Measurement of morphological and functional changes of the vessel wall during the progression of atherosclerosis in the ApoE-/- mouse model by MR-Microscopy at 17.6T

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Introduction

Atherosclerosis and accompanied cardiovascular disease is one of the major causes of death in the western world. To investigate its pathophysiology, animal models such as the ApoE-/- mouse are commonly used. In this follow up study, we measured the changes of the morphology and the function of the vessel wall that occur during the formation and progression of atherosclerotic plaque in ApoE-/- and control mice at the age of 6, 18 and 30 weeks. The morphology of the vessel wall was evaluated by ascertaining the mean thickness of the arterial wall. The function was determined by measuring the local pulse wave velocity (local PWV) which is an indicator for the stiffness of the vessel wall. Both parameters were measured in the upper abdominal aorta. Thereby we found, that the local PWV increases clearly before morphological changes are detectable, which makes the local PWV a very sensitive parameter for the examination of early stages of atherosclerosis.

Methods

All MR-experiments were performed on a Bruker Avance 750 (Bruker Biospin, Rheinstetten, Germany) with a vertical main magnetic field of 17.6 T and a max. gradient strength of 1000 mT/m. As receiver coil, we used two home build Bird Cage resonators with an inner diameter of 20 mm for mice of less than 24.0 g bodyweight and 25 mm for mice over 24.0 g bodyweight.

Morphology: We used a multi-slice-multi-echo spin echo sequence (N slices = 8; N echoes = 3; TE = 9 ms; TR = approx. 1 s; slice thickness = 0.4 mm; interslice dist. = 0.8 mm) which was positioned perpendicular to the abdominal aorta, beginning at the aortic hiatus. A respiratory gated cardiac trigger was realized by the use of a pneumatic sensing balloon and a home build trigger unit. To realize a black blood effect, a trigger delay was applied to start data acquisition at the beginning of the systolic flow. The mean arterial wall thickness was calculated out of the area of the vessel lumen and the whole cross sectional area of the vessel which were segmented by the use of Amira 5.2.0 (Visage Imaging GmbH, Berlin, Germany).

Local PWV: Under the assumption of a reflectionless and unidirectional waveform in the early systolic flow pulse, the local PWV can be approximated by PWV=dQ/dA (Q(t): volume flow through the vessel; A(t): cross sectional area of the vessel) with the data of a single slice [1, 2]. For the measurement of the time course of the parameters Q and A, a high resolution PC-Cine-FLASH sequence was performed perpendicular to the arterial vessel with through plane flow encoding (TE = 1.7 ms; TR = 5 ms; slice thickness = 1 mm; frames per heart cycle: 40). By the use of an interlaced acquisition mode, a temporal resolution of 1 ms could be achieved. The evaluation was performed with the help of Matlab (The MathWorks, Inc.; Natick; USA) and Amira 5.2.0 (Visage Imaging GmbH, Berlin, Germany) software.

Animal model: Morphology and local PWV were examined in seven C57Bl/6 mice and in eight ApoE-/- mice at the age of 6, 18 and 30 weeks while one data acquisition of each group could not be evaluated at the age of 30 weeks due to cardiac arrhythmia. The ApoE-/- group was fed a high cholesterol diet (TD88137; ssniff GmbH; Soest; Germany) starting at the age of 4 weeks, whereas the control group was on chow for the whole time. For the experiments the mice were anaesthetized with 1.5 – 2.0 vol.% isoflurane. All experimental procedures were in accordance with institutional guidelines and were approved by an external ethics committee.

Results

Figure 1 shows the development of the mean arterial wall thickness in the abdominal aorta of ApoE-/- and control mice. Until the age of 18 weeks there is no significant difference in vessel wall thickness between ApoE-/- and control mice. The formation of plaque becomes detectable at the age of 30 weeks, where the vessel wall thickness of ApoE-/- increases highly significant compared to 18 week old ApoE-/- mice and compared to the age matched control group. The local PWV in ApoE-/- mice increases highly significantly between the 6th und the 18th week and rests significantly above the level of the age matched control group at the age of 18 and 30 weeks as depicted in Figure 2. Table 1 displays a synopsis of all data.

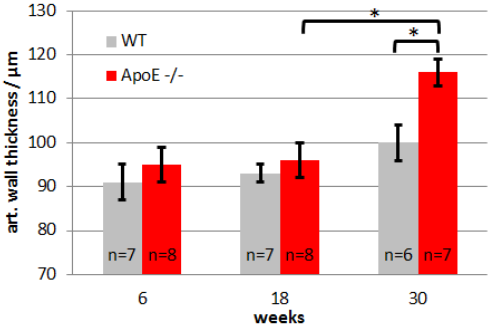

Figure 1: Mean arterial wall thickness in the upper abdominal aorta **(*P < 0.01)**

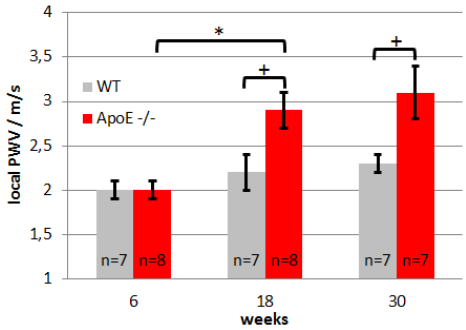

Figure 2: Local PWV in the upper abdominal aorta **(*P < 0.01 / +P < 0.05)**

	ApoE-/- group		Control group	
Age	**local PWV**	**art. wall thickness**	**local PWV**	**art. wall thickness**
6 weeks	(2.0 ± 0.1) m/s	(95 ± 4) µm	(2.0 ± 0.1) m/s	(91 ± 4) µm
18 weeks	(2.9 ± 0.2) m/s	(96 ± 4) µm	(2.2 ± 0.2) m/s	(93 ± 2) µm
30 weeks	(3.1 ± 0.3) m/s	(116 ± 3) µm	(2.3 ± 0.1) m/s	(100 ± 4) µm

Table 1: Results of the local PWV measurements and the measurements of the mean arterial wall thickness in the upper abdominal aorta. Data are presented as mean ± SE.

Conclusion

In this study we investigated the degree of morphological and functional changes at different stages of the atherogenesis in the abdominal aorta of ApoE-/- mice. Our data indicate that, by the use of MR-Microscopy, the functional changes, represented by the increase of the local PWV are detectable earlier than the morphological changes of the vessel wall. This could be useful in an experimental setup, to enhance the capability of detecting the effect of e.g. nutrition or medication on the plaque progression earlier and more sensitive. Furthermore the clinical application of this method could help to diagnose early stages of atherosclerosis, as the PWV assessed by ultrasound has already been described as an early indicator of vascular damage in humans [3].

References

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