Mitochondrial Dysfunction and Senescence in Age-Related Aortic Disease

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Background

- **What causes aortic disease?[1]**
  - Hypertension, smoking, adrenergic substance use, and genetic disease are known risk factors
  - Aging is perhaps the most common risk factor
- **Aging is driven by multiple established biologic hallmarks[2]**
  - Mitochondrial dysfunction and senescence are two well-known hallmarks
- **Genetic aortopathies seem to have an early-aging phenotype[3-4]**

1. LeMaire SA, Russell L. Epidemiology of thoracic aortic dissection. *Nat Rev Cardiol*. 2011;8(2):103-113. doi:10.1038/nrcardio.2010.187
2. López-Otín C, Blasco MA, Partridge L, Serrano M, Kroemer G. Hallmarks of aging: An expanding universe. *Cell*. 2023;186(2):243-278. doi:10.1016/j.cell.2022.11.001
3. You W, Hong Y, He H, Huang X, Tao W, Liang X, Zhang Y, Li X. TGF-β mediates aortic smooth muscle cell senescence in Marfan syndrome. Aging (Albany NY). 2019 May 30;11(11):3574-3584. doi: 10.18632/aging.101998. PMID: 31147528; PMCID: PMC6594817.
4. Balint B, Yin H, Nong Z, et al. Seno-destructive smooth muscle cells in the ascending aorta of patients with bicuspid aortic valve disease. *EBioMedicine*. 2019;43:54-66. doi:10.1016/j.ebiom.2019.04.060

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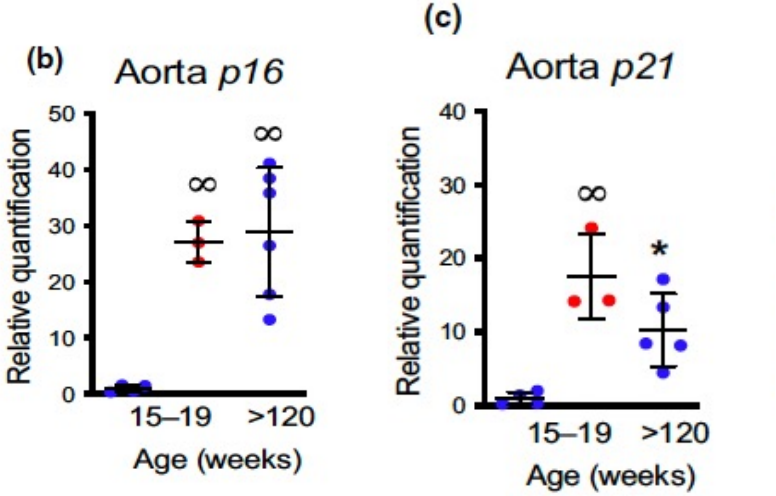
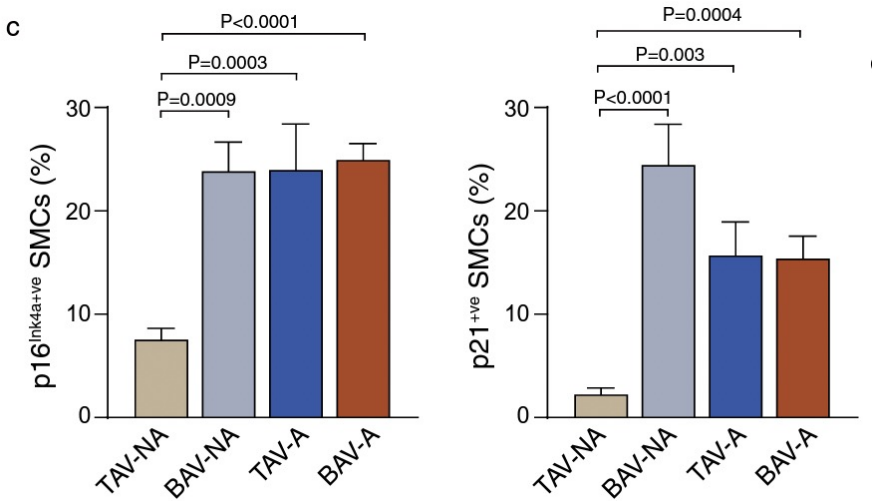
Aged and Diseased Aortas are Highly Senescent[4-5]



- p16 and p21 are known markers of senescence[4-5]
- This study revealed higher expression in aged wild-type mice (blue) and genetically progeroid mice (red)[5]

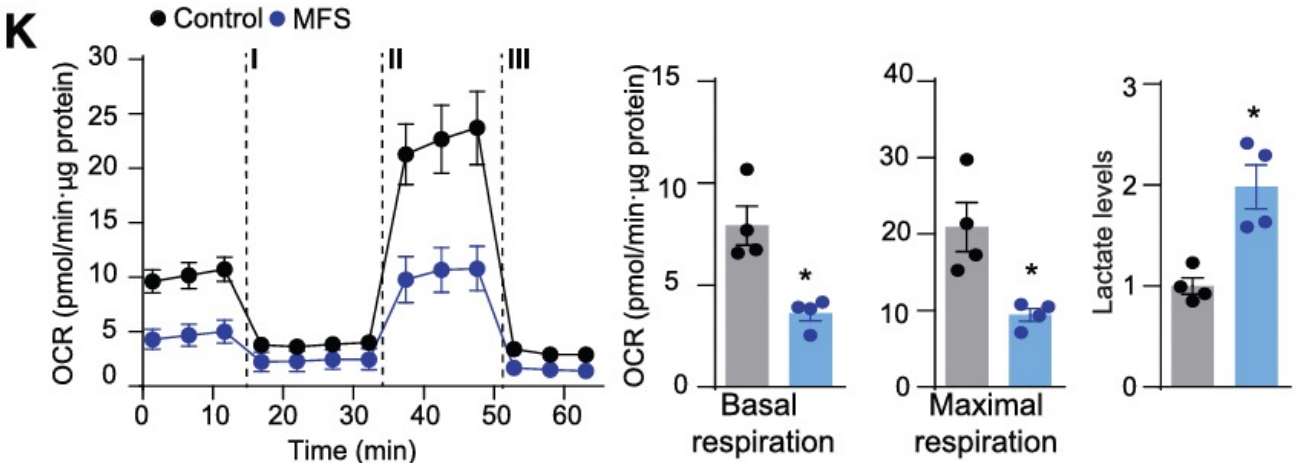


- This study looked at p16 and p21 expression in human tricuspid aortic valve (TAV) and bicuspid (BAV) aortas[4]
- Non-aneurysmal BAV aortas and all aneurysmal aortas have higher p16 and p21 levels
- NA = no aneurysm; A = aneurysm

5. Yousefzadeh MJ, Zhao J, Bukata C, et al. Tissue specificity of senescent cell accumulation during physiologic and accelerated aging of mice. *Aging Cell*. 2020;19(3):e13094. doi:10.1111/acel.13094

4. Balint B, Yin H, Nong Z, et al. Seno-destructive smooth muscle cells in the ascending aorta of patients with bicuspid aortic valve disease. *EBioMedicine*. 2019;43:54-66. doi:10.1016/j.ebiom.2019.04.060

Diseased Aortas have altered Mitochondrial Function[6]



- Aortas with Marfan Syndrome have decreased respiratory capacity
- OCR = oxygen consumption rate

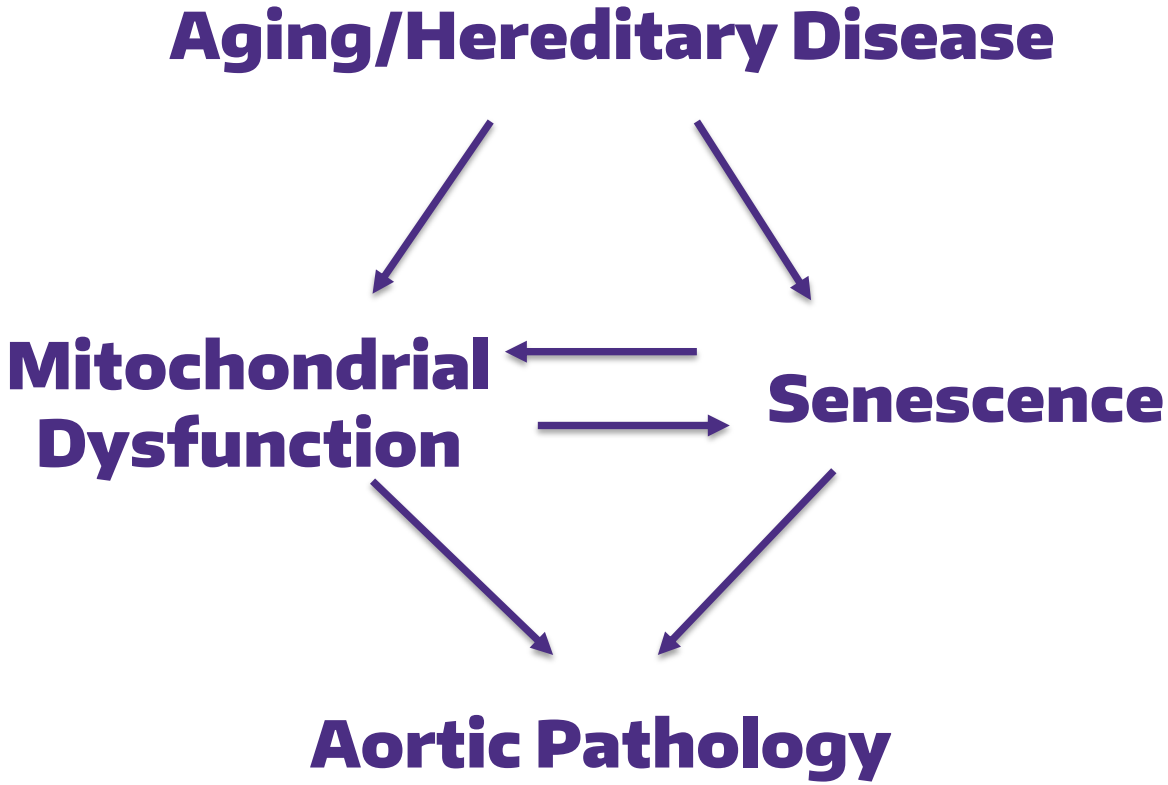
6. Oller J, Gabandé-Rodríguez E, Ruiz-Rodríguez MJ, Desdín-Micó G, Aranda JF, Rodrigues-Diez R, Ballesteros-Martínez C, Blanco EM, Roldan-Montero R, Acuña P, Forteza Gil A, Martín-López CE, Nistal JF, Lino Cardenas CL, Lindsay ME, Martín-Ventura JL, Briones AM, Redondo JM, Mittelbrunn M. Extracellular Tuning of Mitochondrial Respiration Leads to Aortic Aneurysm. Circulation. 2021 May 25;143(21):2091-2109. doi: 10.1161/CIRCULATIONAHA.120.051171. Epub 2021 Mar 12. PMID: 33709773; PMCID: PMC8140666.

Targeting mitochondrial function

- Mitochondrial-targeted peptides (MT) can improve age-related mitochondrial dysfunction
- This has been shown to treat age-related organ dysfunction in multiple tissues[7-10]
  - Heart, kidney, abdominal aorta
- Ameliorates senescence, as well[7-10]

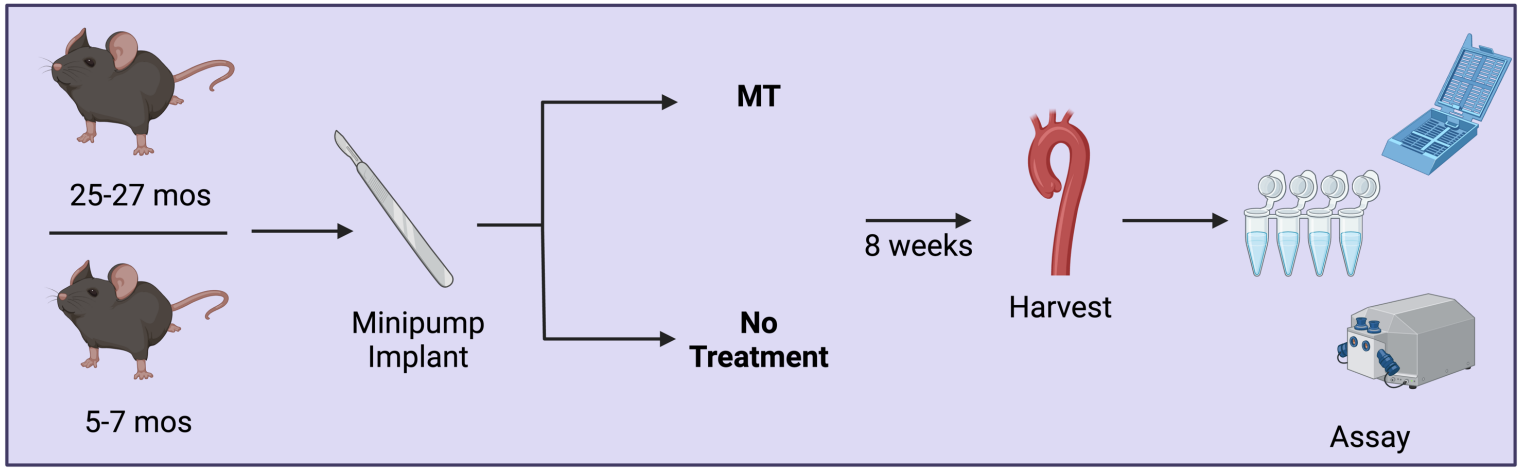
7. Chiao YA, Zhang H, Sweetwyne M, Whitson J, Ting YS, Basisty N, Pino LK, Quarles E, Nguyen NH, Campbell MD, Zhang T, Gaffrey MJ, Merrihew G, Wang L, Yue Y, Duan D, Granzier HL, Szeto HH, Qian WJ, Marcinek D, MacCoss MJ, Rabinovitch P. Late-life restoration of mitochondrial function reverses cardiac dysfunction in old mice. Elife. 2020 Jul 10;9:e55513. doi: 10.7554/eLife.55513. PMID: 32648542; PMCID: PMC7377906.
8. Whitson JA, Martín-Pérez M, Zhang T, Gaffrey MJ, Merrihew GE, Huang E, White CC, Kavanagh TJ, Qian WJ, Campbell MD, MacCoss MJ, Marcinek DJ, Villén J, Rabinovitch PS. Elamipretide (SS-31) treatment attenuates age-associated post-translational modifications of heart proteins. Geroscience. 2021 Oct;43(5):2395-2412. doi: 10.1007/s11357-021-00447-6. Epub 2021 Sep 4. PMID: 34480713; PMCID: PMC8599536.
9. Navas-Madroñal M, Almendra-Pegueros R, Puertas-Umbert L, et al. Targeting mitochondrial stress with Szeto-Schiller 31 prevents experimental abdominal aortic aneurysm: Crosstalk with endoplasmic reticulum stress. *Br J Pharmacol*. 2023;180(17):2230-2249. doi:10.1111/bph.16077
10. Sweetwyne MT, Pippin JW, Eng DG, Hudkins KL, Chiao YA, Campbell MD, Marcinek DJ, Alpers CE, Szeto HH, Rabinovitch PS, Shankland SJ. The mitochondrial-targeted peptide, SS-31, improves glomerular architecture in mice of advanced age. Kidney Int. 2017 May;91(5):1126-1145. doi: 10.1016/j.kint.2016.10.036. Epub 2017 Jan 4. PMID: 28063595; PMCID: PMC5392164.

Hypothesis


Aging/Hereditary Disease
Mitochondrial Dysfunction
Senescence
Aortic Pathology

Methods: Aim 1

Test the hypothesis that treatment with MT (mitochondrial targeted therapy) improves mitochondrial dysfunction, senescence, and structural changes in the aged mouse thoracic aorta (25-27 months old) compared to young controls (5-7 months old)



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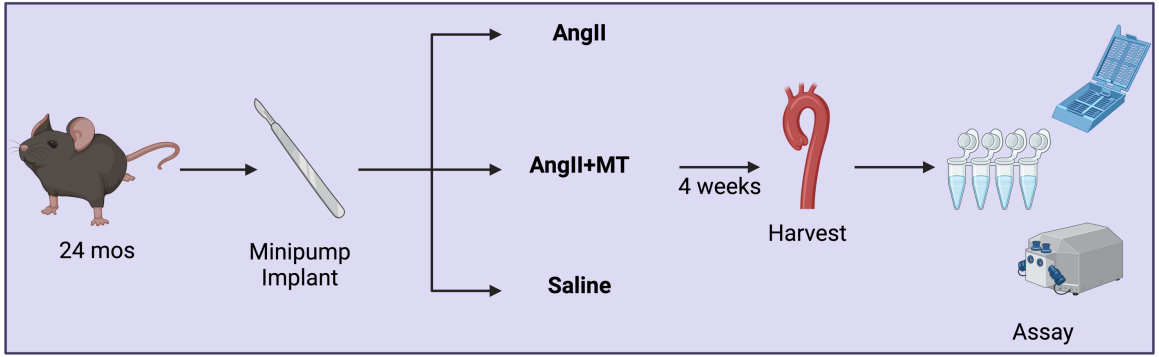
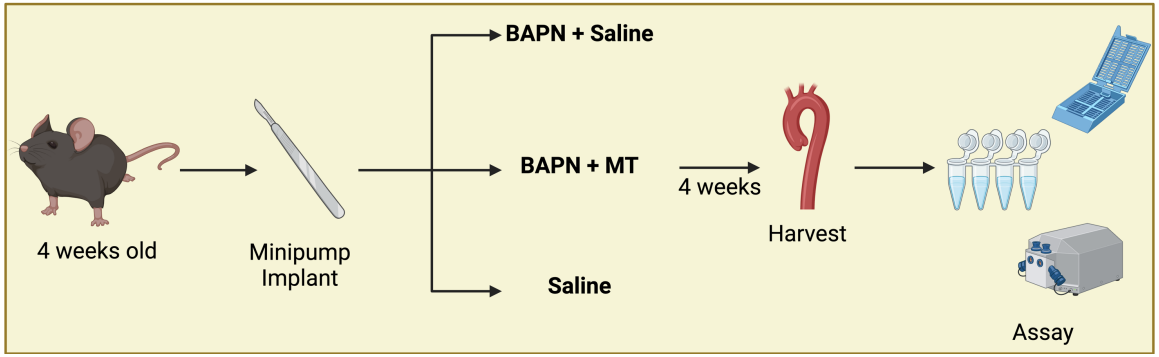
Methods: Aim 2

Test the hypothesis that treatment with MT improves mitochondrial dysfunction, senescence, and structural changes in the diseased mouse thoracic aorta.



AngII = Angiotensin II

Induces hypertensive aortic disease



BAPN = Beta-Aminoproprionitrile

Induces connective tissue disorder via lysyl oxidase inhibition

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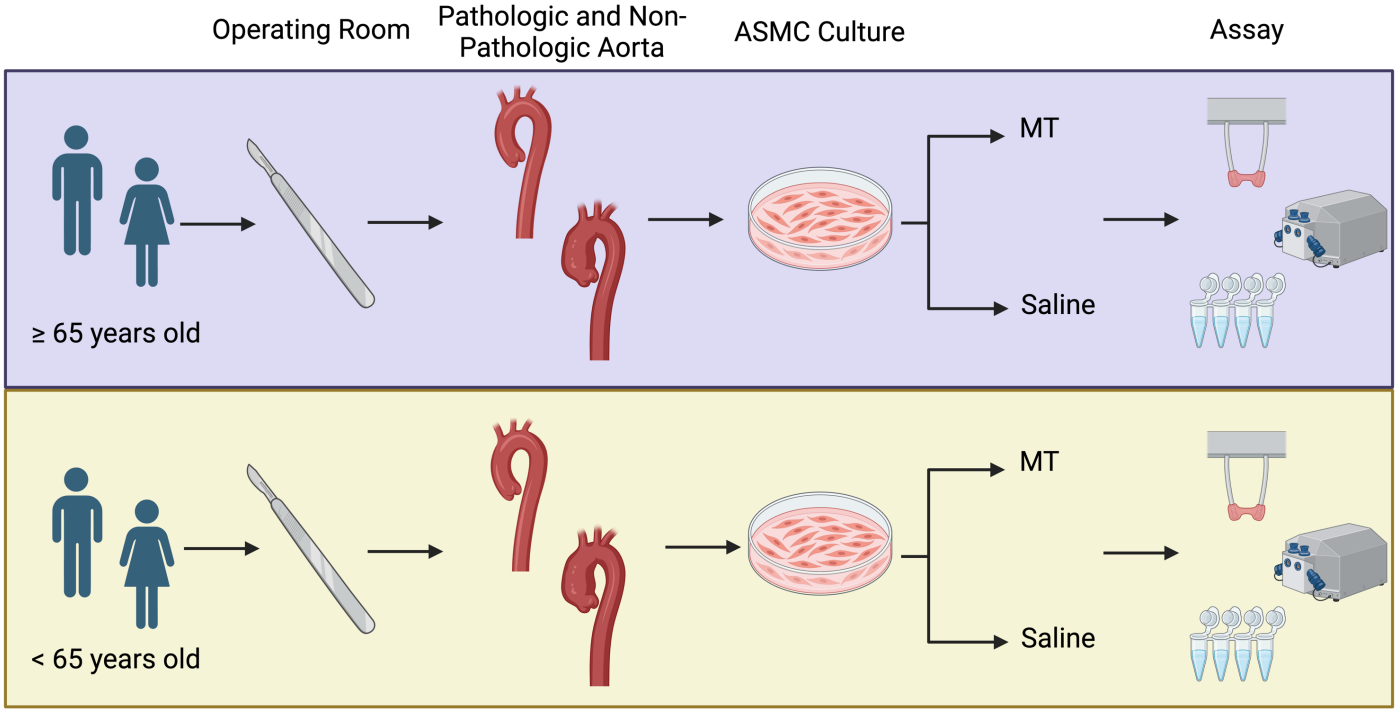
Methods: Aim 3

Test the hypothesis that treatment of primary human aortic smooth cell culture from both aged and pathologic aortas with MT reduces mitochondrial dysfunction, senescent cell burden, and a destructive extracellular matrix phenotype.



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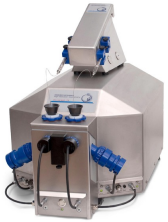
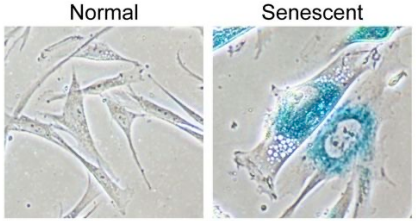
Methods: Assays

Mitochondrial Function



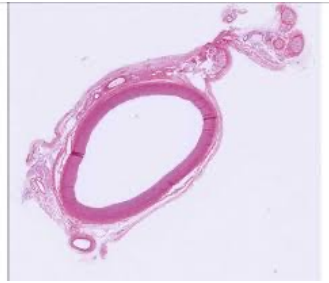
- Respiration
- Mitochondrial Content
- Redox State

Senescent Expression



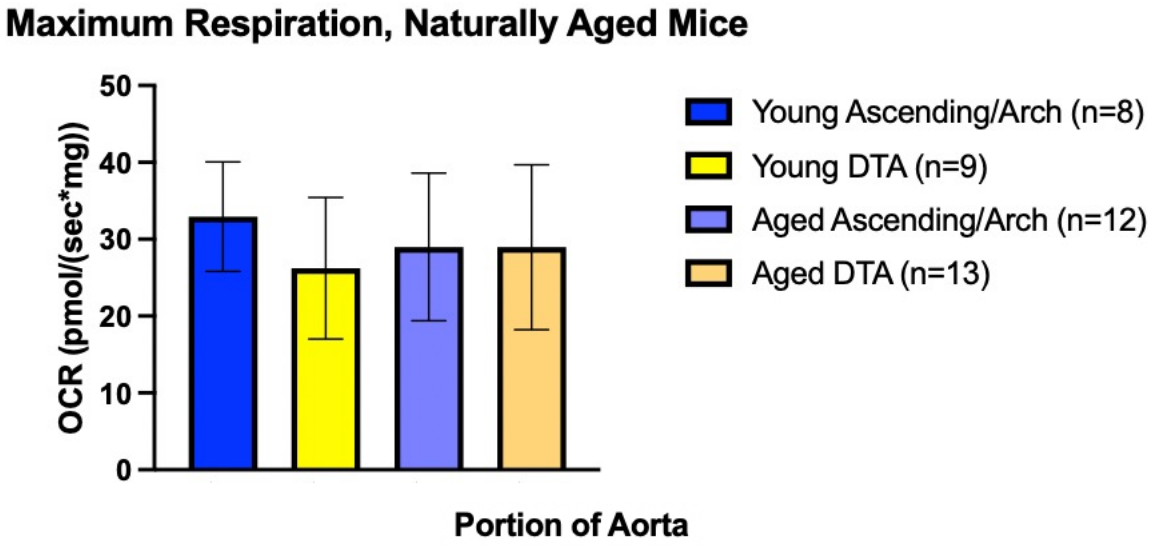
- SA-Bgal Staining
- p16, p21 expression
- SASP expression

Histology, Anatomy, Physiology



- Echocardiography
- Blood Pressure
- Aortic Compliance
- Gross Structure
- Media Thickness
- Elastin Breaks

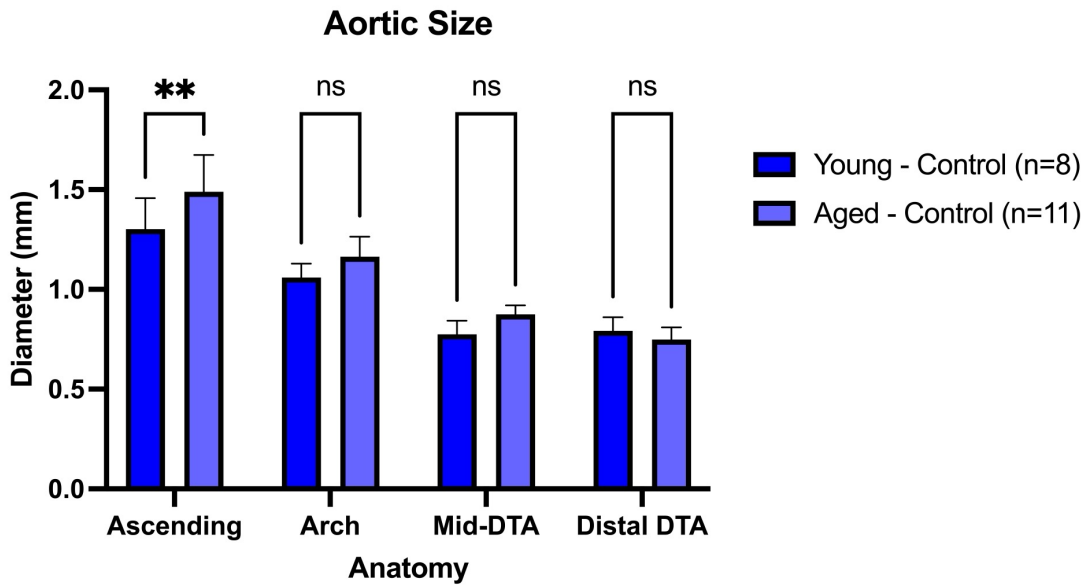
Aim 1 Results



No significant difference, but data still being collected

OCR = oxygen consumption rate

Aim 1 Results



Ascending significantly larger in the aged, non-treated group

Data is still being collected

Next Steps

- Data collection ongoing in all aims
- Potential therapeutic effects of MT will need to be assessed
- Aim 1 and Aim 2-AngII arms to be complete by July 2024

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