Intravascular Ultrasound-Guided Catheter-Based System

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Introduction

Intravascular brachytherapy is a rapidly evolving therapeutic modality. Its efficacy in reducing restenosis after percutaneous coronary interventions (PCIs) has been demonstrated in randomized clinical trials mainly involving in-stent restenosis patients. Despite some unresolved clinical issues, such as late total occlusion, the marked benefits of intravascular brachytherapy over conventional PCI in the setting of in-stent restenosis has contributed to the enthusiasm characterizing this new brachytherapy application. The widespread use of these systems in the near future is likely to greatly benefit patients.

Our interest in intravascular brachytherapy is centered on the development of second-generation systems. The goals of our developmental work are increasing efficacy and decreasing toxicity by using a new guidance strategy that is attuned to the biology and anatomy of PCI procedures. We present an intravascular ultrasound (IVUS)-guided catheter-based system generated from cooperation between interventional cardiology and radiation oncology and sympathetic to the needs of both specialties.

Background

The first generation systems are varied in their design. On the surface there does not appear to be many shared qualities. These devices take many forms including afterloading catheters (with and without centering capability), stents, liquid-filled balloons, gas-filled balloons, and x-ray tubes mounted on catheters. The diverse embodiments of these devices belie their dosimetric similarities. All of them generate a radiation dose profile that is concentric perpendicular to the long axis of the delivery device. In contrast, the vessel wall is most often eccentrically narrowed by atherosclerosis. This dichotomy leads to a mismatch between the axial vascular anatomy and the radiation dose profile (Fig. 1). Both the radiation oncologist and the interventional cardiologist must try to solve this dosimetric prob-
Figure 1. Axial image of a coronary artery ~24 hours after percutaneous coronary intervention. A radiation source (black dot) is centered in the lumen and 20 Gy is prescribed to a 1.5-mm radius. Note the inhomogeneity of dose to the adventitia.

Our developmental goals center on the perceived need to match dosimetry with the complex anatomy of vascular lesions. Viewed in the axial plane, the anatomy may best be characterized as eccentric. With interventions that target the lumen, such as balloon angioplasty, the axial anatomy is of little proven importance. However, the treatment targets for intravascular brachytherapy are likely to be located in the vascular wall. There is also some evidence that the entire vascular wall, not just the periluminal portion, should be targeted. Clinical correlations to these basic science observations are emerging. The efficacy of treatment with a $^{192}$Ir-based system is closely linked to the minimum dose to the external elastic lamina (EEL) of the vessel as estimated from IVUS. Although there is less direct evidence, the toxicity of intravascular brachytherapy may also be related to dose. For example, in the porcine animal model, a focal area of vascular wall necrosis, with or without overlying thrombus, was produced in a vessel 1 month after 15 to 25 Gy of $^{192}$Ir was prescribed, to a 1.5 mm distance from the source. The histologic pictures from that study look strikingly similar to the IVUS images of patients who developed delayed thrombosis in various clinical trials that predominately used beta emitters. With these histologic and IVUS findings of focal vascular wall necrosis/thinning, one may hypothesize that late total
occlusion after intravascular brachytherapy is the result of excessive dose from a catheter that lies too close to the vessel wall. Preventing focal areas of excessive dose, while ensuring that the remainder of the vessel wall gets adequate coverage, is the main goal of our development.

Three characteristics of an optimal device were ultimately decided upon. The first is the ability to conform the radiation dose to the vascular anatomy. This was the one quality of the device that could not be compromised because it alone would allow the dosimetric match with the vascular anatomy we sought. With the recognition that the axial anatomy of most vessels is eccentric, we investigated ways to create an eccentric radiation dose profile. The most reliable way of doing this is by partially shielding the circumference of the catheter segment containing the radiation source. The result is a radiation dose profile that resembles the vascular wall (Fig. 2). In our mind's eye we imagined the overlay of this dose profile on an axial section of a diseased vessel (Fig. 3) and thought that this is what we wanted to achieve. The second quality is the ability to image the axial anatomy of the vessel and know how this image relates to the radiation dose profile. Phased array IVUS is the most reasonable choice because it permits axial imaging, is small enough to be integrated into a catheter that can hold a radiation source, and has no moving.

![Figure 2](image-url)

**Figure 2.** Axial image of a radiation dose profile from the Brigade catheter. The 10% of maximum iso-dose line is at about 3 mm from the center of the catheter (12 o'clock position) at the unshielded portion of the catheter, and at 2 mm from the center of the catheter (6 o'clock position) at the shielded portion of the catheter. The very intense areas of dose (red) are not present adjacent to the shielded portion of the catheter allowing it to lie against the vascular wall with impunity.
Figure 3. Overlay of the dose profile from Figure 2 on an axial section of a coronary after percutaneous coronary intervention. This orientation delivers a homogeneous dose to the adventitia.

parts so it can be linked with the radiation shield in a fixed orientation. The linking of the radiation dose profile and the vessel wall image is crucial because it allows the user see the best match between the dose profile and the image. The third characteristic enables the user to make the aforementioned match happen by mounting the radiation shield/IVUS combination on a torqueable shaft.

After many iterations, we arrived at a design-freeze that captured all of the aforementioned elements (Fig. 4). The device is named the Brigade (Beta Radiation with IVUS Guidance and Directed Energy) catheter. This catheter-based system has a maximal outer diameter (OD) of 3.5 F. This occurs at the IVUS transducer. The shaft distal to the IVUS transducer has an OD of 2.5 F. This area contains the radiation shield and is where the radiation source dwells during use. The proximal shaft is 3.0 F and is composed of a combination of polymer and metal in order to transmit torque effectively while maintaining flexibility. The compromise between torque and flexibility was the developmental hurdle that took the most effort to overcome. The catheter travels over a 0.014" guidewire passed through a monorail system at the catheter's tip. A novel feature of this tip is the ability to rotate freely about the long axis of the catheter. This not only permits torque but also prevents guidewire prolapse because torque cannot build up as the catheter negotiates a curved pathway. The radiation source (OD of 0.45 mm) is passed into the catheter through the proximal port of the catheter. The central lumen of the catheter is closed to the patient.

The combination of the radiation shield, IVUS, and torque shaft suggests the method of use for this device. At the proper time during the intervention, the
catheter is inserted into the vessel and a survey of the vessel wall is done with the integrated IVUS. The orientation of the dose profile relative to the vessel's anatomy is noted. The dose profile is then altered to effect a match with the vascular anatomy by torquing the catheter (Fig. 5). The torquing is made easier by having real-time IVUS images of the vessel during manipulation.

**Figure 4.** Schema of the Brigade Catheter.

**Figure 5.** A. Intravascular ultrasound (IVUS) of a coronary artery with the Brigade catheter in situ prior to proper orientation. Cursors indicate the position of the shield (lower right is unshielded). B. IVUS of the same coronary artery with the Brigade catheter in situ after proper orientation. The unshielded portion of the dose profile is directed at the external elastic lamina furthest from the catheter.
The radiation oncologist is now able to prescribe a dose of radiation to the vessel wall that is relatively homogeneous. Software that is linked to the IVUS unit provides the computing power to generate a treatment plan in seconds by simply indicating a point on the image to use for dose normalization. Not only will the dose to various points of interest be listed, but the dwell time of the source will also be displayed (Fig. 6). The source is now loaded into the catheter for the length of the dwell time and removed at its completion. The source material chosen for the initial trials is $^{188}$W/$^{188}$Re, a mixed beta and gamma emitter that can be used in activities yielding treatment times of ~2 minutes. No additional shielding is necessary to protect the medical personnel.

**Pre-Clinical Experimentation**

The safety of this device was determined by experimentation in the porcine animal model of balloon overexpansion coronary injury. A group of 6 animals was sacrificed 3 days after treatment. Another group of 16 animals was sacrificed 6 months after treatment. The animals each received a balloon overexpansion injury of two coronary arteries. One of these injury sites received the brachytherapy catheter
alone and one received the catheter and radiation (dose prescribed was 30 Gy to the EEL nearest the catheter). All animals survived the radiation procedure. Prior to sacrifice, all animals had an angiogram taken. After angiography, the animals were sacrificed and the hearts explanted and fixed under arterial pressure.

The primary endpoint of this series of experiments was safety. The assessment of safety was based on examination of the arterial segments by both light and electron microscopy. Under light microscopy there was no evidence of radiation necrosis or delayed thrombosis (Fig. 7). Electron microscopy of the

**Figure 7.** A. Coronary artery 6 months after balloon overstretch injury. Significant neointimal formation is present. B. Coronary artery 6 months after balloon overstretch injury and intravascular brachytherapy. Limited neointimal formation present and no evidence of radiation necrosis.
endothelium demonstrated complete endothelialization of all arterial segments (Fig. 8). Efficacy was superficially addressed by examining the angiographic restenosis (>50% stenosis, angiographically) rate; in the 6-month group, it was 0% for the irradiated segments and 12% for the untreated segments.

Figure 8. A. Electron microscopy of the endothelium of a coronary artery 6 months after balloon overstretch injury. Endothelialization is complete. B. Electron microscopy of the endothelium of a coronary artery 6 months after balloon overstretch injury and intravascular brachytherapy. Endothelialization is also complete.
Clinical Plan

The initial clinical investigation will consist of two phase I trials addressing the populations at high risk for restenosis after PCI, namely patients with in-stent restenosis and de novo lesions in diabetics. So far, most of the intravascular brachytherapy studies have involved patients with in-stent restenosis. However, diabetic patients may also have enhanced benefits from brachytherapy. In fact, the pathophysiological mechanisms leading to restenosis in diabetics may partially differ from nondiabetics. Whereas, following balloon angioplasty in nondiabetics, negative remodeling leading to vessel shrinkage appears to be more important than neointimal proliferation in producing late lumen loss, the converse may be true in diabetics. The predominant role of neointimal proliferation in restenosis makes this population, similarly to the in-stent restenosis population, particularly suitable for brachytherapy because of the ability of radiation to prevent neointimal formation. Moreover, conventional percutaneous revascularization, including debulking devices, has shown limited efficacy in the treatment of both in-stent restenosis and lesions in diabetic patients. Two phase I registries involving 30 in-stent restenosis patients and 30 diabetics are planned. The study summaries are reported in Table 1. The antiplatelet regimen consists of clopidogrel 75 mg daily for 6 months in addition to aspirin. Independent core laboratories will perform quantitative angiographic analysis and IVUS analysis at baseline and follow-up. Since late thrombosis following intravascular brachytherapy occurs more frequently after stenting than after balloon angioplasty, the protocols favor provisional stenting, ie, stent deployment only for suboptimal balloon angioplasty results. In order to provide standard care and to minimize the

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<th>Table 1</th>
<th>Summary of Brigade In-Stent Restenosis Trial and Brigade Diabetic Trial</th>
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<tr>
<td><strong>In-Stent Restenosis Trial</strong></td>
<td></td>
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<tr>
<td><strong>Objective</strong></td>
<td>Safety and feasibility of IVUS-guided brachytherapy for in-stent restenosis.</td>
</tr>
<tr>
<td><strong>Design</strong></td>
<td>Prospective, nonrandomized trial.</td>
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<tr>
<td><strong>Population</strong></td>
<td>30 patients with in-stent restenosis.</td>
</tr>
<tr>
<td><strong>Primary endpoints</strong></td>
<td>30-day and 9-month composite endpoint of target vessel revascularization, death, and myocardial infarction.</td>
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<tr>
<td><strong>Secondary endpoints</strong></td>
<td>Angiographic restenosis (&gt;50%) of the target vessel at 9-months Subacute/late thrombosis at 30 days and 9 months.</td>
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<tr>
<td><strong>Diabetic Trial</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Objective</strong></td>
<td>Safety and feasibility of IVUS-guided brachytherapy in diabetics.</td>
</tr>
<tr>
<td><strong>Design</strong></td>
<td>Prospective, nonrandomized trial.</td>
</tr>
<tr>
<td><strong>Population</strong></td>
<td>30 diabetic patients with de novo or restenotic lesions ≥9 mm of length.</td>
</tr>
<tr>
<td><strong>Primary endpoints</strong></td>
<td>30-day and 9-month composite endpoint of target vessel revascularization, death, and myocardial infarction.</td>
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risks of treatment effect based on different antithrombotic regimens, glycoprotein IIb/IIIa receptor inhibitors will be routinely administered, if no contraindications to the drugs are present.21

Conclusion

The Brigade system is a second generation brachytherapy system. It combines the input of both the interventional cardiologist and the radiation oncologist. Its design is intended to conform to the lesions treated so as to maximize efficacy and decrease toxicity. Based on the failure patterns of preexisting devices, this device seems poised to make improvements to the field of intravascular brachytherapy.

References