TS	1	1	199	0	0	-

[1]Loecher M, et al (2016). *JMRI* 43(4)

Results – Intra-observer Agreement

- Observer 1 re-analyzed 30 cases
  - 1 month between analysis
- Excellent reliability in 32/34 flow and pulsatility measures
  - Basilar artery and right VA only moderate reliability for pulsatility

		Volumetric Flow Rates (mL/min)					Pulsatility Indices (a.u.)				
Vessel Segment	N	r	ICC*	Bias	Upper LOA	Lower LOA	r	ICC*	Bias	Upper LOA	Lower LOA
LICA_C1	30	0.995	0.997	0.932	-8.124	9.988	0.973	0.986	-0.004	-0.098	0.089
RICA_C1	30	0.996	0.998	0.171	-8.494	8.835	0.97	0.98	-0.009	-0.123	0.105
LICA_C3	30	0.993	0.997	0.007	-10.934	10.948	0.93	0.964	0.006	-0.134	0.145
RICA_C3	30	0.997	0.998	-0.539	-9.114	8.036	0.892	0.927	-0.041	-0.188	0.106
LMCA	30	0.998	0.999	-0.296	-4.276	3.683	0.94	0.968	0.016	-0.139	0.171
RMCA	29	0.999	1	0.127	-1.943	2.196	0.992	0.99	0	-0.179	0.179
LACA	29	0.999	1	-0.103	-2.126	1.921	0.997	0.997	-0.012	-0.125	0.1
RACA	30	0.993	0.996	1.365	-4.282	7.012	0.937	0.968	0.005	-0.142	0.153
BA	30	0.99	0.995	0.271	-6.442	6.983	**0.49**	**0.623**	**-0.038**	**-0.541**	**0.465**
LVA	30	0.991	0.995	-0.102	-7.434	7.229	0.933	0.966	-0.009	-0.207	0.188
RVA	29	0.991	0.996	0.558	-5.952	7.069	**0.555**	**0.545**	**0.075**	**-1.061**	**1.211**
LPCA	30	0.944	0.971	0.623	-5.971	7.217	0.871	0.931	-0.022	-0.278	0.233
RPCA	30	0.985	0.993	0.312	-3.71	4.334	0.903	0.948	0.004	-0.161	0.169
SSS	30	0.997	0.998	-0.03	-8.12	8.059	0.922	0.951	-0.021	-0.159	0.116
STR	30	0.978	0.989	0.419	-6.942	7.78	0.87	0.931	-0.016	-0.238	0.207
LTS	24	0.999	1	0.788	-4.982	6.559	0.921	0.96	0.007	-0.222	0.236
RTS	29	1	1	0.079	-5.787	5.945	0.953	0.976	0.007	-0.122	0.135

*ICC(3,k) – Two-way mixed-effects model, absolute agreement, mean of measurements

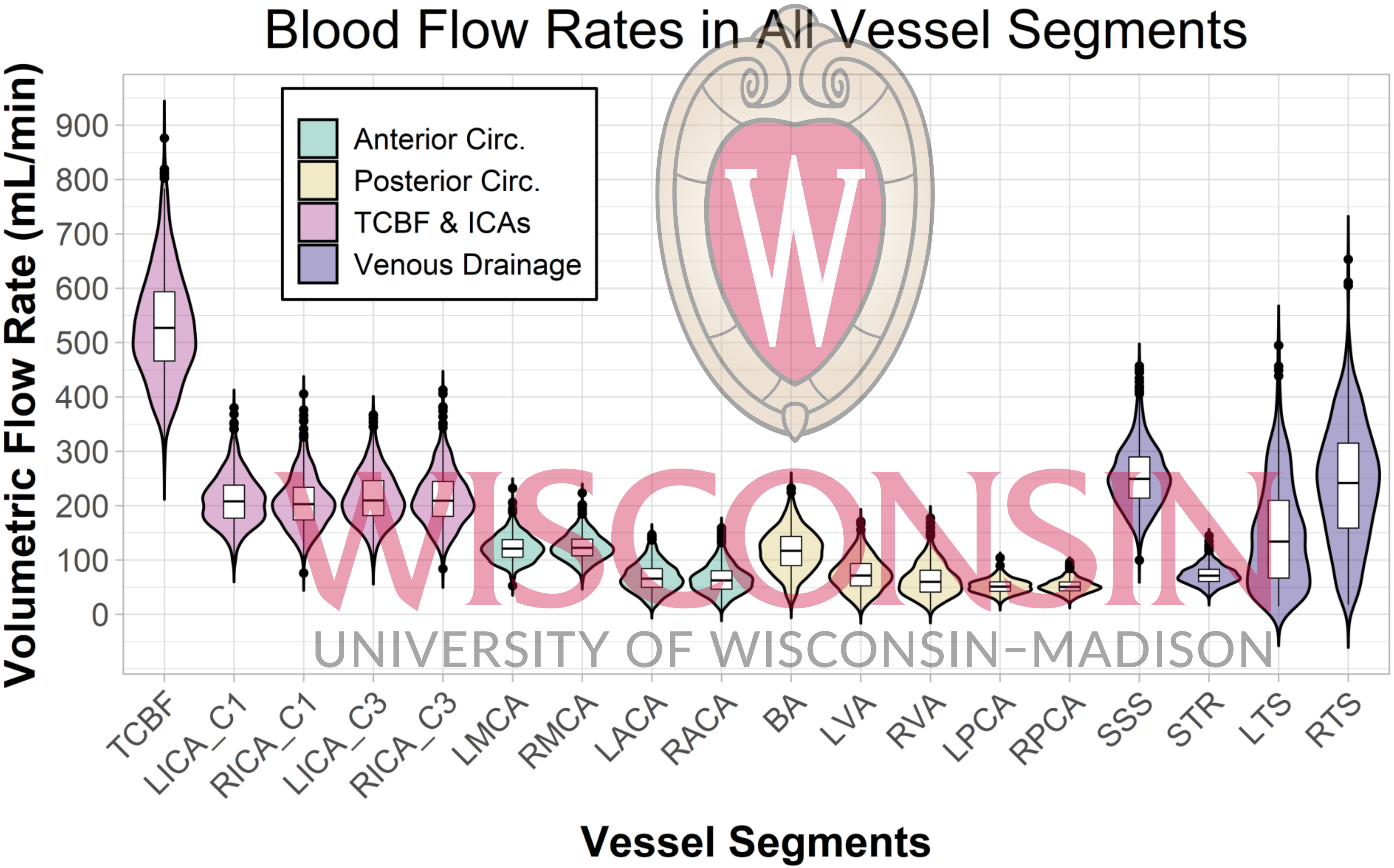
Results – Inter-observer Agreement

- Observer 2 analyzed same 30 cases
  - 1 month between analysis
- Excellent reliability in 32/34 flow and pulsatility measures
  - Right VA and left transverse sinus moderate reliability for pulsatility

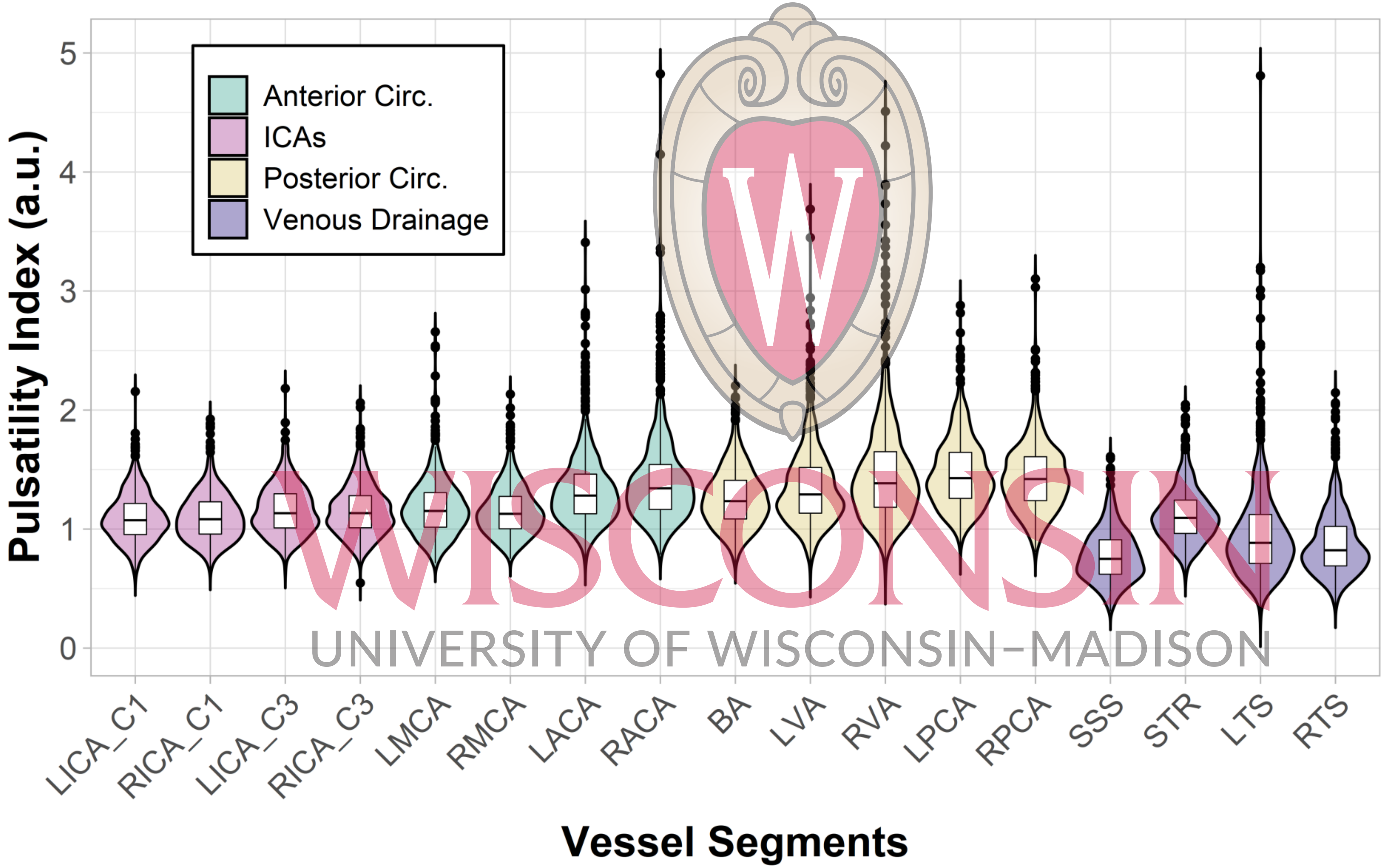
Vessel Segment	N	Volumetric Flow Rates (mL/min) r	ICC*	Bias	Upper LOA	Lower LOA	Pulsatility Indices (a.u.) r	ICC*	Bias	Upper LOA	Lower LOA
LICA_C1	30	0.986	0.992	2.979	-12.176	18.134	0.966	0.981	-0.019	-0.122	0.085
RICA_C1	30	0.993	0.996	0.498	-11.36	12.356	0.959	0.971	-0.034	-0.152	0.085
LICA_C3	30	0.987	0.993	1.745	-13.519	17.008	0.866	0.927	-0.01	-0.215	0.195
RICA_C3	30	0.98	0.987	5.039	-16.93	27.007	0.842	0.913	-0.01	-0.189	0.169
LMCA	30	0.981	0.99	1.867	-11.762	15.495	0.829	0.902	0.027	-0.228	0.281
RMCA	29	0.993	0.996	1.233	-5.846	8.311	0.939	0.968	-0.041	-0.372	0.29
LACA	29	0.968	0.981	-2.843	-14.494	8.807	0.926	0.952	0.047	-0.371	0.465
RACA	30	0.945	0.972	0.27	-15.288	15.827	0.924	0.959	0.018	-0.139	0.175
BA	30	0.99	0.995	0.343	-6.346	7.033	0.943	0.971	0.005	-0.119	0.129
LVA	30	0.983	0.992	-0.206	-9.862	9.45	0.919	0.955	0.031	-0.18	0.241
RVA	29	0.986	0.993	1.213	-7.111	9.537	**0.47**	**0.466**	**0.067**	**-1.123**	**1.256**
LPCA	30	0.891	0.94	-0.202	-10.189	9.784	0.9	0.949	-0.007	-0.237	0.222
RPCA	30	0.94	0.969	-0.686	-8.785	7.412	0.843	0.908	-0.025	-0.267	0.217
SSS	30	0.993	0.996	0.055	-11.954	12.064	0.971	0.985	-0.012	-0.098	0.075
STR	30	0.989	0.994	-0.737	-6.01	4.536	0.895	0.945	0.009	-0.192	0.209
LTS	24	0.996	0.998	2.223	-12.972	17.418	**0.778**	**0.86**	**0.05**	**-0.302**	**0.403**
RTS	29	0.999	0.999	0.457	-11.045	11.959	0.886	0.941	0	-0.191	0.191

*ICC(3,k) – Two-way mixed-effects model, absolute agreement, mean of measurements

Results – Blood Flow

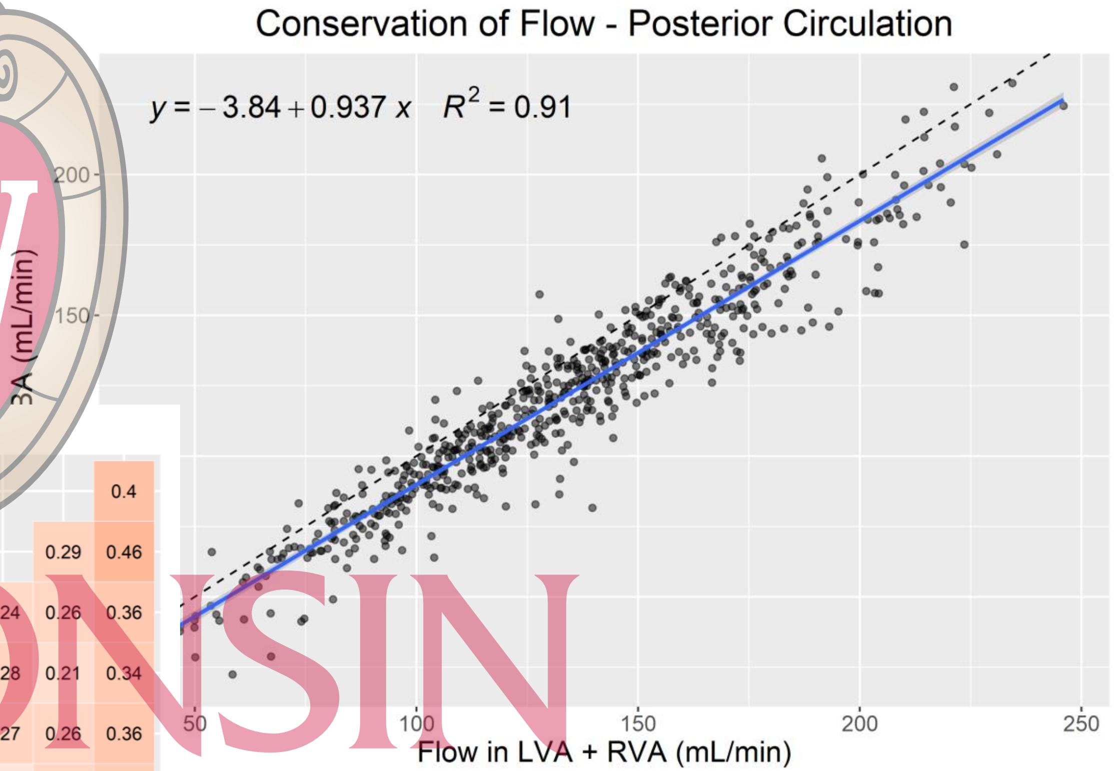


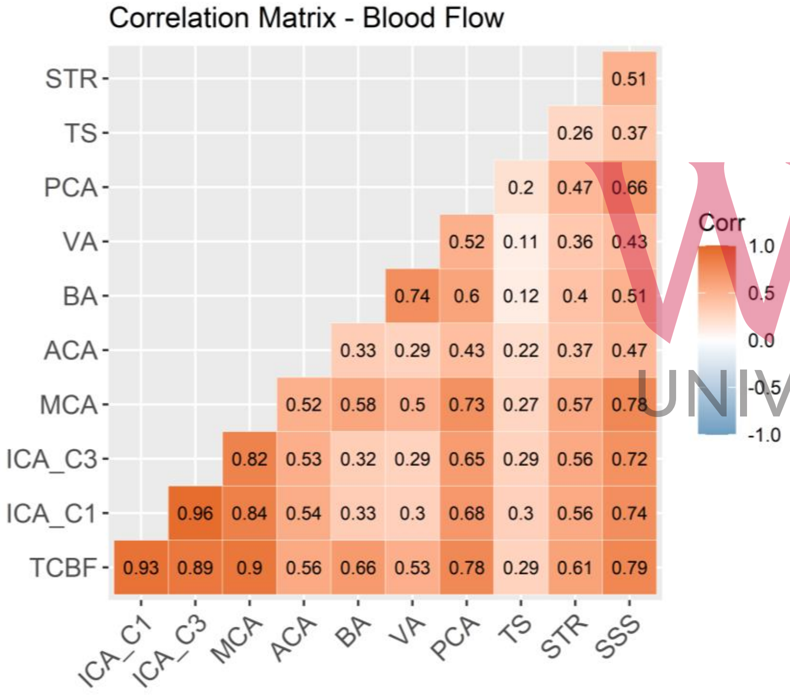
Results – Vascular Pulsatility

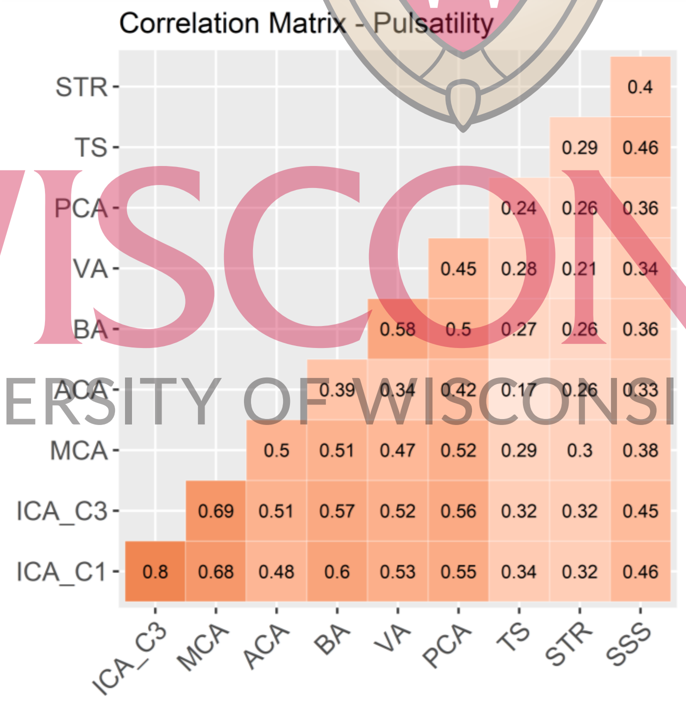


Results – Blood Flow

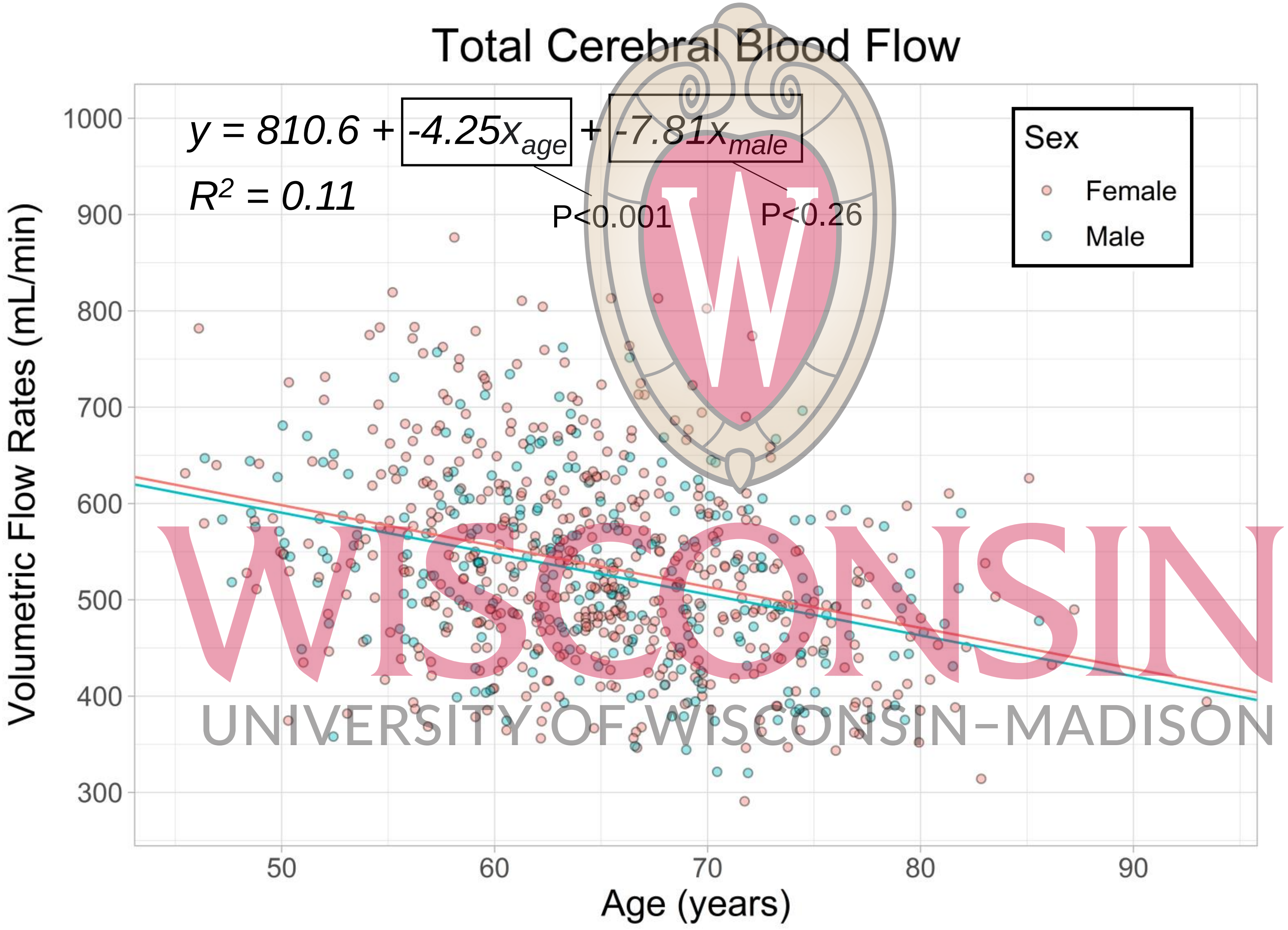
- Conservation of flow
  - LVA + RVA ≈ BA
  - Similar results for ACA + MCA ≈ ICA
- Flow and PI were significantly correlated between all vessel segments







Results – Flow vs. Age/Sex

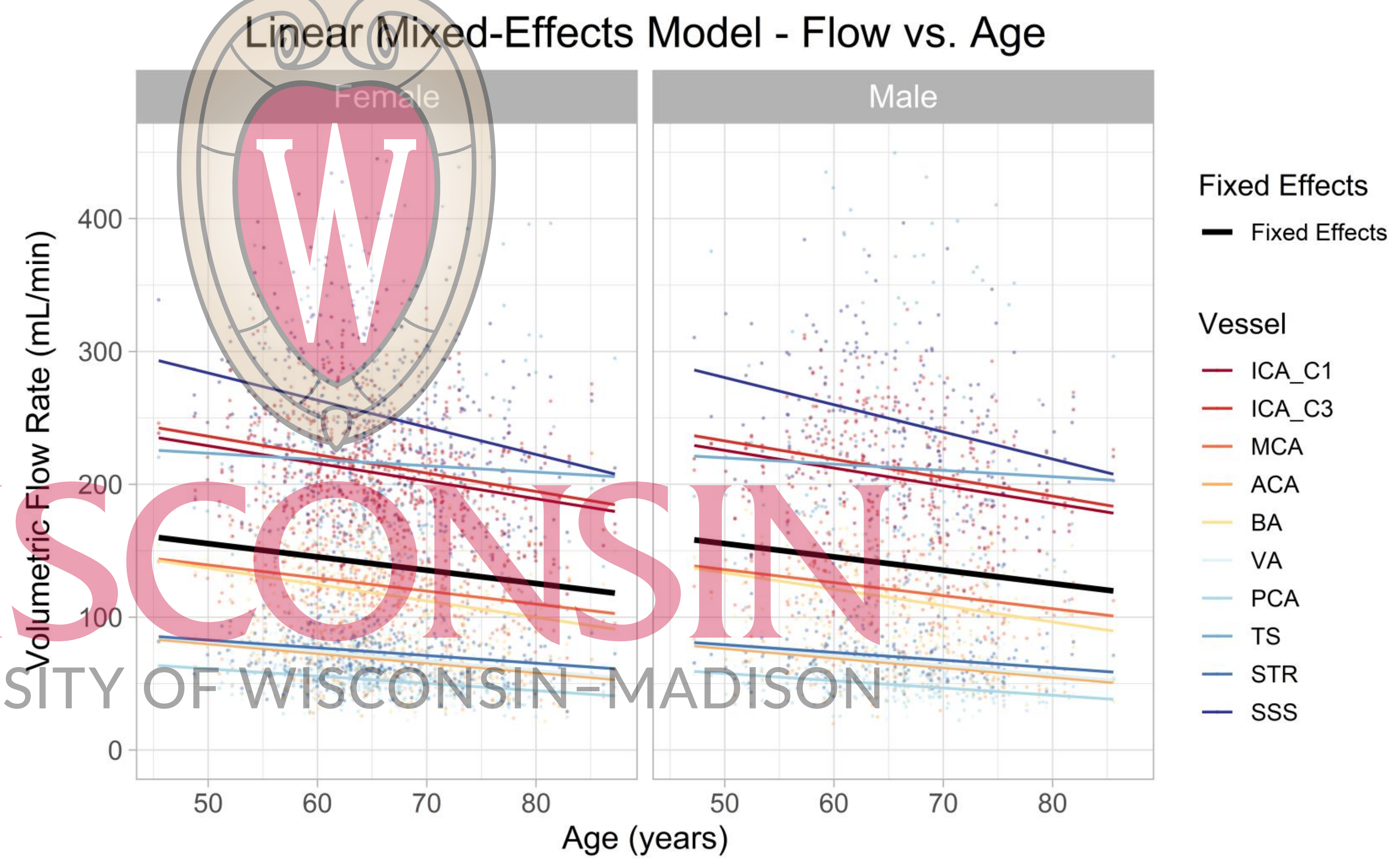


Results – Flow vs. Age/Sex

Flow ~ Age + Sex + (1 + Age | Vessel)

	β (coefficients)		
	Intercept	Age	Sex (male)
FIXED EFFECT	**205.4*** **	**-1.00*** **	**-3.46** **
ICA_C1	295.4	-1.33	-3.46
ICA_C3	305.4	-1.38	-3.46
MCA	188.4	-0.98	-3.46
ACA	115.9	-0.72	-3.46
BA	198.4	-1.23	-3.46
VA	117.6	-0.72	-3.46
PCA	88.5	-0.55	-3.46
TS	247.0	-0.47	-3.46
STR	111.7	-0.58	-3.46
SSS	386.0	-2.04	-3.46

T-tests using Satterthwaite's method
**p<0.01
***p<0.001

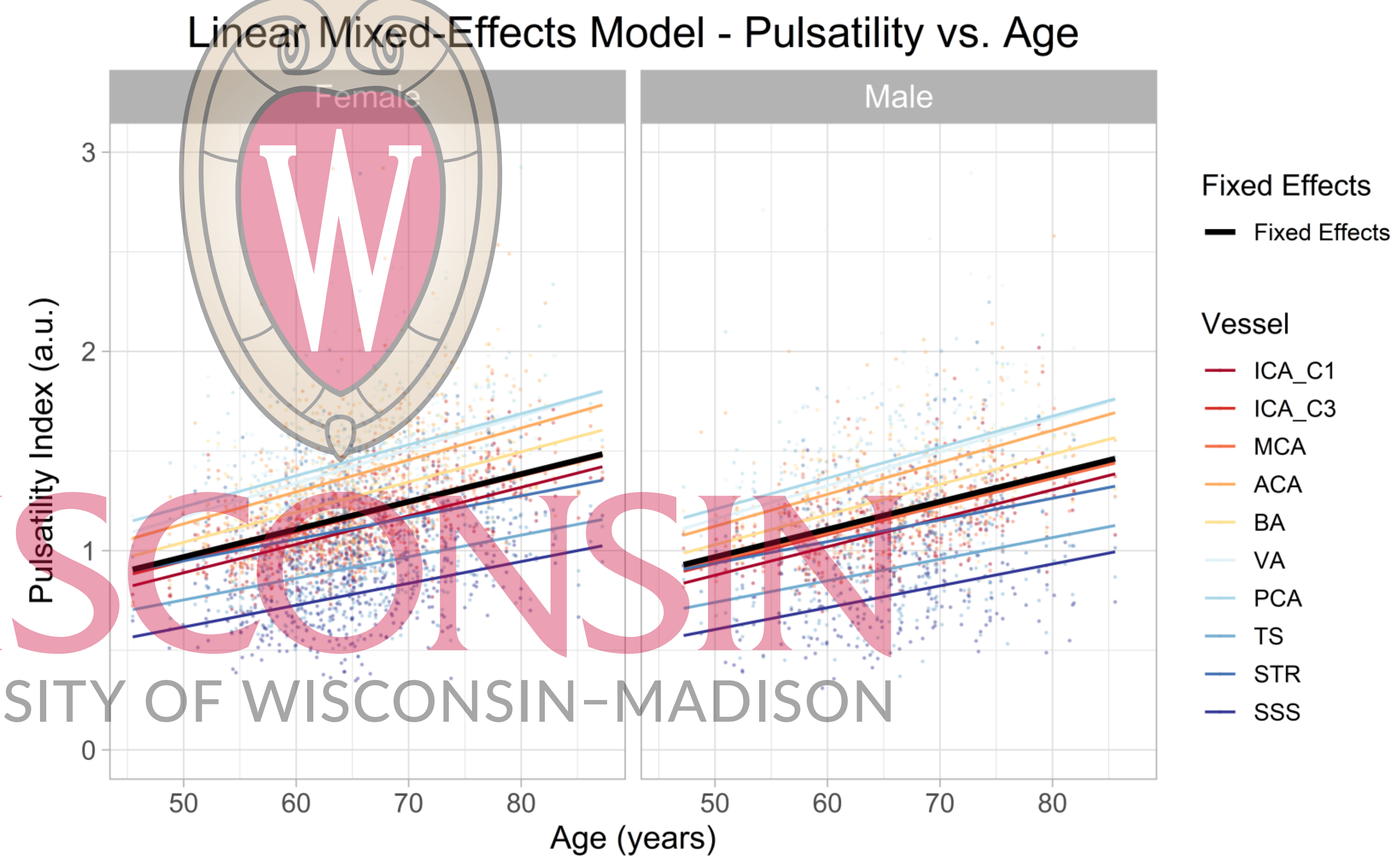


Results – Pulsatility vs. Age/Sex

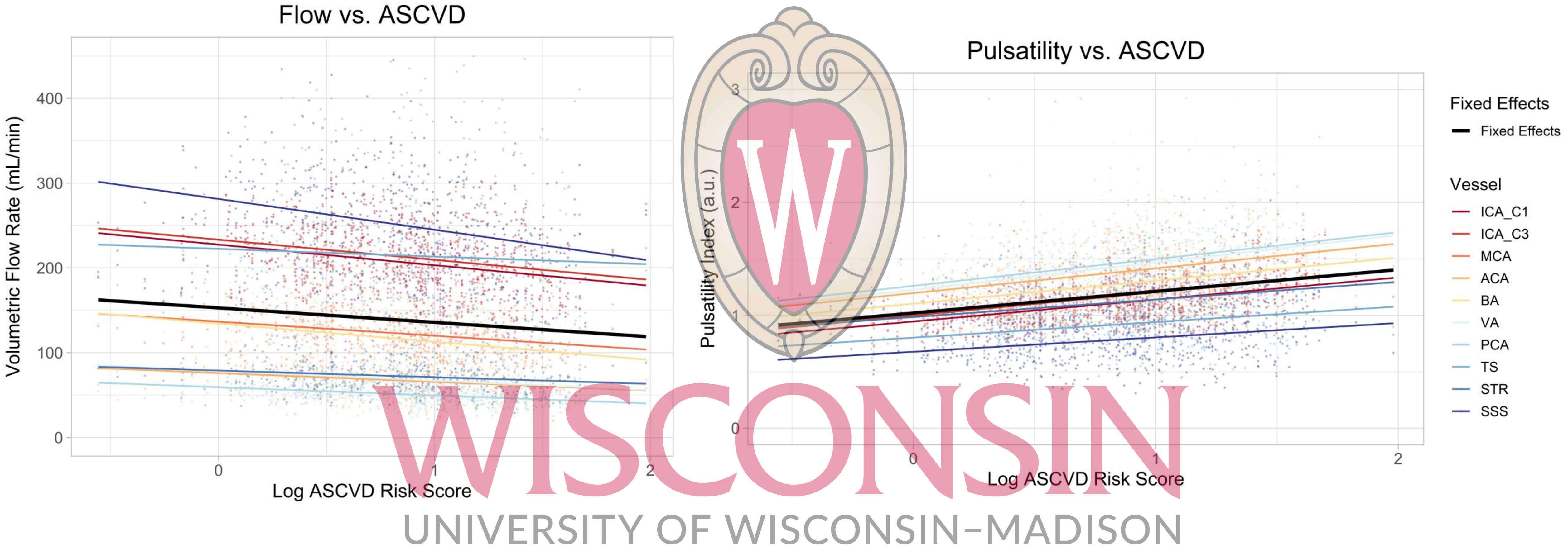
PI ~ Age + Sex + (1 + Age | Vessel)

	β (coefficients)		
	Intercept	Age	Sex (male)
FIXED EFFECT	**0.275*** **	**0.014*** **	-0.012
ICA_C1	0.174	0.014	-0.012
ICA_C3	0.227	0.014	-0.012
MCA	0.271	0.014	-0.012
ACA	0.333	0.016	-0.012
BA	0.286	0.015	-0.012
VA	0.329	0.017	-0.012
PCA	0.441	0.016	-0.012
TS	0.211	0.011	-0.012
STR	0.405	0.011	-0.012
SSS	0.069	0.011	-0.012

T-tests using Satterthwaite's method
***p<0.001



Results – ASCVD



Discussion

- 4D flow MRI allowed for hemodynamic assessment in 17 vessels in 759 subjects
  - One of the most comprehensive intracranial flow studies
  - Possible with our semi-automated tool
- **Flow decreases** and **pulsatility increases** with **increasing age**
  - Contributing factors:
    - Decreased brain metabolism[1]
    - Decreased parenchyma[1]
    - Increased arterial stiffness[2]
- **Flow decreases** and **pulsatility increases** with **increasing cardiovascular risk score**
  - Reflects effect of systemic cardiovascular disease on neurovascular health

[1]Leenders KL, et al (1990). *Brain* 113(1).
[2]Rosenberg AJ, et al (2020). *J Appl Physiol* 128.

Conclusion

- Future studies will investigate how flow/pulsatility is related to:
  - APOE genotype
  - White matter hyperintensities
  - Other risk scores (Framingham risk score, LIBRA)
- **First-step towards defining normal cerebral blood flow and pulsatility values in older adults**
  - **Determine abnormal hemodynamic ranges**
  - **Help power future neurovascular studies**

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