Role of Sympathetic Nervous System in Abdominal Aortic Aneurysm Pathogenesis

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Introduction

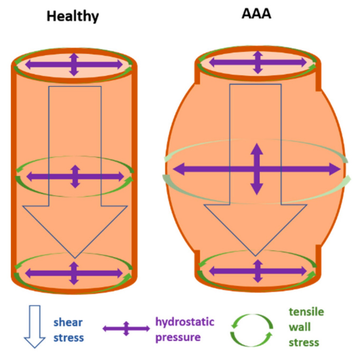
- Despite remarkable advancements in surgical technique, particularly in the endovascular space, no pharmacologic therapy has successfully slowed or halted abdominal aortic aneurysm (AAA) growth[1].
- Aortic vascular smooth muscle cells (VSMCs) are innervated by the abdominal aortic plexus and the aortic wall is subject to three principle hemodynamic forces: 1) wall shear stress, 2) hydrostatic pressure, and 3) relative wall strain[2].
- Biomechanical strain induce changes in VSMC phenotype, gene and protein expression, as well as apoptosis. [2] Aortic wall homeostasis is thus balanced, in part, by biomechanical forces derived from sympathetic nervous system (SNS) innervation and subsequent derangement may play a fundamental role in the aortic wall degeneration seen in AAA.

GOAL:

Investigate the relationship between SNS dysregulation and abdominal aortic wall morphology to further elucidate the mechanism of AAA pathogenesis and expansion.

HYPOTHESIS:

Dysfunction of sympathetic innervation to the abdominal aortic smooth muscle is an important factor to the onset of aortic dilatation and progression of aneurysmal disease.

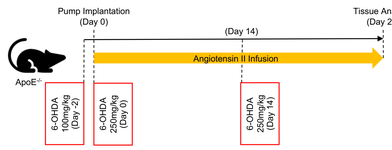


Methods

Animals: ApoE KO mice, male, age 12-weeks

Procedures:

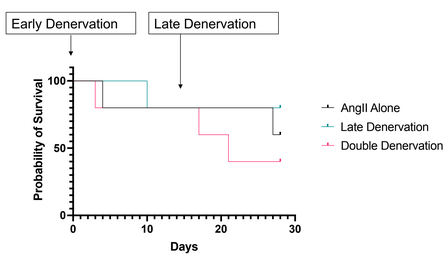
- Subcutaneous osmotic mini-pump implantation (ALZET Model 1004) for continuous Angiotensin II (**AngII**) infusion
- Intraperitoneal (IP) injection of 6-hydroxydopamine (**6-OHDA**) or buffer control



	Pump Implantation	Day -2 & 0 Denervation	Day 14 Denervation
Control Group	-	-	-
AngII Group	+	-	-
Late Denervation Group	+	-	+
Double Denervation Group	+	+	+

Results

Double denervation reduces survival in comparison to AngII and late denervation



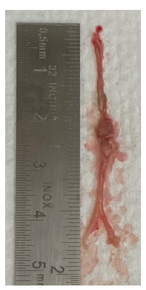


Figure 1: Kaplan-Meier curve of survival from aortic-related mortality across experimental timeline (28 days). Early denervation (Day -2, Day 0), and late denervation (Day 14) in relation to aortic related mortalities (left). Representative gross specimen of aorta harvested after model completion on day 28 (right).

Results

Systemic denervation, when paired with AngII infusion, induces greater max aortic diameter in surviving mice

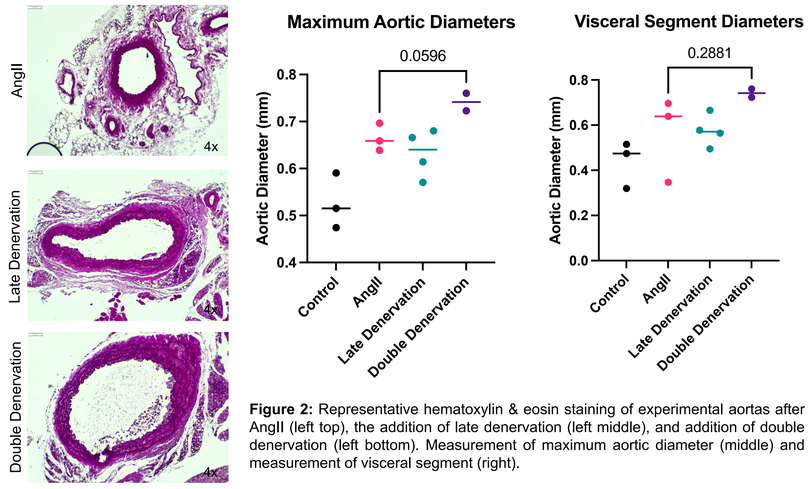


Figure 2: Representative hematoxylin & eosin staining of experimental aortas after AngII (left top), the addition of late denervation (left middle), and addition of double denervation (left bottom). Measurement of maximum aortic diameter (middle) and measurement of visceral segment (right).

Systemic 6-OHDA administration reduces sympathetic nerve fibers in AngII-treated aortas

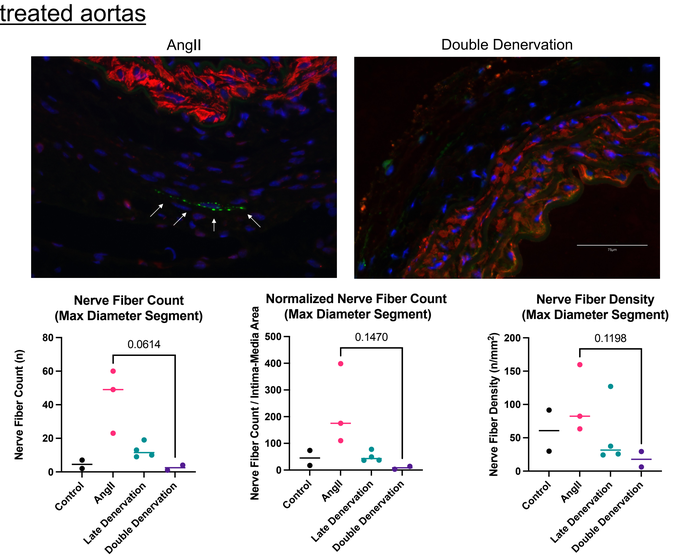


Figure 2: Representative immunohistochemical staining of aorta after AngII infusion (top left) and AngII infusion paired with double denervation (top right). Nerve fiber count of maximum diameter aortas (bottom left), nerve fiber count normalized to intima-media area (bottom middle), and nerve fiber density (bottom right).

Control aortas demonstrate low level of sympathetic nerve fibers in comparison to AngII-treated aortas

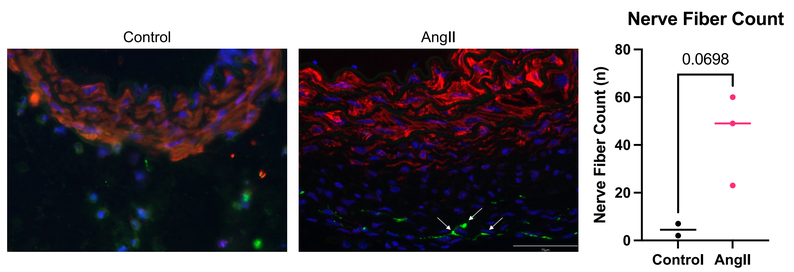


Figure 3: Representative immunohistochemical staining of control aorta (left) and experimental aorta after AngII infusion (middle) Red=alpha smooth muscle actin (αSMA); Blue=Hoechst; Green=tyrosine hydroxylate (TH). Nerve fiber count of maximum diameter aorta (right).

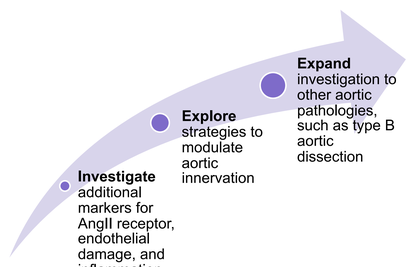
Conclusions

1. **Mortality:** Double denervation, when paired with AngII infusion, is associated with increased aortic-related mortality
2. **Aortic Diameter:** Double denervation, when paired with AngII infusion, is associated with greater aortic diameter in surviving mice
3. **Nerve Fiber Density:** Aortas from control ApoE$^{-/-}$ mice demonstrate low nerve fiber count with subsequent increase after AngII infusion
4. **Denervation:** Systemic denervation is achievable with IP 6-OHDA and double denervation confers sustained effects through aneurysm model timeline (28 days)

IMPACT:

Solidifying the connection between the SNS and AAA pathogenesis will provide a pivotal platform to to investigate future pharmacologic, cellular, and even surgical therapies for AAA. Modulation of aortic sympathetic innervation remains a promising strategy with potential for cardiovascular disease broadly.

Future Directions



Systemic sympathetic denervation can be achieved via IP injection of 6-OHDA, however there is evidence of neural regeneration at two weeks

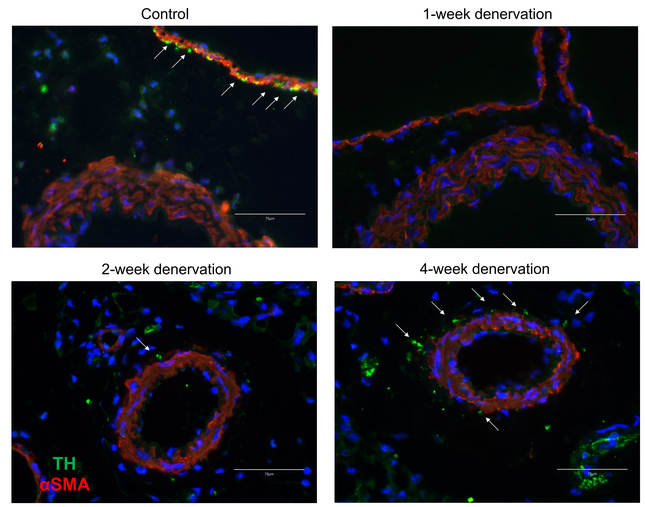


Figure 4: Representative immunohistochemical staining of aorta and vena cava after vehicle only (top left) and one week after 6-OHDA (top right). Representative immunohistochemical staining of mesenteric branch artery two weeks after 6-OHDA (bottom left) and four weeks after 6-OHDA (bottom right).

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