Ex vivo magnetic particle imaging of vascular inflammation in abdominal aortic aneurysm in a murine model

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Background

- An **abdominal aortic aneurysm** (AAA) is a weakening and dilatation of the abdominal aorta.
- AAAs are currently one of the leading causes of death in developed countries.
- Chronic **inflammation** is fundamental for the development of AAA.
  It is characterized by the infiltration of inflammatory cell types, mainly macrophages and monocytes in the thrombus and throughout all layers of the aortic wall, leading to vascular smooth muscle cell apoptosis and degradation of the aortic tunica media.
- **Magnetic particle imaging (MPI)** is an innovative imaging modality, enabling the highly sensitive detection of magnetic nanoparticles **(MNP**s), suitable as surrogate marker for molecular targeting of vascular infammation.
- We assessed the potential of sensitive *ex vivo MP* imaging for the characterization of relevant parameters in AAA development and progression.

Methods

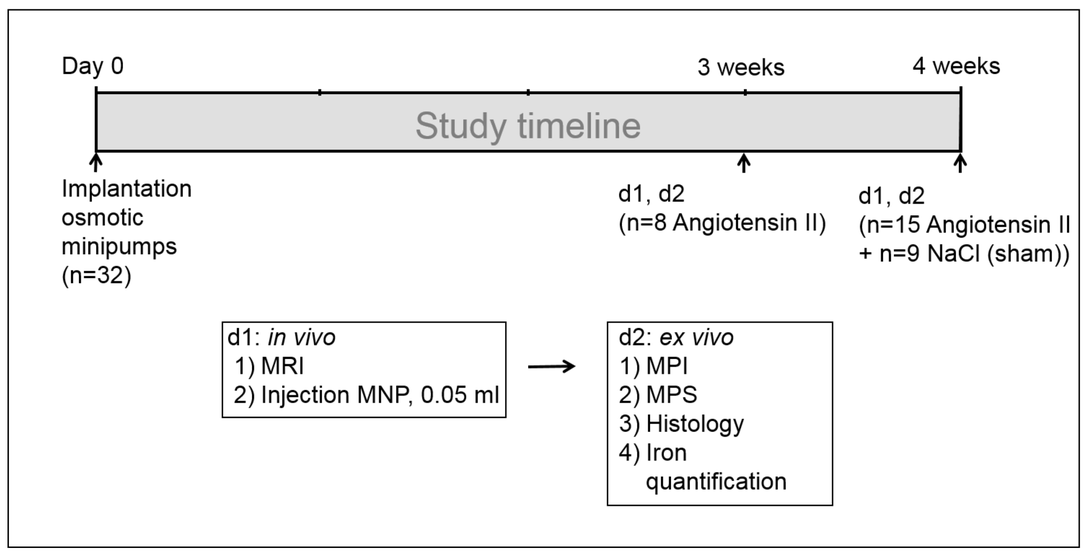

Figure 1: Experimental setup of animal experiments

Osmotic minipumps were implanted subcutaneously in the dorsal neck area. Angiotensin II was continuously infused with a rate of 1,000 ng/kg/min for 3 weeks (group 1, n = 8) or 4 weeks (group 2, n = 15), respectively. Sham-operated ApoE−/− mice (n=9) delivered saline over 4 weeks serving as the control group.
In order to verify the development of AAA, native *in vivo* **MR imaging** was performed afer 3 weeks (group 1) or 4 weeks (group 2 and control group), followed by i.v. injection of **ferucarbotran** to the tail vein (50 µl ferucarbotran). 24 h later, animals were sacrifced and the abdominal part of the aorta was harvested for *ex vivo* analysis.
For correlation of *in vivo* and *ex vivo* data, *ex vivo* **MPI**, magnetic particle spectroscopy (**MPS**), histological staining with **Perls' Prussian blue** to visualize the iron ions and **Miller's Elastica van Gieson** stain (EvG) to visualize the elastic fibers were performed. Hematoxylin and Eosin (HE) staining were additionally performed. The spatial distribution of MNPs within the aneurysmal wall was visualized using **Laser Ablation Inductively Coupled Plasma Mass Spectrometry** (LA-ICP-MS). Immunofluorescence **CD68 staining** was performed for evaluation of localization and density of macrophages.

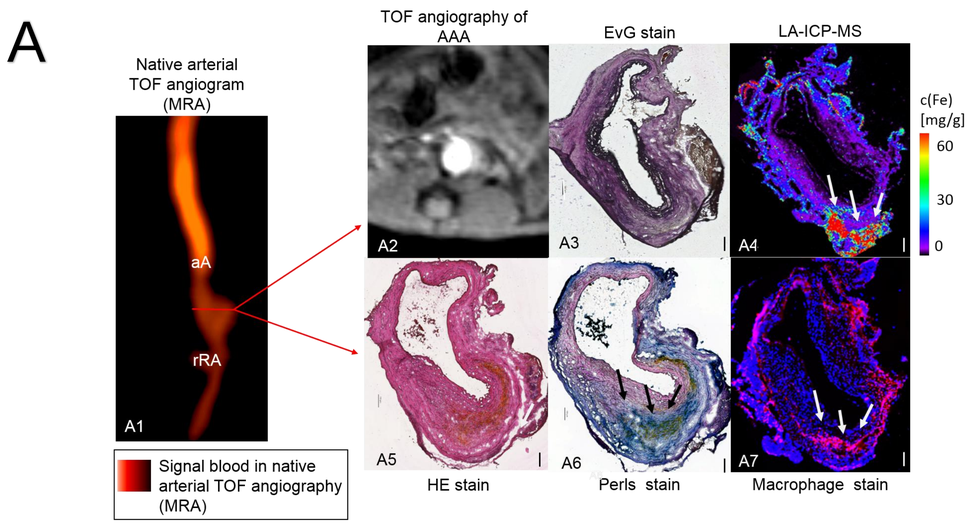

Figure 2: *In vivo* MRI and *ex vivo* analysis of inflammatory-activity during the development of AAA

Results

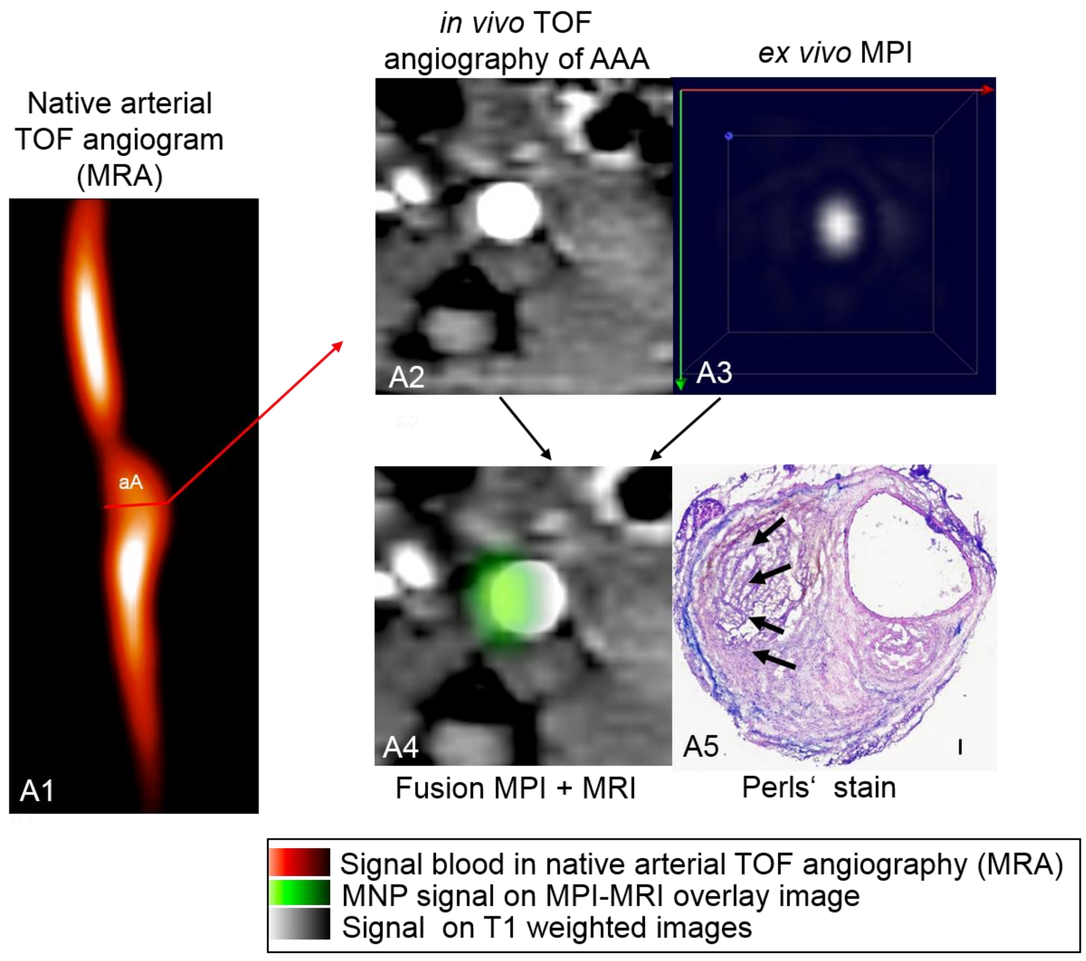

Figure 3*: In vivo* MRI and *ex vivo* MPI of inflammatory activity during the development of AAA

In the control group, consisting of sham-operated mice (n=9) that received a continuous saline infusion for 4 weeks, AAA development was not observed. In the experimental group (n=23), the continuous infusion of angiotensin II (Ang II) via osmotic minipumps led to **the formation of suprarenal aortic aneurysms.**
MR-angiography enabled the visualization of **aneurysmal development** and dilatation in the experimental group. A close correlation (R= 0.87) with histological area assessment was measured. No side effects or adverse reactions to the imaging agent were observed in the investigated animals.
Ex vivo MPS revealed **abundant iron deposits in AAA** samples and *ex vivo* histopathology measurements were in good agreement (R= 0.76). *Ex vivo* MPI and MPS results correlated greatly (R= 0.99). CD68 immunohistology stain and Perls' Prussian Blue stain confrmed the **colocalization of macrophages and MNPs.**

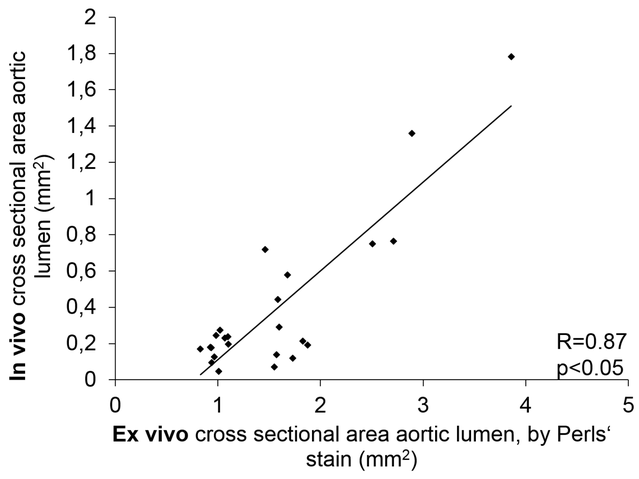

Figure 4: Correlation of *in vivo* MRI and *ex vivo* histological cross sectional AAA area measurements

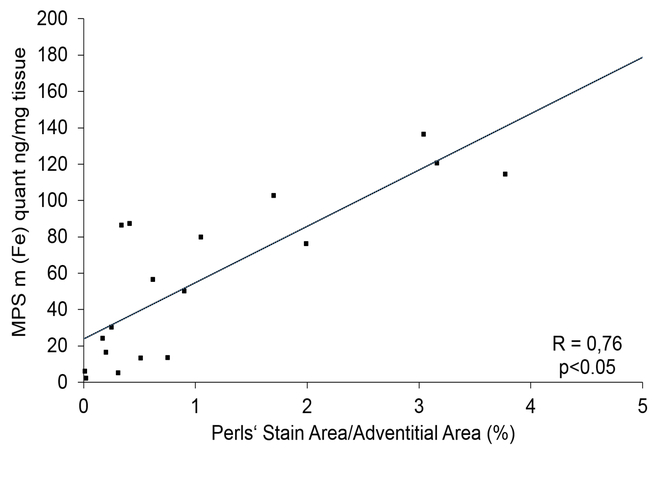

Figure 5: Correlation of MPS iron oxide particle measurements and Perls' Prussian Blue stained histological measurements

Conclusions

To our knowledge, this is the first study that demonstrates the potential of a combined *in vivo MR—ex vivo* MP imaging for the assessment of inflammatory activity in the aneurysmal wall of an Ang II-infused ApoE −/− mouse model using the MNP ferucarbotran. Future research could examine the feasibility of a combined MR-MP imaging in order to improve the *in vivo* characterization of AAAs.

References

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