Role of a Transient Receptor Potential Channels in Marfan Syndrome-induced Aortopathy and Cardiomyopathy

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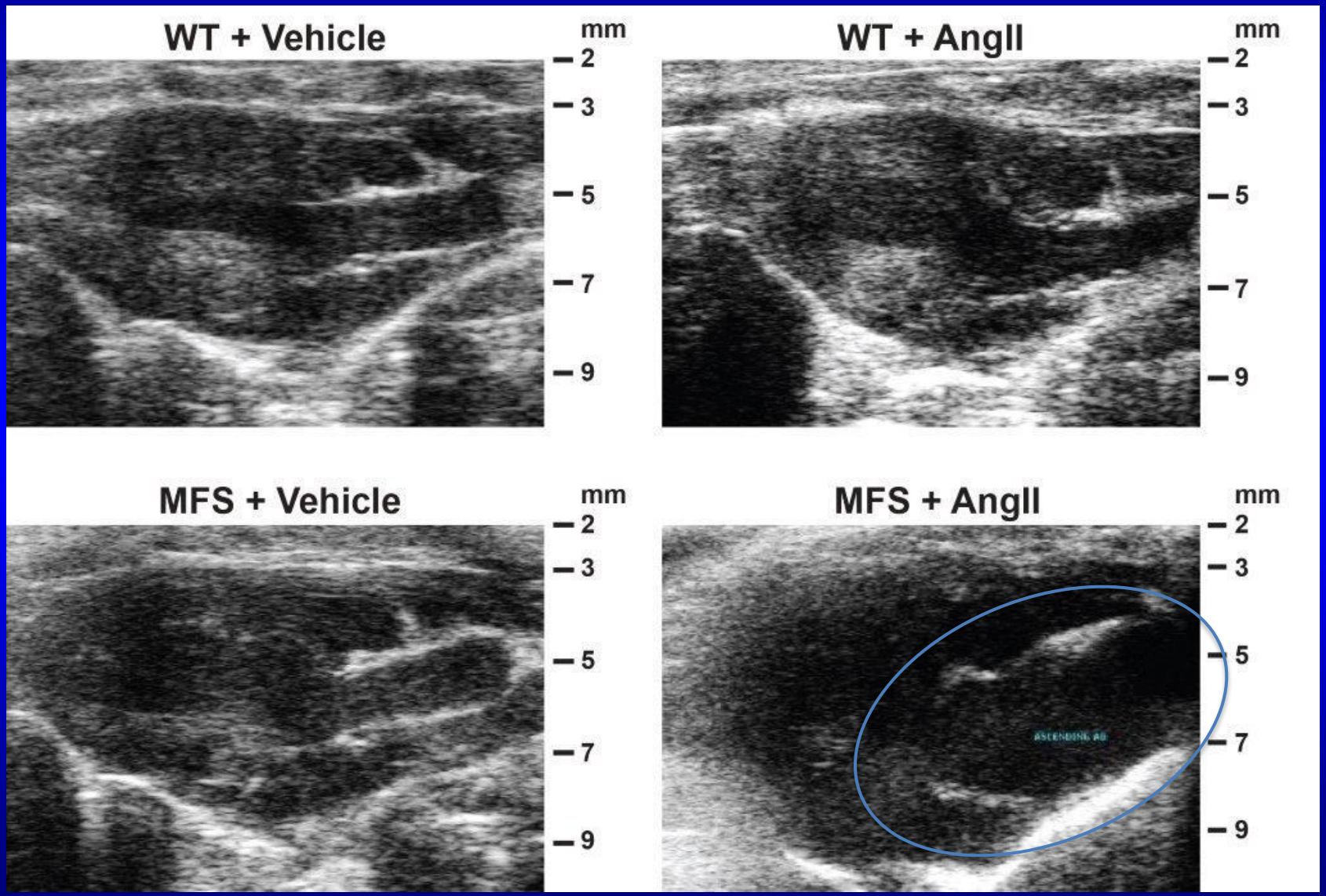
Current Limitations for Investigating Marfan Syndrome

- Previous murine models can take years to develop a mild aortopathy
- Cardiomyopathies are rare and inconsistent
- Losartan alone does not completely attenuate aortic aneurysm formation, suggesting a need for multi-modal treatment and alternate signaling pathways must be elucidated.

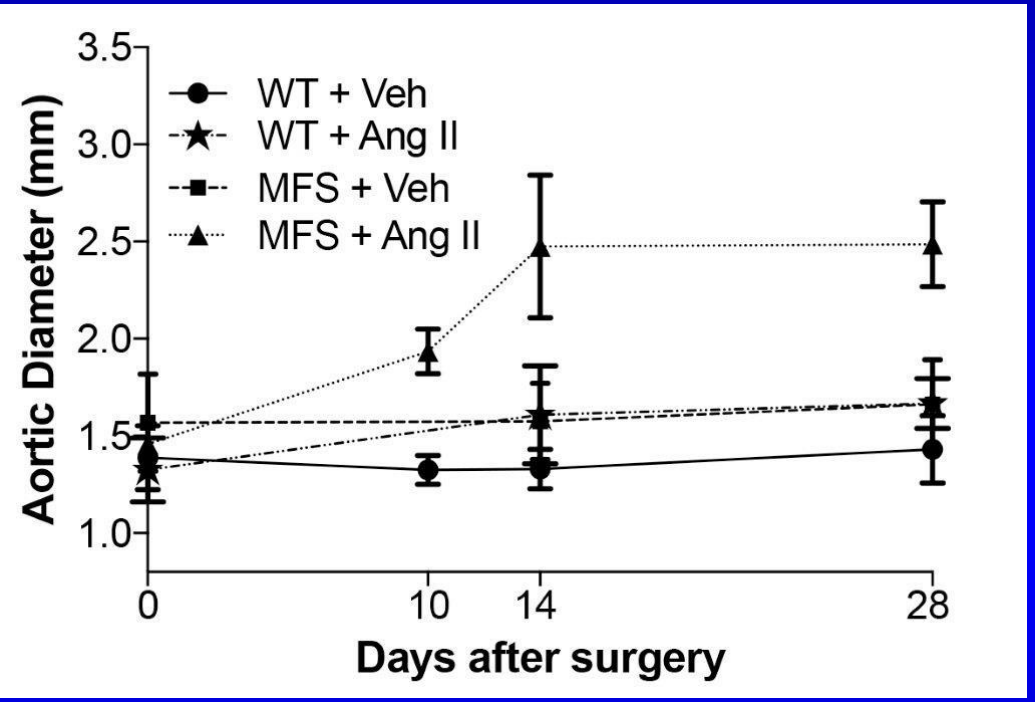
Development of Marfan Syndrome Murine Model

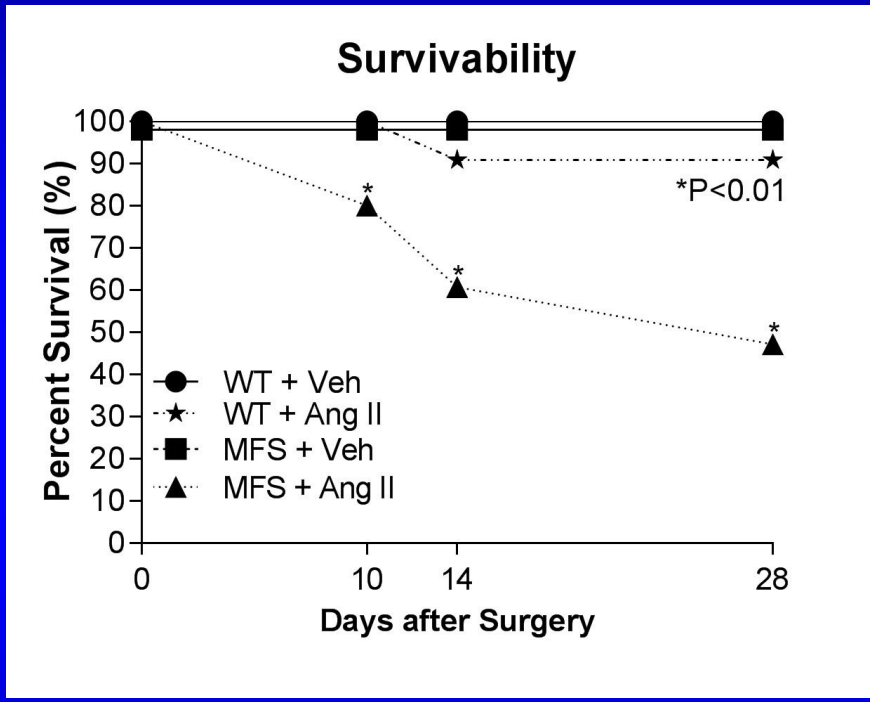
- B6.129 (Wild-type) and Fbn1C1039G/+ (MFS)
- Creation of an accelerated MFS-induced cardiomyopathy via subcutaneous osmotic mini-pump installation for 14 days in 3 treatment groups: Wild-type + 0.9% saline (vehicle); MFS + vehicle; MFS + angiotensin II (4.5mg/kg/day) (accelerated treatment group).
- Wild-type + Angiotensin II was insignificantly different from our vehicle.

Does the model really work…



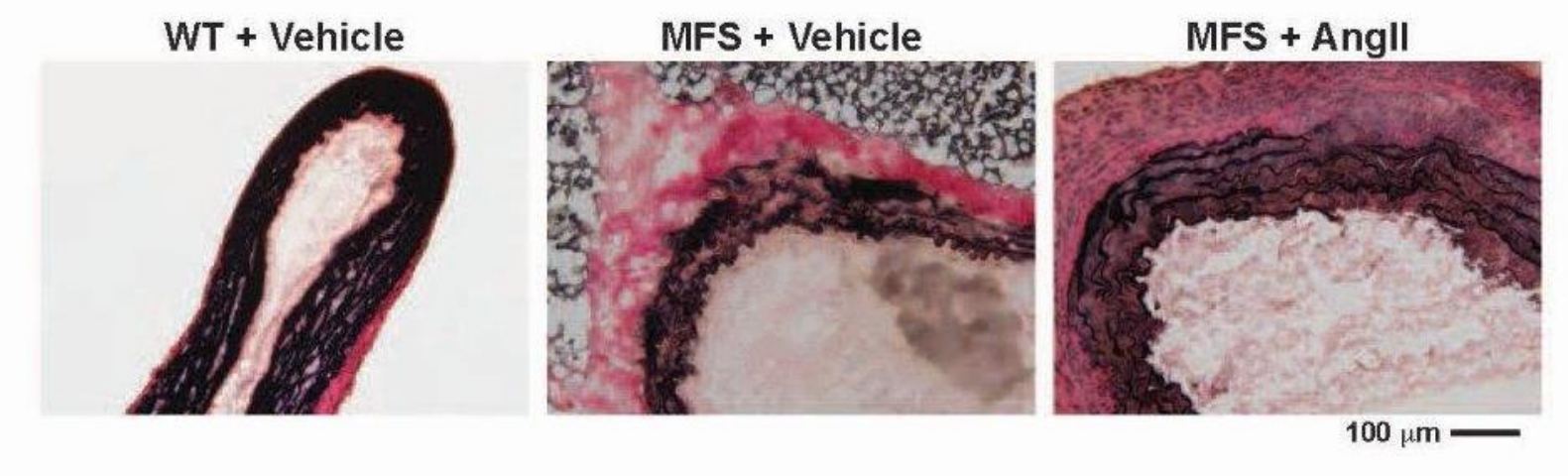
Accelerated MFS Model Phenotype

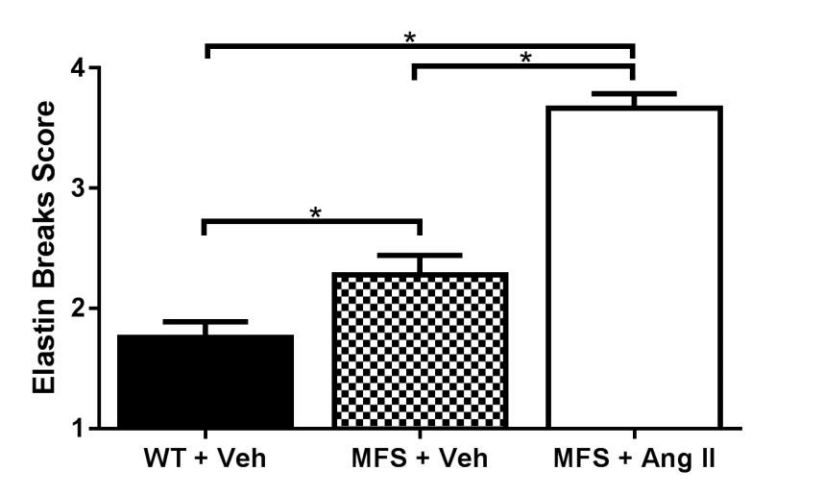




- Aortic diameter nearly doubles
- Over half of MFS + Ang II mice are deceased at 28 days

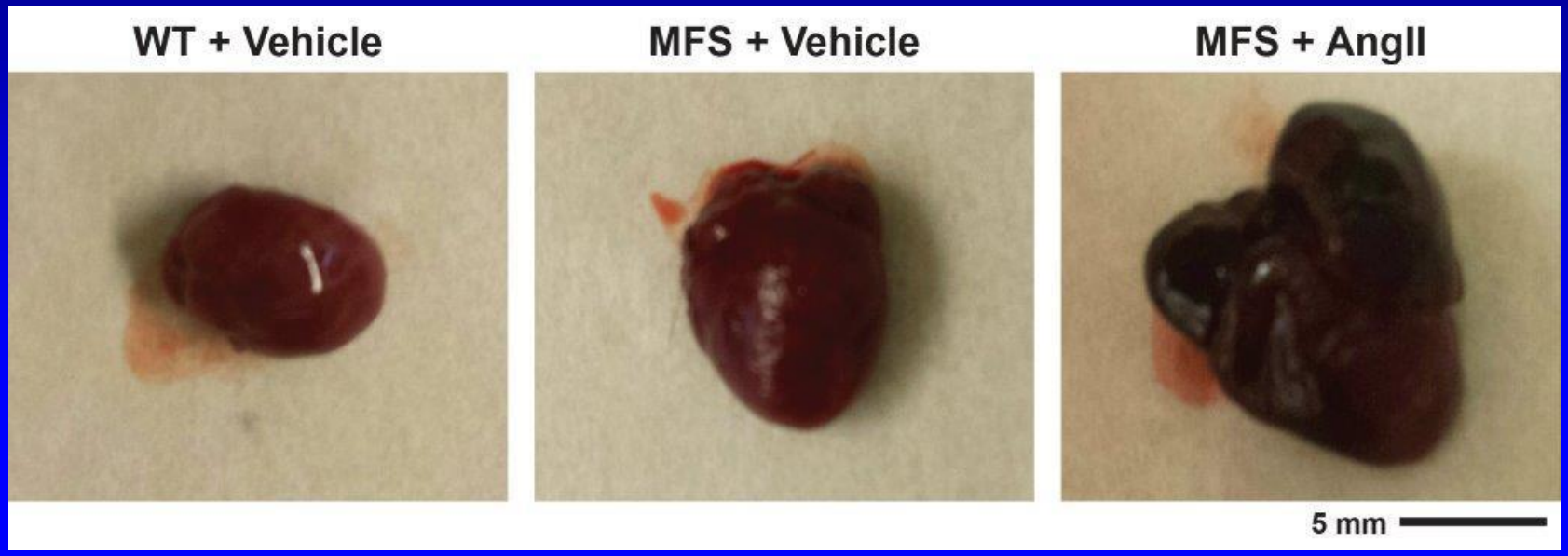
Aortic Verhoeff–Van Gieson stain

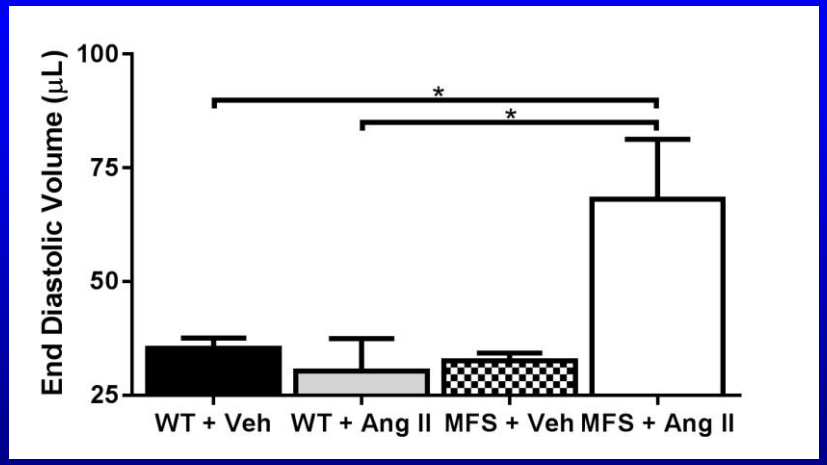


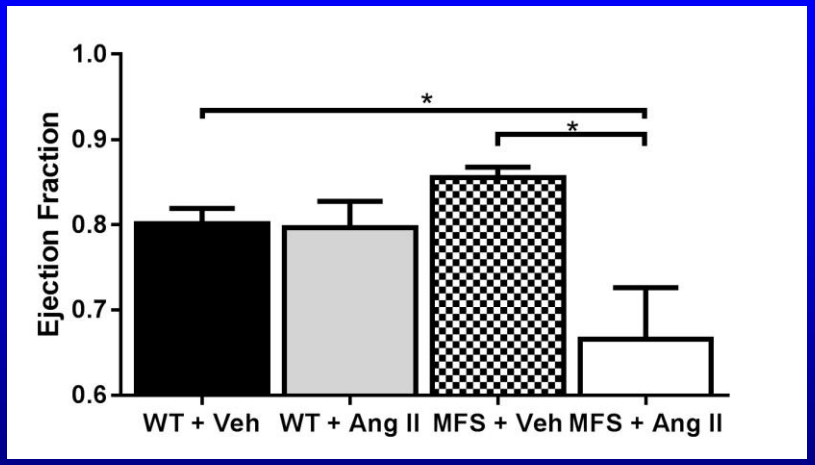


- Elastin (black) is blindly scored, ranking 1 (no breaks) to 4 (highly fractionated)
- Note increase in adventitia in MFS + Angiotensin II

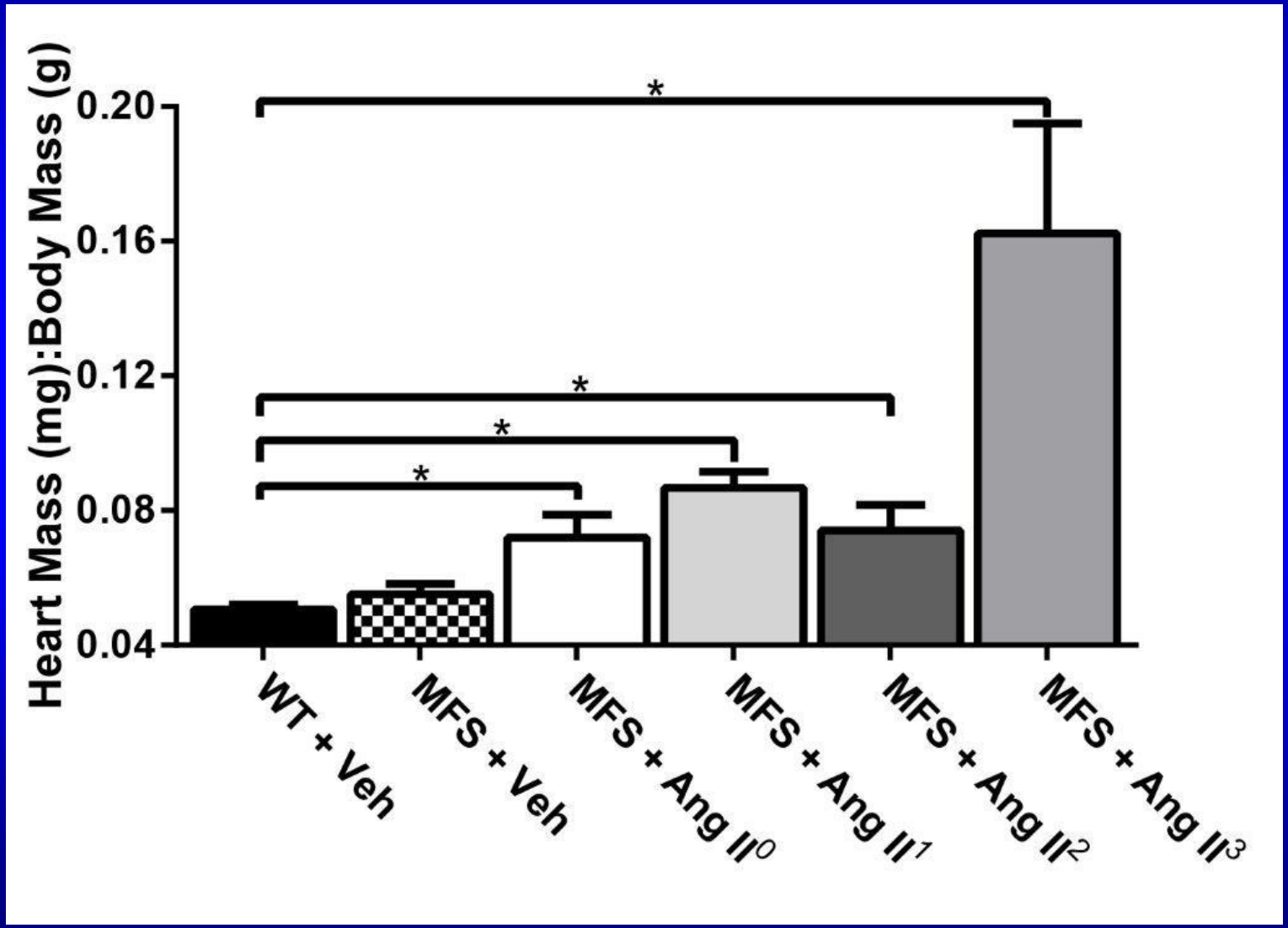
Presence of Cardiomyopathy







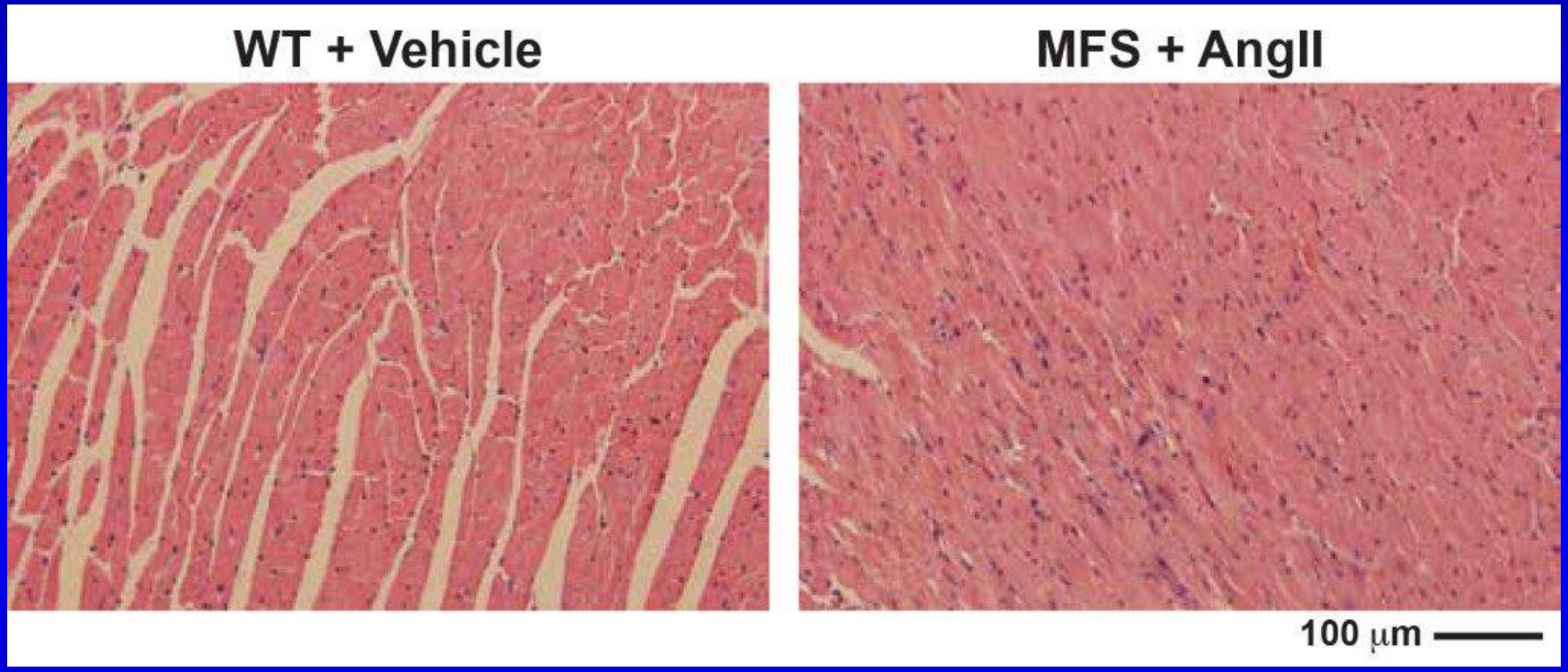
Cardiomyopathy with Respect to Aortic Insufficiency



Intrinsic Cardiomyopathy

- Ejection fraction <80% and an indexed left ventricular end diastolic volume >1.75 µl/g.
- No dilated cardiomyopathies in wild-type mice
- 60% of surviving accelerated MFS mice revealed dilated cardiomyopathies at 14 days.
- Just under half of the cardiomyopathic accelerated MFS mice occurred in the presence of either none or mild aortic insufficiency.

Cardiac Hematoxylin & Eosin Stain

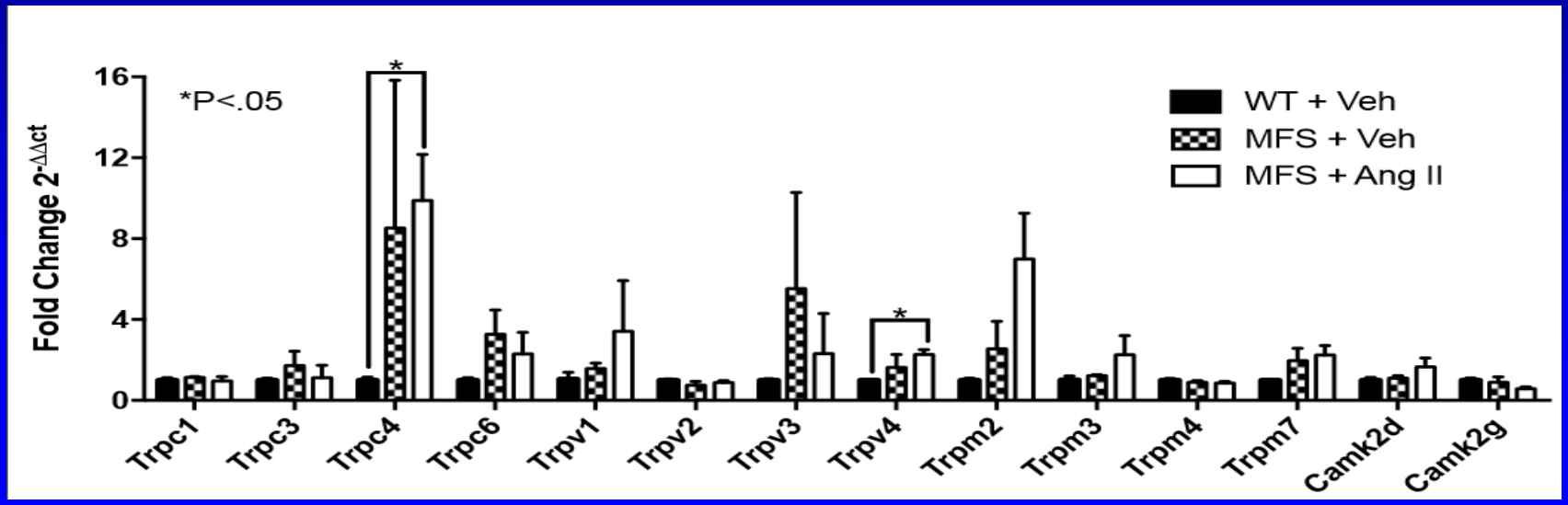


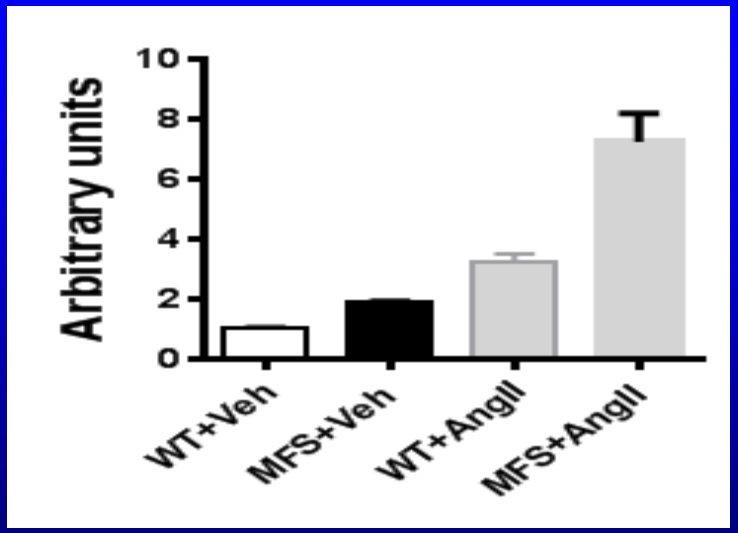
- Cross sectional stains are taken from left ventricle
- Vehicle cells are mononucleated, while MFS + Ang II are polynucleated and muscle fibers are distended

Relevance of Transient Receptor Potential Channels

- Members of the family of transient receptor potential channels (TRP) have emerged as likely regulators of VSMC activity.
- Additionally, newer research suggests TRP channels may regulate various forms of cardiomyopathy.

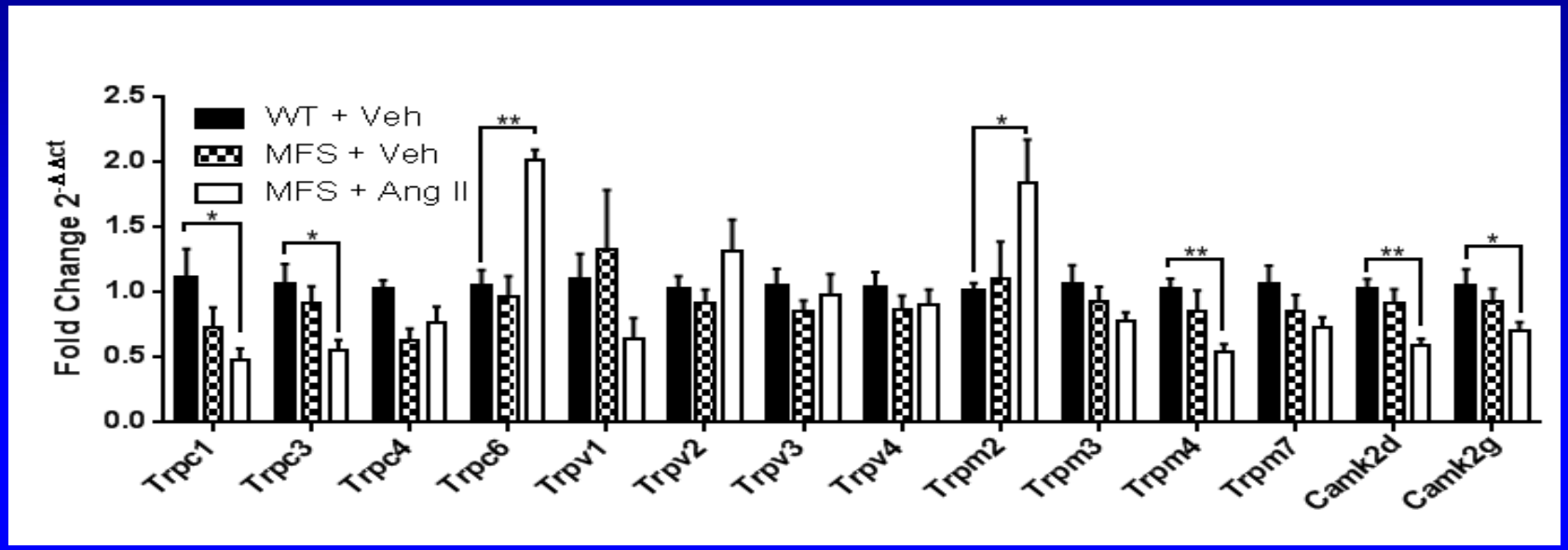
Aortic Expression in Murine MFS Model

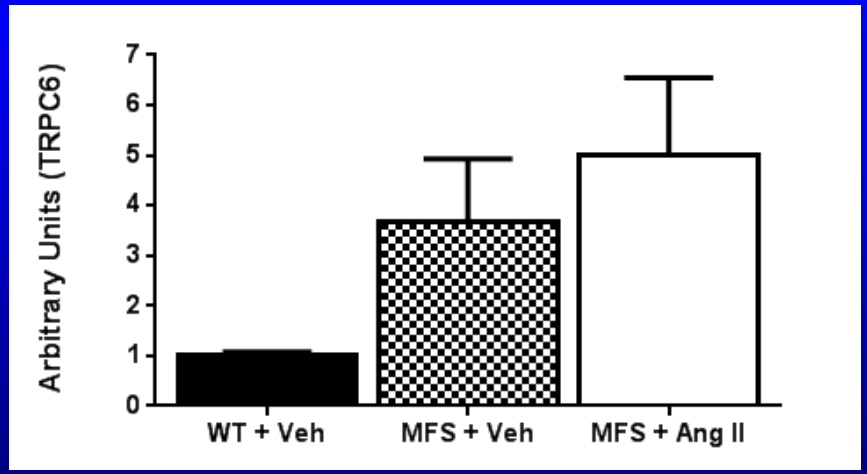




- TRPC4 demonstrated a 9.9 fold increase at DNA level
- TRPC4 demonstrated a 7.2 fold increase at protein level
- Aortic tissue is not of quality RNA Integrity to utilize in RNA-seq

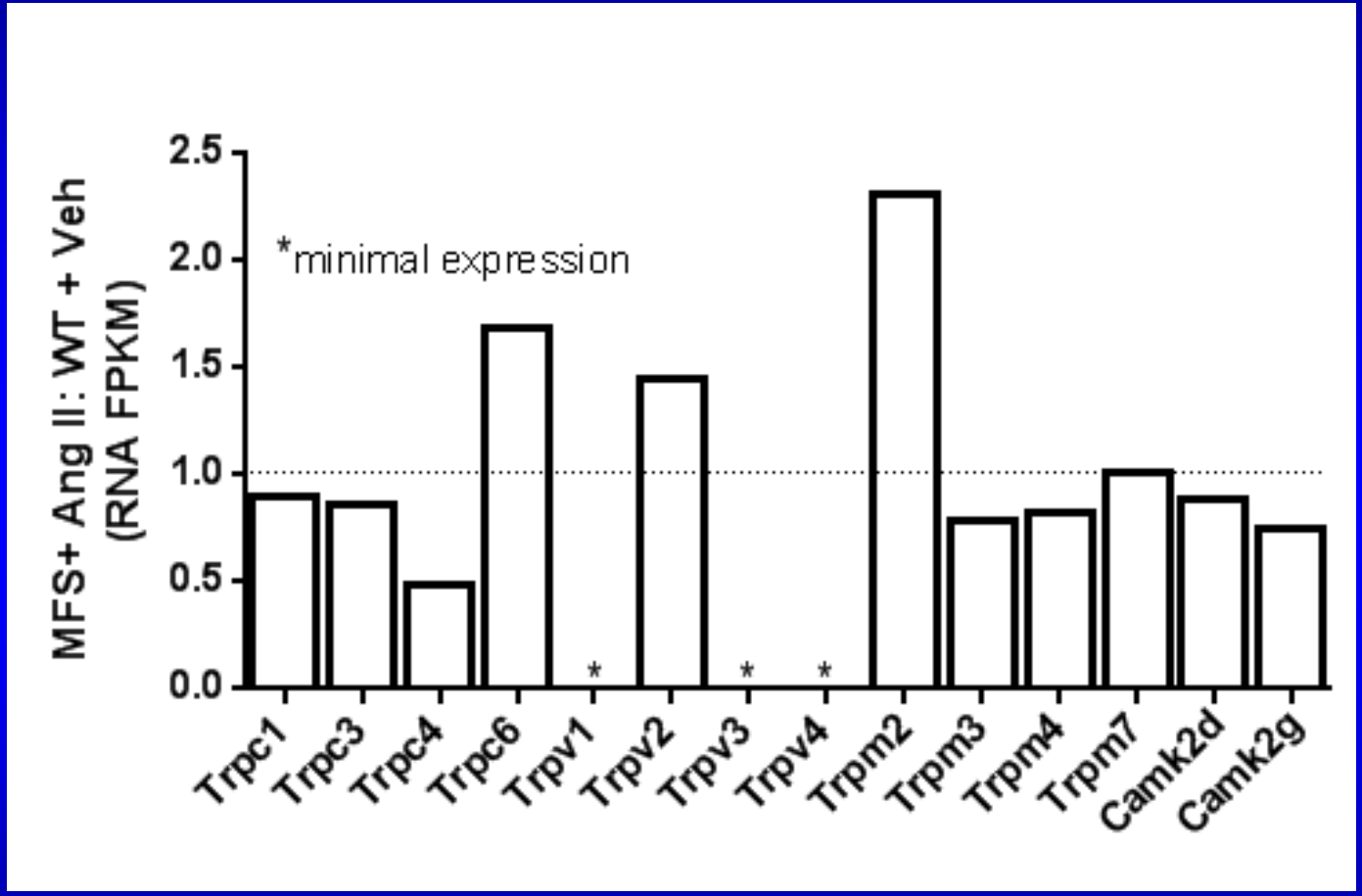
Cardiac Expression in Murine MFS Model





- TRPC6 demonstrated a 2-fold increase at the DNA level
- TRPC6 demonstrated a 5-fold increase at protein level

Cardiac RNA Expression in Murine MFS Model



- FPKM should be thought of as comparable to # of reads
- TRPC6 demonstrated a 1.7 fold increase at RNA level

Current Studies

- We are investigating multiple signaling cascades that delineate the role of TRPC4 in aneurysm formation and TRPC6 in a MFS-induced cardiomyopathy.

Questions?