Negative Magnetic Resonance Contrast of Peri-Aortic Lymph Nodes created by Uptake of Ultrasmall Superparamagnetic Particles of Iron Oxide (USPIOs) May Mask the Aortic Lumen and Lead to False Positive Results with Regard to the Diagnosis of Atherosclerosis.

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Background:
Ultrasmall superparamagnetic particles of iron oxide (USPIOs) are intravenously administered cellular MR contrast agents with a strong T2* shortening effect. It has been shown, that USPIOs are taken up by lymph nodes and USPIO-enhanced MRI is clinically used for staging of cancer metastases. Recently, USPIO-enhanced MRI has been reported as a tool for investigating atherosclerotic plaque in rabbit and mouse aortas. Lymph nodes are lying adjacent to the aorta at standard positions along the aorta. The strong T2* effect may lead to darkening of a larger area or an area not corresponding with the location of the USPIOs on gradient echo images, which is called "glooming". In this study, we want to investigate the disturbing effect of lymph node uptake of USPIOs on MR images of atherosclerotic aortas.

Materials & methods:
5 ApoE-/- and eNos-/- mice (age: 5-7 months) were fed a Western-type diet (42% of total calories from fat; 0.15% cholesterol added; Harlan-Teklad) for 17 weeks and baseline MRI (9.4 T) of the abdominal aorta was performed after this diet period immediately followed by intravenous administration of 75 microliter (=100 micromole/kg) USPIOs (Sinerem, Guerbet). For all mice, MRI measurements were repeated at 72 hours and 120 hours after USPIO administration. MRI protocol: transverse images of the abdominal aorta (0-10 mm above right renal artery) were acquired with a T2* weighted gradient echo (TR= 35 ms, TE=2.20 ms) and a T2 weighted fast spin echo sequence (TR=2800 ms, TE= 29.3 ms). After the final measurement, the aorta of each animal was perfusion-fixed in formaldehyde 4% and histology was performed. Sections corresponding with MRI levels were stained with hematoxylin and eosin, elastin von Giesson, Prussian blue (iron) and MAC-3 (macrophages). As a control, in a very old apoE -/- mouse saline was administered instead of USPIOS. Three adult mice (Balb-c) were fed a standard chow diet and further treated as animals in group A. In these mice, MRI of respectively the abdominal aorta, the abdominal aorta including the bifurcation to the common iliac arteries and the thoracic aorta including the innominate artery was performed.

Results:
In both, apoE-/- eNOS-/- mice and wild type mice, the aortic wall on T2* weighted MR images showed dark holes, which after histology appeared to predominantly correspond with USPIO uptake by peri-aortic lymph nodes. USPIO uptake in lymph nodes did explain dark holes at the aortic arch and at the iliac bifurcation of wild type mice, too. Some aortic plaques showed USPIO uptake, but this was, when compared to lymph node uptake, very little.

Conclusions:
The versatility of USPIOs as a negative MR contrast agent for both lymph node staging and atherosclerosis poses important limits to its use for detection of macrophage-rich atherosclerotic lesions in the aorta and probably in the coronary ostia at the clinically found useful dose of 100 micromole USPIOs per kg, due to the presence of adjacent lymph nodes. Use of more specific molecular targeted contrast agents for detection of high-risk plaques is recommended.

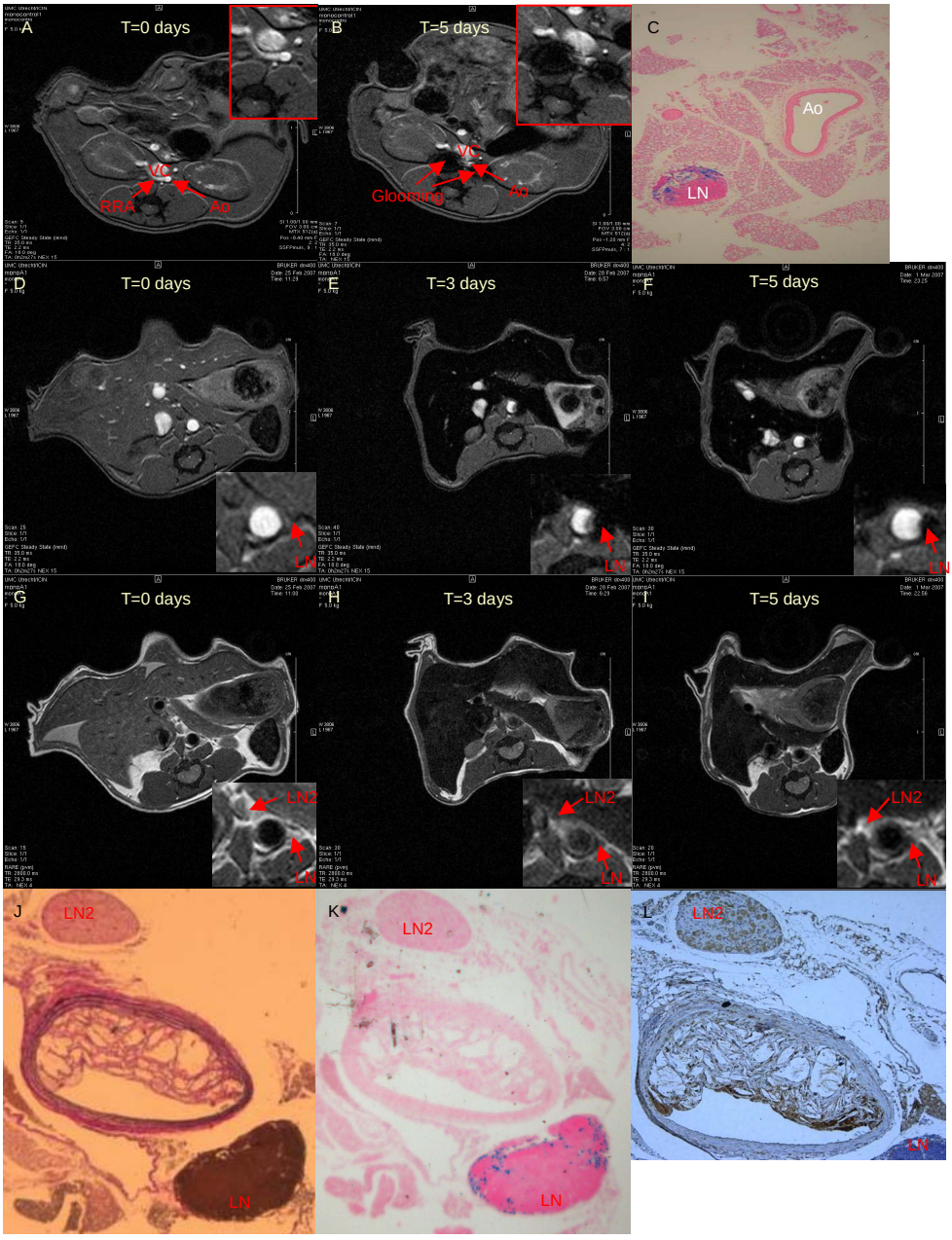

Figure 1. T2* weighted GE images of the abdominal aorta of a wild type mouse (balb-c) before (A) and 120 hours after (B) administration of USPIOs at the level of the right renal artery. Corresponding iron stained section (C). T2* weighted GE images (D, E, F) and T2 weighted FSE images (G, H, I) of the abdominal aorta of an apoE-/- eNOS-/- mouse before (D, G), 72 (E, H) and 120 (F, I) hours after administration of USPIOs. Level: 3 mm above the right renal artery. Corresponding histological sections, Elastin-von Giesson (J), iron (K) and macrophage stained (L).