6. Summary

Magnetic resonance tomographical, histological and fluorescencemicroscopical studies on localization of contrastagents with affinity to atherosclerotic plaques of WHHL rabbits

Atherosclerosis, leading to stroke and coronary artery disease, is a major cause of morbidity and mortality in the Western world.

In the early stages atherosclerotic plaques are invisible with luminographic techniques, because they develop without narrowing the arterial lumen. Therefore all luminographic techniques, conventional X-ray angiographie as well as magnetic resonance (MR) or computed tomography (CT) angiographie, frequently underestimate the true burden of atherosclerosis and are not able to predict sites of subsequent clinical events.

It is well etablished that the risk of an acute cardiologic event mediated by plaque rupture is predicated upon the composition of atherosclerotic plaque rather than the degree of luminal narrowing. Plaques with a large necrotic lipid core and a thin fibrous cap must be considered „vulnerable“ and are associated with a high risk of plaque rupture. However, not all vulnerable plaques must to yield to cardiovascular events.

Several groups reported that high resolution MR is capable of detecting and characterizing atherosclerotic plaque. However, these high resolution MR techniques are restricted to superficial vessels, need highly qualified scientists, or are invasive, because the use of intravascular coils is required.

A contrast agent that selectively enhances atherosclerotic plaque or plaque compounds could clearly improve the non-invasive detection and/or characterization of atherosclerotic lesions and would be of a great clinical interest.

In the present examination two Gd-based MRI contrast agents (model compounds) from the Schering AG Berlin were investigated on the basis of a WHHL rabbit atherosclerosis model.

After MR imaging (24h , resp. 48h post contrast agent application, respectifly), the WHHL rabbits were sacrified and their aortic arches were taken for histological investigations.

For this purpose, the model-compounds were histologically detected in immunhistochemical and histochemical characterized plaques by fluorescence microscopy.

In the MRI examination the compounds were able to raise the signal intensity in the rabbit aorta. The atherosclerotic changes in arterial wall were validated with help of histological examination after imaging.

Both compounds enrich in the extracellular, lipid-rich, collagen-rich, edemateus and acellular

plaquematrix. The cells from the MPS are not involved in contrast agent enrichement in the plaque. The target of the contrast agents seems to be the acellular, fibrous, fatty and necrotic core, which plays an important role in vulnerabilty of plaques.

In addition the optimal time for MR-examination after application of the contrast agent could be identified.

On plain MR images –without contrast agent injection- no plaques in the aorta were detectable. In control rabbits (without plaques) no enhancement of the vessel wall was observed post contrast-agent administration.

In a second study the mechanism of contrast agent enrichment was examined wih atherosclerotic aortic sections from WHHL-rabbits in vitro. This should help to develop a new in vitro model for examinations of human atherosclerotic material. Aortic sections were exposed to contrast agents for 5, 15, 30, 60 and 120 minutes.

Gadophrin-2 was able to enrich qualitative and quantitative likewise the in vivo studies after 5 minutes inkubation. Not so Gadofluorine-M: It enriched just behind the endothelial layer. A third contrast agent, ultrasmall superparamagnetic oxids (USPIOs), did not enrich anywhere. In vivo USPIOs are known to migrate with help of monocytes per phagocytosis in the blood into the plaque.