X-ray phase-contrast grating interferometry for atherosclerosis imaging in mice

Ruud B. van Heeswijk[1,2], Peter Modregger[3,1], Simone Coppo[1,2], Gabriele Bonanno[1,2], Maxime Pellegrin[4], Jean-François Aubert[4], Marco Stampanoni[3,5], Lucia Mazzolai[4] and Matthias Stuber[1,2]

[1]Department of Radiology, University Hospital (CHUV) and University (UNIL) of Lausanne, Switzerland, [2]Center for Biomedical Imaging (CIBM), Lausanne, Switzerland, [3]Swiss Light Source, Paul Scherrer Institut, Villigen, Switzerland, [4]Service of Angiology, University Hospital of Lausanne (CHUV), Switzerland, [5]Institute for Biomedical Engineering, University and ETH Zürich, Zürich

Introduction: Obtaining images of atherosclerotic plaque in the mouse vasculature can be challenging with traditional non-invasive methods. However, X-ray phase-contrast grating interferometry (PCI) [1] has been applied for the ultra-high resolution depiction of atherosclerotic plaque in the excised mouse aorta and the characterization of its components [2]. The contrast in PCI is based on the phase difference that highly parallel synchrotron X-rays obtain at tissue interfaces, and in our current setup allows the depiction of intact three-dimensional structures with an isometric resolution down to 4µm, although *in vivo* imaging is currently not possible. The goal of this study was to take the next step in mouse atherosclerosis imaging and to analyze the three-dimensional structure of atherosclerotic plaque in the carotids and coronary arteries, and to compare the results to high-resolution magnetic resonance imaging (MRI) and histological staining.

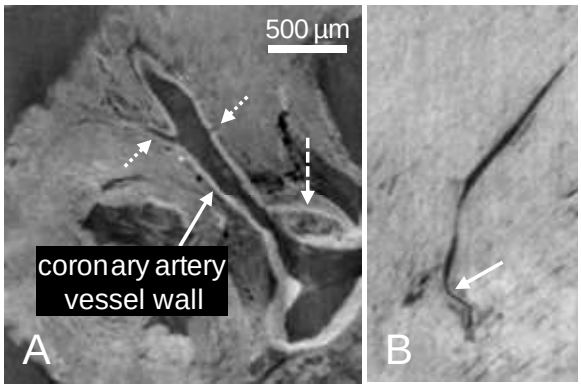

Figure 1. PCI of coronary arteries. A) *Proximal right coronary artery (RCA) next to atherosclerotic plaque (dashed arrow). The interior and cap of the plaque can be clearly differentiated. The RCA vessel wall can be discerned in the RCA itself as well as in its branches (dotted arrows).* ***B)*** *Distal left anterior descending coronary artery (LAD), where the coronary vessel wall can also be identified.*

Methods: Two ApoE-KO mice [3] were fed a high-fat diet for 12 weeks to allow for the development of atherosclerotic plaque. These mice and two C57Bl6 control mice were then sacrificed, after which their hearts and aortic arches were excised and fixed in formalin. After fixation, the samples were embedded in agarose gel and mounted on the TOMCAT beamline at the Swiss Light Source synchrotron of the Paul Scherrer Institute in Villigen, Switzerland. Multiple image volumes with a size of 15x15x3.7mm^3 and an isotropic pixel size of 7.4µm were acquired. Next, 3D gradient echo MRI was performed (TR/TE=10/3.8ms, field of view=15x15x15mm^3, 64 averages, isometric resolution 78µm) on a 14.1T Varian animal scanner with a 30mm diameter volume coil. The samples were subsequently sectioned at the level of atherosclerotic plaques and Movats pentachrome histological staining [3] was performed. Finally, all three modalities were visually compared for the identification of plaque structures.

Results and Discussion: Ultra-small structures including the coronary artery vessel wall and the fibrotic cap could be discerned In the PCI images (Fig. 1). With a pixel size of 7.4µm and a vessel wall thickness of 25-65µm, 3-7pixels are available for analysis of the vessel wall cross-section. The internal structure of the plaque also corresponded with both histology and MRI (Fig.2). Although the MR images had a lower resolution and the internal structure of the plaque could not be discerned, the fibrous cap could still be detected. In conclusion, PCI enables the three-dimensional investigation of the coronary artery vessel wall and atherosclerotic plaque with a very high spatial resolution.

References: [1] S McDonald et al., J Synchrotron Radiation 6(4):p56, 2009 [2] M Shinohara et al., Am J Physiol Heart Circ Physiol 294: H1094 (2008) [3] P Menu et al., Cell Death Dis 2:e137 (2011)

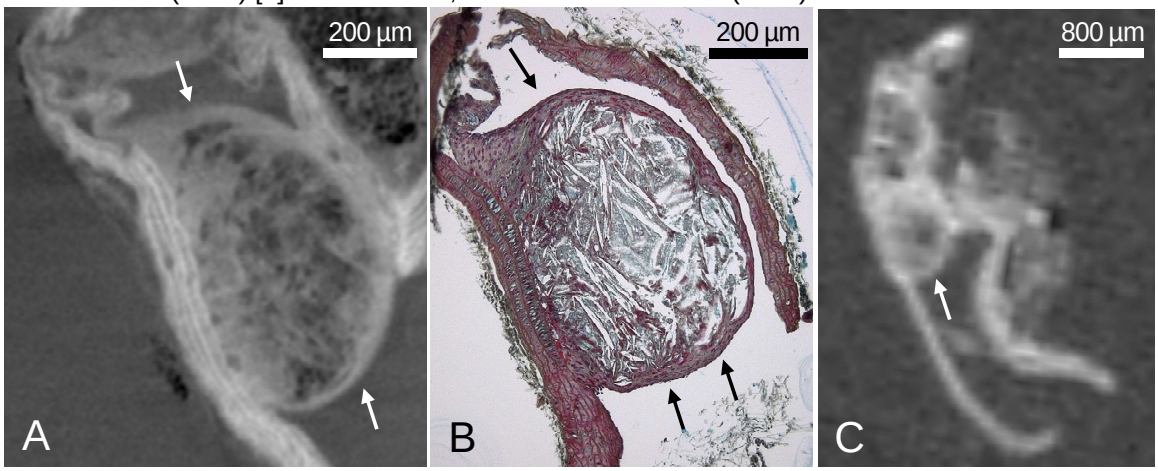

Figure 2. Large atherosclerotic plaque in the excised right common carotid artery. A) *The fibrous cap (arrows) can be clearly differentiated from the interior.* ***B)*** *Histology confirms the structure of the plaque characterized by a fibrous cap (black arrows) and a necrotic/lipid core containing numerous cholesterol clefts (white) as well as cellular and extracellular components (blue).* ***C)*** *Interpolated 14.1T MR image of the carotid with the plaque branching of from the aorta. The fibrous cap can still be discerned.*

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