Molecular Imaging of Benfluorex Treatment in Diabetic Rats with $\alpha_v\beta_3$-integrin Targeted Nanoparticles

K. Cai[1], T. A. Williams[1], S. D. Caruthers[1,2], G. M. Lanza[1], S. A. Wickline[1], and P. M. Winter[1]
[1]Washington University, Saint Louis, MO, United States, [2]Philips Medical Systems, Andover, MA, United States

INTRODUCTION: The metabolic syndrome, characterized by obesity, hypertension, hyperlipidemia and insulin resistance, is highly associated with cardiovascular disease, including atherosclerosis. The development of atherosclerotic lesions is accompanied by increased angiogenesis within the arterial wall. The $\alpha_v\beta_3$-integrin is an ideal biomarker of angiogenesis because it is expressed on neovascular endothelial cells, but not on mature vessels. The JCR:LA-cp obese rat is homozygous for the cp gene and mimics the metabolic syndrome and mild type II diabetes. Benfluorex, a hypolipidemic agent, could prevent the progression of cardiovascular disease by curbing the metabolic abnormalities. Molecular imaging of angiogenesis using $\alpha_v\beta_3$-targeted gadolinium nanoparticles could sensitively detect the development of atherosclerosis associated with metabolic syndrome and monitor the therapeutic responses.

METHODS: Five month old male JCR:LA-cp lean rats (n=2) and JCR:LA-cp obese rats (n=5) were studied. Three obese rats received benfluorex in their feed (0.069% wt/wt) for 15 weeks, while all other animals received regular rodent diet. Body weights and food consumption were recorded weekly. Fasting serum insulin, leptin and triglycerides were measured. The abdominal aorta was imaged using a 3.0 T whole-body MRI scanner and a T1-weighted, fat-suppressed, black-blood, multi-slice turbo spin echo imaging sequence (TR/TE=296/10 ms, resolution= 213µm*213µm*2mm, 4 slices, ~11.6 min). Imaging was preformed before (baseline) and up to 2 hours post IV injection of $\alpha_v\beta_3$-targeted gadolinium nanoparticles (1.0 ml/kg). Images were normalized based on a reference gadolinium standard. The aorta wall was segmented manually for each slice at 2 hours post-injection, and automatically fit to earlier imaging points. The signal intensity of the aortic wall was averaged at each imaging point and enhancement was calculated. A balanced one-way ANOVA of the 2 hour enhancement was performed.

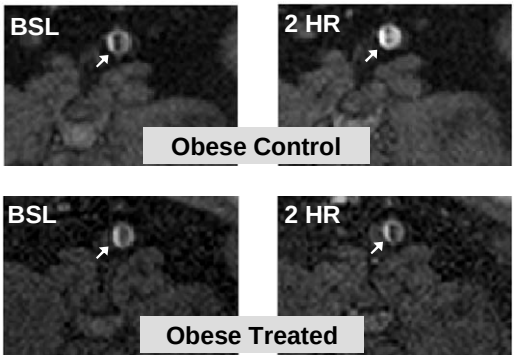

Fig. 1. Images of the aortic wall pre- and 2 hours post-injection of targeted nanoparticles show clear enhancement in the control animal (Top), reflecting angiogenesis supporting atherosclerotic plaques. Benfluorex treatment reduced aortic enhancement (Bottom).

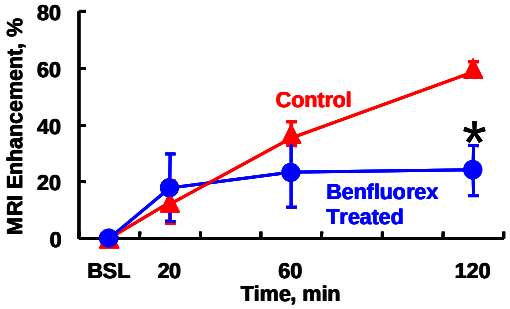

Fig. 2. Molecular imaging of aortic angiogenesis in JCR obese rats on control (Triangles) or benfluorex diet (Circles) before (BSL=baseline) and after injection of targeted nanoparticles. Decreased angiogenesis in treated rats (* $p < 0.05$) indicates reduction of atherosclerosis with benfluorex treatment.

RESULTS: Treatment of obese JCR:LA rats with benfluorex decreased weekly food consumption (127±11g vs. 175±4g) and reduced body weight by an average of 119g. The serum insulin, leptin and triglyceride of obese control animals were 3.6±1.8, 75.6±19.5 and 305,500±39,500 ng/ml, and were decreased by 38.0%, 39.8% and 36.8% in benfluorex treated animals. At 2 hours post-injection, MRI signal enhancement in the obese treated rats (23.9±8.8%) and the lean rats (31.4±3.2%) was significantly lower than in obese control rats (60.0±2.2%, $p<0.05$), indicating that treatment decreased angiogenesis in the aortic wall and possibly inhibited atherosclerotic burden (Fig. 1). The signal enhancement (Fig. 2) steadily increased in obese control rats during the 2 hours, reflecting accumulation of targeted nanoparticles, while the treated rats reached a constant level by about 20 minutes.

CONCLUSION: Benfluorex treatment lowers serum lipid and insulin and also reduces angiogenesis feeding atherosclerotic plaques in this model of the metabolic syndrome. Molecular imaging of angiogenesis with targeted gadolinium nanoparticles may be used to detect cardiovascular disease associated with metabolic syndrome and monitor the treatment response.