Using Optical Coherence Tomography to Evaluate Atherosclerotic Lesion Formation in the Watanabe Heritable Hyperlipidemic (WHHL) Rabbit Model

Michael Frie (BA), Mitchell Troutman (DVM), Mark Smith (PhD)

American Preclinical Services, Minneapolis, MN, USA

Introduction

A reproducible animal model of atherosclerotic plaque exhibiting similar properties to those observed in the human population has proven difficult to develop. One of the more promising models is the Watanabe Heritable Hyperlipidemic (WHHL) rabbit. The WHHL rabbit is a well studied and characterized model for hypercholesterolemia in which atherosclerotic lesions develop naturally. Lipid-dense atheromas, similar to those found in human cases of atherosclerosis, can be found throughout the aorta and iliac arteries, at varying levels of severity. Since the extent of these lesions are not always apparent when viewed under fluoroscopy, we evaluated the use of optical coherence tomography (OCT) imaging as a guide for identifying animals with adequate plaque burden and then target optimum lesion sites for treatment within a region of vessel.

Characteristic of the WHHL Rabbit Model

The hypercholesterolemia observed in WHHL rabbits is due to a genetic deficiency in the LDL (low-density lipoprotein) receptor.

Plasma Lipid	Normal Rabbits	WHHL Rabbits
Total Cholesterol (mg/dL)	65 ± 35	643 ± 94

Methods

Six WHHL rabbits were sedated and prepped sterilely for the implant procedure. An introducer sheath was placed in the carotid artery for vascular access. An angiogram of the infra-renal aorta and Iliac bifurcation was obtained (**figure 1**).

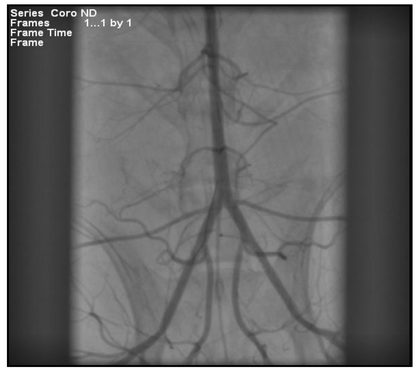

Figure 1. Infra-renal aorta and iliac bifurcation.

OCT images were acquired and the overall plaque burden was evaluated. Target implant sites were selected based on vessel size and the severity of plaque burden and treated with a balloon expandable stent. OCT images of the implanted stents were acquired after stent placement and stent to vessel wall apposition was evaluated. The animals were then recovered and transferred to long-term animal housing.

Pre-Implant OCT Image Analysis

The atherosclerotic lesions observed in WHHL rabbit arteries were not easily identifiable via fluoroscopy and were typically diffuse in nature; with moderate atheroma formation observed in the infra-renal aorta and marked atheroma formation observed in the iliac arteries. Animal to animal variability was observed, with some animals demonstrating lesions throughout the aorta (**figure 2**), while others were more focal in nature (**figure 3**).

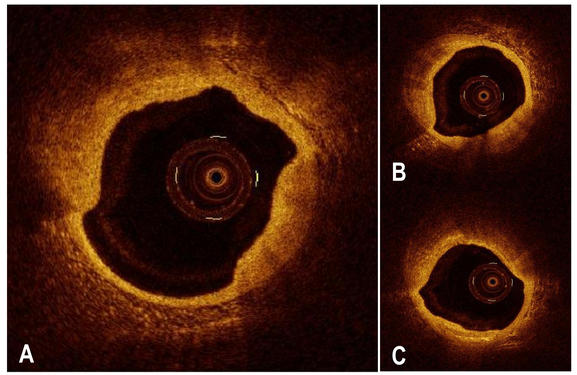

Figure 2. OCT image of vessel site targeted for stent deployment (A). OCT image of reference vessel 10 mm proximal (B) and 10 mm distal (C) to treatment site.

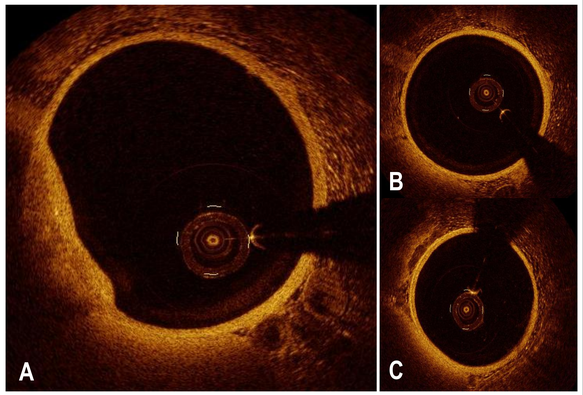

Figure 3. OCT image of vessel site targeted for stent deployment (A). OCT image of reference vessel 10 mm proximal (B) and 10 mm distal (C) to treatment site.

Using the pre-implant OCT images as guidance, in conjunction with the fluoroscopic images, these specific regions within the vessels were targeted for implantation with balloon expandable bare metal stents.

Post-Implant OCT Image Analysis

Eight stents were successfully implanted in either the aorta and/or the external iliac artery in a targeted region of vessel that displayed a suitable amount of plaque burden. All stents demonstrated appropriate vessel wall apposition, with increased lumen diameter, when compared to pre-stent OCT images (**figure 5**).

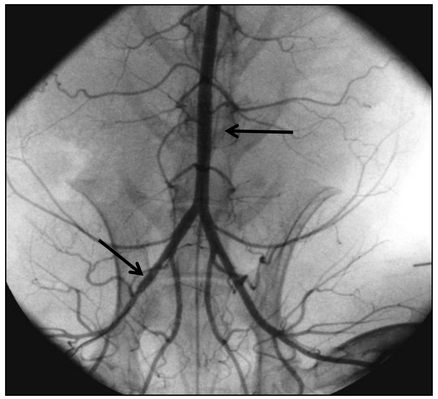

Figure 4. Post stent angiogram of the infra-renal aorta and external iliac arteries. Implanted stents are denoted by the arrows.

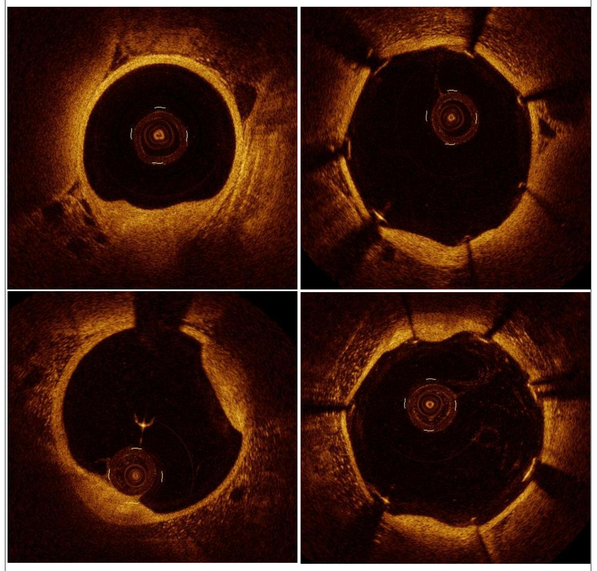

Figure 5. OCT images of vessel sites targeted for stent deployment (upper and lower left images). Post stent OCT images of stented vessels (upper and lower right images).

Histopathology

Representative lesions (shown in **figure 6**) displayed moderate numbers of spindle shaped cells (smooth muscle cells and myofibroblasts) separated by intervening variable amounts of collagen, free and intracellular lipid (phagocytized by foamy macrophages), and cholesterol clefts. Small amounts of free lipid multifocally aggregated which created necrotic cores within the neointima. On occasion, the necrotic cores examined exhibited minimal amounts of dystrophic calcification.

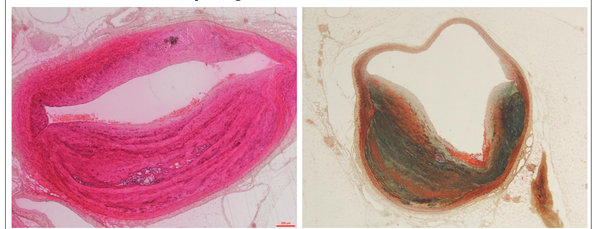

Figure 6. Non-stented region of Watanabe aorta displaying moderate to severe amount of atherosclerotic plaque.

The abluminal surface of the stent either abutted the compressed, non-circumferential atherosclerotic plaque or abutted the tunica media (if there was no atherosclerotic plaque present), thereby increasing the overall lumen diameter (**figure 7**).

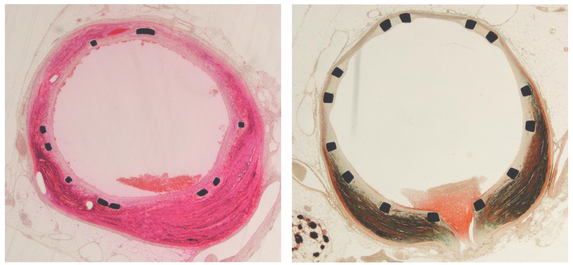

Figure 7. Stented region of Watanabe aorta. Animal were survived ninety days post stent implant.

Conclusion

Optical coherence tomography is a necessary tool to ensure that a subject animal has suitable overall atheroma formation and that an experimental therapeutic device, such as a stent, will be delivered to and evaluated within a lesion-rich portion of test vessel. The plaques observed were variable in location and severity, and could not reliably be visualized or assessed via fluoroscopy. This new imaging technique can allow for in-life evaluation of lesion development and aided in optimizing site selection for stent or DEB placement.

For Further Information

Please contact *mfrie@apsemail.com*. More information on this and related subjects can be found at www.americanpreclinicalservices.com.