The effect of Ivabradine on plaque size, biomechanics, and microvasculature in atherosclerotic rabbits measured using MR and Ultrasound Imaging

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Target Audience: Researchers interested in imaging techniques and new treatment strategies for atherosclerosis.

Purpose: Atherosclerotic plaque development is associated with increased oxidative stress, promoting angiogenesis, lipid oxidation and uptake, and ensuing cell death. In addition, biomechanical stress (blood-pressure variations with every heart beat), may further enhance plaque vulnerability. Ivabradine, a heart-rate lowering drug, is associated with reduced oxidative stress and diminished atherosclerotic plaque formation in mice[1]. Yet it's role on plaque microvasculature and biomechanical stress is unknown. The purpose of the present study was to investigate the effect of Ivabradine on plaque formation using MR and ultrasound (US) imaging.

Methods: Atherosclerosis formation was induced in 19 New-Zealand White rabbits with a high cholesterol diet (1.0% for 10 weeks and 0.3% for 4 weeks). After two weeks, endothelial denudation (balloon-injury) of the abdominal aorta was performed[2]. Nine rabbits were treated with Ivabradine (17 mg/kg/day) dissolved in their drinking water during the entire study period. After 14 weeks, MRI (7.0 T Bruker BioSpec 70/30, Bruker, Germany) and US (Esaote Picus, Genoa, Italy) examination of the rabbits was performed. Plaque size was measured using contrast-enhanced T1w-Double Inversion Recovery black-blood MR images[3] (TR/TE/TI: 1000/10/350 ms, FOV 120x120 mm, acq/reco matrix 384x384/512x512), while plaque microvasculature was determined using a dynamic T1w black blood TSE pulse sequence[4] (TR/TE/TI: 300/9.5/120 ms, FOV 120x120 mm, acq/reco 192x192/384x384 matrix, temporal resolution 7.2 sec, 100 time phases) with 0.2 mmol/kg Gadobutrol (Bayer Healthcare, Germany) injected after one minute through a marginal ear vein. Quantification of DCE-MRI was done both semi-quantitatively by means of the area under relative signal time-enhancement curve (AUC) and quantitatively by means of pharmacokinetic modelling using a muscular region as reference[5], with K^{trans} and v_e values of muscle taken from literature[6]. Pulse pressure and relative distension were measured using a pressure catheter in the central auricular ear artery and high frame-rate ultrasound, respectively.

Results: Failure of contrast injection occurred in one rabbit and three rabbits died during the study period. Therefore, successful MRI and US examination was performed on 15 rabbits (six Ivabradine treated animals). Ivabradine resulted in a 15% heart rate reduction, both in conscious state ($p=0.026$) and under anaesthesia ($p=0.031$). Pulse pressure and relative distension, as measured with US, were similar between the Ivabradine and control group (both $p>0.5$). But, due to the reduction in heart-rate, the aorta's in the Ivabradine group are less often exposed to the biomechanical stress. MRI plaque size (Figure 1) was similar between the groups ($p=1.0$). DCE-MRI analysis showed a decrease in plaque microvasculature with a 25% decrease in the AUC from 0 till 7 minutes after contrast injection ($p=0.029$) and a 30% decrease in K^{trans} ($p=0.040$) for Ivabradine-treated animals compared to controls.

Discussion and Conclusion: Use of Ivabradine led to lowered AUC and K^{trans} on DCE-MRI, indicating decreased plaque microvascular density, flow, or leakiness, which is thought to be an important determinant of reduced plaque vulnerability. Ivabradine did not lead to reduced vessel wall area, despite reduced repetitive biomechanical stress. Histological analysis is still ongoing and is expected to provide further insights on the effect of Ivabradine on atherosclerosis.

References: [1]Custodis et al., Circulation. 2008;117:2377-87, [2]Lobbes et al., Radiology. 2009;250:682-91, [3]Phinikaridou et al., Circ Cardiovasc Imaging. 2010;3:323-32, [4]Calcagno et al., ATVB. 2008;28:1311-17, [5]Yankeelov et al. MRM. 2005;23:519-29, [6]Jaspers et al., Med Phys. 2010;37:5746-55. **Acknowledgements**: This research was performed within the framework of CTMM, project PARISk (grant 01C-202), and supported by the Netherlands Heart Foundation.

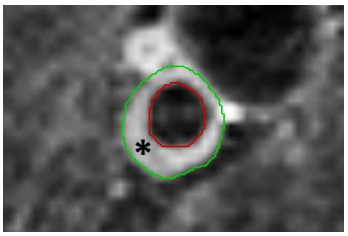

Figure 1: Contrast-enhanced T1w-DIR BB MR image showing the atherosclerotic plaque in the rabbit aorta (indicated with *).

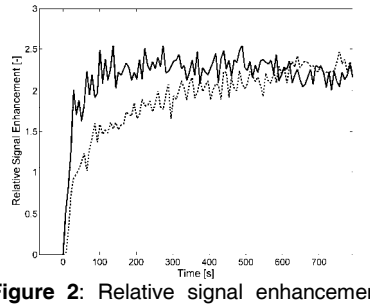

Figure 2: Relative signal enhancement-time curve of DCE MRI for a control rabbit (black line) and a rabbit that was treated with ivabradine (dashed line).