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Response to Letters Regarding Article, “Segmental Aortic Stiffening Contributes to Experimental Abdominal Aortic Aneurysm Development”

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We thank Dr. Han and colleagues as well as Dr. Murakami and colleagues for their interest in our study¹ and for discussing our proposed pathomechanism of segmental aortic stiffness (SAS) in the context of experimental and clinical aortic coarctation.

We read with great interest the report of an alternative rabbit model that combines external elastase application with proximal aortic coarctation to model accelerated abdominal aortic aneurysm (AAA) development². Although post-stenotic turbulent flow caused by experimental aortic constriction may critically contribute to aortic dilation in this model, aortic coarctation also results in segmental aortic stiffness and may therefore generate substantial axial wall stress during systolic aortic expansion that we believe is a critical driver of early AAA development.

In our study mild aortic infusion of porcine pancreatic elastase (PPE; 1.5 U/mL for 5 minutes) was sufficient to induce initial elastin damage and aortic stiffening that eventually resulted in pervasive elastin fragmentation after 14 days. As PPE is biologically active for no more than 24 hours after perfusion³, we believe that the mechanisms leading to severe aneurysmal elastin destruction and wall remodeling are not directly due to the (artificial) PPE injury and may therefore be relevant in the human disease context.

We observed fibrotic stiffening of the aneurysm-adjacent aorta at day 14 after PPE induction (represented by Figure 2D in the manuscript) leading to subsequent reduction of aneurysm growth rate. However, even though aneurysm growth was contained through this “healing mechanism”, we did not find a subsequent regeneration of elastin lamellae.

We agree on the complex role of matrix metalloproteinases (MMPs) in ECM remodeling, although experimental studies suggest a deleterious net effect of MMP2 and MMP9 in the context of AAA^{3, 4}.

We thank Dr. Murakami and colleagues for highlighting aortic root expansion in patients with (repaired) aortic constriction as a phenomenon that may be mechanistically due to segmental aortic stiffness resulting pulse wave reflection⁵. Although we did not test the impact of SAS on pulse wave reflection in our experimental model, we believe it is entirely possible that pulse pressure augmentations proximal of the stiff segment may enhance wall stress at the interface between the stiff and compliant vessel segments and therefore promote aneurysmal remodeling.

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