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Computational study to assess arterial function recovery in PAD patients with micro-vascular insufficiency and integration of smart screening technology using skin patch biosensor to predict the severity of peripheral artery disease

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**COMPUTATIONAL STUDY TO ASSESS ARTERIAL FUNCTION RECOVERY
IN PAD PATIENTS WITH MICRO-VASCULAR INSUFFICIENCY AND
INTEGRATION OF SMART SCREENING TECHNOLOGY USING SKIN PATCH
BIOSENSOR TO PREDICT THE SEVERITY OF PERIPHERAL ARTERY
DISEASE**

A Thesis by

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Submitted to the Department of Industrial and Manufacturing Engineering
and the faculty of the Graduate School of
Wichita State University
in partial fulfillment of
the requirements for the degree of
Master of Science

July 2015

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**COMPUTATIONAL STUDY TO ASSESS ARTERIAL FUNCTION RECOVERY IN
PAD PATIENTS WITH MICRO-VASCULAR INSUFFICIENCY AND INTEGRATION
OF SMART SCREENING TECHNOLOGY USING SKIN PATCH BIOSENSOR TO
PREDICT THE SEVERITY OF PERIPHERAL ARTERY DISEASE**

The following faculty members have examined the final copy of this thesis for form and content and recommend that it be accepted in partial fulfillment of the requirement for the degree of Master of Science with a major in Industrial Engineering

Kim Cluff, Committee Chair

Krishna Krishnan, Committee Member

Klaus A. Hoffmann, Committee Member

DEDICATION

Dedicated to my family and dear friends

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ABSTRACT

Peripheral arterial disease (PAD) is characterized by atherosclerotic blockages of the arteries supplying blood to the lower extremities, which cause a progressive accumulation of ischemic injury. Despite revascularization treatment intervention some PAD patients require follow up secondary treatment due to a continued decline in limb function, quality of life and walking parameters. Standard revascularization surgical procedures restore blood flow in the main arteries via bypass surgical grafting. However, nutrient transport and oxygen transfer take place at the level of the microvasculature and capillaries. Nevertheless, an assessment of the microvascular circulation is lacking. Multi-physics simulation software was used to model the phenomena to assess the effectiveness of the standard lower limb revascularization treatment in PAD patients who may have microvascular dysfunction. It was observed that there was 71.73 % decrease in the oxygen transferred to the surrounding tissues when there was blockage at the microvascular level. This model identifies the need to measure the microvascular circulation in the compromised limbs of PAD patients to optimize diagnosis and treatment strategies that reflect the underlying pathophysiology. Also the study suggests for early detection of PAD through screening methods. Current screening methods require trained personnel, special equipment and less accurate. In this study, we present a new sophisticated smart skin technology that could be used as a point-of-care continuous monitoring system for PAD screening. The smart skin biosensor was attached to a human arm phantom to detect blood flow changes. As a result the biosensor was able to detect blood flow in arm phantom and was also be able to record pulse volume changes in the blood flow. The result was then validated using ultrasound technique and found that the biosensor had 94% accuracy with the ultrasound measure.

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CHAPTER 1 : INTRODUCTION

1.1 BACKGROUND OF PERIPHERAL ARTERIAL DISEASE (PAD)

Peripheral artery disease (PAD) is very common in adults that one third of the affected population are over 70 years (Grenon et al., 2014). Elevated blood cholesterol, diabetes, smoking, hypertension and obesity are some of the risk factors for PAD (Kenneth Ouriel, 2001). PAD is characterized by narrowing of blood vessels that carry blood to leg and arm muscles. The vessel narrowing is due to the fatty deposit and plaque formation on the walls of the arteries. Approximately 12% - 14% of the population are affected by PAD (M. Al-Qaisi, Nott, D. M., King, D. H., & Kaddoura, S., 2009). Leg pain after inactivity (from rest) is the primary symptom for PAD. Claudication is a term used to stage PAD based on its severity. ABI is a standard and non-invasive diagnostic method to predict the severity of the disease to an extent. In most cases ABI method was proved to be appropriate, however, for some complicated scenarios such as asymptotic PAD, the ABI can give inaccurate measure. Also, this measure could predict the risks of cardiovascular events (Arain & Cooper, 2008). Generally PAD is diagnosed and treated at the intermittent claudication stage, when patients will experience pain in their calf muscle or thigh (Kenneth Ouriel, 2001). Once a patient is diagnosed with PAD at claudication stage, they should be treated to prevent the most common risk factors stated above, that could contribute to developing lower extremity PAD. Intermittent claudication (IC) relates to functional ischemia measured during exercise and not at rest. At rest, oxygen consumption or saturation in the limb muscles of PAD patients is low (Komiya et al., 2002). Later stages of claudication would result in non-healing wounds and to avoid spreading of wound complications, patients are treated through amputation (removal of limbs). Claudication develops to critical limb ischemia level in

patients if untreated, and is a prime risk factor for many cardiovascular and cerebrovascular events.

1.2 SIGNIFICANCE OF PAD

PAD is a highly prevalent atherosclerotic syndrome that affects approximately 8 to 12 million individuals in the United States (Hirsch et al., 2001). This condition becomes more common as one gets older and the number of affected Americans is expected to increase with an increase of the elderly population. It is estimated that the PAD prevalence in the United States has ranged from 3% to 30% in the US adult population. Patients with PAD are compounded with six fold greater risk for underlying cardiovascular events (Stein et al., 2006).

Peripheral artery disease is a serious vascular diseases and is a primary risk factor for cardiovascular events such as stroke and myocardial infarction. Patients presenting with PAD symptoms are also likely to have widespread accumulation of fatty deposits in the arteries and have coexisting forms of vascular disease. As a consequence of coexisting other vascular disease, there is an increased risk of MI, stroke and cardiovascular death in patients with lower extremity PAD (Hirsch, Haskal, Hertzler, Bakal, Creager, Halperin, Hiratzka, Murphy, Olin, Puschett, Rosenfield, Sacks, Stanley, Taylor, White, White, White, Antman, Smith, Adams, Anderson, Faxon, Fuster, Gibbons, Hunt, et al., 2006). The annual mortality rate from studies of patients with lower extremity PAD is 4% to 6% and increases as the severity of the disease increases (Vogt et al., 1993).

1.2.1 Economic impact

PAD is becoming increasingly recognized as a major cardiovascular burden due to its increased risk of vascular disease and the increased probability of patients suffering from major cardiovascular ischemic events. For elderly individuals with PAD, Medicare expense were estimated to be \$1450 approximately and the total expense for PAD related treatment was calculated to cross \$4.37 billion (Hirsch et al., 2008). A total of \$4.37 billion was spent on PAD related treatment and 88% of the expenses were of inpatient care (Hirsch et al., 2008). With the progression of PAD, the effective treatment is limited and only choice is amputation of legs. It is reported that more than 60000 amputations are performed per year in the United States (Presern-Strukelj & Poredos, 2002). Amputation is considered to be a medical failure to treat the disease and controlling the health care costs of PAD represents a major challenge.

1.2.2 Severity of PAD and its stages

Critical limb ischemia (CLI) involves pain in the limbs at rest and tissue loss (non-healing ulcers and gangrene) in patients resulting in poor wound healing. In CLI stage, there is a severe reduction in blood flow through the arterial bed and thus stopping the complete metabolism in the affected extremities (Gresele et al., 2011). When there is no metabolism, the tissue cells may become necrotic as there is insufficient oxygen exchange taking place and this prevents the healing of wounds in the legs leading to ulceration. This slow progressive disorder if ignored might be a risk factor for stroke, amputation and death (Lyn M. Steffen et al., 2008).

To avoid major amputation, wound healing is very important in patients with CLI. In worst cases, there is a need to perform minor amputation in patients, to avoid wound complications from spreading and risks toward end organ failure (Kobayashi et al., 2014). Healing wounds is

directly dependent on the tissue restoration. During revascularization procedures, arteries in main arterial beds are bypassed and blood flow is restored. This means the metabolism at the lower extremities will also be restored and the dead tissue cells already will be replaced by new tissues, thus healing of wounds. However vascular surgeons have reported that patients who underwent endovascular surgery often required secondary treatment due to lack of wound healing because of insufficient tissue oxygenation (Bae et al., 2013; Klevsgard et al., 2001).

Microvascular dysfunction, a concept of no reflow phenomenon refers to the state of tissue hypoperfusion (Jaffe et al., 2008). No reflow results from the obstruction in microvascular bed resulting in microvasculature injury. In coronary artery disease, the similar no reflow phenomenon is due to myocardial ischemia, which often ends up injuring the coronary microvasculature structurally and the dysfunction is directly associated to the risks of heart attacks and death (Ito, 2014). Similarly, in limbs, microvascular obstruction leads to microvasculature structural damage that would lay a foundation for target organ failure and reperfusion injuries (Aoqui et al., 2014). When there is a microvascular dysfunction, the blood flow in the main arteries doesn't reach the tissue level. The pathophysiology of microvascular dysfunction in legs has not been addressed properly due to lack of proper diagnostic method to investigate blood at the microvascular level and there are very limited studies that focus on the microcirculation (Michaels et al., 2000).

1.3 STATEMENT OF THE PROBLEM

Peripheral arterial disease (PAD) is an aging-related disease affecting more than 10 million patients in the United States (Norgren et al., 2007). PAD is a major component of the overall burden of cardiovascular disease in the United States (Ranson, 2012). The lack of advanced

diagnostic method for PAD risks patients with underlying effect of cardiovascular events. About 65% of patients, have clinically relevant cerebral or coronary artery disease, and few researchers concluded that patients with PAD had a six-fold higher risk of death from cardiovascular disease than those without PAD (Peach et al., 2012). People should be made aware about the causes and implication of this disease through education and awareness programs.

Patients continue to experience declining limb function even after surgical intervention by revascularization procedures (Rush et al., 1989). Lack of advancement in the management of PAD is one of the reasons that depletes the quality of patient's life. , Ankle Brachial Index (ABI) is one of the oldest screening method that is being practiced in clinics till date. This diagnostic method needs trained personnel to use the Doppler techniques and calculate the measure, to predict the severity of risk towards the developing lower extremity PAD (Allison et al., 2009). This screening method has been studied and reported to be less sensitive and accurate in many cases (M. Al-Qaisi et al., 2009).Lack of diagnostic methods for underlying problems that exist in the microvascular level should be addressed to avoid limb amputations, and the underlying risks towards many cardiovascular events. These points imply the need of a new approach in diagnostic and screening methods that could eliminate the risk of developing lower extremity PAD at the earliest stage and benefit PAD patients.

1.4 OBJECTIVES

Our main objective in this study is to present that the insufficient oxygen transfer to the tissues that results in poor wound healing and end organ failure in patients with PAD even after revascularization is due to microvascular dysfunction in limbs and to optimize the screening method for PAD with a point of care monitoring system. The two rationale that underlies this

study is that if we can diagnose the existence of microvascular dysfunction in patients before the surgery, an alternate treatment method can be implicated. The current method of screening for PAD can be upgraded as a cost-effective and sophisticated tool that a patient can use it from their homes as a point of care monitoring system.

1.4.1 Specific aims

- i. A computational study to assess the effectiveness of revascularization treatment in PAD patients with microvascular dysfunction.
- ii. To develop a point-of care screening method for PAD that would be a sophisticated tool for patients to use it from their homes and predict the severity of the disease.
- iii. The outcome of the objective would suggest an alternate diagnostic and screening approach for PAD. This would improve treatment strategies and could save some patients from major amputation. Also, the proposed method shall be integrated with the current screening methods to improve the sensitivity and accuracy of the current methods.

1.5 DISSERTATION ORGANIZATION

Chapter 2 presents a literature review of key concepts related to this thesis work, including the significance of PAD, risk factors, and diagnostic methods. The chapter will also include concepts related to micro-circulation and its significance and how they are related to PAD.

There are two more main phases of this thesis work. Objective I, covered in Chapter 3, deals with the assessment of arterial function recovery after surgical intervention in PAD patients

with microvascular insufficiency using computational modelling. Objective II, covered in Chapter 4, proposes a new screening method for PAD that shall be integrated with the current methods to make it cheaper and sophisticated.

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CHAPTER 2 : LITERATURE REVIEW

2.1 SIGNIFICANCE OF PAD, RISK FACTORS AND DIAGNOSIS

Peripheral artery disease (PAD) is characterized by decreased blood flow due to blockage in the arteries. Although there are many problems related to PAD, we mainly focus on the arterial occlusive disease in the arteries to the legs. PAD is more common in people of age over 60 years. PAD affects 12 -14% of the total population (M. Al-Qaisi et al., 2009). Still, this disease is underestimated and awareness to diagnose PAD is low among the population (Hirsch et al., 2001). Intermittent claudication, usually defined as pain in the muscles is a primary symptom in patients with lower extremity PAD and the disease progresses with increased muscle pain at rest. Later stages of PAD include tissue hypo perfusion that progresses to ischemic ulceration and gangrene, and finally amputation. Annually 20% of patients with PAD suffer from limb threatening manifestations and fewer than 10% of patients die from PAD complications (K. Ouriel, 2001; Ranson, 2012).

2.1.1 *Risk factors*

Major risk factors of PAD would include age, hypertension, diabetes, smoking, hypercholesterolemia, hyperhomocysteinemia, and C-reactive protein (Hirsch, Haskal, Hertzler, Bakal, Creager, Halperin, Hiratzka, Murphy, Olin, Puschett, Rosenfield, Sacks, Stanley, Taylor, White, White, White, Antman, Smith, Adams, Anderson, Faxon, Fuster, Gibbons, Hunt, et al., 2006; Norgren et al., 2007). Firstly, on the age factor, we see an increase in prevalence of lower extremity PAD as age increases. The prevalence of lower extremity PAD among adults aged over 40 years in the United States was 4.3% which corresponds to 5 million individuals. Among those adults aged over 70 years, the prevalence was 14.5% (Selvin & Erlinger, 2004). The

number of cigarette packs smoked per year has a direct correlation with an increased risk of limb amputation, increased disease severity, and mortality. Chain smokers have a fourfold higher risk involved in developing PAD than the non-smokers (Jensen et al., 2005; Norgren et al., 2007). Diabetes is also associated with the developing lower extremity PAD and its duration and severity is directly correlated with the severity of PAD. Diabetes alters the nature of PAD, patients with diabetes commonly get affected by arterial occlusive disease. The risk of intermittent claudication increases by 3.5 fold in men and 8.6 fold in women (Beckman et al., 2002). An elevated systolic blood pressure of 140 mm Hg or greater leads to hypertension, and this involves risk to all forms of cardiovascular diseases (Selvin & Erlinger, 2004). But hypertension involves lesser risk towards developing lower extremity PAD compared to diabetes and smoking (Norgren et al., 2007). Figure 2.1 presents the range of these risks of developing lower extremity PAD

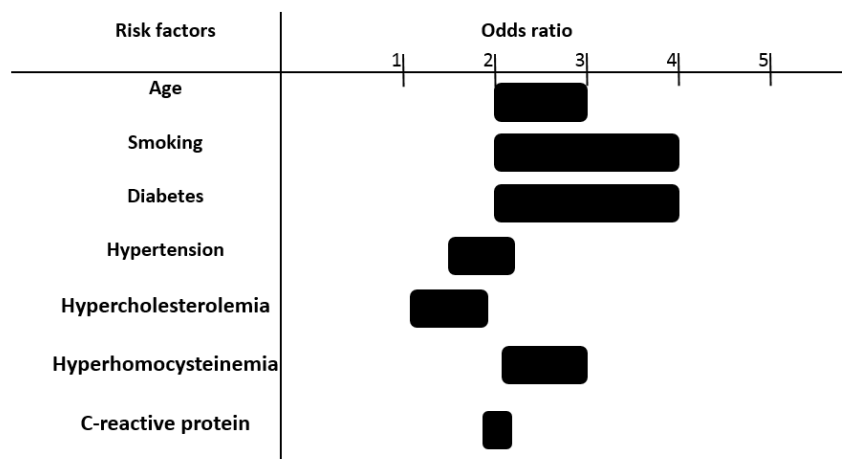


Figure 2.1: Range of odds ratios of risk factors for developing lower extremity peripheral arterial disease. Modified from (Hirsch, Haskal, Hertzler, Bakal, Creager, Halperin, Hiratzka, Murphy, Olin, Puschett, Rosenfield, Sacks, Stanley, Taylor, White, White, White, Antman, Smith, Adams, Anderson, Faxon, Fuster, Gibbons, Hunt, et al., 2006)

2.1.2 Claudication

Claudication is one of the main symptoms when patients feel pain in their legs on exertion and relieved at rest (Leng et al., 2000). It is generally muscular leg pain that occurs when blood flow in the artery bed fails to meet the metabolic demand in the leg musculature (Gardner, Parker, et al., 2008). In one of the studies, researchers have characterized leg symptoms into 6 mutually exclusive groups using a San Diego claudication questionnaire (Criqui et al., 1996). Claudication is an initial indication for people to check for the existence of PAD. Claudication involves main features such as disease progression and limb functioning declining over time (Beebe, 2001). Figure 2.2 shows the classification of leg symptoms group based on San Diego claudication questionnaire.

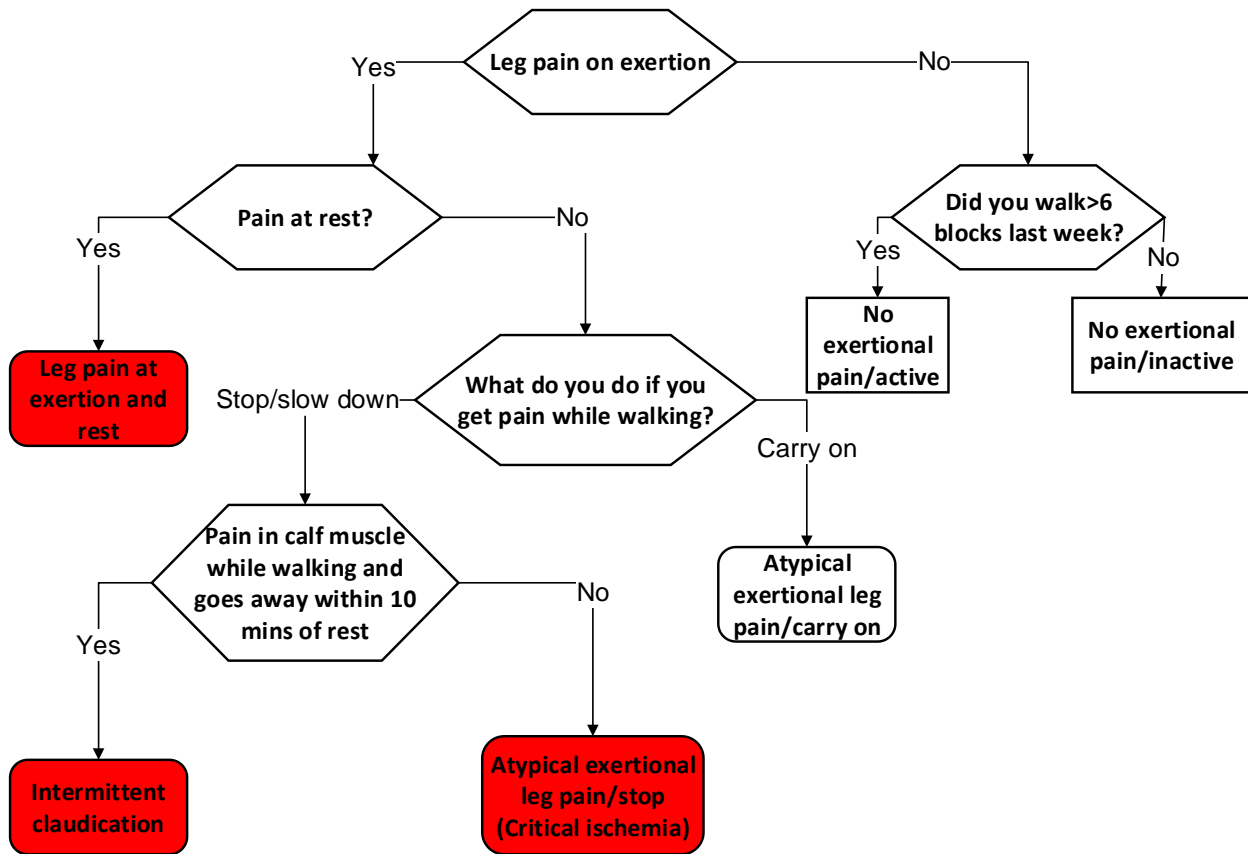


Figure 2.2: Leg Symptoms that are commonly present in PAD, grouped based on questionnaire Courtesy of (McDermott et al., 2001).

The pathophysiology of claudication is more complex than what can be explained by the mismatch of blood flow and oxygen demand (Hirsch, Haskal, Hertzler, Bakal, Creager, Halperin, Hiratzka, Murphy, Olin, Puschett, Rosenfield, Sacks, Stanley, Taylor, White, White, White, Antman, Smith, Adams, Anderson, Faxon, Fuster, Gibbons, Hunt, et al., 2006). Patients with claudication have a significantly higher mortality of about 12% a year (Cassar, 2006). The pathophysiology of claudication involves more complex events such as metabolic, neurological, and inflammatory responses (Brunelle & Mulgrew, 2011). In fact, all of the physiological changes that occur during claudication are not fully understood. In one of the studies, they say 50% of patients with Intermittent Claudication (IC) experience death from cardiovascular disease and 20% of patients are affected from cerebrovascular disease (Casey et al., 2004). Though IC is

not life threatening, it is a bio marker for the developing lower extremity PAD and other vascular disease (Fletcher, 2006). Supervised walking exercise is the advised primary care treatment for patients with claudication (Bartelink et al., 2004).

2.1.3 Critical limb ischemia and acute limb ischemia

As PAD worsens, claudication leads to limb ischemia where patients begin to feel pain in their muscular leg even at rest. Both ischemia needs proper attention at the earliest to avoid amputation. During this stage, the arterial bed functioning should be studied thoroughly and restored through revascularization procedures. This stage is analogous to the myocardial infarction as in coronary artery disease in heart (Shishehbor, 2014). Acute limb ischemia (ALI) is when the patients experience sensory loss in their limbs. The sudden cessation of blood flow in the arteries to the affected limb leads to neuromuscular impairment (Falluji & Mukherjee, 2014). In one study, they have classified ALI based upon their severity and suggested a recommended method for each stage as shown in Table 2.1.

Table 2.1: Categories of Acute limb ischemia. Modified from (Adam & Bradbury, 2007; Falluji & Mukherjee, 2014)

Class	Description	Neuromuscular Symptoms	Recommended treatment
I	Viable	No loss	Revascularization
IIa	Marginally threatened	Sensory loss	Revascularization
IIb	Immediate threatened	Sensory loss and some motor loss	Revascularization
III	Irreversible	Paralysis and Insensate	Amputation

Critical limb ischemia (CLI) is the final stage of developing lower extremity PAD. This ischemia includes muscular leg pain at rest and tissue damage that results in poor wound healing. Like in ALI, Critical limb ischemia is classified from pain at rest to gangrene level in the Rutherford classification as shown in table (Shishehbor, 2014). Researchers say that roughly 5-10% of people progresses from claudication to CLI in less than 5 year span (Falluji & Mukherjee, 2014). The primary goal for a vascular surgeon at this stage would be to control pain, improve wound healing, and prevent amputations. Revascularization is a common treatment for CLI where a bypass surgery is performed to restore the arterial bed functioning and preventing further tissue damage losses. In a study, a new treatment procedure combining revascularization and free tissue transfer was discussed (Briggs et al., 1985). Using this concept, a study was performed on 7 patients who fell into category 6 based on Rutherford classification (Table 2.2). All of them underwent tissue transfer and grafting surgery that resulted in 85% flap survival rate and 100% limb salvage rate (Igari et al., 2013).

Table 2.2: Rutherford categories for critical limb ischemia. Modified from (Shishehbor, 2014)

Category	Clinical Symptoms
1	Mild Claudication
2	Moderate Claudication
3	Severe Claudication
4	Pain at rest
5	Tissue loss
6	Gangrene

Both acute and critical limb ischemia is to be properly diagnosed in their early stages and should be aggressively treated to avoid amputation of limbs. Annually, large number population

is diagnosed with PAD at CLI level, which means that there is no effective preventive methods at early stages till date (Falluji & Mukherjee, 2014). Proper awareness about the risk factors associated with developing lower extremity PAD towards cardiovascular and cerebrovascular disease is still lacking among the population.

2.1.4 Diagnosis

National Institute for Health and Clinical Excellence (NICE) has recommended some guidelines for the management and diagnosis of PAD (Layden et al., 2012). Leg pain at rest is a symptom of PAD, but this symptom is not an accurate prediction of the disease and requires diagnostic methods to stage the severity of lower extremity PAD. There has been different methods to detect peripheral artery disease (PAD) as listed below:

2.1.4.1 Physical Examination:

Identifying signs of PAD while having a general check-up is not a cumbersome task for the physician. There are several signs for detecting PAD like the whooshing sound (bruits) that can be detected with the help of a stethoscope, sickness, confinement of the blood flow in the ruptured areas, variation in blood pressure in the ruptured leg.

2.1.4.2 Ankle-brachial index (ABI):

One of the most prominent test used for PAD detection is ABI. The main concept behind ABI is to find the ratio of blood pressure between arm and ankle. Instruments used for the detection of pressure are normal blood pressure sleeve and on a few occasions ultrasound is also used to evaluate flow and pressure. Sometimes, patients may stroll on a treadmill and have readings taken before and instantly after the end of practicing to catch the seriousness of the contracted arteries at the time of walking.

2.1.4.3 Ultrasound:

Doppler ultrasound imaging can help the physicians calculate blood pressure and velocity through the blood vessels and also help to locate blockages or contracted arteries.

2.1.4.4 Angiography:

In angiography, a dye is being injected into blood vessels and this helps in detecting the blood flow. Blood flow is being tracked with the help of advanced imaging techniques like magnetic resonance angiography (MRA) or computerized tomography angiography (CTA). Catheter angiography is a method which involves insertion of a tube like structure into the affected region and then injecting the dye in the blood vessel. Even though this method is invasive, it can simultaneously offer diagnosis and cure at the same time. Initially, the ruptured area is identified, then the blood vessel is broadened and provide the necessary treatment in order to enhance the blood flow.

There are few other non-invasive diagnostic techniques like Doppler ultrasonography, and near infrared spectroscopy that will be generally used to localize and quantify the severity of arterial damage in patients before surgery is considered.

2.1.5 Clinical approach

Once the patient is diagnosed with developing lower extremity PAD at CLI level, vascular surgeons or clinicians recommend them for endovascular revascularization treatment.

Revascularization procedures involve restoring the arterial bed functioning by grafting a bypass and thus the blood flows in the grafted bypass artery, thereby the metabolism in the limb is restored and patients should experience no leg pain, normal limb functioning and effective wound healing. In a study, researchers have concluded that endovascular vascularization is a

better therapy for patients with CLI, as they are effective in facilitating healing of wounds (Bae et al., 2013). Once revascularization is performed, patients should be thoroughly under supervision for at least 6 months – 2 year period as there is a greater probability of graft failure in patients, resulting in a secondary treatment (Hirsch, Haskal, Hertzler, Bakal, Creager, Halperin, Hiratzka, Murphy, Olin, Puschett, Rosenfield, Sacks, Stanley, Taylor, White, White, White, Antman, Smith, Adams, Anderson, Faxon, Fuster, Gibbons, Halperin, et al., 2006). A study clarifies that up to 25% of patients after vascularization experience wound complications and 1% of all patients after revascularization will develop a secondary infection with a mortality rate of 15% and 40% of major limb loss (Nehler et al., 2003).

2.2 SCREENING FOR PAD

Peripheral artery disease is a progressive disease and is considered to contribute risk towards the underlying cardiovascular events. So screening for PAD is an essential requirement for patients with symptoms, to avoid complications. The dominance of PAD, evaluated utilizing the ankle brachial blood pressure (ABI), has been assessed to be 10 to 20% of people beyond 65 years (Criqui, 2001). Shockingly, PAD has been under-estimated and under-treated, with most patients lacking knowledge of ideal administration, which take account of treatments demonstrated to diminish mortality (Criqui et al., 1992). Traditional discontinuous claudication (i.e. limb discomfort calmed by rest) is just noted by 10–30% of patients with PAD (Hirsch et al., 2001; McDermott et al., 2004). Appropriately, clinical evaluation for PAD has a moderately poor prescient worth (<10%) (Criqui, Fronek, Klauber, et al., 1985). Organized polls, for example, the Edinburgh Claudication Questionnaire has enhanced affectability and specificity when contrasted with clinician evaluation yet these surveys just recognize patients with the traditional set of symptoms (Leng & Fowkes, 1992). Since the present acknowledgment of PAD is

imperfect, and on the grounds that successful treatment that enhances mortality is accessible for these people, an adequate method to screen the populace for PAD is profoundly engaged. Some of the common screening methods and their limitations are discussed in the following literature.

2.2.1 ABI

Ankle Brachial Pressure Index (ABI) is a commonly used non-invasive technique used by practitioners to predict the severity of PAD. Among diagnosis techniques for examination to angiography, the ABI can identify blocked vessels with a sensitivity in the scope of 80–95 per cent, and a specificity in the scope of 95–100 per cent (Fowkes, 1988; Lijmer et al., 1996). The ABI is figured out from Doppler-inferred estimations of the systolic weight at the brachial and arterial areas. By tradition, for every lower end, the higher of the two lower limb artery pressure is utilized for the ABI computation. The ABI for that furthest point is the higher, lower limb pressure separated by the higher of the two brachial pressure. In simpler terms, the index is measured as the ratio of pressure difference between ankle systolic blood pressure and brachial systolic pressure (M. Al-Qaisi et al., 2009). In a healthy patient the ABI value at rest will be approximately equal to 1, meaning that the systolic blood pressure in the brachial artery of the arm is similar to that of the systolic blood pressure of the ankle. Figure 2.3 shows the standard clinical procedure to measure ABI. Table 2.3 shows the interpretation of ABI used by practitioners.

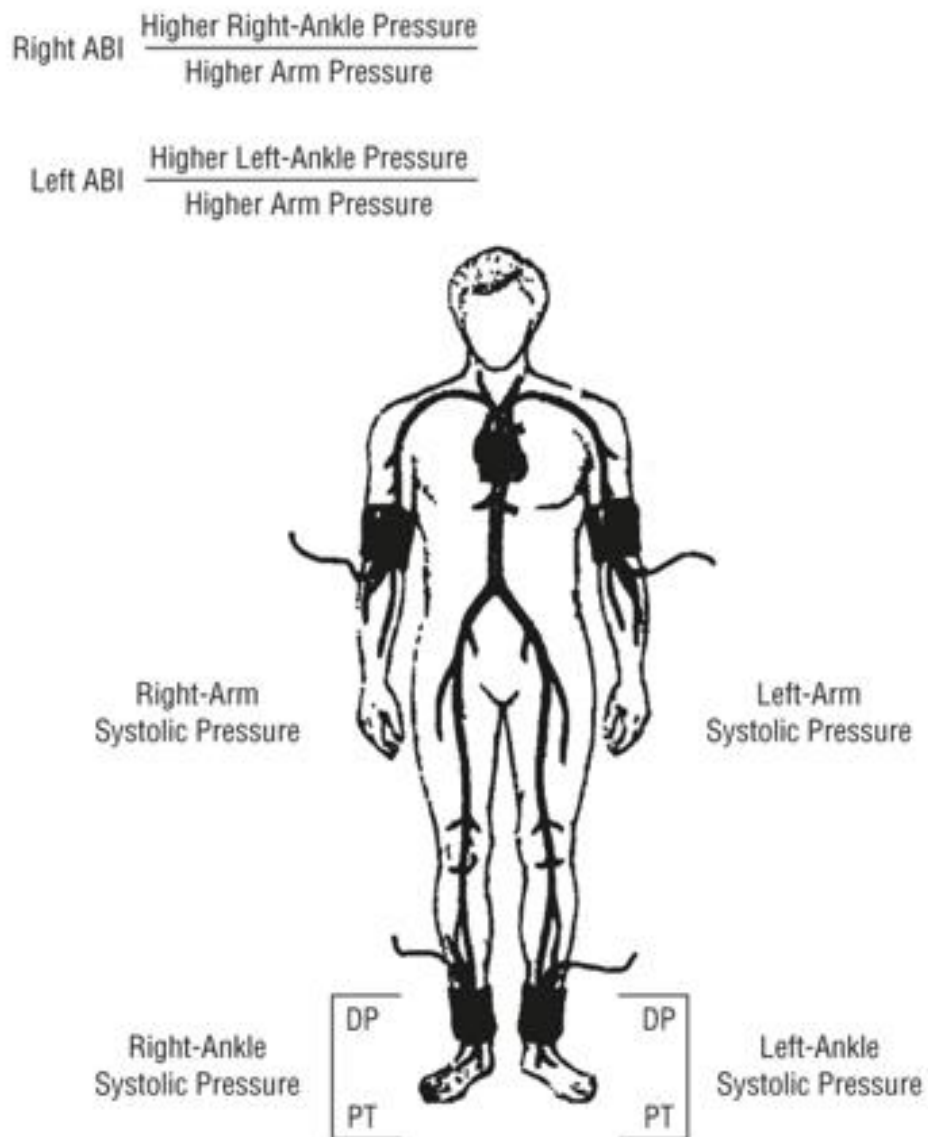


Figure 2.3: Measurement of ABI. DP indicates dorsalis pedis artery; PT indicates posterior tibial artery. Modified from (Mohler, 2003)

Table 2.3: Interpretation of ABI. Modified from: (M. Al-Qaisi et al., 2009)

ABI	Severity of disease
>1.4	Calcification may be present
>1.0	Probably no arterial disease
0.81–1.00	No significant arterial disease, or mild/insignificant disease
0.5–0.80	Moderate disease
<0.5	Severe disease
<0.3	Critical limb ischemia

ABI can be measured in 15 minutes to predict the developing lower extremity PAD in clinics. In a literature, researchers studied the accuracy of ABI to predict PAD and concluded that patients with $ABI \leq 0.3$ have poor survival rate than the patients with ABI 0.5-0.8 (McDermott et al., 1994). Other literature also reports a U shaped association between ABI measure of PAD and mortality risk rates and suggest the ABI value should not exceed 1.40 (Resnick et al., 2004). Figure 2.4 shows the U shaped association between mortality risk and measured ABI value. Another analysis by ABI reported, patients with ABI 1.1 to 1.4 had the lowest mortality rate per 1000 patient years, however these rates increased as the ABI measure decreases, resulting in about 6 fold increased risk factor for developing lower extremity PAD or amputation (Diehm et al., 2009).

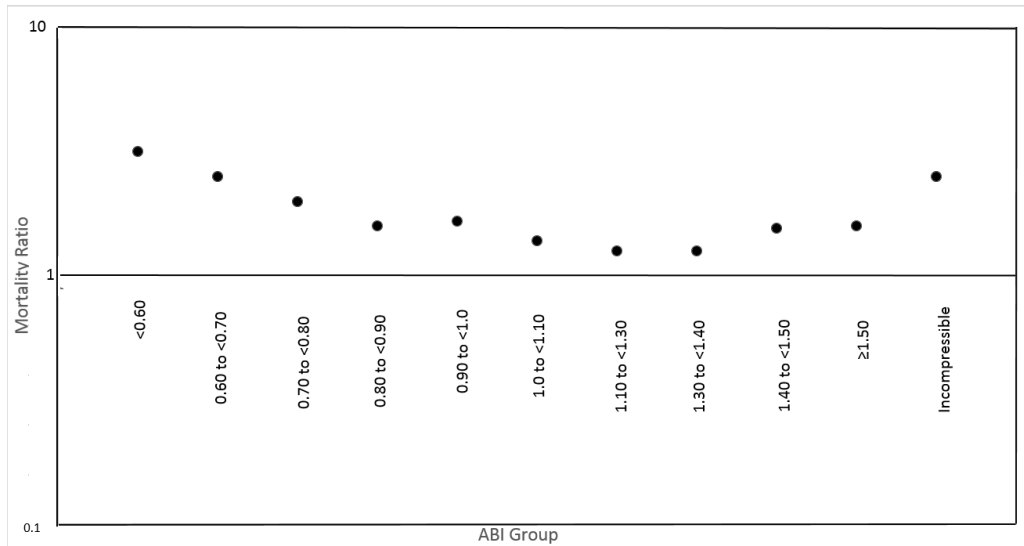


Figure 2.4: Adjusted Mortality ratio by baseline ABI value plot. Modified from (Resnick et al., 2004)

ABI also has limitations in diagnosing lower extremity PAD in patients with diabetes, which results in high ABI values due to incompressible arterial beds (Mohler, 2003). ABI measure is not sensitive enough to assess the progression of the disease with an overall accuracy rate of 68% (McLafferty et al., 1997). These accuracy rates in detecting developing PAD do not seem to be suitable in monitoring the progression of the disease. Also in another study, they highlight the difference is the measure of ABI value during rest and after exercise. In a clinical study of 396 patients, 31% who had normal readings at rest measured abnormal readings after exercise (Stein et al., 2006). These studies have clearly given us a picture that this non-invasive diagnosing method, though useful in many prediction of developing PAD has some limitations in predicting mild PAD and fail to predict subsequent cardiovascular events. After revascularization, ABI was measured to monitor the functional recovery of the arteries. But the accuracy to predict the failure of revascularization was very poor with 67% sensitivity and this is because ABI cannot distinguish between graft failure and progression of PAD (Aboyans et al.,

2012). Researchers and clinicians continued to notice a decline in limb functioning even after the surgery procedures. In this case ABI is not an essential method to diagnose PAD.

2.2.2 Biomarker screening

In this method, biomarkers are being used for screening and treating PAD. Biomarkers are natural measures of a biological state. By definition, a biomarker is a trademark that is neutrally measured and assessed as a marker of various processes like pathogenic, biological etc.

Biomarkers have a variety of purposes in the medical field, for example, pulse or high level of cholesterol indicator and is utilized to perform various tests in order to anticipate wellbeing state in people.

The biomarker index score is one of the methods that is utilized by many clinicians in order to provide improved and advanced form of diagnosis. For instance, these index scores help in predicting the probability of recurrence of breast cancer and other such diseases (Paik et al., 2004; Snyder et al., 2007). The end results of such index scores are way better than individual markers (E. T. Fung et al., 2008). This is the reason why these index scores are being used with other markers in order to differentiate individuals on the basis of their score. This will help in segregating individuals according to their level of seriousness of PAD.

Prediction, diagnosis, and treatment have been simplified with the use of biomarkers. The new innovative technique used to identify any kind of disorder is the biological media. For example, to predict the difference in the functioning of any part of our body during normal and unhealthy state can be performed with the help of biological media (Mayeux, 2004). Biological media comprises of blood, muscle, nerve etc. With the help of these components, once can

determine the functioning of the body in health and unhealthy state. The general biomarker panel comprises of various types of biomarkers.

In a research study (Cooke & Wilson, 2010), 540 individual were selected for screening using biomarkers. This study revealed that among many biomarkers, β_2 M, cystatin C and CRP showed high correlation with the ABI readings. So these biomarkers would best suit for the screening of PAD. Some of the common features of these biomarkers are listed in Table 2.4. Out of the three markers, β_2 M protein had high predicting value for PAD (Shinkai et al., 2008).

Table 2.4: Ideal characteristics of Biomarker (Cooke & Wilson, 2010)

Characteristics of an ideal Biomarker
Sensitive for the presence of disease
Specific, good negative predictive value
Correlates with prognosis
Measurable with high-throughput techniques
Correlates with disease-specific features: ABI, walking time
Levels minimally or predictably affected by confounding factors
Reproducible
Cost effective
Acceptable to patients and clinicians
Complementary to current strategies

Selecting or creating a new protein biomarker is not an easy task and there are lots of obstacles to the discovery of new biomarkers that can be used for screening of PAD. The most discouraging issue is because of the significant variety of the proteome (Gerszten & Wang, 2008). To be clinically successful, the biomarkers used should be maintained to remain stable to

be easily measured and provide accurate results (Cooke & Wilson, 2010). There is a strong clinical need for more specific biomarkers for PAD.

2.2.3 *Edinburgh Claudication Questionnaire*

Pain, cramp in the legs and thighs are the primary criteria for characterization of intermittent claudication. The main reason for such of pain is due to insufficient blood supply to the specific parts of the body. Edinburgh claudication questionnaire and measurement of ABI were used for screening PAD based on its symptoms (Fernandez, 2002).

In Rabia and Khoo (2007), a study was performed on patients (18 years and above) who were diabetic. The patients were told to answer a set of questionnaire in order to find the existence of Intermittent Claudication (IC). There were six questions as follows:

Edinburgh Claudication Questionnaire	
Question 1	Assesses whether patients get any pain or discomfort on walking.
Question 2	Evaluates whether patients get this pain when they are standing still or sitting.
Question 3	Estimates whether patients get pain when they walk uphill or walk in a hurry.
Question 4	Determines whether patients get this pain walking at an ordinary pace on level ground.
Question 5	Assesses whether if patients stand still the pain continues for more than 10 min or disappears within 10 min.
Question 6	Requires patients to mark on a diagram, where they actually get pain or discomfort

As a result of this study, the individuals were classified with or without claudication on the basis of answers to the questionnaire. An individual possessing claudication will point out

pain in the calf without referring to pain in another part of the body. Also, if someone states pain in thigh without any pain in calf is considered to possess a typical kind of claudication. Pain in joints, shin etc. are not considered in the list of claudication (Leng & Fowkes, 1992). Figure 2.5 shows a sample ECQ used commonly to screen vascular disease such as PAD and CVD in clinical practice. Figure 2.6 briefs the method to confirm the existence of intermittent claudication through ECQ.

The Edinburgh Claudication Questionnaire:
CAD/PVD

* A positive questionnaire diagnosis of claudication is made only if the **“correct”** answer is given to **all questions**

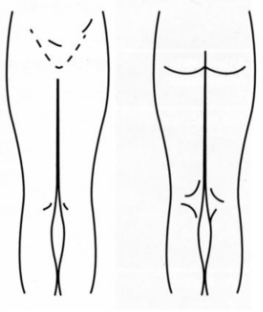
Questions	Correct Answer	
1. Do you get pain or discomfort in your legs(s) when you walk? <input type="radio"/> Yes <input type="radio"/> No <input type="radio"/> Unable to walk <ul style="list-style-type: none"> • If you answered “yes” to question 1, please answer the following questions 	Yes	
2. Does the pain ever begin when you are standing or sitting still?	No	
3. Do you get it when you walk uphill or in a hurry?	Yes	
4. Do you get it when you walk at an ordinary pace on the level?	Yes	
5. What happens if you stand still? <ul style="list-style-type: none"> • Usually continues for more than 10 minutes? • Usually disappears in 10 minutes or less? 	No Yes	
6. Where do you get this pain or discomfort? <ul style="list-style-type: none"> • Mark the places with an “X” on the diagram 		

Figure 2.5:Edinburgh claudication questionnaire for screening PAD (Leng & Fowkes, 1992)

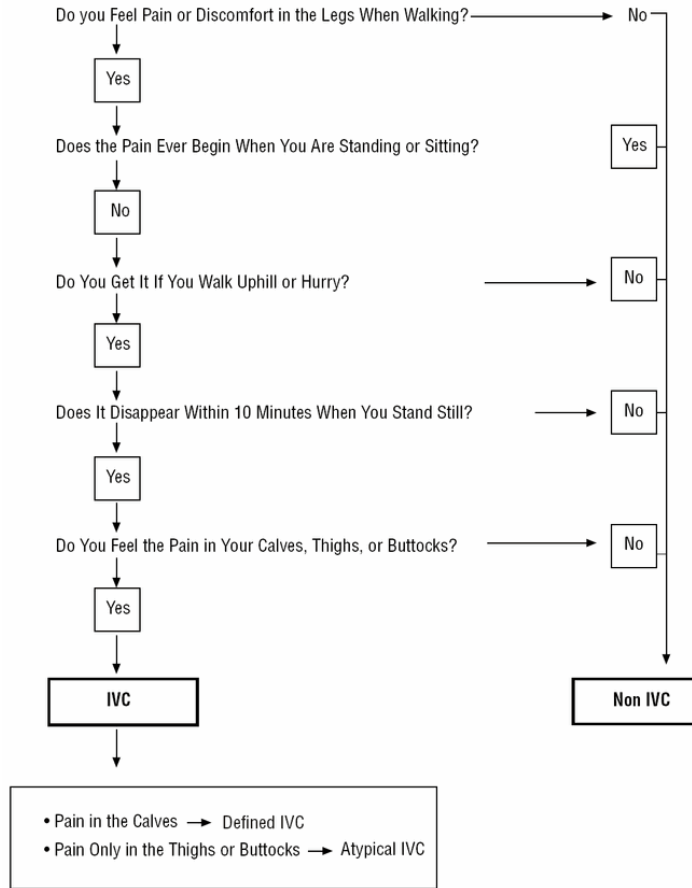


Figure 2.6: A technique based on ECQ to conclude the existence of IC (Manzano et al., 2006). Researchers observed some disparity with ECQ screening for PAD, that diagnosed 16% of patients with PAD while actually 4.5% of the patients were suffering from IC (Rabia & Khoo, 2007). This was because the study was done in general individuals with diabetes were not considered. Chao and Koh (2003) proved that 15.1% of the individuals possessed PAD on the basis of ABI and on the basis of EQC existence of IC was 2.71%. As in ABI, this screening method will work less effective for asymptomatic PAD and in diabetes patients as they would not feel pain in their legs. So it is clear that many researchers conclude that ECQ is not a preferred screening method for PAD.

2.2.4 Pulse volume recording (PVR)

PVR, also termed as plethysmography is a non-invasive vascular test to obtain information about arterial blood flow in the arms and legs. It is a screening method to diagnose obstruction in the blood vessel. Based on the testing, we could categorize the disease based on its severity and also could locate the obstruction in blood vessels.

This system uses cuff that detect volume changes in the blood vessel as shown in **Error! eference source not found.** Based on the analysis of the output pulse wave form and amplitude of the peak, the condition of the underlying vessels can be determined.

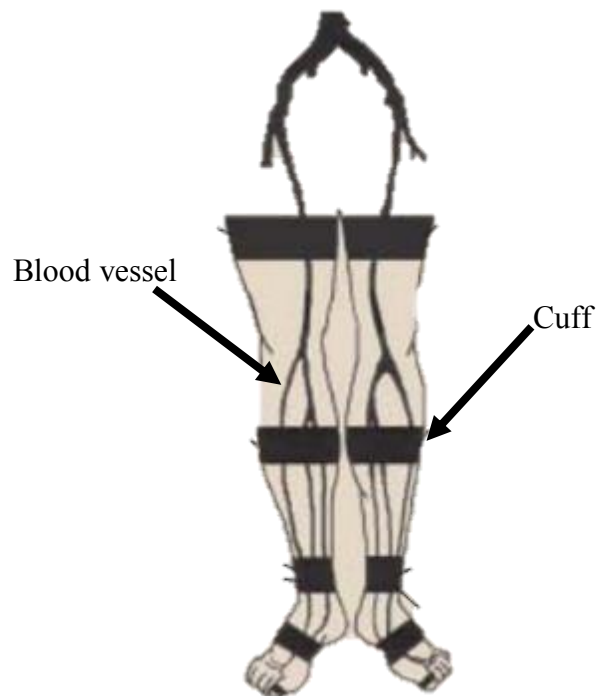


Figure 2.7: Cuffs used at thigh, upper calf, ankle, metatarsal, and digits to obtain pulse volume recordings. modified from (Begelman & Jaff, 2006).

2.2.4.1 Method of screening

PVR screening method normally would take 45 minutes. The patient will be asked to lie on the test bed and the physician would mount the pressure cuffs in the desired sites.

Measurement sites commonly include the high thigh, above the calf, below the knee, the ankle and the toe. The cuff is inflated and they measure the volume of blood that passes through the blood vessel underneath the cuff. This volume of blood is registered as a waveform pattern as shown in Figure 2.8. The physician can determine if there is any blockage in the arteries above or at the level of the cuff by looking at the size and shape of the waveform.

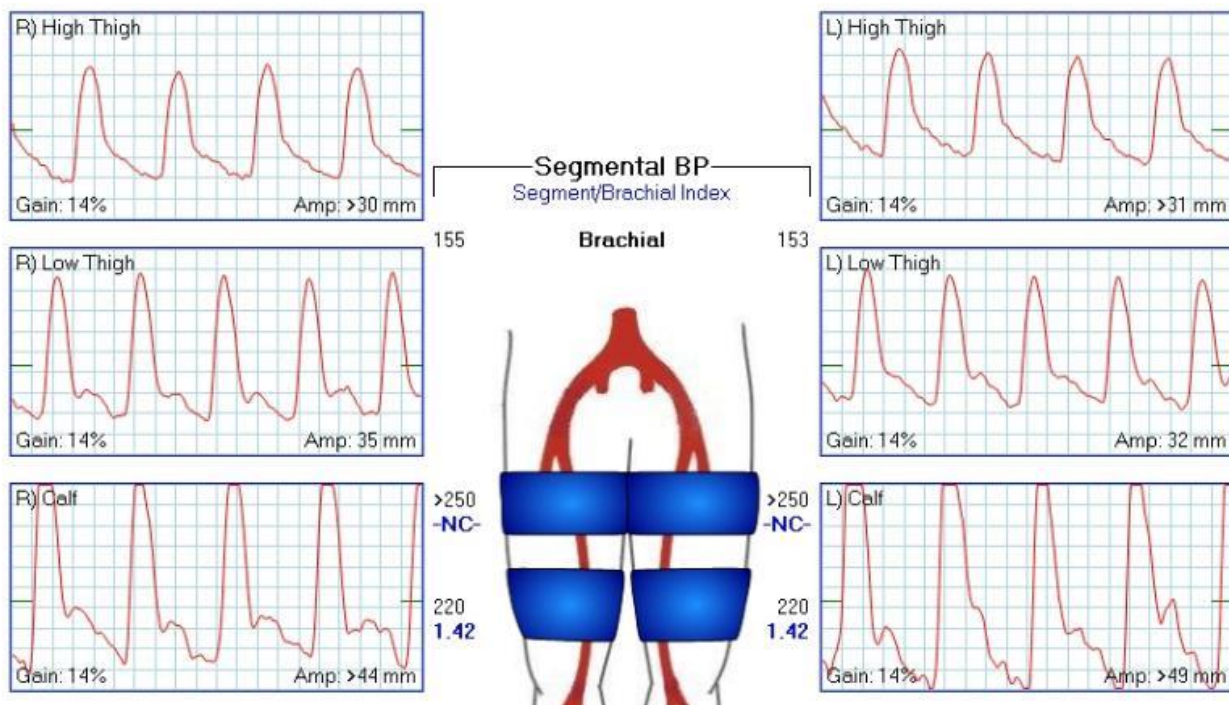


Figure 2.8: Pulse waveform pattern at the upper and lower thigh. Retrieved June 22, 2015, from <http://www.angiologist.com/arterial-disease/pulse-volume-recordings-interpretation-pitfalls/>

2.2.4.2 PVR analysis

Waveform pattern is analyzed to determine the severity of the disease. To interpret the pulse waveform, it is important to understand the four important patterns in a single waveform.

Absence of any one of these patterns is an indication of abnormality in the underlying blood vessel.

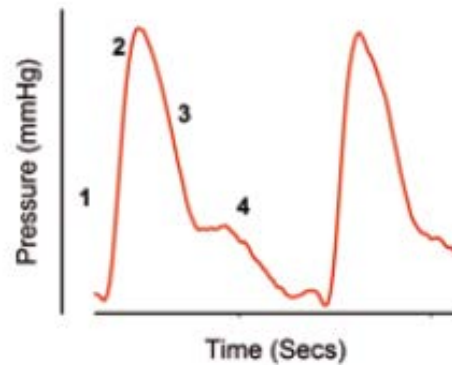


Figure 2.9: Normal PVR waveform (Davies, Lewis, & Williams, 2014).

The four distinct features of the pulse waveform in Figure 2.9 are as follows:

1. A steep rise in the upstroke during systole cycle
2. A sharp peak at maximum amplitude
3. A gradual down stroke
4. Presence of a dichrotic notch

Absence of dichrotic notch is the prime indication of possible abnormality. And as the disease progresses, the peak amplitude flattens and also the blockages in the blood vessel will show a decreased slope of the upstroke steep and descending down stroke. As the disease is in the critical stage, the PVR will record a flat waveform. Based on the features, the severity of the disease is categorized (Davies et al., 2014) as shown in Figure 2.10

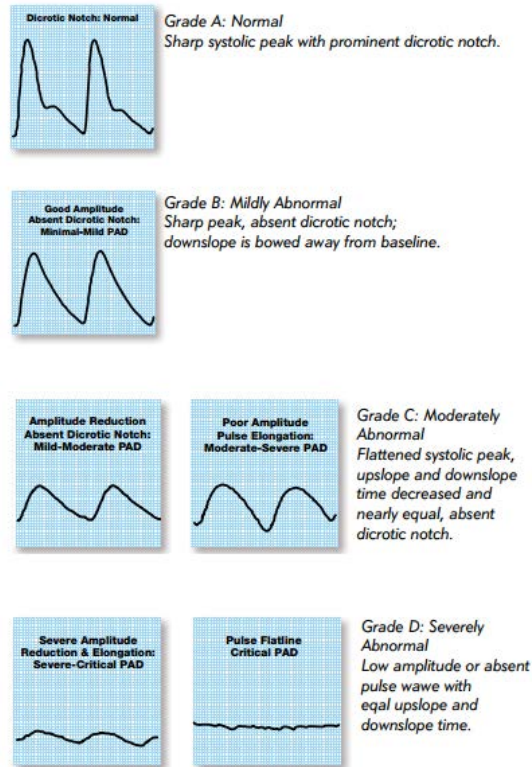


Figure 2.10: PVR grading system (Davies et al., 2014)

2.3 SENSORS TECHNOLOGY TO DETECT BLOOD FLOW

2.3.1 Wearable Photoplethysmographic Sensors

Photoplethysmography (PPG) sensor technology has been developed to continuously monitor pulse rate. The sensor consists of infrared light emitting diodes and photodetectors to monitor the pulse rate non-invasively. The PPG sensor monitors the pulse rate changes with the changes in the light intensity (Tamura et al., 2014). The wearable PPG sensors operates on two modes (Figure 2.11); 1) transmission mode and 2) reflectance mode. The sensor is capable of obtaining good signal when operated in transmission mode, however the measurement sites are limited. The sensor will be effective, when the sensor is located at sites like fingertip, nasal septum, cheek, tongue or earlobe (Tamura et al., 2014).

In reflectance mode the measurement sites are not limited as this method eliminates the problem associated with the transmission mode. Any physical movement may corrupt the transmitted signal due to motion artifacts and pressure disturbances and thus limit the measurement accuracy of physiological parameters (Tamura et al., 2014).

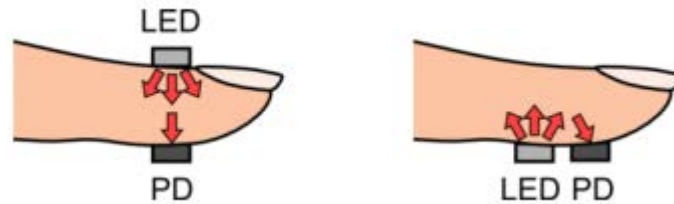


Figure 2.11: Placement of sensor for transmission and reflectance mode photoplethysmography (PPG). Courtesy (Tamura et al., 2014)

The PPG sensors are yet to be developed as a prototype. However a great progress has been achieved in the signal processing. Using green light sources in the sensor would eliminate motion artifacts and could offer better results (Tamura et al., 2014).

2.3.2 *Micro optical blood flow sensor*

These sensors were developed and used to monitor blood flow of chicken to prevent bird flu. The sensor uses MEMS technology to monitor flood flow and this sensor is considered to be the smallest sensor in the world to measure the blood flow. The sensor setup would need a battery source to function as shown in Figure 2.12. This technology is a low power and low cost micro sensor and researches are working on to reduce the power consumption and size. Also the sensor is yet to be tested on human studies to label this as a more practical sensor (Seto et al., 2009).

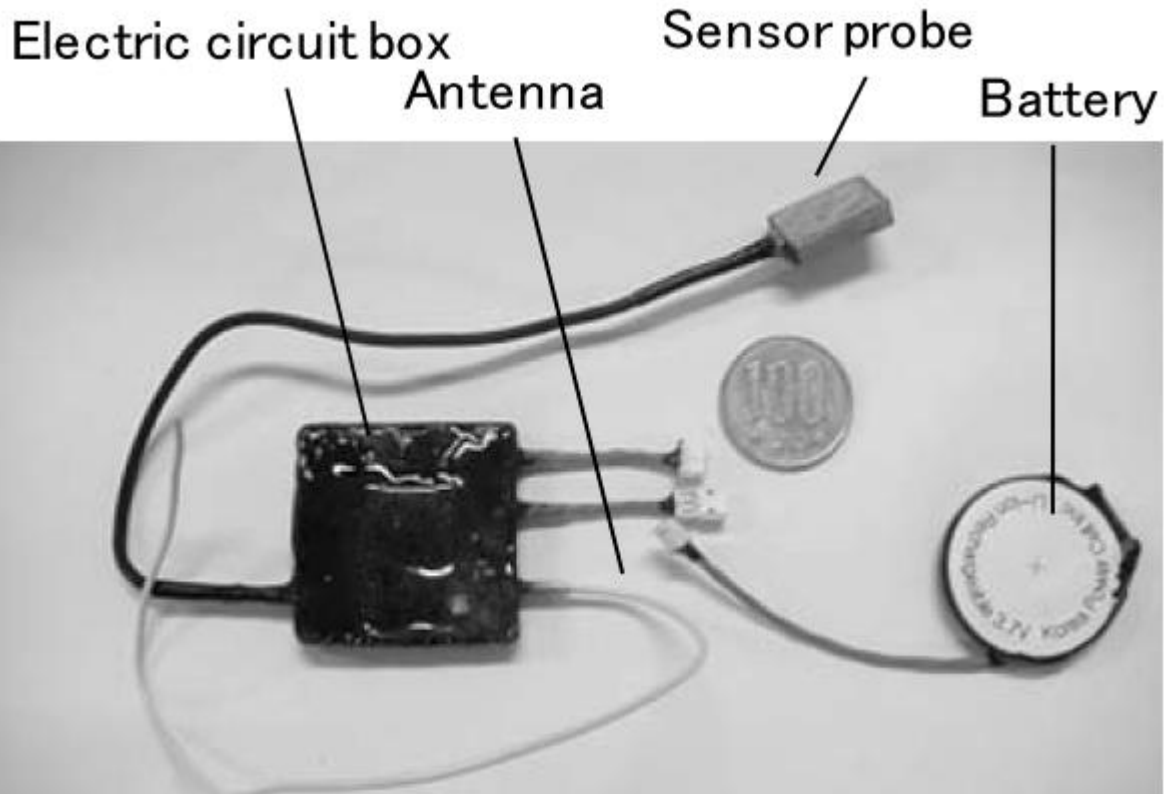


Figure 2.12: MEMS blood flow sensor setup. Courtesy (Seto et al., 2009)

2.4 VASCULAR SYSTEM

Vascular system in the human body, consists of blood vessels, whose purpose is to transfer blood from the heart through the body. Heart act as a pump to receive and send out blood through the vascular system. The blood vessels that include arteries, arterioles, precapillary sphincters, capillaries, venules, and veins are responsible for distribution of blood throughout the body (Tortora & Nielsen, 2014). The circulation is more clearly explained in the flow model below in Figure 2.13.

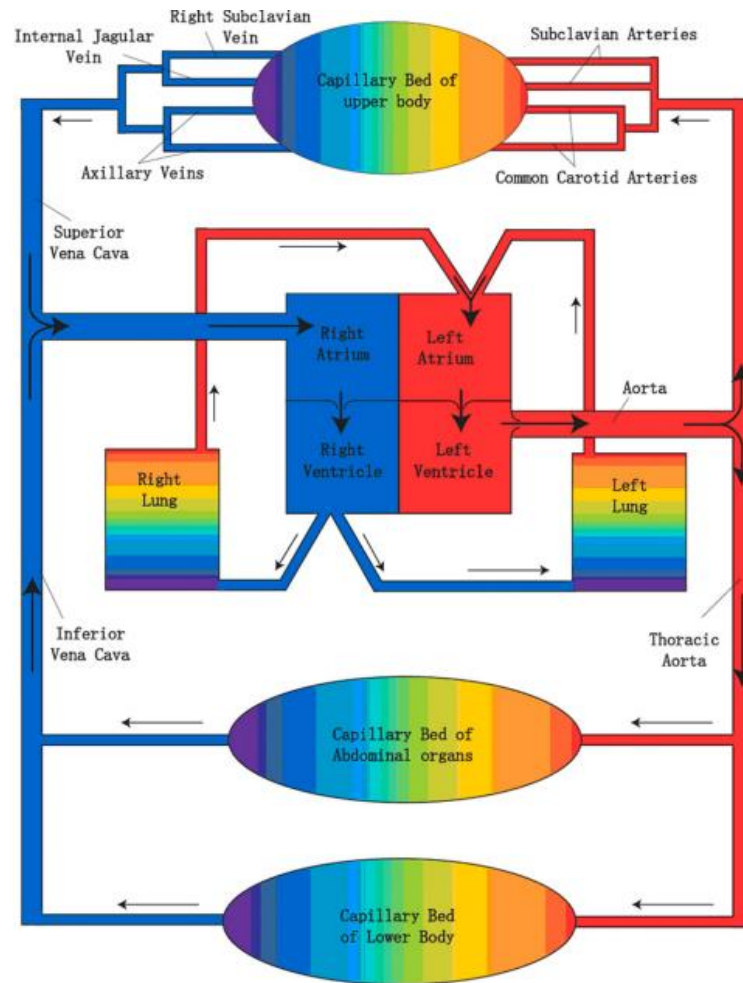


Figure 2.13: A schematic of human blood circulation system Courtesy from (Khakpour & Vafai, 2008)

Blood vessels transport blood to and from the heart. These vessels can be divided into three major classes: arteries, veins and capillaries. Arteries carry blood from the heart and transfer to the capillaries. Capillaries are small blood vessels that are responsible for oxygen and nutrient transfer from blood to surrounding tissues. Also waste from the tissues are transferred to capillaries and transported to veins. Through veins, circulated blood reaches heart. This whole process takes place in a matter of seconds through systolic and diastolic cycle. During systole, the blood vessels contract to gain pressure and during diastole, the vessels expand and blood flows (Y. C. Fung, 1997).

2.4.1 Microcirculation

In a study, researchers demonstrated that PAD is not confined to conduit vessels, but also affect skeletal muscle flow and it is important to study microvascular flow (Wu et al., 2009). To understand the mechanism of microvascular flow, blood microcirculation should be studied in depth. Microcirculation is that part of the vascular system where oxygen, nutrients, and waste products are exchanged between circulating blood and surrounding tissues (Cohen et al., 2002). The microcirculation includes network of blood vessels less than 100 μm in diameter. According to anatomical features and the direction of the blood flow, these micro vessels are subdivided into arterioles, capillaries, and venules (Peters et al., 2001).

In addition to the general architecture of microcirculation, physiologists confirmed the existence of precapillary sphincters and metarterioles (Sakai & Hosoyamada, 2013). The arterioles contain vascular smooth muscle and are the major site of systemic vascular resistance. In skeletal muscle and other tissues, a large number of capillaries remain closed for long periods due to contraction of the precapillary sphincter. These capillaries provide a reserve flow capacity and can open quickly in response to local conditions such as a fall in pO_2 when additional flow is required. Figure 2.14 shows the two factors that controls the transfer of oxygen across capillary membrane.

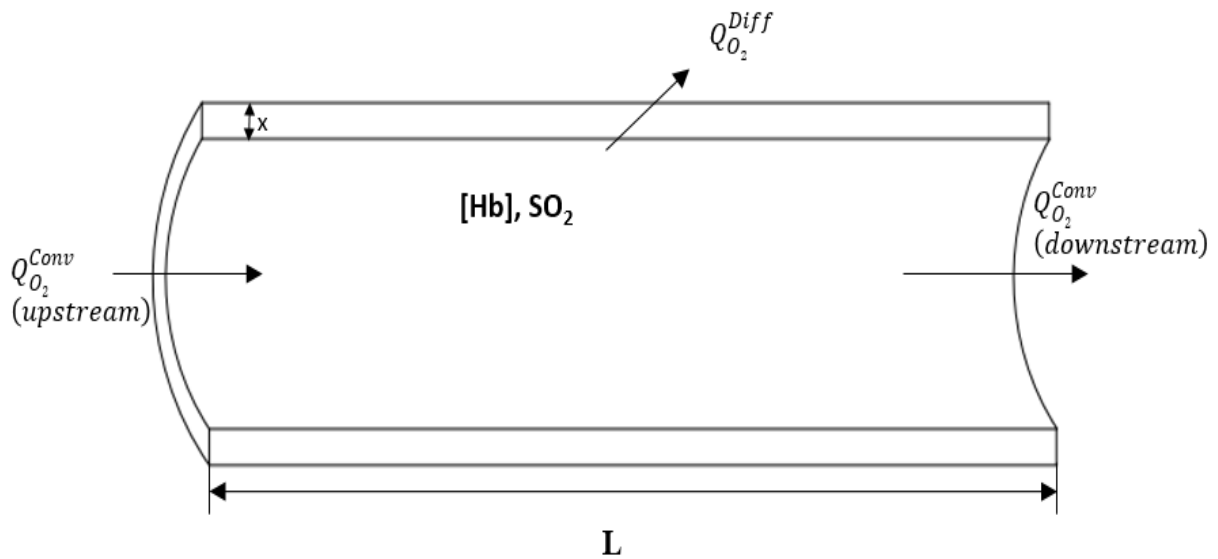


Figure 2.14: Two factors associated with oxygen transfer in the microcirculation. Upstream is from the arterial side; downstream is to the venal side and diffusion is in the tissues surrounding the capillaries. Modified from (Pittman, 2005)

There are very few studies that focused on the microvascular flow in progressive PAD. In Wu et al. (2009), they have introduced a new method to measure the calf perfusion in PAD patients. The assessment method includes the supplication of continuous arterial spin-labeling (CASL) magnetic resonance imaging (MRI). In this study 40 subjects were chosen with varying degrees of PAD and CASL method was used to quantitate the blood perfusion in the microvascular level. CASL is a non-invasive MRI technique that uses two scanning: the tagged uses radiofrequency pulses to acquire arterial blood flow and the control is obtained without net magnetization. Then the signal difference is computed to measure the perfusion rate in the calf muscle of PAD patients.

In (De Backer et al., 2002), a microvascular blood flow study was conducted on animal model with sepsis. The study population included 50 patients with severe sepsis. The microvascular blood flow was imaged using orthogonal polarization spectral (OPS) imaging technique. OPS imaging is another non-invasive technique that can be used to investigate the

blood flow in microvascular level (Groner et al., 1999). Figure 2.15 shows the image of the microvascular structure in human obtained from OPS technique. The vessel walls are not visible in Figure 2.15, however if they contain some red blood cells in the blood vessels, the walls will be visible and this has been validated in experimental models (Mathura et al., 2001).

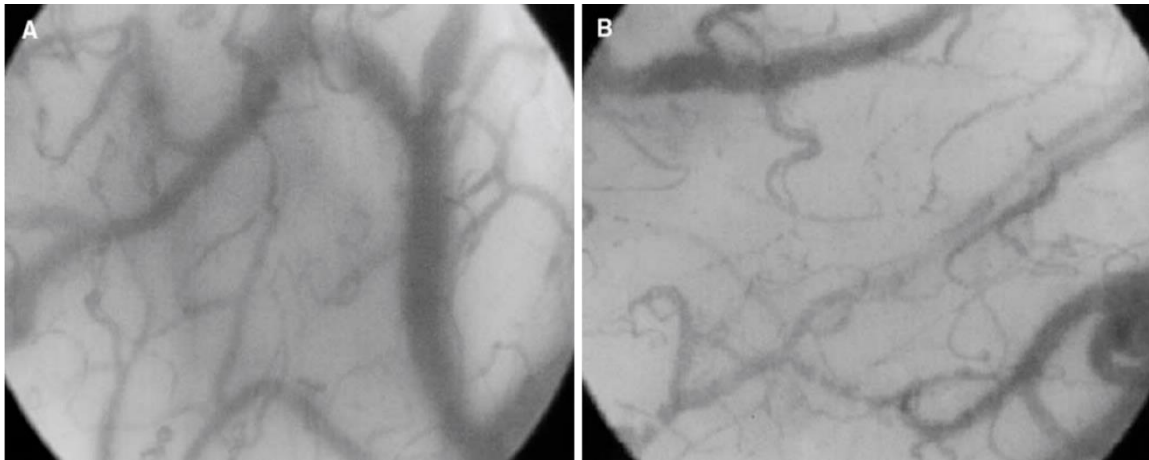


Figure 2.15: Microvasculature in A) Healthy patient B) patient with sepsis. Courtesy from (De Backer et al., 2002)

2.4.2 Regulation of blood flow

The cardiovascular system regulates blood flow to individual organs by following ways; by maintaining arterial pressure within narrow limits and by allowing each organ to adjust its vascular resistance to blood flow so that each organ receives an appropriate fraction of the blood flow. There are three major mechanisms that regulate blood flow in the cardiovascular system: neural, humoral, and local (Bagher & Segal, 2011). The neural system and circulating hormonal changes, both provide overall vasoregulation, and thus coarse flow control, to all vascular beds. The local mechanisms provide finer regional control within a tissue, usually in response to local changes in tissue activity or local trauma.

2.4.2.1 Local regulation of blood flow

When blood pressure (arterial pressure minus venous pressure, $P_A - P_V$) initially decreases, blood flow (F) falls because of the following relationship between pressure, flow and resistance (Zubieta-Calleja & Paulev):

$$F = (P_A - P_V) / R \quad \text{Equation 2.1}$$

When blood flow falls, arterial resistance (R) falls as the resistance vessels (small arteries and arterioles) dilate. There are two important theories that could explain local regulation of blood flow. They are (1) the myogenic mechanism based on the ability of vascular smooth muscle to actively adjust its resistance in response to the blood pressure; (2) the metabolic mechanism, based on the demand due to tissue metabolism (Jones & Berne, 1965).

The myogenic theory considers regulation of blood flow is as result of the myogenic response which is an intrinsic property of vascular smooth muscle. The blood vessel reacts to the blood pressure within the vessel. So if the pressure is increased, the vessel stretches and constricts the flow and on the other way, the vessel is relaxed causing vasodilation. Both these constriction and vasodilation are controlled by the smooth muscles in the blood vessels. This process is termed as vasomotion. The metabolic theory suggests that blood flow is altered is caused due to the changes in tissue metabolites. Based on the oxygen demand in the tissues, they release vasodilator substances that would alter the blood vessels through smooth vessels (Starc, 2004).

2.5 MICROVASCULAR DYSFUNCTION

The obstruction in the microvascular bed results in ‘no flow’ phenomenon that actually points out the absence of reperfusion after an intervention. Microvascular dysfunction is more common in the coronary arterial bed and there are several case studies reported in the journals. In one of the research, case studies, a 50 year old man, despite undergoing a revascularization surgery the main coronary flow was achieved and he later developed heart failure (Jaffe et al., 2008). Literatures depict that 50% of CAD patients are diagnosed with microvascular coronary dysfunction after the surgical intervention (Kothawade & Bairey Merz, 2011). Researchers relate the dysfunction towards poor wound healing in the legs of the PAD patients and is the main reason for ulceration. Researchers are still working towards effective diagnostic method to measure and study on the microvascular dysfunction in detail. Figure 2.16 shows the pathophysiological mechanisms that may contribute to reperfusion no reflow phenomenon.

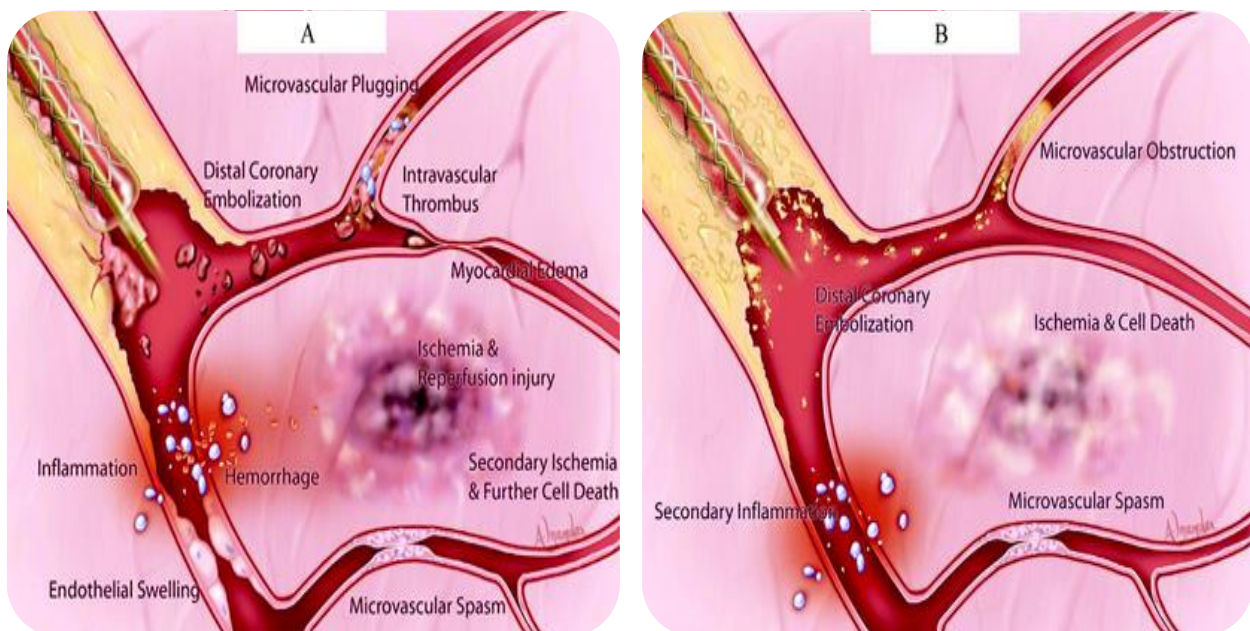


Figure 2.16: Obstructions in the microvasculature showing ischemia & reperfusion injury (Jaffe et al., 2008)

2.6 SUMMARY

PAD has been a common threat to the people of the United States that, since 1999 to 2004 almost 6 percent of the United States adults in the age limit of 40 or more are prone to be diagnosed with PAD (Virginia A Moyer, 2013). It is also estimated that the prevalence rate is almost 10%, rising to 15-20% in people of age over 70 years (Hiatt, 2001). PAD is almost recognized and confirmed to have equivalent mortality and morbidity rate compared to coronary artery disease and ischemic stroke (Desormais et al., 2014). The fundamental problem in PAD patients is the presence of atherosclerotic blockages in the arteries supplying blood to their legs. The pathophysiology of PAD is complex and involves changes occurring on multiple levels, including, reduced blood flow, altered metabolic processes, and muscle degeneration (Stewart et al., 2002). The current treatment strategies include endovascular surgical intervention to restore blood flow in the main arteries. Despite revascularization, patients continue to experience decline in limb functioning and walking parameters. This may be related to microvascular dysfunction as in coronary artery disease. A computational assessment of arterial functional recovery was performed as a part of this thesis work to determine the effectiveness of revascularization procedures. The nutrient and oxygen transfer takes place at the level of microvasculature and so reduced blood flow in the capillaries may impair tissue oxygenation (Tortora & Nielsen, 2014). This results in wound complications and later removal of legs and also the prevalence of PAD in patients are a risk factor towards major cardiovascular events (Chenzbraun et al., 2001). The computational study to assess the effect of microvascular insufficiency in PAD patients could give an insight and awareness to optimize the current diagnostic methods that can image at microvascular level. The literature also listed some screening methods for PAD that are currently

practiced and also highlighted some of their limitations. While all the screening methods are specific for PAD, their sensitivity is fairly low as in Table 2.5.

Table 2.5: Sensitivity values for the screening methods of PAD (Dachun et al., 2010; Khan et al., 2006)

Sensitivity of PAD detection methods	
Edinburgh Claudication Questionnaire	56%
Examination: absence of both pedal pulses	72%
Examination: femoral bruit	28%
Ankle-brachial index	77%

In this thesis work, we have proposed a new technology that could be used as a screening method for PAD. The technology works as a point of care screening method and this method can also be integrated with current methods to improve the quality of life of the people.

2.7 REFERENCES

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**CHAPTER 3 : ASSESSMENT OF ARTERIAL FUNCTION RECOVERY AFTER
SURGICAL REVASCULARIZATION IN PAD PATIENTS WITH MICRO-
VASCULAR INSUFFICIENCY USING COMPUTATIONAL MODEL ANALYSIS**

3.1 ABSTRACT

Peripheral arterial disease (PAD) is characterized by atherosclerotic blockages of the arteries supplying blood to the lower extremities, which cause a progressive accumulation of ischemic injury. Despite revascularization treatment intervention, some PAD patients require follow up secondary treatment due to a continued decline in limb function, quality of life and walking parameters. Standard revascularization surgical procedures restore blood flow in the main arteries via bypass surgical grafting. However, nutrient transport and oxygen transfer take place at the level of the microvasculature and capillaries. Nevertheless, an assessment of the microvascular circulation is lacking. Microvascular dysfunction, a ‘no flow’ phenomena that may occur at the level of the microvasculature, may impair tissue oxygenation as well as nutrient transport and may therefore be a contributor to the continued decline in limb function and walking parameters. Microvascular dysfunction may be one of the dominating factors that should be studied, to understand the failure of the arterial function recovery. Multi-physics simulation software was used to model the phenomena to assess the effectiveness of the standard lower limb revascularization treatment in PAD patients, who may have microvascular dysfunction. Typical invasive revascularization surgery using artificial bypass grafts to restore blood flow may fail to be effective if the PAD patient has microvascular dysfunction. It was observed that there was 71.73 % decrease in the oxygen transferred to the surrounding tissues when there was blockage at the microvascular level. This model identifies the need to measure the microvascular circulation in the compromised limbs of PAD patients to optimize diagnosis and treatment strategies that reflect the underlying pathophysiology.

Keywords: Microvascular dysfunction, revascularization, microvasculature, peripheral artery disease, oxygen consumption.

3.2 INTRODUCTION

Peripheral artery disease (PAD) is very common in adults that one third of the affected population are over 70 years (Grenon et al., 2014). Elevated blood cholesterol, diabetes, smoking, hypertension and obesity are some of the risk factors involved for PAD (Kenneth Ouriel, 2001). PAD is characterized by narrowing of blood vessels that transport blood to leg and arm muscles. The vessel narrowing is due to fatty deposits and plaque formation on the walls of the arteries. Approximately 12 - 14% of the population are affected with PAD (M. Al-Qaisi, Nott, D. M., King, D. H., & Kaddoura, S., 2009). Discomfort in the leg after inactivity (claudication) is the primary symptom of PAD, which is used to stage PAD based on its severity. The Ankle Brachial Index (ABI) is a standard and non-invasive diagnostic method to predict the severity of the disease to an extent. In most cases ABI method was proved to be appropriate, however, for some complicated scenarios such as asymptotic PAD, the ABI can give inaccurate measures. Also, this test could predict the risks of cardiovascular events (Arain & Cooper, 2008). Generally PAD is diagnosed and treated at the intermittent claudication stage, when patients experience pain in their calf muscle or thigh to prevent the most common risk factors, that could contribute to developing lower extremity PAD (Kenneth Ouriel, 2001). Intermittent Claudication (IC) relates to functional ischemia measured during exercise and not at rest. At rest, oxygen consumption or saturation in the limb muscles of PAD patients is minimal (Komiya et al., 2002). Later stages of claudication would result in non-healing wounds and to avoid spreading of wound complications, patients are treated through amputation (removal of limbs). Claudication progresses to critical limb ischemia stage in patients if untreated, and is a prime risk factor for many cardiovascular and cerebrovascular events.

Critical limb ischemia (CLI) involves pain/discomfort in the limbs at rest and tissue loss (non-healing ulcers and gangrene) in patients resulting in incomplete recovery from wounds. When the disease progresses to critical limb ischemia, there is a severe reduction in blood flow through the arterial bed, thus preventing the metabolic processes from taking place in the affected extremities (Gresele et al., 2011). When there is no metabolism, the tissue cells may become necrotic, as there is insufficient oxygen transfer to the tissues and this prevents the healing of wounds in the legs leading to ulceration. This slow progressive disorder, if ignored, might be a risk factor for stroke, amputation and death (Lyn M. Steffen et al., 2008).

To avoid major amputation, wound healing is very important in patients with CLI. In worst cases, there is a need to perform minor amputation in patients, to avoid wound complications from spreading and risks toward end organ failure (Kobayashi et al., 2014). The healing of wound(s) is directly dependent on the tissue restoration. During revascularization procedures, the arteries in main arterial beds are bypassed and blood flow is restored. This means the metabolism at the lower extremities will also be restored and the dead tissue cells will be replaced by new ones, thus healing the wound(s). However, vascular surgeons have reported that patients who underwent endovascular surgery often required secondary treatment due to lack of wound healing because of insufficient tissue oxygenation (Bae et al., 2013; Klevsgard et al., 2001). Actual oxygen and nutrient transfer takes place at the level of microvasculature.

Microvascular dysfunction, a syndrome that results from an obstruction in the microvascular bed, refers to the state of tissue hypo-perfusion (Jaffe et al., 2008). In coronary artery disease, the similar no reflow phenomenon is due to myocardial ischemia, which often ends up injuring the coronary microvasculature structurally and the dysfunction is directly associated to the risks of heart attacks and death (Ito, 2014). Similarly, in the limbs, microvascular obstruction may lead to

microvasculature structural damage that would lay a foundation for organ failure and reperfusion injuries (Aoqui et al., 2014). When there is a microvascular dysfunction, the blood flow in the main arteries doesn't reach the tissue level. The knowledge about the effects of microvascular dysfunction in the lower extremity is lacking. Also there is no proper diagnostic method to study the microvascular perfusion level and also the pathophysiology of microvascular dysfunction has not been successfully addressed completely (Michaels et al., 2000).

The objective of this study is to assess arterial function recovery after surgical revascularization and determine if microvascular obstruction may be an important factor responsible for continued declining limb function in PAD patients. Our central hypothesis is to justify that the poor wound healing and end organ failure cases in patients with PAD, even after revascularization, may be due to microvascular dysfunction in limbs similar to the myocardial ischemia that results from abnormal coronary microcirculation. The rationale that underlies this research is that if the existence of microvascular dysfunction in patients can be diagnosed before the surgery, an alternate treatment method can be implicated. This diagnostic approach to PAD could save money and time, and ease the discomfort of patients by avoiding endovascular surgery.

3.3 METHODS

To analyze the effectiveness of the treatment before and after the surgical revascularization intervention procedures in PAD patients who may have microvascular dysfunction, we studied the change in oxygen concentration at the walls of capillaries. Oxygen transfer in a vascular network that is essential for the tissue metabolism takes place at the level of microvasculature and capillaries through convection and diffusion. Oxygen delivery (convective flow of oxygen to the capillaries) and oxygen extraction (diffusive transport of oxygen from hemoglobin (Hb) to

tissue cells are the two limiting factors associated with oxygen transfer in a vascular network (Pittman, 2000).

In order to quantify the transfer rate of oxygen from capillaries to the surrounding tissues, micro-circulation in the vascular network was modeled in a virtual simulation platform using a chemical reaction module. The two mechanisms associated with the oxygen transfer included, oxygen from the blood transferred to the inner wall through convection and blood oxygen from the inner capillary wall to the surrounding tissue via diffusion phenomena, are shown in Figure 3.1.

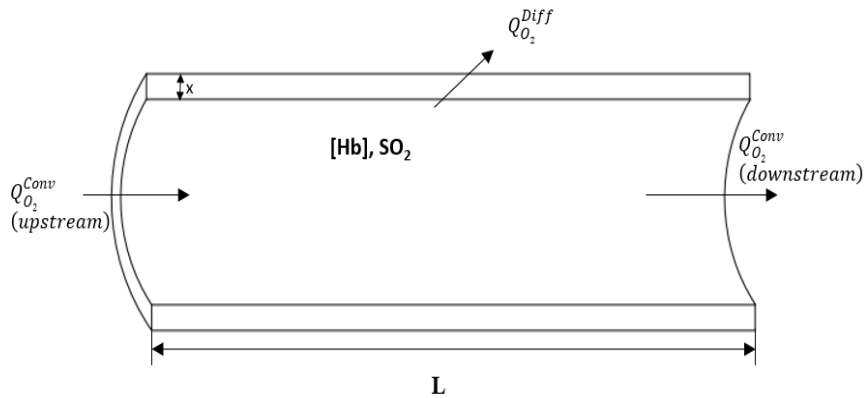


Figure 3.1: Two factors associated with oxygen transfer in the microcirculation. Modified from (Pittman, 2005)

3.3.1 Mathematical model

Microcirculation includes both delivery and extraction that is governed by Fick's Principle (conservation of mass) as shown in Equation 1.

$$Q_{O_2}^{Diff} = Q_{O_2}^{Conv}(upstream) - Q_{O_2}^{Conv}(downstream) \quad \text{Equation 2}$$

The inflow in **Error! Reference source not found.** represents the blood pumped from the heart through arterioles. The incoming flux of blood releases the blood cells with Hb content to the walls of the capillaries through convection as it passes through the length of capillaries. The blood exits the capillaries through venules and recirculates back to the heart. The hemoglobin (Hb) in blood cells contains saturated oxygen which is released through diffusion, from the capillary walls to the surrounding tissue. As the blood is released, the oxygen rich blood cells also collect the depleted blood cells via lymphatic node transfer and reach the heart through venules for purification. The model also includes the reaction involved during the oxygen transfer at the capillaries and the kinetics of Hb-O₂, which is an important factor involved in the oxygen transfer (Goldman, 2008). Fick's law of diffusion states the amount of gas transferred per unit time ($\Delta N/\Delta t$) across a membrane of thickness Δx is proportional to the area (A) available for exchange and the partial pressure difference (ΔP) of the gas across the membrane. It can be incorporated to quantify the amount of oxygen transferred to the surrounding tissues. The diffusion rate is given by the equation 2,

$$\Delta N/\Delta t = kA\Delta P/\Delta x \quad \text{Equation 3}$$

where k is the Krogh's diffusion coefficient (Pittman, 2011).

The saturation of oxygen SO₂ in the blood is generally calculated using Hill's equation. This equation, evaluates the binding characteristics of hemoglobin and oxygen in the blood. The saturation level of O₂ increases from 0 to 100% for each dissociation curve associated with Hill's equation (Turri & Yanagihara, 2011),

$$SO_2 = \frac{\left(\frac{P_{O_2}}{P_{50}}\right)^n}{1 + \left(\frac{P_{O_2}}{P_{50}}\right)^n} \quad \text{Equation 4}$$

Where, n is the Hill's coefficient. It is about 2.7 for human adult hemoglobin and is related to the degree of dissociation of oxygen binding to hemoglobin.

A healthy vascular network as shown in Figure 3.2 was structured and imported to a virtual simulation environment to study blood reperfusion and oxygen transfer in a vascular network. The vascular network is comprised of arteries, capillaries and veins. Blood circulates from the heart through arteries to every end organ and reaches the heart through veins.

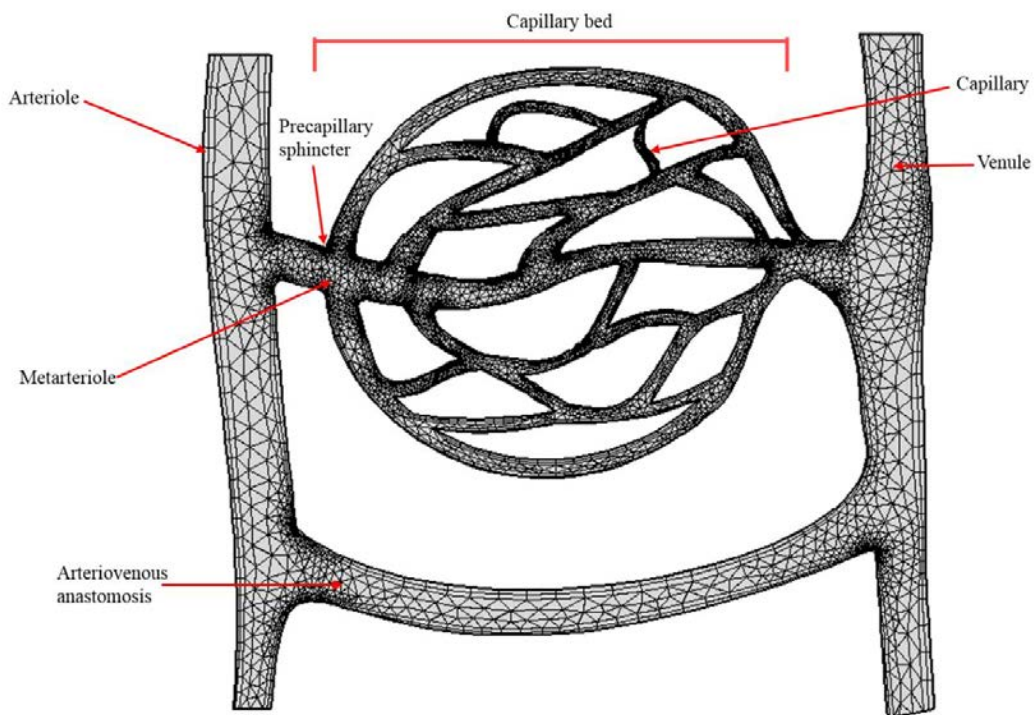


Figure 3.2: A model of vascular network that comprises of arteries, capillaries and veins.

When there is a blockage in the vascular network, the blood flow is interrupted and results in reduced blood flow through arteries that impairs tissue oxygenation in the downstream of the blockage. Revascularization treatment, bypasses the blockage through a graft to restore blood flow in the main arteries. Although the blood flow is restored, patients continue to experience declining limb function even after revascularization and the reason could have been due to microvascular obstructions as in myocardial ischemia. So the effectiveness of surgical treatment was evaluated by inducing small blockages at the level of microvasculature. Oxygen saturation in the capillaries was analyzed to demonstrate the decreased arterial function recovery in PAD patients.

Inlet blood flow was assumed to be pulsatile (Figure 3.3), incompressible, laminar and a Non-Newtonian fluid. This is justified by the Navier-Stokes equations (Conservation of momentum) in the fluid domain,

$$\rho (\mathbf{u}_{fluid} \cdot \nabla) \mathbf{u}_{fluid} = \nabla \cdot [-p\mathbf{I} + \mu (\nabla \mathbf{u}_{fluid} + (\nabla \mathbf{u}_{fluid})^T)] + \mathbf{F} \quad \text{Equation 5}$$

$$\rho \nabla \cdot \mathbf{u}_{fluid} = 0 \quad \text{Equation 6}$$

where \mathbf{u} is the velocity, ρ is the fluid density ($\sim 1050 \text{ kg/m}^3$), μ is the fluid viscosity, t is the time, and p is the pressure. The different terms correspond to the inertial forces ($\rho (\mathbf{u}_{fluid} \cdot \nabla) \mathbf{u}_{fluid}$), pressure forces ($-p\mathbf{I}$), viscous forces ($\mu (\nabla \mathbf{u}_{fluid} + (\nabla \mathbf{u}_{fluid})^T)$), and the external forces applied to the fluid (\mathbf{F}).

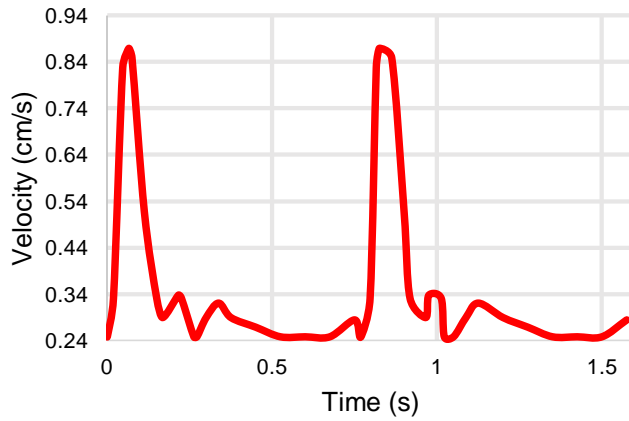


Figure 3.3: The boundary condition in the inlet was a pulsatile velocity profile.

To compute the oxygen saturation at the capillaries, a branch of the vascular network as shown in Figure 3.4 was modelled and imported into the simulation platform.

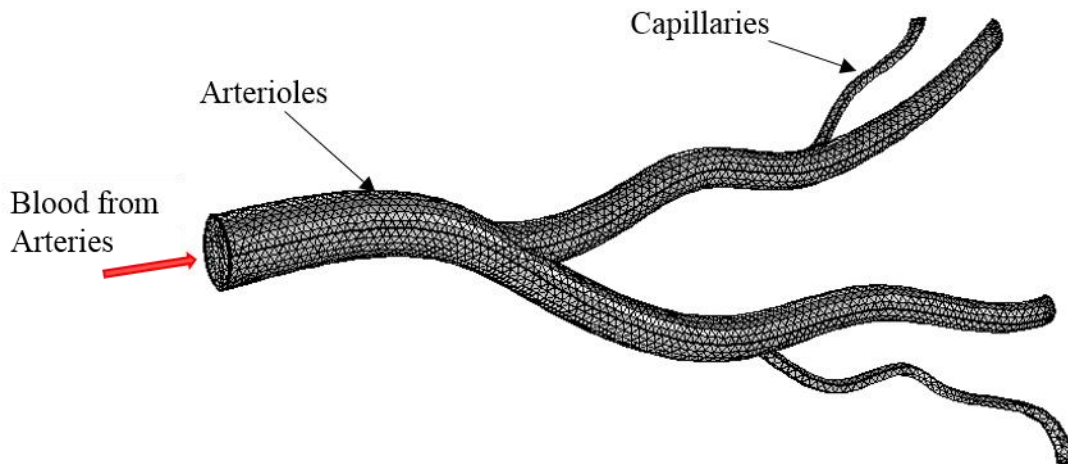


Figure 3.4: A branch of the vascular system to represent the level of microvasculature

It is governed by the convection-diffusion equation as follows:

$$\nabla \cdot (D_i \nabla c_i) + \mathbf{u} \cdot \nabla c_i = R_i \quad \text{Equation 7}$$

where \mathbf{u} is the velocity, c is the oxygen concentration in the blood, R is the reaction rate at the capillary walls, and D is the oxygen diffusivity. The values for oxygen diffusivity were $D = 1.08 * 10^{-9} \text{ m}^2/\text{s}$ and reaction rate were $R = -4.89 * 10^{-2} \text{ 1/s}$ (Sun et al., 2009).

Microvascular deficiency was induced by reducing the flow with a blockage in the vessel as shown in Figure 3.5. Oxygen concentration available at the capillary walls was computed with the above listed equations to prove that the blockage in the microvascular level would decrease the oxygen available to the surrounding tissues resulting in tissue injury and muscle damage.

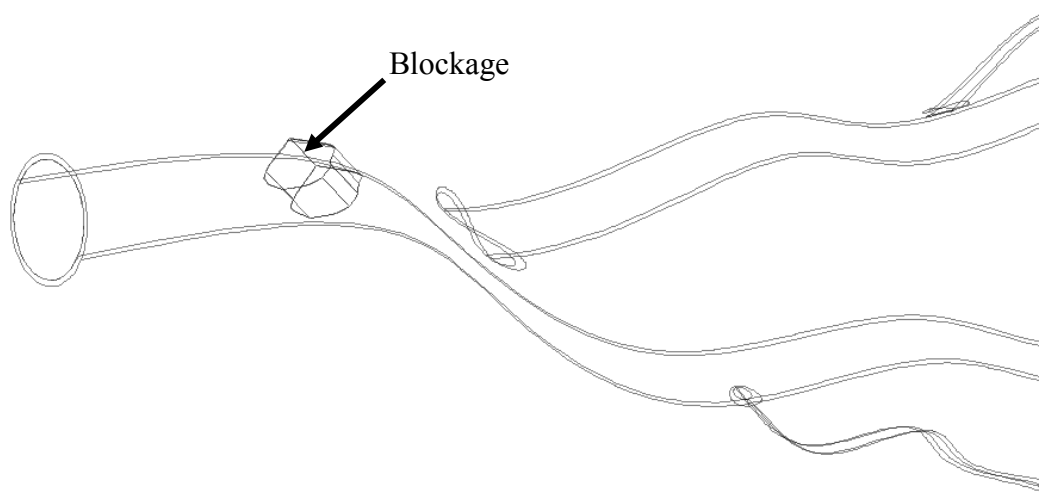


Figure 3.5: Vascular network with blockage modelled at the level of microvasculature.

3.4 RESULTS AND DISCUSSIONS

Using the model, we solved for velocity and oxygen concentration in the vascular network. Figure 3.6, shows the velocity profile ($t=0.8 \text{ sec}$) of the vascular network without any blockages and a normal velocity plot through the arteries is observed with an increased velocity at narrow

regions and almost zero velocity near the walls. The model vascular network also depicts the role of sphincter action (as marked in Figure 3.6) to regulate flow through the capillaries. In this model, the sphincter action is incorporated by inducing a vascular contraction through a narrowed region and forcing the blood to flow through the capillaries. The pre-capillary sphincters are the smooth muscles in the arterioles that would regulate the blood flow by opening and closing the number of capillaries that are required to meet the tissue oxygen demand.

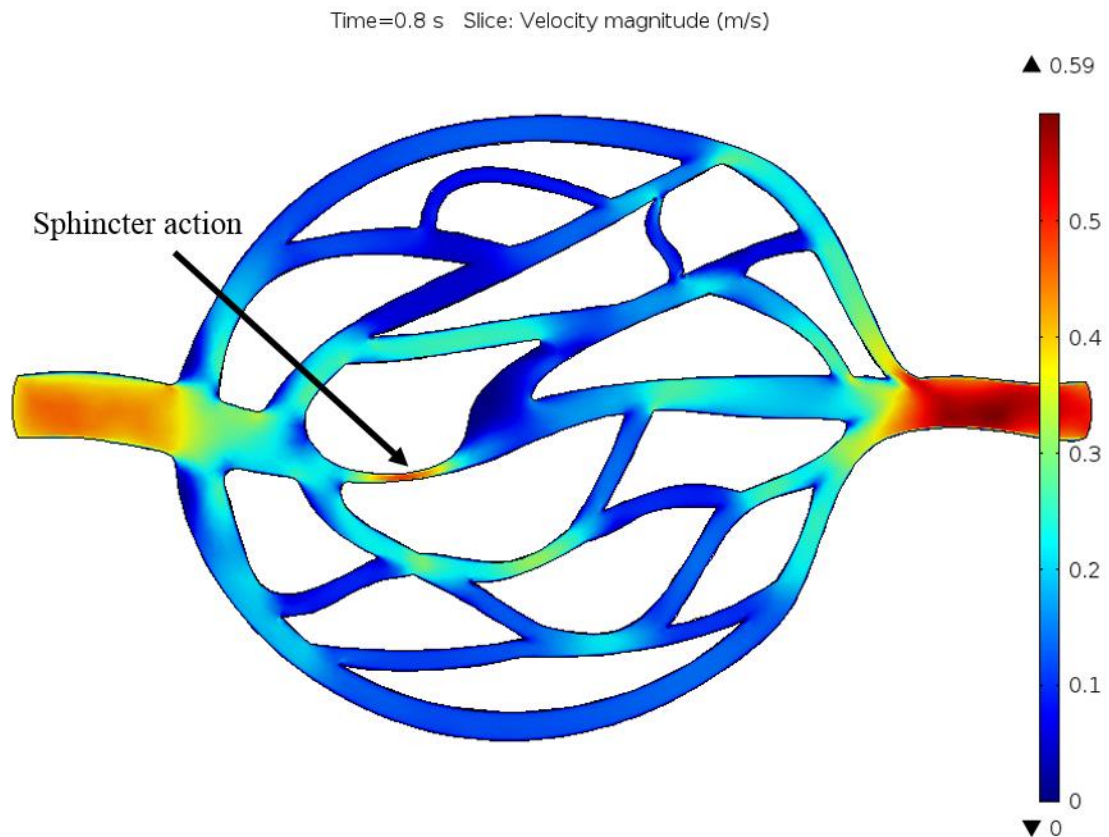


Figure 3.6: Velocity profile of the blood circulation in the vascular network

A branch of this vascular network was considered for our oxygen concentration study. The inlet boundary condition was assumed to be the same pulsatile flow; and the velocity profile was

plotted as in Figure 3.7. The average velocity was used for computing oxygen concentration. A multi-physics study was integrated to solve for oxygen concentration. Two studies in the chemical reaction module were used for our study: the transport of diluted species and species transport in porous media.

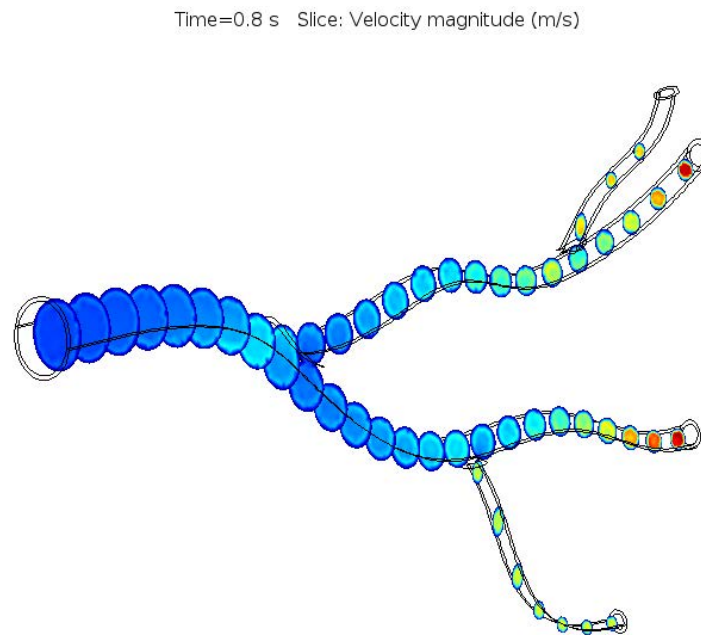


Figure 3.7: Velocity profile in a branch of the vascular network.

Oxygen concentration available at the capillary wall was computed to assess the arterial function recovery. Surgical intervention bypasses the blocked artery in the larger arteries and restore the blood flow but the actual oxygen transfer takes place at the level of microvasculature. The blood flow in the larger arteries may be restored, but a no-reflow phenomenon occurs at the microvascular level due to microvascular insufficiency as shown in Figure 3.8. Due to the blockage at the micro level blood vessels, no blood reperfusion takes place and subsequently there is not enough oxygen for the surrounding tissues through the capillaries. Due to this reason patients will continue to experience declining limb functioning and walking parameters. This

microvascular obstruction is very similar to myocardial ischemia that results in abnormal coronary microcirculation.

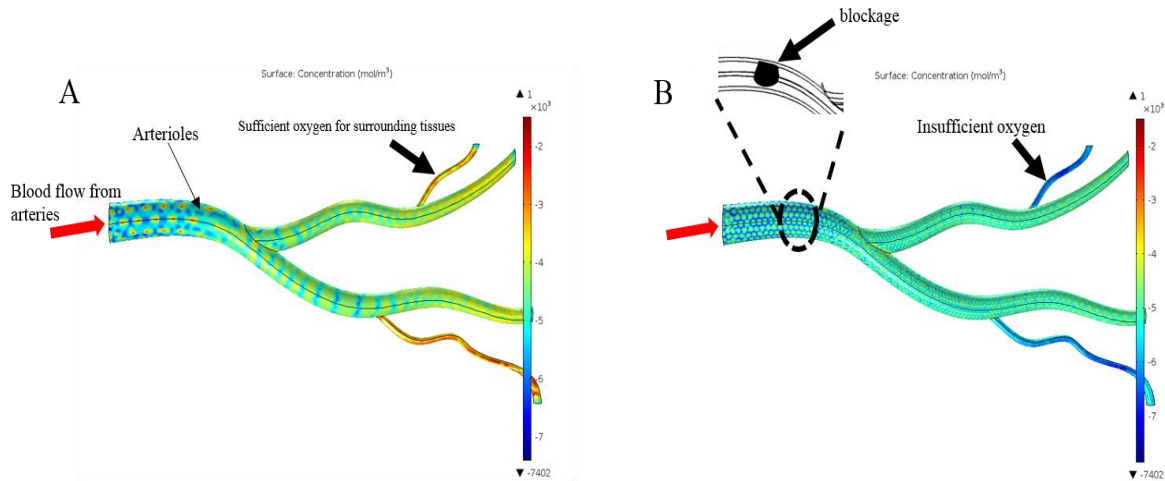


Figure 3.8: A) Concentration color plot in microvascular network without blockage. B) Concentration color plot in microvascular network with blockage

From the results, it was observed that oxygen concentration decreased 71.73% significantly at the capillaries in a vascular network with blockage. From literature, we see that lack of sufficient oxygen to tissue will result in tissue injury and ultimately lead to tissue death. This eventually leads to muscle damage, wound complications and could possibly be a risk towards end organ failure. Our computational results were consistent in proving that when there is a blockage at the microvascular level, the oxygen concentration at the capillaries is reduced significantly.

As a result of our assessment, microcirculation seems to play an important role in PAD and complications. Matsubara and Sano (1972) had studied the effect of smoking on pre-capillary sphincters. Pre-capillary sphincters are smooth muscles in the arterioles that are responsible for the micro-circulation. Sphincter action decides the number of functional capillaries based on the oxygen demand due to tissue metabolism. Smoking is considered as the primary risk factor for PAD; the nicotine in cigarettes is a vasoactive substance that stimulates

vasoconstriction causing reduced blood flow through the arterioles (Matsubara & Sano, 1972). This study correlates with our theory in that it suggests successful treatment strategies would be more accurate to include larger vessels, microvascular vessels and muscle damage.

3.5 CONCLUSION AND FUTURE WORKS

The effectiveness of the revascularization treatment in PAD patients with microvascular dysfunction was assessed by comparing the oxygen concentration at the micro-vascular level. As expected, the oxygen concentration was far less in patients with a microvascular obstruction leading to tissue death and poor wound healing. Despite surgical intervention, 15-25% of PAD patients suffer from continuing wound complications, out of which 5-10% result in leg amputation (Rush et al., 1989). This research could offer novel insight into the factors which may contribute to the successful treatment of PAD. Typical invasive revascularization surgery using artificial bypass grafts to restore blood flow, may fail to be effective if the PAD patient has microvascular dysfunction. This model identifies the need to measure the microvascular circulation in the compromised limbs of PAD patients to optimize diagnosis and treatment strategies that reflect the underlying pathophysiology. Our future objective would be to develop a diagnostic tool that would be powerful and effective at imaging at the level of microvasculature, and to develop alternate successful treatment strategies for PAD, considering all the possible contributors.

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**CHAPTER 4 : SMART SCREENING TECHNOLOGY USING SKIN PATCH SENSOR
TO PREDICT THE SEVERITY OF PERIPHERAL ARTERY DISEASE.**

4.1 ABSTRACT

Peripheral arterial disease (PAD) is characterized by blockages in the arteries that supply blood to lower extremities, resulting in reduced blood flow, causing ischemic injury to the skeletal muscles of the lower limbs. PAD is a progressive disease that requires early detection and management and a continuous monitoring system is suggested. Delayed detection of this progressive disease at the ischemic stage would result in amputation of limbs. Current screening methods require trained personnel, specialized equipment, and are associated with increased cost and time. Also, in some cases the current screening measure is not very accurate, and frequently fails to predict asymptomatic PAD. In this study, we present a new sophisticated technology that would complement the current screening methods and can be used as a point of care screening method for PAD. The smart skin biosensor was attached to a human arm phantom to detect blood flow changes. As a result the biosensor was able to detect blood flow in arm phantom and was also able to record pulse volume changes in the blood flow. The result was then validated using ultrasound technique and found that the biosensor had 94% accuracy with the ultrasound measure. The biosensor screening could be integrated with current screening methods to improve ease of use and make PAD screening cost effective.

Keywords: atherosclerosis, peripheral artery disease, blood flow detection, smart band, health care

4.2 INTRODUCTION

Peripheral artery disease (PAD) is characterized by atherosclerotic blockages of the arteries that supply blood to the lower extremities. It is estimated that people of age over 70 and above are prominently affected by this progressive disease (Peach et al., 2012). Approximately 10 million US population are affected by PAD (Bertoia et al., 2013). Hypertension, smoking, diabetes and obesity are some of the common risk factors toward the developing lower extremity PAD (Jang et al., 2013; K. Ouriel, 2001). The blood flow is reduced due to the fatty deposits and plaque formation on the walls of the arteries. Pain in the muscles of the leg is the earliest and common symptom for PAD (K. Ouriel, 2001). PAD is usually considered as an indicator for an increased risk of cardiovascular events (Ranson, 2012), so early detection of this disease is usually recommended. Claudication is the most used factor to diagnosis PAD based on its severity (Gardner, Montgomery, et al., 2008).

Generally PAD is diagnosed and treated at the intermittent claudication (IC) stage, when patients experience pain in their calf muscle or thigh (Kenneth Ouriel, 2001). The distance walked by PAD patients decreased by as much as 50%, when compared to healthy individuals of the same age (da Cunha-Filho et al., 2007). Intermittent claudication develops to the ischemic level in patients if left untreated, and is a prime risk factor for many cardiovascular and cerebrovascular events. Critical limb ischemia (CLI) involves pain in the limbs at rest (claudication) and tissue loss (non-healing ulcers and gangrene) in patients, resulting in poor wound healing (Komiyama et al., 2002). In CLI stage, there is a severe reduction in blood flow through the arterial bed, which reduces the oxygen and nutrient transfer in the affected extremities (Gresele et al., 2011).

Sequentially, this results in tissue damage resulting in poor healing of wounds in the legs leading to non-healing ulcers. This slow progressive disorder, if ignored, might be a risk factor for stroke, amputation and death (Lyn M. Steffen et al., 2008). Early detection of PAD in patients before the intermittent claudication stage is primarily considered, as it may reduce potential risks involved towards developing lower extremity PAD and CVD (V. A. Moyer & Force, 2013). Ankle brachial pressure index (ABI) is a standard and non-invasive screening method to predict the severity of the disease to an extent.

ABI is a measure of blood flow, done by comparing the systolic blood pressure of the legs with the brachial pressure of the arm (Manfredini et al., 2013). Based on the ratio, the severity of PAD is determined. ABI measures are recorded when patients are at rest and after exercise to predict the outcome. This diagnostic method needs trained personnel to use the Doppler techniques and calculate the measure, to predict the severity of risk towards the developing lower extremity PAD (Allison et al., 2008).

However, in most cases this measure is not accurate or appropriate in some complicated cases when ABI gave inaccurate results (M. Al-Qaisi et al., 2009). The current screening methods for PAD needs improvements to predict the disease with good accuracy and sensitivity. The design of this smart sensor is based on a wireless application that could detect changes in the physical quantity, independent of the source. This sensor concept has great potential that it can be used in various applications in the field of engineering.

Interpretation of ABI can be done by using an ABI index (Ghannam et al., 2012). If ABI is greater than 1.3, it indicates that the patient has incompressible arteries. If this index is between 1-1.29 the patient health condition is normal and has no arterial disease. If the index value lies between 0.4-0.9, the patient is suffering from mild to moderate disease and an index value less

than 0.4 indicates the patient is suffering from severe PAD. This stage is termed as critical limb ischemia and the patients are advised to undergo surgical intervention treatment.

The basic design of the smart skin biosensor, is a resonant spiral of conductive material configured as open circuit without any electrical connections (Wang & Taylor, 2011). The biosensor consists of a resonant spiral of conductive material configured as open circuit without any electrical connections (Wang & Taylor, 2011). These sensors can be tailored and can be used for many biomedical applications. Our objective is to develop a point of care biosensor for PAD screening to make it more sophisticated, so that patients could use it from their homes to predict the severity of the disease. Our central hypothesis is to demonstrate that the smart skin biosensor would detect volumetric changes in blood flow through blood vessels and could report abnormalities, whenever patients want/need to evaluate their health conditions. The rationale behind this study is to upgrade the current method of screening for PAD in a smarter and simpler way such that a patient can use this screening method from his/her home. Ultimately, this technology would be designed as a screening method for PAD that would be more precise and accurate than the current methods and more importantly, save time and money for PAD patients.

The rationale behind this study is to upgrade the current method of screening for PAD to improve the ease of use and make it cost effective. Ultimately, this technology would be designed as a screening method for PAD that would be more precise and accurate than the current methods and more importantly, save time and money for PAD patients.

4.3 METHODS AND MATERIALS

4.3.1 *Sensor design and governing equations*

The sensor is a self-resonating spiral pattern of conductive material that does not need any electrical connections to function (Wang & Taylor, 2011). The basic design of the biosensor consists of a single physical component of conductive material in spiral form. Figure 4.1 illustrates the sensor geometry in a square pattern.

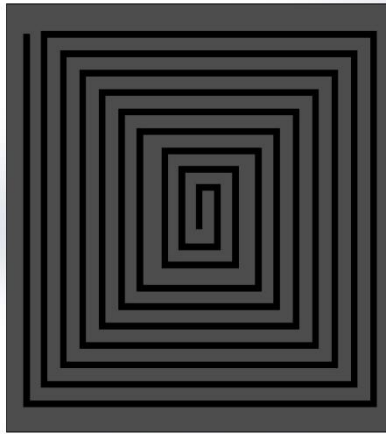


Figure 4.1: Open circuit Biosensor

The sensor can be technically compared to an RLC circuit with inductance L , capacitance C and resistance R Figure 4.2.

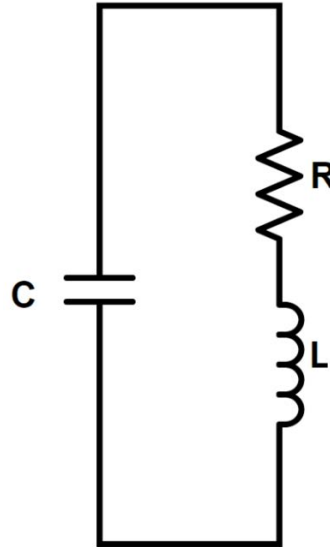


Figure 4.2: Schematic representation of sensor.

The basic principle behind the function of this biosensor is the principle of resonance, where the first principal resonant frequency of the sensor is mathematically given by,

$$f = \frac{1}{2\pi\sqrt{LC}} \quad \text{Equation 8}$$

where, f is the resonant frequency of the sensor. The quality factor of sensor Q , is the amount of stored energy over the energy loss in one cycle. It is expressed as

$$Q = \frac{2\pi fL}{R} \quad \text{Equation 9}$$

Q is the quality factor which has a direct relation with the bandwidth; higher the value of Q narrows the bandwidth and lower Q results in wider bandwidth.

The resonant frequency and properties of the sensor mainly depend on the design geometry. The overall dimensions of the resonant sensor along with trace width, trace spacing and total length establish inductance, capacitance, resistance and corresponding operational characteristics. Thus, based on the geometry and dimensions, the sensor exhibits different

properties. As in Figure 4.3, we could fabricate the sensor in any of the geometric patterns shown. For our study, we preferred to use a rectangular geometric pattern as it has desirable resonance performance and, it could be easily modified to function as a smart skin patch.

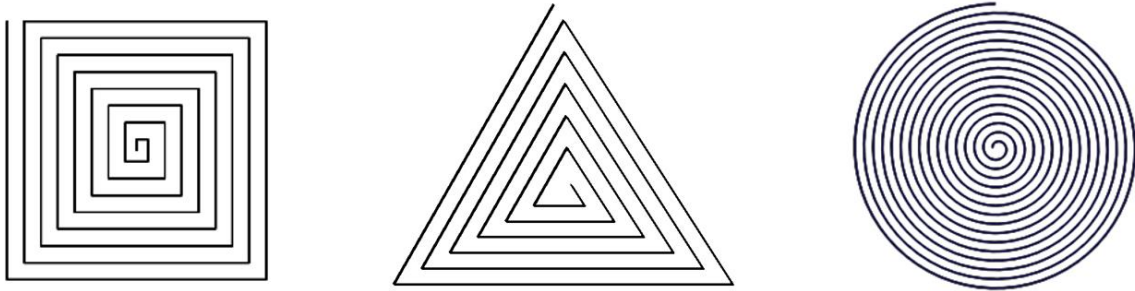


Figure 4.3: Different geometry patterns for sensor

The dimensions of the sensor were chosen based on the sensing depth required. For deeper penetration, a low frequency combination was preferred. For our study, in order to detect volumetric changes in blood flow through the arteries, we preferred to use a low frequency sensor.

The sensor is wirelessly powered using an antenna (external oscillating magnetic fields) and when excited responds with its own magnetic fields whose frequency, amplitude and bandwidth can be correlated with the magnitude of multiple unrelated physical quantities. Based on antenna theory, there would be an external time varying magnetic field developed around the sensor, inducing an electromotive force (emf) in the biosensor sensor. Alteration in physical quantity of the substrate will subsequently change the dielectric properties of the substrate, which will have an impact on the resonant frequency of the sensor. The change in resonant frequency can be correlated with the physical parameter that we measured.

The Smart Skin Biosensor can be used as a point of care screening method for developing lower extremity PAD. Figure 4.4: *Position of smart skin biosensor on the legs to detect blood flow changes*

shows the skin patch having an open-circuit conductive pattern adhered to a human leg. The smart skin patch is composed of an open-circuit conductive pattern with sensitive dielectric material exposed to the sensor's responding electric field, or with a sensitive magnetic permeable material exposed to the sensor's responding magnetic field.

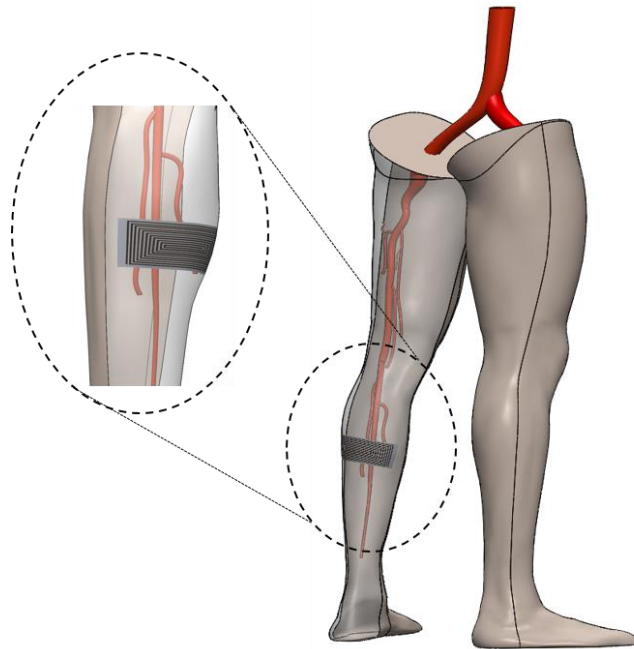


Figure 4.4: Position of smart skin biosensor on the legs to detect blood flow changes

4.3.2 Experimental study

In this study, a human arm phantom (Figure 4.5) with simulated blood flow was chosen. The phantom has artificial skin that has acoustic properties of human skin, while the blood used in the phantom arm mimics human blood, with simulated red blood cells.

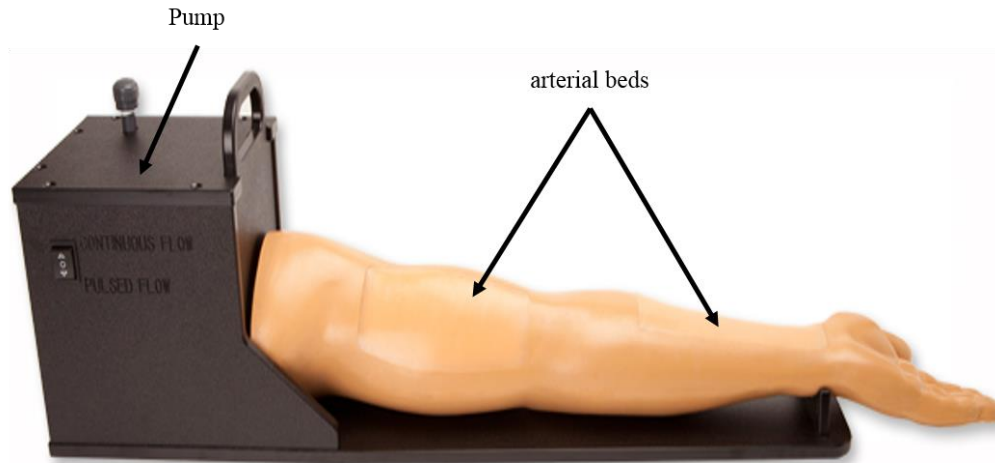


Figure 4.5: Human arm phantom with vascular network consisting of arteries, veins, and synthetic blood.

The sensor itself, when excited with the antenna, had a magnetic and electric field developed around it. Figure 4.6 shows the field around the sensor and its corresponding resonant frequency in the air. The peaks were identified where changes were observed when the sensor was in contact with the substrate (arm). When the sensor was moved in the air, the peak shifting according to changes in the surroundings was observed.

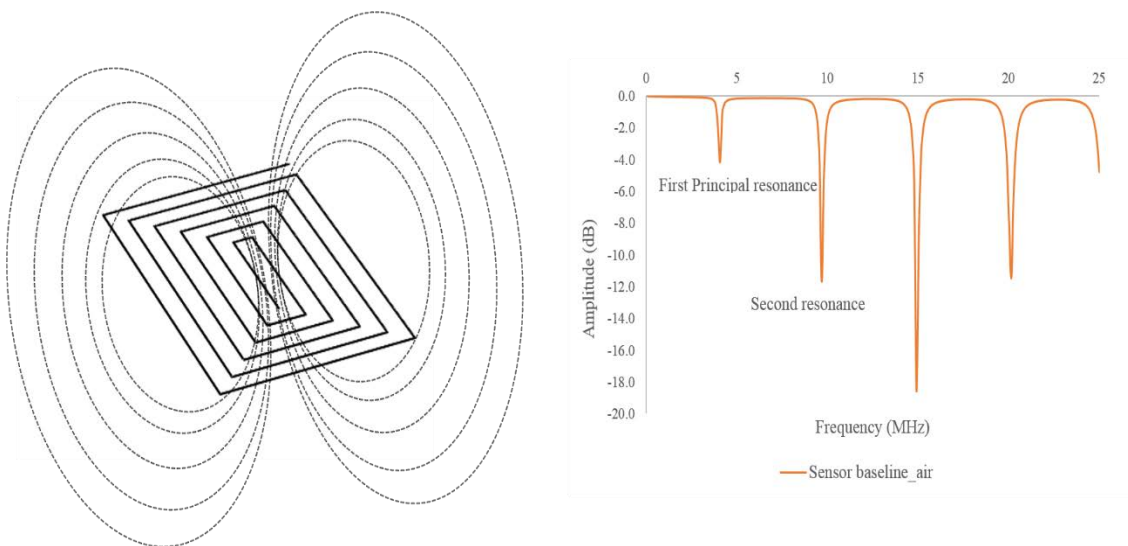


Figure 4.6: Baseline resonant frequency of the biosensor in air.

When the sensor was placed on the arm phantom there was a shift in frequency (Figure 4.7) corresponding to the change in dielectric properties of the substrate. The new shift in frequency was set as the baseline resonance frequency for an arm with no flow, and the peak resonance was identified. The blood was then pumped through the system in a pulsatile manner. This change in volumetric blood through the arteries would alter the dielectric properties of the arm. This change was expected to be detected by skin patch that was attached to the arterial bed on arm phantom, as resonance peaks shift back and forth corresponding to the pulsatile flow.

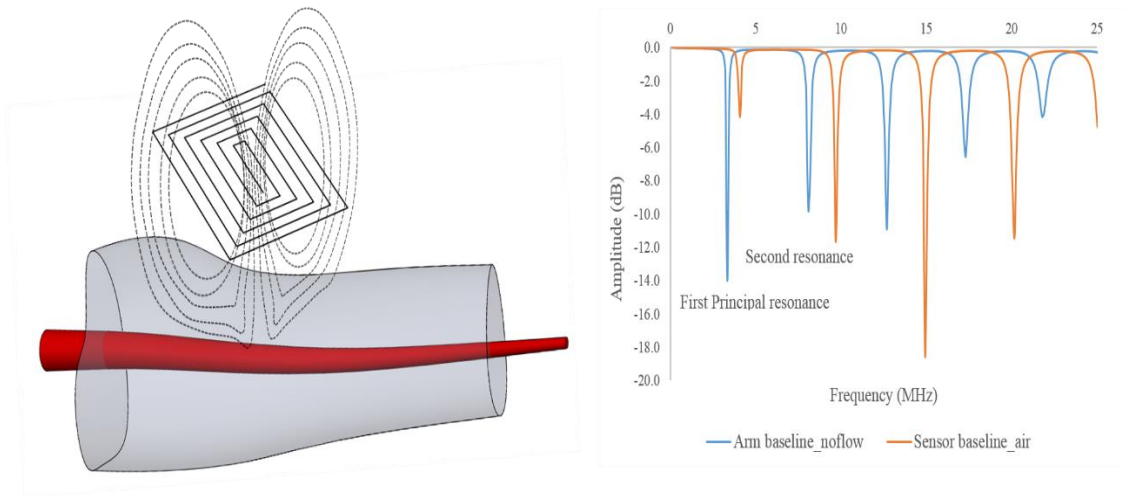


Figure 4.7: Change in the magnetic field when sensor placed on the substrate and corresponding resonance change.

4.4 RESULTS AND DISCUSSIONS

Initially, the expected outcome was tested with water, where the volume of water was changed in a cup. The sensor could sense the volume of cup as we filled it with water as in

Figure 4.8. The peak resonance shifted as the water in the cup increased in volume, which gave an insight that the sensor could sense and respond to volumetric change. Similarly, in the case of a human arm, the volume of blood continuously changes during a cycle. A cycle includes systole and diastole strokes which relate to the contraction and dilation of the arteries, indicating a volumetric change of blood in the arteries. The resonance peak shifted back and forth corresponding to the stroke cycle as expected, which added an evidence to the fact that the biosensor could detect volumetric changes in the substrate and not just respond to the flow.

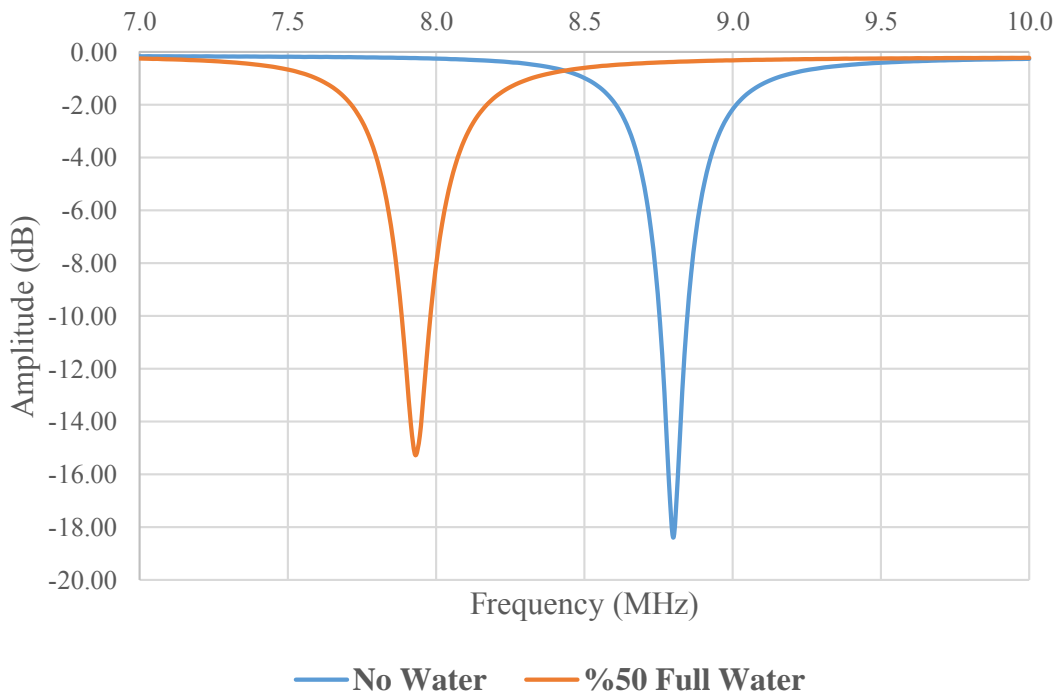


Figure 4.8: Smart sensor response to volumetric change of water in a cup.

As the biosensor was able to detect changes in the volumetric flow, we extended our study to perform pulse volume recording and compare it with the real time peaks. For this we used the same human arm phantom with the inflow as pulsatile blood flow. We calibrated the biosensor to trace a single identified peak with respect to time. This means that the sensor was

able to detect the shift for a certain time period. With this data collection, the pulse volume was chartered for the selected frequency.

For the blood flow measurement, two resonance peaks were chosen from the baseline resonance of arm with no flow: 1. First principal resonance and 2. Second resonance. The smart skin biosensor picked up changes in the volumetric blood flow and recorded as resonance shifts. In this case, the sensor patch picked up the pulsatile flow signal and recorded the change in the volume of blood through the arteries as corresponding resonance shifts. A single resonance shift at one moment of time from the selected resonance peaks was recorded.

From the first principle resonance curve, the sensor detected the blood flow and reported it as a change in amplitude (dB) as in Figure 4.9. The systole and diastole peaks were identified from these recorded plots as the volume of blood changed during its flow through arteries. The smart skin patch sensor can be used to continuously monitor these peaks for a specific instance of time, and it would report any disruption in the volumetric blood flow.

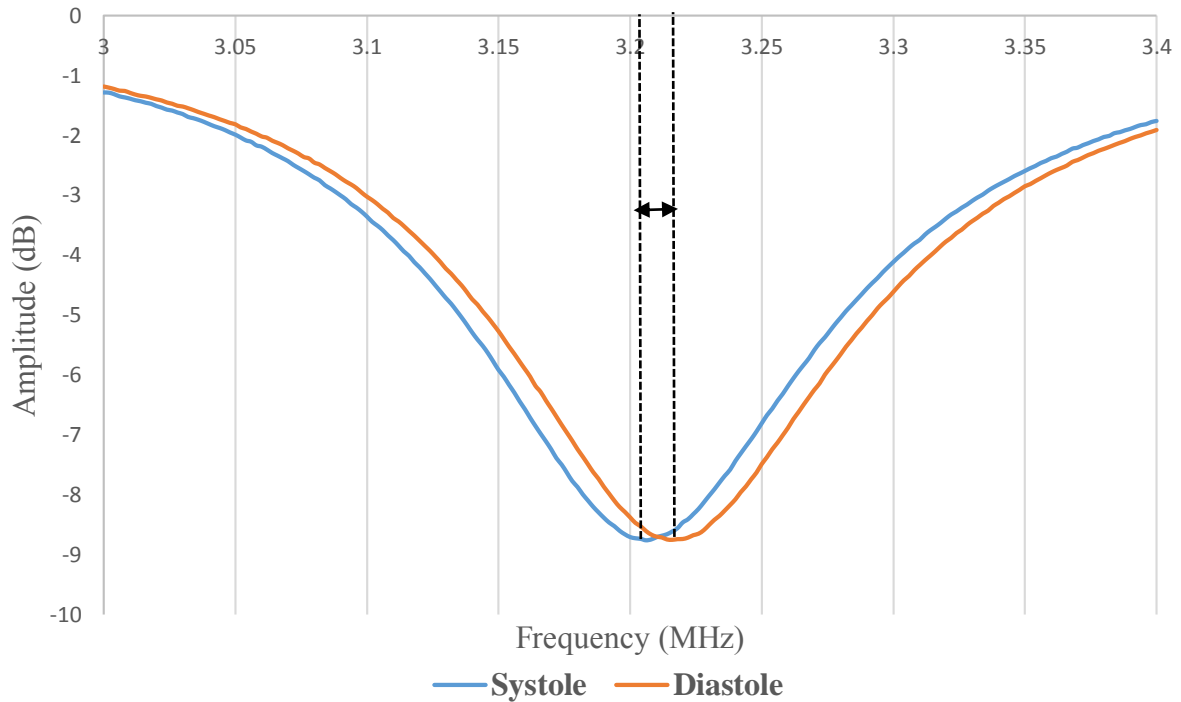


Figure 4.9: Skin patch sensor’s resonance response to pulsatile arterial blood flow (one moment of time)

Using the frequency shift as in Figure 4.9, the timing from systole to diastole was noted and was reported to be 1.26 sec/cycle. From here we were able to calculate the heart rate as $60/1.26 = 47$ Bpm, which would be the pumping rate measurement of the arm phantom using a smart skin patch.

The sensor data was later verified and validated using ultrasound measurement on the arm phantom. The pulse wave form plotted using ultrasound (Figure 4.10) correlated with the resonance shifts from the skin patch sensor. To validate the heart rate of the arm phantom, the time for one cycle (systole to diastole) was measured as 1200ms, which calculated the heart rate to be 50Bpm with peak velocity of 77.72 cm /sec using ultrasound. In spite of this, the measure from the smart skin patch sensor report was suggested to be more accurate than that of the

ultrasound. As the sensor could detect volumetric change in blood flow, the biosensor can be used as a pulse volume recorder and as a screening method for PAD.



Figure 4.10: Ultrasound image of pulsatile arterial blood flow on arm phantom

The sensor was calibrated to obtain pulse volume changes of blood through the arteries. A single peak was identified and selected as in Figure 4.11. The peak was traced for a certain time interval and the corresponding impedance values were recorded. Then, the frequency point was selected based on the point at the peak.

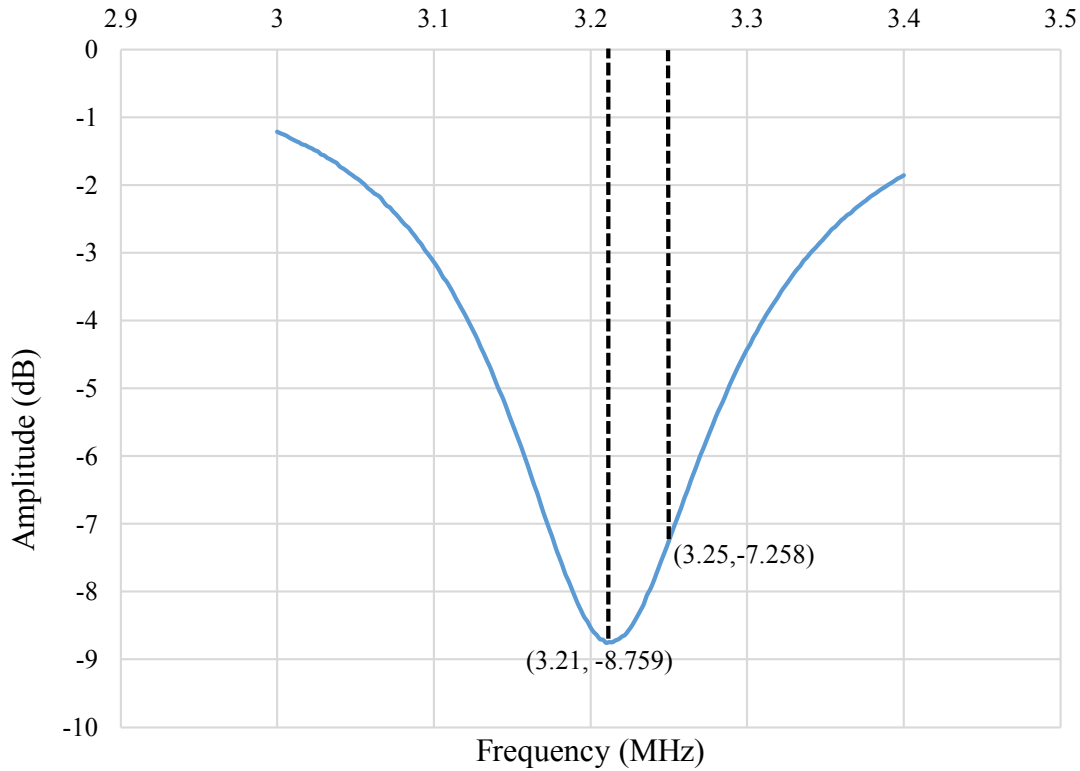


Figure 4.11: A single peak selected for recording pulse volume changes in blood flow through arteries.

The selected two points were charted against time as in Figure 4.12 to record the pulse volume change of blood flow in arm phantom. The pattern of the plots was different for the selected frequency points; the frequency point that was away from the maximum dip was very similar to pulse volume recordings with distinct peaks. The presence of the dicrotic notch with the peak amplitude suggested that there is no abnormality in the arterial blood flow in human arm phantom.

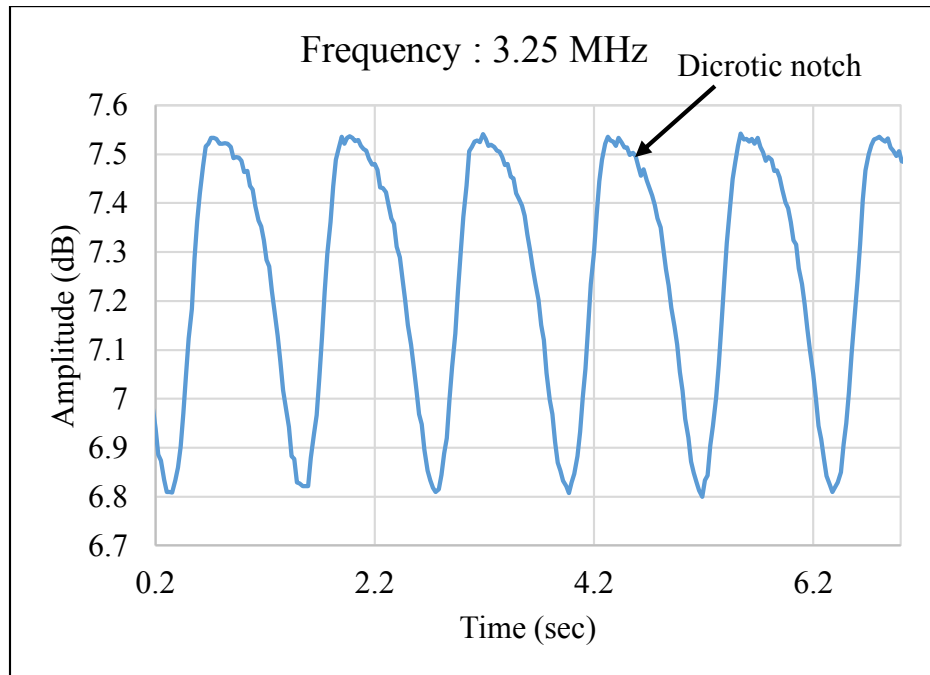
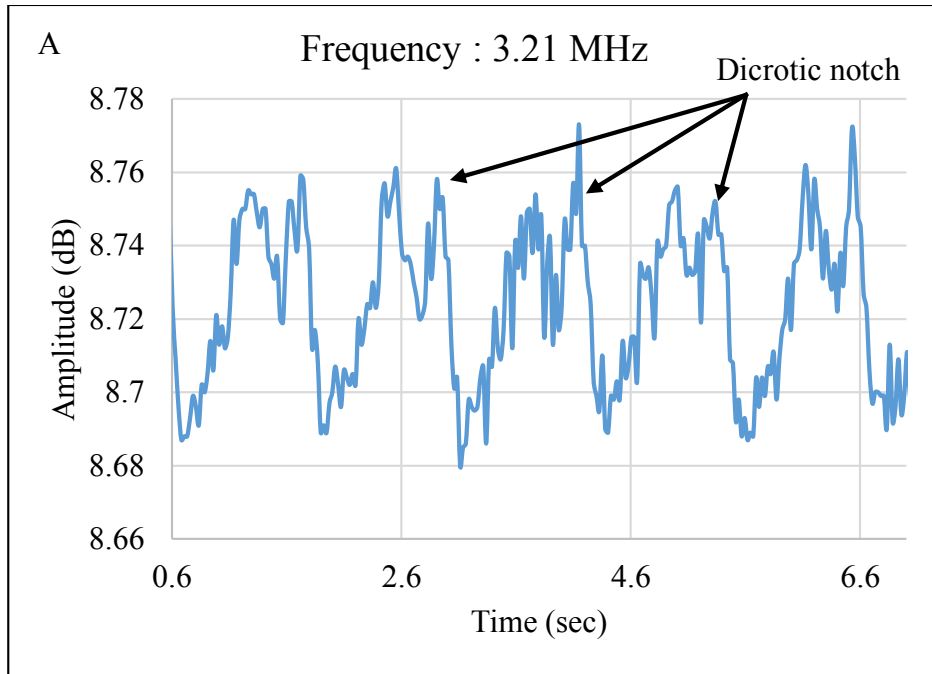


Figure 4.12: A) Plot of pulse volume at the maximum dip frequency point; B) Plot of pulse volume at the frequency point right to the maximum dip.

The plot at the maximum dip frequency was then processed to remove any additional noise and smoothing of the curve was performed. As in Figure 4.13 a very similar PVR waveform with the presence of prominent notch was seen. The time between two strokes was measured to be 1.2 sec. The biosensor measure had 94% accuracy with the ultrasound measure validating our experiment results.

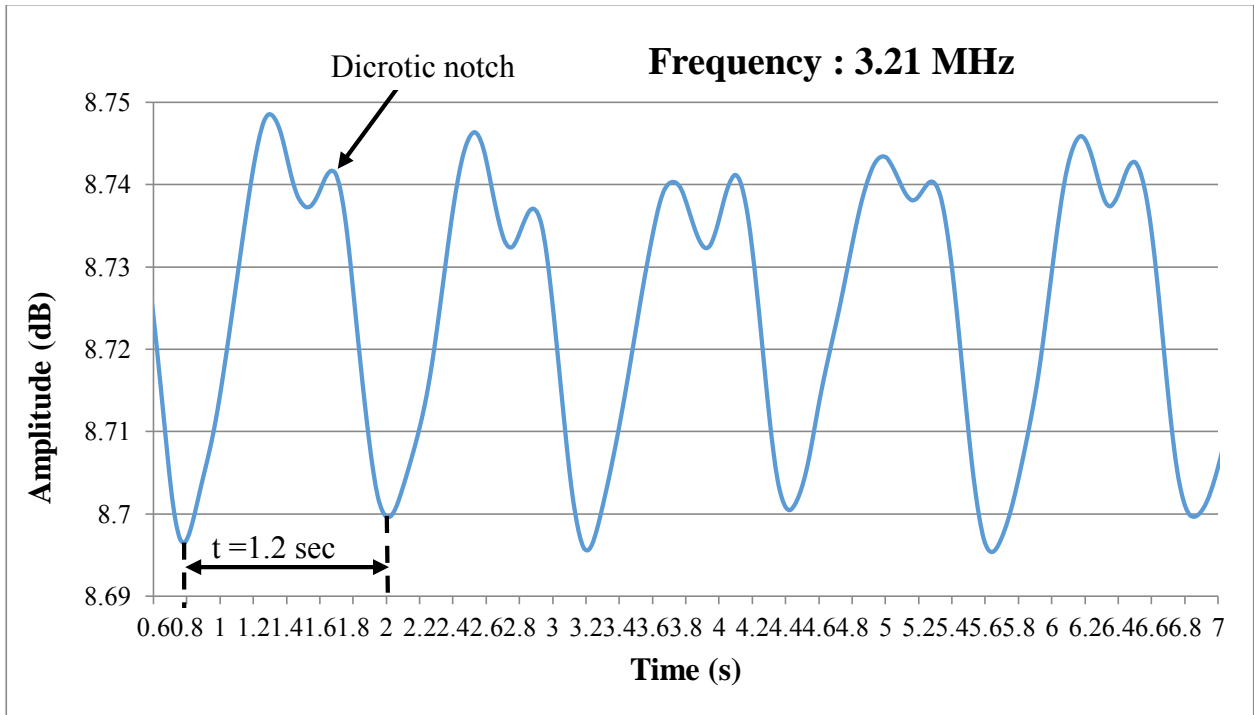


Figure 4.13: Plot of pulse volume at the maximum dip frequency point

In PAD patients, the arteries are narrowed and reduced blood flow through them due to atherosclerosis blockage. When the smart skin patch senses this disrupted blood flow and change in volume of blood through the arteries, there would always be a corresponding change in resonance that deviates from the healthy baseline resonance. Patients could maintain a record of the variations from the past and perform this screening method from their home without much effort. Current screening methods such as ABI and PVR, could integrate the smart skin patch technology to predict the severity of PAD.

4.5 CONCLUSION AND FUTURE WORKS

The smart skin patch lays a new platform of developing technology in health care applications. It is unique in that it is very light (like a bandage) and it does not require any electrical connection. The sensor uses the concept of resonance and the smart skin patch would respond to the corresponding change in dielectric or permeability properties of the substrate. PAD screening can be made sophisticated with this upgraded sensing technology. Patients can carry this patch in their pockets, and can even use the technology when they feel the basic symptoms of this disease like pain in their calf muscle. This PAD screening method can be labelled as a failure free method as the smart skin patch is constructed without any electrical connections.

Future work with this smart skin patch sensor would be to integrate mobile technology to communicate wirelessly with the sensor. The smart phone can replace the antenna to send and receive signals from the sensor and the smart phone can show the condition of the disease. Also the biosensor patch can include an array of other sensors that could sense and report EMG signals from arms and legs.

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