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Four Surgical Modifications to the Classic Elastase Perfusion Aneurysm Model Enable Haemodynamic Alterations and Extended Elastase Perfusion

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WHAT THIS PAPER ADDS

The elastase induced murine aneurysm model is considered the most advanced disease mimicking model for experimental *in vivo* abdominal aortic aneurysm research. In this detailed microsurgical study, the classical model is evolved through modifications based on surgical practice with alterations to the aortic outflow and by enabling elastase perfusion in additional segments to the classic infrarenal part of the aorta. This technical study will increase the translational value by enabling futures studies of embryologically different segments of the aorta, as well as varying aneurysm morphologies assessed through molecular biology and imaging modalities.

Objective/Background: Abdominal aortic aneurysm (AAA) is an individual and socioeconomic burden in today's ageing society. Treatment relies on surgical exclusion of the dilated aorta by open or endovascular repair. For research purposes, animal models are necessary and the elastase induced aneurysm model closely mimics end stage human aneurysm disease. To improve the translational value of this model, four modifications to the classic elastase perfusion procedure (PPE) in relation to human aneurysm morphology were conducted.

Methods: In ten week old male C57BL/6J wild type mice the PPE procedure was modified in four ways using two different techniques. Flow alteration was simulated by partial ligation of the common iliac artery or the distal aorta. Additionally, careful exploration of the abdominal aortic branches allowed PPE induction at the suprarenal and iliac level. Molecular biology, ultrasound, and immunohistochemistry were used to evaluate these pilot results.

Results: Two aortic outflow obstructions simulating distal aortic or iliac stenosis significantly increase murine AAA diameter ($p = .046$), and affect local vascular wall remodelling. Suprarenal aortic dissection allows a juxtarenal aneurysm to be induced, similar to the angiotensin II induced aneurysm model. A separate investigation for canonical activation of transforming growth factor β in the two embryonically distinct juxtarenal and infrarenal segments showed no distinct difference. Creating an aortoiliac bifurcated aneurysm completes the mimicry of human aneurysm morphology.

Conclusion: The alteration of the classic PPE aneurysm by outflow modulation and further elastase perfusion to the juxtarenal and aortoiliac segment modifies morphology and diameter, and thus increases the translational value in future research.

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INTRODUCTION

Abdominal aortic aneurysm (AAA) is a daily concern in vascular surgery, as successful treatment is exclusively achieved by open or endovascular repair. Its prevalence is 2–11% among male smokers, and rupture the major complication, is associated with unacceptably high morbidity and mortality rates.[1]

Studies on human aneurysm tissue resulted in a theory of transmural chronic inflammation with proteolytic imbalance and characteristic remodelling of the extracellular matrix, possibly based on activation of canonic transforming growth factor (TGF)-β signaling.[2,3] Activation of the innate immune system and the phenotype change of vascular smooth muscle cells represent compensatory vascular wall repair

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mechanisms.[4,5] However, this is observation based on tissue from end stage disease, yet lacking the final clue for the initial stimulus of aneurysm formation. Thus, clinical studies targeting such mechanisms have been unable to abrogate the natural course of disease, prevent rupture, or alter aneurysm growth.[6–8]

Therefore, mouse models of AAA are necessary for mechanistic insights, as well as growth simulation. For translational research purposes, the porcine pancreatic elastase (PPE) perfusion model is widely used, applying short-term luminal perfusion to the infrarenal aorta, resulting in aortic wall thickening and a diameter increase to approximately 170% after 8 weeks (Fig. 1A and B).[9] Vessel wall morphology, cytokine expression, and signaling mechanisms have been very well characterised, revealing a time dependent pathogenesis with acute to chronic inflammation, and distinct vascular wall remodelling (Fig. 1A).[10–12] Many of these features become prominent in the later stages of the PPE model and are characteristic of end stage human aneurysm disease (Fig. 1B).[2,5,13] However, the fusiform shape, restricted to the infrarenal aorta, only partly mimics human aneurysm morphology, and studying the influence of haemodynamics, such as aortic outflow, is currently not possible.[14–16]

In this study, the aim was to improve the current shortcomings of the classic PPE model by microsurgical modifications enabling aortic and iliac flow modulation and elastase perfusion of segments other than the infrarenal aorta in order to mimic different human aneurysm morphologies for translational research.

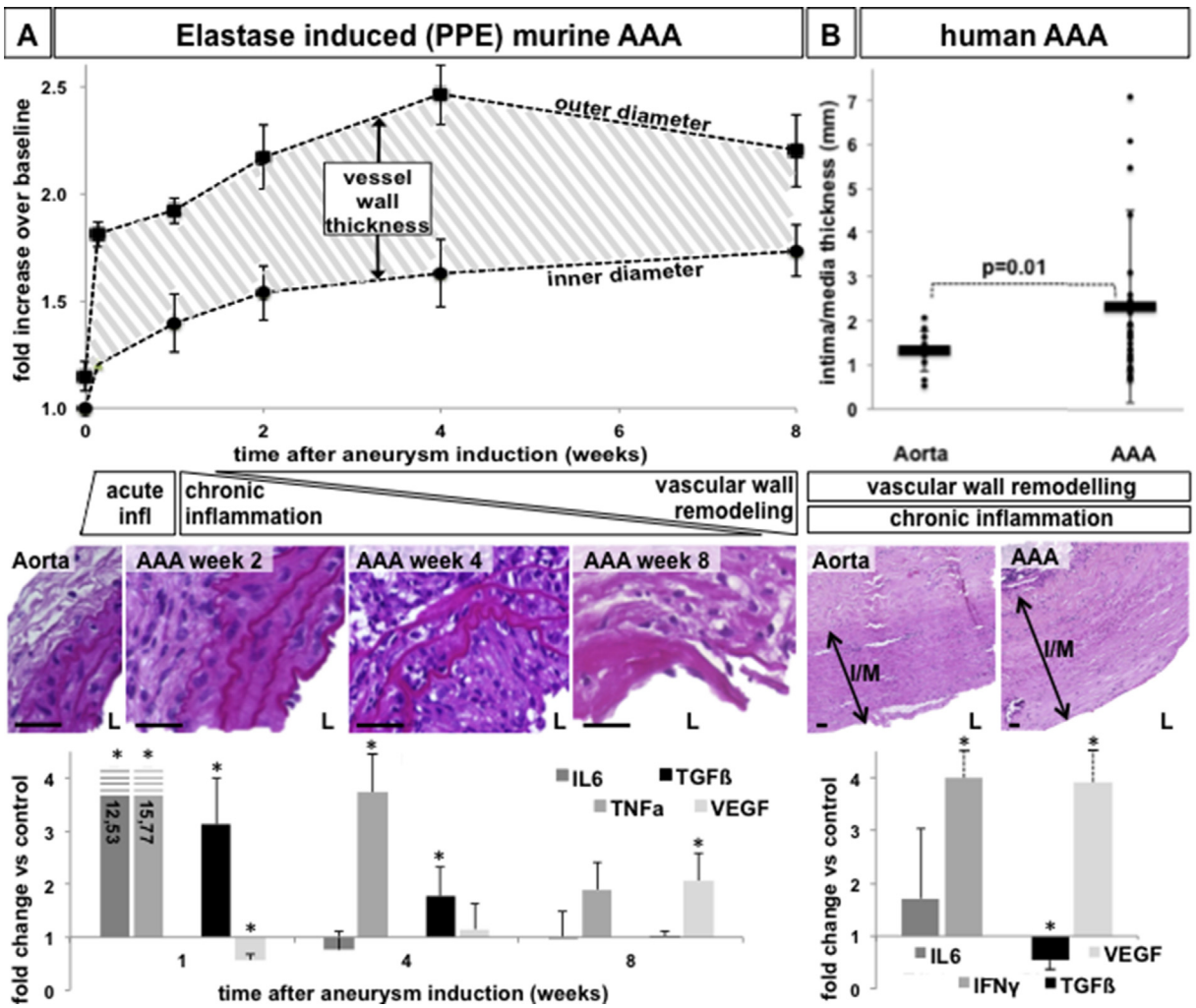

Figure 1. Comparison of murine porcine pancreatic elastase (PPE) aneurysm and human abdominal aortic aneurysm (AAA). (A) The murine aortic wall (0.1 mm thick, inner/outer diameter: 0.59 ± 0.03 mm/0.68 ± 0.07 mm) quickly thickens after elastase application, owing to an acute inflammatory reaction. The lumen (L) dilates to approximately 170% after 8 weeks. Increased inflammatory cellularity vanishes and chronic vessel wall remodelling, i.e. angiogenesis and tissue fibrosis, becomes more prominent. Accordingly, inflammatory markers and transforming growth factor (TGF)-β are downregulated and vascular endothelial growth factor (VEGF) is upregulated. (B) Human AAA samples show chronic inflammation and vascular remodelling at the histological and mRNA level. Compared with non-aneurysmal control aorta, the intima/media (I/M) thickness doubles (1.32 ± 0.4 6 mm vs. 2.32 ± 2.18 mm; $p = .01$).[2] *Note.* Scale bar 50 µm; magnification ×200/×100 for murine/human; $n = 5–6$ mice for each time point for histology/polymerase chain reaction (PCR); diameter measured by ultrasound ($n = 22$ mice; mean ± SD); $n = 13$ non-aneurysmal aortas, $n = 21$ human AAA for PCR, and $n = 43$ AAA for histological analysis; mRNA expression shown as fold change vs. non-aneurysmal control aorta. IL = interleukin; IFN = interferon. *Significant p value $< .05$.

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