Cerebral Arteriovenous Malformations: Their Features, Management, and A Look Into Their Natural History

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June 5, 2021

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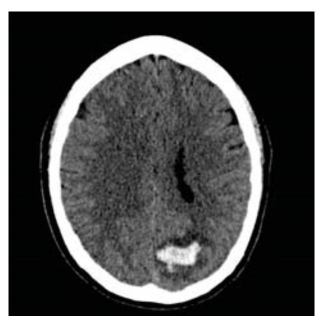
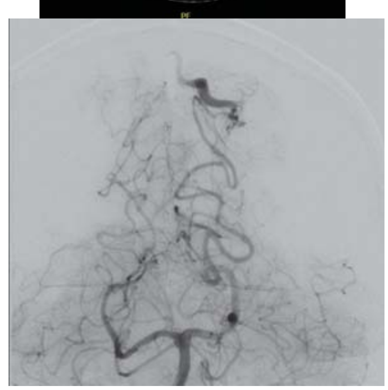
Cerebral Arteriovenous Malformations (AVMs)

- Comprised of abnormal high flow artery to vein connections
- Annual risk of hemorrhage between 2 to 4%[1-6]
- When symptomatic, present with seizures, hemorrhage, headache, neurologic deficits from vascular "steal" phenomenon or venous hypertension

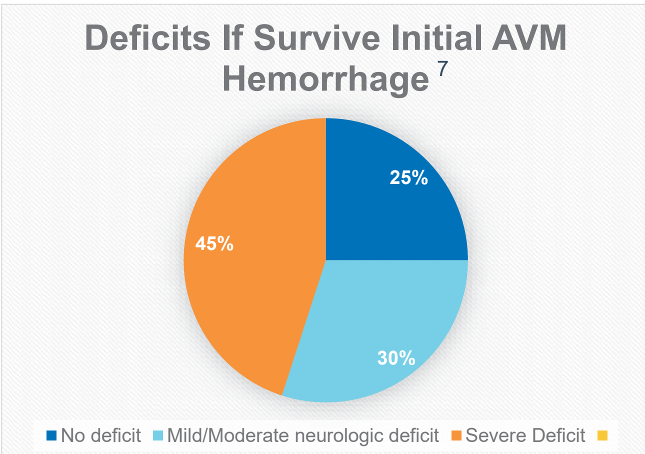


25 year old male with new onset right inferior quandrantanopsia and headache.



Found to have Spetzler-Martin Grade I AVM. Arterial supply: left PCA with drainage to stenosed cortical draining vein and 2.5 mm perinidal aneurysm

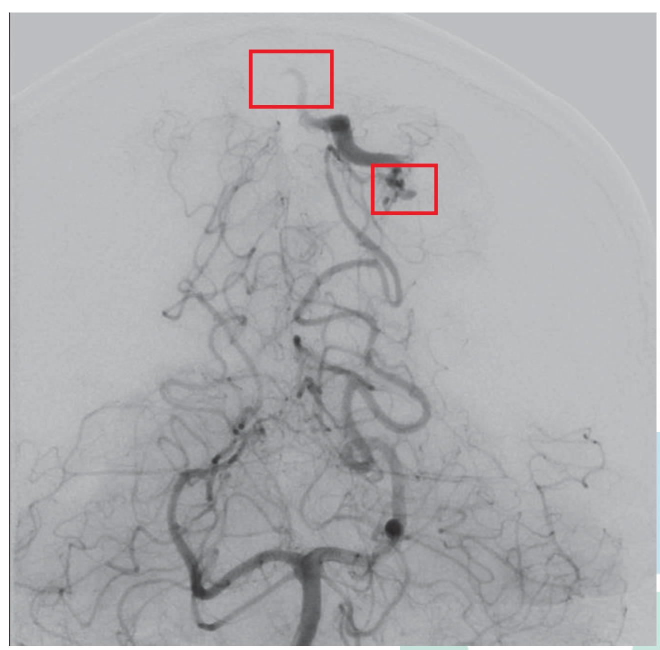
Morbidity and mortality is high after AVM hemorrhage



20% of initial survivors die in the first three months, with a third of the remaining survivors having moderate disability[8]

High risk features of AVMs

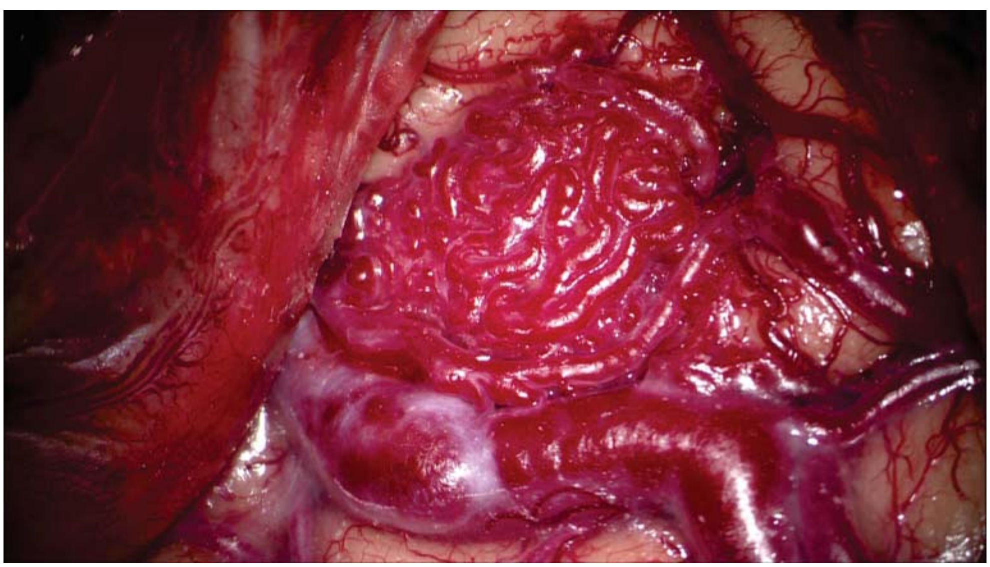
- Intranidal aneurysm: 9.8% per year risk rate of bleeding[10]
- Prior hemorrhage: 4.5% per year risk rate of rebleed[9]
- Venous outlet stenosis[9]
- Deep location of AVM[9]
- Sole deep venous drainage[9]
- Small size of AVM
- Associated flow related aneurysms[9,10]



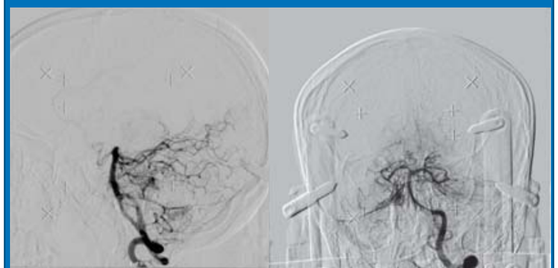
Current Management Strategies

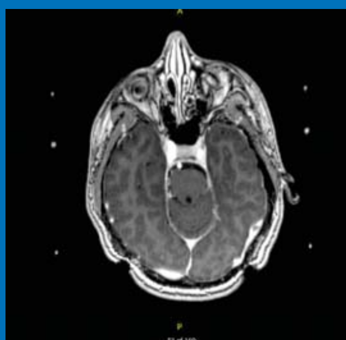
- Medical management alone:
  - blood pressure control, high risk behavior reduction, routine surveillance
- Microsurgical resection
- Gamma knife radiation
- Microsurgical resection with adjunct embolization
- Gamma knife radiation with prior embolization
- Embolization alone
- Combined strategies

Microsurgical Resection



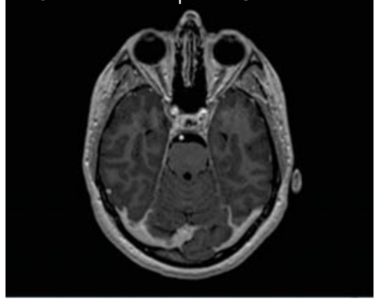
Gamma Knife Radiation



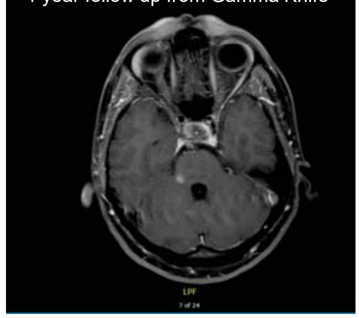


Gamma Knife Planning Angiogram and MRI for Pontine AVM

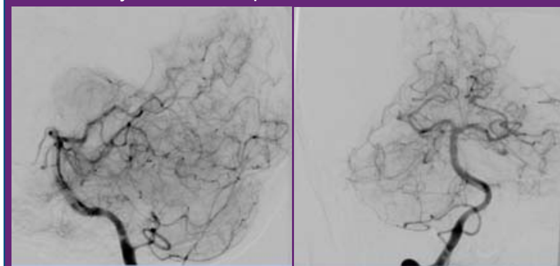
6 month follow up from Gamma Knife



1 year follow up from Gamma Knife



2 year Follow up from Gamma Knife



Significant reduction in AVM nidus

The question

- When is treatment indicated in arteriovenous malformations?
- When surgery is indicated, what modality should be used?

Current Methodology for Determining Treatment Strategy

- Retrospective Clinical Case Series
- Rare Prospective Randomized Control Trials
  - Limitations: outcome measurements, patient selection, physician experience/bias
- The “Art of Medicine”: ie Expert Opinion and Experience Crafted Algorithms

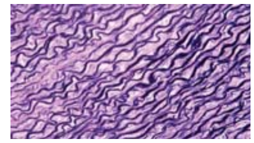
New Strategies for Approaching Treatment

- Applying engineering fundamentals to medical pathologies
- Artificial Intelligence analysis of “Big Data”

Goal of Personalized Medicine

Multi-Phase Project

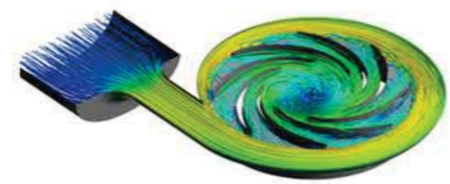
- Phase 1: Histologic analysis of cerebral blood vessel walls for elastin using Van Gieson Staining



- Phase 2: In vivo measurement of inflow and outflow of AVMs using 4D angiography and intraoperative flow monitoring

- Phase 3: Mechanical testing of human cerebral vasculature

- Phase 4: Fluid Structure Interaction modeling of a simple AVM incorporating the histologic properties and inflow and outflow parameters from Phases 1 and 2.



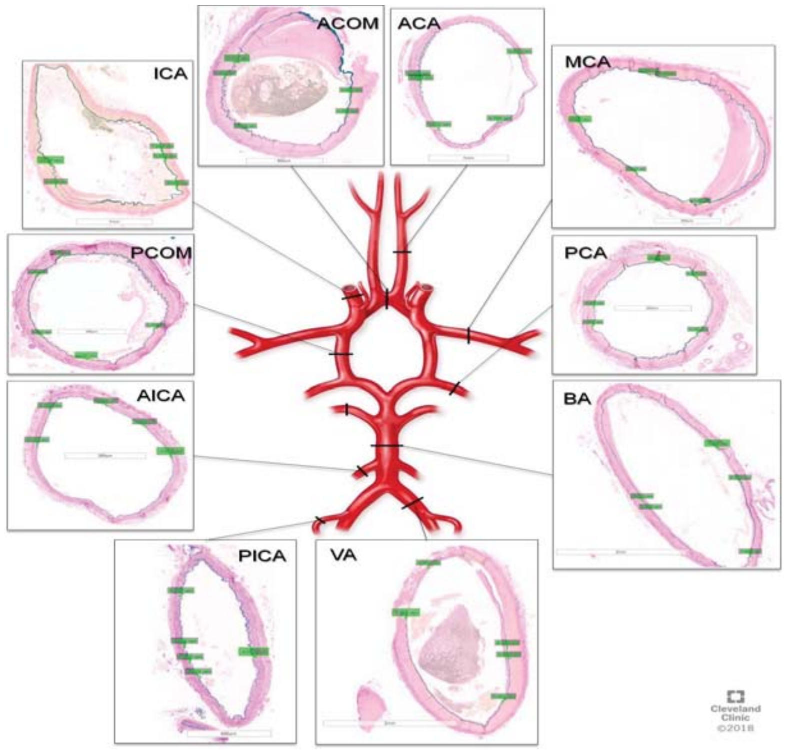
Phase 1

Measurement of Normal Cerebrovascular Vessel Elastin

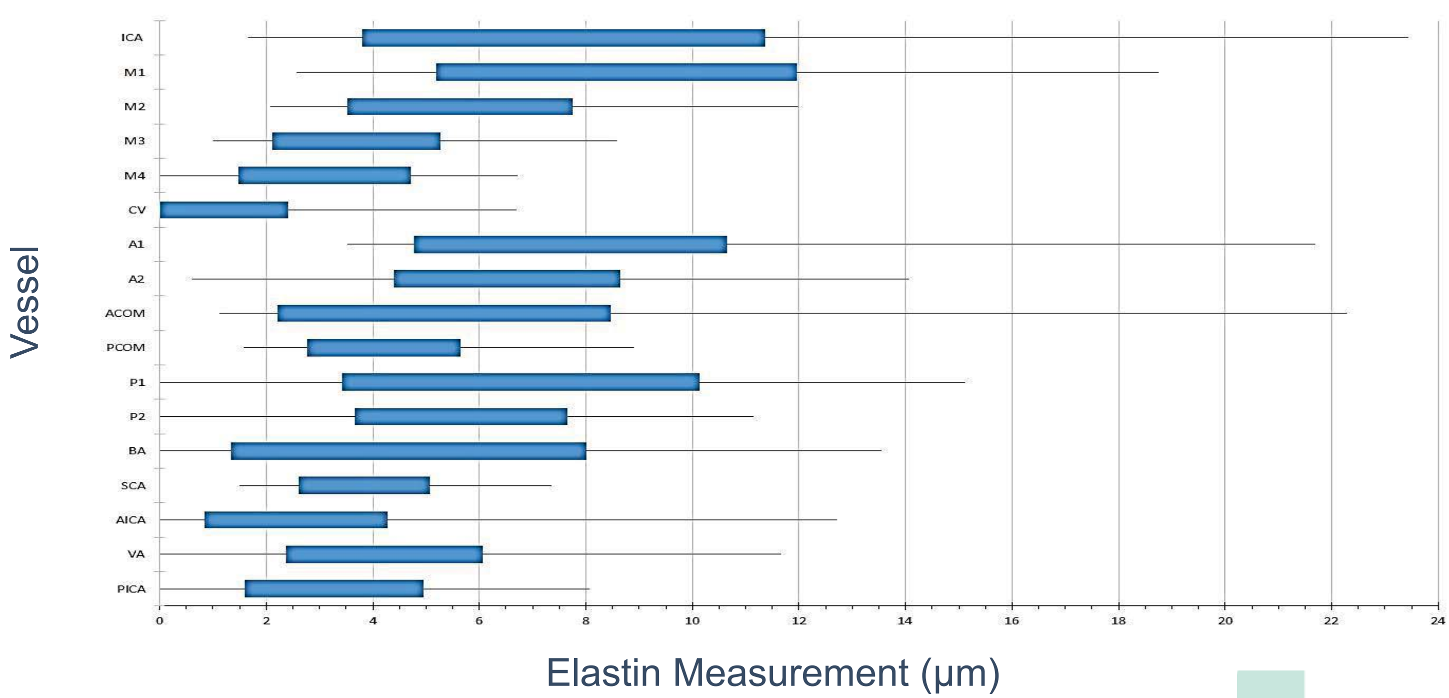
- 5 purchased cadaveric heads
  - housed in the Cleveland Clinic Neurosurgery Skull Base Laboratory were used to obtain specimens of blood vessels in each vascular distribution.
  - Fixed in formaldehyde
  - Processed by Cleveland Clinic Lerner Research Institute Histology Laboratory and stained with Verhoeff's Van Gieson stain
    - identifies the elastic layer thickness as the color black, collagen thickness as red and other tissue as yellow.

Van Gieson Stain: Elastin

Elastin and Normal Cerebrovascular: Results



Elastin Measurements of Blood Vessels of the Brain



Anterior versus Posterior Elastin

Table 1: Elastin Thickness vs Anterior/Posterior Only				
Parameter	Class Values	Coefficient	Std Error	P-Value
Intercept		4.46	.43	<.0001
Anterior/Posterior	Anterior = 1, Posterior = 0	1.45	.61	.044

There is a statistically significant difference between anterior and posterior elastin.

Table 2: Elastin Thickness (µm) vs Vessel Diameter and Anterior/Posterior				
Parameter	Class Values	Coefficient	Std Error	P-Value
Intercept		2.32	.46	.001
Anterior/Posterior	Anterior = 1, Posterior = 0	1.01	.61	.139
Vessel Diameter (mm)		1.27	.07	<.0001
Location Right/Left	Left = 1 Right = 0	.38	.14	.024
Observer 1 vs 2	Observer 1 = 1 Observer 2 = 0	-.043	.14	.77

There is a statistically significant association between elastin thickness, vessel diameter and anterior posterior circulation.

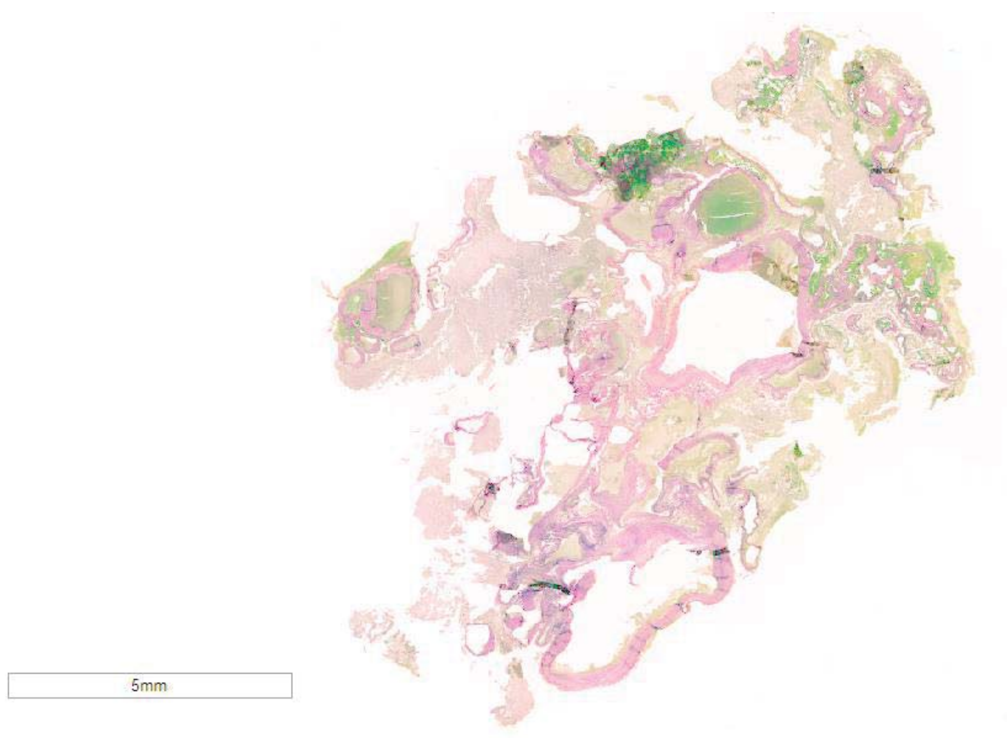
Results

- Elastin thicknesses are significantly different between anterior and posterior circulation vessels (P<0.05)
  - This may explain the differences seen in aneurysm rupture risk for anterior versus posterior circulation aneurysms
  - This may explained the propensity of flow related aneurysms to be seen in cerebellar AVMs.
- These findings support the need for fluid-structure interaction modeling parameters to be more precise and help explain findings seen in cerebrovascular aneurysm and AVM pathology.
- We are generating a predictive model of elastin thickness based off of vessel diameter and wall thickness which may help apply mechanical properties to models based off of angiographic images.

AVM staining

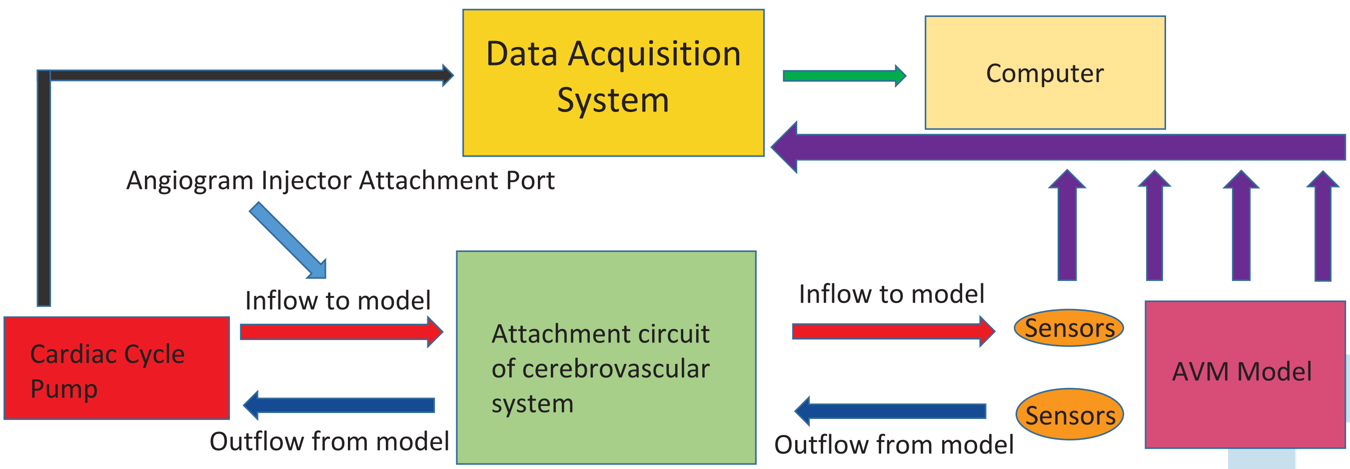
- 8 human AVM specimens currently stained with Van Gieson
- Currently measuring each size of vessel within specimen and measure corresponding elastin thickness and proportion to vessel caliber
- This number will be compared to normal brain vessel elastin thickness/proportion

AVM Measurements



Phase 2

In vivo measurement of inflow and outflow of AVMs using 4D angiography and intraoperative flow monitoring



3D printed AVM rendering

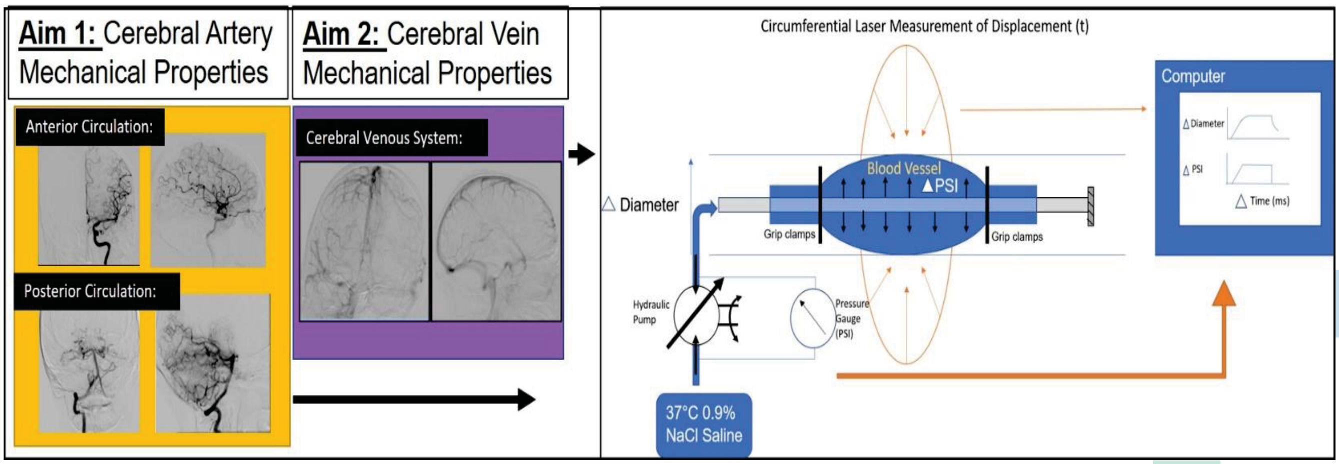
Results Goal: To generate patient specific flow and pressure information through AVM for Fluid Structure Interaction modeling parameters

Phase 3:

Mechanical testing of human cerebral vasculature

5 purchased fresh frozen cadaveric heads and 5 autopsy dissections

- housed in the Cleveland Clinic Neurosurgery Skull Base Laboratory are being used to obtain specimens of blood vessels in each vascular distribution for both arteries and veins



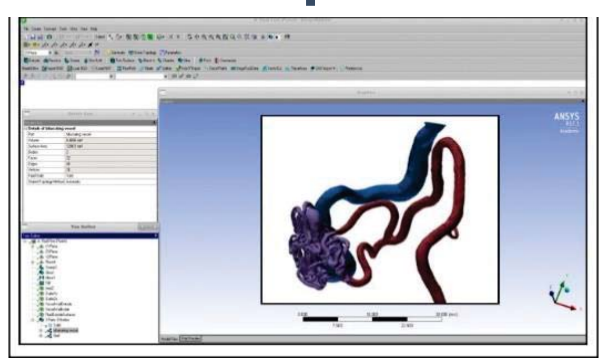
Phase 4:

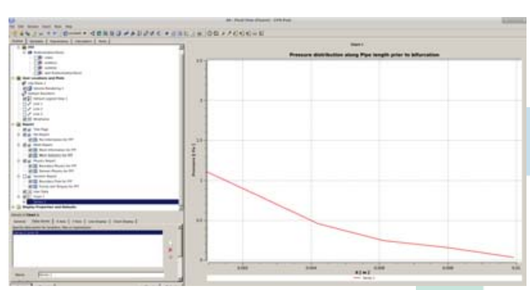
Fluid-Structure Interaction Computations

- ANSYS Fluent and Mechanical software (Ansys, Inc., Canonsburg, PA, USA) is being used to perform a combined CFD and structural failure analysis of the simple AVM geometries.

- Geometries are generated within ANSYS design software from 3D printed simulations.

- Fluid information is obtained from Phase 2 for patient specific AVM. Mechanical properties are being varied: linear elastic, nonlinear elastic and nonlinear viscoelastic. Plan is then to include mechanical parameters from Phase 3.





Conclusions

- Prediction of natural history of a patient anatomy specific would be greatly beneficial in selecting treatment strategy and timing.
- A predictive model of both rupture risk and treatment approach may be possible with a coupled fluid dynamics-structural analysis with the appropriate properties.

References

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