

Market Application of a Novel Stent-based Patency Monitor to the management of Ischemic Vascular Disease

By

Baruch Schori

B.Sc. (Cum Laude) Information Systems Engineering, Technion, Israel, 2001

SUBMITTED TO THE HARVARD – MIT DIVISION OF HEALTH SCIENCES AND TECHNOLOGY AND THE MIT SLOAN SCHOOL OF MANAGEMENT IN PARTIAL FULFILLMENT OF THE REQUIREMENTS FOR THE DEGREES OF

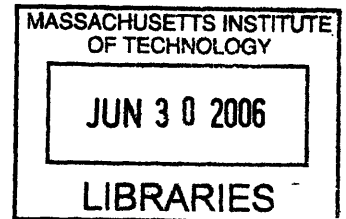
MASTERS OF SCIENCE IN HEALTH SCIENCES AND TECHNOLOGY

and

MASTERS OF BUSINESS ADMINISTRATION

at the

MASSACHUSETTS INSTITUTE OF TECHNOLOGY



The author hereby grants to MIT permission to reproduce and to distribute an electronic copy of this thesis document in June 2006. No part of this document may be reproduced or transmitted in any form or by any means electronic or mechanical, including photocopying and recording, or by any information storage or retrieval system, without permission in writing from the author.

© 2006 Baruch Schori. All rights reserved.

ARCHIVES

Signature of Author: _____
Harvard-MIT Division of Health Sciences and Technology
MIT Sloan School of Management

Certified by: _____
Richard J. Cohen, MD, Ph.D.
Whitaker Professor of Biomedical Engineering
Thesis Supervisor, Harvard – MIT Division of Health Science and Technology

Certified by: _____
T. Forcht Dagi, MD, MPH, MBA, Senior Lecturer
Thesis Supervisor, Harvard – MIT Division of Health Science and Technology

Accepted by: _____
Martha Gray, Ph.D.
Edward Hood Taplin Professor of Medical and Electrical Engineering
Director, Harvard – MIT Division of Health Science and Technology

List of Contents

Abstract.....	5
1. Introduction.....	7
2. Background.....	10
3. Related Work.....	14
3.1. Existing applications.....	14
3.2. Prior art.....	17
4. Significance.....	23
4.1. Literature Survey.....	23
4.2. Preliminary Questionnaire.....	26
4.3. Interpretation of results.....	36
4.4. Clinical Need.....	37
5. Analysis.....	40
5.1. Available techniques.....	40
5.2. Proposed Approach.....	43
5.3. Design and implementation.....	48
5.4. Value Proposition.....	54
6. Feasibility Assessments.....	56
6.1. In-vitro Experiment.....	56
6.2. Interpretation of results.....	66
7. Critical assessment of own work.....	68
7.1. Significance.....	68
7.2. Feasibility.....	69
8. Work Provision.....	70
8.1. Market Applications.....	70
8.2. Commercialization.....	72
8.3. Risk Mitigation.....	73
8.4. Impact.....	74
9. Summary Conclusions.....	76
9.1. Acknowledge of Contribution.....	77
Bibliography.....	79

Abstract

The use of stents following angioplasty in ischemic arterial beds is limited by complications and continuing vascular deterioration. A phenomenon called stent restenosis post procedure exists which puts patients at a relatively high risk for vessel stenosis and occlusion^{1,2,3}. Stent restenosis may eventually lead to clinical symptoms such as myocardial infarction, stroke or limb loss, and if overlooked might lead to death⁴. Within five years of stenting, a significant portion of patients require additional surgical intervention⁵.

A novel stent-based, implantable, and wireless approach for real-time monitoring of vessel patency at the site of coronary stents is proposed, will provide a measure of efficacy of stenting and of the pharmacologic regiment to mitigate the risk of vessel stenosis and narrowing due to the underlying.

The purpose of this thesis is to explore and test the Hypotheses that **there is a market for a direct, non-invasive monitoring of vessel patency at the site of a coronary stent; and that an implantable, wireless, stent-based device to monitor blood flow rate through a coronary stent can be designed and built.**

A literature survey of late clinical studies and the opinion of numerous specialist clinicians collected in interviews and preliminary questionnaire, demonstrate sufficient clinical ambiguity regarding the safety of coronary stents, including Drug-Eluting Stents (DES) portrait an underserved clinical need to justify the introduction of a direct, non-invasive modality for post-op monitoring of vessel patency at the site of a coronary stent.

A research of existing techniques establishes that measurement techniques are available for such monitoring. Preliminary results of an in-vitro experiment further support the proposed approach and lay the foundations for further work.

While not in the scope of this thesis project, additional potential applications for such an approach are far more reaching than coronary stents and might as well position this technique as a platform technology for numerous clinical applications.

1 Introduction

This thesis project is about a potential application of a novel stent-based patency monitor to the follow-up management of ischemic vascular disease in patients post angiography and stenting procedure.

The proposed approach is of an implantable device, which will incorporate multidisciplinary technology and will utilize current clinical knowledge and emerging technologies such as Micro-Electro-Mechanical Systems (MEMS) and wireless communication in order to measure in vivo blood flow velocity at the site of a coronary stent, and communicate data to a wireless, external reading device. The primary purpose of this device is to facilitate minimally invasive, ongoing monitoring of patency in blood vessels that have been augmented using angioplasty followed by stenting. The device is believed to provide a significant improvement in standard of care and quality of life by allowing earlier diagnosis and thus better end results of related treatment administration.

I have set two Hypotheses to be tested within the scope of this thesis:

1. ***Hypothesis 1: There is a market for a direct, non-invasive monitoring of vessel patency at the site of a coronary stent; and***
2. ***Hypothesis 2: An implantable, wireless, stent-based device to monitor blood flow rate through a coronary stent can be designed and built.***

The objectives of this thesis project are therefore two folds:

1. Assess the significance of the proposed approach, by testing the first Hypothesis that there is a market for such a device.

Relevant questions will include the following:

- a. Is there a need? Is there sufficient clinical ambiguity to justify the proposed approach?
- b. Are physicians interested? Is this interest economically driven or clinically driven?
- c. Would such a device make a difference in outcome by facilitating the real-time, long-term study and treatment of underlying conditions and vessel patency? Would such a device be welcomed in the optimization of management of these conditions?

The first Hypothesis will be tested using the methodologies of a literature survey, a preliminary questionnaire gauging potential of such approach by medical specialists, and by framing the value proposition of such an approach.

2. Assess the feasibility of the proposed approach, by testing the second Hypothesis that such a device can be designed and built.

Relevant questions will include the following:

- a. Are measurement techniques available?
- b. Design considerations – functionality, biocompatibility
- c. Proof of concept

The second Hypothesis will be tested using the methodologies of an overview of existing technologies, a detailed description of the selected technology and design

of the proposed device, and by building a proof of concept prototype, and showing preliminary results of an in-vitro experiment using the prototype.

In order to achieve these objectives, the structure of thesis will be as follows:

Chapter 2 - Background will demonstrate a wide appreciation of the context of the problem in hand, thus providing motivation to address this problem.

Chapter 3 - Related Work will include a survey and critical assessment of available techniques, and prior art related to methods for monitoring of stented vessel patency. A literature review will follow to demonstrate existing controversy regarding the use of stents.

Chapter 4 – Significance will gauge the clinical need and market characteristics by showing data and interpretation the results of a clinician preliminary questionnaire.

Chapter 5 –Analysis will describe the proposed novel approach to address the problem in hand. A theoretical assessment will be followed by practical design and implementation specifications.

Chapter 6 - Feasibility Assessments will detail the In-vitro Experiment design and methods followed by an interpretation of preliminary results.

Chapter 7 - Critical assessment of owns work will confront my findings with my hypotheses, and weigh advantages and disadvantages of the proposed approach.

Chapters 8 - Work Provision will describe risk mitigation and necessary next steps on the way to commercialization.

Chapter 9 - Summary Conclusions will be followed by **Bibliography**.

2 Background

Coronary artery disease affects approximately seven million Americans, causing 1.5M Myocardial Infarctions and over half a million deaths per year at an estimated cost exceeding \$100B⁶. Coronary artery disease is the result of a complex, years-long process called Atherosclerosis, in which cellular intimal and mineral additives, fatty and clotting debris accumulate and deposit in the arterial walls, forming a plaque comprised of cells, lipids (fats or cholesterol) and fibrous tissue (mostly collagen). This process may lead to a narrowing of the vessel lumen (stenosis), and reduction of blood flow (ischemia). Symptoms include angina pectoris (chest pain), and myocardial infarction (heart attack). In addition, the formed plaque is susceptible to rupture, resulting in an inflammatory process culminating in thrombus (clot) formation and acute cessation of blood flow to the heart, and leading to acute coronary syndrome, myocardial infarction, stroke or sudden death⁷.

Nearly a million new angioplasty constructions followed by implantation of a coronary stent - a mechanical device designed to keep the artery open - are performed every year in the United States in order to treat and overcome arterial stenosis related to blood vessel diseases (see Table 1 for procedure breakdown)^{6,7}.

Although such procedures are relatively common and have been proven to save hundreds of thousands of lives every year, they do not eliminate the underlying pathophysiology that initially led to arterial stenosis, and pose additional challenges. Post surgery patients implanted by bare-metal stents are still at a relatively high risk for vessel stenosis and occlusion at the site of the stent, and in 20-30% of the cases, stenosis persists

and leads to narrowing and reblocking of the stented artery (stent restenosis) over time (typically at six-months)¹⁻⁵. This occurs due to the body's response to the "controlled injury" of angioplasty which is characterized by vascular smooth muscle cells migration into the lumen of the stent and proliferation, thus forming scar tissue which encroaches on the lumen and forces the stent to close and restrict blood flow in the arteries. Drug-eluting stents - coated with a thin polymer that slowly releases an antiproliferative drug - were recently approved for use. While clinical trials assessing the efficacy of drug-eluting stents after 1 year of patient follow-up have shown encouraging results - reducing the frequency of vessel retreatment to less than 5%⁸⁻¹⁸ - it remains unclear whether the drug-eluting stents are inhibiting or simply delaying restenosis. Ongoing clinical trials of two dominant drug-coated stents - Johnson & Johnson's Cypher stent^{19,20} and Boston Scientific Corp.'s Taxus stent²¹ - presented new evidence of longer-term blood clots raising concerns that there is an increase in potentially deadly blood clots in patients' arteries that have been implanted with drug-coated stents^{22,23}.

Stenosis and blood clotting at the site of the stent may eventually lead to clinical symptoms such as myocardial infarction, stroke or limb loss, and if overlooked might lead to death, which raises two major questions - which stent will fail, and how to monitor the entire post surgery population in a cost effective manner. Nevertheless, the progress of restenosis as well as the formation of blood clots in these patients is nearly impossible to monitor with current imaging technologies (see Table 2), consisting of extremely invasive, costly and risky methods such as Catheter Angiography (CA), or non-invasive, but extremely expensive tests such as Magnetic Resonance Imaging (MRI) scan and specifically Coronary Magnetic Resonance Angiography (MRA). For instance,

MRA fail to provide imaging of vessels containing a stent and often show signal void at the location of a metallic implant, rendering evaluation of the lumen impossible to monitor^{24,25}.

The gold standard treatment therefore remains indirect stress tests of symptomatic patients only, which if positive, is followed by diagnostic CA^{26,27}. These techniques, being used selectively and periodically, and being conducted in a stationary setup, results in a very late diagnosis, if at all, only when the stent is over seventy percent occluded. Such a high percent of occlusion coupled with late diagnosis place the patient at very high risk and leads to expensive inefficiencies – all treated patients are administered extensive long-lasting anti-clotting medications as a preventive mean, and a significant portion of patients necessitates a repeat procedure or further treatment to reduce blockage and restore perfusion. These inefficiencies result in extensive burdens, both financial and clinical, on the health system, such as surveillance direct costs, repeat intervention risks and caregiver expenses.

Type of Operation	Case Load per Year (US 2004)	Stenosis and Occlusion	Comments
Angioplasty & Stenting	900,000	20-30%	Bare Metal Stents
		5%	Drug Eluting Stents

Table 1- Statistics on stenting surgeries performed in order to treat and overcome arterial stenosis related to blood vessel diseases

Diagnostic Modality	Cost per Procedure (US\$)	Comments/Complications
Catheter Angiography	5,000 - 10,000	<ul style="list-style-type: none"> • Invasive • Renal failure • Bleeding
Magnetic Resonance Angiography	2,000 - 4,000	<ul style="list-style-type: none"> • Poor resolution • Poor sensitivity & specificity
Nuclear Imaging	1,000 - 2,000	<ul style="list-style-type: none"> • Indirect measurement
Duplex Ultrasound	200 - 500	<ul style="list-style-type: none"> • Insensitive to small vessels • Physician dependent

Table 2 - Current Diagnostic Methods

For coronary stents current surgical interventions are palliative and do not cure the underlying disease, leaving the patients highly susceptible to vessel restenosis and occlusion. Invasive and non-invasive methodologies with improved specificity and sensitivity are therefore critical for vessel surveillance and subsequent treatment of vessel stenosis and occlusion.

3 Related Art

3.1 Existing Applications

Current surveillance methodologies include broad categories of survey to assess vessel patency²⁶. In general, these methodologies can be separated into two categories - DIRECT flow observation by using radiological techniques, that are dangerous, uncomfortable and invasive; and INDIRECT flow measurements, such as scans, stress tests etc that infer flow characteristics by watching the reaction of the heart, that are less specific and less sensitive.

DIRECT - the current most common method of blood flow assessment, Catheter Angiography (CA), often called Arteriography – which involves skin and arterial puncture with vessel catheterization by insertion of a thin plastic tube (catheter) into an artery in the arm or leg, advancement of it into the coronary arteries, and injection of a dye visible by X-ray into the bloodstream which can then be visible on X-ray pictures - is highly invasive, with associated long-term risk of renal failure, bleeding, and stroke.

Computed Tomography Angiography (CTA) is a less invasive procedure and uses small peripheral vein instead of artery for dye injection, but the technology can not reliably image small, twisted arteries or vessels in rapidly moving organs such as the heart, and therefore is not readily a substitute for CA.

Nuclear Imaging tests such as Radionuclide Ventriculography or Multiple-Gated Acquisition Scanning (MUGA), Positron Emission Tomography (PET) or Thallium Stress test - all involve injecting a radioactive dye into a vein, then using tomographic imaging to take pictures of the heart as it pumps blood – suffer rapid dissolution of dye,

require expensive gamma imaging cameras and are able to give a positive result only above 70% vessel occlusion.

Another invasive technique, referred to as “intravascular ultrasound”, where a miniature ultrasound transducer is inserted by a catheter to monitor blood vessel acoustic impedance has yet to prove its efficacy.

INDIRECT - Diagnostic Ultrasound or Echocardiography – a safe, painless test, which gives off a sound wave that bounces off the heart, creating images of its chambers and valves to examine its structure and motion - has gained popularity in assessing non-coronary flow velocities but remains insensitive in general to coronary vessels and can not detect an occlusion less than 50% of vessel lumen.

Magnetic Resonance Imaging (MRI) and specifically Magnetic Resonance Angiography (MRA) which produces images of flowing blood, became the modality of choice for angiography due to its non-invasiveness, but suffers low spatial resolution and is not adequate for diagnosis and treatment planning of small vessels (3 to 4 mm in diameter) and, in particular, the coronary arteries due to not only their size, but also their tortuous and complex pathway, the abundant signal from surrounding epicardial fat, and the significant motion associated with both respiration^{28,29} and cardiac motion. In addition and of special interest for this thesis, a major obstacle for coronary MRA imaging is the use of intracoronary stents. Although not a contraindication for MRA³⁰, local signal voids or artifact associated with implanted metallic objects such as intravascular stents preclude assessment of the stented portion of the vessel³¹.

A stress test, sometimes called a treadmill test or exercise test - which gradually increases heart demand for oxygen, thus requiring the heart to pump more blood and revealing coronary insufficiencies - remains the gold standard to assess heart performance, but is limited in nature for some patients and can subject patients with a dysfunctional heart to exercise loads and therefore pose additional risk.

Currently employed methodologies are unable to screen the asymptomatic, general population of post-surgery patients for vessel occlusion. Traditional testing methods are time consuming, invasive, expensive and associated with risk to patients. Large groups of post-surgical patients are therefore at risk for clinically silent vessel occlusion leading to myocardial infarction, loss of limb, stroke and sudden death. In addition, currently available methodologies are not specialized for frequent blood flow determinations during the convalescent period. By ignoring the changing physiology of coronary arteries blood flow, data from current techniques provide static anatomical measurements and misinterpret physiological, hemodynamic changes seen in these vessels. A better invention would be capable of monitoring hemodynamic conditions over extended periods of time to allow dynamic assessment of such changes.

Besides the blood flow measurement mechanism used, other aspects of modern vessel surveillance and care are non-optimal. Currently employed techniques require outpatient hospitalization, critical operator expertise and have traditionally been restricted to cardiac catheterization laboratories and intensive care units (ICUs). Such measurements can not be made easily in ambulatory settings, or under conditions of

cardiac loading, such as exercise, and therefore result in inconsistent information. A better invention would permit simplified, rapid and real-time vessel interrogation.

A preferred arterial flow measurement approach would include: (1) non-invasive technique, (2) easy deployment of the measuring element (3) efficacy for all types of coronary stents, and (4) optimal post-surgical assessment and care of the vessel.

3.2 Prior Art

The description herein describes systems and devices for measuring coronary artery flow rate and arterial blood velocity.

Ohlsson et al³² describe implantation of a pressure sensor and an oxygen sensor, the IHM-1, Model 10040 (Medtronic, Inc.). However, in this study, 12 out of 21 oxygen sensors within the first 6 months of implantation failed, probably because sensors were being coated by fibrous tissue. In addition, surgical implantation of this pacemaker-style device requires a 2-3 hour procedure in the operating room, which is more costly than a catheterization procedure to insert a pressure sensor. Data from this study, however, points to the importance of long-term, continuous pressure monitoring, as opposed to one-time measurements using standard cardiac catheterization techniques.

In U.S. Pat. No. **6053873: Pressure-sensing stent** issued Apr. 25, 2000 to Govari, Assaf et al, a method of monitoring flow rates within a stent is described. In particular, the use of ultrasonic sensors to monitor blood flow rates is described. However, due to the change in composition and thickness of the biological material present on the sensor

blood flow in a blood vessel issued Mar. 1, 1994 to Swartz, William M., where an ultrasonic transducer-conductor wire assembly is removably attached to non-removable cuff around vessel, to monitor blood flow within the blood vessel. After completion of monitoring the ultrasonic transducer-wire assembly, but not the cuff are removed from the patient. This method is clearly highly invasive and allows monitoring of blood flow during the procedure only.

In U.S. Pat. No. **6729336: In-stent restenosis detection** issued May 4, 2004 to Da Silva, Luiz B., et al., an apparatus is described which can presumably be used to detect in stent restenosis by comprising an acoustic sensor to detect stent acoustic oscillations. In U.S. Pat. No. **6308715: Ultrasonic detection of restenosis in stents** issued Oct. 30, 2001 to Weissman, Eric M., et al., a diagnosing method is described which utilizes a similar concept of exciting the stent structure to produce acoustic signal indicative of the diagnosis. The acoustic signal is then analyzed to predict a degree of restenosis experienced by the stent. In both methods disclosed, ultrasonic waves are used to assess **INDIRECTLY** the level of stenosis within the stent, by predicting material composition and the thickness of the wall around the stent rather than to assess blood flow velocity. Such an indirect approach can only assist estimating the vessel patency and is not complete – material composition, as well as wall thickness, might present asymmetric patterns which make it nearly impossible to accurately assess. In addition, exciting an intraluminal acoustic vibration at a site of potential stenosis might pose additional risk of plaque rupture and thrombosis.

intraluminally to measure the resultant temperature change of blood, produced by a heater, to indicate the blood flow rate through the blood vessel or artery. By using a rigid tube this approach suffers several drawbacks – a rigid tube may limit the device usage, by constraining its deliverability by a catheter, limiting the treated arteries to ones with a relatively larger diameter. A rigid structure may infringe vessel elasticity and induce friction or irritation of surrounding tissues, such as the vessel endothelium, the epicardium, and the visceral layer of the pericardium. It may also increase the long-term risk of thrombosis along the tube. In addition, the amount of energy required to significantly increase the blood volume that flows through the tube to a measurable levels is higher to allow an external induction in physiological conditions.

In U.S. Pat. No. **5271408: Hydrodynamic system for blood flow measurement** issued Dec. 21, 1993 to Breyer, Branko, et al., a hydrodynamic system for blood flow measurement is disclosed - two spaced passive transducers are mounted at the exterior surface of a catheter implanted within the vascular vessel, the first with a protrusion in the form of a hydrofoil profile, and the other with a flat surface at the exterior of the catheter. The transducer having the hydrofoil profile generates a signal due to the quasi-static pressure acting on the transducer as well as due to the drag force acting on the transducer caused by the blood flow. The other transducer generates a signal solely due to the quasi-static pressure; their respective signals can be subtracted in a differential amplifier, so that a signal proportional to the axial flow velocity is obtained. The insertion of the catheter into the vessel lumen for a long term period, as well as the transducers required interactability with the blood flow, pose a significant risk of thrombosis formation on the catheter or transducers' surfaces, and makes its long-term functionality

questionable after transducers' surface is coated by endothelium or restenosis.

Notwithstanding the extensive efforts in the prior art, however, there remains a need for an implantable *blood velocity/flow* sensor, which can provide useful *flow measurements* for an extended period of time, without material interference from thrombus formation, embolization, or other foreign body response. Preferably, the sensor is capable of continuous or near continuous monitoring, making data available to the patient or medical personnel.

4 Significance

4.1 Literature Survey

A novel method for treating coronary artery stenosis, termed Percutaneous Transluminal Coronary Angioplasty (PTCA), commonly called balloon angioplasty, was introduced in 1977 by Dr. Andreas Gruentzig (Switzerland), which can be performed using minimally invasive catheter procedure. In PTCA, the occluding plaque is compressed by the inflated balloon while no material is removed, and vessel patency is restored. Although the successful opening of the artery, in a small percentage of cases, the artery would collapse immediately after the balloon was deflated, requiring an emergency bypass graft surgery to repair the problem. In addition, in about one-third of cases, re-narrowing of the treated segment (restenosis) may occur in the immediate six months period post procedure, necessitating a repeat procedure or an invasive coronary artery bypass surgery. Despite intensive research effort and several drug trials, a solution to this phenomenon remains elusive^{33,34}.

In order to reduce restenosis rates and maintain vessel patency, a device called a stent - a metal tube or "scaffold", mounted on the balloon and able to be opened once inside the coronary artery - was first inserted into a human coronary artery in 1986, in Toulouse, France, by Drs. Jacques Puel and Ulrich Sigwart. In 1994 the first Palmaz-Schatz stent was approved for use in the United States. Over the next decade, several generations of bare metal stents were developed, with each succeeding one being more flexible and easier to deliver to the narrowing. But while bare metal stents nearly eliminated acute artery occlusion post procedure, in about 25% of cases restenosis persisted and occlusion at the treated site occurs, typically at six-month post

procedure^{33,34}. It was learned that restenosis, was not only the sole result of the coronary artery disease, but rather was the recurrence of the underlying disease combined with the body's response to the "controlled injury" of angioplasty, characterized by growth of smooth muscle cells roughly analogous to a scar forming over an injury.

New research efforts moved away from the purely mechanical bare metal stents and toward pharmacologic advances of a variety of drugs targeted at interrupting the biological processes that caused restenosis. Drug-eluting stent - first introduced in 2003 - incorporate a normal metal stent which is being coated with a pharmacologic agent (drug) which is sometimes imbedded in a thin polymer for time-release^{35,36}.

Currently two drug-eluting stents have received FDA approval for sale in the United States as well as the CE mark for sale in Europe - the Cordis CYPHER™ sirolimus-eluting stent in April 2003 (which later became Johnson & Johnson's product), and the Boston Scientific TAXUS™ paclitaxel-eluting stent in March 2004. Medtronic's Endeavor stent which uses ABT-578, a drug made by Abbott, was approved in Europe in April 2005. Additional drug-eluting stents – Abbott's own Zomaxx stent and Guidant's Xience stent – are currently undergoing clinical trials.

But while in recent clinical trials drug-eluting stents have been extremely successful in reducing restenosis - both the TAXUS™ and CYPHER™ stents have shown significant reduction of restenosis from the 20-30% range to single digits, and also a dramatic reduction in reinterventions in diabetics, a population that has been highly susceptible to restenosis in the past⁸⁻¹⁸ – leading market analysts to predict that the current

world market for drug-eluting stents will double to \$5 billion annually, new concern arise. It still remains unclear whether the drug-eluting stents are inhibiting or simply delaying restenosis^{19,21-23}. In addition, the issue of stent thrombosis is being scrutinized and concerns have been raised regarding an increase in potentially deadly blood clots in patients' arteries that have been implanted with drug-coated stents - In October 2003, the FDA issued a warning regarding cases of Sub-Acute Thrombosis (SAT or blood clotting) with the CYPHER™ stent that resulted in some deaths²⁰. Ongoing clinical trial of the CYPHER™ stent and the TAXUS™ stent have suggested an increase in the incidence of late stent thrombosis in patients implanted with drug-eluting stents, where the blood-clotting inside the stent can occur one or more years post-stenting. While this has been seen rarely in both the TAXUS™ and CYPHER™ stent trials, thrombosis is extremely dangerous, fatal in over one-third of cases.

To prevent thrombosis, patients are being administered a long-term antiplatelet therapy post-stenting to prevent the blood from reacting to the new device by thickening and clogging up the newly expanded artery and to allow a smooth, thin layer of endothelial cells to grow over the stent during this period, thus reducing the tendency for clotting. The therapy consists of anti-clotting or antiplatelet drugs such as aspirin, clopidogrel (Plavix) or ticlopidine (Ticlid) for six or more months after the stenting^{37,38}.

New stent designs exist but have yet to demonstrate a superior outcome in relation with restenosis and thrombosis. An example is the Conor MedSystems' CoStar stent which was approved in Europe in February 2006 - by utilizing a bioresorbable polymer to deliver the anti-restenosis drug, the CoStar stent, after eluting drug for a few months,

becomes in effect a bare metal stent - which may eliminate the concern of late stent thrombosis present in permanent polymer stents. In addition, Germany-based Biotronik is testing a completely bioabsorbable stent which will totally disappear after its role is fulfilled.

In addition to susceptibility to restenosis and thrombosis, literature suggests that several decisions made by the interventional cardiologist are of equal importance, and have been shown to have high correlation with the procedure clinical outcome post stenting²⁷ - the correct sizing of the stent, both length-wise to match the length of the lesion, and diameter-wise to match the artery lumen are two of these decisions and can be considered and determined prior to the procedure itself to ensure best result. Sufficient deployment of the stent, however, is equally crucial and must be evaluated in real time during the procedure. The physician has to verify that the stent, once optimally placed at the stenosis site, is expanded fully to the arterial wall – under-expansion can result in small gaps between the stent and arterial wall which can lead to serious complications such as blood clots, or Sub-Acute Thrombosis (SAT). Such assessments of stent expansion are made by viewing the real-time angiogram in the cath lab. Intravascular ultrasound imaging might provide more detailed information, but due to this technique operational complexity it is nearly never being utilized. Direct, easy-to-use methodologies for monitoring vessel patency during and immediately post stent deployment are therefore necessary to improve procedure outcome.

4.2 Preliminary Questionnaire

4.2.1 Overview

Ten specialist clinicians²⁷ were approached with a preliminary questionnaire (see Figure 1) followed by a face-to-face interview to assess the clinical need and gauge the potential market for the proposed approach to of a Novel Stent-based Patency Monitor to the management of Ischemic Vascular Disease.

To avoid any potential bias, no information was delivered to the clinician prior to questionnaire filling (such as the purpose of the questionnaire, the proposed approach, or any other subjective evaluation of clinical conditions and standard of care).

4.2.2 Materials and Method

Clinical Need

To define the nature and scope of the clinical need, clinicians were asked the following two questions:

- 1. What is the main post-op risk associated with patients who undergo a coronary angioplasty and Stenting procedure? What is the symptom/complication prevalence?*

This question intended to assess whether there is a status-queue in the medical community or are different specialists present different perspectives regarding the risk associated with such procedures. By asking of the prevalence, a second insight was gained regarding the awareness of such a risk within the medical community.

2. *How do you follow-up these patients to avoid/detect this symptom/complication?*

In this question physicians were asked to fill relevant screening modalities, medications and other modalities and to quote the frequency of post procedure follow-up visits, to gauge existing standards of care two folds – the first being to assess whether sufficient screening and interventions exist to mitigate the previously described risk and overcome its clinical outcomes, the second being to evaluate if existing imaging applications fulfill the clinical need associated with that risk.

Relatively similar inputs in response to these questions with high correlation to literature data would suggest a well-defined need with high awareness, whereas higher spread would suggest the contrary.

Physician Interest

To find out if physicians were at all interested in improving the current clinical status, and if so what drives this interest, clinicians were asked the following two questions:

- 3. If you had the ability to monitor a single parameter in these patients as part of the follow-up, in a non-invasive, instantaneous screening procedure which could be performed in an office or a clinic, what would you monitor?***

In this question physicians were asked to circle the most indicative parameter of clinical significance for the symptom/complication from the following blood characteristics:

- a. Systolic Pressure within the stent
- b. Diastolic Pressure within the stent
- c. Flow Rate (Volume/Time) through the stent
- d. Flow Velocity through the stent
- e. Hematocrit Level
- f. Blood Viscosity
- g. Blood Conductivity
- h. Specific Enzyme Levels

This question intended to define a clinician interest in monitoring a specific blood character of clinical significance - to find if there is indeed a wide spread, common interest that can be addressed.

4. If you had the ability to detect significant change within a stent of this parameter, at a simple, office-based screening procedure, would that affect the follow-up regimen and how?

In this question physicians were asked to specify if such monitoring process would or would not affect the follow-up treatment and how – as an insight to whether or not they would welcome utilization of such approach and the associated paradigm shift for follow-up vessel patency monitoring.

Physician inputs in response to these questions will reveal whether there is a strong, unified interest in monitoring a single, most significant character, and will help estimate their openness and potential acceptance of a modality that would address this interest, if exists.

Change in Clinical Outcome

To find out if physicians believe, based on current available clinical information and best practice, that the use of such monitoring might change clinical outcome, clinicians were asked the following question:

5. Do you believe such monitoring and sequential adjusted treatment can change the clinical outcome of these patients?

Physician inputs in response to this question will help understand the perceived value associated with such monitoring process.

Clinician Questionnaire – January 2006

Clinician Name: _____

1. What is the main post-op risk associated with patients who undergo a coronary angioplasty and Stenting procedure? What is the symptom/complication prevalence?
- _____

2. How do you follow-up these patients to avoid/detect this symptom/complication? (fill relevant)

a. Screening

Modality	Frequency (exams/Yr)
Angiography/Arteriography	
Computed Tomography Angiography (CTA)	
Magnetic Resonance Angiography (MRA)	
Duplex Ultrasound	

b. Medications

Drug Name	Dosage and Frequency

c. Outpatient visits – Frequency _____

d. Other _____

3. If you had the ability to monitor a single parameter in these patients as part of the follow-up, in a non-invasive, instantaneous screening procedure which could be performed in an office or a clinic, what would you monitor? (circle the most indicative parameter of clinical significance for the symptom/complication in q.1)

- a. Systolic Pressure within the stent
- b. Diastolic Pressure within the stent
- c. Flow Rate through the stent
- d. Flow Volume through the stent
- e. Hematocrit Level
- f. Blood Viscosity
- g. Blood Conductivity
- h. Specific Enzyme Levels _____

4. If you had the ability to detect significant change within a stent of this parameter, at a simple, office-based screening procedure, would that affect the follow-up regimen and how?

- a. Yes (please explain) _____
- b. No (please explain) _____

5. Do you believe such monitoring and sequential adjusted treatment can change the clinical outcome of these patients? _____

Thank you!

Figure 1 - Clinician Questionnaire

4.2.3 Results

Question 1

All clinicians stated stent restenosis and SAT as the leading post-op complications.

Clinicians specified the prevalence of restenosis to range from 4% to 15% in DES and 20% to 30% in bare metal stents, while in literature the estimated prevalence of drug-eluting stent (DES) is 5-10% and of bare metal stent is 20%-30%.

Acute Thrombosis was mentioned as another serious complication, which while is much less prevalent, is associated with much more severe outcome, with approximately 40% mortality AND >80% acute MI. Clinicians specified the prevalence of SAT to be 1-2%, while in literature the estimated prevalence of SAT is 1%.

Clinicians stated to be using DES in 80-90% of cases.

Question 2

Screening – for asymptomatic patients no screening methodology is undertaken at post-op follow-up. This finding is somewhat surprising, but sits in agreement with the technical deficiency of current modalities to image patency of stented vessels.

When patients become symptomatic with angina a stress test is performed, which if positive leads to either an Angiography or a CTA test, to evaluate restenosis progress.

For SAT, as it is an acute event, no screening modality is available.

Medications – patients are unanimously administered anticoagulative drugs such as Aspirin (325mg QD), Plavix (75mg QD), CHOL, or BP Rx.

Frequency of Outpatient Visits – patients are followed-up, in general, by an outpatient visit to the interventional cardiologist two weeks post procedure and 2-4 additional visits per year thereafter. These visits are conducted regardless of additional, parallel visits to PCPs and cardiologists.

Question 3

All clinicians selected *Flow Rate through the stent* as the most clinically significant parameter indicative of vessel patency and stent underlying restenosis conditions, which would be their first choice if were able to monitor as part of the follow-up.

Question 4

All clinicians but one answered *Yes* believing that monitoring Flow Rate through the stent may change the follow-up regimen. In their aggregated view, it would provide better information than stress test does, and might increase the frequency of follow-up visits and stress tests, while at the same time might reduce the need for angiography testing and augment its results when done, and facilitate earlier reintervention if so required.

One clinician answered *No* claiming that as no effective medications exist to prevent restenosis, such monitoring, while has the potential to diagnose asymptomatic patients and facilitate earlier reintervention, would not change the medication administration.

Question 5

Half of clinicians answered *Yes* believing that monitoring vessel patency on its own has the potential to improve clinical outcome by better understanding the disease progress and responding accordingly.

The other half was uncertain, stating that there is lack of knowledge to estimate the potential outcome, and that the superiority of such approach relative to a stress test is yet to be proven.

In addition to these five questions, clinicians specified an additional complication when there is an incomplete expansion of the stent during deployment, which requires immediate reintervention. There is no screening modality to detect such event except for intra-vascular ultrasound immediately post procedure which is rarely used due to its cumbersome operation.

All clinicians showed great interest in such a technology, stated that if such technology existed they would use it on all of their patients, and asked to be followed-up with the progress of this project.

4.3 Interpretation of results

The literature survey reveals the existence of vibrant controversy regarding the safety and effectiveness of DES in preventing restenosis – clinical studies have been performed for relatively short periods of no more than two years, and the findings are still eluded. It is yet to be proven that DES actually prevent restenosis rather than delay it. New evidence of higher risk of thrombosis when DES is used further fuel the debate within the medical community.

The results obtained in the preliminary questionnaire, clearly suggest that there exist a clinical need to monitor vessel patency post-op. The survey results suggest that clinicians are highly aware of the existence and prevalence of restenosis and thrombosis which suggest that this need is well defined and accepted.

Current modalities are not sufficient for such broad monitoring process, and due to multiple reasons are rarely, if at all, utilized for such objective.

The most important factor indicative of vessel patency and stent underlying restenosis conditions is synonymally believed to be *Flow Rate through the stent*.

Monitoring of vessel patency is perceived advantageous in order to accurately detect the natural history progress of underlying disease, to allow earlier reintervention or regimen adjustment and reduce complication rate in post-op patients.

Integrating the results, I believe there is sufficient evidence of clinicians' interest in a novel approach to address this need. Given that the perceived value added is in changing current standard of care in what is believed to be an opportunity to improve clinical outcome, and from the other hand there is minimal utilization of existing imaging modalities, this interest is likely to be clinically rather than economically driven. A detailed cost-effective analysis is required to establish economically driven incentives for the health care system as a whole in utilizing such a novel approach.

According to this preliminary survey, clinicians believe that there may be a difference in clinical outcome by facilitating a real-time, long-term monitoring of vessel patency and a real option to better manage post-op follow-up and related treatment. Therefore, it is reasonable to estimate that a novel approach which while would yet need to be evaluated in the field, might allow such improvement, would be welcomed in the optimization of management of these conditions.

4.4 Clinical Need

As described previously, the use of stents following angioplasty in ischemic arterial beds is limited by complications and continuing vascular deterioration. A phenomenon called stent restenosis post procedure exists which puts patients at a relatively high risk for vessel occlusion. Stent restenosis may eventually lead to clinical symptoms such as myocardial infarction, stroke or limb loss, and if overlooked might lead to death¹⁻⁵.

Within five years of stenting, a significant portion of patients require additional surgical intervention. Additional complications result from insufficient stent expansion at deployment, which in turn can lead to serious complications such as blood clots, or Sub-Acute Thrombosis (SAT)^{6,7}.

Post procedural assessment of vessel patency at the site of a stent is therefore critical to optimal post-operative outcome.

Based on the literature survey and the results of the preliminary physician survey, it is reasonable to estimate that the most significant factor clinically to monitor vessel patency at the site of a stent would be blood flow rate, meaning the volume of blood transferred through the stent lumen in a time constant. In clinical settings, the most common flow rate unit used is cc/min, although other flow rate units such as cc/hr are in use as well.

In an optimal case where the vessel cross-sectional area is known and remains constant along time, blood flow rate can be determined inferentially by retrieving the blood average velocity. In such case blood velocity depends nearly entirely on the pressure differential that is forcing the blood through the vessel, and either direct fluid velocity or indirect pressure differential along a known distance would allow flow rate assessment.

In real life scenarios, however, and especially for our interest, vessel cross-sectional area in patients suffering from a vascular disease deteriorate over time due to

restenosis and therefore average velocity or pressure differential alone are not sufficient and more information is required to assess flow rate.

Additional factors that affect blood flow rate include the blood viscosity and density. These factors tend to remain constant in most physiological conditions with only minor fluctuations.

A device that will allow a real time measure of efficacy of stenting and pharmacologic regimen is therefore required, to mitigate the risk of vessel restenosis and occlusion due to the underlying disease and the body reaction to the controlled injury at the site of stenting.

5 Analysis

5.1 Available Techniques

Several techniques are available to be used in flowmeters, which might be candidates for DIRECT non-invasive monitoring of vessel patency. In general, these techniques can be classified as either differential pressure sensors or velocity sensors³⁹⁻⁴².

Less common techniques include laser or light flowmeters and hydrodynamic flowmeters.

Differential pressure devices⁴³

The basic operating principle of differential pressure flowmeters is based on the premise that the pressure drop across the vessel segment is proportional to the square of the flow rate within that segment. The flow rate is obtained by measuring the pressure differential and extracting the square root.

Differential pressure flowmeters have a primary and secondary element. The primary element causes a change in kinetic energy, which creates the differential pressure in the vessel segment. The secondary element measures the differential pressure and provides the signal or read-out that is converted to the actual flow value. The sensor must be properly matched to the vessel size, flow conditions, and the blood properties, and therefore might require frequent calibration events.

Velocity Sensors

Velocity sensor techniques consist of Electromagnetic, Ultrasonic and Thermodilution designs.

Electromagnetic flowmeters⁴⁴ operation is derived from Faraday's law of electromagnetic induction that states that a voltage will be induced when a conductor moves through a magnetic field. The blood, being an electrically conductive liquid serves as the conductor; the magnetic field is generated by either energized coils outside the vessel or induced from outside the body. Two electrodes mounted in opposite sides of the vessel lumen detect the voltage, which is measured by a secondary element. The amount of voltage (E) developed across the electrodes will be proportional to the diameter of the vessel (D), the magnetic field density (B) generated by the coils, and the velocity (V) of the blood flow:

$$E = V \times B \times D$$

If B and D are known (which in this case will be the distance between the electrodes), the blood flow velocity V can be easily deduced by measuring E.

The voltage that develops at the electrodes is a millivolt signal. This signal is typically converted into a standard current (4-20 mA) or frequency output (0-10,000 Hz) at or near the sensor and then can be converted into a digital output, allowing for wireless communication with an external reader outside the body.

Magnetic flowmeters expected inaccuracy is from 0.2-1% of rate.

Ultrasonic flowmeters⁴⁵ can be divided into Doppler-shift flowmeters and time-of-travel (or transit) meters.

Doppler-shift flowmeters measure the frequency shifts caused by blood flow. Two transducers are attached to one side of the vessel, one of them is a receiver element.

The transducer sends a signal of known frequency ultrasonic pulse into the blood stream. Blood particles, such as RBCs, cause the pulse to be reflected to the receiver element. Because the blood causing the reflection is moving, the frequency of the returned pulse is shifted. The frequency shift is proportional to the blood velocity. Measurement inaccuracy ranges from $\pm 1\%$ to $\pm 5\%$.

laser Doppler flowmeters use the same concept but utilize a coherent, low powered laser beam, and are therefore more suitable for artificial applications such as measuring the blood flow within the microcirculatory beds under the skin and less so for deeper applications such as coronary arteries.

Transit Time flowmeters use wide-beam illumination, and two transducers mounted on each side of the vessel - one upstream and one downstream - to pass ultrasonic signals back and forth, alternately intersecting the flowing liquid in the upstream and downstream directions. The configuration is such that the sound waves traveling between the devices are at a 45 deg. angle to the direction of blood flow. The speed of the signal traveling between the transducers increases or decreases with the direction of transmission. The Flowmeter derives an accurate measure of the 'transit-time' it took the wave of ultrasound to travel from one transducer to the other. The difference between the upstream and downstream integrated transit times is a measure of flow velocity.

Theoretically, transit-time ultrasonic meters are very accurate (inaccuracy of $\pm 0.1\%$ of reading is sometimes claimed).

These flowmeters can measure two different outputs - Pulsatile, which is the real-time flow waveform and Mean which gives out a filtered signal of mean flow.

Thermodilution measurement⁴⁶ is performed by sensing temperature gradient of blood along a specific time period. The initial blood temperature change is produced either by injection of iced saline through a catheter to locally cool the blood, or by a heater, to locally heat the blood. A thermocouple or sensing element retrieves the resultant temperature change of blood, which is indicative of the blood flow rate through the blood vessel or artery.

5.2 Proposed Approach

5.2.1 Overview

The proposed device is an implantable, wireless sensor, able to measure flow rate and communicate its retrieved data to an external device. It will be incorporated within a stent in order to measure blood flow velocity in the stent post angioplasty and stenting surgery. The device will be adhered to the stent wire mesh and its layout will not infringe the stent footprint, thus allowing for vascular spontaneous contraction and dilation, while ensuring mechanical flexibility and fixation to the stent. The device will be attached to the stent as part of the stent's manufacturing process and will be delivered to the patient's vascular system together with the stent. The device is a Class III device by the standards used by the FDA to classify medical devices.

The device will allow a non-invasive, on-demand, and dynamic information about the blood flow velocity characteristics within the stent. Readings from the device by an

external reader will be taken frequently, starting during and immediately after the procedure and continuing during regular PCP (Primary Care Physician) visits, Cath lab follow up visits, or visits to the cardiac specialist treating the patient. Since normal and pathological blood flow rates within native and stented arteries are well characterized, the data obtained from the device will have significant meaning to the physician. By accurately measuring blood flow velocity in the stent on a long-term, continuous basis, the device will allow understanding of the flow fluctuations and underlying physiological changes within the stent post stenting procedure. This information will provide an opportunity for an early diagnosis and treatment for restenosis, as well as facilitate an ongoing monitoring to assess the prescribed treatment efficacy. Based on the patterns observed from the readings, the physician will be able to determine whether a more invasive and thorough examination is needed before large percent of the stent is occluded.

The proposed approach is the only one to directly and non-invasively give ongoing blood flow measurements, and as such, there really is no competing alternative.

5.2.2 Device Requirements

The requirements of such a device consist of both Efficacy issues (Functional Requirements) and Safety issues (Anatomical, Biological and Physiological requirements), detailed herein.

Functional Requirements

1. The device is required to measure absolute flow rate (cc/min) within a stented vessel at the location of the stent.
2. The device shall be able to measure blood flow 'upon request', meaning while it is temporarily activated.
3. Each measurement shall be a single assessment of the blood flow rate.
4. The measurement accuracy shall be within 5% of the actual flow rate, in order to truly reflect blood flow changes over time and be able to correlate with existent stenosis.
5. The device shall communicate wirelessly with an external reading device to allow non-invasive blood flow measurement post angioplasty and stenting procedure.
6. The device shall function within the body for an unlimited period of time, without the need for invasive intervention. Practically, it should function for the entire longevity of the underlying stent.

Anatomical Requirements

7. The device footprint would be minimal, $<0.5\text{mm}^3$ including all subcomponents.
8. The device should not interfere with stent elasticity, to avoid stent kinking and occlusion due to the device stiffness.
9. The device shall be fixated to the stent, to avoid longitudinal movement along the blood vessel or complete migration into the pericardial cavity.
10. The device shall not interfere with stent deliverability into target site, to allow insertion of the stent and adhered device as a single implant with current procedure methodology and know-how.

Biological Requirements

11. The device and its components should be biocompatible:
 - The device shall not induce any unnatural responses or remodeling of the surrounding organs, tissues and cells.
 - The device shall not induce any toxicity to the surrounding organs, tissues and cells.
 - The device and its components will be made of materials with no short term irritation or sensitization, no cytotoxicity, no acute systemic toxicity, No chronic toxicity.
 - Hemocompatibility of outer layer of the device
12. The device and its components shall not degrade within the body, thus preventing immune system responses and generation of small particle disease.
13. The device shall not induce scar formation due to friction or irritation of any of the surrounding tissues, such as the vessel endothelium, the epicardium, myocardium, and endocardium, and the visceral layer of the pericardium.
14. The device shall not induce hyperplasia, hypoplasia or hypertrophy in any of the surrounding tissues, such as the vessel endothelium, the epicardium, myocardium, and endocardium, and the visceral layer of the pericardium.

Physiological Requirements

15. The device shall not interfere with heartbeat rhythm.
16. The device shall not form pressure on surrounding tissues and organs.

The device preliminary concept of design and main components are illustrated in Figure 2, 3, and 4 herein.

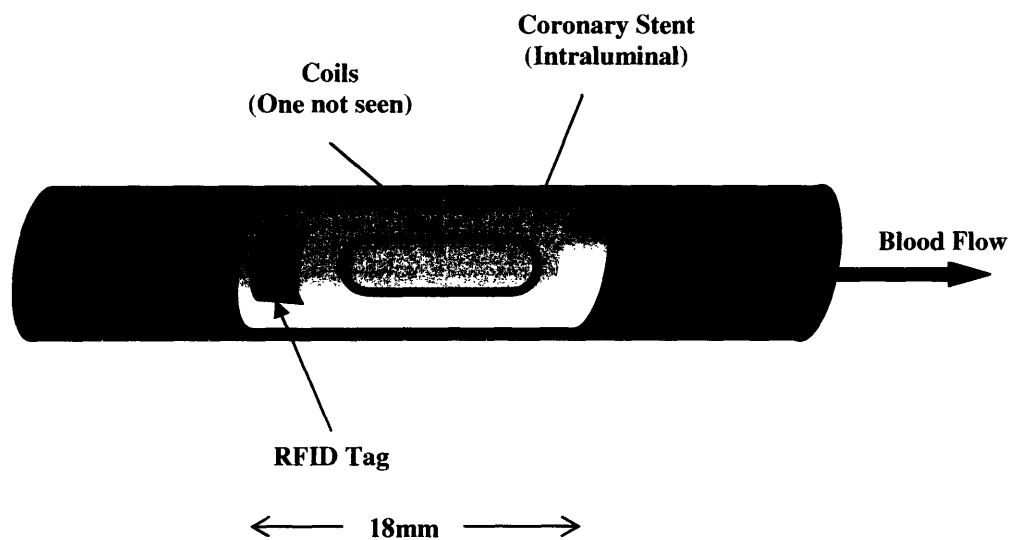


Figure 2 - The EM device is mounted on the stent

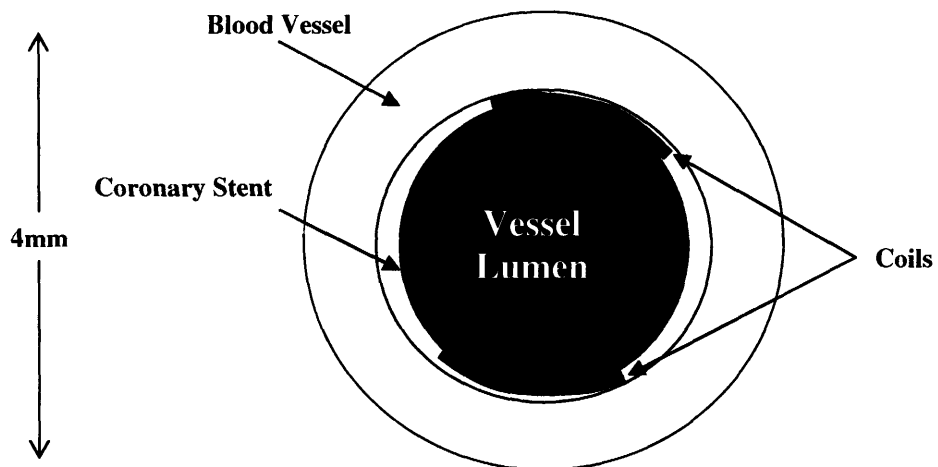


Figure 3 - A cross-sectional view of the EM device

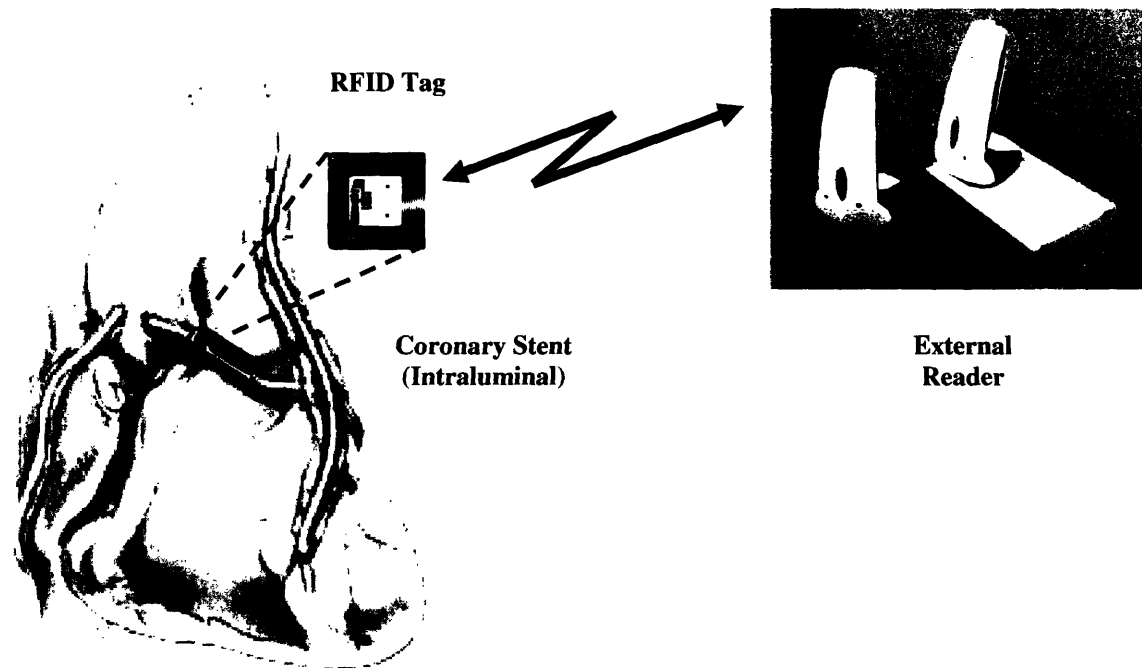


Figure 4 - System Concept. RFID Tag facilitates wireless communication with External reader.

5.3 Design and Implementation

5.3.1 Design Concept

The device will be incorporated within an arterial coronary stent.

In order to measure flow the device shall utilize one of the following techniques:

1. Electromagnetic induction (EM prototype) – based on Faraday's Law, an initial electric field within the stent, induced by an external electromagnetic field, will be altered by the blood flow which is a conductive fluid and will cause a voltage gradient across the

blood vessel. Thus flow characteristics will be deduced by applying an electromagnetic field to a coil of wire adhered to the stent, and then measuring the voltage across the loop, which is proportional to the blood flow velocity through the stent.

2. Thermodilution (TD prototype) – based on Thermodilution Laws, a constant heating of a thermistor adhered to the stent wire mesh, induced by an external electromagnetic field, will be altered by the blood flow which facilitates rapid dissipation of heat off the thermistor and into the blood stream. Thus flow characteristics will be deduced by measuring, after a time shift from initial heating, the thermistor resistance which is proportional to the thermistor temperature. The thermistor temperature is in turn proportional to the blood flow velocity through the stent.

Either measurement, indicative of the flow velocity through the stent, will then be transmitted by the device wirelessly to the external reader, by utilizing a wireless communication such as RFID technology.

Other techniques and especially ultrasound-based techniques such as Doppler-Shift flowmeters and Transit Time flowmeters were excluded based on preliminary estimates of power consumption that were reasonably higher than the proposed techniques.

In order to simplify the initial development process a simple design was chosen. Thus, the first generation device will be a ‘passive’ sensor - it will only measure blood flow ‘upon request’, meaning upon temporarily activation from outside the body. The

measurements will be initiated from outside the body by an external reader that will power the device and stimulate its components to produce flow measurement and related readings that can be directly correlated to a fluid velocity and flow rate. This will be done through an electromagnetic process of induction and will allow the device to perform without a self electrical power source, eliminating the need to implant a battery, and thus eliminating associated risks. Furthermore, the first generation of this device will incorporate unidirectional data transfer to only signal the flow measurement outside of the body to be received by the external reader.

Future generations would potentially allow data storage of blood flow ‘upon defined events’, requiring an internal electrical power source, and would potentially incorporate bidirectional data transfer – to allow both inward communications, to allow control, initiation and calibration of the device, and outward communications, to allow signaling the flow measurement to the external reader.

5.3.2 Sub Components

In order to fulfill its required functionality, the device shall consist of the following major components (see Table 3 for details):

1. Silicon-coated Chip

The Chip shall provide the support frame for all of the device components. The Chip shall be made of unalloyed, grade 2 titanium (ASTM B-338-95; Tico Titanium, Inc., Farmington Hills, MI). This material was chosen as the substrate for the Chip based on its long history of use the cardiovascular experimentation. The entire surface of the

Chip will be coated with Silicon to ensure biocompatibility, and to avoid friction or pressure on surrounding tissues while arterial contraction and dilation.

2. Electrical Source

The device will have no internal electrical power source – its operation will be initiated from outside the body by an external reader that will power the device and stimulate its components through an electromagnetic induction.

3. Measuring Element

a. EM prototype – Coils will serve as the flow measurement electromagnetic sensor, to actually measure a momentarily blood flow through the stent. The coils shall be made of a conductive, biocompatible metal. Preliminary choices would be either tungsten or gold, based on current findings which suggest that even if the tungsten corrodes, cell function is not affected⁴⁷.

b. TD prototype – A thermistor adhered to the stent wire mesh will be heated by a point heater. The thermistor resistance after a time shift from initial heating, which is proportional to the thermistor temperature, which is in turn proportional to the fluid velocity through the stent, will be measured to deduce blood flow velocity through the stent.

4. Data Processing

Analog measurement of voltage will be converted to digital signals by using an A/D converter located on the Chip.

5. Communication

A RFID tag shall facilitates wireless communication of the digital signal between the device and the external reader using radio frequency waves. The tag consists of an integrated circuit to encode and hold information (specific identification code, and voltage gradient parameter). The stent wire mesh would serve as the tag antenna to transmit data to the external reader. The tag profile will be attached to the Chip.

The first generation device will include a 'Passive tag', which derive its energy from radio frequencies generated by the external reader and do not require a self electrical power source, and therefore are much smaller and less expensive compared to 'Active tags', which do require an internal power source. A characteristic radio frequency initiated by the external device, shall induce electrical current in the antenna and the tag shall reflect back its identification code and a voltage gradient parameter.

The RFID tag shall operate low frequency radio waves of 125-134 KHz. Low frequency waves, while limiting the read range potential to around 1.5 meters, will demonstrate the following advantages:

- Works well near metal, such as the Stent and Coils
- Does not affect human tissues
- Does not induce heart electrical stimulation or interfere with heartbeat

Currently, 'Passive tags' are commercially available and are manufactured to well defined engineering specifications, defined as Class 0 or Class 1 in North America.

The smallest such devices are measured 0.4 mm × 0.4 mm, and cost from US\$0.40. The 134.2 kHz RFID chips, from VeriChip Corp., a subsidiary of Applied Digital Solutions Inc., was recently approved by the FDA to be the first RFID chips that can be implanted in humans.

6. External reader

The external reading device will be designed as a handset and serve a number of functions. The external device shall place an electromagnetic field across the body to power the device, by stimulating a current in the coils to create the local magnetic field and by activating the RFID tag to sense and transmit the vessel voltage gradient. Readings of voltage gradient shall be directly correlated to a fluid velocity and flow.

The external reader shall operate low frequency radio waves of 125-134 KHz, to demonstrate the same advantages as the RFID tag.

The external reader shall consist of an antenna packaged with a transceiver and decoder, to decode the data encoded in the tag's chip, present it as a fluid flow parameter and send the data to a host computer for processing.

Component	Prototype	Beta version
Electrical Source	Power Supply	External
Measuring Element	EM prototype: 1. Electrodes - Copper tape 2. Wire - 30 AWG Wire	MicroChip elements
	TD prototype: 1. Thermistors (GE. Edison, NJ, US) 2. Resistive Wire (JLC Eletromet. RI, US)	

Data Processing	Digital Multimeter (John Fluke, WA, US)	A/D Converter
Transmission	NA	RFID tag
Receiving	NA	Receiver

Table 3 - Component Breakdown

5.4 Value Proposition

The device will provide a significant improvement in standard of care and quality of life for patients suffering from ischemic vascular disease, and would improve diagnosis and end results of related treatment administration by allowing physicians to monitor the success of ongoing treatments between surgery and stenosis. The device will offer many advantages compared to current techniques, including:

For Physicians -

- Implanted during existing procedure - easy adoption
- Allows intra and post operative dynamic monitoring
- Allows a longitudinal surveillance of each stent performed
- Reliable and reproducible results
- Ease of use, rapidly performed readings
- Allows a lengthwise study along the stent (by placing and reading from multiple devices placed in different locations on a single stent)

For Patients -

- Peace of mind
- Early detection of restenosis allowing earlier, safer and more effective intervention – to improve outcome and reduced mortality of occlusions

- No documented side-effects of related materials
- Non-invasive measurements - avoid risks of invasive procedure

For 3rd Party Payers and Hospitals -

- Cost effectiveness - inexpensive surveillance
- Out-patient clinical readings
- Earlier, safer and more effective intervention – fewer re-operations
- Improved standard of care

The utilization of the proposed device may provide a new, superior diagnostic tool within existing implantable devices – such as the coronary stent, allowing earlier, more efficient intervention, thus further reducing patients' risk, improving clinical outcome, and reducing cost to society⁴⁸.

6 Feasibility Assessment

6.1 In-vitro Experiment

6.1.1 Overview

The purpose of the In vitro experiment is to demonstrate a proof-of-concept for the proposed approach as a mean to monitor flow rate within a stented vessel.

A Stented Coronary Artery (SCA) model was constructed to host the coronary stent and the device.

Three prototypes of the device were constructed to be used in this experiment, each utilizing a different technology to monitor flow rate – either EM or TD (see Figure 6). Each prototype was incorporated within a coronary stent deployed within the SCA model.

A flow apparatus was constructed to provide a controlled setup for measuring flow rate within a stent by generating fluid flow through the SCA model, thus partially mimicking the coronary artery blood flow.

The scope of this preliminary experiment was the ability to measure flow rate through a stented vessel. Both prototypes represent an initial, limited design of the measurement unit of such a device, and therefore do not encapsulate all desired components and features. Miniaturization of the device, as well as external power

induction, and wireless communications were not represented in these prototypes and were accounted for by other means as described later on.

6.1.2 Materials and Method

In vitro Stented Coronary Artery (SCA) model

A simplified planar model of a Coronary Artery was fabricated from a paper straw with diameter of 4mm (Chenille-Kraft-Company, IL, USA). This represents the diameter of a normal non-diseased LM coronary artery, which is 4.5 ± 0.5 mm in men and 3.9 ± 0.4 mm in women⁴⁹. The angulations and tortuosity of the Coronary Artery segment were not reproduced.

The stent used was a commercial coronary stent (ACS Multi-Link RX Tristar 3.0 x 18mm Coronary Stent System, Guidant, Advanced Cardiovascular Systems, Inc., CA, USA). A metal spring substituted the actual stent in the experiments conducted as part of this thesis..

During intravascular deployment, the stent (of diameter 3 mm when fully expanded) is located inside the paper straw. To allow flow rate measurements and data retrieval the straw was penetrated by thin-wire. As in clinical practice, the device was deployed by a delivery system pressurized in 2 ATM increments until the stent is completely expanded.

Flow circuit

The flow apparatus served the functions of partially mimicking the coronary artery blood flow, by providing a constant flow rate of 13.6 cc/min, which translates into flow velocity of 1.15 cm/sec which is comparable to flow rate within coronary arteries⁵⁰. Pulsatile flow rate was not generated at this setup. This apparatus provided a controlled setup for measuring flow rate within a stent.

The flow apparatus is shown in Figure 5. The inlet section into the SCA model was a straight PVC pipe (silicone tubes) of inner diameter 5mm and length 0.3m which incorporated a temperature-controlled reservoir, a large volume infusion pump (Deltec® 3000, Graseby Medical, Watford, UK), and an ultrasonic cannulating flow probe (24N, Transonic System Inc., Ithaca, NY, USA). After the SCA model fluids were collected to a fluid container.

Flow rate was generated by the infusion pump which produced a pre-defined steady flow rate.

The actual mean flow rates were determined by measuring the volume of fluid collected at the container over a known time interval. The flow probe served as control to provide an additional indication of the flow rate through the SCA model.

For flow rate measurement with the EM prototype, the fluid was a 10% sucrose and sodium chloride solution with conductivity comparable to that of human blood⁵¹.

For the EM prototype measurements, a constant, linear electromagnetic field was induced at the stented site, by placing two magnets (S1030 Square magnet, N38 Nickel, 4mm thick) at opposite locations around the SCA model at a distance of 13mm. The electromagnetic field density, measured using a Gauss meter, was 0.192 Tesla.

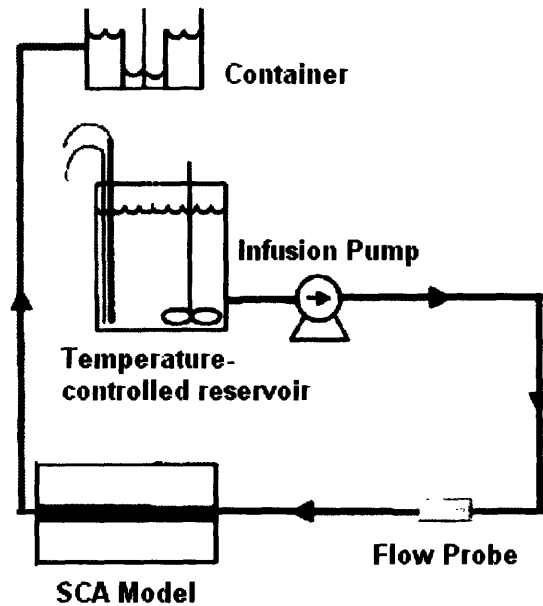


Figure 5 - Flow circuit

Flow Measurement Device

To measure blood flow through the stent, one of three different prototypes was adhered to the stent, and measurements were made in the following three ways:

The EM prototype - two electrodes were attached to the stent at opposite locations along its longitudinal axis. The voltage gradient induced at these electrodes by the local electromagnetic field generated by the two magnets was measured at fixed interval of 30 seconds after setting a specific flow rate. Faraday's Law infers that this voltage gradient is proportional to the fluid velocity.

The TD prototype – a transistor was used initially to point heat the stent wire mesh at its proximal end (upstream). The resistance level of a thermistor in contact with the transistor was measured with no flow after a period of 60 seconds post heating, and then again with a constant flow. This initial setup was abandoned after generating a transient voltage and was substituted by inducing constant voltage of 12V across the thermistor and measuring its resistance with no flow and again with a constant flow. The thermistor resistance is proportional to its temperature, and the difference in resistance ΔR is then converted into a difference in temperature ΔT , which is proportional to fluid velocity.

A third prototypes was built comprising of two thermistors adhered to the stent – one upstream with no voltage across to provide a control and another downstream with similar functionality as described in the case of a single thermistor.

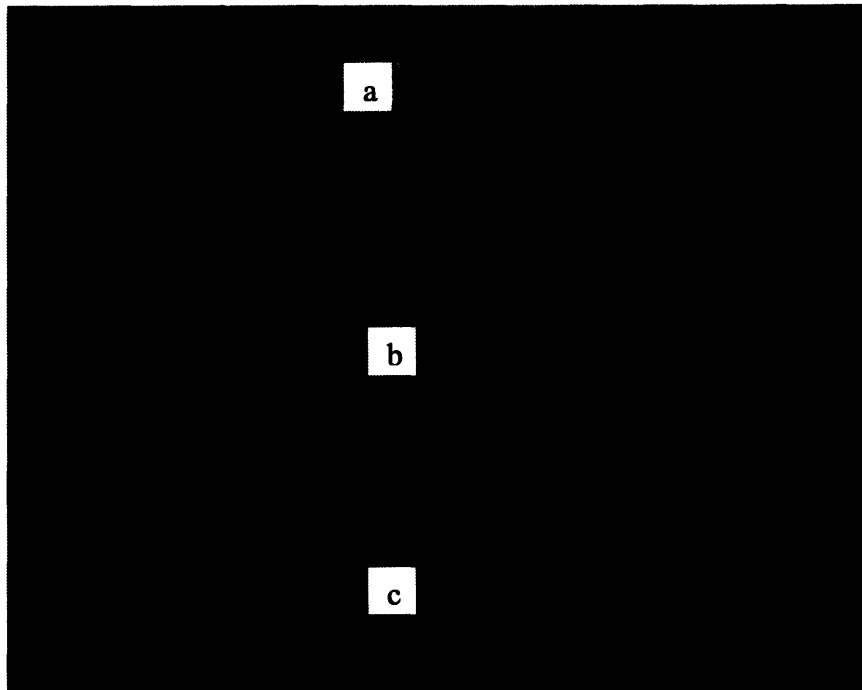


Figure 6 - Device prototypes: (a) EM prototype, (b) Single-Thermistor TD prototype, (c) Dual-Thermistor TD prototype

6.1.3 Results

In the present study, longitudinal velocity component was measured and presented. Velocity measurements were made in the stented site at the locations shown in Figure 5. Each data point represents an average of the velocity derived from 5-15 consecutive measurement cycles at a constant flow rate, with SD associated with these cycles. Flow rate was then calculated out of the deduced fluid velocity.

The EM prototype

Based on Faraday's law, the amount of voltage (E) developed across the electrodes will be proportional to the diameter of the vessel (D), the magnetic field density (B) generated by the coils, and the velocity (V) of the blood flow:

$$E = V \times B \times D \quad (\text{where } B=0.192 \text{ Tesla and } D=5\text{mm})$$

As B and D are known in this setup (which in this case will be the local magnetic field and the distance between the electrodes, respectively), the fluid velocity V can be easily deduced by measuring E, and is given by m/sec units. V is then converted into cm/min units to comply with flow rate units.

Flow Rate is calculated by:

$$\text{Flow Rate} = \text{Fluid Velocity} * \text{Lumen Area}$$

Lumen Area is given by Πr^2 and in this setup where $r=2.5\text{mm}$ the area equals 0.19635cm^2 .

Two sets of measurements were conducted, in which the average flow rate calculated were 13.13 cc/min and 54.14 cc/min and the measurement standard deviation were 0.47 and 21.64 respectively (see Table 4 for detailed results). The voltage across the electrodes with no flow, which served as a control, was zero.

First measurement - mean

No.	Actual Flow rate (cc/min)	E Voltage after 30 sec with flow (mV)	V Fluid Velocity (m/sec)	V Fluid Velocity (cm/min)	Calculated Flow Rate (cc/min)
1.	13.6	88.76	0.0108	64.89	12.74
2.	13.6	86.16	0.0111	66.85	13.13
3.	13.6	85.70	0.0112	67.21	13.20
4.	13.6	89.02	0.0108	64.70	12.70
5.	13.6	81.55	0.0118	70.63	13.87

Second measurement

No.	Actual Flow rate (cc/min)	E Voltage after 30 sec with flow (mV)	V Fluid Velocity (m/sec)	V Fluid Velocity (cm/min)	Calculated Flow Rate (cc/min)
6.	13.6	19.55	0.0491	294.63	57.85
7.	13.6	17.92	0.0536	321.43	63.11
8.	13.6	36.09	0.0266	159.60	31.34
9.	13.6	13.50	0.0711	426.67	83.78
10.	13.6	32.65	0.0294	176.42	34.64

Table 4 – EM prototype - results of first and second measurements

The TD prototype

Based on Thermodilution laws, the heat conduction for a spherical heating element of radius a in an infinite medium with no flow can be modeled[†]:

$$\vec{J}_H = -k\vec{\nabla}T = k\vec{\nabla}\tau \text{ where } \tau = T - T_\infty$$

Heat Flux (J_H) equals the product of thermal conductivity (k) and temperature gradient ($\vec{\nabla}T$), and τ is the difference in temperature at a location in the medium (T) and at an infinity (T_∞).

In steady state $\vec{\nabla} \cdot \vec{J}_H = 0 \Rightarrow \nabla^2 \tau = 0$. The solution for τ in the case of spherical symmetry is $\tau = \frac{\tau_s \times a}{r}$, where r is the radial distance from the origin at the center of the sphere and τ_s is the temperature at the surface of the sphere. Therefore for

the heat conduction:
$$Q' = 4 \times \Pi \times r^2 \times k \times \left| \vec{J}_H \right| = \frac{4 \times \Pi \times r^2 \times k \times \tau_s \times a}{r^2}$$

or
$$Q' = 4 \times \Pi \times k \times \tau_s \times a$$

In this setup, where $k_{\text{water}}=0.001622 \text{ cal/cm}^*\text{s}^*\text{C}$, τ_s is approximately 1°C , and $a=1\text{mm}$, $Q' = 0.0144 \text{ Watts}$. Solving for τ_s we obtain a value of 1.7°C which is in good *ballpark* agreement with our observations ($\sim 1^\circ\text{C}$) in the no flow states given the very different geometry of our set up.

As for heat conduction under dynamic flow conditions, that involves complex thermodynamic algorithms and would require a computer simulation and building an empirical model to take into account the specific setup and dynamics. For the scope of this thesis, the fact that the measured ΔT comparing the flow and no flow states is quite

consistent across different measurements suggest that such simulation and empirical model can be further developed to accurately deduce fluid velocity.

One set of measurements was conducted for the single-thermistor prototype, in which the difference in resistance and deduced temperatures across the thermistor with and without flow were measured (see Table 5 for detailed results).

Single Thermistor

No.	Actual Flow rate (cc/min)	Current (mA) after 60 sec heating with water	Current (mA) after 60 sec heating with flow	ΔR Resistance (Ω)	ΔT ($^{\circ}C$)
1.	13.6	1.218	1.199	155.47	0.35824
2.	13.6	1.154	1.135	173.35	0.37547
3.	13.6	1.157	1.138	172.44	0.37463
4.	13.6	1.170	1.148	195.73	0.43007
5.	13.6	1.171	1.153	159.31	0.35108
6.	13.6	1.181	1.163	156.61	0.34849
7.	13.6	1.189	1.170	163.21	0.36577
8.	13.6	1.232	1.197	283.62	0.65786
9.	13.6	1.196	1.156	345.73	0.77219
10.	13.6	1.177	1.154	202.35	0.44745
11.	13.6	1.189	1.163	224.69	0.5019
12.	13.6	1.183	1.162	182.56	0.40643
13.	13.6	1.188	1.165	198.59	0.44383
14.	13.6	1.187	1.169	155.02	0.34696

Table 5 - TD prototype - results of single-thermistor measurements

Additional set of measurements was conducted for the dual-thermistor prototype, in which both downstream thermistor and the upstream control thermistor temperature differences were measured (see Table 6 for detailed results).

Dual Thermistor - Downstream

No.	Actual Flow rate (cc/min)	Current (mA) after 60 sec heating with water	Current (mA) after 60 sec heating with flow	ΔR Resistance (Ω)	ΔT ($^{\circ}C$)
1.	13.6	1.289	1.249	296.90	0.72304
2.	13.6	1.259	1.219	311.46	0.73814
3.	13.6	1.239	1.210	231.16	0.54062
4.	13.6	1.243	1.222	165.21	0.38927
5.	13.6	1.237	1.217	158.76	0.37210
6.	13.6	1.257	1.218	304.40	0.72044
7.	13.6	1.261	1.221	310.45	0.73712
8.	13.6	1.252	1.220	250.35	0.59175
9.	13.6	1.256	1.222	264.72	0.62741
10.	13.6	1.258	1.234	184.75	0.44071

Dual Thermistor – Upstream Control (power applied to downstream thermistor)

No.	Actual Flow rate (cc/min)	Resistance (K Ω) after 60 sec with water	Resistance (K Ω) after 60 sec with flow	ΔR Resistance (Ω)	ΔT ($^{\circ}C$)
11.	13.6	11.056	11.190	0.134	0.27014
12.	13.6	11.315	11.415	0.1	0.19671
13.	13.6	11.398	11.417	0.019	0.03721
14.	13.6	11.422	11.390	-0.032	-0.06271
15.	13.6	11.360	11.419	0.059	0.1158
16.	13.6	11.307	11.398	0.091	0.17925
17.	13.6	11.247	11.367	0.12	0.23747
18.	13.6	11.313	11.374	0.061	0.12027
19.	13.6	11.398	11.371	-0.027	-0.05302
20.	13.6	11.572	11.290	-0.282	-0.5512

Table 6 - TD prototype - results of dual-thermistor measurements

6.2 Interpretation of Results

All prototypes were shown to enable the interpretation of flow velocity. However, the observed results, as well as several technical obstacles that were encountered along the way, give rise to important technical considerations.

These considerations might affect factors such as the required setup, the calibration process and the repeatability of measurements and must, therefore, be taken into account when evaluating the best approach for an implantable device.

The EM prototype posed several technical difficulties, which would disfavor utilizing this approach in an implanted device.

The voltage measurements across the electrodes fluctuated when the electrodes were placed such that they contacted the stent wire mesh. This is believed to be due to circuit shortage conducted by the mesh itself. In addition, this approach requires that the electrodes would be in contact with the fluid itself, to measure voltage gradient across the vessel lumen. However, such direct contact mode is not guaranteed in-vivo when the stent is coated with endothelium cells or plaque, in the case of restenosis. This would require an undesired post-procedure calibration involving a catheter as a reference scale.

Another technical uncertainty relates to the external magnetic field induced to allow the measurement – varying orientation and distance of the external device relative to the implanted device would reduce the repeatability and accuracy of the measurements. While this variation can be compensated by certain constrains such as external reader design, it increases system complexity and pose limitation on the operator.

The TD prototype seems to facilitate a more comprehensive approach, independent of external reader properties. However, several feasibility issues should be considered in this approach as well.

The initial design comprising of a transistor as a heating element and a thermistor as the measurement element, generated a transient voltage increase at each measurement. The transient voltage is believed to be due to convection flow resulting of the point heating technique used. To eliminate this transient voltage, different approaches was tested - to directly heat the thermistor and measure its resistance after a predefined time period – and indeed the transient voltage was not observed.

The use of two thermistors provided a less accurate measurement of flow velocity, probably due to the downstream location of the measurement element. The upstream control element maintained its emperature. This dual setup can be advantageous in vivo to compensate for different blood temperature in different physiological conditions without recalibration, but on the other end contributes increased technical complexity and requires additional hardware incorporated within the stent.

The accuracy and repeatability in the presence of a coated stent with either endothelium or plaque of varied composition is yet another uncertainty which should be evaluated in further in-vitro and in-vivo studies.

7 Critical Assessment of Own Work

7.1 Significance

In previous sections of this work I have demonstrated a sufficient clinical ambiguity and a vibrant controversy regarding the use of stents, especially DES, following angioplasty in ischemic arterial beds. This use is limited by complications and continuing vascular deterioration. My findings, both in a literature survey and a preliminary questionnaire answered by specialists dealing with patients suffering ischemic arterial beds, suggest that there is a clear clinical need, well defined and highly diffused within the medical community in regards with the importance of such monitoring as well as the short reaching of existing modalities in addressing this need. There is a broad agreement of the parameter which is most indicative of vessel patency – flow rate through the stent, and a shared anticipation that monitoring this parameter might change standard of care and improve clinical outcome.

While further, more comprehensive and of larger scale studies should be complete to better gauge and quantify the potential market - market economics such as potential demand, margins, price points, and growth drivers, market mechanics such as channels, barriers to entry and power distribution, and other important factors - the findings described herein are encouraging enough to support the Hypothesis that there exists a market for a novel approach facilitating monitoring of vessel patency post procedure.

7.2 Feasibility

Previous sections of this work have described multiple available techniques to enable the in-vivo measurement of blood flow rate through a stent, to establish vessel patency and the need for treatment adjustment or reintervention, as a real-time, wireless, and non-invasive monitoring paradigm.

The proposed approach address, in theory, various requirements and design consideration to enable the development and assembly of a novel device that would address the clinical need identified.

While further development is required to mitigate technical uncertainties and comply with physiological and biological requirements, a proof of concept was demonstrated by building a prototype and running an in-vitro experiment. Although simple and limited, the preliminary results of that experiment have shown that the fundamental concept is feasible and that flow rate can be measured at the stent intraluminally.

Next developmental steps to achieve miniaturizing, external power induction, and wireless communication - are all based on proven technologies which have been demonstrated in practice in multiple other applications. Therefore I believe the findings described in this work sufficiently support the Hypothesis that such a device can be designed and built.

8 Work Provision

8.1 Market Application

The market for coronary stents and drug-eluting stents in particular is the leading stent market at approximately \$5 billion annually and predicted to maintain its growth. This is therefore the most lucrative market application for the proposed approach discussed in this thesis.

However, additional in-vivo applications exist, which would potentially be enhanced by the proposed approach, providing physicians the means to monitor patency and flow rate in a non-invasive method - the use of stents in other parts of the body, such as carotid stents, vascular stents in the lower extremities, and biliary stents, is rapidly expanding both in clinical indications and in volume of procedures. Additional candidate modalities include vascular grafts, both native and synthetic⁵², and shunts, such as Cerebrospinal Fluid shunts (CSF) to treat high intracranial pressure, and Transjugular Intrahepatic Portosystemic shunts (TIPS) to treat high blood pressure in the liver.

Extensive market research should be conducted to quantify the potential of each application, but the following factors should be considered as a first step to validate the fit for a specific application⁵³:

- Clinical need – How important is patency/flow rate monitoring? What is the level of susceptibility to narrowing/blockage?

- Uniqueness – Are there any other modalities to monitor patency/flow rate in the specific location/device?
- Feasibility - What accuracy level would the proposed approach achieve? What would it take to incorporate the proposed approach in the modality?
- Ease of use – Would the proposed approach allow a simple, quick measurement?
- Resistance – What proof of efficiency is required to facilitate adoption? Are there external factors that would limit the use/adoption of the proposed approach?

Carotid stents, vascular stents in the lower extremities would pose a lower technical challenge – by allowing a larger device due to the wider vessel lumen, and also by providing a more ‘friendly’ environment – with minimal vessel movement and more adjacent to the skin – which can improve measurement accuracy. However, other modalities and especially ultrasound can nearly fulfill the clinical need and therefore the uniqueness of the proposed approach is less vivid.

CSF shunts and TIPS would also pose lower technical constraints, they are highly susceptible to blockage requiring their replacement, and there is no available technique to monitor their patency. However, the flow rate in these shunts is very slow compared to the rate in coronary arteries, and therefore a different measurement technique might be required to fulfill that need.

Synthetic grafts might be a good candidate to start with, as the incorporation of the proposed measurement device is quite straight forward, and there is no other modality to monitor graft patency. However, the market trend in the last few years was definitely

towards using more non-invasive catheter-delivered stents than bypassed grafts requiring an open chest surgery.

In general, it seems as if a strategy of targeting first a lower hanging fruit such as synthetic vascular grafts or lower extremities vascular stents would be a favorable approach and allow delivering a simpler product quicker, deepen technical knowledge and expertise and gain market feedback. This would facilitate easier adoption and earlier success that would allow then targeting the much more lucrative market of coronary stents.

8.2 Commercialization

The project has past the stage of formulating the general design concept of such a device and identifying its main components and material involved, and is currently at the stage of developing a proof-of-concept prototype to be tested and verified both in-vitro and in-vivo on animal model. For Class III device key next steps after developing a proof-of-concept prototype, and running initial animal trials, would probably require some long-term animal implant studies before proceeding into human trials and a FDA PMA clearance process. These steps will be facilitated by sponsored research support and later on by venture financing. The process of filing for a conceptual patent has started in order to secure IP issues.

8.3 Risk Mitigation

Potential technical uncertainties include efficacy and reliability within the body. The device should be miniaturized utilizing MEMS technology and demonstrate in-vivo efficacy. The development of a proof-of-concept fully functional device prototype and the initial animal studies will clarify technical uncertainties. In order to mitigate the technical risk, all candidate technologies involved have been demonstrated to successfully measure flow in similar applications with somewhat different settings.

Potential clinical uncertainties include safety and biocompatibility within the body. Being incorporated within a coronary stent, intraluminally, the device poses a risk of thrombosis or tissue deposition or encapsulation due to potential fibrotic reactions on its surface. The minimal footprint, $<0.5\text{mm}^3$, as well as the coated silicon should mitigate these risks. In order to mitigate the biocompatibility risk, all the materials which are to be used to compose the device components are well documented and are currently used extensively in the human body including cardiac defibrillators, pace makers and artificial vascular grafts with little or no immune response.

Potential market uncertainties include adoption rates and competing non-invasive imaging techniques. Immediate next step would be to conduct an initial primary market research to reduce market uncertainties. In order to facilitate rapid adoption the project team has started building meaningful close relationships with luminaries and thought leaders within the medical community, and specifically with cardiac and vascular

surgeons, and an on-going field feedback will be maintained through the entire development and clinical studies. Non-invasive imaging techniques are still decades away from reaching the required sensitivity and specificity.

8.4 Impact

Commercial - The introduction of such a device into the medical device market will have a significant commercial effect. It will improve the efficacy and capabilities of the healthcare system – while enhancing best practice surveillance and treatment of post surgery patients; it will have a much broader impact on the specialty of interventional cardiology, as well as other specialties, by facilitating a non-invasive, ongoing monitoring and blood analysis of various relevant hematological factors.

Taking advantage of its non-invasive, simple-to-conduct nature, physicians across the country will be able to conduct precise, fast analysis of restenosis status and progress over time, by simply reading flow values at interest sites, and would potentially improve end results of related treatment administration. Accordingly, such a device will be adopted by the community of interventional cardiologists. As no other comparable device exists to date, it is clear that there will be a significant commercial benefit associated.

Societal - I believe that this technology and its successful commercialization will have a far-reaching societal impact. As described previously, there is currently no available technology for detection of stent occlusion post surgery. The first sign that something is wrong is when the stent is nearly completely blocked, at which stage

interference is usually impossible and this is frequently a fatal occurrence. I believe that this technology will widen the number of early diagnosed patients as undergoing a restenosis progress; offering hope for patients who would only be diagnosed and treated much later with today's capabilities, thus reducing the number of patients requiring repeated intervention or suffering severe adverse events and saving tens of thousands of lives annually. In addition, the device will allow surveillance and sequential treatment that will offer a radical improvement in quality of life and peace of mind for these patients through earlier and more efficient treatment. Various resources, first and foremost human resources, will be freed up to address other medical challenges, increase society's productivity, and significantly reduce health related costs.

Educational - This commercialization effort will advance the education of physicians nationwide. As there are no competing devices available, there is a huge potential for research which has been heretofore impossible - by revealing and quantifying the ongoing progress of restenosis and fibrosis and compare this progress outcome in the presence of various treatments and medications the effect of medication on flow could be directly studied. Additional questions, such as how does flow change with exercise, and does the loss of normal capacity for such change constitute an early indication of trouble can be answered. The technology opens whole new areas of investigation, and it is expected that thought leaders and luminaries who will be involved in utilizing this technology will develop new medical techniques and best practices to be adopted by the rest of the medical community.

9 Summary Conclusion

In this thesis, I have explored and tested the Hypotheses that **there is a market for a direct, non-invasive monitoring of vessel patency at the site of a coronary stent; and that an implantable, wireless, stent-based device to monitor blood flow rate through a coronary stent can be designed and built.**

A literature survey of late clinical studies regarding the safety and efficacious of DES reveals sufficient clinical ambiguity to justify the proposed approach. Results of interviews and preliminary questionnaire with numerous specialist clinicians portrait an underserved clinical need and further justify the introduction of a direct, non-invasive modality for monitoring of vessel patency at the site of a coronary stent as part of the best practice follow-up regimen. Although no comparable modality exists, clinicians were unanimously positive about welcoming the proposed approach and certain that such a tool has the potential to improve clinical outcome. The practitioners' interest, therefore, seems to be clinically driven.

A research of related techniques and existing intellectual property establish the notion that measurement techniques are available for monitoring of vessel patency at the site of a coronary stent. Preliminary results of an in-vitro experiment with a prototype that was built as part of this project demonstrate partial proof-of-concept and together with emerging technologies such as MEMS and wireless communication techniques place the foundations for designing and developing a stent-based, implantable, and

wireless device that would allow a direct, non-invasive efficacious measurement of blood flow rate through coronary stents.

While not in the scope of this thesis project, additional potential applications for such an approach are far more reaching than coronary stents and might as well position this technique as a platform technology for numerous clinical applications.

9.1 Acknowledgements

The author would like to deeply appreciate the valuable support and on-going contribution of Richard J. Cohen.

The author would also like to thank T. Forcht Dagi at the Harvard-MIT Division of Science and Technology and Peter Madras, MD, Associate Prof Surgery Harvard Medical School, Vascular and Transplant Surgeon, Lahey Clinic for their advice and shared experience.

The physical task of building the prototype was conducted by Antoine Machal-Cajigas, a junior in the department of Electrical Engineering at MIT as a UROP student.

Many thanks are devoted to all the luminaries and clinicians who have spent time for personal meetings and who have responded to the questionnaire included in this study.

A special gratitude is indebted to my wife Tami and my daughters Ziv and Gali for their love, patience and endless support, not only on this thesis project but also in the past two years, and to my parents, Gadi and Mina, for their support and central role in realizing my dreams.

Bibliography

1. Kuntz RE, Gibson CM, Nobuyoshi M, et al. Generalized model of restenosis after conventional balloon angioplasty, stenting and directional atherectomy. *J Am Coll Cardiol.* 1993;21:15–25.
2. Cutlip DE, Chauhan MS, Baim DS, et al. Clinical restenosis after coronary stenting: perspectives from multicenter clinical trials. *J Am Coll Cardiol.* 2002;40:2082–2089.
3. Ho KKL, Senerchia C, Rodriguez O, et al. Predictors of angiographic restenosis after stenting: pooled analysis of 1197 patients with protocolmandated angiographic follow-up from 5 randomized stent trials. *Circulation.* 1998;98(suppl I):I-362. Abstract.
4. Hausleiter J, Kastrati A, Mehilli J, et al. Predictive factors for early cardiac events and angiographic restenosis after coronary stent placement in small coronary arteries. *J Am Coll Cardiol.* 2002;40:882–889.
5. de Feyter PJ, Vos J, Rensig BJ. Anti-restenosis trials. *Curr Interv Cardiol Rep.* 2000;2:326–331.
6. Heart Disease and Stroke Statistics - 2006 Update: A Report From the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. *Circulation* 2006;113:e85.
7. Heart and Stroke Facts, American Heart Association, <http://www.americanheart.org/>
8. David RH, Jr, Martin BL, et al. Analysis of 1-Year clinical Outcomes in the SIRIUS Trial: A Randomized Trial of a Sirolimus-Eluting Stent Versus a Standard Stent in Patients at High Risk for Coronary Restenosis. *Circulation* 2004;109:634-640
9. Gregg WS, Stephen GE, David AC, et al. for the TAXUS-IV Investigators. One-Year Clinical Results With the Slow-Release, Polymer-Based, Paclitaxel-Eluting TAXUS Stent: The TAXUS-IV Trial. *Circulation* 2004;109:1942-1947.
10. Alexandra JL, Ricardo AC, Gary SM, et al. for the DELIVER Clinical Trial Investigators. Non-Polymer-Based Paclitaxel-Coated Coronary Stents for the Treatment of Patients With De Novo Coronary Lesions Angiographic: Follow-Up of the DELIVER Clinical Trial. *Circulation* 2004;109:1948-1954.
11. Sousa JE, Costa MA, Abizaid A, et al. Lack of neointimal proliferation after implantation of sirolimus-coated stents in human coronary arteries: a quantitative coronary angiography and three-dimensional intravascular ultrasound study. *Circulation.* 2001;103:192–195.

12. Morice MC, Serruys PW, Sousa JE, et al. A randomized comparison of a sirolimus-eluting stent with a standard stent for coronary revascularization. *N Engl J Med.* 2002;346:1773–1780.
13. Moses JW, Leon MB, Popma JJ, et al. Sirolimus-eluting stents versus standard stents in patients with stenosis in a native coronary artery. *N Engl J Med.* 2003;349:1315–1323.
14. Rensing B, Vos J, Smits P, et al. Coronary restenosis elimination with a sirolimus-eluting stent: first European human experience with six month angiographic and intravascular ultrasonic follow up. *Eur Heart J.* 2001; 22:2125–2130.
15. Colombo A, Drzewiecki J, Banning A. Randomized study to assess the effectiveness of slow and moderate release polymer based paclitaxel-eluting stents for coronary artery lesions. *Circulation.* 2003;108:788–794.
16. Liistro F, Stenkovic G, Di Mario C, et al. First clinical experience with a paclitaxel derivative-eluting polymer stent system implantation for in-stent restenosis: immediate and long-term clinical and angiographic outcome. *Circulation.* 2002;105:1883–1886.
17. Drug-Eluting Stents and multiple articles, [Angioplasty.Org](http://www.angioplasty.org), <http://www.angioplasty.org/>
18. Thomas M. Drug-Eluting Stents To Transform Cardiovascular Medicine. *Managed Care Magazine* July 2003.
19. Allen J, Brett S, Jonathan B, et al. Stent Thrombosis After Successful Sirolimus-Eluting Stent Implantation. *Circulation* 2004;109:1930-1932.
20. Unraveling the Cypher™ : An [Angioplasty.org](http://www.angioplasty.org) Editorial on the FDA Warnings About Johnson & Johnson's Drug Eluting Stent, October 30, 2003, [Angioplasty.org](http://www.angioplasty.org/), <http://www.angioplasty.org/>
21. Patrick WS, Muzaffer D, Kengo T, et al; for the TAXUS II Study Group. Vascular Responses at Proximal and Distal Edges of Paclitaxel-Eluting Stents: Serial Intravascular Ultrasound Analysis from the TAXUS II Trial. *Circulation* 2004;109:627-633.
22. Sylvia PW. Some Doctors See Long-Term Clot Risk In Stent Patients. *The Wall Street Journal*, October 21, 2005.
23. David M, Jacqueline I. Stent Showdown. *Wood Mackenzie Limited* March 16th 2004.
24. Kent Y, Charles MA, Robert RE, et al. Magnetic Resonance Angiography: Update on Applications for Extracranial Arteries. *Circulation* 1999;100:2284-2301.

25. Lambertus WB, Henk FMS, Chris JGB, and Max AV. MR Imaging of Vascular Stents: Effects of Susceptibility, Flow, and Radiofrequency Eddy Currents. *J Vasc Interv Radiol* 2001; 12:365–371.

26. Tests To Diagnose Heart Disease, American Heart Association, <http://www.americanheart.org/>

27. Interviews with physicians at leading research hospitals (Boston Medical Center, Massachusetts General Hospital, Lahey Clinic).

28. Lambertus WB, Chris JGB, Jan LV, Max AV. Improved Lumen Visualization in Metallic Stents and Filters by Reduction of Susceptibility and RF Artifacts. *Proc. Intl. Soc. Mag. Reson. Med* 2001; 9: 305.

29. Wang Y, Riederer SJ, Ehman RL. Respiratory motion of the heart: kinematics and the implications for the spatial resolution in coronary imaging. *Magn Reson Med*. 1995;33:713–719.

30. Scott NA, Pettigrew RI. Absence of movement of coronary stents after placement in a magnetic resonance imaging field. *Am J Cardiol*. 1994;73:900–901.

31. Duerinckx AJ, Atkinson D, Hurwitz R, Mintorovitch J, Whitney W. Coronary MR angiography after coronary stent placement. *AJR Am J Roentgenol*. 1995;165:662–664.

32. Ohlsson A, et al., Continuous ambulatory monitoring of absolute right ventricular pressure and mixed venous oxygen saturation in patients with heart failure using an implantable hemodynamic monitor: Results of a one year multicentre feasibility study. *Eur Heart J* 2001; 22:942-954.

33. Fischman DL, Leon MB, Baim D, et al, for the STRESS Trial Investigators. A randomized comparison of coronary-stent placement and balloon angioplasty in the treatment of coronary artery disease. *N Engl J Med*. 1994;331:496–501.

34. Serruys PW, de Jaegere P, Kiemeneij F, et al, for the Benestent Study Group. A comparison of balloon-expandable-stent implantation with balloon angioplasty in patients with coronary artery disease. *N Engl J Med*. 1994;331:489–495.

35. Paul ST. A Chicken in Every Pot and a Drug-Eluting Stent in Every Lesion. *Circulation* 2004;109:1906-1910.

36. John WH, JR., Robert LW. Drug-eluting stents are here - now what? Implications for clinical practice and health care costs. *Cleveland Clinic Journal of Medicine* 2004; 71.

37. Brenda G. Questions Are Raised About the Safety of a Major Heart Drug. *The New York Times*, March 13, 2006.

38. A Drug Is Found to Reduce Plaque in Arteries. *Reuters* March 14, 2006

39. OMEGA Complete Flow and Level Measurement Handbook and Encyclopedia®, *OMEGA Press*, 1995.
40. Miller RW, McGraw H. Flow Measurement Engineering Handbook, 1996.
41. Spitzer DW. Flow Measurement, *Instrument Society of America*, 1991.
42. Ginesi D. Flow Sensing: The Next Generation, *Control Engineering*, November 1997.
43. Siebes M, Verhoeff BJ, Meuwissen M, et al. Single-Wire Pressure and Flow Velocity Measurement to Quantify Coronary Stenosis Hemodynamics and Effects of Percutaneous Interventions. *Circulation* 2004;109:756-762.
44. Khazan AD. Transducers and Their Elements: Electromagnetic Flowmeter. *Prentice Hall PTR*, 1994.
45. Committee Report: Transit Time Ultrasonic Flowmeters. AWWA Subcommittee on Ultrasonic Devices, *AWWA Journal*, July 1997.
46. McGee, H.; McInerney, J.; and Harrus, A. The Virtual Cook: Modeling Heat Transfer in the Kitchen. *Physics Today* 52, 30-36, Nov. 1999.
47. Peuster M, Kaese V, Wuensch G, et al. Composition and in vitro biocompatibility of corroding tungsten coils. *J Biomed Mater Res B Appl Biomater*. 2003 Apr 15;65(1):211-216.
48. Lammers D. Micro medical devices could transform health care. *EE Times* June 2002.
49. Dodge JT Jr, Brown BG, Bolson EL, Dodge HT. Lumen diameter of normal human coronary arteries: influence of age, sex, anatomic variation, and left ventricular hypertrophy or dilation. *Circulation* 1992; 86: 232–246.
50. Chong1 CK, How TV. Flow patterns in an endovascular stent-graft for abdominal aortic aneurysm repair. *Journal of Biomechanics* 2004; 37, 89–97.
51. Frederic GH, Texter EC, JR., Wood LA, et al. The Electrical Conductivity of Blood: Relationship to Erythrocyte Concentration. *Blood*. 1950 Nov;5(11):1017-35.
52. Sperker W, Glogar D, Gyöngyösi M. Percutaneous Treatment of Left Main Coronary Artery Stenoses. *Journal of Clinical and Basic Cardiology* 2002; 5 (Issue 2), 163-169.
53. How To Invest in Cardiac Surgical Devices. Thomson Financial Inc. Venture Capital *Journal*, November 01, 2003