MRI of Intracoronary Local Delivery of Motexafin Gadolinium: Towards Molecular MRI-Guided Gene Therapy

Yanfeng Meng[1], Jinnan Wang[2], Jihong Sun[1], Feng Zhang[1], Patrick Willis[1], Jiakai Li[1], Han Wang[1], Tong Zhang[1], Stephanie Soriano[1], Bensheng Qiu[1], and Xiaoming Yang[1]

[1]*Radiology, University of Washington, Seattle, WA, United States,* [2]*Clinical Sites Research Program, Philips Research North America*

Introduction: Atherosclerotic heart disease is the leading cause of death in the United States. Surgery-based artery bypass grafting and percutaneous transarterial interventions are currently available methods for reducing the risk of myocardial infarction. However, surgical bypass grafting is an invasive approach, while percutaneous transarterial intervention has approximate 9%-20% in-stent restenosis. Gene therapy is one of the frontiers in preventing in-stent restenosis. This study was to develop a new technique, using molecular MRI to monitor local agent delivery to coronary artery walls for potential MRI-guided prevention of in-stent restenosis.

Materials and Methods: This study was divided into three phases: in vitro confirmation, ex vivo evaluation, and in vivo validation. For the in vitro confirmation, we used human arterial smooth muscle cells (SMCs) to determine the optimum dose of Motexafin Gadolinium (MGd, Pharmacyclics Inc.), a multifunctional intracellular T1 MR contrast/anti-atherosclerotic agent. The different groups of SMCs were exposed to solutions of 0, 25, 50, 75, 100, 125,175, 200, 225 and 250-μM MGd, respectively, for 24 hours. Then the cells were washed to remove un-uptake MGd. The cells were transferred into Eppendorf tubes and dispersed in agarose. T1-weighted MR images of these cell-tubes were obtained on a 3T MR scanner. For the ex vivo evaluation, we placed a custom-made microporous delivery balloon catheter into the coronary arteries of three cadaveric pig hearts, which were placed in a saline-filled phantom. We locally infused 2-ml MGd/Trypan blue mixture into the coronary arterial wall under MRI. Axial spin echo T1-weighted MRI was performed pre- and post-MGd/blue infusion. For the in vivo validation, we placed the custom microporous delivery balloon into the left coronary arteries of three living pigs under fluoroscopy guidance. We then delivered 2-mL MGd/blue mixture into arterial walls under ECG- and respiratory-gated MRI using spin echo sequence, 385ms TR and 21ms TE. MR signal-to-noise ratios of the coronary arterial walls were measured, and targeted coronary arteries were then harvested for subsequent MRI-histologic correlation.

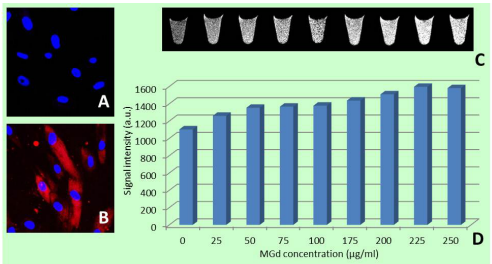

Fig. 1. (A&B) Fluorescent microscopic images. Human smooth muscle cells cultured with MGds, showing cell uptake of MGds as intracellular red fluorescence (B) compared to unlabeled cells (A). (C) In vitro MRI of the cell-tubes with subsequent signal intensity (SI) measurements (D), demonstrating SIs increase as MG concentrations increase.

Results: Cytological examination showed that red fluorescence emitted by MGd was detected in the exposed SMCs. MRI demonstrated a linear increase of signal intensities (SIs) as MGd concentrations increased (Fig. 1). For the ex vivo evaluation, axial T1-weighted MRI showed the enhancement of the coronary artery walls after the MGd/blue infusion in comparison to the control arterial walls. For the in vivo validation, MRI demonstrated the enhancements of coronary arterial walls for post-MGd/blue infusion in comparison to pre-MGd/blue infusion. These MRI findings were confirmed by histology, showing trypan blue as blue-color deposits and MGd-emitted red fluorescent spots through the arterial walls, which were not seen in the control arterial walls (Fig. 2).

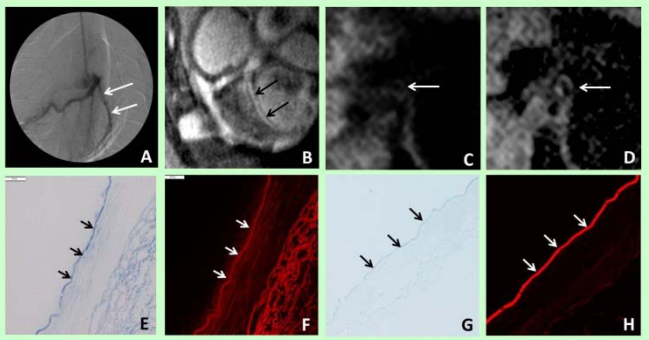

Fig. 2. (A) X-ray coronary angiogram, showing the agent delivery balloon (arrows) placed into the circumflex branch of the left coronary artery. (B) MR angiogram, showing the balloon (arrow) in the left coronary artery. (C&D) Axial MRI of the targeted coronary artery walls (arrows), demonstrating the wall enhancement post MGd/blue infustion (D), compared to pre-MGd/blue infusion (C). (E&F) Histology confirmes successful MGd/blue delivery, presented as blue infiltration (E) and MGd-emitting red fluorosence (F) through the coronary artery walls, which are not seen in the controls (G&H). Arrows indicate intima

Conclusion: This study initially demonstrates the possibility of using MRI to monitor the local agent delivery and distribution in the coronary arterial walls, which establishes groundwork to explore a new technique, molecular MRI-guided intracoronary local gene therapy.

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