



Small Vessels in Aged Brains

Mechanisms in Brain Microvascular Dysfunction



Atticus H Hainsworth

AH Hainsworth disclosures

Honoraria from

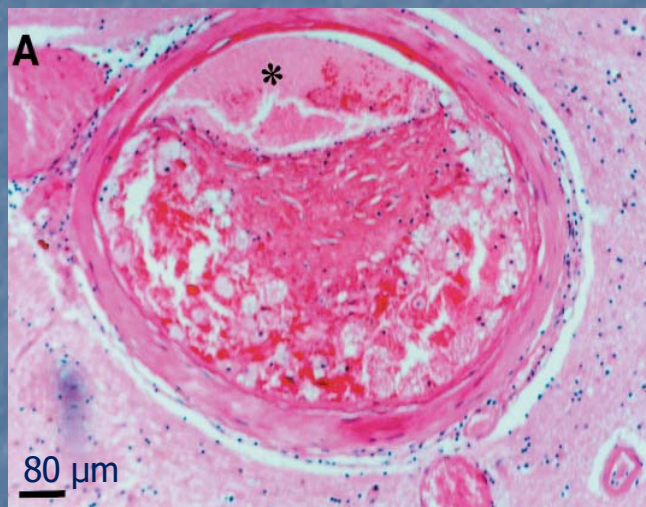
- Eli Lilly Neuroscience
- Dementia Discovery Fund
- NIA

Non-Profit Roles

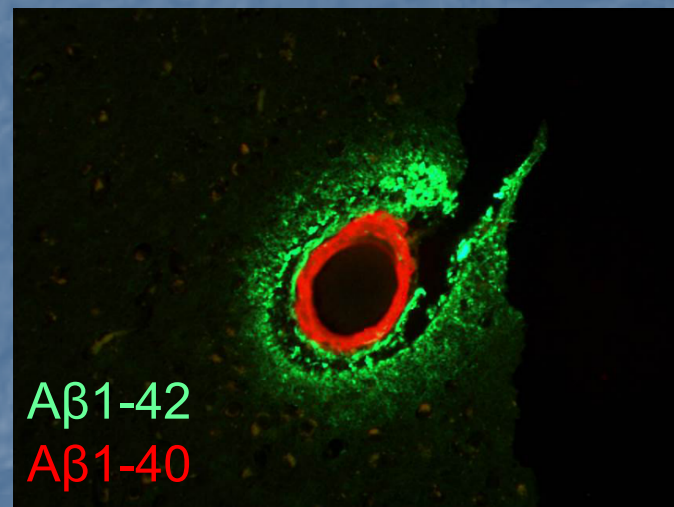
- Chair, Vascular Cognitive Disorders, Alzheimer's Association International Society to Advance Alzheimer's Research and Treatment (ISTAART)
- Chair, Vascular Experimental Medicine, Dementias Platform UK
- Chief Investigator, Perfusion by Arterial Spin Labelling Following Single Dose Tadalafil in Small Vessel Disease (PASTIS)

What is Brain Microvascular Disease?

- *Micro-atheroma*
- *Cerebral amyloid angiopathy*
- *Small vessel disease..*



GA Lammie 2002 Brain Pathol

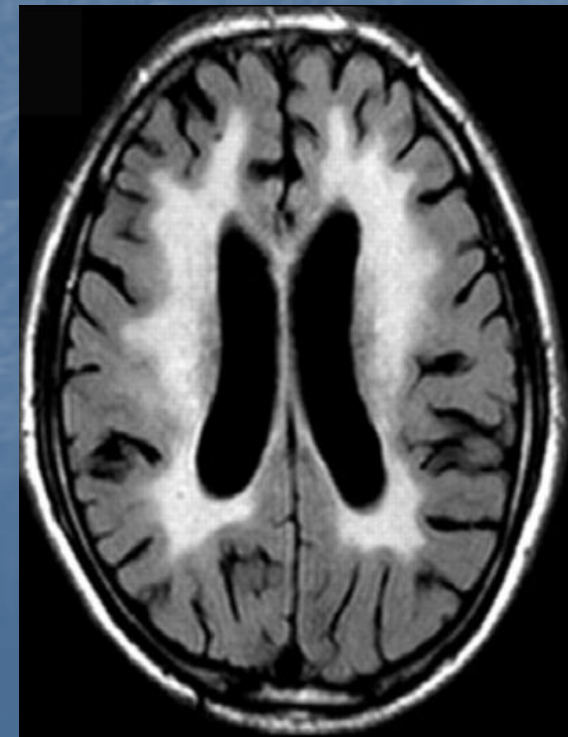
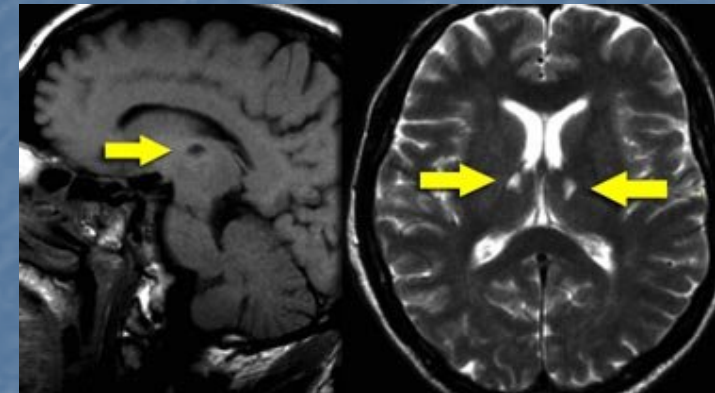
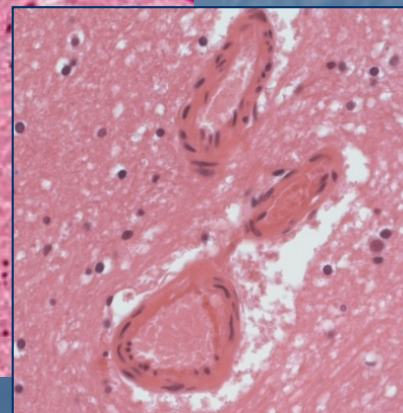
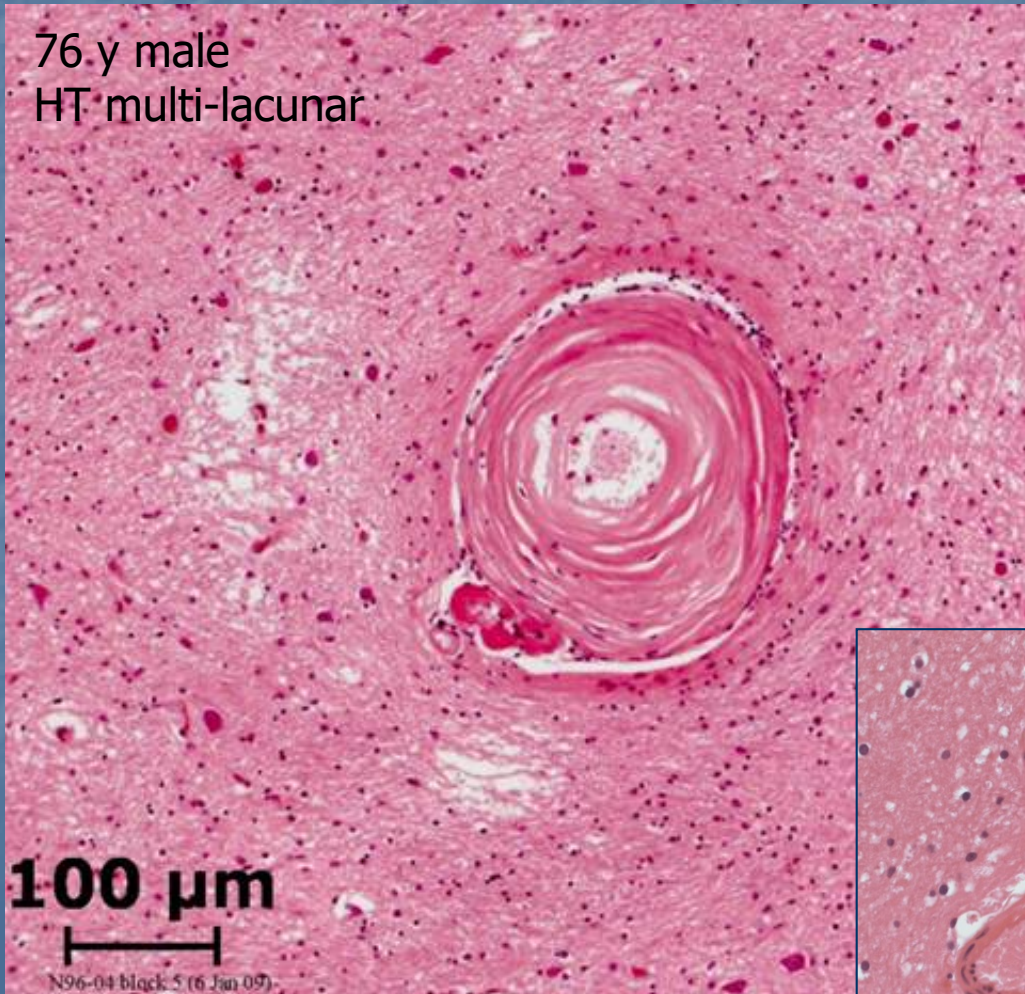


*D Howlett, P Francis, AH Hainsworth
Unpublished data*

Cerebral Small Vessel Disease

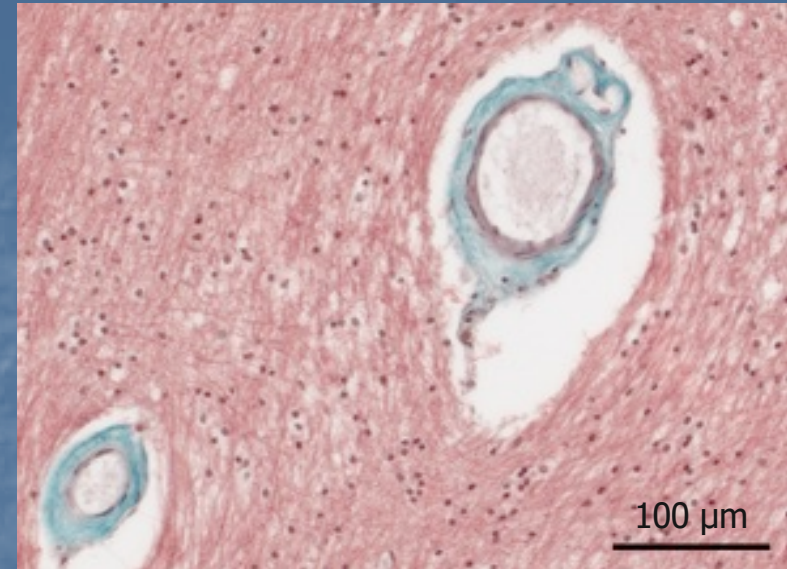
Main Cause of lacunar stroke, white matter hyperintensities, VCI

76 y male
HT multi-lacunar



Small vessel disease

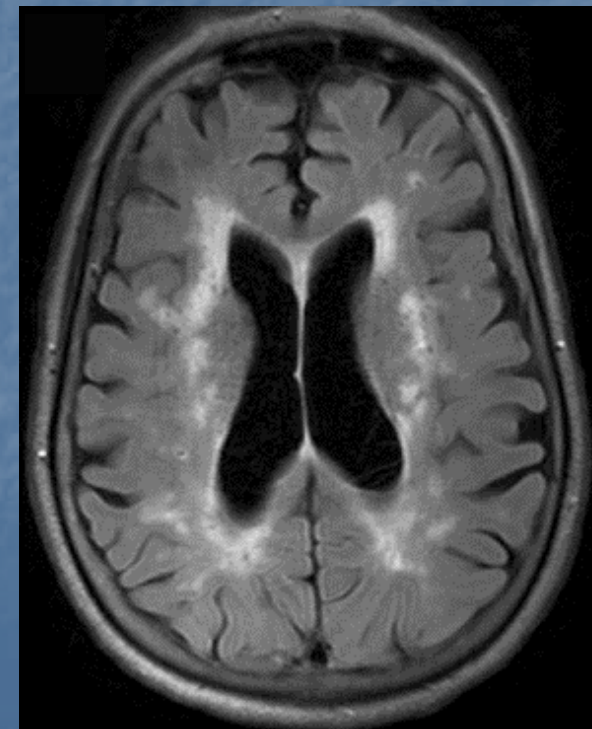
- Concentric fibrous thickening
- Not atheroma
- Not cerebral amyloid angiopathy



Hainsworth et al. 2015 Brain Pathol



G. Salamon et al. 1968. Prog Brain Res.



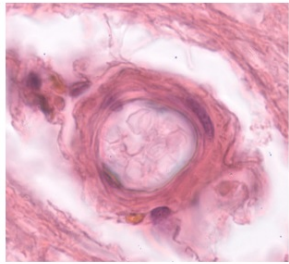
Are Brain Small Arteries the same as Heart Small Arteries..?

Yes	No
Same diameter	Brain: astrocytes, BBB
Same blood	Less surrounding matrix (collagen?)
Similar lumen pressure	Lower parenchymal pressure
Similar pharmacology (?)	Peri-vascular trafficking, fluid clearance

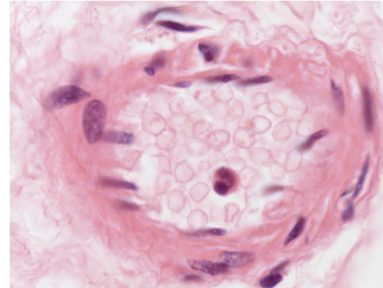
Small-Vessel Disease in the Heart and Brain: Current Knowledge, Unmet Therapeutic Need, and Future Directions. Berry C, Sidik N, Pereira AC, Ford TJ, Touyz RM, Kaski JC, Hainsworth AH (2019) JAHA

Brain and Heart Small Arteries

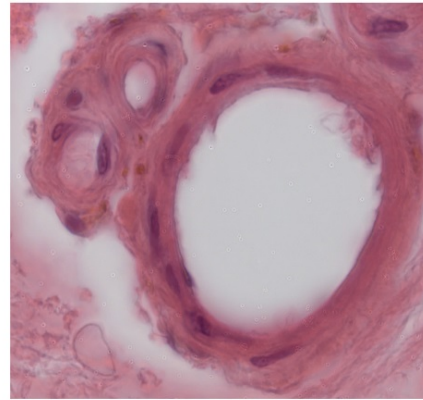
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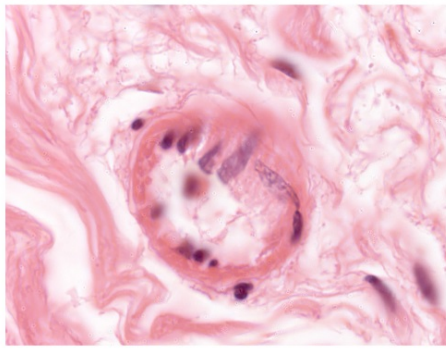
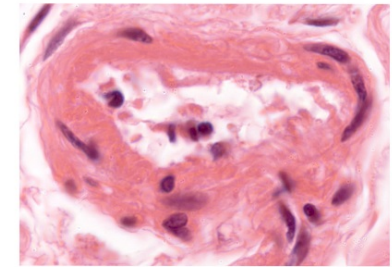
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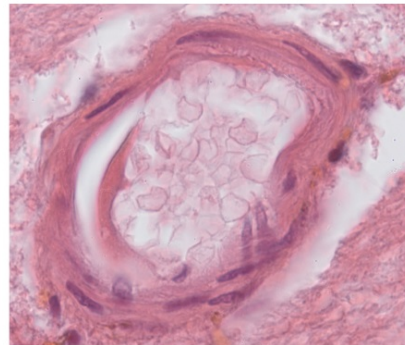
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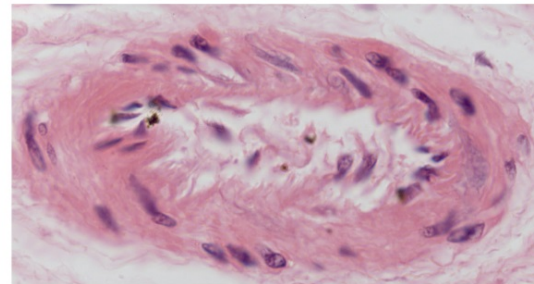
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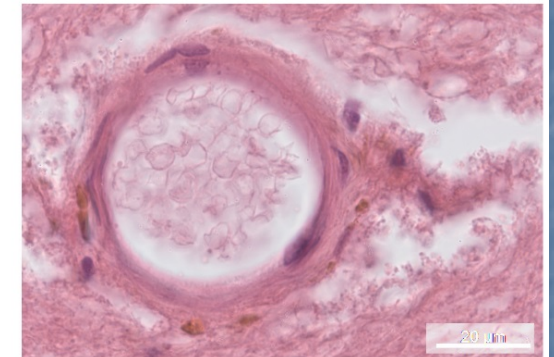
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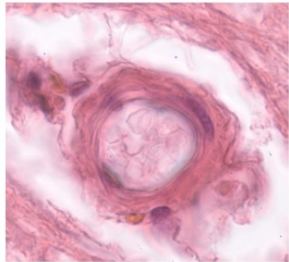
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Brain and Heart Small Arteries

1



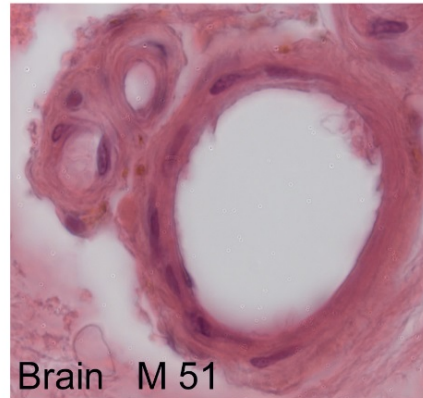
Brain M 51

2



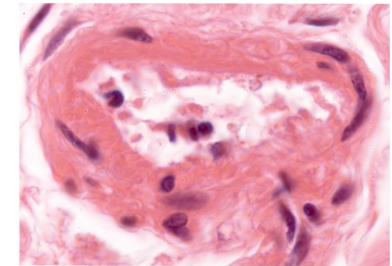
Heart M 27

3

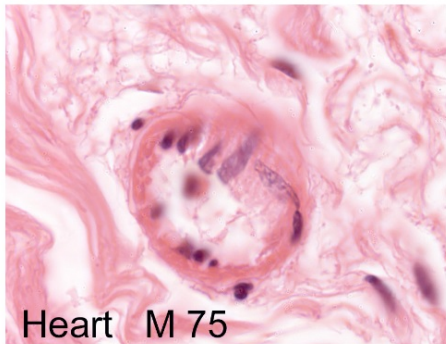


Brain M 51

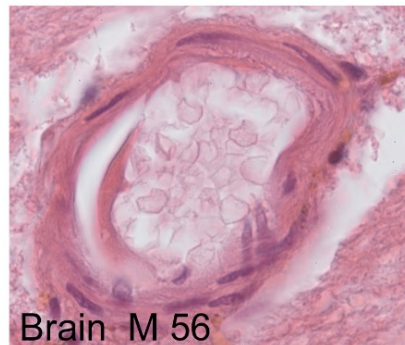
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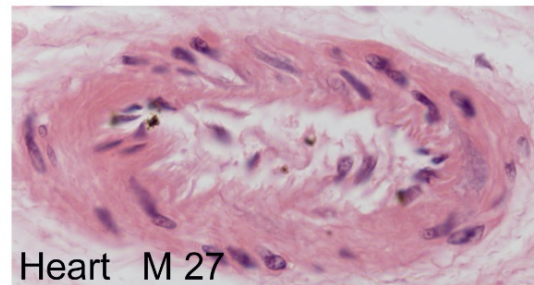
Heart M 70



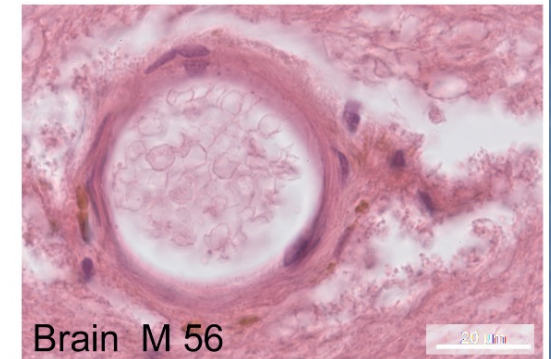
Heart M 75



Brain M 56



Heart M 27



Brain M 56

5

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SVD Mechanism / Pathogenesis

Risk factors:

- Old age
- Hypertension

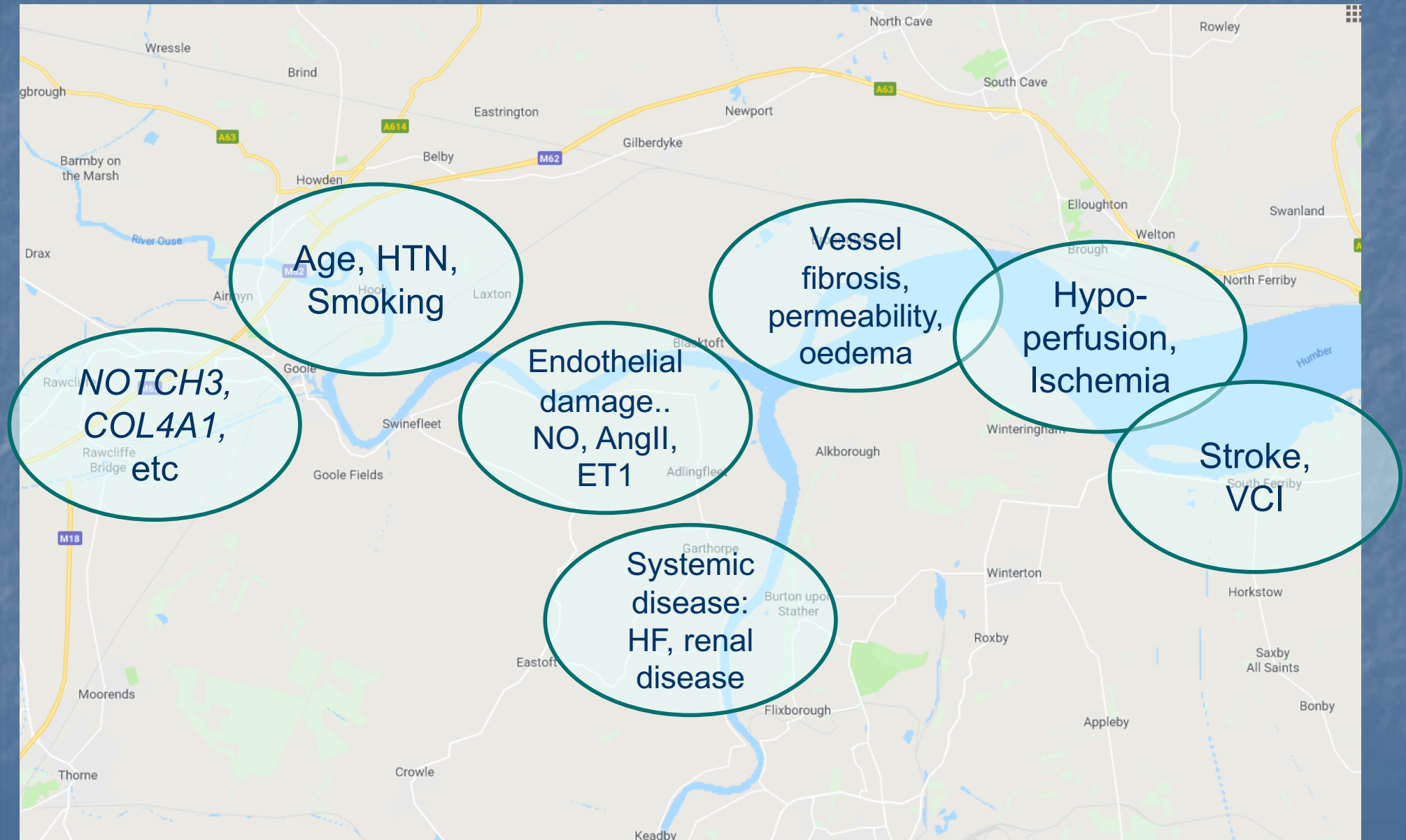
- Smoking
- Diabetes mellitus type 2
- Elevated homocysteine
- *Err... that's it*

SVD Mechanism / Pathogenesis

Genetic factors:

- *NOTCH3* Myocyte receptor (CADASIL)
- *COL4A1/COL4A2* BM Collagen IV
- *EDNRA* Endothelin Receptor A
- *FOXF2* Forkhead Transcription factor
- *MMP12* Matrix metalloproteinase

SVD Mechanisms



We Need

- 1) Correlative pathology in Brain & Heart
- 2) Large animal models



Joycelyn Andoh
 Nadim Jiwa
 Moji Giwa
 Cheryl Khoong
 Ekta Vasita
 Emma Norton
 Mathilde Pauls
 Lauren Binnie
 Adam Anad
 Miriam Barker
 Dot Bennett
 Tom Barrick
 Anan Shtaya

Les Bridges
 Anthony Pereira
 Jamuna Jeevahan
 Kay Elderfield
 Jeremy Madigan
 Jeremy Isaacs



Colin Berry
 Tom van Agtmael
 Del Graham
 Anna Dominiczak
 William Holmes
 Mhairi Macrae



Wayne Poon



Barry Moynihan



Thais Minett
 Hugh Markus
 Andrew Lawrence



Margaret Esiri
 Jonathan Williams
 Rebecca Llewellyn-Bennett



Steve Wharton
 Paul Ince
 Gill Forster



Raj Kalaria



Christina Kruuse
 Egill Rostrup



Lawrence Kenyon

