

**Intraoperative Physiologic Monitoring During Endovascular Revascularization  
for Atherosclerotic Peripheral Arterial Disease**

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requirements for the MSc degree in Epidemiology

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## **Preface**

Mark Rockley (MR) is the student. MR was involved in all stages of protocol inception, study conduct and data collection, and preparation of all manuscripts. Dr. George Wells (GW) is the thesis supervisor. GW is the director of the Cardiovascular Research Methods Center at the University of Ottawa Heart Institute, professor in the School of Epidemiology and Public Health at the University of Ottawa, and senior scientist affiliate in the Ottawa Hospital Research Institute. GW was involved in overseeing all protocol inceptions, study conduct, and preparation of thesis. Dr. Prasad Jetty (PJ) is a Thesis Advisory Committee (TAC) member. PJ is a vascular surgeon at The Ottawa Hospital, director of research of the Ottawa Division of Vascular Surgery, and clinical investigator in the Ottawa Health Research Institute. PJ served as an expert content advisor to the conception and conduct of individual studies and overall thesis preparation. The specific roles of each author are listed within each component article.

Ethics approval was required for two component studies of this thesis. The Ottawa Health Science Network Research Ethics Board (OHSN-REB) approval for the retrospective study presented in Chapter 4 is included in Appendix A (Approval Number 20180682-01H), and the OHSN-REB approval for the prospective study presented in Chapter 5 is included in Appendix B (Approval Number 20180656-01H).

## **Abstract**

Peripheral vascular disease (PVD) is defined by insufficient blood flow to limbs and can result in pain, gangrene, and amputation. Minimally invasive angioplasty treatments for PVD are common but suffer from high failure rates. We conducted three studies: 1) a systematic review to describe methods of intraoperative blood flow assessment; 2) a retrospective cohort study to describe the correlation between outpatient blood flow assessment and clinical outcomes; and 3) a prospective observational study to describe the reliability and association between intraoperative blood flow assessment and clinical outcomes. While limb blood flow is routinely assessed before and after interventions, intraoperative assessment has not been well described. Postoperative blood flow assessments are strongly correlated with clinical outcomes. Intraoperative blood flow assessment is feasible and strongly correlated with clinical outcomes. Intraoperative blood flow assessment may be a useful tool to guide intraoperative decision making.

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# Chapter 1: Introduction

## 1.1 Rationale

Peripheral vascular disease (PVD) is a condition caused by arterial blockages causing inadequate blood flow, resulting in pain and gangrene of the legs. The prevalence of PVD in the North American general population over 50 years of age is estimated at 17.4%, and is rising in association with the increasing prevalence of diabetes(1). While bypass surgery is reserved for patients with severe forms of PVD, the minimally invasive options of angioplasty is the treatment of choice for most patients with PVD. The annual rate of endovascular peripheral vascular interventions in the USA Medicare population has risen to 419.6 per 100,000 Medicare beneficiaries(2). Angioplasty is the foundational treatment of endovascular therapy, which may be augmented by treatments such as stenting or atherectomy. Unfortunately, the two-year patency of balloon angioplasty for PVD has been poor, reported between 50 – 80%, depending on lesion location and characteristics(3). Subsequently, the 1-year amputation rate despite endovascular revascularization has been reported as high as 32% in patients with lower leg critical limb ischemia(4). This high failure rate has prompted investigation into the predictors of failure, and potential solutions to optimize the success rate of revascularization.

The goal of peripheral vascular revascularization, whether via open bypass or endovascular angioplasty, is to improve the delivery of arterial blood to the affected leg. Because flow rate is inversely related to resistance, improvement of peripheral blood flow is achieved by decreasing peripheral vascular resistance. This relationship was described in the 18<sup>th</sup> century by Poiseuille's Equation:

$$Q = \frac{\pi P r^4}{8 n l}$$

Where:

Q = Flow Rate

P = Systemic Pressure

r = Vessel Radius

n = Fluid Viscosity

l = Length of Vessel

The severity of peripheral vascular resistance is measured by the blood pressure of the limb, distal to the site of arterial blockage. Accordingly, a hallmark of lower extremity peripheral arterial disease is reduced blood pressure in the affected leg. This measurement is performed by applying a blood pressure cuff at the level of either the lower leg or the great toe. When compared with the blood pressure in the arms (brachial pressure), the Ankle-Brachial Index (ABI) or Toe-Brachial Index (TBI) can be calculated, depending on whether the blood pressure cuff was applied to the lower leg or great toe, respectively. Traditionally, the maximal systolic pressure is used as the measured pressure.

ABI and TBI measurement is standard procedure to diagnose peripheral arterial disease, and improvement of ABI or TBI after open vascular bypass surgery has been established as a strong predictor of limb salvage after vascular bypass(5). Conversely, a minimal ABI improvement of <0.1 has also been associated with significantly worse functional status and quality of life following bypass(6). Because ABI relies on blood pressure measured in the mid-leg, the blood pressure cuff placement may not encompass more distal arterial blockages in the lower leg and the ankle. Unfortunately, distal arterial blockages are a common disease pattern in patients with diabetes, and is more commonly managed with endovascular procedures. As a result, toe pressure measurement has been proposed as an alternative method of blood pressure measurement in the limb, and represents a key component of the Society for Vascular Surgery 'WIFI' peripheral vascular revascularization guidelines(7).

Although toe pressure logically correlates with ankle pressure, and the benefits of ankle pressure improvement after bypass logically correlates with the benefits of toe pressure improvement after endovascular procedures, there is limited evidence to support these theories. In a 2017 analysis subgroup analysis of subjects in the IN.PACT DEEP trial, an improvement of toe pressure  $>1\text{mmHg}$ , or TBI of  $>0.025$ , was significantly associated with reduced hazard of major adverse limb events within 1 year (HR=0.15 and HR=0.24 respectively)(8). Major adverse limb events ('MALE') is defined as a composite outcome of mortality, clinically-driven target limb reintervention, and major or minor amputation.

Currently, the primary intraoperative feedback used to determine procedural success is the anatomic appearance of the angiogram upon completion of the procedure. While an angiogram may depict the improvement of focal arterial narrowing, which is represented in the Poiseuille's Equation as vessel radius, the angiogram does not provide a physiologic feedback to the operator. Small vessel disease or tandem lesions may instead be the primary culprit of the peripheral vascular disease, and may not be represented adequately by the angiogram. Consequently, a hemodynamically significant lesion may not be anatomically significant, resulting in a falsely reassuring angiogram. Because limb pressure measurements encompass these variables that are not represented by angiogram, limb pressure measurement could be more predictive of procedural success than angiogram. The current practice of waiting until the postoperative period to assess physiologic limb perfusion may miss opportunities to guide intraoperative decision making.

The intraoperative divergence of anatomic and physiologic results during endovascular therapy has been emphasized in the cardiac literature by the FAME 1 trial, which investigated intraluminal pressure gradients across stenoses versus angiogram alone in coronary endovascular treatment(9). The added benefit of intraoperative physiologic assessment during cardiac angioplasty and stenting in reducing major adverse cardiac events was supported by a meta-analysis(10). The FAME 2 Trial demonstrated that physiologic-guided intervention is

superior to medical therapy in reducing major adverse cardiac events in stable coronary artery disease, where angiogram-guided interventions were traditionally inferior to medical therapy when based on anatomy alone(11).

Physiologic feedback during peripheral vascular intervention is less established. There are several reasons why intraoperative feedback in the peripheral vascular surgery could be of even greater utility. The length of potentially diseased arteries in the lower extremity is substantially greater than in coronary arteries, and the hemodynamic importance of each vascular lesion along this length if multiple lesions exist is not evident anatomically. While tandem lesions may exist in coronary arteries, there is significantly less length of vasculature to develop tandem lesions. It is also possible to visualize perfusion of peripheral vascular tissue in a still state over several seconds, while observation over the same timeframe would require cardiac arrest in coronary arteries. Another important distinction with coronary endovascular therapy is that the tissue being reperfused by a peripheral intervention, such as skin, is readily accessible to the operator during the procedure. Therefore, more direct measures of tissue perfusion are feasible.

Real-time intraoperative physiologic feedback would be highly relevant to care providers who perform endovascular revascularization procedures. This knowledge may help determine the appropriate course of management following attempted endovascular revascularization, such as early conversion to bypass surgery. Furthermore, if intraoperative feedback of limb blood pressure is predictive of outcomes, the results of this thesis could guide further investigation into using instant blood pressure to guide intraoperative decision making and ultimately improve the success of endovascular revascularization.

## 1.2 Objectives

The overarching purpose of this thesis is to investigate intraoperative measurement of limb perfusion during endovascular revascularization. In context of the existing evidence, there are three successive research objectives that will be addressed by this thesis:

***Objective 1: Review Currently Reported Intraoperative Physiologic Measures***

In patients undergoing endovascular revascularization for atherosclerotic peripheral vascular disease, what intraoperative physiologic measurements have been associated with postoperative clinical outcomes?

***Objective 2: Association between Hemodynamic Response and Reintervention***

In patients undergoing endovascular revascularization for atherosclerotic peripheral vascular disease, is change in toe blood pressure measured at least one day after surgery associated with need for reintervention?

***Objective 3: Association between Intraoperative Hemodynamic Measurement and Postoperative Outcomes***

In patients undergoing endovascular revascularization for atherosclerotic peripheral vascular disease, is the change in intraoperative measurement of toe blood pressure associated with postoperative clinical outcomes including amputation and reintervention?

## 1.3 Chapter Descriptions

The objectives of this thesis will be addressed in the following chapters.

- Chapter 2 provides a summary of evidence supporting methods used to assess limb perfusion, with a focus on potential intraoperative application.
- Chapter 3 addresses Objective 1 and includes two articles: a protocol and a completed systematic review. These articles summarize the existing evidence describing the

relationship between intraoperative physiologic limb perfusion assessments and postoperative clinical outcomes.

- Chapter 4 addresses Objective 2 and contains a retrospective review manuscript. This article evaluates the association between perioperative anatomic or physiologic feedback mechanisms and subsequent postoperative clinical outcomes. Anatomic feedback is the current standard of care in the form of intraoperative angiogram, and physiologic feedback is represented by postoperative limb pressure measurements.
- Chapter 5 addresses Objective 3 and contains two articles: a protocol and a completed prospective study. The prospective study introduced limb pressure assessments during the time of surgery, and observed the association between intraoperative changes in limb hemodynamics and postoperative clinical outcomes.
- Chapter 6 is a discussion chapter which summarizes and unifies the thesis components, and provides insights into future research.

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## Chapter 2: Background

### 2.1: Non-Invasive Arterial Pressure Measurement

#### *2.1.1 Ankle Pressure*

Several studies described an increase in ankle-brachial index (ABI) within 1 day after endovascular procedures(1), and sustained over a month(2, 3). No studies have reported intraoperative monitoring of ABI. O'Mara et al described the first use of hemodynamic monitoring following endovascular therapy in 1981, and found that treatment of iliac lesions resulted in greater prevalence of hemodynamic improvement when compared with femoropopliteal lesions (73.8% vs 44.4% respectively)(4).

An increase in ABI of at least 0.15 after surgery has been associated with freedom from amputation (14.4% vs 6.0%,  $p < 0.01$ )(5). Alback et al noted that subjects undergoing femoropopliteal angioplasty with more severe tibial disease based on the Tibial Run-Off Score were less likely to experience hemodynamic improvement(6). Jacomella et al found that peripheral revascularization was associated with not only an increase in ABI, but also an improvement in the aortic augmentation index, which is an indicator of peripheral arterial stiffness(7). Postoperative ABI has often been used as a comparator for other methods of perfusion assessment, which will be described in the following sections.

A limitation of ankle pressure measurement is the incompressibility of calcified tibial vessels. ABI was not recordable in up to 57% of patients in one study of critical limb ischemia(8).

#### *2.1.2 Toe Pressure*

Similar to ankle pressures, changes in postoperative toe pressures have been detected 1 day after surgery, which were sustained for one month following treatment(9). Hammad et al

assessed ankle and toe pressure measurements for subjects before and after below-knee angioplasty(10). This study identified a perioperative threshold of toe pressure increase that is associated with freedom from major adverse limb events (Toe Pressure Threshold=1mmHg, HR=0.15 respectively). Similarly strong associations between increase in TBI and freedom from major adverse limb events were found by Young et al (TBI Threshold=0.04, HR=0.32)(11), and Reed et al (TBI Threshold=0.21, HR=0.27)(12). After infrageniculate procedures, the great toe pressure can change substantially, reported by Ruzsa as improving from 27mmHg to 79 mmHg on average, and correlates with intraoperative intraarterial pressure measurement ( $r=0.37$ )(13). Mustapha et al found conflicting results; they did not find an association between perioperative ABI or TBI change and clinical improvement(14). However, they investigated infrageniculate procedures with a modest mean postoperative TBI change (from 0.42 to 0.49) with a very low reported amputation rate of 5%, suggesting that their population was at low risk of developing symptoms regardless of endovascular results.

The studies by Hammad et al and Reed et al also compared the association with major adverse limb events between ABI and TBI, and both found the associations with TBI to be stronger than ABI. Intraoperative toe pressure measurement has not been evaluated.

## 2.2: Invasive Arterial Pressure Measurement

Four articles reported on intra-arterial pressure measurement during peripheral endovascular therapy. One study used a pull-back catheter method to evaluate the pressure drop across a lesion(15), and three studies recorded trans-lesional pressure gradients using a pressure-sensing wire to calculate the Fractional Flow Reserve (FFR) (13, 16, 17). The Fractional Flow Reserve is then used as an estimation of the hemodynamic significance of a lesion. To calculate FFR, a zero resistance peripheral bed is assumed. Therefore, peripheral hyperemia is often induced prior to measurement by intraarterial injection of vasodilators. Kobayashi et al noted that accurate measurement of FFR requires maximal peripheral vasodilation, which is achieved

after intra-arterial injection of 30mg of Papaverine(17). Cho et al compared subjects who received angioplasty with those who received stenting, and found that stenting had was significantly associated with greater decrease in FFR(16).

Using the catheter pull-back method, De Smet et al found that the mean and systolic pressure gradients across iliac lesions significantly improved after therapy(15). Ruzsa et al compared intraoperative FFR with postoperative laser Doppler, tcpO<sub>2</sub>, and toe pressures, and found significant correlations with laser Doppler and toe pressure, but only weakly with tcpO<sub>2</sub>(13). This study also evaluated wedge pressure by performing proximal balloon occlusion, and demonstrated that limbs with multivessel disease have a significantly lower wedge pressure than limbs with more robust collateral circulation.

It is important to distinguish a more global measure of limb perfusion such as wedge pressure, with a location-specific measure of lesion hemodynamic significance such as FFR. Regardless, the association between intraluminal measurement of arterial pressure and postoperative clinical outcomes has not been reported.

## 2.3: Skin Perfusion Measurement

### *2.3.1 Laser Doppler*

Laser Doppler is a method that leverages the Doppler effect on reflected laser wavelengths to estimate blood flow in tissue. The Doppler effect is often used in ultrasound applications, however a distinguishing characteristic of laser Doppler is its relatively shallow tissue penetration of less than 5mm. Martini et al demonstrated a correlation between static-state laser Doppler measurements and ABI before and one month after in-line revascularization, defined as restoring blood flow through the native circulation pathway(18). However, their laser Doppler measurements did not change after indirect revascularization, while ABI detected

improved distal pressure. Indirect revascularization is defined as relying on collateral circulation to bypass an occluded artery which was not treated.

Hoffmann et al described a distinction between high frequency (22.6 cycles/minute) and low frequency waves (2.2 cycles/minute)(19). They found that high frequency laser doppler waves decreased in 6 of 11 anatomically successful cases, but remained unchanged in 7 unsuccessful cases. The importance of evaluating specific spectral waves with laser Doppler was corroborated by Ticcinelli et al, who found increased amplitude of frequencies between 3.02-3.22 cycles/minute, while frequencies between 1.13-1.75 cycles/minute decreased in amplitude after revascularization(20).

Rona et al identified the utility of laser Doppler in measuring the capacity of tissue to produce further hyperemia by comparing measurements at ambient temperature and after heat challenge(21). After revascularization, they found the change in laser Doppler flow in response to heat was significantly greater than baseline, suggesting that the after revascularization, the tissue was adequately perfused and not requiring constant hyperemia. This change in the reactivity to hyperemia was associated with wound healing; subjects with wound healing demonstrated significantly greater heat-induced laser Doppler flow change after intervention, when compared with subjects whose wounds did not heal. They also found that the changes in flow continued to improve between the immediate post-procedure measurement and the follow-up measurements 3 and 12 months postoperatively. Ruzsa et al also found that the hyperemia-stress capacity measured by laser Doppler before and after surgery correlates with intraoperative cross-lesion pressure gradients measured by fractional flow reserve(13).

The intraoperative application of laser Doppler was assessed by Takayama et al, who reported 2 cases of subclinical distal embolization during 112 procedures(22). Both cases of distal embolization were detected by depression of the laser Doppler flowmeter, and these findings prompted intraoperative thrombolysis. The association between intraoperative laser Doppler findings and postoperative outcomes has not been reported.

Laser doppler wave frequency appears to be important to discriminate the source of measured blood flow. Hoffmann et al propose that higher frequency waves of approximately 22.6 cycles per minute most accurately represent terminal arteriole flow, which would be maximally dilated in the hemodynamic regulation of critical ischemia(19). Beyond measuring flow at a steady state, laser Doppler can measure tissue reactivity to hyperemia, induced by either heat(21) or intraarterial vasodilators such as naftidrofuryl(23). This is an indication of the chronic state of tissue ischemia, as chronically ischemic tissue has less capacity to further vasodilate when compared with well perfused tissue(21, 24).

### *2.3.2 Photoplethysmography*

Two articles investigated the intraoperative and postoperative changes of PPG. Peltokangas et al measured PPG waveforms during and one month after peripheral angioplasty(25). They found significant changes in the PPG waveform intraoperatively, which became significantly more pronounced after one month. On follow-up, the ratio of the amplitude of the diastolic PPG wave and the peak systolic PPG wave was most reliably associated with postoperative hemodynamic measurements ( $k=0.91$  and  $k=0.71$  for ABI and TBI respectively). However, Laine et al found that a reliable PPG waveform was only attainable in 78% of the endovascular procedures(26).

### *2.3.3. Skin Perfusion Pressure*

One study evaluated skin perfusion pressure before and after endovascular treatment of infrageniculate lesions(27). The study found that baseline plantar skin perfusion pressure was significantly correlated with both angiogram contrast arrival time and wash-in rate ( $r=0.42$ ,  $p=0.034$  and  $r=.45$ ,  $p=0.020$  respectively).

## 2.4: Oxygen Content Measurement

### 2.4.1 Transcutaneous Oxygen Tension

Six articles reported on the perioperative measurement of transcutaneous oxygen tension, of which one measured intraoperative transcutaneous oxygen tension. Faglia et al found post-intervention tcpO<sub>2</sub> threshold of 34mmHg was discriminatory for reintervention (c-statistic = 0.89)(28), which was reiterated by Redlich et al finding a similar tcpO<sub>2</sub> threshold of 33mmHg (c-statistic = 0.892)(29).

Two papers specifically investigated the role of leg exercise for dynamic tcpO<sub>2</sub> measurements. Stalc et al demonstrated that postoperative exercise-induced drop in pedal tcpO<sub>2</sub> is more pronounced in patients with symptom relief when compared with those without symptom relief(30). This reduction in exercise-induced tcpO<sub>2</sub> drop is apparent 1 day after surgery, and became more pronounced 6 weeks after surgery. Wagner et al confirmed that tcpO<sub>2</sub> increased a day after surgery, however continued to significantly increase at 6 weeks after surgery(30). Interestingly, they also found that control subjects undergoing angiogram alone experienced a significant transient decrease in tcpO<sub>2</sub> the day after angiogram, which returned to baseline 6 weeks post-procedure.

Wildgruber et al compared intraoperative and postoperative tcpO<sub>2</sub> values in claudicants undergoing angiogram, with or without angioplasty(31). The measurements were static and the subjects did not perform exercise stress testing. All subjects experienced an immediate post-procedure decrease in tcpO<sub>2</sub>, which was more pronounced in subjects that underwent balloon angioplasty experienced. The two cohorts had no difference in tcpO<sub>2</sub> measurements one day after surgery, however the subjects who received angioplasty experienced increased tcpO<sub>2</sub> pedal measurements at 2 weeks after surgery, which became even more apparent at 4 weeks after surgery. These findings are contrasted with the ABI measurements 1 day after surgery, which found early signs of increased pressure in the cohort receiving angioplasty, and

sustained at 2 and 4 weeks postoperatively. However, authors also found that postoperative ABI and tcpO<sub>2</sub> at 4 weeks correlated ( $r=0.460$ ,  $p=0.001$ ). The lack of immediate response of tcpO<sub>2</sub> was also noted by Ruzsa et al, who demonstrated that immediate intravascular pressure changes measured by pressure wire are not associated with tcpO<sub>2</sub> monitoring(13).

#### *2.4.2 Transcutaneous Oxygen Saturation*

A single study evaluated transcutaneous measurement of oxygen saturation, using micro-lightguide spectrophotometry(32). By comparing measurements before and after endovascular therapy in subjects with chronic leg wounds, they found that pedal oxygen saturation increases postoperatively by 26.35% in subjects experiencing wound healing, and decreases by 4.27% in subjects without wound healing.

### **2.5: Infrared Thermography**

Instead of analyzing specific wavelengths of infrared signals to infer the oxygen saturation, infrared data can be used to estimate the thermal energy of the surface of a structure. A single article analyzed the estimated skin thermal energy of the plantar aspect of the foot using an infrared sensor, measuring before and after peripheral angioplasty(33). This study required significant efforts to standardize ambient temperature and rest the subjects to produce reliable results, but found a significant correlation between change in skin temperature and change in ABI. Therefore, the intraoperative application of infrared thermography to ascertain the temperature change in the limb during revascularization may be limited due to the distance required for infrared camera acquisition, ambient temperature, and time required to reach a steady state.

### **2.6: Angiogram Perfusion**

Angiogram is performed during most endovascular procedures. This involves intra-arterial injection of radiopaque contrast, often containing iodine, to opacify the lumen of the arteries. The purpose of angiogram is typically to provide anatomic interpretation based on static images. Angiogram perfusion methods capitalize on the use of angiogram to measure the dynamic passage of contrast through the target arteries, as a measure of blood flow. There are several definitions in angiogram perfusion: area-under-the-curve refers to the density of contrast over a given time, time-to-peak refers to the time from either injection or contrast arrival until peak opacification, and peak density refers to the maximal density of contrast observed.

The area-under-the-curve appears to change the most after endovascular therapy when compared with time-to-peak contrast and peak density values(34-36), however Kim et al found significant improvements in all measures following endovascular intervention(37). Hinrichs et al demonstrated that by using a ratio between regions of interest proximal and distal to the target lesion, hand-injections could produce significant changes before and after endovascular repair, without requiring a standardized pump injection(38). Reekers et al noted that motion artifact limits the generalizability of this technique in 10% of their sample(35). Inducing hyperemia to increase accuracy has been proposed by Ikeoka et al, who found that arrival time ratio between baseline and hyperemic states were associated with skin perfusion pressure with an ROC c-statistic of 0.77(27).

## 2.7: Injection of Perfusion Marker

### 2.7.1 Indocyanine Green

Indocyanine green is an inert substance which can fluoresce when exposed to a laser light source. The arrival characteristics of indocyanine green, known as ingress and ingress rate, and the wash-out characteristics known as egress and egress rate, can provide information about tissue blood flow. This method has been evaluated by four studies before and after

endovascular procedures(8, 39-41), and one study applied the method in the operating room(42).

To obtain measurements, indocyanine green is systemically injected, and the charge-coupled camera is positioned perpendicular to the tissue and records for approximately 136 seconds(39). Braun et al assessed 13 subjects who had measurements performed before and after interventions, and found that the ingress, ingress rate, egress, egress rate, area under the curve and maximum intensities all improved significantly after intervention(39). Toe pressures demonstrated the highest correlation with ingress rate ( $R=0.636$ ,  $p=0.006$ ) and ABI demonstrated highest correlation with egress rate ( $0.503$ ,  $p=0.017$ ). Using a similar methodology, Patel et al found that improvement in the ingress, ingress rate, and maximum intensity were significantly improved after endovascular procedures resulting in wound healing, however there was minimal change after procedures not resulting in wound healing(40). This was contrasted with ABI and tcpO<sub>2</sub>, which improved for all patients regardless of wound healing.

### *2.7.2 Radionuclide*

Systemic injection of radionuclides to assess tissue perfusion was reported by two studies. Gehani et al injected 400 MBq of systemic technetium-99m, while a tourniquet was inflated on the proximal affected leg for 3 minutes to induce hyperemia(43). Following deflation, a gamma camera monitored the radionuclide flow into the leg at a rate of 1 frame per second for 100 seconds. Using the time-activity curve, a blood flow rate was calculated. The authors reported significant increases in blood flow rates when measured 3 weeks after the index procedure (6.20 to 8.53 mL/100mL blood/minute). These findings were confirmed by Li et al who found that within 5 minutes after radionuclide injection, muscle perfusion parameters were improved after endovascular intervention(44). This process requires a gamma camera, and has not been evaluated intraoperatively.

### *2.7.3 Contrast-Enhanced Ultrasound*

Contrast-enhanced ultrasound is a modification of traditional B-mode ultrasound, which requires an injection of aggrivated Sulphur hexafluoride suspension to produce microbubbles. The depth of ultrasound interrogation can be modified to interrogate any tissue within view of an ultrasound. All identified studies interrogated muscle perfusion. Amarteifio et al found that the time to maximal contrast density was significantly shorter after endovascular treatment, and correlated strongly with ABI ( $r=0.659$ ,  $p<0.001$ )(45). While contrast-enhanced ultrasound measures and ABI both significantly improve following revascularization, Duerschmied et al reported that the change in ABI may be more profound ( $-9\%$ ,  $p=0.05$ )(46). These findings are consistent with Seinturier et al, who reported that contrast enhanced ultrasound measures did not substantially improve in subjects who experienced postoperative symptom improvement, while both toe pressures and tcpO<sub>2</sub> did significantly improve(47).

## **2.8: Other Macrovascular Assessment**

### *2.8.1 Doppler Ultrasound*

Doppler ultrasound is a ubiquitous tool in preoperative and postoperative vascular surgery assessment. However, most Doppler ultrasound protocols focus on surveillance of specific lesions, and do not perform a global assessment of limb perfusion.

One article evaluated the change in Peak Systolic Velocity (PSV) of the three tibial vessels before and after endovascular therapy(48). This report did not distinguish between endovascular therapy on proximal inflow compared with specific tibial vessels. Regardless, after endovascular therapy the PSV increased significantly in the anterior tibial, posterior tibial, and peroneal arteries (34cm/s, 18cm/s, 25cm/s respectively,  $p<0.1$  for all).

There are also several reports on the use of ultrasound to guide endovascular interventions, often with the intent of minimizing the need for radiopaque contrast administration in patients

with renal failure(49). While intraoperative ultrasound is being used to guide endovascular therapy, there are no reports of intraoperative global assessment of limb perfusion with Doppler ultrasound.

### *2.8.2 Air Plethysmography*

Air plethysmography relies on compliant vessels, and requires the below-knee leg to be surrounded by an air chamber for volume measurement with a proximal tourniquet(50). A single study investigated the change in air plethysmography measurements before and after peripheral endovascular treatment, which correlated with postoperative ABI and Doppler waveform analyses(50). There were no reports of the intraoperative application of air plethysmography, nor the correlation with clinical outcomes.

The practical application of surrounding the leg within an air chamber for intraoperative measurements presents a barrier to applying this method during surgery. While this could be feasible during aortoiliac and proximal femoral disease, this arrangement would encompass tibial vessels and would likely produce inaccurate readings if the target lesions are in tibial arteries.

## **2.9: Cross-Sectional Perfusion Assessment**

### *2.9.1 Magnetic Resonance Imaging*

There are three described magnetic resonance (MR) based perfusion techniques; blood oxygenation level-dependent, dynamic contrast-enhanced, and arterial spin labelling(51). Most reports in the peripheral circulation use variants of the arterial spin labelling method.

Salles-Cunha et al first described MRI blood flowmeter measurement averaged over 20 cardiac cycles, and directed at a location 30cm proximal to the ankle malleoli(52). They found an increase in estimated limb blood flow from 53 to 75mL/minute following femoral angioplasty.

Allouche-Cometto et al compared MRI perfusion with ABI, and found that the change in ABI after surgery was evident one day after surgery, and stable at one month after surgery. While the estimated blood flow on MRI increased significantly one day after surgery, the flow continued to significantly increase a month after surgery(2).

Chen et al found that if hyperemia were induced by transient proximal cuff vascular occlusion, hypoxia-induced changes in microvascular sensitivity as measured by gATP were associated with improvement in ischemia following endovascular therapy (8.72 vs 4.93,  $p=0.047$ ). The value of inducing hyperemia was reiterated by Grozinger et al, who found that the duration of hyperemia in calf muscles was reduced after endovascular therapy(53). West et al used a gadolinium-enhanced MRI method to estimate calf muscle phosphocreatine recovery time after maximally tolerated exercise(54). This method demonstrated that calf muscle metabolic function improved significantly following endovascular revascularization.

### *2.9.2 Computed Tomography*

A single article evaluated a method of perfusion assessment using dynamic volume perfusion computed tomography (CT)(55). Similar to MR perfusion, CT perfusion scans perform serial interrogations of tissue over time to assess dynamic changes in the tissue. A CT perfusion scan using 32mL of iodinated contrast assessed the rate of contrast arrival on six subjects before and after endovascular revascularization. This article identified the plantar dermis as the most sensitive region of perfusion monitoring, with a mean increase in estimated perfusion of 153% after endovascular therapy.

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# Chapter 3: Systematic Review of Physiologic Perfusion Monitoring Methods During Endovascular Revascularization for Atherosclerotic Peripheral Arterial Disease

## **Chapter Overview**

**Chapter 3** addresses Objective 1: Review Currently Reported Intraoperative Physiologic Measures. Prior to this thesis, there were no published reviews of intraoperative methods to assess limb perfusion during endovascular revascularization for peripheral vascular disease. No ethics approval was required for the conduct of the systematic review.

## **Chapter Contents**

**Section 3.1** includes the published protocol manuscript for the systematic review titled *Physiologic Perfusion Monitoring Methods during Endovascular Revascularization for Atherosclerotic Peripheral Arterial Disease*.

**Section 3.2** includes the prepared manuscript of the systematic review titled *Physiologic Perfusion Monitoring Methods during Endovascular Revascularization for Atherosclerotic Peripheral Arterial Disease*.

## **Section 3.1: Protocol for a Systematic Review**

### **Section Overview**

This section includes the protocol manuscript titled ‘Physiologic Perfusion Monitoring Methods During Endovascular Revascularization for Atherosclerotic Peripheral Arterial Disease: Protocol for a Systematic Review’. The protocol outlines the plan to summarize the existing evidence describing the intraoperative application of physiologic limb perfusion assessment.

### **Manuscript Status**

This manuscript has been published in the Systematic Reviews journal. We received permission from the journal to present the text of this manuscript in the thesis.

### **Author Contributions**

Mark Rockley was involved in all stages of the protocol inception and preparation of the protocol manuscript. Prasad Jetty was involved in the protocol inception and preparation of the manuscript. George Wells was involved in all stages of the protocol inception and preparation of the manuscript.

### **Related Thesis Appendices**

The published article is presented in Appendix C. We received permission from the Systematic Reviews journal to present the PDF of the complete manuscript in the thesis.

**Physiologic Perfusion Monitoring Methods During Endovascular Revascularization for  
Atherosclerotic Peripheral Arterial Disease: Protocol for a Systematic Review**

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*Keywords:* Angioplasty, Peripheral Arterial Disease, Perfusion, Intraoperative Monitoring

*Registration:* PROSPERO CRD42019138192

## **Abstract**

**Background:** Endovascular therapy is a fundamental treatment for peripheral arterial disease. However, the success rate of endovascular therapy remains poor, as a third of patients with critical limb ischemia ultimately require a major amputation for gangrene despite endovascular treatment. This failure rate has prompted investigation into methods of determining physiologic procedural success before and after treatment, before clinically apparent outcomes occur such as gangrene. The aim of this systematic review is to evaluate if in patients undergoing endovascular surgery for lower extremity atherosclerotic peripheral arterial disease, do changes in physiologic measures of perfusion during surgery correlate with clinical outcomes?

**Methods:** In compliance with PRISMA, two independent reviewers will conduct a systematic review of EMBASE, MEDLINE, CENTRAL, trial registries, grey literature, and ancestry and citation search. The primary outcome of interest will be Major Adverse Limb Events. Data abstraction and qualitative analysis will be performed according to pre-specified criteria. Data analysis and synthesis will be qualitative; no meta-analysis is planned, as the anticipated homogeneity of measurement and outcome reporting standardization is low.

**Discussion:** The treatment of peripheral arterial disease is unique in that the tissue of the ischemic leg is easily accessible for direct monitoring during procedures. This is contrasted with cardiac and neurologic monitoring during cardiac and cerebral procedures, where indirect or invasive measures are required to monitor organ perfusion. Currently synthesized evidence

describing limb perfusion focuses on static states of ischemia, and does not evaluate the value of change in perfusion measurement as an indicator of endovascular treatment success. These methods could potentially be applied to optimize procedural outcomes by guiding perfusion-based decision making during surgery.

**Systematic Review Registration:** PROSPERO CRD42019138192

## **Manuscript**

### **Background**

#### **Rationale**

Peripheral vascular disease (PVD) is a condition caused by arterial blockages causing inadequate blood flow, resulting in pain and gangrene of the legs. The prevalence of PVD in the North American general population over 50 years of age is estimated at 17.4%, and is rising in association with the increasing prevalence of diabetes(1). Bypass surgery is typically reserved for patients with severe forms of PVD, and minimally invasive options of angioplasty ('endovascular surgery') is emerging as the treatment of choice for most patients with PVD. Angioplasty is the foundational treatment of endovascular therapy, which may be augmented by treatments such as stenting and atherectomy. Unfortunately, the two-year patency of balloon angioplasty for PVD is poor, reported between 50 – 80%, depending on lesion location and characteristics(2). The 1-year amputation rate despite endovascular revascularization has been reported as high as 32% in patients with lower limb critical limb ischemia(3). This has prompted investigation into the predictors of failure, and potential solutions to optimize the success rate of revascularization. One proposed method is to evaluate the physiologic

improvement in limb perfusion intraoperatively, to provide the operator with an opportunity to evaluate the procedural success and potentially guide intraoperative decision making.

One of the most important predictors of clinical success following endovascular surgery for PVD is the post-procedure Ankle-Brachial Index (ABI)(4). This measurement is performed by applying a blood pressure cuff at the level of the lower leg ('Ankle Pressure') and the arm. The ABI is a ratio of the blood pressure at the ankle when compared with the arm. Similarly, a smaller cuff around the great toe can determine the absolute Toe Pressure, which can also be used to calculate the Toe-Brachial Index (TBI). The change in ABI following endovascular surgery can be detected a day after the procedure, and remains stable throughout the month following the procedure(5). Several other post-operative markers of limb perfusion have also been investigated. Magnetic resonance arterial spin labelling correlates with postoperative ABI and clinical outcomes(6). Furthermore, some authors have investigated markers of limb perfusion during surgery, finding correlation between post-operative ABI and intra-operative 2-dimensional perfusion angiography(7) and indocyanine green intra-arterial injection(8). Other methods such as laser doppler(9), near-infrared spectroscopy(10, 11), transcutaneous oxygen saturation(12), and micro-oxygen sensors(13) have also been evaluated. While these methods have been established as markers of perfusion in the outpatient setting, their role in guiding intraoperative decision making is unclear.

The potential of physiologic measures to predict clinical outcomes after endovascular revascularization presents several opportunities. The current practice of waiting until the

postoperative period to measure the limb pressure after surgery may miss opportunities to guide intraoperative decision making. While angiogram is currently the primary form of intraoperative feedback, conventional angiogram provides only anatomic feedback, which may not correlate with physiologic perfusion of blood due to microvascular disease and diffuse disease.

## **Objectives**

The aim of this systematic review is to evaluate if in patients undergoing endovascular surgery for lower extremity atherosclerotic peripheral arterial disease, do changes in physiologic measures of limb perfusion during surgery correlate with clinical outcomes? Physiologic measures include non-invasive and invasive arterial pressure measurements, transcutaneous oxygen measurement, infrared spectroscopy, laser doppler flowmetry, and angiogram perfusion calculations.

Secondary questions that will be addressed by this review will investigate the correlation of intraoperative physiologic measures with non-clinical postoperative outcomes such as radiographic patency and hemodynamic outcomes.

## **Methods**

### **Eligibility Criteria**

#### **Study Designs**

We will include randomized controlled trials (RCT) and quasi-experimental trials, non-randomized controlled trials, cluster trials, interrupted time series studies, controlled before-after studies (CBA), prospective or retrospective cohort studies, and case-control studies. Case series less than 5 participants and case reports will be excluded.

### Participants

We will include studies examining human adults (age 18 or older) who received elective arterial angioplasty for atherosclerotic peripheral vascular disease. The angioplasty must be the primary purpose of the intervention, and not be performed concurrently with a hybrid open vascular procedure on an in-line flow artery. The intervention must be performed on lower extremity peripheral arteries, ranging from the infrarenal aorta proximally to the toes distally. The balloons may be drug-coated or lined with cutting ribs, and alternate adjunctive endovascular procedures stent placement, orbital atherectomy, laser atherectomy, rotational atherectomy, or directional atherectomy. We will exclude venous angioplasty, arteriovenous fistula angioplasty, and studies examining emergency settings.

### Intervention and Comparators

The intervention of interest is intraoperative physiologic measurement of limb perfusion. Examples of established physiologic measurements of perfusion include non-invasive and invasive arterial pressure measurements, transcutaneous oxygen measurement, infrared spectroscopy, laser doppler flowmetry, and angiogram perfusion. Any further methods of physiologic measurement which are currently unknown to the authors and are discovered

during the review will be considered individually. They will be included in the review if they meet our definition of intraoperative physiologic limb perfusion measurement; dynamic measures of blood flow within the target limb performed during surgery. Strictly anatomic measurements which are available on standard angiogram, such as residual stenosis or patency, will be excluded.

### Outcomes

The primary outcome of interest will be Major Adverse Limb Events (MALE). MALE is defined as a composite outcome of clinically-driven target limb reintervention, and major amputation proximal to the ankle(14).

Secondary clinical outcomes include amputation, reintervention, mortality, and clinical symptomatic improvement based on the Rutherford's Classification of Peripheral Vascular Disease(15). Secondary non-clinical outcomes include non-invasive limb hemodynamic results, and radiographic results of vessel patency and stenosis.

### Timing

Studies will be selected for inclusion if they report intraoperative monitoring results in addition to follow-up outcomes reported at least 30 days after the index surgery, categorized into clinical, radiographic, and hemodynamic outcomes.

### Setting

There are no restrictions regarding setting of the study.

### Language

We will include all language studies, with a list of titles requiring translation into English included in an appendix.

### **Information Sources**

A literature search strategy using medical subject headings and text words has been developed. We will search MEDLINE (OVID interface), EMBASE (OVID interface), and the Cochrane Central Register of Controlled Trials (Wiley interface).

To ensure capture of all relevant trials, all selected studies will also undergo ancestry search, in addition to citation search using SCOPUS. OpenGrey will be interrogated for unpublished relevant literature.

### **Search Strategy**

Both qualitative and quantitative studies will be collected. All searches will be limited by date of publication (January 1977 – September 2018). The initial year of 1977 has been chosen as the first in-human use of angioplasty was performed that year. No language limit will be placed on the search. The search strategy and syntax has been guided by a Health Sciences librarian with systematic review experience. The MEDLINE search syntax will be adapted to accommodate the remaining database searches. Please see Appendix 1 for a complete search

syntax used for the MEDLINE search. The search syntax is intentionally broad to include any potentially relevant methods of perfusion measurement. Of note, the PROSPERO database has been searched, and no ongoing or recently completed systematic review on this topic has been performed.

## **Study Records**

### Data Management

Literature search results will be aggregated in EndNote, including where duplicate articles will be removed. The results will then be uploaded to the Distiller SR software, which will facilitate collaboration among all reviewers.

The two screening authors will independently screen titles and abstracts resulting from the combined search of all selected databases. The full text of an article will be obtained for any articles that appear to meet eligibility criteria, at which point the full text will be screened and confirmation of article inclusion will be made. Any reasons for exclusion following full text screening will be explicitly documented and listed in an appendix.

Once both reviewers have created a complete list of eligible articles, the lists will be compared. Discrepancies in article selection will be addressed with discussion with a third-party author experienced in systematic review conduct. No authors will be blinded to journal titles, study authors, or study location of origin.

### Data Collection Process

A standardized form created in Distiller SR will be used as the data collection method. Both reviewers will have a separate form for each article, which will be compared for consistency after data collection has completed. Any discrepancy will be addressed with discussion with a third-party author experienced in systematic review conduct. Study authors will not be contacted to resolve unclear or inadequate reporting of data.

### **Data Items**

The trial design, setting, and any accessory measures such as observer or operator blinding will be assessed. We will collect patient population information including level of endovascular procedure, claudication versus critical limb ischemia, use of vasodilators such as cilostazol or pentoxifylline, and comorbidity data. We will extract perfusion monitoring information including method of perfusion monitoring, timing of monitoring, and any objective serial outcomes, their confidence measures, variability, and inter-rater reliability. We will also note any author comments on feasibility or obstacles in using the method. Extracted outcomes will be guided by the definitions below.

### **Outcomes and Prioritization**

#### Primary Outcome

The primary outcome of interest will be Major Adverse Limb Events (MALE). MALE is defined as a composite outcome of clinically-driven target limb reintervention, and major amputation proximal to the ankle(14).

### Secondary Outcomes

Secondary clinical outcomes include:

- Amputation
  - Minor Amputation (*Toe(s) or Foot*)
  - Major Amputation (*Above the Ankle*)
  - Amputation-Free Survival
- Re-Intervention
  - Target:
    - Lesion
    - Vessel
    - Limb
  - Endovascular
  - Bypass
  - Thrombectomy
  - Thrombolysis
- Mortality
- Improvement in Rutherford's Classification of Peripheral Vascular Disease(15)

Secondary non-clinical outcomes include:

- Postoperative Hemodynamic
  - Ankle pressure

- Ankle-Brachial Index (ABI)
- Toe pressure
- Toe-Brachial Index (TBI)
- Postoperative Radiographic
  - Target Vessel Patency
    - Primary (*Absence of target vessel occlusion or restenosis >50%*)
    - Primary Assisted (*Patency requiring assistance of subsequent procedure to maintain patency of target vessel*)
    - Secondary (*Patency requiring assistance of subsequent procedure to restore patency of target vessel*)

### **Risk of Bias of Individual Studies**

To assess individual studies for potential risk of bias, we will collect information guided by the Cochrane Collaboration tool for assessing risk of bias. In summary, this includes sequence generation, allocation concealment, blinding, incomplete outcome data, and selective outcome reporting. For each category, each study will be determined to be at either Low or High risk. Alternately, if the report includes insufficient information to determine the level of risk, the category will be labelled as Unclear. Determination of the level of bias will be made by the two reviewers independently, and compared following complete assessment of all studies. Any discrepancy will be addressed with discussion with a third-party author experienced in

systematic review conduct. The resulting risk of bias for each study, in each category, will be graphically represented by RevMan software.

## **Data Synthesis**

### Quantitative Synthesis

Due to the anticipated heterogeneity of reports, including the methods of perfusion monitoring, clinical outcomes, and type of endovascular surgery, we will not perform quantitative data synthesis.

### Qualitative Synthesis

We will summarize the described methods of intraoperative perfusion measurement. Specifically, we will describe the reported association of these methods with postoperative outcomes. We will comment on the reported variations in methods, and assess the volume of published experience in utilizing each method. We will also comment on any practical information gleaned from the review. This will include comments on feasibility, reliability, and accessibility. We will also describe any reported patient characteristics that may affect the method's usability. Where there is missing data, we will contact the authors of the original study to obtain complete data where possible.

### A Priori Subgroup Analyses

We will stratify our qualitative analysis into the three postoperative outcome categories: clinical, hemodynamic, and radiographic. Where possible, we will stratify the qualitative

analysis by vascular level of intervention (aortoiliac, femoropopliteal, or tibial), symptom status (claudication or critical limb ischemia), diabetic status, and use of peripheral vasodilators such as cilostazol or pentoxifylline.

### Meta-Bias

As there is no planned quantitative data synthesis, we will not perform statistical analysis of meta-bias. We will however comment on the risk of bias of each study, as well as qualitatively describe

### Confidence in Cumulative Estimate

There will not be a cumulative estimate produced by this study, and therefore there will be no assessment of confidence. However, the generalizability of the findings to the PVD patient population will be qualitatively judged.

### Discussion

In summary, the success of endovascular therapy for PVD is relatively poor despite technological advancements, resulting in a high re-intervention rate. A component of this challenge may be inadequate revascularization during the initial procedure, despite a reassuring anatomic result on angiogram. Physiologic measures of limb perfusion may provide insight into which patients are incompletely revascularized during the initial procedure. If intraoperative feedback of limb perfusion is predictive of outcomes, these methods could be

used to guide intraoperative decision making and ultimately improve the success of endovascular revascularization.

### **List of Abbreviations**

PVD = Peripheral Vascular Disease

MALE = Major Adverse Limb Events

ABI = Ankle-Brachial Index

TBI = Toe-Brachial Index

### **Declarations**

**Ethics Approval:** Ethics is waived for a systematic review of published papers.

**Consent for Publication:** Not applicable

**Availability of Data and Materials:** The datasets generated and analyzed during the current study will be available from the corresponding author on reasonable request.

**Competing Interests:** The authors declare that they have no competing interests.

**Funding:** There are no funding contributions to declare for this study.

**Authors' Contributions:** MR conceived of the project and developed the first draft of the protocol. PJ was a major contributor of project concept and subgroup analysis overview.

GW oversaw all stages of the manuscript.

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## **Appendix**

**Appendix 1:** Proposed search syntax for MEDLINE, using OVID interface

### **Peripheral Vascular Disease**

1. Peripheral Vascular Diseases/
2. GANGRENE/
3. INTERMITTENT CLAUDICATION/
4. Peripheral Arterial Disease/
5. PVD.tw.
6. peripheral vascular disease\*.tw.
7. Peripheral angiopath\*.tw
8. peripheral arterial disease\*.tw.
9. gangrene\*.tw.
10. claudica\*.tw.
11. critical limb ischemia\*.tw.
12. (1 to 11, OR)

### **Endovascular Revascularization**

13. Angioplasty/
14. ENDOVASCULAR PROCEDURES/
15. Stents/
16. angioplast\*.tw.
17. endovascular\*.tw.
18. stent\*.tw.

19. atherectom\*.tw.
20. (Endoluminal adj3 repair\*).tw.
21. (13 to 20, OR)

### **Intraoperative Monitoring**

22. Monitoring, Intraoperative/
23. (intraoperative adj3 monitor\*).tw.
24. (perfusion adj3 angio\*).tw.
25. Ankle Brachial Index/
26. Arterial Pressure/
27. ankle brachial.tw.
28. (ankle adj3 pressur\*).tw.
29. toe brachial.tw.
30. (toe adj3 pressur\*).tw.
31. ABI.tw.
32. TBI.tw.
33. Blood Gas Monitoring, Transcutaneous/
34. (transcutaneous adj2 oxygen pressur\*).tw.
35. tcpo2.tw.
36. Spectrophotometry, Infrared/ or Spectroscopy, Near-Infrared/
37. infrared spectro\*.tw.
38. correlation spectroscop\*.tw.
39. Pulse volume\*.tw.
40. PVR.tw.
41. Tomography, Optical Coherence/
42. (optic\* adj2 coheren\*).tw.
43. Laser-Doppler Flowmetry/
44. (laser adj2 doppler).tw.
45. (22 to 44, OR)
46. (12 AND 21 AND 45)

## **Section 3.2: Systematic Review**

### **Section Overview**

This section includes the completed manuscript titled ‘Physiologic Perfusion Monitoring Methods During Endovascular Revascularization for Atherosclerotic Peripheral Arterial Disease: A Systematic Review’. Following the protocol in Section 3.1, this chapter provides results of the completed systematic review which summarizes the existing evidence describing the intraoperative application of physiologic limb perfusion assessment.

### **Manuscript Status**

This manuscript has been prepared for submission to the Cardiovascular and Interventional Radiology (CVIR) journal.

### **Author Contributions**

Mark Rockley was involved in all stages of the protocol inception, conduct of the review, and preparation of the review manuscript. Prasad Jetty was involved in the protocol inception and preparation of the manuscript. Kathleen Rockley was in involved in the conduct of the review and preparation of the manuscript. George Wells was involved in all stages of the protocol inception, conduct of the review, and preparation of the manuscript.

# **Physiologic Perfusion Monitoring Methods During Endovascular Revascularization for Atherosclerotic Peripheral Arterial Disease: A Systematic Review**

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*Support:* There are no funding disclosures related to the conduct of this review.

*Keywords:* Angioplasty, Peripheral Arterial Disease, Perfusion, Intraoperative Monitoring

*Registration:* PROSPERO CRD42019138192

## **Introduction**

The prevalence of Peripheral vascular disease (PVD) in the North American general population over 50 years of age is estimated at 17.4%, and is rising in association with the increasing prevalence of diabetes<sup>1</sup>. Minimally invasive treatment options in the form of 'endovascular surgery' is emerging as the treatment of choice for most patients with PVD. Endovascular surgery is traditionally represented by angioplasty, which may be augmented by adjunctive procedures such as stenting and atherectomy. Unfortunately, the two-year patency of balloon angioplasty for PVD is poor, reported between 50 – 80%, depending on lesion location and characteristics<sup>2</sup>. The 1-year amputation rate despite endovascular revascularization has been reported as high as 32% in patients with lower limb critical limb ischemia<sup>3</sup>. This has prompted investigation into the predictors of failure, and potential solutions to optimize the success rate of revascularization. One proposed method is to evaluate the physiologic improvement in limb perfusion intraoperatively, to provide the operator with an opportunity to evaluate the procedural success and potentially guide intraoperative decision making.

The potential of physiologic measures to predict clinical outcomes after endovascular revascularization presents several opportunities. The current practice of waiting until the postoperative period to measure the limb pressure after surgery may miss opportunities to guide intraoperative decision making. While angiogram is currently the primary form of intraoperative feedback, conventional angiogram provides only anatomic feedback, which may not correlate with physiologic perfusion of blood due to microvascular disease and tandem lesions.

Several measures of limb perfusion have been evaluated in open peripheral revascularization procedures. Indocyanine green fluorescence ingress of the skin is strongly associated with postoperative wound healing<sup>4</sup>. Skin perfusion pressure greater than 27mmHg and transcutaneous oxygen pressure (tcpO<sub>2</sub>) greater than 40mmHg have demonstrated strong associations with wound healing in a steady state<sup>5,6</sup>. Other methods such as laser doppler<sup>7</sup>

have been evaluated in the outpatient setting. While these methods have been evaluated as assessing limb perfusion in a steady state, their role in guiding intraoperative decision making is unclear.

The aim of this systematic review is to evaluate if in patients undergoing endovascular surgery for lower extremity atherosclerotic peripheral arterial disease, is there an association between intraoperative changes in physiologic measures of perfusion and postoperative clinical outcomes? Physiologic measures of perfusion are defined as methods with the intent to assess blood flow to tissue, rather than assess anatomic vascular disease. The primary postoperative clinical outcome is Major Adverse Limb Events (MALE), which is defined as a composite outcome of clinically-driven target limb reintervention, and major amputation proximal to the ankle<sup>8</sup>.

## **Methods**

The protocol is registered on PROSPERO (CRD42019138192). EMBASE, MEDLINE, and CENTRAL databases were searched with a pre-specified search strategy generated with assistance of a health sciences librarian (Appendix 1). The ClinicalTrials.gov registry was searched for trial registry data, and OpenGrey was interrogated for unpublished relevant literature. Following an initial abstract screen, full-text review of potentially relevant articles was conducted. To ensure capture of all relevant trials, all eligible studies also underwent ancestry search, in addition to citation search using SCOPUS.

All discovered studies were aggregated into EndNote X8.2, before undergoing screening using DistillerSR. Data abstraction was performed independently by two reviewers on DistillerSR, and any disagreements were addressed by a third reviewer. Finally, RevMan 5.3 was used for data analysis and synthesis. All studies were assessed for risk of bias using the Cochrane Collaboration tool.

Eligible study designs included randomized controlled trials (RCT) and quasi-experimental trials, non-randomized controlled trials, cluster trials, interrupted time series studies, controlled before-after studies (CBA), prospective or retrospective cohort studies, and case-control studies. Case series of less than 5 participants and case reports were excluded. The search included studies examining human adults (age 18 or older) who received angioplasty for atherosclerotic stenotic or obstructive vascular disease. Studies published between January 1977 – October 2018 were considered. The start year of 1977 was chosen as the first in-human use of angioplasty was performed that year.<sup>11</sup> Studies which only reported on procedures performed concurrently with a hybrid open vascular procedure on an in-line flow artery, such as an endarterectomy or bypass, were excluded. We included endovascular interventions performed on any lower extremity arterial structure below the aortic bifurcation. Studies were selected for inclusion if they report intraoperative monitoring results in addition to follow-up outcomes reported at least 30 days after the index surgery, categorized into clinical, radiographic, and hemodynamic outcomes. There are no restrictions regarding setting of the study.

The primary outcome of interest was Major Adverse Limb Events (MALE), which is defined as a composite outcome of clinically-driven target limb reintervention, and major amputation proximal to the ankle<sup>8</sup>. Secondary objectives that will be addressed by this review will be to describe feasibility and reliability of intraoperative physiologic measures, and evaluate the association between changes in perfusion measures with postoperative clinical outcomes. Clinical outcomes are defined as symptom status or wound healing. The risk of bias was assessed for each study, guided by the Cochrane Collaboration tool. The quality of cohort studies were assessed using the Newcastle-Ottawa Scale for the assessment of cohort studies<sup>9</sup> and the quality of case-control studies were assessed by the Institute for Health Economics Quality Appraisal Checklist for case series studies<sup>10 11</sup>.

In addition to collecting data regarding the accuracy and results of the perfusion monitoring method, we also commented on any practical information gleaned from the review.

This will include comments on feasibility, reliability, and accessibility. Due to the anticipated heterogeneity of reports, including the methods of perfusion monitoring, clinical outcomes, and type of endovascular surgery, we did not perform quantitative data synthesis. Instead, each article was qualitatively assessed and described.

## **Results**

A total of 2064 articles were evaluated, of which 53 full text articles were reviewed and 2 articles ultimately met study inclusion criteria. The most common reasons for exclusion after full-text assessment was the absence of a clinical outcome (n=26) or the lack of an intraoperative physiologic assessment of limb perfusion (n=26). The study selection process can be seen in Figure 1. A summary of excluded studies and the reasons for exclusion are described in Appendix 2.

Of the two included studies, one was a retrospective review and the other a prospective case series study. No randomized trials were identified. The two articles are summarized in Table 1. Utsunomiya et al<sup>12</sup> described the association of intraoperative angiogram perfusion measurements with clinical outcomes. This was a retrospective cohort study of 93 limbs in 77 subjects undergoing peripheral endovascular revascularization for critical limb ischemia. The method of perfusion assessment used angiogram perfusion to assess the binary presence of 'wound blush'. Wound blush was determined by observer blinded assessment, and defined as an iodinated contrast accumulation in the target tissue wound bed at the final angiogram after endovascular therapy. The clinical outcome was limb salvage rate, defined as freedom from major amputation.

They found that 60.2% of limbs demonstrated wound blush at the time of procedure completion, while 30.8% of the limbs did not demonstrate wound blush. The k-value was 0.75 for interobserver agreement of wound blush. The subjects were followed for a mean of 631

days. At three years, the limb salvage rate was significantly higher if a wound blush was present at the completion of the procedure (96.4% vs 56.8% respectively,  $p < 0.01$ ). However, the presence of a wound blush prior to intervention was not recorded, and it is unclear whether the injection rate, volume, and density of contrast was standardized.

The second study evaluated indocyanine green fluorescence perfusion assessment. Mironov et al performed a prospective case series of 28 endovascular procedures<sup>13</sup>. The method of perfusion assessment used the SPY Elite Fluorescent Imaging System to assess density of indocyanine green in tissue. Unlike prior reports of indocyanine green perfusion assessment, this study injected the indocyanine green dye directly into the arterial sheath. The camera then recorded 137 seconds of perfusion imaging of the dorsal foot. Based on the continuous video of limb fluorescence, the inflow intensity and speed of indocyanine green were calculated, known as ingress and ingress rate, and the wash-out intensity and speed known as egress and egress rate were calculated. The clinical outcomes were changes in Rutherford score and wound healing, which were reported for 25 patients at 6 months.

They found that the baseline severity of symptoms based on Rutherford classification and pre-intervention ingress rate were correlated (Spearman  $\rho = 0.398$ ,  $p = 0.036$ ). 39% of subjects experienced decreased ingress rate and 57% had decreased ingress after the procedure. At 6 months of follow-up, 8 (32%) of subjects did not experience wound healing, and one required amputation.

Of the changes between the pre-intervention and post-intervention intraoperative measurements of ingress, ingress rate, egress, and egress rate, the study reported that none of these changes were significant predictors of wound healing. There were no statistics reported describing these associations.

Both studies were at risk of multiple forms of bias (Figure 2). The study designs without a priori definitions and potential for intraoperative performance bias were major factors

introducing potential bias. The quality of the studies were assessed using the Newcastle-Ottawa Scale for assessment of cohort studies, and the Institute for Health Economics for assessment of case series studies. The completed checklists are found in Appendices 3 and 4.

## **Discussion**

This systematic review found two studies which reported on the association of intraoperative measure of perfusion during peripheral vascular endovascular revascularization with postoperative clinical outcomes. Both studies analyzed relatively small study samples with high risk of bias. Utsunomiya et al found that the subjectively assessed presence of iodinated contrast infiltrating leg wound tissue during angiogram was strongly associated with freedom from amputation. Conversely, Mironov et al did not report any significant association between wound healing and objectively measured indocyanine green perfusion measures.

Although the studies arrived at different conclusions, there are close similarities between these methods. Both capitalized on the existing intravascular devices to directly inject a foreign material, which could be detected with a tissue-penetrating camera. Utsunomiya et al injected iodinated angiogram contrast, and used an xray fluoroscopy machine which penetrates the entire depth of the tissue to trace the flow of this foreign material. Mironov et al injected indocyanine green, and used the SPY Elite Fluorescent camera which analyzes the surface of tissue to trace the flow of the foreign material. A significant difference is that angiogram perfusion techniques rely on resources already readily available during standard endovascular procedures, while indocyanine green requires injection of a foreign material and a separate fluorescent camera that would not otherwise be required. Perhaps the similarities of these methods is not surprising, as they both conveniently exploit the intra-arterial devices during standard endovascular procedures to perform the assessment.

A key requirement of intraoperative measurement is a rapid response following revascularization, to provide the operator with timely feedback. In the process of revascularization, hemodynamic changes precede metabolic and thermal changes.

Furthermore, changes in blood flow through large arteries occurs more quickly than flow through capillaries after revascularization, which may be influenced by distal microvascular disease<sup>14</sup>. Therefore, while metabolic and microvascular perfusion indicators may provide reliable assessments in a steady preoperative or postoperative state, they are unlikely to be useful intraoperative adjuncts.

The postoperative timing of perfusion feedback is demonstrated by several studies. A comparison of intraoperative and postoperative transcutaneous oxygen partial pressure (tcpO<sub>2</sub>) values in claudicants undergoing angiogram found that subjects actually experienced an immediate post-procedure decrease in tcpO<sub>2</sub><sup>15</sup>. The subjects who received angioplasty experienced increased tcpO<sub>2</sub> pedal measurements at 2 weeks after surgery, which became even more apparent at 4 weeks after surgery. These findings are contrasted with ankle pressure measurements which were increased 1 day after surgery, and sustained at 2 and 4 weeks postoperatively. The authors suggested that while macrovascular blood flow is immediately altered during endovascular procedures, changes in microvascular perfusion may take days to week to normalize. Similarly, a comparison of MRI perfusion with hemodynamic results suggested that the postoperative ABI changes are evident within a day after surgery, while the blood flow rates estimated by MRI continues to increased over a month after surgery. Yu et al demonstrated that while near-infrared diffuse optical spectroscopy detected immediate improvement in blood flow is detectable intraoperatively, changes in muscle oxygenation are not evident until hours after revascularization<sup>16</sup>. The lack of immediate response of tcpO<sub>2</sub> was also noted by Ruzsa et al, who demonstrated that immediate intravascular pressure changes are not associated with tcpO<sub>2</sub> monitoring, while toe pressures improved from a mean of 27mmHg to 79mmHg and correlated with intraarterial pressure<sup>17</sup>.

The SPY Elite camera used to detect indocyanine green perfusion has a tissue penetration of 5mm, and therefore would be expected to only represent microvascular tissue perfusion. Indocyanine green perfusion has previously been reported to demonstrate a strong association between measurements and wound healing outcomes in a steady postoperative

state<sup>18</sup>. Therefore, the discrepancy between the previously reported postoperative results and the intraoperative results reported by Mironov et al could be attributed to the delay in microvascular tissue perfusion change after revascularization.

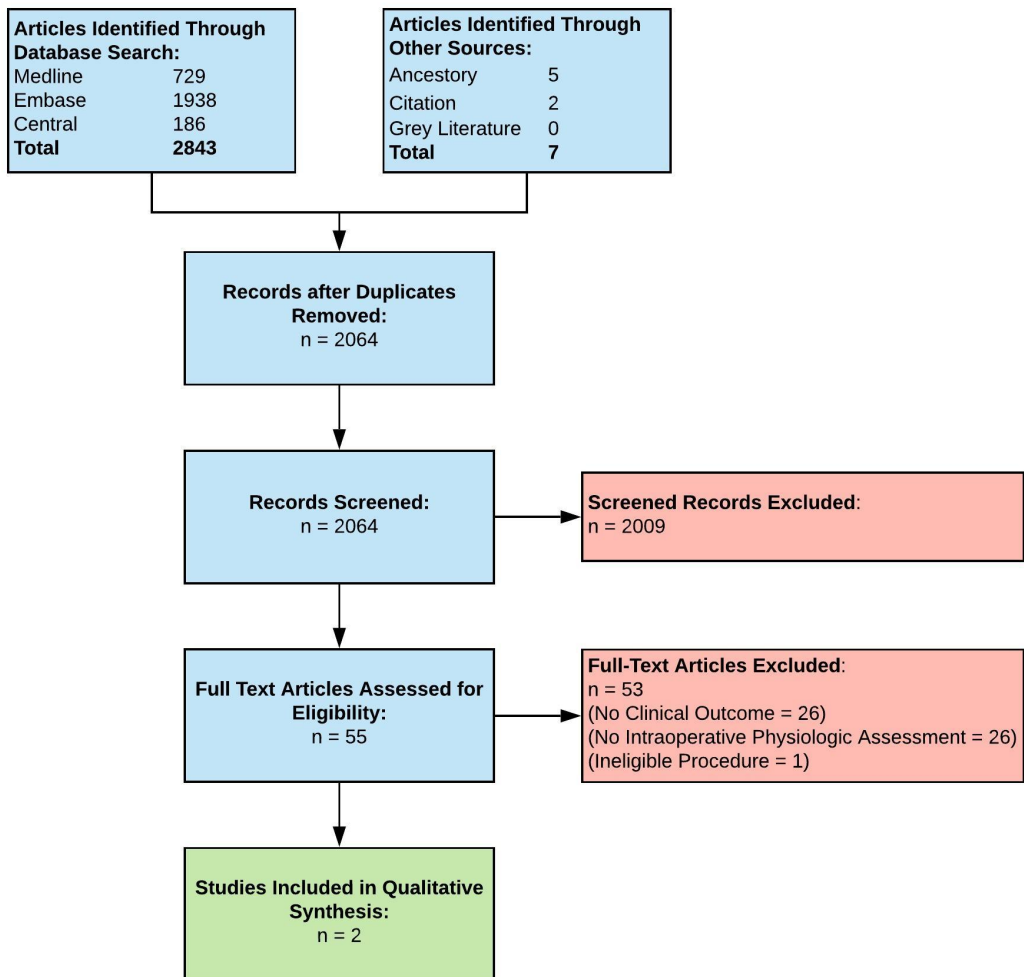
While the intraoperative application of indocyanine green injection faces challenges, iodinated contrast perfusion assessment also has barriers to practical application. Utsunomiya et al did not describe the status of contrast wound blush prior to intervention, and it is unclear whether the intervention itself was responsible for establishing this indicator of wound perfusion. To make an assessment before-and-after intervention, serial measurements would be required. The relatively rapid rate of contrast flow through the limb during angiogram introduces possible confounding measurements if a standardized injection rate, volume, and density of contrast is not used. This could be mitigated by mechanical contrast power injectors, however this process can be more cumbersome than traditional 'hand injection' of a syringe of contrast material.

The main limitation of this study is the limited quality of studies which addressed our research question. Both identified studies were small studies at high risk of bias. While thirteen excluded studies reported on intraoperative assessment of perfusion, there was no practical data on their association with postoperative clinical outcomes. The reports of intraoperative perfusion assessment only report the association with clinical outcomes, and do not comment on the potential of perfusion assessments to guide intraoperative decision making and the potential to modify outcomes. In addition, both studies provided incomplete reporting of data and analyses, and have not responded to our inquiries for more complete data.

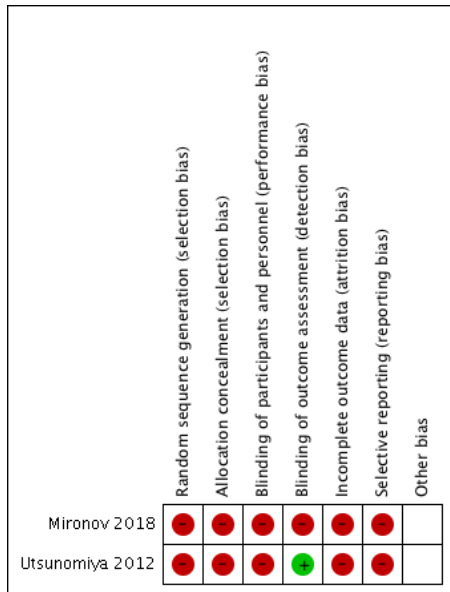
Of note, the complete manuscript of the study by Utsunomiya et al was published outside of the search time range. However, the study was identified through an abstract publication of this study which was published during the time range, and therefore the study was deemed eligible for inclusion.

In conclusion, this systematic review identified two methods of assessing intraoperative perfusion by assessing the flow of iodinated contrast and indocyanine green, both injected through an arterial sheath. The presence of iodinated contrast accumulation in the distal leg wound at the completion of a procedure was associated with freedom from amputation, while the measures of indocyanine green flow through tissue was reported to not be associated with wound healing. The ability to detect changes in perfusion during surgery introduces unique considerations when compared with perfusion assessment in a steady state, therefore an ideal intraoperative perfusion assessment likely measures macrovascular rather than microvascular perfusion. Further research should evaluate the potential of intraoperative perfusion assessment to modify outcomes, focusing on rapidly responding measures detectable during surgery which potentially include iodinated contrast perfusion and hemodynamic assessment.

## Tables and Figures



**Figure 1:** Study selection flow chart.



**Figure 2:** Risk of Bias Summary for included studies.

Article	Study Design	Vascular Intervention	Symptom Status	Control	Number of Subjects	Type of Perfusion Assessment	Timing of Measurement With Respect to Intervention	Clinical Outcomes
Utsunomiya 2012 <sup>12</sup>	Retrospective cohort	Peripheral endovascular treatment	Critical limb ischemia	None	93 limbs in 77 subjects	Iodinated angiogram perfusion	Intraoperative, at completion	Limb salvage
Mironov 2019 <sup>13</sup>	Prospective case series	Peripheral vascular angioplasty	Critical limb ischemia	None	28 subjects	Indocyanine green	Intraoperative, before and after angioplasty	Wound healing, Rutherford stage

**Table 1:** Summary of studies which met inclusion criteria.

## **Appendices**

**Appendix 1:** Search syntax for MEDLINE, using OVID interface.

### **Peripheral Vascular Disease**

47. Peripheral Vascular Diseases/
48. GANGRENE/
49. INTERMITTENT CLAUDICATION/
50. Peripheral Arterial Disease/
51. PVD.tw.
52. peripheral vascular disease\*.tw.
53. Peripheral angiopath\*.tw
54. peripheral arterial disease\*.tw.
55. gangrene\*.tw.
56. claudica\*.tw.
57. critical limb ischemia\*.tw.
58. (1 to 11, OR)

### **Endovascular Revascularization**

59. Angioplasty/
60. ENDOVASCULAR PROCEDURES/
61. Stents/
62. angioplast\*.tw.
63. endovascular\*.tw.
64. stent\*.tw.
65. atherectom\*.tw.
66. (Endoluminal adj3 repair\*).tw.
67. (13 to 20, OR)

### **Intraoperative Monitoring**

68. Monitoring, Intraoperative/
69. (intraoperative adj3 monitor\*).tw.
70. (perfusion adj3 angio\*).tw.
71. Ankle Brachial Index/
72. Arterial Pressure/
73. ankle brachial.tw.
74. (ankle adj3 pressur\*).tw.
75. toe brachial.tw.
76. (toe adj3 pressur\*).tw.
77. ABI.tw.
78. TBI.tw.
79. Blood Gas Monitoring, Transcutaneous/
80. (transcutaneous adj2 oxygen pressur\*).tw.
81. tcpo2.tw.

82. Spectrophotometry, Infrared/ or Spectroscopy, Near-Infrared/
83. infrared spectro\*.tw.
84. correlation spectroscop\*.tw.
85. Pulse volume\*.tw.
86. PVR.tw.
87. Tomography, Optical Coherence/
88. (optic\* adj2 coheren\*).tw.
89. Laser-Doppler Flowmetry/
90. (laser adj2 doppler).tw.
91. (22 to 44, OR)
  
92. (12 AND 21 AND 45)

**Appendix 2:** Summary of excluded studies.

<b>Reason for Study Exclusion</b>	<b>Study</b>
No reported clinical outcome (26)	Cho 2014 <sup>19</sup> , Kobayashi 2015 <sup>20</sup> , De Smet 2000 <sup>21</sup> , Jacomella 2013 <sup>22</sup> , Hoffman 1990 <sup>7</sup> , Ticcinelli 2014 <sup>23</sup> , Laine 2000 <sup>24</sup> , Wagner 2003 <sup>25</sup> , Bouroz 1997 <sup>26</sup> , Garnet 2014 <sup>27</sup> , Reekers 2016 <sup>28</sup> , Rodt 2016 <sup>29</sup> , Kim 2017 <sup>30</sup> , Hinrichs 2017 <sup>31</sup> , Braun 2013 <sup>32</sup> , Abdul 2018 <sup>33</sup> , Li 2017 <sup>34</sup> , Allouche 1999 <sup>35</sup> , Wildgruber 2007 <sup>15</sup> , Martini 2014 <sup>36</sup> , Pardo 2015 <sup>37</sup> , Takayama 2016 <sup>38</sup> , Settembre 2017 <sup>39</sup> , Ruzsa 2018 <sup>17</sup> , Peltokangas 2018 <sup>40</sup> , Ikeoka 2018 <sup>41</sup>
No intraoperative physiologic assessment (26)	O'Mara 1981 <sup>42</sup> , Ray 1997 <sup>43</sup> , Alback 1998 <sup>44</sup> , Papoutsi 2013 <sup>45</sup> , Young 2016 <sup>46</sup> , Mustapha 2017 <sup>47</sup> , Hammad 2017 <sup>48</sup> , Reed 2017 <sup>49</sup> , Bischoff 2018 <sup>50</sup> , Faglia 2007 <sup>51</sup> , Staffa 2017 <sup>52</sup> , Amarteifio 2013 <sup>53</sup> , Salles 1989 <sup>54</sup> , West 2011 <sup>55</sup> , Grozinger 2013 <sup>56</sup> , Chen 2018 <sup>57</sup> , Hur 2016 <sup>58</sup> , Labropoulos 1997 <sup>59</sup> , Stalc 2002 <sup>25</sup> , Duerschmied 2010 <sup>60</sup> , Redlich 2011 <sup>61</sup> , Weber 2014 <sup>62</sup> , Rona 2017 <sup>63</sup> , Seinturier 2017 <sup>64</sup> , Patel 2018 <sup>18</sup> , Wilson 2018 <sup>65</sup>
Ineligible revascularization method (1)	Gehani 1992 <sup>66</sup>

**Appendix 3:** Institute for Health Economics Quality Appraisal Checklist for case series studies<sup>10 11</sup>.

<b>Criteria</b>	<b>Mironov 2019</b>
<b>Study Objective</b>	
Was the hypothesis /aim/objective of the study clearly stated?	Yes
<b>Study Population</b>	
Was the study conducted prospectively?	Yes
Were the cases collected in more than one centre?	No
Were patients recruited consecutively?	No
<b>Study Population</b>	
Were the characteristics of the patients included in the study described?	Yes
Were the eligibility criteria (i.e. inclusion and exclusion criteria) for entry into the study clearly stated?	Yes
Did patients enter the study at a similar point in the disease?	Yes
<b>Intervention and Co-Intervention</b>	
Was the intervention of interest clearly described?	Yes
Were additional interventions (co-interventions) clearly described?	Partial
<b>Outcome Measure</b>	
Were relevant outcome measures established a priori?	Unclear
Were outcome assessors blinded to the intervention that patients received?	No
Were the relevant outcomes measured using appropriate objective/subjective methods?	Partial
Were the relevant outcome measures made before and after the intervention?	Yes
<b>Statistical Analysis</b>	
Were the statistical tests used to assess the relevant outcomes appropriate?	Yes
<b>Results and Conclusions</b>	

Was follow-up long enough for important events and outcomes to occur?	Yes
Were losses to follow-up reported?	Yes
Did the study provided estimates of random variability in the data analysis of relevant outcomes?	Yes
Were the adverse events reported?	Partial
Were the conclusions of the study supported by results?	Yes
<b>Competing Interests</b>	
Were both competing interests and sources of support for the study reported?	Yes

**Appendix 4:** Newcastle-Ottawa Scale for the assessment of cohort studies<sup>9</sup>.

Criteria	Justification	Utsunomiya 2012
<b>Selection</b>		
Representativeness of the intervention cohort	Truly representative of the population	*
Selection of the non intervention cohort	Drawn from the same community as the intervention cohort	*
Ascertainment of intervention	Secure record	*
Demonstration that outcome of interest was not present at start of study	Yes	*
<b>Comparability</b>		
Comparability of cohorts on the basis of the design or analysis	No	
<b>Outcome</b>		
Assessment of outcome	No description	
Was follow up long enough for outcomes to occur	Yes; median follow-up 631 days	*
Adequacy of follow up of cohorts	Follow up rate < 80% (select an adequate %) and no description of those lost	

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## Chapter 4: Association between Hemodynamic Response and Reintervention following Endovascular Revascularization for Atherosclerotic Peripheral Vascular Disease

### **Chapter Overview**

**Chapter 4** addresses Objective 2: Association between Hemodynamic Response and Reintervention. The chapter contains the manuscript of a retrospective cohort study titled ‘Association Between Hemodynamic Response and Clinical Outcomes following Endovascular Revascularization for Atherosclerotic Peripheral Vascular Disease’. The article evaluates the association between perioperative anatomic or physiologic feedback mechanisms and subsequent postoperative clinical outcomes. Anatomic feedback is represented by the current standard of care of intraoperative angiogram, and physiologic feedback is represented by postoperative limb pressure measurements.

### **Manuscript Status**

This manuscript has been prepared for submission to the Journal of Interventional Radiology (JVIR).

### **Author Contributions**

Mark Rockley was involved in all stages of the project inception, study conduct, and preparation of the manuscript. Celine Sayed was involved in study conduct as a blinded observer and subsequently preparation of the manuscript. Prasad Jetty was involved in project inception and preparation of the manuscript. George Wells was involved in all stages of the project inception, study conduct, and preparation of the manuscript.

### **Related Thesis Appendices**

A letter of Institutional Approval from the Ottawa Hospital Research Ethics Board is attached in Appendix A.

# **Association Between Hemodynamic Response and Clinical Outcomes following Endovascular Revascularization for Atherosclerotic Peripheral Vascular Disease**

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## **Compliance with Ethical Standards:**

This study was not supported by any funding. The authors declare that they have no conflict of interest. Ethics approval was obtained by the local ethics board (OHSN-REB). For this type of study, formal informed consent is not required. For this type of study consent for publication is not required.

## **Abstract**

### **Purpose**

Current endovascular practice relies on feedback from intraoperative angiogram results rather than hemodynamics to make intraoperative decisions on the end-point of treatment. The objective of this study is to determine if the outpatient hemodynamic response following endovascular revascularization for atherosclerotic peripheral vascular disease is associated with clinical outcomes.

### **Methods**

We performed a retrospective cohort study of lower extremity endovascular revascularization procedures in Ottawa ON between 2012-2018. The change in outpatient ankle brachial index (ABI) and toe brachial index (TBI) before and after intervention were determined, and clinical outcomes including clinical status improvement, reintervention, and amputation were assessed by a blinded observer. Binary outcomes were handled with mixed effects logistic regression, and time-to-event outcomes assessed with Cox proportional hazards model with competing risk. All analyses clustered limbs by patient. Youden's method was used to determine the optimal threshold change in ankle and toe pressures to discriminate clinical outcomes.

### **Results**

In total, 183 limbs of 156 subjects were included for analysis, of which 48.6% suffered critical limb ischemia. Postoperatively, 51.4% of limbs clinically improved, 10.9% experienced a major adverse limb event (MALE), and 29.5% required reintervention, including 24.0% receiving treatment on an accessory lesion which was not addressed during the index procedure. Angiographic result of change in stenosis was correlated with hemodynamic result, however there was substantial variability (ABI  $p < 0.01$   $R^2 = 0.34$  and TBI  $p < 0.01$   $R^2 = 0.54$ ). In addition to intraoperative angiographic result, factors associated with poor hemodynamic response to treatment included chronic kidney disease ( $p < 0.01$ ). Adjusting for critical limb ischemia and vascular level of intervention, the angiographic and hemodynamic results were all significantly associated with both clinical improvement and MALE outcomes. However, the angiographic result was not significantly associated with freedom from reintervention (Adj HR 0.95 [95% CI 0.85-1.06]  $p = 0.38$  for intraoperative change in residual stenosis), while the hemodynamic results were strongly associated with freedom from reintervention (Adj HR = 0.62 [95% CI 0.50-0.78]  $p < 0.01$  and Adj HR = 0.56 [95% CI 0.48-0.66]  $p < 0.01$  for change in ABI and TBI respectively). A minimum increase in ABI = 0.09 and TBI = 0.12 were the ideal thresholds for determining reintervention.

### **Conclusions**

Although the intraoperative angiographic result was one of several factors associated with hemodynamic results, the angiographic result was not significantly associated with reintervention. Conversely, the hemodynamic response based on ABI or TBI was strongly associated with all clinical outcomes. This information suggests that the angiographic result alone may not be sufficient for determining the end-point of treatment. There could be an

opportunity to apply intraoperative hemodynamic assessment of limb perfusion in the operating room to guide operative decision making.

**Keywords**

Peripheral Vascular Disease, Vascular Surgery, Hemodynamic Measurement, Intraoperative Monitoring, Endovascular Therapy

## **Manuscript**

### **Association Between Hemodynamic Response and Reintervention following Endovascular Revascularization for Atherosclerotic Peripheral Vascular Disease**

#### **Introduction**

Interventional treatment of peripheral vascular disease (PVD) has doubled in the last decade(1). This increase is driven primarily by a threefold increase in endovascular procedures, while open bypass procedures have decreased by 42% during that time(1). Unfortunately, the success of endovascular revascularization remains limited. Failure of endovascular intervention can be defined anatomically by patency, functionally by clinical improvement and wound healing, or ultimately by limb salvage. Primary failure rate of endovascular procedures for PVD after one year ranges from 19% to 37%(2, 3), corresponding with reported one-year amputation rates between 12% to 31%(4).

There are several potential mechanisms for failure after endovascular revascularization. The initial treatment may not be possible due to inability to cross the lesion with the endovascular wire, which occurs in approximately 11% of critical limb ischemia procedures(5). After angioplasty, incomplete dilation of the artery resulting in residual stenosis may occur and is associated with clinical failure(6). Furthermore, concurrent disease processes such as infection, venous, and lymphatic disease may render an isolated arterial procedure insufficient to preserve the leg(7). Following the initial procedure, the treated arterial lesion may acutely occlude due to thrombosis or dissection, or restenosis secondary to intimal hyperplasia(8-10). These events may lead to target-lesion revascularization, which is reported in approximately 12.3% of cases after one year(11). However, atherosclerosis is typically a diffuse arterial disease that often affects multiple regions within the same leg, rather than a single lesion. Failure to address multilevel disease is another potential mechanism for failure of the initial procedure, and may require reintervention on the same leg that does not involve the initial target lesion, which occurs after approximately 35% of below-knee angioplasty(12).

When diffuse multi-level atherosclerotic disease is present, the end-point of treatment is unclear. Intraoperative feedback during endovascular procedures is typically entirely based on the anatomic result of the angiogram. Multi-level treatment during the initial procedure has been associated with reduced need for reintervention(13), and a randomized trial suggested that multiple tibial vessel intervention at the initial procedure is associated with improved wound healing(14). However, unnecessary interventions can result in iatrogenic injury such as arterial dissection and embolization, and some lesions are not amendable to exclusively endovascular treatment, and require a hybrid open and endovascular procedure(15). Beyond a small cohort study that retrospectively examined wound 'blush' of contrast during angiogram, there are no reports of intraoperative methods to assess physiologic blood flow that are associated with clinical outcomes(16). The significance of a specific lesion can be assessed using fractional flow reserve(17) or optical coherence tomography(18), but these lesion-specific methods have not been generalized to assessment of the whole leg perfusion.

While the evidence supporting intraoperative assessment of perfusion is limited, there are several postoperative methods to assess limb perfusion which have been associated with clinical outcomes. These include non-invasive blood pressure assessment(19), skin perfusion pressure(20), transcutaneous oxygen pressure(21), infrared thermography(22), indocyanine green fluorescence(23), and computed tomography or magnetic resonance perfusion(24, 25). Of these methods, non-invasive limb blood pressure is the most ubiquitous diagnostic tool and has repeatedly demonstrated a strong association with clinical outcomes. A postoperative increase in ankle pressure of at least 73mmHg and toe pressure of at least 1mmHg was associated with reduced major adverse limb events (MALE) (HR=0.51 and HR=0.15 respectively)(19). This was confirmed by Young et al who found an increase in toe-brachial index of 0.04 correlated with freedom from MALE (HR=0.32)(26), and Reed et al who found an increase in toe-brachial index of at least 0.21 was associated with wound healing (HR=1.57).(27)

Unfortunately, the current evidence does not address whether the lack of improvement in limb perfusion following revascularization is simply reflective of the nature and burden of PVD, or if this lack of improvement potentially demonstrates incomplete revascularization during the index surgery and an opportunity to further optimize perfusion. We hypothesize that subjects who do not experience robust increase in limb perfusion following revascularization are most likely to receive reinterventions, particularly on accessory vascular lesions that were not addressed during the index procedure. If a lack of postoperative hemodynamic response is indeed predictive of need for reintervention, intraoperative application of perfusion assessment may guide intraoperative decision making and reduce the need to repeat interventions in the future. This study seeks to describe the association between physiologic response and clinical outcomes. First, the study will investigate factors associated with hemodynamic outcomes in subjects undergoing endovascular revascularization for de-novo atherosclerotic peripheral vascular disease. Second, the study will assess the association between hemodynamic outcomes and long-term clinical outcomes.

## **Methods**

Ethics approval was obtained by the local ethics board (OHSN-REB). We performed a retrospective review of all subjects undergoing endovascular revascularization for lower extremity peripheral vascular disease by the Division of Vascular Surgery in Ottawa ON. To ensure complete data capture, we leveraged the status of this vascular service as the only vascular surgical service in the Champlain LHIN public health region, which serves 1.3 million people.

Eligible subjects were age 18 or older who underwent elective or semi-urgent endovascular procedures on the native iliac, femoral, popliteal, or tibial arteries for de-novo symptomatic atherosclerotic peripheral vascular disease between October 2012 and January 2018. The starting date of October 2012 represents the transition of the division of vascular surgery to a common billing system where procedures could be retrospectively identified. We completed data collection in January 2018 so that all subjects were followed until January 2019, to ensure a minimum follow-up opportunity of one year. Subjects were excluded if they required concurrent open surgery

requiring vascular clamping for any period of time, prior history of vascular surgery on the affected leg, required urgent intervention defined as symptoms lasting less than 14 days, or had treatment isolated to the non in-line flow vessels of the internal iliac or profunda femoral arteries. Peripheral vascular disease was defined as a baseline ankle-brachial index (ABI) of less than 0.9 or toe-brachial index (TBI) of less than 0.7, associated with consistent symptoms. Subjects must have a recorded preoperative and postoperative ankle or toe pressure measurement within one year of the procedure, and were excluded if they received an interval vascular reintervention prior to their first postoperative pressure assessment.

Baseline comorbidity and symptom status were ascertained through assessor-blinded chart review, and vascular anatomic features were ascertained through assessor-blinded evaluation of preoperative computed tomography angiograms and intraoperative pre-intervention angiogram. Anatomic features including the calcium score, runoff score and TASC classification were recorded as outlined by the Society for Vascular Surgery Reporting Standards(28).

Preoperative and postoperative limb pressures were defined as toe or ankle blood pressure, and were measured concurrently with the highest arm pressure to determine TBI or ABI. To be eligible for inclusion, a limb must have had the same of either TBI, ABI, or both assessed before and after surgery. These assessments were obtained by vascular sonographers in The Ottawa Hospital Vascular Diagnostic Center. Intraoperative anatomic outcomes were determined by assessor-blinded evaluation of pre-intervention and post-intervention angiogram. Adjunctive procedures to plain angioplasty such as drug-eluting balloon, stenting, thrombectomy and atherectomy were recorded. The degree of stenosis was determined by comparing the maximal degree of stenosis of a lesion, compared with the vessel width of a non-diseased segment.

Postoperative outcomes were collected through The Ottawa Hospital's Oacis electronic health record. Symptom driven re-interventions were detected and stratified by open and endovascular reinterventions, emergent reintervention, target limb reintervention, target vessel reintervention, and target lesion reintervention. Symptom-driven vascular interventions are any arterial intervention on the ipsilateral limb following the index procedure which was prompted by symptoms, rather than prophylactic procedures based on surveillance. Furthermore, accessory lesion reintervention was defined as a vascular reintervention procedure in the limb's target arterial path that did not address the lesions treated during the index procedure. Other outcomes include any clinical improvement as defined by the Rutherford's classification of peripheral vascular disease(29), minor amputation defined as amputation below the ankle joint, major amputation above the level of the ankle, and all-cause mortality. Major adverse limb events (MALE) is defined as a composite outcome of major amputation above the ankle or major reintervention in the form of thrombolysis, thrombectomy, or bypass as defined by the Society for Vascular Surgery Reporting Standards(28). All postoperative outcomes were performed by an independent blind observer.

The units of analysis are individual legs; subjects who contribute both legs to the study were treated as a cluster of two units. The univariate associations between angiographic result and hemodynamic outcomes were first assessed with simple linear regression. The associations between angiographic result and hemodynamic outcomes were then assessed with multivariate linear mixed models with random coefficients, using the Kenward-Rodger adjustment to degrees of freedom. Regression models accounted for clustering of two legs from the same subject using an unstructured covariance matrix. Variables that required inclusion in the multivariate models based on existing evidence and relevance to practitioners include critical limb ischemia, diabetes, presence of aortoiliac or femoropopliteal disease, tibial vessel runoff disease, level of intervention (iliac, femoropopliteal, and tibial), and angiographic result defined as absolute reduction in lesion stenosis. Inclusion of further variables was identified through forward selection.

We then analyzed the association between hemodynamic outcomes and clinical outcomes. Clinical improvement is a binary outcome and variables associated with clinical improvement was assessed with univariate and multivariate mixed effects logistic regression, clustering limbs by subject with an unstructured covariance matrix.

Reinterventions and MALE are time-to-event outcomes and were evaluated with univariate and multivariate Cox regression analysis incorporating a competing risk for mortality, and clustering limbs by subject with a robust sandwich estimate. Multivariate models were performed separately for ankle and toe assessments. All multivariate models adjusted for critical limb ischemia status and vascular level of intervention. Inclusion of further variables was identified through forward selection, limiting the number of included variables to prevent over-fitting. If intervention was performed on multiple levels, the residual stenosis was presented as a composite average of lesions.

Finally, ideal thresholds for change in ABI and TBI associated with clinical outcomes were identified using Youden's method to maximize sensitivity and specificity, and reported with corresponding positive and negative likelihood ratios.

## **Results**

In total, 183 limbs in 156 subjects were included in this study and followed for a median of 1.7 years (Figure 1). All subjects had at least one documented postoperative encounter. The baseline comorbidity and symptom status are presented in Table 1. Critical limb ischemia was the indication for treatment in 52% of limbs. The overall tibial runoff scores and Trans-Atlantic Inter-Society Consensus classification (TASC Score) for the aortoiliac, femoropopliteal, and tibial vascular levels and are summarized in Table 2. A TASC score of at least A in multiple levels was present in 112 (61.2%) of limbs, a TASC score of at least B in multiple levels was present in 53 (30.0%) limbs, and a TASC Score of at least C was present in 18 (9.8%) of limbs. Conversely, the index procedure involved multiple vascular anatomic levels in 18 (9.8%) limbs. The target lesion baseline and post-intervention anatomic characteristics are summarized in Table 3. Overall, the degree of target lesion stenosis improved from 82.1% to 11.3% after intervention.

### Hemodynamic Outcomes

Follow-up limb pressure measurements after surgery occurred at a mean of 44 days. Complete ankle and toe pressure measurements were available in 153 and 100 limbs respectively. All hemodynamic measures increased significantly postoperatively on univariate paired t-test comparison (Table 4).

The univariate association between the intraoperative change in lesion stenosis and change in outpatient ABI and TBI are demonstrated in Figure 2. The angiographic result was significantly correlated with outpatient change in both ABI and TBI, however there was significant unexplained variability (ABI  $p < 0.01$   $R^2 = 0.34$ , TBI  $p < 0.01$   $R^2 = 0.54$ ). Multivariate linear mixed models were then used to assess factors associated with change in ABI and TBI after surgery (Figures 3 and 4, Appendices 1 and 2 respectively). Chronic kidney disease and lesion calcium score added significant accuracy during forward selection and were included in the models. Omitted variables including smoking status, antiplatelet use, and anticoagulation use did not provide additional benefit to the models and were not included. As expected, the degree of stenosis reduction observed on the completion intraoperative angiogram was significantly and positively associated with change in both ABI and TBI ( $p < 0.01$  for both ABI and TBI). Conversely, factors that were significantly associated with limited hemodynamic response were presence of chronic kidney disease for both ABI and TBI ( $p < 0.01$ ) and increased runoff score for ABI ( $p = 0.04$ ). Evaluation of the residuals of the multivariate ABI and TBI models demonstrated a relatively constant variance without substantial heteroskedasticity (Appendices 3 and 4).

### Clinical Outcomes

Overall, 51.4% of limbs experienced clinical improvement of at least one category of the Rutherford's classification during follow-up (Figure 5, Table 5). 54 (29.5%) limbs required reintervention at a median of 332 days (SD=656), including 42 (23.0%) which were performed via endovascular means, and 44 (24.0%) accessory lesion reinterventions (Table 6). Ultimately 10 (5.5%) limbs required minor amputation and 12 (6.6%) limbs required major amputation at a median of 225 (SD=262) and 291 (SD=401) days respectively (Table 5). 20 (10.9%) limbs experienced the composite outcome of MALE and 10 (5.5%) patients died during the study period.

Univariate analysis was performed to assess factors associated with clinical improvement, non-target lesion endovascular reintervention, and MALE (Appendices 5 and 6). We then created multivariate models to assess the association between clinical outcomes and ABI, TBI, and the intraoperative angiographic result, adjusting for baseline critical limb ischemia and infrainguinal level of intervention (Figure 6, Appendices 7-9). The reduction of stenosis on angiogram, improvement in ABI, and improvement in TBI were significantly associated with clinical improvement and freedom from MALE. However, residual stenosis was not associated with reintervention (Adj HR=0.95 [95% CI 0.85-1.06]  $p = 0.38$ ), whereas increase in ABI and TBI were associated with reintervention (Adj HR=0.62 [95% CI 0.50-0.78]  $p < 0.01$  and Adj HR=0.56 [95% CI 0.48-0.66]  $p < 0.01$  respectively). Stenosis reduction remained unassociated with reinterventions when excluding reinterventions on index lesions, while change

in ABI and TBI remained strongly associated (Adj HR=0.60 [95% CI 0.45-0.79]  $p<0.01$  and Adj HR=0.55 [95% CI 0.47-0.64]  $p<0.01$  respectively).

The optimal thresholds to maximize sensitivity and specificity of limb pressure changes after intervention are presented in Table 7. Of note, the optimal ABI improvement threshold following revascularization to discriminate from future limb reintervention was 0.09 (Positive LR=2.92, Negative LR=0.12) and the optimal TBI threshold was 0.12 (Positive LR=3.60, Negative LR=0.17).

## **Discussion**

This study identified a broad range of subjects undergoing endovascular management suffering from PVD. The subjects suffered from numerous comorbidities and approximately half of the included limbs demonstrated critical limb ischemia. While the overall ankle and toe pressures significantly increased following revascularization, half of the limbs did not experience clinical improvement, and a quarter required reintervention. This study reiterates that patients presenting with peripheral vascular disease are a frail cohort with challenging treatment options.

However, the clinical failure rates demonstrated in this study are comparable to previous reports. The reintervention rate of 29.5% in this study is similar to the 28% reintervention rate in the endovascular arm of the BASIL randomized trial, and our clinical improvement rate of 51.4% is comparable to the unassisted clinical success rate of 49.5% in the BASIL endovascular arm(30). While advancements such as drug-eluting technology have resulted in improved outcomes in the last decade, the high failure rates have not been eliminated. In the IN.PACT SFA trial, the 5-year clinically-driven target vessel reintervention rate remained at 29.3% in the drug-eluting arm(31). The thresholds of limb pressure improvement identified by this study are also comparable to previous reports. Reed et al identified an ABI threshold of 0.23 and TBI threshold of 0.21 to discriminate postoperative wound healing(27).

The association between positive intraoperative anatomic results and improved symptoms is expected. The lack of association between reduction in stenosis and target limb reintervention may simply be a result of a threatened treated lesion, due to delayed vessel recoil or early postoperative thrombosis. These factors wouldn't be observed on the immediate post-intervention angiogram, but would potentially be apparent at the time of postoperative hemodynamic assessment. However, when we excluded reinterventions on the initially treated lesions, the pattern remained. Reinterventions on these accessory lesions are not expected to be associated with treatment of the index lesion. Instead, it is insightful that the lack of hemodynamic improvement remained strongly associated with accessory lesion reintervention. This suggests that hemodynamic assessment could identify subjects who may be incompletely revascularized during the index procedure. If this feedback was known at the time of the procedure, perhaps this information could guide the operator to make more informed decisions about further treatment of ambiguous remaining lesions.

While the use of reintervention as an outcome potentially introduces treatment selection bias, clinically-driven reintervention remains an important indicator of clinically significant disease that is amendable to revascularization. Furthermore, although the outcome of reintervention can be prone to treatment selection bias, the consistent results of other objective outcomes support the reintervention findings. Beyond the burden of repeat reintervention and potential amputation, subjects who do not demonstrate increase in limb pressure following revascularization have demonstrated worse quality of life measures(32). These results suggest that there is a potential opportunity to identify and address subjects prone to require reintervention soon after the index procedure, without waiting to determine whether persistent clinical symptoms necessitate reintervention.

This study identified a reduced hemodynamic response to treatment in subjects with chronic kidney disease and likely those with diseased tibial vessel runoff. While these factors are known to affect the accuracy of hemodynamic assessment particularly at the level of the ankle(33), patients with chronic kidney disease(34), poor tibial vascular runoff(35, 36), and higher burden of arterial calcium(37) are known to have relatively poor clinical outcomes following endovascular procedures for peripheral vascular disease. Therefore, our results suggest a pathway through which these factors result in poor initial hemodynamic results and resulting poor outcomes. In patients predisposed to small vessel disease such as chronic kidney disease, the distribution of disease affects tibial vessels more often than iliac vessels, but most significantly affects microvasculature that is not amendable to current endovascular technology (38). When tibial vessel lesions are amendable to treatment, the clinical outcomes of isolated treatment of tibial vessels are inferior to multilevel treatment(39). The physiologic response of tibial vessel spasm is significantly different than large vessels, and disease in these vessels likely impacts the success of interventions on tibial vessel disease(40). While there are many challenges to revascularization of patients with tibial and microvascular disease, perhaps there is an opportunity for physiologic feedback to guide calculated more aggressive revascularization strategies, particularly by ensuring adequate inflow from large vessels.

Conversely, current endovascular treatment is not durable and/or possible in all vascular disease. Disease may not be ideal for endovascular treatment due to flexion points(41) or long chronically occluded lesions(42), and aggressive treatment of small vessels has a propensity for complications(43). Furthermore, there is potential for error in hemodynamic assessment, particularly the ABI in calcified or distal disease(44). Therefore, the use of hemodynamic assessment to determine the physiologic effect of revascularization should not dictate surgical decision making. Instead, it could assist in patient selection for more aggressive treatment. Alternatively, a positive early hemodynamic result may avoid further planned interventions.

This study benefits from the Ottawa vascular surgical division's status as the only vascular surgical service in the public health region, which maximizes follow-up of the study participants. Detailed review of all operative and follow-up procedures allowed us to discriminate between target lesion and accessory lesion reintervention, which has not previously been explored. Limitations of this study include risk of selection bias which potentially excluded subjects who required an interval procedure such as amputation prior to a surveillance pressure assessment. The low

number of events limits the inclusion of all variables in the multivariate models. There is a potential for performance bias; a poor hemodynamic response may have prompted reintervention. However, this performance bias would be less likely to impact other measures such as clinical improvement and major amputations. These retrospective results need to be confirmed with prospective data with immediate pressure assessment to ensure broad generalizability.

In conclusion, patients presenting with diffuse multilevel disease are common, and subsequent reinterventions after the index procedure often occur on lesions not addressed by the index procedure. The anatomic result of endovascular revascularization for peripheral vascular disease is one of several factors associated with the resulting hemodynamic result of treatment. Both anatomic and hemodynamic results are associated with clinically relevant outcomes such as symptom improvement and major adverse limb events, however only hemodynamic results are associated with reintervention. This information suggests that the angiographic result alone may not be sufficient for determining the end-point of treatment. There may be an opportunity to apply hemodynamic assessment of limb perfusion in the operating room to guide intraoperative decision making, to potentially reduce the need for reintervention and the associated morbidity.

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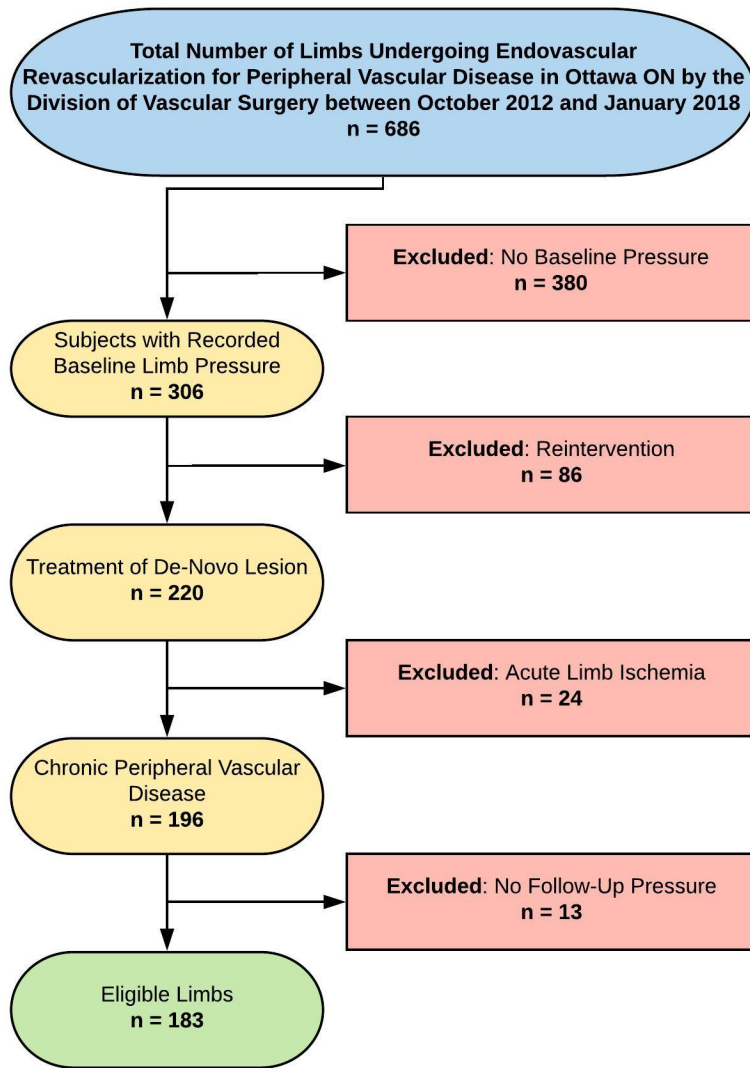
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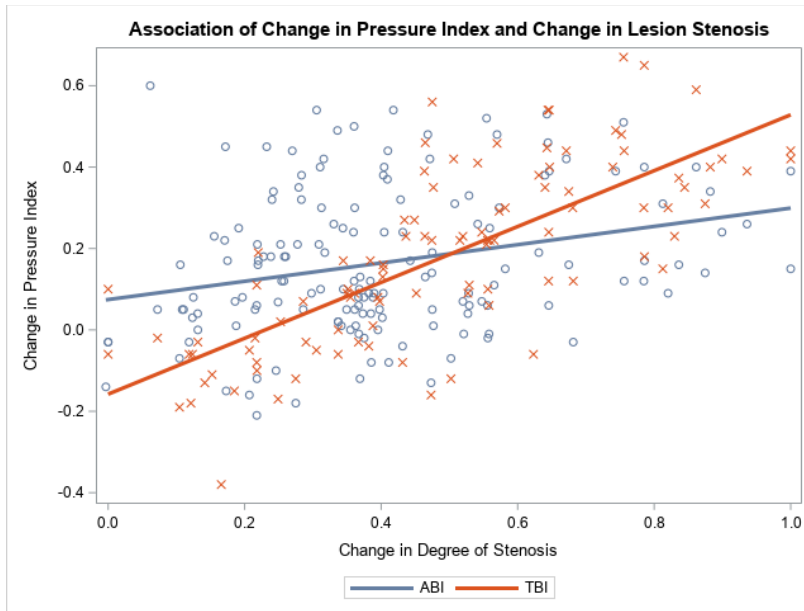
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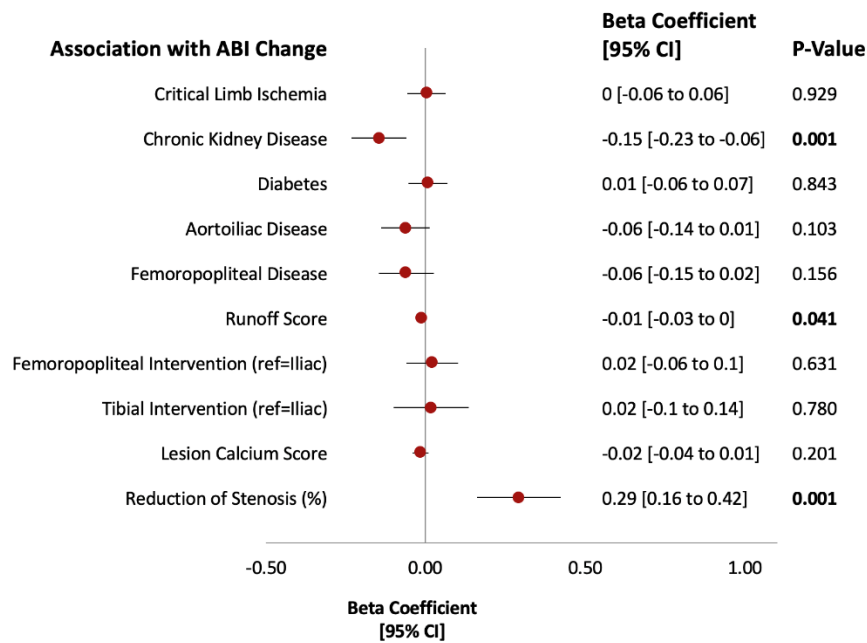
**Figures**



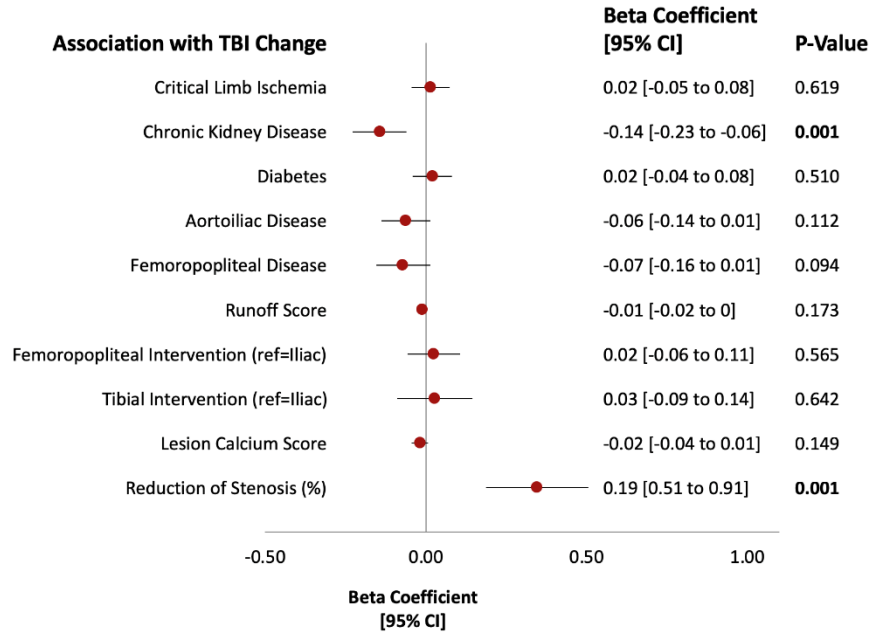
**Figure 1:** Cohort selection and reasons for exclusion.



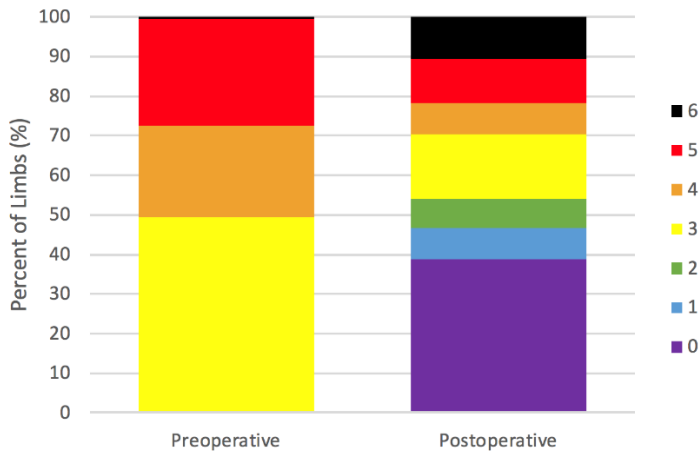
**Figure 2:** Univariate association between intraoperative change in degree of lesion stenosis and resulting outpatient change in ABI and TBI pressure indices. ABI  $p < 0.01$   $R^2 = 0.34$ , TBI  $p < 0.01$   $R^2 = 0.54$ .



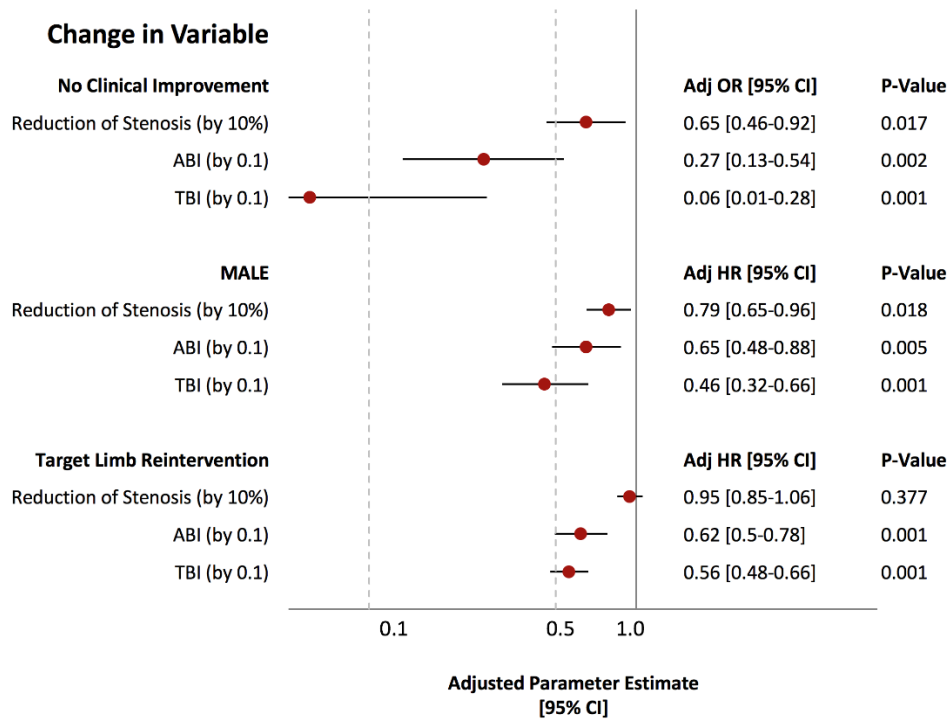
**Figure 3:** Multivariate associations between baseline and intraoperative anatomic factors, and the resulting outpatient change in ABI pressure index. Aortoiliac Disease and Femoropopliteal Disease refer to the presence of disease as defined by TASC score greater than 0. Femoropopliteal and tibial refer to the vascular level of intervention.



**Figure 4:** Multivariate associations between baseline and intraoperative anatomic factors, and the resulting outpatient change in TBI pressure index. Aortoiliac Disease and Femoropopliteal Disease refer to the presence of disease as defined by TASC score greater than 0. Femoropopliteal and tibial refer to the vascular level of intervention.



**Figure 5:** Distribution of clinical status by Rutherford category in preoperative and postoperative states.



**Figure 6:** Summary of association between anatomic or hemodynamic results and clinical outcomes. All estimates are adjusted for baseline critical limb ischemia and level of intervention.

## Tables

	Value (%)
Age (Years)	67.2
Male	104 (66.7%)
Current Smoker	69 (44.2%)
Former Smoker	71 (45.5%)
Diabetes	66 (42.3%)
HTN	111 (71.2%)
DLP	118 (75.6%)
Antiplatelet	114 (73.1%)
Anticoagulant	10 (6.4%)
Statin	111 (71.2%)
COPD	21 (13.5%)
CAD	69 (44.2%)
CVA	21 (13.5%)
CKD	30 (19.2%)
Dialysis	5 (3.2%)
Critical Limb Ischemia	89 (48.6%)
<b>Rutherford Classification</b>	
3	94 (51.4%)
4	42 (23.0%)
5	45 (24.6%)
6	2 (1.1%)

**Table 1:** Baseline demographic, comorbidity, and symptom severity characteristics of study participants.

	Total	Aortoiliac	Femoropopliteal	Tibial
<b>Number</b>	183	88	97	16
<b>Aortoiliac TASC</b>				
No Disease	78 (43%)	0 (0%)	70 (72%)	15 (94%)
A	48 (26%)	31 (35%)	23 (24%)	1 (6%)
B	45 (25%)	44 (50%)	4 (4%)	0 (0%)
C	11 (6%)	12 (14%)	0 (0%)	0 (0%)
D	1 (1%)	1 (1%)	0 (0%)	0 (0%)
<b>Femoropopliteal TASC</b>				
No Disease	45 (25%)	39 (44%)	0 (0%)	6 (38%)
A	46 (25%)	15 (17%)	33 (34%)	3 (19%)
B	47 (26%)	12 (14%)	40 (41%)	4 (25%)
C	25 (14%)	10 (11%)	15 (16%)	2 (13%)
D	20 (11%)	12 (14%)	9 (9%)	1 (6%)
<b>Tibial TASC</b>				
No Disease	94 (51%)	59 (67%)	40 (41%)	0 (0%)
A	41 (22%)	17 (19%)	25 (26%)	1 (6%)
B	27 (15%)	8 (9%)	18 (19%)	5 (31%)
C	15 (8%)	3 (3%)	9 (9%)	6 (38%)
D	6 (3%)	1 (1%)	5 (5%)	4 (25%)
<b>Tibial Runoff Score [SD]</b>	3.36 [2.78]	2.42 [2.07]	3.93 [2.95]	7.81 [2.67]

**Table 2:** Anatomic severity of disease overall, and stratified by level of intervention.

	Total	Aortoiliac	Femoropopliteal	Tibial
<b>Baseline Lesion Characteristics</b>				
Length in cm [SD]	7.24 [7.97]	3.88 [4.67]	10.8 [9.4]	10.9 [8.5]
Chronic Total Occlusion	72 (39.3%)	20 (22.7%)	51 (52.6%)	12 (75%)
Calcium Score [SD]	1.50 [1.08]	1.70 [1.08]	1.26 [1.02]	1.25 [1.18]
Severity of Stenosis % [SD]	82.1 [20.4]	76.2 [21.0]	86.5 [18.9]	90.0 [18.3]
<b>Intervention Characteristics</b>				
Plain Angioplasty	58 (31.7%)	13 (16.5%)	30 (34.1%)	15 (93.8%)
Bare Metal Stent	120 (65.6%)	66 (83.5%)	53 (60.2%)	1 (6.3%)
Drug-Eluting Balloon	5 (2.7%)	0 (0%)	5 (5.7%)	0 (0%)
Residual Stenosis % [SD]	11.3 [17.0]	7.56 [12.3]	13.8 [19.8]	15.0 [12.1]

**Table 3:** Baseline and intraoperative characteristics of treated lesions.

	Preoperative Mean [SD]	Postoperative Mean [SD]	p-value
<b>Ankle Pressure: n=153 limbs</b>			
Overall Ankle Pressure (mmHg)	93 [27]	118 [37]	<0.001
Claudication	99 [23]	128 [32]	<0.001
Critical Limb Ischemia	85 [30]	105 [40]	<0.001
<b>Overall ABI</b>			
Overall ABI	0.64 [0.18]	0.80 [0.24]	<0.001
Claudication	0.69 [0.16]	0.87 [0.21]	<0.001
Critical Limb Ischemia	0.57 [0.18]	0.71 [0.24]	<0.001
<b>Toe Pressure: n=100 limbs</b>			
Overall Toe Pressure (mmHg)	55 [23]	73 [34]	<0.001
Claudication	60 [20]	81 [36]	<0.001
Critical Limb Ischemia	52 [24]	67 [32]	<0.001
<b>Overall TBI</b>			
Overall TBI	0.38 [0.15]	0.49 [0.22]	<0.001
Claudication	0.42 [0.14]	0.54 [0.23]	<0.001
Critical Limb Ischemia	0.36 [0.15]	0.46 [0.20]	<0.001

**Table 4:** Hemodynamic assessments, stratified by baseline symptom status. P-values reflect the result of univariate paired t-test.

	Clinical Improvement	Amputation		MALE	Mortality
		Minor	Major		
<b>Overall</b>	94 (51.4%)	10 (5.5%)	12 (6.6%)	20 (10.9%)	10 (5.5%)
<b>Baseline Status</b>					
Claudication	57 (60.6%)	1 (1.1%)	0 (0.0%)	5 (5.3%)	5 (5.3%)
Critical Limb Ischemia	37 (41.6%)	9 (10.1%)	12 (13.5%)	15 (16.9%)	5 (5.6%)
<b>Level of Intervention</b>					
Aortoiliac	53 (60.2%)	2 (2.3%)	2 (2.3%)	5 (5.7%)	5 (5.7%)
Femoropopliteal	43 (44.3%)	7 (7.2%)	9 (9.3%)	15 (15.5%)	6 (6.2%)
Tibial	7 (43.8%)	4 (25.0%)	4 (25.0%)	4 (25.0%)	0 (0.0%)

**Table 5:** Clinical outcomes. Clinical improvement is defined by an increase of at least one Rutherford's category.

	<b>Target Lesion</b>	<b>Accessory Lesion</b>	<b>Target Vessel</b>	<b>Target Limb</b>
<b>Overall</b>	17 (9.3%)	44 (24.0%)	29 (15.9%)	54 (29.5%)
<b>Method of Reintervention</b>				
<b>Endovascular</b>	10 (5.5%)	39 (21.3%)	21 (11.5%)	42 (23.0%)
<b>Open</b>	7 (3.8%)	5 (2.7%)	8 (4.4%)	12 (6.6%)
<b>Mean Years Until Reintervention [SD]</b>	1.50 [2.35]	1.24 [1.42]	1.38 [1.87]	1.39 [1.80]
<b>Baseline Status</b>				
<b>Claudication</b>	12 (12.8%)	18 (19.2%)	18 (19.2%)	26 (27.7%)
<b>Critical Limb Ischemia</b>	5 (5.6%)	26 (29.2%)	11 (12.4%)	28 (31.5%)
<b>Level of Index Intervention</b>				
<b>Aortoiliac</b>	6 (6.8%)	18 (20.5%)	11 (12.5%)	21 (23.9%)
<b>Femoropopliteal</b>	12 (12.4%)	26 (26.8%)	19 (19.6%)	33 (34.0%)
<b>Tibial</b>	0 (0.0%)	4 (25.0%)	1 (6.3%)	4 (25.0%)

**Table 6:** Reinterventions on limbs based on target lesions, target vessel, and target limb. Accessory lesion reinterventions are any target limb reintervention excluding procedures that were performed on the index target lesion.

	<b>Clinical Improvement (Positive LR, Negative LR)</b>	<b>MALE (Positive LR, Negative LR)</b>	<b>Target Limb Reintervention (Positive LR, Negative LR)</b>
<b>ABI</b>	0.12 (5.27, 0.23)	0.08 (2.21, 0.33)	0.09 (2.92, 0.27)
<b>TBI</b>	0.16 (10.0, 0.04)	0.19 (2.39, 0.20)	0.12 (3.60, 0.17)

**Table 7:** Optimal thresholds for change in ankle and toe pressure measurements to discriminate from the outcomes of clinical improvement, MALE, and accessory lesion reintervention.

## Appendices

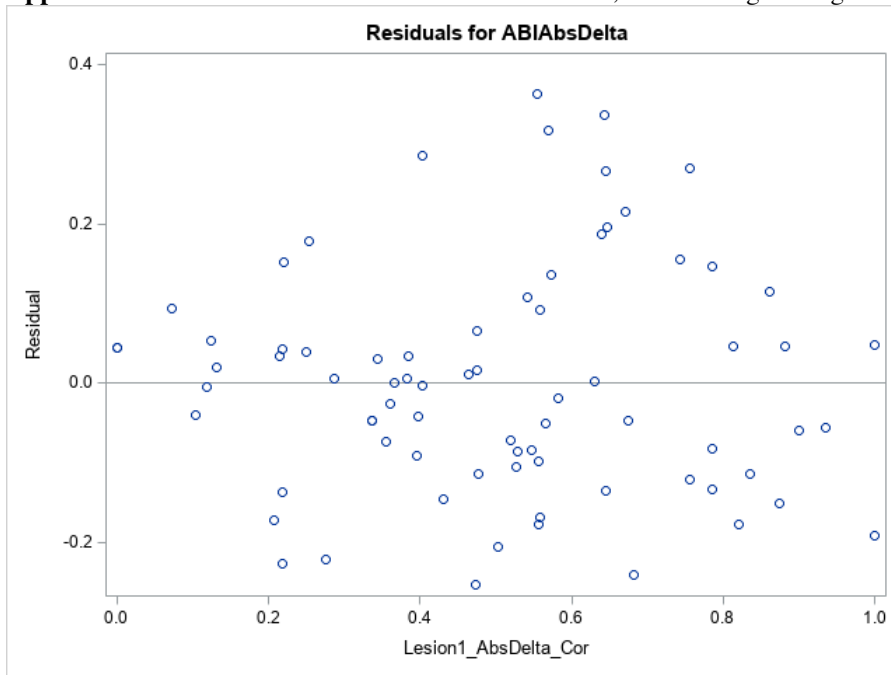
**Appendix 1:** ABI Linear Mixed Model. This model evaluates the association between the change in ABI (pre-operative to post-operative) and baseline and intraoperative anatomic factors. Aortoiliac Disease and Femoropopliteal Disease refer to the presence of disease as defined by TASC score greater than 0. Femoropopliteal and tibial refer to the vascular level of intervention.

Effect	Estimate	Standard Error	P Value	95% Upper CI	95% Lower CI
<b>Intercept</b>	0.023	0.079	0.768	-0.133	0.179
<b>Critical Limb Ischemia</b>	0.00273	0.03049	0.9288	-0.05754	0.063
<b>CKD</b>	-0.1459	0.04325	0.001	-0.2316	-0.06015
<b>Diabetes</b>	0.006175	0.031	0.8425	-0.05538	0.06773
<b>Aortoiliac Disease</b>	-0.06359	0.03877	0.1031	-0.1402	0.01303
<b>Femoropopliteal Disease</b>	-0.06121	0.04287	0.1563	-0.1462	0.02379
<b>Runoff Score</b>	-0.01417	0.006866	0.0408	-0.02775	-0.0006
<b>Femoropopliteal (ref=Iliac)</b>	0.02014	0.0418	0.6307	-0.06249	0.1028
<b>Tibial (ref=Iliac)</b>	0.01681	0.05998	0.7796	-0.1018	0.1354
<b>Lesion Calcium Score</b>	-0.01679	0.01305	0.2005	-0.04262	0.009028
<b>Reduction of Stenosis (%)</b>	0.291	0.06718	0.001	0.1593272	0.4226728

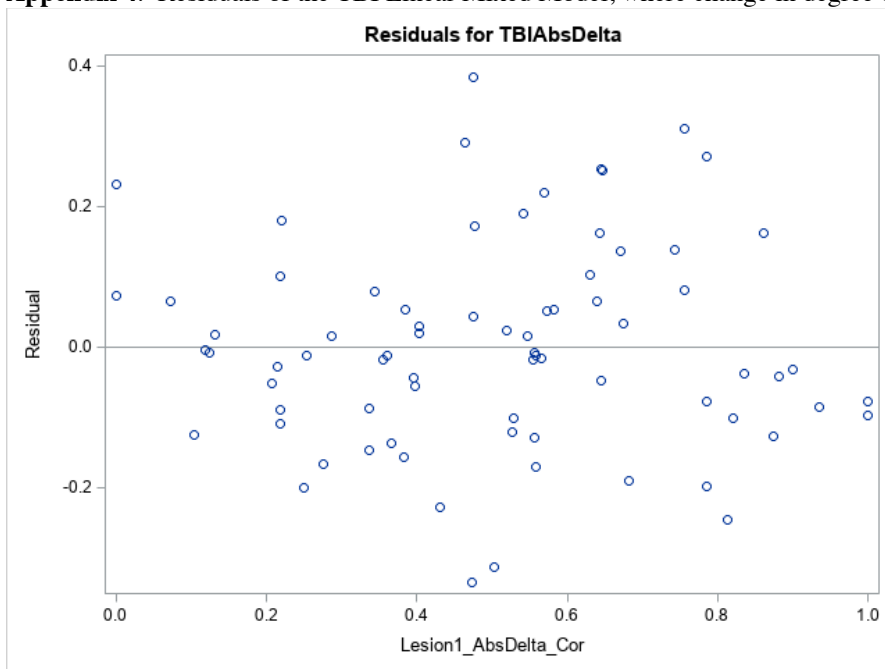
**Appendix 2:** TBI Linear Mixed Model. This model evaluates the association between the change in TBI (pre-operative to post-operative) and baseline and intraoperative anatomic factors. Aortoiliac Disease and Femoropopliteal Disease refer to the presence of disease as defined by TASC score greater than 0. Femoropopliteal and tibial refer to the vascular level of intervention.

Effect	Estimate	Standard Error	P Value	95% Upper CI	95% Lower CI
<b>Intercept</b>	0.019	0.082	0.819	-0.143	0.180
<b>Critical Limb Ischemia</b>	0.01522	0.03051	0.6187	-0.04511	0.07555
<b>CKD</b>	-0.1441	0.04258	0.001	-0.2285	-0.05969
<b>Diabetes</b>	0.02051	0.03101	0.51	-0.04107	0.08209
<b>Aortoiliac Disease</b>	-0.06127	0.03826	0.1115	-0.1369	0.01436
<b>Femoropopliteal Disease</b>	-0.07143	0.04222	0.0937	-0.1552	0.01229
<b>Runoff Score</b>	-0.00975	0.007122	0.1733	-0.02383	0.004335
<b>Femoropopliteal (ref=Iliac)</b>	0.02391	0.04141	0.5645	-0.05794	0.1058
<b>Tibial (ref=Iliac)</b>	0.02754	0.05905	0.6417	-0.08922	0.1443
<b>Lesion Calcium Score</b>	-0.01867	0.01288	0.1494	-0.04415	0.006804
<b>Reduction of Stenosis (%)</b>	0.3468	0.08099	0.001	0.1880596	0.5055404

**Appendix 3:** Residuals of the ABI Linear Mixed Model, where change in degree of lesion stenosis is on the x axis.



**Appendix 4:** Residuals of the TBI Linear Mixed Model, where change in degree of lesion stenosis is on the x axis.



**Appendix 5:** Summary of univariate analyses of the associations between baseline factors and clinical outcomes including clinical improvement, MALE, and target limb reintervention.

Variable	No Clinical Improvement		Major Adverse Limb Events		Target Limb Reintervention	
	OR [95% CI]	p-value	HR [95% CI]	p-value	HR [95% CI]	p-value
<b>Baseline Comorbidities</b>						
Age	0.985 [0.943-1.029]	0.491	0.946 [0.893-1.003]	0.062	0.995 [0.95-1.042]	0.817
Male	0.907 [0.441-1.864]	0.784	1.254 [0.435-3.614]	0.675	0.964 [0.49-1.894]	0.915
Current Smoker	0.828 [0.389-1.761]	0.615	2.097 [0.822-5.349]	0.121	1.099 [0.576-2.097]	0.775
Ex-Smoker	0.742 [0.356-1.548]	0.417	0.356 [0.127-1.002]	0.051	0.634 [0.333-1.21]	0.167
Diabetes	1.474 [0.701-3.098]	0.297	1.402 [0.566-3.473]	0.465	0.784 [0.411-1.495]	0.460
Hypertension	1.496 [0.629-3.557]	0.353	0.878 [0.321-2.404]	0.801	1.308 [0.6-2.85]	0.500
Dyslipidemia	0.559 [0.247-1.263]	0.157	0.738 [0.281-1.934]	0.536	0.716 [0.372-1.377]	0.317
Antiplatelet	0.481 [0.194-1.191]	0.110	0.395 [0.157-0.994]	0.049	0.819 [0.424-1.579]	0.550
Anticoagulant	0.681 [0.139-3.342]	0.627	0.933 [0.147-5.934]	0.942	0.487 [0.06-3.949]	0.501
Statin	0.691 [0.313-1.527]	0.351	0.89 [0.339-2.333]	0.812	0.89 [0.465-1.701]	0.724
COPD	1.08 [0.358-3.254]	0.889	0.854 [0.198-3.683]	0.832	1.787 [0.718-4.451]	0.212
Coronary Artery Disease	1.047 [0.494-2.22]	0.902	0.532 [0.199-1.419]	0.207	0.886 [0.469-1.673]	0.709
Cerebrovascular Disease	2.484 [0.817-7.559]	0.106	0.781 [0.179-3.411]	0.742	1.317 [0.484-3.579]	0.590
Chronic Kidney Disease	3.898 [1.655-9.18]	0.003	1.66 [0.632-4.361]	0.304	1.004 [0.48-2.1]	0.991
Dialysis	1.843 [0.2-16.955]	0.580	1.541 [0.23-10.306]	0.656	0.57 [0.098-3.308]	0.531
Critical Limb Ischemia	1.742 [0.849-3.572]	0.126	2.976 [1.088-8.142]	0.034	1.469 [0.792-2.725]	0.222
Tissue Loss	1.775 [0.676-4.661]	0.229	2.658 [1.112-6.352]	0.028	1.419 [0.767-2.623]	0.265
Rutherford's 4 (ref=3)	1.271 [0.528-3.059]	0.583	2.483 [0.7-8.804]	0.159	1.303 [0.612-2.775]	0.493
Rutherford's 5 (ref=3)	2.18 [0.89-5.342]	0.086	3.799 [1.155-12.49]	0.028	1.428 [0.698-2.923]	0.329
Rutherford's 6 (ref=3)	1.249 [0.046-33.744]	0.892	18.067 [1.98-164.861]	0.010	6.143 [0.562-67.119]	0.137

**Appendix 6:** Summary of univariate analyses of the associations between vascular anatomic or hemodynamic factors and clinical outcomes including clinical improvement, MALE, and target limb reintervention.

Variable	No Clinical Improvement		Major Adverse Limb Events		Target Limb Reintervention	
	OR [95% CI]	p-value	HR [95% CI]	p-value	HR [95% CI]	p-value
<b>Baseline Anatomic</b>						
TASC Aortoiliac						
A	2.106 [0.408-10.886]	0.351	4.059 [0.925-17.857]	0.063	0.733 [0.332-1.614]	0.440
B	1.388 [0.324-5.939]	0.639	1.841 [0.493-6.897]	0.364	1.002 [0.437-2.296]	0.996
C	4.721 [0.234-95.279]	0.290	3.698 [1.105-12.74]	0.031	1.053 [0.383-2.894]	0.921
D						
TASC Femoropopliteal						
A	1.961 [0.43-8.942]	0.361	2.207 [0.428-11.398]	0.3444	1.808 [0.495-6.613]	0.371
B	3.246 [0.542-19.442]	0.182	3.235 [0.666-15.701]	0.1453	2.248 [0.714-7.081]	0.166
C	8.051 [0.747-86.719]	0.081	4.782 [0.954-23.963]	0.057	8.591 [2.883-25.596]	0.000
D	13.783 [0.714-266.16]	0.079	1.03 [0.102-10.44]	0.979	3.705 [1.1-12.476]	0.035
Tibial Runoff Score	1.268 [1.055-1.525]	0.013	1.107 [0.964-1.271]	0.149	1.107 [1.006-1.218]	0.036
<b>Baseline Hemodynamic</b>						
Ankle Pressure	0.986 [0.97-1.001]	0.070	0.976 [0.955-0.997]	0.027	0.987 [0.974-1.001]	0.059
Ankle Brachial Index (ABI)	0.109 [0.011-1.054]	0.055	0.096 [0.003-3.621]	0.205	0.088 [0.013-0.61]	0.014
Toe Pressure	0.998 [0.978-1.019]	0.834	0.997 [0.978-1.015]	0.724	0.987 [0.971-1.004]	0.126
Toe Brachial Index (TBI)	0.86 [0.034-21.425]	0.922	1.045 [0.054-20.27]	0.977	0.063 [0.005-0.83]	0.036
<b>Lesion of Intervention</b>						
Lesion Length (cm)	1.046 [0.998-1.097]	0.062	1.034 [0.995-1.074]	0.088	1.038 [1.005-1.071]	0.024
Degree of Stenosis (%)	1.002 [0.985-1.02]	0.776	0.992 [0.972-1.012]	0.413	1.019 [1.003-1.037]	0.024
Chronic Total Occlusion	0.785 [0.308-2.002]	0.594	0.899 [0.377-2.141]	0.809	1.649 [0.901-3.02]	0.105
Calcium Score	1.023 [0.729-1.437]	0.893	0.789 [0.497-1.252]	0.314	0.91 [0.672-1.232]	0.541
Infrainguinal	1.839 [0.683-4.951]	0.213	3.991 [1.204-13.227]	0.024	1.427 [0.735-2.771]	0.293
Femoropopliteal (Ref=Aortoiliac)	1.523 [0.585-3.968]	0.368	2.579 [0.963-6.906]	0.059	1.397 [0.745-2.621]	0.298
Tibial (Ref=Aortoiliac)	1.419 [0.329-6.119]	0.621	2.051 [0.661-6.365]	0.214	0.989 [0.329-2.972]	0.984
<b>Intraoperative</b>						
Reduction in Degree of Stenosis (%)	0.978 [0.96-0.996]	0.017	0.979 [0.96-0.998]	0.030	0.148 [0.054-0.407]	0.001
Residual Stenosis (%)	1.072 [1.02-1.127]	0.008	1.024 [1.003-1.045]	0.027	1.027 [1.014-1.039]	0.001
<b>Postoperative Hemodynamic</b>						
Increase in Ankle Pressure (by 10)	0.723 [0.602-0.869]	0.001	0.823 [0.683-0.993]	0.042	0.765 [0.647-0.9]	0.002
Increase of ABI (by 0.1)	0.41 [0.299-0.561]	0.001	0.622 [0.454-0.852]	0.003	0.584 [0.438-0.779]	0.001
Increase in Toe Pressure (by 10)	0.226 [0.115-0.445]	0.000	0.635 [0.507-0.794]	0.000	0.63 [0.548-0.724]	0.001
Increase of TBI (by 0.1)	0.053 [0.012-0.239]	0.001	0.536 [0.428-0.671]	0.001	0.566 [0.472-0.679]	0.001

**Appendix 7:** Mixed effects logistic regression parameter estimates for three models, modelling the association between clinical improvement and changes in anatomic or hemodynamic results, adjusting for critical limb ischemia status or intralingual level of intervention.

**Outcome = No Clinical Improvement**

<b>Reduction of Stenosis Model</b>	<b>Estimate</b>	<b>SE</b>	<b>DF</b>	<b>t Value</b>	<b>p</b>
Intercept	2.1798	1.0584	82	2.06	0.0426
Lesion Stenosis Reduction by 10%	-0.4276	0.1601	16	-2.67	0.0168
Critical Limb Ischemia	0.5424	0.526	16	1.03	0.3178
Infrainguinal Level	0.9127	0.5634	16	1.62	0.1248
<b>ABI Model</b>					
Intercept	0.9392	0.587	58	1.6	0.1151
ABI by 0.1	-1.3136	0.3208	13	-4.09	0.0023
Critical Limb Ischemia	-0.06346	0.6504	13	-0.1	0.9238
Infrainguinal Level	1.0975	0.661	13	1.66	0.1208
<b>TBI Model</b>					
Intercept	4.8131	1.6518	82	2.91	0.0046
TBI by 0.1	-2.8097	0.7185	16	-3.91	0.0012
Critical Limb Ischemia	-0.07547	0.9672	16	-0.08	0.9388
Infrainguinal Level	0.5743	1.0344	16	0.56	0.5864

**Appendix 8:** Cox proportional hazard regression parameter estimates for three models, modelling the association between major adverse limb events (MALE) and changes in anatomic or hemodynamic results, adjusting for critical limb ischemia status or intralingual level of intervention.

**Outcome = MALE**

<b>Reduction of Stenosis Model</b>	<b>DF</b>	<b>Parameter Estimate</b>	<b>SE</b>	<b>Chi-Square</b>	<b>p</b>
Lesion Stenosis Reduction by 10%	1	-0.23427	0.09899	5.6006	0.018
Critical Limb Ischemia	1	0.91358	0.51059	3.2014	0.0736
Infrainguinal Level	1	1.33915	0.65034	4.2402	0.0395
<b>ABI Model</b>					
ABI by 0.1	1	-0.42887	0.15178	7.9839	0.0047
Critical Limb Ischemia	1	1.27983	0.64189	3.9754	0.0462
Infrainguinal Level	1	1.58725	0.79751	3.9612	0.0466
<b>TBI Model</b>					
TBI by 0.1	1	-0.78221	0.18794	17.3224	<.0001
Critical Limb Ischemia	1	0.07108	0.56955	0.0156	0.9007
Infrainguinal Level	1	1.8163	0.76964	5.5692	0.0183

**Appendix 9:** Cox proportional hazard regression parameter estimates for three models, modelling the association between target limb reinterventions and changes in anatomic or hemodynamic results, adjusting for critical limb ischemia status or intralingual level of intervention.

**Outcome = Target Limb Reintervention**

<b>Reduction of Stenosis Model</b>	<b>DF</b>	<b>Parameter Estimate</b>	<b>SE</b>	<b>Chi-Square</b>	<b>p</b>
Lesion Stenosis Reduction by 10%	1	-0.0503	0.05691	0.7812	0.3768
Critical Limb Ischemia	1	-0.00524	0.2958	0.0003	0.9859
Infrainguinal Level	1	0.4321	0.32234	1.7969	0.1801
<b>ABI Model</b>					
ABI by 0.1	1	-0.47325	0.11663	16.4655	<.0001
Critical Limb Ischemia	1	-0.04829	0.32454	0.0221	0.8817
Infrainguinal Level	1	0.69836	0.31607	4.8819	0.0271
<b>TBI Model</b>					
TBI by 0.1	1	-0.57451	0.08275	48.1996	<.0001
Critical Limb Ischemia	1	-0.35407	0.37455	0.8936	0.3445
Infrainguinal Level	1	0.3868	0.42833	0.8155	0.3665

## Chapter 5: Association between Intraoperative Hemodynamic Measurement and Postoperative Outcomes

### **Chapter Overview**

Chapter 5 addresses Objective 3: Association between Hemodynamic Response and Reintervention. The chapter contains the protocol for a prospective study which has been published in the BMJ Open, and a manuscript of the completed study which has been prepared for submission to the Journal of Vascular Surgery. A letter of Institutional Approval from the Ottawa Hospital Research Ethics Board is attached in Appendix B.

### **Chapter Contents**

**Section 5.1** presents the published protocol manuscript for the *Intraoperative Simultaneous Limb Perfusion Monitoring (INSTANT) Study*.

**Section 5.2** presents the prepared manuscript of the *Intraoperative Simultaneous Limb Perfusion Monitoring (INSTANT) Study*.

## **Section 5.1: Protocol for Prospective Observational Study**

### **Section Overview**

**Section 5.1** presents protocol manuscript for a prospective study titled 'Protocol for a prospective observational diagnostic study: intraoperative simultaneous limb pressure monitoring (INSTANT) study'. This protocol outlines a prospective study that observes limb pressure measurements during surgery and the associated postoperative outcomes.

### **Manuscript Status**

This manuscript has been published in the BMJ Open journal, and the text is included in this thesis with the permission of the journal.

### **Author Contributions**

Mark Rockley was involved in all stages of the protocol inception and preparation of the protocol manuscript. Prasad Jetty was involved in the protocol inception and preparation of the manuscript. George Wells was involved in all stages of the protocol inception and preparation of the manuscript.

### **Related Thesis Appendices**

The published article is presented in Appendix D. We received permission from the BMJ Open journal to present the PDF of the complete manuscript in the thesis.

# Protocol for a Prospective Observational Diagnostic Study: Intraoperative Simultaneous Limb Pressure Monitoring (INSTANT) Study

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*Registration* This study has been registered on ClinicalTrials.gov (ID NCT03875846).

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## **ABSTRACT**

### **Introduction**

Peripheral Vascular Disease (PVD) is a condition caused by arterial blockages causing inadequate blood flow, resulting in pain and gangrene of the legs. Endovascular therapy such as angioplasty can be used to treat PVD, however the operator feedback during surgery is primarily anatomic based on the angiogram. Because physiologic blood perfusion can be difficult to determine based on anatomic images, we propose introducing physiologic measurements into the operating room. This study will investigate whether change in intraoperative monitoring of hemodynamic measurements such as the toe-brachial index during endovascular surgery for lower extremity atherosclerotic PVD is associated with clinical outcomes such as major adverse limb events (MALE).

### **Methods and Analysis**

This study will be a prospective, operator-blinded and blinded end-point adjudicated observational diagnostic cohort study. A total of 80 legs will be enrolled in the study. Ankle and toe blood pressures will be measured non-invasively at pre-determined timepoints before, during, and after surgery, and we will assess associations between changes in intraoperative pressure measurements and postoperative clinical and hemodynamic outcomes. The primary outcome will be MALE within one year, and secondary outcomes include follow-up pressure measurements, vessel patency, reintervention, clinical staging improvement, amputation, and death.

### **Ethics and Dissemination**

Regional hospital ethics approval has been granted (OHRI-REB, Protocol 20180656-01H). Upon completion of data analysis, the study will be submitted for presentation at international vascular surgical society meetings, in addition to submission for publication in publicly accessible medical journals.

**Registration**

This study has been registered on ClinicalTrials.gov (ID NCT03875846).

## **Article Summary**

### **STRENGTHS AND LIMITATIONS OF THIS STUDY**

- Novel application of intraoperative physiologic monitoring using ankle and toe blood pressure during revascularization procedures
- Prospective, operator-blinded and blinded end-point adjudicated
- Observational cohort study
- Resource intensive pressure measurement

## **MANUSCRIPT**

### **INTRODUCTION**

Peripheral vascular disease (PVD) is a condition caused by arterial blockages causing inadequate blood flow, resulting in pain and gangrene of the legs. The prevalence of PVD in the North American general population over 50 years of age is estimated at 17.4%, and is rising in association with the increasing prevalence of diabetes<sup>1</sup>. While bypass surgery is reserved for patients with severe forms of PVD, the minimally invasive options of angioplasty ('endovascular surgery') is emerging as the treatment of choice for most patients with PVD. The annual rate of endovascular peripheral vascular interventions in the USA Medicare population has risen to 419.6 per 100,000 Medicare beneficiaries<sup>2</sup>. Angioplasty is the foundational treatment of endovascular therapy, which may be augmented by treatments such as stenting.

Unfortunately, the two-year patency of balloon angioplasty for PVD has been poor, reported between 50 – 80%, depending on lesion location and characteristics<sup>3</sup>. Subsequently, the 1-year amputation rate despite endovascular revascularization has been reported as high as 32% in patients with lower leg critical limb ischemia<sup>4</sup>. This high failure rate has prompted investigation into the predictors of failure, and potential solutions to optimize the success rate of revascularization.

One of the most significant predictors of clinical success following endovascular surgery for PVD is the post-procedure Ankle-Brachial Index (ABI)<sup>5</sup>. This measurement is performed by applying a blood pressure cuff at the level of the lower leg ('Ankle Pressure') and the arm. The ABI is a

ratio of the blood pressure at the ankle when compared with the arm. Similarly, a smaller cuff around the great toe can determine the absolute Toe Pressure, which can also be used to calculate the Toe-Brachial Index (TBI). The change in ABI following endovascular surgery can be detected a day after the procedure, and remains stable throughout the month following the procedure<sup>6</sup>. While the ABI is commonly used for monitoring hemodynamic improvement after endovascular surgery, postoperative surveillance TBI has been demonstrated to have a significantly stronger correlation with clinical outcomes such as Major Adverse Limb Events (MALE)<sup>7</sup>. Major adverse limb events ('MALE') is defined as a composite outcome of clinically-driven target limb reintervention, and major amputation<sup>8</sup>. While the TBI is an important marker for postoperative outcomes, attempting these measurements during the procedure has never been reported.

Other post-operative markers of limb perfusion have also been investigated. Magnetic resonance arterial spin labelling correlates with postoperative ABI and clinical outcomes<sup>9</sup>. Furthermore, some authors have investigated markers of limb perfusion during surgery, finding correlation between post-operative ABI and intra-operative 2-dimensional perfusion angiography<sup>10</sup> and indocyanine green intra-arterial injection<sup>11</sup>. Other methods such as laser doppler<sup>12</sup>, near-infrared spectroscopy<sup>13 14</sup>, transcutaneous oxygen saturation<sup>15</sup>, and micro-oxygen sensors<sup>16</sup> have demonstrated delayed feedback of perfusion that would not be rapid enough to guide intraoperative decision making.

The potential utility of limb blood pressure to predict clinical outcomes after endovascular revascularization presents several opportunities. Measurement of limb blood pressure is relatively simple to perform intraoperatively, particularly during endovascular procedures. The intraoperative use of ankle or toe blood pressure measurement has never been described. Therefore, while limb blood pressure measurements may be significant predictors of outcomes, the current practice of waiting to measure the limb pressure after surgery may miss opportunities to guide intraoperative decision making.

Currently, the primary intraoperative feedback used to determine procedural success is the anatomic appearance of the angiogram upon completion of the procedure. While an angiogram may depict the improvement of focal arterial narrowing, it does not provide physiologic feedback to the operator. Small vessel disease or tandem lesions may instead be the primary culprit of the peripheral vascular disease, and would not be demonstrated adequately by the angiogram. Consequently, an anatomically significant lesion may not be hemodynamically significant, resulting in a falsely reassuring angiogram. Because limb pressure measurements encompass these variables that are not accounted for by angiogram, limb pressure measurement could be more predictive of procedural success than angiogram. This study investigates the diagnostic association between intraoperative non-invasive limb blood pressure measurement and postoperative outcomes. If applying limb blood pressure monitoring into the operating room is predictive of outcomes, the results of this study will guide further investigation into using instant blood pressure feedback to guide intraoperative decision making and ultimately improve the success of endovascular revascularization.

## **OBJECTIVES**

### **Primary Objective**

The primary objective of this investigation is to determine if the magnitude of change of intraoperative Toe-Brachial Index (TBI) during endovascular revascularization (pre-angioplasty and post-angioplasty) for atherosclerotic peripheral vascular disease is associated with freedom from Major Adverse Limb Events (MALE) within 1 year post-procedure.

Intraoperative TBI change is defined as the difference between the pre-intervention and post-intervention time point measurements, which are described in detail under the 'Data Collection' heading. MALE is defined as a composite outcome of major amputation above the ankle, major re-intervention in the form of catheter-directed thrombolysis, open bypass or thrombectomy<sup>17</sup>.

## **Secondary Objectives**

In addition to a the magnitude change in intraoperative TBI, we will also evaluate the association of the binary intraoperative perfusion marker change on symptom improvement, major and minor amputation, target lesion/vessel/limb reintervention, target vessel patency, and association between intraoperative and postoperative measurements.

Beyond analyzing TBI, we will analyze other intraoperative measures of change in limb perfusion including ABI, absolute toe pressures, and absolute ankle pressures. All measures of intraoperative changes perfusion will be calculated as the difference between the pre-intervention and post-intervention time point measurements. Ideal acceptable threshold improvements in intraoperative TBI and ABI will be determined using Youden's method, to potentially use as a clinical decision rule in further research. The study will also report feasibility measures including rate of enrollment and reported anticipated or unanticipated disruptions to patient flow during intraoperative data collection.

## **METHODS AND ANALYSIS**

### **Study Design**

This study will be a prospective observational cohort study. The surgical operators will be blinded to intraoperative pressure measurements. All radiographic and postoperative clinical end-points will be assessor blinded.

### **Setting**

Patients undergoing treatment by the Division of Vascular Surgery at The Ottawa Hospital, Civic Campus. All patients will be under the care of the Vascular Surgery Division, both inpatients and outpatients. All outpatient limb pressure measurements will have been performed at the Vascular Ultrasound Diagnostic Lab, and all endovascular procedures and intraoperative limb pressure measurements performed in the operating theatres of the Civic Campus. We will

leverage our status as the only vascular surgical service in the medical region (Champlain LHIN) to maximize capture of outcomes following the index procedure.

## **Study Population**

### *Inclusion Criteria*

- Patients undergoing elective or semi-urgent endovascular procedures on de-novo lesions of the aorta, iliac, femoral, popliteal, or tibial arteries
- Symptomatic, atherosclerotic Peripheral Vascular Disease
- Age 18 years old or greater
- Detectable toe pressure

### *Exclusion Criteria*

- Concurrent hybrid open procedure during endovascular revascularization requiring vascular clamping for any period of time, such as endarterectomy
- Prior open vascular surgery performed on the affected leg
- Emergent intervention for Acute Limb Ischemia, defined as symptoms lasting less than 14 days
- Non-femoral vascular access

### *Recruitment*

Recruitment for this study will be performed just after consent for the procedure is obtained, by notification of the attending vascular surgeon.

## **Variables**

### *Baseline Characteristics*

- Age
- Sex
- Smoking Status
- Diabetes
- Hypertension
- Dyslipidemia

- Antiplatelet Use
- Anticoagulant Use
- Statin Use
- Chronic Kidney Disease (eGFR < 60)
- Dialysis Dependence
- TASC (Trans-Atlantic Inter-Society Consensus) Classification<sup>18</sup>
- Rutherford's Classification of Peripheral Vascular Disease<sup>19</sup>
- WiFi Classification<sup>8</sup>

### *Preoperative Limb Pressures*

- Ankle Pressure
- Toe Pressure
- Brachial Pressure
- Ankle-Brachial Index
- Toe-Brachial Index

### *Procedural Characteristics*

- Vessel(s) of Intervention
- Anatomic Level (Iliac, Femoropopliteal, and Infrageniculate)
- Severity of Stenosis
  - <50%, 50 – 75%, or >75% Stenosis
  - Complete Occlusion
- Residual Stenosis
- Adjunctive Procedures
  - Drug-Eluting Balloon
  - Stenting
    - Balloon-Expandable
    - Self-Expanding
    - Bare-Metal
    - Covered
  - Thrombectomy

- Atherectomy

### *Intraoperative Perfusion Markers of Interest*

- Ankle Pressure
- Toe Pressure
- Brachial Pressure
- Ankle-Brachial Index
- Toe-Brachial Index

### **Primary Outcome**

The primary outcome is freedom from MALE (Major Adverse Limb Event) within 1 year post-intervention. MALE is defined as a composite outcome of major amputation above the ankle, major re-intervention in the form of catheter-directed thrombolysis, open bypass or thrombectomy.

### **Secondary Outcomes**

Note: All clinical outcomes are assessed within 1 year post-index procedure, and hemodynamic outcomes assessed at 1-3 months post-index procedure.

- Improvement in Rutherford's Classification of Peripheral Vascular Disease
- Amputation
  - Minor (Toe(s) or Foot to the Ankle)
  - Major (Above the Ankle)
- Minor Amputation (*Toe(s) or Foot*)
- Major Amputation (*Above the Ankle*)
- Target Limb Re-Intervention
  - Endovascular
  - Bypass
  - Thrombectomy
  - Thrombolysis
- Target Vessel Re-Intervention
- Target Lesion Re-Intervention

- Target Vessel Patency
  - Primary (*Absence of target vessel occlusion or restenosis >50%*)
  - Primary Assisted (*Patency requiring assistance of subsequent procedure to maintain patency of target vessel*)
  - Secondary (*Patency requiring assistance of subsequent procedure to restore patency of target vessel*)
- Mortality
- Amputation-Free Survival
- Correlation between immediate post-operative limb pressure and 1-3 month follow-up limb pressure measurement

### **Feasibility Outcomes**

- Enrollment
  - Enrollment rate
  - Consent rate for subjects approached for study participation
- Data Capture
  - Rate of complete intraoperative data capture of consenting subjects
  - Postoperative subject involvement retention rate
- Disruptions to Patient Flow
  - Total time of procedures
  - Reported unexpected disruptions

### **Sample Size**

Due to the nature of investigating a novel technique, there is limited established evidence to guide expected results for a sample size calculation. The most closely related published data is found in a subgroup analysis of the IN.PACT DEEP trial, which followed patients for 12 months after infrainguinal angioplasty<sup>7</sup>. In patients who experienced any improvement of TBI immediately post-operatively, this study identified a Hazard Ratio of 0.15 [95% CI 0.04-0.57] of Major Adverse Limb Events ('MALE') within one year, defined as major limb amputation above the level of the ankle, or major target lesion revascularization in the form of thrombolysis,

thrombectomy or bypass. The study also found a sampling distribution ratio of patients demonstrating an improvement in TBI to no improvement in TBI of 2.14. On survey of regional attending vascular surgeons to depend on an intraoperative monitoring system, a hazard ratio of 0.15 would be appropriate as a minimum to guide intraoperative decision making.

This study includes patients undergoing endovascular procedures for a spectrum of symptomatic PVD, including those with claudication and critical limb ischemia. The primary outcome of this study will be defined as MALE. The expected 1-year event rate of MALE is higher in subjects with Critical Limb Ischemia (20.5%<sup>7</sup>) versus subjects with Claudication (3.2%<sup>20</sup>). Based on a recent 10-year audit of endovascular procedures performed at the investigational center (The Ottawa Hospital, Civic Campus) the expected proportion of eligible subjects with Critical Limb Ischemia (vs. Claudication) is 0.625. Therefore, we will need to calculate an overall expected event rate based on the relative proportion of each disease severity, in addition to their respective event rates. This calculation can be seen in Table 1, and ultimately the overall expected event rate is 14%. The Division of Vascular Surgery at The Ottawa Hospital is the sole vascular surgical provider for the region, therefore the expected loss to follow-up is minimal and estimated at less than 5%. The anticipated rate of inclusion of bilateral legs of the same subject is less than 20%, and therefore the expected loss of analytic power due to robust sandwich estimate cluster modelling is minimal and will be accounted for in our inflation adjustment of 10%. In light of an alpha of 0.05, beta of 0.20, buffer for loss to follow-up and cluster modelling of 10%, sampling distribution of 2.14 : 1, Hazard Ratio of 0.15, a total of **80 legs** will be enrolled.

Variable	Value
Alpha	0.05
Power	0.80
Sampling Distribution	2.14 : 1
Overall Event Probability	0.140
<i>Critical Limb Ischemia</i>	<i>0.205</i>
<i>Proportion of Subjects with Critical Limb Ischemia</i>	<i>0.625</i>
<i>Claudication</i>	<i>0.032</i>
<i>Proportion of Subjects with Claudication</i>	<i>0.375</i>
<i>Calculation of Overall Event Probability</i>	<i>(0.205*0.625)+(0.032*0.375)</i>

Hazard Ratio	0.15
Inflation: Loss to Follow-Up, Cluster Analysis	10%
<b>Total Sample Size</b>	<b>80 Legs</b>

**Table 1:** Sample Size Calculation

### Planned Analyses

The unit of analysis will be individual legs; one subject may contribute two eligible legs to the study. Therefore, all analyses will account for clusters of legs to each subject. Survival analysis of the primary outcome (MALE) as a function of the magnitude of improvement of perioperative TBI will be performed with Cox Proportional Hazards, using robust sandwich estimate cluster modelling, competing risk adjustment, and adjusting for pre-operative Rutherford’s classification, anatomic level of disease, and discrepant baseline characteristics. An unadjusted univariate Log Rank Test will also be reported.

The following time-to-event secondary outcomes compared between those with positive limb pressure change and those without improvement or negative change will be analyzed using Cox Proportional Hazards with Generalized Estimating Equations for clustering, competing risk adjustment, and adjustments for pre-operative Rutherford’s classification and anatomic level of disease: major and minor amputation, re-intervention, target vessel patency, mortality, and amputation-free survival. An unadjusted univariate Log Rank Test will also be reported.

Logistic regression with Generalized Linear Mixed Model, clustering by patient and adjusted for pre-operative Rutherford’s classification and anatomic level of disease, will be used to analyze the binary outcome of any symptomatic improvement based on the post-operative Rutherford’s classification. An unadjusted univariate logistic regression will also be reported.

Using ROC curves developed by models correlating MALE based on intraoperative change in toe and ankle pressures, the ideal threshold will be identified using Youden’s Method. This new threshold will then be used to replicate the primary analysis with binary toe and ankle pressure thresholds.

The correlation between immediate post-operative toe and ankle pressure measurements and follow-up pressure measurements will be assessed using Pearson's coefficient, Intra-Class Correlation, and Bland-Altman Plots. We will repeat these correlation analyses when comparing pre-procedure and pre-intervention measurements, as well as a comparison of post-intervention and post-procedure measurements (Table 2). In addition, analysis of the variability in measurement of both preoperative and postoperative values will be performed. As these measurements are repeated three times during both of these timepoints, we will report both Standard Deviation and Standard Error of the Mean.

Planned subgroup analyses include stratification for the three vascular levels (iliac, femoropopliteal, and tibial), critical limb ischemia vs. claudication, stenting vs. angioplasty alone, and pre-operative TASC II (Trans-Atlantic Inter-Society Consensus) Classification.

Feasibility outcomes including enrollment, consent, intraoperative data capture, and postoperative retention rates will be reported as absolute values and fractions. Qualitative descriptions of reported unexpected disruptions to patient flow will be described. Total operative times will be presented alongside the allocated timeframe for the procedures. No statistical analysis are planned for feasibility outcomes.

### **Missing and Incomplete Data**

If no clinical contact is made with a subject following the index procedure, the subject will be considered lost to follow-up and will be excluded from analysis. Missing postoperative pressure measurements due to missed appointments will be addressed with Mixed Model Repeated Measures imputation. Missing postoperative pressure measurements due to amputation or mortality will be excluded from correlation analyses.

The primary outcome, MALE, is a composite outcome that accommodates potential intercurrent events such as reintervention and amputation, however it does not include mortality. In the case of mortality, this will be labelled as a competing risk and will be

accommodated by the survival analyses models. The secondary outcomes will use a Treatment Policy strategy, where the variable will be included regardless of intercurrent events. However, specific intercurrent events of amputation, mortality, or in certain outcomes intercurrent bypass surgery, will be included as competing risks in the survival analysis models.

## **STUDY ADMINISTRATION**

### **Feasibility and Study Duration**

Between the Division of Vascular Surgery and the Division of Radiology, approximately 6 lower extremity endovascular revascularization procedures per week are performed at the Civic Campus. Approximately half of these cases are expected to be eligible based on an audit of the prior year. With a target enrollment of 80 legs, enrollment could be achieved within 7 months if all cases are enrolled. The enrollment rate of eligible cases is expected to be moderate, given the non-invasive nature of this study. In total, 11 months have been allocated to study enrollment.

### **Data Sources**

Baseline and post-operative follow-up clinical data will be collected through vOACIS-PROD (version r7.3.0\_20130320). vOacis is the central electronic medical record system used by The Ottawa Hospital, and is where all vascular surgery clinical appointment and operative notes are documented. Perioperative data will be the only data collected in addition to standard medical care. This is the only data source that is a result of study member interaction with the study subjects.

### **Data Collection**

After enrollment into the trial, the study administrator will collect baseline data based on relevant notes in vOacis as described above. Only the Principal Investigator and Study Coordinator will have access to the password and Data Collection forms.

Perioperative data collection will occur on the day of surgery. An automated non-invasive blood pressure cuff (NIBP) will be placed around the patient's arm, and additional ankle and toe blood pressure cuffs will be placed around the patient's leg and great toe with a distal photoplethysmography recorder. Because only femoral vascular access will be considered in this study, the blood pressure cuffs below the knees will be separate from the operative field and will be covered by standard draping procedure to maintain sterility.

The ankle blood pressure cuff size will be a universal Hokanson SC12 straight segmental cuff, 13cm x 85cm. Toe blood pressure cuff size will be chosen as the cuff width closest to 20% wider than the toe diameter. Available toe pressure cuffs are Hokanson UPC2.5 2.5cm x 12cm, and Hokanson UPC3.3 3.3cm x 12cm. The FalconPro Viasonix machine will be used for non-invasive blood pressure measurements, connected to a FalconQuad machine for Viasonix Disk PPG sensor input.

Prior to commencement of the procedure, the ankle and toe blood pressure of the affected limb(s) in addition to the blood pressure of the arms will be measured. If any regional anesthetic such as epidural or spinal analgesia is to be administered, the preoperative measurement must be taken at minimum 15 minutes after anesthetic administration to allow for onset of sympathetic blockade vasodilation. Pre-procedure and post-procedure pressure measurements will be repeated three times at least 5 minutes apart to assess measurement variability.

After vascular access is obtained and the intra-arterial vascular sheath has been inserted, another set of blood pressure measurements will be obtained. This is because the physical presence of the intra-arterial instruments may affect distal leg and toe pressures. Following angioplasty, a repeat set of pressure measurements will be obtained prior to removal of intra-arterial instruments. The post-intervention measurements will be repeated after repeated endovascular treatment on the same leg during the procedure, such as multi-lesion angioplasty,

stent, or atherectomy. Finally, after the completion of the procedure and removal of all intra-arterial instruments, a final set of post-operative measurements will be obtained.

If an ulcer or infection precludes great toe pressure measurement, an alternate toe will be used to measure toe pressure. If the baseline ABI or TBI is greater than 1.5, we will infer incompressible vessels and deem the measurement unreliable.

Postoperatively, patients will follow routine follow-up scheduled clinic and ultrasound appointments at 1-3 months, which will not involve any active study intervention. The angiograms will be de-identified and presented to a blinded investigator to determine procedural anatomic success. Data will be collected from these images and appointments, during which the observer collecting postoperative data will remain blinded to the intraoperative results. Upon completion of follow-up data collection, the datasets will be frozen and merged for analysis. The schedule of assessments is presented in Table 2.

		Time Point							
		Preoperative	Perioperative				Postoperative		
		Recruitment	Pre-Procedure	Pre-Intervention	Post-Intervention	Post-Procedure	1 Month Follow-Up	0 - 12 Month Follow-Up	
Clinical	Baseline Characteristics	X							
	Rutherford's Score	X						X	
	Ipsilateral Endovascular Reintervention							X	
	Ipsilateral Open Reintervention							X	
	Minor Amputation							X	
	Major Amputation							X	
	Mortality							X	
Pressure	Toe Pressure		X	X	X	X	X		
	Ankle Pressure		X	X	X	X	X		
	Arm Pressure		X	X	X	X	X		
Radiographic	Severity of Lesion Stenosis	X				X			
	SVS Runoff Score	X				X			
	Primary Patency							X	
	Primary Assisted Patency							X	

	Secondary Patency							X
	Feasibility	X				X	X	X

**Table 2:** Schedule of Assessments. See below for specific Time Point Definitions.

Time Point Definitions:

Pre-Procedure: Lying supine, on day of procedure, prior to arterial puncture.  
 Pre-Intervention: Balloon deflated but while catheter across lesion.  
 Post- Intervention: Balloon deflated but while catheter across lesion.  
 Post-Procedure: Lying supine, after all catheters/sheaths are removed, and after manual pressure applied to the puncture site has been released.

Subject retention will be primarily promoted by the design of the study, which completes intraoperative measurements in a single and non-intrusive patient encounter during surgery. Postoperatively, the study leverages the Ottawa Division of Vascular Surgery as the only vascular surgical service in the public health region, to ensure complete data capture of postoperative outcomes. Because there is no further study-specific subject contact after surgery, we anticipate high postoperative retention rates. Subjects will be encouraged to attend all postoperative appointments at the time of enrollment, but will not be contacted by study personnel to promote postoperative appointment adherence.

**Blinding**

The surgical operator, operating assistant, scrub nurse, and any other member participating in the patient’s circle of care will be blinded from the intraoperative results of this study. The operators will rely on standard of care intraoperative feedback mechanisms such as intraoperative angiogram to guide the procedures. This blinding applied both to the intraoperative period as well as the postoperative period, such that the intraoperative pressure results will not factor into postoperative decision making by members of the subject’s circle of care.

As well as blinding clinicians involved in the administration of health care, all ultrasound technologists responsible for postoperative blood pressure measurements will be blinded from the intraoperative limb pressure results. Finally, the intraoperative pressure measurement data collection file will be ‘frozen’ and provided to our statistician before any postoperative clinical

outcome data collection is performed. The study official who will then perform postoperative outcome data collection will be separate from the study members who performed intraoperative pressure measurements, and will be blinded from these results while performing postoperative outcome data collection.

### **Data Monitoring and Management**

This is a single center study and all data will be stored locally. All intraoperative data collection will initially occur on hard copy datasheets, which will be stored in a locked container in a locked room within the study hospital, which is only accessible by the study member performing intraoperative data measurement. Each limb is assigned a 'Study Specific Identification Number' which will be used to link data for analysis.

All intraoperative data will be transferred to a password-protected spreadsheet locally, which is held on The Ottawa Hospital server and will be updated until recruitment is complete, at which time the intraoperative dataset will be 'frozen' and sent to a statistician. Double data entry will be performed by a second study member who will separately repeat data entry from the paper form to another password-protected spreadsheet, which will also be sent to the statistician to ensure accurate data coding between the two members.

Independent source verification will be performed by the statistician, by reviewing at random 20% of all paper case report forms. In addition, the intraoperative pressure data will be screened for outliers by flagging any pressure measurement value falling outside 2 standard deviations of the baseline measurement for review. The statistician will have access to paper case report forms to ensure accuracy of data entry in these cases.

Postoperative outcome assessment will not start until recruitment is complete, and will be performed by two additional study members who will not have access to intraoperative results. Double data entry will be performed by each member into independently password-protected electronic datasets for all postoperative outcomes including the primary outcome of MALE.

Upon completion of postoperative outcome measurements, the outcome datasets will also be available to the statistician for final analysis and confirmation of accuracy between the double-entry files. At any point, discrepancy between double-entry files will be brought to the attention of the principal investigator for resolution.

The individual study members conducting intraoperative data collection will have separate password access to their individual files, in addition to the Principal Investigator and local ethics board who have access to all files as required by the ethics committee. This is designated as a minimal-risk study, and there will be no interim analysis for the purposes of safety monitoring. Due to the relatively short duration of the study, these passwords will remain constant during the study unless a security breach is suspected. All paper and electronic datasets will be retained for 10 years following completion of the study.

#### **Access to Data**

The OHRI-REB will have access to anonymized data at their discretion, as per REB policy. However, no third party investigators, or corporate bodies will have access to study data prior to synthesis and dissemination.

#### **Confidentiality**

All data and records generated during this study will be kept confidential in accordance with institutional and OHRN-REB policies. The investigators will not use such data and records for any purpose other than conducting the study. Only necessary personal identification data will be collected, and deleted or destroyed at the earliest feasible time. Data will be collected and stored securely and anonymously in password protected files and on a hospital server, as described above.

#### **Study Timeline**

Enrollment Start Date: October 2018

Enrollment Stop Date: August 2019

Data Collection Stop Date: August 2020

Submission for Publication: September 2020

### **Funding**

This study will not receive dedicated funding.

### **Competing Interests**

The authors have no relevant conflicts of interest to disclose.

### **Author Contributions**

MR and PJ contributed to the concept of designing this study. MR and GW defined the study design and analytic plan. MR, PJ, and GW all contributed to writing and critical review of the manuscript.

## **ETHICS AND DISSEMINATION**

### **Ethics Approval**

This study has received OHRI-REB approval (Protocol 20180656-01H), which was most recently provided following an amendment on January 10, 2019.

### **Risk Assessment**

The only procedure affecting study subjects beyond the standard of care is a benign non-invasive blood pressure measurement of the lower extremities, which they already routinely receive serially in the same fashion before and after surgery at ultrasound appointments. On review of literature, there have been no reported adverse events resulting from blood pressure measurement of the lower extremity. However, cuff inflation at the ankle immediately following a lower tibial intervention such as angioplasty may theoretically encourage vessel thrombosis; the ankle cuff will not be inflated following any lower tibial interventions. The transiently inflated blood pressure cuff of the leg may be uncomfortable for the duration of

inflation, similar to blood pressure measurement of the arm. This will be minimized by inflating the lower extremity blood pressure cuffs to appropriate pressures standardized by the upper extremity inflations. The blood pressure cuffs will be applied several feet away from the operative field, addressing any potential compromise of surgical field sterility.

### **Reportable Events**

Any suspected (confirmed or unconfirmed) breach in confidentiality will be immediately reported to the OHRI-REB. This will include coordination with the review board for rapid notification of the patient(s) in question.

Any significant interruption in the flow of the operating theatre may be reported by any member of the operating theatre to the OHRI-REB. The study protocol, in addition to Primary Investigator, Study Coordinator, and OHRI-REB contact information will be posted and freely accessible in all vascular surgical operating theatres to ensure study transparency.

The study subjects will also be encouraged to report any irregular events to the Study Coordinator, Principal Investigator, and/or OHRI-REB as described in the consent forms.

### **Consent**

Consent for this study is necessary as there are measurements that will occur beyond the standard of care. These measurements, while they qualify as minimal-risk, will be fully explained to the subjects prior to obtaining consent. The access to electronic health records will also be discussed. The coordinator obtaining consent will have no direct involvement in the medical care of the subject.

### **Protocol Amendments**

All protocol amendments will require REB approval, in addition to Principal Investigator and Study Coordinator consensus.

### **Patient and Public Involvement**

There were no funds or time allocated for patient and public involvement, however we have invited patients to help us develop our dissemination strategy.

### **Dissemination**

Following completion of data analysis, the study will be synthesized and submitted for presentation at national and international vascular surgical society meetings, in addition to submission for publication in publicly accessible medical journals. All publicly presented and published data will describe the cohorts as a whole anonymously and will not include any direct identifiers.

### **Limitations**

The eligibility criteria may unintentionally exclude subjects with a history of unrelated venous procedures such as great saphenous venous stripping, and include aortic stenting for occlusive disease which is a relatively unique and rare procedure. Although these are anticipated to affect only a small subset of patients and will likely not have a differential effect, this eligibility criteria was established at the time of enrollment and will not be changed during the course of the study to maintain integrity.

The original protocol guiding enrollment of the majority of subjects did not explicitly state that both arm blood pressures will be measured and that the highest systolic pressure will be used for calculations of pressure indices. This is the standard protocol for assessment of ABI and TBI, and this method of determining the arm laterality for use in calculations has been performed in all instances, but has not been explicitly described in the protocol until a revision on June 21, 2019.

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## Section 5.2: Prospective Observational Study

### **Section Overview**

**Section 5.2** presents the completed manuscript of a prospective study titled ‘Intraoperative Simultaneous Limb Perfusion Monitoring (INSTANT) Study’. This study is a prospective, operator-blinded, and blinded end-point adjudicated observational cohort study, and to our knowledge is the first reported application of intraoperative limb pressure measurements during endovascular treatment of peripheral arterial disease.

### **Manuscript Status**

This manuscript has been prepared for submission to the Journal of Vascular Surgery.

### **Author Contributions**

Mark Rockley was involved in all stages of protocol inception, study conduct, and preparation of the study manuscript. Prasad Jetty was involved in all stages of protocol inception, study conduct, and preparation of the study manuscript. Adnan Hadziomerovic was involved in the conduct of the study as the head of Angiography and Interventional Radiology in Ottawa. Chanhee Seo was involved in study conduct as a blinded observer. Melanie Bouthillier participated as the head of the Vascular Diagnostic Center which facilitated conduct of intraoperative and postoperative hemodynamic assessments. George Wells was involved in protocol inception and preparation of the study manuscript.

## **Intraoperative Simultaneous Limb Perfusion Monitoring (INSTANT) Study**

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### **Keywords:**

Vascular Surgery, Hemodynamic Measurement, Intraoperative Monitoring

### **Conflicts of Interest:**

The authors have no relevant conflicts of interest.

### **Registration:**

This study is registered on ClinicalTrials.gov (NTC 03875846) and a-priori protocol is published<sup>1</sup>.

## Article Highlights:

**Type of Research:** Single-center, prospective, operator-blinded and blinded endpoint adjudicated cohort study

**Key Findings:** Intraoperative TBI assessment is reliable, and the magnitude of change in the intraoperative TBI measurements sustained a strong association with clinical outcomes such as MALE (Adj HR = 0.19 [95% CI 0.07 – 0.49],  $p < 0.01$ , per change in TBI of 0.1).

**Take Home Message:** These findings suggest that intraoperative perfusion assessment may be a useful tool in guiding intraoperative decision making.

## Table of Contents Summary:

In this prospective cohort analysis of patients undergoing endovascular treatment for peripheral vascular disease, we performed intraoperative TBI assessments and monitored for postoperative clinical outcomes such as MALE. Intraoperative TBI assessment was reliable and correlated with postoperative clinical outcomes, suggesting that intraoperative perfusion assessment may be a useful tool in guiding intraoperative decision making.

## Abstract

### Objectives

The primary objective of this study is to determine if the magnitude of change of intraoperative toe-brachial index (TBI) during endovascular procedures for atherosclerotic peripheral vascular disease (PVD) is associated with major adverse limb events (MALE) within 1 year post-procedure

## **Methods**

We performed a prospective, operator-blinded and blinded endpoint-adjudicated observational cohort study based on an a-priori published protocol. The TBI was assessed at multiple time points before, during, and after the procedures. The reliability and correlation between intraoperative and pre- or post-operative TBI assessments was evaluated with Pearson's and intraclass correlation coefficients. The association between intraoperative change in TBI and postoperative outcomes were analyzed with Cox Proportional Hazards, accounting for clustering of legs within subjects, accounting for the competing risk of mortality, and adjusted for baseline clinical status of limb ischemia and vascular level of intervention.

## **Results**

80 limbs of 67 patients were enrolled. The intraoperative TBI assessments were slightly depressed compared with pre- and post-operative TBI assessments, however they remained strongly correlated. During one year follow-up, MALE occurred in 21% of limbs. The magnitude of change in the intraoperative TBI measurements sustained a strong association with clinical outcomes such as MALE (Adj HR = 0.19 [95% CI 0.07 – 0.49],  $p < 0.01$ , per change in TBI of 0.1). However, the magnitude of intraoperative change in TBI did not was not associated with systemic outcomes such as mortality ( $p=0.93$ ). The ideal threshold of improvement in intraoperative TBI to maximize sensitivity and specificity of MALE is 0.08.

## **Conclusion**

Intraoperative TBI assessment during endovascular procedures for PVD is reliable and strongly correlated with postoperative clinical outcomes such as MALE. These findings suggest that intraoperative perfusion assessment may be a useful tool in guiding intraoperative decision making, which should be evaluated with a clinical trial.

## Manuscript

### **Introduction**

Peripheral vascular disease (PVD) is a systemic condition that may involve multiple levels of arterial disease in the affected legs. Diffuse multilevel PVD is becoming more prevalent and is associated with an increasing prevalence of diabetes and renal failure<sup>2,3</sup>. Multilevel and small vessel disease has traditionally been challenging to treat<sup>4</sup>, however new technologies and techniques are widening the scope of PVD potentially treatable by endovascular therapy. Accordingly, the number of procedures for PVD in the United States has doubled in the last decade, which is driven by a tripling of endovascular procedures<sup>5</sup>. Because the current standard of intraoperative feedback is exclusively anatomical based on angiogram, the end-point of successful treatment can be challenging to define anatomically in the setting of diffuse and distal disease. Despite the increased endovascular treatment of multilevel disease<sup>6</sup>, a physiologic end-point indicating adequate limb revascularization has not been established.

A similar void of intraoperative physiologic feedback has been addressed in cardiology through fractional flow reserve (FFR)<sup>7</sup>. This technique has also been tested in PVD<sup>8</sup>, however FFR determines the hemodynamic significance of individual lesions without quantifying the overall distal organ perfusion. PVD is unique because the ischemic tissue is physically accessible for assessment, and a more global assessment of tissue perfusion is feasible through non-invasive toe-brachial index monitoring (TBI). The TBI and ankle-brachial index (ABI) are traditionally used in outpatient settings to diagnose and monitor PVD, where TBI is the more reliable measure in the setting of diabetes<sup>9</sup>. Improvement of TBI following endovascular treatment is a powerful predictor of clinical success<sup>10</sup>, but has not been used to guide intraoperative decision making.

We propose the application of physiologic perfusion assessments within the operating room. If intraoperative markers of perfusion are associated with improved clinical outcomes, these perfusion assessments may be used to determine adequate revascularization during

procedures. The primary objective of this study is to determine if the magnitude of change in intraoperative TBI assessments during endovascular procedures for atherosclerotic PVD is associated with clinical outcomes such as major adverse limb events (MALE). Secondary objectives are to describe the correlation between intraoperative TBI assessment and pre-operative or post-operative measurements, describe the association between intraoperative change in TBI and other clinical outcomes such as vessel patency and reinterventions, and to identify an optimal threshold of intraoperative TBI change that is associated with freedom from MALE. Finally, this study will describe the feasibility of performing intraoperative TBI assessment during endovascular procedures.

## **Methods**

We performed a prospective, operator-blinded and blinded endpoint-adjudicated observational cohort study. This study is registered on ClinicalTrials.gov (NTC 03875846) and the a-priori protocol is published<sup>1</sup>. Ethics approval for this study was obtained by the local ethics board (OHSN-REB), and informed consent was obtained from participants.

We enrolled patients undergoing elective or semi-urgent endovascular revascularization of de-novo symptomatic atherosclerotic PVD at The Ottawa Hospital in Ottawa, Canada. Procedures performed by both vascular surgeons and interventional radiologists were included. Subjects were 18 years of age or older and demonstrated a detectable toe pressure during the procedure. Detectable toe pressure was defined as a consistent toe photoplethysmography waveform rate consistent with ECG monitoring, which was obliterated with inflation of toe cuff to a pressure less than 1.5 the systemic systolic pressure. Procedures were excluded if a prior or concurrent ipsilateral open vascular procedure was performed, emergent indication with symptoms of less than 14 days, or non-femoral vascular access was obtained (Appendix 1).

Baseline patient-specific variables were recorded. Severity of ischemia was defined by Rutherford's and WiFi classification<sup>11</sup>. Baseline anatomic disease was characterized by the

TASC<sup>12 13</sup> and runoff classifications, as well as lesion-specific features including the length, severity of stenosis, and calcium score. Intraoperative angiograms were de-identified and presented to a blinded investigator for assessment. Procedural characteristics included the method of treatment, residual stenosis after treatment, and vascular level of treatment defined as suprainguinal aortoiliac, and infrainguinal femoropopliteal or tibial vessels.

Limb pressure assessments were performed in five distinct phases; pre-procedure immediately prior to vascular access, pre-intervention after vascular sheath had been placed but no treatment had been performed, post-intervention upon completion of treatment but prior to sheath removal, post-procedure after the vascular sheath had been removed and access hemostasis achieved, and follow-up in an outpatient setting 1 to 3 months post-procedure (Figure 1). Detectable toe pressures were required for inclusion in the study, however if ankle pressures were also detectable these measurements were also performed. All limb pressure measurements were obtained by a study member using Hokanson UPC 2.5 or 3.3 cuffs, Viasonix Disk Photoplethysmography sensors, and FalconPro Viasonix machines. At every time point, automated non-invasive arm blood pressure was obtained from the arm demonstrating highest systolic pressure at time of enrollment. The TBI is calculated by dividing the great toe systolic pressure by the brachial systolic pressure. Throughout the study, surgeons were blinded to the results of intraoperative pressure assessments.

The primary outcome of this study is major adverse limb events (MALE) within 1 year post-procedure, defined as a composite outcome of amputation above the ankle, or major reintervention in the form of endovascular thrombolysis or open revascularization surgery. Other clinical outcomes included minor and major amputation, target limb reintervention, target vessel patency (primary, primary assisted, and secondary), mortality, and amputation-free survival. All clinical outcomes were assessed within 1 year post-procedure, and definitions were consistent with the SVS reporting standards<sup>14</sup>. In addition, routine follow-up pressure measurements were performed according to institutional protocol between 1 to 3 months following the procedure by vascular ultrasonographers blinded to the intraoperative pressure

results. We leveraged the Ottawa Division of Vascular Surgery's status as the only vascular surgical service in the public health region to ensure data capture, using the local EPIC electronic health record system to ascertain outcomes. The observer who ascertained postoperative clinical outcomes was blinded to all pressure assessments.

The unit of analysis in this study is individual legs. One patient may contribute two eligible legs to the study, and therefore all analyses will account for clustering of legs to each subject. The previously published sample size calculation based on an expected MALE event rate of 14%, expected hazard ratio of 0.15, alpha of 0.05, and power of 80%, yielded a total number of 80 legs required to enroll<sup>1</sup>. Individual datasets of intraoperative and postoperative data were frozen prior to analysis, and an independent study member also performed independent source verification at random.

Survival analysis of the association between the magnitude of change of intraoperative TBI (post-intervention compared with pre-intervention) and the primary outcome (MALE) was performed with Cox Proportional Hazards modelling. We used a robust sandwich estimate cluster model to account for clustering of legs within subjects, and used the Fine and Gray method to account for the competing risk of mortality. We adjusted for baseline clinical status of critical limb ischemia vs claudication, and for any infrainguinal anatomic level of treatment. An unadjusted univariate model is also reported. Planned subgroup analyses of the primary outcome included stratification of the anatomic vascular levels, baseline clinical status of critical limb ischemia vs claudication, and the use of stenting during the procedure.

All time-to-event secondary outcomes were similarly analyzed with Cox proportional hazards accounting for clustering and competing risks, adjusting for baseline ischemic status and anatomic level of intervention. An unadjusted univariate model is also reported. The binary secondary outcome of clinical improvement, defined as an improvement in the Rutherford's classification scale, was analyzed with logistic regression with generalized linear

mixed model, clustering by patient and adjusted for baseline ischemic status and anatomic level of intervention. An unadjusted univariate logistic regression model is also reported.

We assessed the correlation of TBI assessments between successive time points by determining the Pearson's coefficient, intraclass correlation, and analysis of Bland-Altman plots. We compared the pressure assessment timepoint pairs of pre-procedure versus pre-intervention, and post-intervention versus post-procedure, to assess the impact of the removal of vascular sheaths on the toe pressures. We also assessed the correlation between the immediate post-procedure measurements and the outpatient follow-up measurements.

## **Results**

The study recruited 67 subjects contributing 80 limbs undergoing endovascular treatment for de-novo PVD between October 2018 and March 2019 (Figure 2). The eligibility rate of all limbs undergoing isolated endovascular peripheral vascular revascularization procedures was 58%. The ineligible limbs were excluded due to repeat interventions (n=29), acute limb ischemia (n=17), and previous below-knee-amputation (n=2). Of the 89 eligible limbs, overall enrollment rate was 90% due to 2 subjects who declined consent, and 7 limbs in which intraoperative pressure measurements were unobtainable. Of the 80 limbs in which intraoperative TBI pressures were obtainable, ABI was detectable in 56 limbs. The mean follow-up duration was 10.9 months (SD=2.3) with no limbs lost to follow-up, however the follow-up period was abbreviated in 5 limbs due to mortality.

The mean age of the participants was 72.8 years. The demographics of study participants are presented in Table 1. 54 (68%) limbs suffered from critical limb ischemia prior to intervention, including 34 (43%) with tissue loss (Table 2). A summary of the TASC and Tibial Runoff anatomic classifications are presented in Table 3. Treated lesion-specific characteristics are presented in Table 4. Treated iliac lesions were shorter, less stenotic, and less commonly occluded than the femoropopliteal and tibial lesions.

Forty-two (53%) limbs were treated by interventional radiologists, and the remaining 38 limbs were treated by vascular surgeons. The 80 procedures were performed by 12 operators, each contributing a range of 1 to 15 procedures per operator. A mean of 2.3 anatomic levels were treated in each limb. An antegrade femoral access was utilized in 39% of procedures, and upon completion a vascular closure device was used in 41% of access sites. The mean duration of the procedures was 1.9 hours (SD=0.9 hours) which was longer than the mean allocated booking duration of 1.4 hours, however there were no disruptions to intraoperative flow as a result of the study reported to the investigators or REB.

The mean TBI measurements at discrete time points are displayed in Figure 3. The presence of a vascular sheath appears to depress the TBI assessments; the placement of a vascular sheath decreased the TBI by a mean of 0.039, and upon completion the removal of the sheath increased the TBI by 0.035 (Table 5, Appendices 2 and 3). However, these assessments remained strongly correlated with Pearson's and intraclass correlation coefficients of 0.89 and greater (Table 5). The mean follow-up outpatient pressure recordings were performed 2.5 months after the index procedure (SD=2.1). The immediate postoperative and outpatient follow-up TBI measurements were comparable, with Pearson's and intraclass correlation coefficients of 0.74 and 0.78 respectively (Table 5). The Bland-Altman plot comparing these assessments (Figure 4) does not demonstrate a differential effect at extreme values.

A summary of the clinical outcomes is presented in Table 6. The primary outcome of MALE occurred in 21% of participants. The majority of these outcomes occurred within two months of the index procedure (Figure 5). Half (49%) of the limbs did not experience improvement in the Rutherford's classification following endovascular treatment at any point during follow-up.

The magnitude of intraoperative change in TBI was strongly associated with the primary outcome of MALE (Adj HR = 0.19 [95% CI 0.07 – 0.49],  $p < 0.01$ , per change in TBI of 0.1) (Figure 6). Subgroup analyses evaluating the anatomic level of intervention and method of treatment

did not demonstrate significant interactions between these factors and the outcome of MALE (Appendix 4). Limb-specific outcomes including lack of clinical change, target limb reintervention, vessel patency, and amputation-free survival were also strongly associated with the magnitude of intraoperative TBI change (Table 7). However, post-procedure mortality was not associated with the intraoperative change in TBI (Adj HR = 1.09 [95% CI 0.16 – 7.29] p=0.93).

Using an unadjusted ROC curve (Appendix 5) and Youden's method to maximize sensitivity and specificity, an intraoperative increase of TBI by 0.08 was the ideal threshold to identify a MALE outcome (Positive LR = 2.14, Negative LR = 0.20). In our cohort, half of the 80 limbs reached the threshold increase in TBI of at least 0.08. Similarly, in the 56 limbs in which ABI was detectable, the optimal calculated threshold for intraoperative change was 0.13 (Positive LR = 2.00, Negative LR = 0.65).

## **Discussion**

This prospective observational study found that intraoperative toe pressure assessment is strongly correlated with pre- and post-procedure measurements. The magnitude of change of the intraoperative TBI between the start and end of a procedure is strongly associated with post-procedure clinical outcomes such as MALE. MALE was five times less likely for every increase in intraoperative TBI of 0.1. The ideal threshold of improvement in intraoperative TBI to avoid MALE is 0.08.

Previous authors have also attempted to correlate clinical outcomes with intraoperative indicators of perfusion during endovascular procedures for PVD. Utsunomiya et al<sup>15</sup> found that an angiographic contrast 'wound blush' in subjects with gangrene indicated improved wound perfusion, and was associated with improved wound healing. This method appears useful in patients with gangrene, however is not objective nor practical in patients without wounds. Mironov et al<sup>16</sup> evaluated the utility of indocyanine green fluorescence during endovascular

procedures, but did not find perfusion indicators that were correlated with clinical outcomes. Because indocyanine green fluorescence can only evaluate superficial skin perfusion, perhaps the changes in arteriole perfusion were not instantaneously apparent during the procedures. In contrast, toe and ankle hemodynamic assessments assess the perfusion pressures of larger arteries, and are therefore more likely to immediately reflect macrovascular changes.

The finding that the majority of limbs received treatment in multiple vascular locations highlights the premise of this study. PVD is a diffuse disease, and obtaining an angiographically 'normal' result is often not feasible due to chronic occlusions and small vessel disease. As a result, operators are often required to declare the end-point of a procedure while leaving residual disease. Our finding that intraoperative physiologic assessment is feasible indicates that physiologic-guided revascularization may provide useful information to the operator.

This study was adequately powered (Appendix 6). The sample size target of 80 limbs was met, including only 16% of bilateral legs in the same subjects. The overall primary outcome event rate was 21%, which was greater than the anticipated 14%. The rate of MALE in our cohort is likely related to the high proportion of advanced critical limb ischemia, and our center's tendency to attempt revascularization rather than primary amputation. Clinical follow-up data was available for all limbs. Hemodynamic follow-up data was missing for 17 limbs, of which 13 were a result of postoperative amputations.

The results of this study must be interpreted with caution. The total number of limbs in this study limits multivariate adjustment of all relevant factors. While we demonstrated that intraoperative assessment of toe pressures is reliable and indicative of post-procedure outcomes, it remains unclear whether changing intraoperative decision making based on this feedback has the potential to modify outcomes. It is possible that positive response to intraoperative toe pressures simply stratifies patients with disease amenable to endovascular treatment, versus disease that is not treatable by endovascular means. Aggressive pursuit of intraoperative hemodynamic results may incur greater risk. Even if this is true, intraoperative

feedback may still play a role by indicating an end-point of adequate revascularization before pursuit of more aggressive treatments and their associated risks. We therefore plan to pursue a prospective trial to examine the impact of intraoperative physiologic feedback to the operator.

A potential source of performance bias is that the operators were not blinded to the routine follow-up limb pressure assessments. The blinded intraoperative results were closely correlated with the unblinded follow-up pressure assessments. Therefore, reinterventions guided by the follow-up results may be confounding our analysis of the association between intraoperative pressures and postoperative outcomes. However, we feel that this bias is minimal for two reasons. The association between intraoperative pressures and postoperative outcomes persistent when considering clinical outcomes that are unlikely to be affected by pressure assessments such as vessel patency and major amputation. In addition, over half of the MALE events occurred within two months after the index procedure, while the follow-up pressure assessments typically occurred later at a mean of 2.5 months after the index procedure.

In conclusion, intraoperative TBI assessment during endovascular procedures for PVD is reliable and strongly correlated with postoperative clinical outcomes. These findings suggest that intraoperative perfusion assessment may be a useful tool in guiding intraoperative decision making.

## Tables

	Value (%)
<b>Number of Participants</b>	67
<b>Age (Years)</b>	73.4
<b>Male</b>	43 (64%)
<b>Current Smoker</b>	13 (19%)
<b>Former Smoker</b>	40 (60%)
<b>Diabetes</b>	30 (45%)
<b>HTN</b>	55 (82%)
<b>DLP</b>	49 (73%)
<b>Antiplatelet</b>	52 (78%)
<b>Anticoagulant</b>	10 (15%)
<b>Statin</b>	44 (66%)
<b>COPD</b>	8 (12%)
<b>CAD</b>	34 (51%)
<b>CVA</b>	13 (19%)
<b>CKD</b>	20 (30%)
<b>Dialysis</b>	6 (9%)

**Table 1:** Demographics of participants.

	Value (%)
<b>Number of Limbs</b>	80
<b>Critical Limb Ischemia</b>	54 (68%)
<b>Rutherford Classification</b>	
3	26 (32%)
4	20 (25%)
5	25 (31%)
6	9 (11%)
<b>WiFi Classification</b>	
<b>Wound</b>	
0	46 (57%)
1	8 (10%)
2	16 (20%)
3	10 (13%)
<b>Ischemia</b>	
0	28 (35%)
1	22 (28%)
2	9 (11%)
3	21 (26%)

<b>Foot Infection</b>	
0	48 (60%)
1	17 (21%)
2	10 (13%)
3	5 (6%)

**Table 2:** Clinical presentation by limb.

	<b>Value (%)</b>
<b>Aortoiliac TASC Score</b>	
<i>None</i>	29 (36%)
<i>A</i>	22 (28%)
<i>B</i>	13 (16%)
<i>C</i>	12 (15%)
<i>D</i>	4 (5%)
<b>Femoropopliteal TASC Score</b>	
<i>None</i>	17 (21%)
<i>A</i>	13 (16%)
<i>B</i>	27 (34%)
<i>C</i>	19 (23%)
<i>D</i>	4 (5%)
<b>Runoff Score [SD]</b>	8.3 [5.9]

**Table 3:** Baseline anatomic characteristics by limb.

	<b>Iliac</b>	<b>Femoropopliteal</b>	<b>Tibial</b>
<b>Total Number of Interventions</b>	70	70	45
<b>Mean Lesion Length (mm) [SD]</b>	17 [19]	72 [76]	167 [101]
<b>Mean Degree of Stenosis (%) [SD]</b>	67 [17]	83 [18]	89 [18]
<b>Chronic Total Occlusion (%)</b>	4 (6%)	22 (31%)	20 (44%)
<b>Mean Calcium Score [SD]</b>	1.9 [1.0]	0.9 [0.8]	1.4 [1.3]
<b>Stent Placed</b>	60 (86%)	43 (61%)	0 (0%)

**Table 4:** Treated lesion characteristics.

Time Point (Comparison Time Period)	Pre-Intervention (Pre-Procedure)	Post-Procedure (Post-Intervention)	Follow-Up (Post-Procedure)
<b>Participating Limbs</b>	80	80	63
<b>Absolute Change in TBI [SD]</b>	- 0.039 [0.067]	0.035 [0.048]	0.019 [0.031]
<b>Pearson's Coefficient (p value)</b>	0.91 (<0.01)	0.91 (<0.01)	0.74 (<0.01)
<b>Intraclass Correlation</b>	0.89	0.90	0.78

**Table 5:** Correlations between measurement time points.

	Value (%)
<b>Limbs Participating in Follow-Up</b>	80
<b>Lack of Clinical Improvement</b>	39 (49%)
<b>Target Limb Reintervention</b>	11 (14%)
<i>Endovascular without Thrombolysis</i>	7 (9%)
<i>Catheter Directed Thrombolysis</i>	2 (2%)
<i>Bypass</i>	1 (1%)
<i>Thromboembolectomy</i>	1 (1%)
<b>Target Vessel Patency</b>	
<i>Primary</i>	69 (86%)
<i>Primary Assisted</i>	75 (94%)
<i>Secondary</i>	76 (95%)
<b>Amputation</b>	
<i>Minor</i>	8 (10%)
<i>Major</i>	13 (16%)
<b>Mortality</b>	5 (6%)
<b>Amputation Free Survival</b>	65 (81%)
<b>Major Adverse Limb Event</b>	17 (21%)

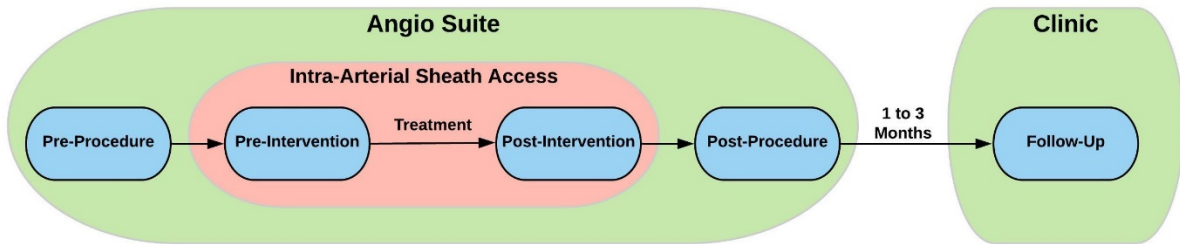
**Table 6:** Clinical outcomes.

	Unadjusted HR [95% CI]	p-value	Adjusted HR [95% CI]	p-value
<b><i>Primary Outcome</i></b>				
<b>Major Adverse Limb Event</b>	0.25 [0.10 – 0.66]	< 0.01	0.19 [0.07 – 0.49]	< 0.01
<b><i>Secondary Outcomes</i></b>				
<b>Target Limb Reintervention</b>	0.09 [0.03 – 0.32]	< 0.01	0.09 [0.02 – 0.32]	< 0.01
<b>Target Vessel Patency</b>				
<i>Primary</i>	0.09 [0.03 – 0.32]	< 0.01	0.08 [0.02 – 0.32]	< 0.01
<i>Primary Assisted</i>	0.06 [0.01 – 0.43]	< 0.01	0.07 [0.01 – 0.66]	< 0.01
<i>Secondary</i>	0.06 [0.01 – 0.47]	< 0.01	0.08 [0.01 – 0.59]	< 0.01

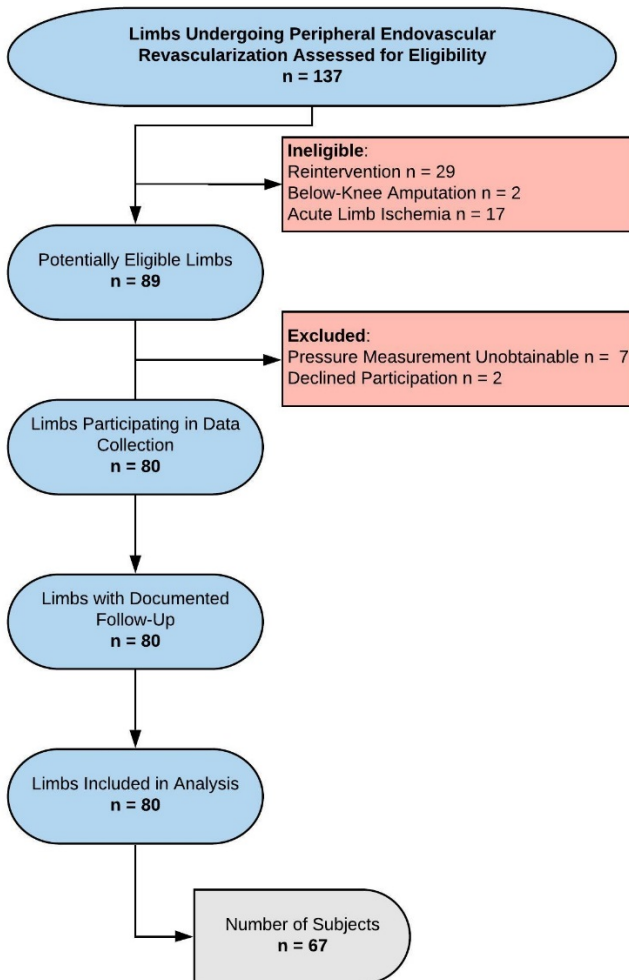
<b>Amputation</b>				
<i>Minor</i>	0.22 [0.05 – 0.96]	0.04	0.17 [0.04 – 0.69]	0.02
<i>Major</i>	0.59 [0.18 – 1.95]	0.39	0.32 [0.10 – 1.08]	0.07
<b>Mortality</b>	1.29 [0.15 – 11.29]	0.82	1.09 [0.16 – 7.29]	0.93
<b>Amputation Free Survival</b>	0.52 [0.18 – 1.54]	0.24	0.33 [0.11 – 0.97]	0.04
	<b>Unadjusted OR [95% CI]</b>	<b>p-value</b>	<b>Adjusted OR [95% CI]</b>	<b>p-value</b>
<b>Lack of Clinical Improvement</b>	0.12 [0.03 – 0.45]	< 0.01	0.09 [0.02 – 0.38]	< 0.01

**Table 7:** Univariate and multivariate associations between intraoperative increase in TBI (by 0.10) and clinical outcomes. Multivariate models were adjusted for the pre-specified variables of critical limb ischemia and infrainguinal level of intervention.

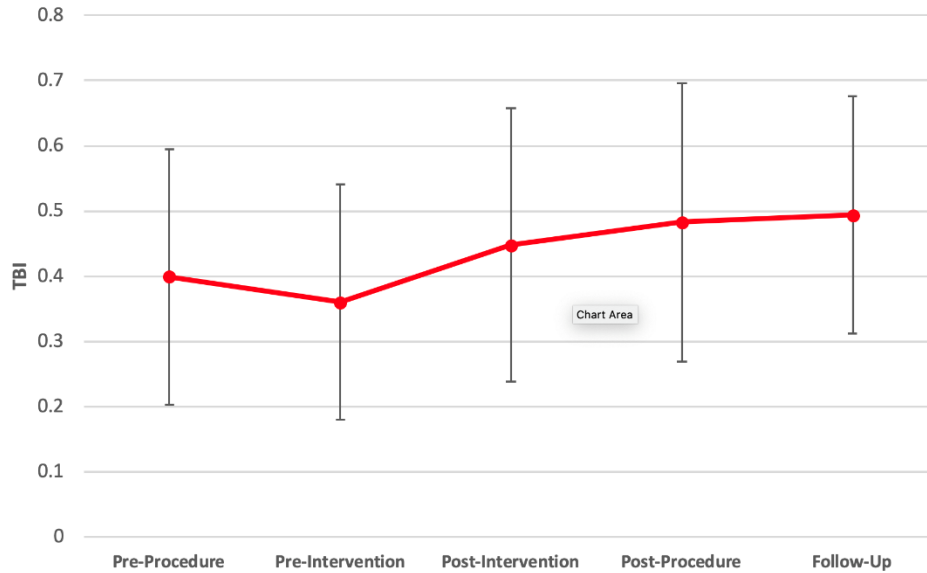
## Figures



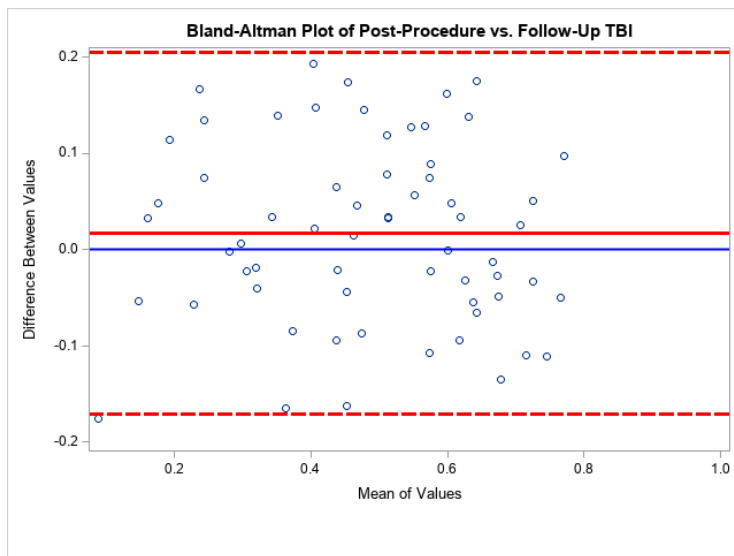
**Figure 1:** Pressure assessment timeline.



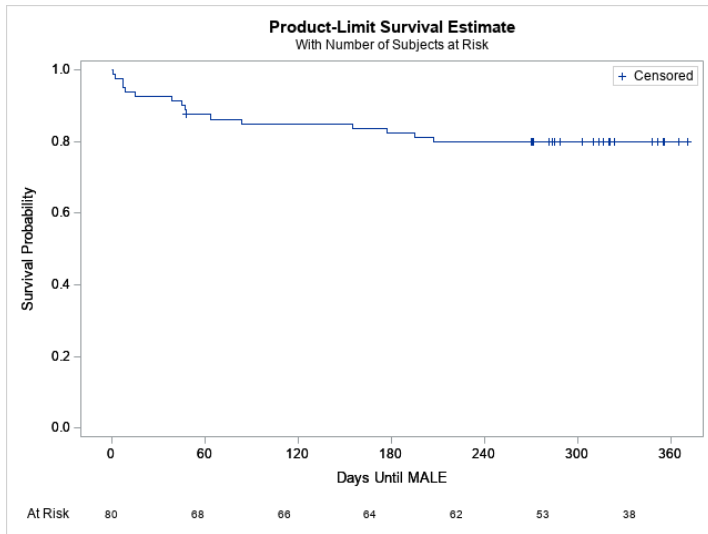
**Figure 2:** Participant selection flow chart.



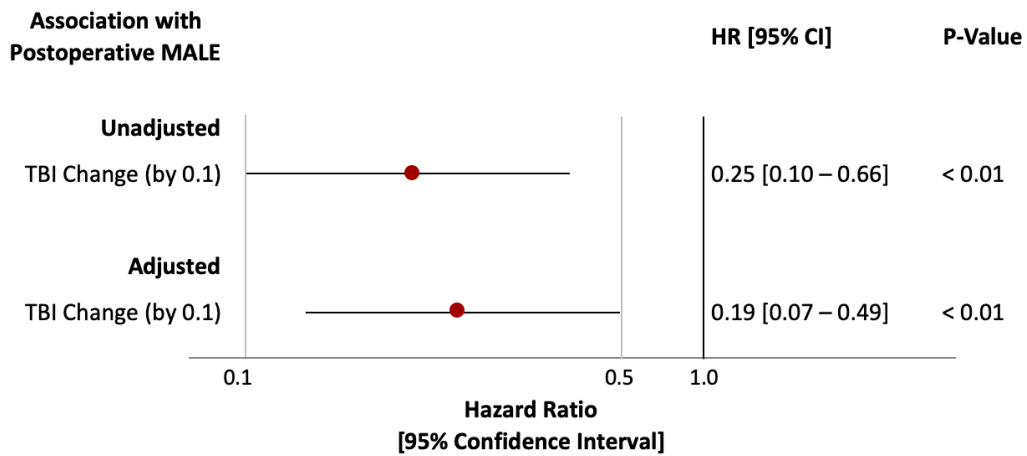
**Figure 3:** Mean TBI values at each time point. Error bars represent the standard deviation.



**Figure 4:** Bland-Altman plot comparing the difference in TBI measurements between immediate post-procedure and follow-up time points, plotted as a function of their mean values.



**Figure 5:** Survival curve representing the timing of the primary outcome (MALE).



**Figure 6:** Forest plot depicting the unadjusted and adjusted hazard ratio of a postoperative MALE outcome, for each intraoperative TBI change of 0.1.

## Appendices

### Appendix 1: Eligibility criteria

#### Inclusion Criteria

Elective or Semiurgent endovascular procedures  
(>14 days symptoms)

De-novo lesions of the aorta, iliac, femoral, popliteal, or  
tibial arteries

Symptomatic atherosclerotic peripheral vascular disease

Age  $\geq$  18 years

Detectable pre-intervention toe pressure after sheath  
insertion

#### Exclusion Criteria

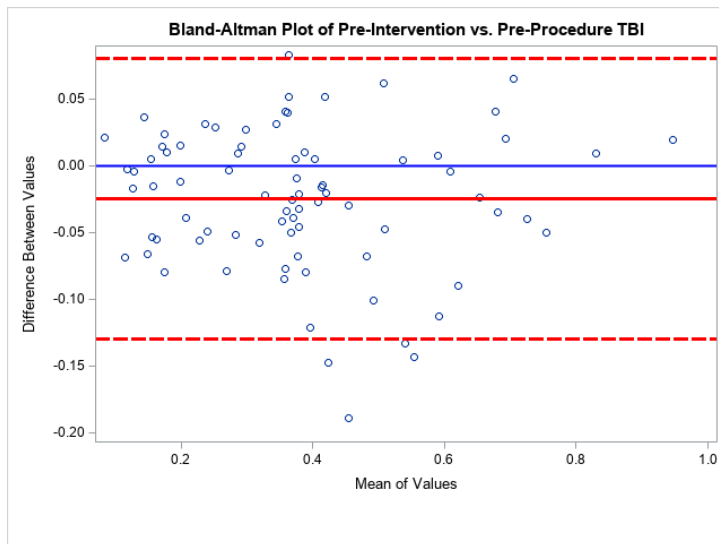
Concurrent hybrid open procedure requiring vascular  
clamping, such as endarterectomy

Prior open vascular surgery performed on the affected leg

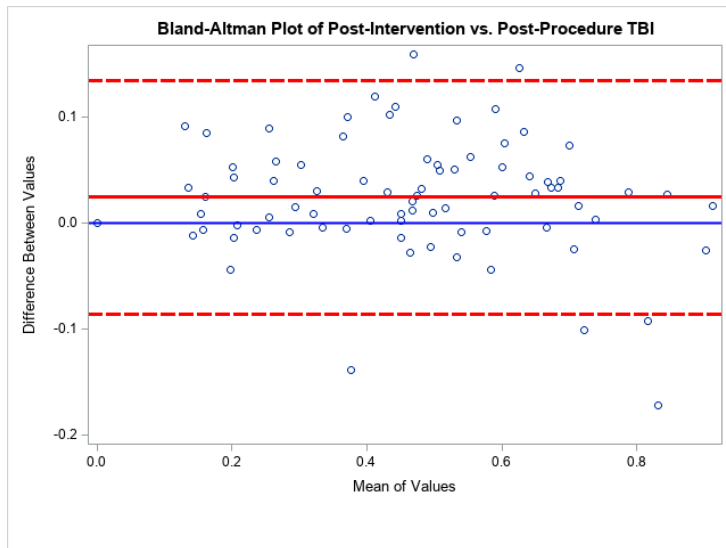
Emergent intervention for acute limb ischemia  
( $\leq$ 14 days of symptoms)

Non-femoral vascular access

**Appendix 2:** Bland-Altman plot comparing the difference in TBI measurements between pre-intervention and pre-procedure time points, plotted as a function of their mean values.



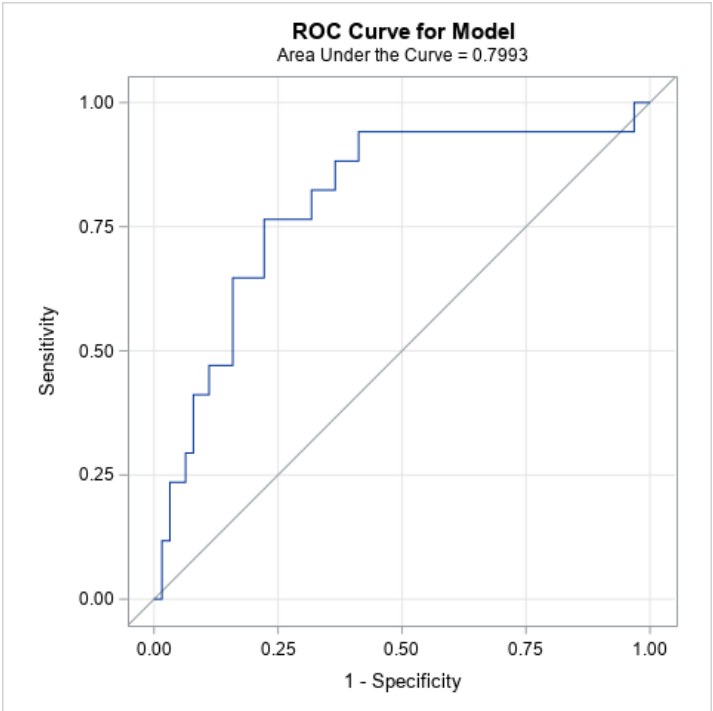
**Appendix 3:** Bland-Altman plot comparing the difference in TBI measurements between post-intervention and post-procedure time points, plotted as a function of their mean values.



**Appendix 4:** Subgroup analysis of the association between the intraoperative change in TBI and MALE outcomes in pre-specified subgroups.

	Number of Eligible Limbs	Unadjusted HR [95% CI]	Interaction p-value
<b>Anatomic Level of Intervention</b>			
<i>Suprainguinal</i>	34	0.80 [0.08 – 7.69]	0.96
<i>Infrainguinal</i>	46	0.40 [0.12 – 1.37]	
<b>Severity of Ischemia</b>			
<i>Claudication</i>	26	No MALE Events	-
<i>Critical Limb Ischemia</i>	54	0.38 [0.12 – 1.25]	
<b>Method of Treatment</b>			
<i>Angioplasty Alone</i>	30	0.47 [0.12 – 1.79]	0.63
<i>Any Stenting</i>	50	0.98 [0.13-7.54]	

**Appendix 5:** Receiver-operator curve depicting the sensitivity and specificity of detecting MALE based on the magnitude of intraoperative TBI change.



**Appendix 6:** Anticipated versus observed values.

	<b>Anticipated</b>	<b>Observed</b>
<b>Units of Analyses (Limbs)</b>	80	80
<b>Subjects</b>	64	67
<b>Proportion of Limbs with Claudication</b>	38%	32%
<b>Loss to Follow Up</b>	10%	0%
<b>Primary Event Rate (MALE)</b>	14%	21%

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## **Chapter 6: Discussion**

### **6.1 Discussion Introduction**

The purpose of this thesis was to explore methods of assessing blood flow to limbs during minimally invasive procedures to restore perfusion. This discussion chapter will summarize the findings of the three study components of the thesis, discuss the practical considerations of applying physiologic monitoring during surgery, consider alternate physiologic monitoring methods, and finally propose a future direction of investigation.

### **6.2 Summary of Findings**

The concept of intraoperative physiologic monitoring during endovascular procedures has been proposed in previous studies. While there are numerous methods to assess limb perfusion in an outpatient setting, very few methods have been evaluated in an intraoperative setting. Our systematic review described in Chapter 3 identified two papers which assessed intraoperative measures of perfusion, of which one found an association between intraoperative presence of wound blush and limb salvage(1). This is a relatively small study with a subjective outcome and high risk of bias, and is not applicable to procedures that are performed in limbs without wounds. We therefore concluded that there was a lack of investigation into the methods of assessing limb perfusion during endovascular revascularization.

Our retrospective cohort study described in Chapter 4 evaluated the association between outpatient measures of perfusion after endovascular procedures and clinical outcomes. This study found that anatomic intraoperative feedback, in the form of an angiogram, was only modestly associated with outpatient measures of perfusion. Furthermore, it identified that outpatient perfusion measures were more significantly associated with clinical outcomes than intraoperative angiographic results. We concluded that angiographic results alone may be

insufficient to predict clinical outcomes, and that if reliable, intraoperative limb perfusion assessment may add valuable information to the operator.

Finally, our prospective cohort study described in Chapter 5 evaluated the reliability of intraoperative toe pressure measurements to assess limb perfusion, and the association of these measures with clinical outcomes. This study identified that intraoperative toe pressure assessment is correlated with perioperative assessments, in addition to follow-up measurements months after the procedure. The intraoperative changes in toe pressure assessments were strongly correlated with tangible postoperative outcomes such as major adverse limb events. In summary, intraoperative assessment of perfusion during endovascular revascularization is possible and is strongly correlated with clinical outcomes.

### **6.3 Practical Considerations of Intraoperative Application**

The ideal intraoperative assessment of perfusion is instantaneous, accurate, and feasible. There are several biologic explanations for why some useful outpatient perfusion assessment methods may not be useful during procedures. In particular, the vessel size being evaluated may play a large role in the ability of the measurement to provide accurate rapid feedback, due to arteriole adaptation and confounding factors such as temperature. Indocyanine green assesses the perfusion of skin, which may not tangibly change during a relatively short operative time(2). Laser Doppler, transcutaneous oxygen, and infrared assessments may all have the same shortcoming. In contrast, large-vessel measures are intuitively more likely to immediately reflect changes in perfusion due to large-vessel surgery. These measures include non-invasive methods such as ankle and toe pressures, and invasive methods such as fractional flow reserve. We would therefore suggest that further investigation of intraoperative measures of perfusion should be cognizant of the ability for these measures to change rapidly during a procedure.

However, there are still several limitations to the intraoperative application of toe pressure assessment. The prospective study required additional intraoperative resources in the form of a study member trained in toe pressure acquisition, and a specialized hemodynamic assessment machine for data acquisition. These resources are not readily available outside the scope of a trial and will likely limit the adoption of this method. Furthermore, there are several measurable and immeasurable factors that could confound toe pressure measurements. These include the hemodynamic significance of intra-arterial sheaths, vasodilation and vasospasm during the course of the measurement, and the effects of iodinated contrast viscosity. While these potential confounders may be clinically relevant, our current data cannot fully explore the significance of these factors.

Finally, the goal of intraoperative physiologic measurement is to guide intraoperative decisions. However, the current state of endovascular surgery has limitations, and operator decision-making based on these results may cause more harm than benefit in certain situations. In particular, current technology is limited when faced with small vessel disease and non-crossable chronic occlusions. Reversible vasospasm of an artery may result in a falsely depressed perfusion assessment which should be managed differently than an atherosclerotic residual stenosis. Alternatively, a procedure resulting in arterial dissection may initially demonstrate a falsely reassuring increase in perfusion, but could result in early failure. We suggest that the application of intraoperative physiologic monitoring should assist decision making, rather than be the sole driver of decisions.

#### **6.4 Future Direction**

This thesis has established that intraoperative physiologic assessment of blood flow during endovascular revascularization for peripheral vascular disease is possible and correlated with postoperative clinical outcomes. Ultimately, the goal is to identify an intraoperative physiologic feedback mechanism that could improve clinical outcomes. While intraoperative toe pressure assessments were accurate, they may not be broadly applicable to everyday practice due to the

additional resources and interpretive skills required. Before determining whether intraoperative feedback can alter outcomes, we would need to explore alternate intraoperative feedback mechanisms.

Beyond intraoperative toe pressure monitoring, assessment of angiogram contrast flow rate may be an ideal assessment. The current purpose of angiogram is simply to highlight the inner lumen of the artery, and to demonstrate the anatomic shape of the blood flow channel. Theoretically, instead of simply analyzing the angiogram as if it were a still image, an operator could also assess the flow rate of the contrast injected into the arteries. Some operators may already subjectively assess the flow rate of contrast during procedures, however it has not been explored quantitatively or correlated with clinical outcomes. This approach would utilize angiogram equipment that is already employed during standard procedures, and would provide real-time feedback of the blood flow through large vessels. It may not be necessary to only examine the blush of contrast noticed during procedures for large wounds, as was described by Utsunomiya(1). Real-time quantitative feedback of flow rate would require additional software, which does not currently exist. Flow rate could be assessed by many approaches, such as the time that it takes the arteries to be fully opacified, or the rate at which the contrast opacity changes after injection.

Similar to intraoperative toe pressures, the assessment of contrast flow rate may be confounded by intraoperative factors. Intra-arterial device placement may temporarily slow arterial flow rate. This could be addressed by only examining flow rate before and after treatment when the intra-arterial sheaths have not changed. Another concern is that variability in the injection rate of contrast may confound the flow rate in the arteries. The volume, concentration, and rate of contrast injections could be standardized by automated power injection machines, rather than syringe 'hand injections'. Instead of only examining the speed of contrast arrival into the arteries, this problem could also be addressed by examining the wash-out rate of contrast after the injection is complete, when the native perfusion is the only factor driving flow rate. A drawback of this solution could be an increase in fluoroscopy time,

increasing radiation exposure to the patient and the operator. Finally, the variability in hand injections could be mitigated by examining the derivative change in contrast opacity over time, rather than simply the rate of contrast flow(3).

To examine the relationship between contrast flow and clinical outcomes, we will perform a post-hoc analysis of the INSTANT study presented in Chapter 5. We will examine the stored angiogram videos for various definitions of flow rate, and assess the relationship between these findings and the clinical outcomes in our cohort. In addition, we will compare the intraoperative contrast flow rate results with the intraoperative toe pressures. If we define a measure of contrast flow rate that is resistant to potential confounders, the next step would be to apply this method in a prospective randomized trial. The objective would be to determine if intraoperative qualitative feedback of angiogram contrast flow rate, when compared with the current standard of care by assessing angiogram in a static state, is associated with reduced postoperative major adverse limb events in patients undergoing endovascular procedures for atherosclerotic peripheral vascular disease.

In addition to studying alternate methods of perfusion assessment, there are opportunities to explore alternate research methods. While we used a traditional systematic review approach in Chapter 3, a systematic review of prognostic studies using the PROGRESS framework would characterize evidence from a number of perspectives. This framework would evaluate the contributors of successful endovascular revascularization by evaluating the fundamental, individual factors, overall models, and stratified components. This thesis demonstrated that the factors influencing outcomes of peripheral arterial disease are complex. Depending on the context, any of these four components could represent an appropriate perspective. Therefore, a review based on the PROGRESS framework would provide a multifaceted summary of current evidence regarding the prognosis of endovascular revascularization, and could serve as a guide for a variety of future research programs.

## **6.5 Conclusions**

The concept of intraoperative physiologic monitoring during endovascular procedures for peripheral vascular disease has been proposed in previous studies, however there is limited evidence to guide the practical application of intraoperative monitoring. We found that intraoperative angiographic results alone are insufficient to predict clinical outcomes, and that physiologic intraoperative monitoring of limb pressure is feasible and strongly correlated with postoperative clinical outcomes.

## 6.6 References

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# Appendices

## Appendix A: Ethics Approval for 'Association Between Hemodynamic Response and Clinical Outcomes following Endovascular Revascularization for Atherosclerotic Peripheral Vascular Disease'



August 15, 2018

Dr. Prasad Jetty

The Ottawa Hospital, Civic Campus Division of Vascular & Endovascular Surgery 1053 Carling Avenue, Room A2-80 Ottawa, ON K1Y 4E9

**Re:** OHRI Institutional Approval for Ottawa Health Science Network Research Ethics Board (OHSN-REB) Submission

20180582-01H;

**Hemodynamic Improvement and Clinical Outcomes in Patients Undergoing Endovascular Revascularization for Atherosclerotic Peripheral Vascular Disease**

Dear Dr. Prasad Jetty,

This letter serves as **Ottawa Hospital Research Institute (OHRI)** Institutional Approval for the above-referenced study. Please maintain this documentation in your investigator study file.

Based on the information you provided about this study through the Clinical Research Registration Form, you have satisfied the requirements for institutional (OHRI) approval. This includes initial research ethics approval by OHSN-REB, appropriate departmental/service area notifications and execution (fully signed versions) of all agreement(s) required to begin the study locally. Please note there may be additional agreement(s) pending execution that are required to send funds, samples, or data to external sites, but are not required for you to begin your study locally.

Changes and/or additions to your study that may require additional agreement(s) or revisions to existing agreement(s) must be communicated to the OHRI Contracts Office. This should be undertaken simultaneously with any related OHSN-REB amendment submission.

Changes and/or additions to your study that affect various hospital/institution departments (e.g., pharmacy, Department of Medical Imaging, EORLA, EEG, etc.) must be communicated to the relevant departments.

As mentioned in the 'Response' tab of the Ethics application, you have 3 months from the date of initial OHSN-REB approval to submit French documents including the translation certificate to OHSN-REB through the Translated Documents section of the ethics application (if applicable).

Should you have any questions, please contact REBadministration@ohri.ca or 613-798-5555 extension 16719.

Nancy Camack, BScN RN MBA CCRP  
Director, Clinical Research Administration  
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## Appendix B: Ethics Approval for 'Intraoperative Simultaneous Limb Perfusion Monitoring (INSTANT) Study'



September 28, 2018

Dr. Prasad Jetty

The Ottawa Hospital, Civic Campus Division of Vascular & Endovascular Surgery 1053 Carling Avenue, Room A2-80 Ottawa, ON K1Y 4E9

**Re:** OHRI Institutional Approval for Ottawa Health Science Network Research Ethics Board (OHSN-REB) Submission

20180656-01H;

### **Intraoperative Simultaneous Pressure Guided Revascularization Study**

Dear Dr. Prasad Jetty,

This letter serves as **Ottawa Hospital Research Institute (OHRI)** Institutional Approval for the above-referenced study. Please maintain this documentation in your investigator study file.

Based on the information you provided about this study through the Clinical Research Registration Form, you have satisfied the requirements for institutional (OHRI) approval. This includes initial research ethics approval by OHSN-REB, appropriate departmental/service area notifications and execution (fully signed versions) of all agreement(s) required to begin the study locally. Please note there may be additional agreement(s) pending execution that are required to send funds, samples, or data to external sites, but are not required for you to begin your study locally.

Changes and/or additions to your study that may require additional agreement(s) or revisions to existing agreement(s) must be communicated to the OHRI Contracts Office. This should be undertaken simultaneously with any related OHSN-REB amendment submission.

Changes and/or additions to your study that affect various hospital/institution departments (e.g., pharmacy, Department of Medical Imaging, EORLA, EEG, etc.) must be communicated to the relevant departments.

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# Appendix C: Published Manuscript 'Physiologic perfusion monitoring methods during endovascular revascularization for atherosclerotic peripheral arterial disease: protocol for a systematic review'.

Rockley *et al. Systematic Reviews* (2020) 9:107  
<https://doi.org/10.1186/s13643-020-01357-y>

Systematic Reviews

PROTOCOL

Open Access

## Physiologic perfusion monitoring methods during endovascular revascularization for atherosclerotic peripheral arterial disease: protocol for a systematic review



Mark Rockley<sup>1\*</sup>, Prasad Jetty<sup>1†</sup> and George Wells<sup>2†</sup>

### Abstract

**Background:** Endovascular therapy is a fundamental treatment for peripheral arterial disease. However, the success rate of endovascular therapy remains poor, as a third of patients with critical limb ischemia ultimately require a major amputation for gangrene despite endovascular treatment. This failure rate has prompted investigation into methods of determining physiologic procedural success before and after treatment, before clinically apparent outcomes occur such as gangrene. The aim of this systematic review is to evaluate if in patients undergoing endovascular surgery for lower extremity atherosclerotic peripheral arterial disease, do changes in physiologic measures of perfusion during surgery correlate with clinical outcomes.

**Methods:** We registered and designed a study protocol for a systematic review. Literature searches will be conducted in MEDLINE, EMBASE, and CENTRAL (from January 1977 onwards). Grey literature will be identified through OpenGrey and clinical trial registries, and supplemented by citation searches. We will include randomized controlled trials, quasi-experimental trials, and observational (cohort, case-control) studies conducted in human adults (age 18 or older) who received elective arterial angioplasty for atherosclerotic peripheral vascular disease. The primary outcome of interest will be major adverse limb events. Two investigators will independently screen all citation, full-text articles, and abstract data. The study quality (risk of bias) will be appraised appropriate tools. Data analysis and synthesis will be qualitative; no meta-analysis is planned, as the anticipated homogeneity of measurement and outcome reporting standardization is low.

(Continued on next page)

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**Discussion:** The treatment of peripheral arterial disease is unique in that the tissue of the ischemic leg is easily accessible for direct monitoring during procedures. This is contrasted with cardiac and neurologic monitoring during cardiac and cerebral procedures, where indirect or invasive measures are required to monitor organ perfusion. Currently synthesized evidence describing limb perfusion focuses on static states of ischemia, and does not evaluate the value of change in perfusion measurement as an indicator of endovascular treatment success. These methods could potentially be applied to optimize procedural outcomes by guiding perfusion-based decision-making during surgery.

**Systematic review registration:** PROSPERO CRD42019138192

**Keywords:** Angioplasty, Peripheral arterial disease, Perfusion, Intraoperative monitoring

## Background

### Rationale

Peripheral vascular disease (PVD) is a condition caused by arterial blockages causing inadequate blood flow, resulting in pain and gangrene of the legs. The prevalence of PVD in the North American general population over 50 years of age is estimated at 17.4%, and is rising in association with the increasing prevalence of diabetes [1]. Bypass surgery is typically reserved for patients with severe forms of PVD, and minimally invasive options of angioplasty (“endovascular surgery”) are emerging as the treatment of choice for most patients with PVD. Angioplasty is the foundational treatment of endovascular therapy, which may be augmented by treatments such as stenting and atherectomy. Unfortunately, the 2-year patency of balloon angioplasty for PVD is poor, reported between 50–80%, depending on lesion location and characteristics [2]. The 1-year amputation rate despite endovascular revascularization has been reported as high as 32% in patients with lower limb critical limb ischemia [3]. This has prompted investigation into the predictors of failure, and potential solutions to optimize the success rate of revascularization. One proposed method is to evaluate the physiologic improvement in limb perfusion intraoperatively, to provide the operator with an opportunity to evaluate the procedural success and potentially guide intraoperative decision-making.

One of the most important predictors of clinical success following endovascular surgery for PVD is the post-procedure ankle-brachial index (ABI) [4]. This measurement is performed by applying a blood pressure cuff at the level of the lower leg (“Ankle Pressure”) and the arm. The ABI is a ratio of the blood pressure at the ankle when compared with the arm. Similarly, a smaller cuff around the great toe can determine the absolute toe pressure, which can also be used to calculate the toe-brachial index (TBI). The change in ABI following endovascular surgery can be detected a day after the procedure, and remains stable throughout the month following the procedure [5]. Several other postoperative markers of limb perfusion have also been investigated. Magnetic resonance arterial spin labeling correlates with postoperative ABI and clinical outcomes [6].

Furthermore, some authors have investigated markers of limb perfusion during surgery, finding correlation between postoperative ABI and intraoperative 2-dimensional perfusion angiography [7] and indocyanine green intra-arterial injection [8]. Other methods such as laser doppler [9], near-infrared spectroscopy [10, 11], transcutaneous oxygen saturation [12], and micro-oxygen sensors [13] have also been evaluated. While these methods have been established as markers of perfusion in the outpatient setting, their role in guiding intraoperative decision-making is unclear.

The potential of physiologic measures to predict clinical outcomes after endovascular revascularization presents several opportunities. The current practice of waiting until the postoperative period to measure the limb pressure after surgery may miss opportunities to guide intraoperative decision-making. While angiogram is currently the primary form of intraoperative feedback, conventional angiogram provides only anatomic feedback, which may not correlate with physiologic perfusion of blood due to microvascular disease and diffuse disease.

### Objectives

The aim of this systematic review is to evaluate if in patients undergoing endovascular surgery for lower extremity atherosclerotic peripheral arterial disease, do changes in physiologic measures of limb perfusion during surgery correlate with clinical outcomes. Physiologic measures include non-invasive and invasive arterial pressure measurements, transcutaneous oxygen measurement, infrared spectroscopy, laser doppler flowmetry, and angiogram perfusion calculations.

Secondary questions that will be addressed by this review will investigate the correlation of intraoperative physiologic measures with non-clinical postoperative outcomes such as radiographic patency and hemodynamic outcomes.

## Methods

### Eligibility criteria

#### Study designs

We will include randomized controlled trials (RCT) and quasi-experimental trials, non-randomized controlled

trials, cluster trials, interrupted time series studies, controlled before-after studies (CBA), prospective or retrospective cohort studies, and case-control studies. Case series less than 5 participants and case reports will be excluded.

#### **Participants**

We will include studies examining human adults (age 18 or older) who received elective arterial angioplasty for atherosclerotic peripheral vascular disease. The angioplasty must be the primary purpose of the intervention, and not be performed concurrently with a hybrid open vascular procedure on an in-line flow artery. The intervention must be performed on lower extremity peripheral arteries, ranging from the infrarenal aorta proximally to the toes distally. The balloons may be drug-coated or lined with cutting ribs, and alternate adjunctive endovascular procedures stent placement, orbital atherectomy, laser atherectomy, rotational atherectomy, or directional atherectomy. We will exclude venous angioplasty, arteriovenous fistula angioplasty, and studies examining emergency settings.

#### **Intervention and comparators**

The intervention of interest is intraoperative physiologic measurement of limb perfusion. Examples of established physiologic measurements of perfusion include non-invasive and invasive arterial pressure measurements, transcutaneous oxygen measurement, infrared spectroscopy, laser doppler flowmetry, and angiogram perfusion. Any further methods of physiologic measurement which are currently unknown to the authors and are discovered during the review will be considered individually. They will be included in the review if they meet our definition of intraoperative physiologic limb perfusion measurement, dynamic measures of blood flow within the target limb performed during surgery. Strictly anatomic measurements which are available on standard angiogram, such as residual stenosis or patency, will be excluded.

#### **Outcomes**

The primary outcome of interest will be major adverse limb events (MALE). MALE is defined as a composite outcome of clinically driven target limb reintervention, and major amputation proximal to the ankle [14].

Secondary clinical outcomes include amputation, reintervention, mortality, and clinical symptomatic improvement based on the Rutherford's classification of peripheral vascular disease [15]. Secondary non-clinical outcomes include non-invasive limb hemodynamic results, and radiographic results of vessel patency and stenosis.

#### **Timing**

Studies will be selected for inclusion if they report intraoperative monitoring results in addition to follow up outcomes reported at least 30 days after the index surgery, categorized into clinical, radiographic, and hemodynamic outcomes.

#### **Setting**

There are no restrictions regarding setting of the study.

#### **Language**

We will include all language studies, with a list of titles requiring translation into English included in an appendix.

#### **Information sources**

A literature search strategy using medical subject headings and text words has been developed. We will search MEDLINE (OVID interface), EMBASE (OVID interface), and the Cochrane Central Register of Controlled Trials (Wiley interface).

To ensure capture of all relevant trials, all selected studies will also undergo ancestry search, in addition to citation search using SCOPUS. OpenGrey will be interrogated for unpublished relevant literature.

#### **Search strategy**

Both qualitative and quantitative studies will be collected. All searches will be limited by date of publication (January 1977–onwards). The initial year of 1977 has been chosen as the first in-human use of angioplasty was performed that year. No language limit will be placed on the search. The search strategy and syntax have been guided by a Health Sciences librarian with systematic review experience. The MEDLINE search syntax will be adapted to accommodate the remaining database searches. Please see [Appendix](#) for a complete search syntax used for the MEDLINE search. The search syntax is intentionally broad to include any potentially relevant methods of perfusion measurement. Of note, the PROSPERO database has been searched, and no ongoing or recently completed systematic review on this topic has been performed.

#### **Study records**

##### **Data management**

Literature search results will be aggregated in EndNote, including where duplicate articles will be removed. The results will then be uploaded to the Distiller SR software, which will facilitate collaboration among all reviewers.

The two screening authors will independently screen titles and abstracts resulting from the combined search of all selected databases. The full text of an article will be obtained for any articles that appear to meet eligibility criteria, at which point the full text will be screened

and confirmation of article inclusion will be made. Any reasons for exclusion following full text screening will be explicitly documented and listed in an appendix.

Once both reviewers have created a complete list of eligible articles, the lists will be compared. Discrepancies in article selection will be addressed with discussion with a third-party author experienced in systematic review conduct. No authors will be blinded to journal titles, study authors, or study location of origin.

#### **Data collection process**

A standardized form created in Distiller SR will be used as the data collection method. Both reviewers will have a separate form for each article, which will be compared for consistency after data collection has completed. Any discrepancy will be addressed with discussion with a third-party author experienced in systematic review conduct. Study authors will not be contacted to resolve unclear or inadequate reporting of data.

#### **Data items**

The trial design, setting, and any accessory measures such as observer or operator blinding will be assessed. We will collect patient population information including level of endovascular procedure, claudication versus critical limb ischemia, use of vasodilators such as cilostazol or pentoxifylline, and comorbidity data. We will extract perfusion monitoring information including method of perfusion monitoring, timing of monitoring, and any objective serial outcomes, their confidence measures, variability, and inter-rater reliability. We will also note any author comments on feasibility or obstacles in using the method. Extracted outcomes will be guided by the definitions below.

#### **Outcomes and prioritization**

##### **Primary outcome**

The primary outcome of interest will be major adverse limb events (MALE). MALE is defined as a composite outcome of clinically driven target limb reintervention, and major amputation proximal to the ankle [14].

##### **Secondary outcomes**

Secondary clinical outcomes include the following:

- Amputation
  - Minor amputation (toe(s) or foot)
  - Major amputation (above the ankle)
- Reintervention
  - Target:
    - Lesion
    - Vessel
    - Limb
- Endovascular
- Bypass
- Thrombectomy
- Thrombolysis
- Mortality
- Improvement in Rutherford's classification of peripheral vascular disease [15]

Secondary non-clinical outcomes include the following:

- Postoperative hemodynamic
  - Ankle pressure
  - Ankle-brachial index (ABI)
  - Toe pressure
  - Toe-brachial index (TBI)
- Postoperative radiographic
  - Target vessel patency
    - Primary (absence of target vessel occlusion or restenosis > 50%)
    - Primary assisted (patency requiring assistance of subsequent procedure to maintain patency of target vessel)
    - Secondary (patency requiring assistance of subsequent procedure to restore patency of target vessel)

#### **Risk of bias of individual studies**

To assess individual studies for potential risk of bias, we will collect information guided by the Cochrane Collaboration Risk of Bias 2.0 tool [16]. In summary, this includes sequence generation, allocation concealment, blinding, incomplete outcome data, and selective outcome reporting. For each category, each study will be determined to be at either low or high risk. Alternately, if the report includes insufficient information to determine the level of risk, the category will be labeled as unclear. The quality of cohort studies will be assessed by the Newcastle-Ottawa Scale [17], and the quality of case series will be assessed by the Institute for Health Economics Quality Appraisal Checklist [18, 19]. Determination of the level of bias will be made by the two reviewers independently, and compared following complete assessment of all studies. Any discrepancy will be addressed with discussion with a third-party author experienced in systematic review conduct. The resulting risk of bias for each study, in each category, will be graphically represented by the RevMan software.

#### **Data synthesis**

##### **Quantitative synthesis**

Due to the anticipated heterogeneity of reports, including the methods of perfusion monitoring, clinical outcomes, and type of endovascular surgery, we will not perform quantitative data synthesis.

**Qualitative synthesis**

We will summarize the described methods of intraoperative perfusion measurement. Specifically, we will describe the reported association of these methods with postoperative outcomes. We will comment on the reported variations in methods, and assess the volume of published experience in utilizing each method. We will also comment on any practical information gleaned from the review. This will include comments on feasibility, reliability, and accessibility. We will also describe any reported patient characteristics that may affect the method's usability. Where there is missing data, we will contact the authors of the original study to obtain complete data where possible.

**A priori subgroup analyses**

We will stratify our qualitative analysis into the three postoperative outcome categories: clinical, hemodynamic, and radiographic. Where possible, we will stratify the qualitative analysis by vascular level of intervention (aortoiliac, femoropopliteal, or tibial), symptom status (claudication or critical limb ischemia), diabetic status, and use of peripheral vasodilators such as cilostazol or pentoxifylline.

**Meta-bias**

As there is no planned quantitative data synthesis, we will not perform statistical analysis of meta-bias. We will however comment on the risk of bias of each study, as well as qualitatively describe.

**Confidence in cumulative estimate**

There will not be a cumulative estimate produced by this study, and therefore there will be no assessment of confidence. However, the generalizability of the findings to the PVD patient population will be qualitatively judged.

**Discussion**

In summary, the success of endovascular therapy for PVD is relatively poor despite technological advancements, resulting in a high reintervention rate. A component of this challenge may be inadequate revascularization during the initial procedure, despite a reassuring anatomic result on angiogram. Physiologic measures of limb perfusion may provide insight into which patients are incompletely revascularized during the initial procedure. If intraoperative feedback of limb perfusion is predictive of outcomes, these methods could be used to guide intraoperative decision-making and ultimately improve the success of endovascular revascularization.

This review may be limited by the anticipated lack of standardized reporting or high-quality evidence including prospective randomized trials. In response, we do not plan to perform any meta-analyses. Qualitative synthesis alone will summarize existing literature, but is

unlikely to directly influence current practice by itself. This review is still warranted however, as even lower quality studies may provide useful insights to guide more robust future investigation, which may help to inform future practice.

If we encounter the need for a protocol amendment, the change must be approved by all study members. The protocol change will be immediately updated in the PROSPERO registration, and the change will be explicitly described in the methods section of the final manuscript.

**Appendix****Appendix: Proposed search syntax for MEDLINE, using OVID interface**

## Peripheral vascular disease

1. Peripheral Vascular Diseases/
2. GANGRENE/
3. INTERMITTENT CLAUDICATION/
4. Peripheral Arterial Disease/
5. PVD.tw.
6. peripheral vascular disease\*.tw.
7. Peripheral angiopath\*.tw
8. peripheral arterial disease\*.tw.
9. gangrene\*.tw.
10. claudica\*.tw.
11. critical limb ischemia\*.tw.
12. (1 to 11, OR)

## Endovascular revascularization

13. Angioplasty/
14. ENDOVASCULAR PROCEDURES/
15. Stents/
16. angioplast\*.tw.
17. endovascular\*.tw.
18. stent\*.tw.
19. atherectom\*.tw.
20. (Endoluminal adj3 repair\*).tw.
21. (13 to 20, OR)

## Intraoperative monitoring

22. Monitoring, Intraoperative/
23. (intraoperative adj3 monitor\*).tw.
24. (perfusion adj3 angio\*).tw.
25. Ankle Brachial Index/
26. Arterial Pressure/
27. ankle brachial.tw.
28. (ankle adj3 pressur\*).tw.
29. toe brachial.tw.
30. (toe adj3 pressur\*).tw.
31. ABL.tw.

32. TBI.tw.
33. Blood Gas Monitoring, Transcutaneous/
34. (transcutaneous adj2 oxygen pressur\*).tw.
35. tcpo2.tw.
36. Spectrophotometry, Infrared/ or Spectroscopy, Near-Infrared/
37. infrared spectro\*.tw.
38. correlation spectroscop\*.tw.
39. Pulse volume\*.tw.
40. PVR.tw.
41. Tomography, Optical Coherence/
42. (optic\* adj2 coheren\*).tw.
43. Laser-Doppler Flowmetry/
44. (laser adj2 doppler).tw.
45. (22 to 44, OR)
46. (12 AND 21 AND 45)

#### Abbreviations

PVD: Peripheral vascular disease; MALE: Major adverse limb events; ABI: Ankle-brachial index; TBI: Toe-brachial index

#### Authors' contributions

MR conceived of the project and developed the first draft of the protocol. PJ was a major contributor of project concept and subgroup analysis overview. GW oversaw all stages of the manuscript. The author(s) read and approved the final manuscript.

#### Funding

There are no funding contributions to declare for this study.

#### Availability of data and materials

The datasets generated and analyzed during the current study will be available from the corresponding author on reasonable request.

#### Ethics approval and consent to participate

Ethics is waived for a systematic review of published papers.

#### Consent for publication

Not applicable

#### Competing interests

The authors declare that they have no competing interests.

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# BMJ Open Protocol for a prospective observational diagnostic study: intraoperative simultaneous limb pressure monitoring (INSTANT) study

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## ABSTRACT

**Introduction** Peripheral vascular disease (PVD) is a condition caused by arterial blockages causing inadequate blood flow, resulting in pain and gangrene of the legs. Endovascular therapy, such as angioplasty, can be used to treat PVD, however, the operator feedback during surgery is primarily anatomic based on the angiogram. Because physiologic blood perfusion can be difficult to determine based on anatomic images, we propose introducing physiological measurements into the operating room. This study will investigate whether the change in intraoperative monitoring of haemodynamic measurements such as the Toe-Brachial Index during endovascular surgery for lower extremity atherosclerotic PVD is associated with clinical outcomes such as major adverse limb events (MALEs).

**Methods and analysis** This study will be a prospective, operator-blinded and blinded endpoint adjudicated observational diagnostic cohort study. A total of 80 legs will be enrolled in the study. Ankle and toe blood pressures will be measured non-invasively at predetermined time points before, during and after surgery, and we will assess associations between changes in intraoperative pressure measurements and postoperative clinical and haemodynamic outcomes. The primary outcome will be MALE within 1 year, and secondary outcomes include follow-up pressure measurements, vessel patency, reintervention, clinical staging improvement, amputation and death.

**Ethics and dissemination** Regional hospital ethics approval has been granted (Ottawa Hospital Research Institute - Research Ethics Board, Protocol 20180656–01H). On completion of data analysis, the study will be submitted for presentation at international vascular surgical society meetings, in addition to submission for publication in publicly accessible medical journals.

**Trial registration number** NCT03875846

## INTRODUCTION

Peripheral vascular disease (PVD) is a condition caused by arterial blockages causing inadequate blood flow, resulting in pain and gangrene of the legs. The prevalence of PVD in the North American general population over 50 years of age is estimated at 17.4%, and is rising in association with the increasing prevalence of diabetes.<sup>1</sup> While bypass surgery

## Strengths and limitations of this study

- Novel application of intraoperative physiological monitoring using ankle and toe blood pressure during revascularisation procedures.
- Prospective, operator-blinded and blinded endpoint adjudicated.
- Observational cohort study.
- Resource intensive pressure measurement.

is reserved for patients with severe forms of PVD, the minimally invasive options of angioplasty ('endovascular surgery') is emerging as the treatment of choice for most patients with PVD. The annual rate of endovascular peripheral vascular interventions in the USA Medicare population has risen to 419.6 per 100 000 Medicare beneficiaries.<sup>2</sup> Angioplasty is the foundational treatment of endovascular therapy, which may be augmented by treatments such as stenting. Unfortunately, the 2-year patency of balloon angioplasty for PVD has been poor, reported between 50% and 80%, depending on lesion location and characteristics.<sup>3</sup> Subsequently, the 1-year amputation rate despite endovascular revascularisation has been reported as high as 32% in patients with lower leg critical limb ischaemia.<sup>4</sup> This high failure rate has prompted investigation into the predictors of failure, and potential solutions to optimise the success rate of revascularisation.

One of the most significant predictors of clinical success following endovascular surgery for PVD is the postprocedure Ankle-Brachial Index (ABI).<sup>5</sup> This measurement is performed by applying a blood pressure cuff at the level of the lower leg ('Ankle Pressure') and the arm. The ABI is a ratio of the blood pressure at the ankle when compared with the arm. Similarly, a smaller cuff around the great toe can determine the absolute toe pressure, which can

also be used to calculate the Toe-Brachial Index (TBI). The change in ABI following endovascular surgery can be detected a day after the procedure, and remains stable throughout the month following the procedure.<sup>6</sup> While the ABI is commonly used for monitoring haemodynamic improvement after endovascular surgery, postoperative surveillance TBI has been demonstrated to have a significantly stronger correlation with clinical outcomes such as major adverse limb events (MALE).<sup>7</sup> 'MALE' is defined as a composite outcome of clinically driven target limb reintervention and major amputation.<sup>8</sup> While the TBI is an important marker for postoperative outcomes, attempting these measurements during the procedure has never been reported.

Other postoperative markers of limb perfusion have also been investigated. MR arterial spin labelling correlates with postoperative ABI and clinical outcomes.<sup>9</sup> Furthermore, some authors have investigated markers of limb perfusion during surgery, finding correlation between postoperative ABI and intraoperative two-dimensional perfusion angiography<sup>10</sup> and indocyanine green intra-arterial injection.<sup>11</sup> Other methods, such as laser Doppler,<sup>12</sup> near-infrared spectroscopy,<sup>13 14</sup> transcutaneous oxygen saturation<sup>15</sup> and micro-oxygen sensors,<sup>16</sup> have demonstrated delayed feedback of perfusion that would not be rapid enough to guide intraoperative decision making.

The potential utility of limb blood pressure to predict clinical outcomes after endovascular revascularisation presents several opportunities. Measurement of limb blood pressure is relatively simple to perform intraoperatively, particularly during endovascular procedures. The intraoperative use of ankle or toe blood pressure measurement has never been described. Therefore, while limb blood pressure measurements may be significant predictors of outcomes, the current practice of waiting to measure the limb pressure after surgery may miss opportunities to guide intraoperative decision-making.

Currently, the primary intraoperative feedback used to determine procedural success is the anatomic appearance of the angiogram on completion of the procedure. While an angiogram may depict the improvement of focal arterial narrowing, it does not provide physiological feedback to the operator. Small vessel disease or tandem lesions may instead be the primary culprit of the PVD, and would not be demonstrated adequately by the angiogram. Consequently, an anatomically significant lesion may not be haemodynamically significant, resulting in a falsely reassuring angiogram. Because limb pressure measurements encompass these variables that are not accounted for by angiogram, limb pressure measurement could be more predictive of procedural success than angiogram. This study investigates the diagnostic association between intraoperative non-invasive limb blood pressure measurement and postoperative outcomes. If applying limb blood pressure monitoring into the operating room is predictive of outcomes, the results of this study will guide further investigation into using instant blood pressure feedback to guide intraoperative decision

making and ultimately improve the success of endovascular revascularisation.

## OBJECTIVES

### Primary objective

The primary objective of this investigation is to determine if the magnitude of change of intraoperative TBI during endovascular revascularisation (preangioplasty and postangioplasty) for atherosclerotic PVD is associated with freedom from MALEs within 1-year postprocedure.

Intraoperative TBI change is defined as the difference between the preintervention and postintervention time point measurements, which are described in detail under the 'Data Collection' heading. MALE is defined as a composite outcome of major amputation above the ankle, major reintervention in the form of catheter-directed thrombolysis, open bypass or thrombectomy.<sup>17</sup>

### Secondary objectives

In addition to the magnitude change in intraoperative TBI, we will also evaluate the association of the binary intraoperative perfusion marker change on symptom improvement, major and minor amputation, target lesion/vessel/limb reintervention, target vessel patency and association between intraoperative and postoperative measurements.

Beyond analysing TBI, we will analyse other intraoperative measures of change in limb perfusion including ABI, absolute toe pressures and absolute ankle pressures. All measures of intraoperative changes perfusion will be calculated as the difference between the preintervention and postintervention time point measurements. Ideal acceptable threshold improvements in intraoperative TBI and ABI will be determined using Youden's method, to potentially use as a clinical decision rule in further research. The study will also report feasibility measures including rate of enrolment and reported anticipated or unanticipated disruptions to patient flow during intraoperative data collection.

## METHODS AND ANALYSIS

### Study design

This study will be a prospective observational cohort study. The surgical operators will be blinded to intraoperative pressure measurements. All radiographic and postoperative clinical endpoints will be assessor blinded.

### Setting

Patients undergoing treatment by the Division of Vascular Surgery at The Ottawa Hospital, Civic Campus. All patients will be under the care of the Vascular Surgery Division, both inpatients and outpatients. All outpatient limb pressure measurements will have been performed at the Vascular Ultrasound Diagnostic Laboratory, and all endovascular procedures and intraoperative limb pressure measurements performed in the operating

theatres of the Civic Campus. We will leverage our status as the only vascular surgical service in the medical region (Champlain LHIN) to maximise capture of outcomes following the index procedure.

### Study population

#### Inclusion criteria

- ▶ Patients undergoing elective or semiurgent endovascular procedures on de novo lesions of the aorta, iliac, femoral, popliteal or tibial arteries.
- ▶ Symptomatic, atherosclerotic PVD.
- ▶ Age 18 years old or greater.
- ▶ Detectable toe pressure.

#### Exclusion criteria

- ▶ Concurrent hybrid open procedure during endovascular revascularisation requiring vascular clamping for any period of time, such as endarterectomy.
- ▶ Prior open vascular surgery performed on the affected leg.
- ▶ Emergent intervention for acute limb ischaemia, defined as symptoms lasting less than 14 days.
- ▶ Non-femoral vascular access.

#### Recruitment

Recruitment for this study will be performed just after consent for the procedure is obtained, by notification of the attending vascular surgeon.

### Variables

#### Baseline characteristics

- ▶ Age.
- ▶ Sex.
- ▶ Smoking status.
- ▶ Diabetes.
- ▶ Hypertension.
- ▶ Dyslipidaemia.
- ▶ Antiplatelet use.
- ▶ Anticoagulant use.
- ▶ Statin use.
- ▶ Chronic kidney disease (estimated Glomerular Filtration Rate (eGFR) <60).
- ▶ Dialysis dependence.
- ▶ Trans-Atlantic Inter-Society Consensus (TASC) Classification.<sup>18</sup>
- ▶ Rutherford's Classification of PVD.<sup>19</sup>
- ▶ WiFi classification.<sup>8</sup>

#### Preoperative limb pressures

- ▶ Ankle pressure.
- ▶ Toe pressure.
- ▶ Brachial pressure.
- ▶ ABI.
- ▶ TBI.

#### Procedural characteristics

- ▶ Vessel(s) of intervention.
- ▶ Anatomic level (iliac, femoropopliteal and infrageniculate).

- ▶ Severity of stenosis.
  - <50%, 50%–75% or >75% stenosis.
  - Complete occlusion.
- ▶ Residual stenosis.
- ▶ Adjunctive procedures.
  - Drug-eluting balloon.
  - Stenting.
    - Balloon expandable.
    - Self-expanding.
    - Bare-metal.
    - Covered.
  - Thrombectomy.
  - Atherectomy.

#### Intraoperative perfusion markers of interest

- ▶ Ankle pressure.
- ▶ Toe pressure.
- ▶ Brachial pressure.
- ▶ ABI.
- ▶ TBI.

#### Primary outcome

The primary outcome is freedom from MALE within 1-year postintervention. MALE is defined as a composite outcome of major amputation above the ankle, major reintervention in the form of catheter-directed thrombolysis, open bypass or thrombectomy.

#### Secondary outcomes

All clinical outcomes are assessed within 1-year postindex procedure, and haemodynamic outcomes assessed at 1–3 months postindex procedure.

- ▶ Improvement in Rutherford's Classification of PVD.
- ▶ Amputation.
  - Minor (toe(s) or foot to the ankle).
  - Major (above the ankle)
- ▶ Minor Amputation (toe(s) or foot).
- ▶ Major amputation (above the ankle).
- ▶ Target limb reIntervention.
  - Endovascular.
  - Bypass.
  - Thrombectomy.
  - Thrombolysis.
- ▶ Target vessel reintervention.
- ▶ Target lesion reintervention.
- ▶ Target vessel patency.
  - Primary (absence of target vessel occlusion or restenosis >50%).
  - Primary assisted (patency requiring assistance of subsequent procedure to maintain patency of target vessel).
  - Secondary (patency requiring assistance of subsequent procedure to restore patency of target vessel).
- ▶ Mortality
- ▶ Amputation-free survival.
- ▶ Correlation between immediate postoperative limb pressure and 1–3months follow-up limb pressure measurement.

**Feasibility outcomes**

- ▶ Enrolment.
  - Enrolment rate.
  - Consent rate for subjects approached for study participation.
- ▶ Data capture.
  - Rate of complete intraoperative data capture of consenting subjects.
  - Postoperative subject involvement retention rate.
- ▶ Disruptions to patient flow.
  - Total time of procedures.
  - Reported unexpected disruptions.

**Sample size**

Due to the nature of investigating a novel technique, there is limited established evidence to guide expected results for a sample size calculation. The most closely related published data are found in a subgroup analysis of the IN.PACT DEEP trial, which followed patients for 12 months after infrainguinal angioplasty.<sup>7</sup> In patients who experienced any improvement of TBI immediately postoperatively, this study identified an HR of 0.15 (95% CI 0.04 to 0.57) of 'MALE' within 1 year, defined as major limb amputation above the level of the ankle, or major target lesion revascularisation in the form of thrombolysis, thrombectomy or bypass. The study also found a sampling distribution ratio of patients demonstrating an improvement in TBI to no improvement in TBI of 2.14. On survey of regional attending vascular surgeons to depend on an intraoperative monitoring system, an HR of 0.15 would be appropriate as a minimum to guide intraoperative decision-making.

This study includes patients undergoing endovascular procedures for a spectrum of symptomatic PVD, including those with claudication and critical limb ischaemia. The primary outcome of this study will be defined as MALE. The expected 1-year event rate of MALE is higher in subjects with critical limb ischaemia (20.5%<sup>7</sup> vs subjects with claudication 3.2%).<sup>20</sup> Based on a recent 10-year audit of endovascular procedures performed at the investigational centre (The Ottawa Hospital, Civic Campus) the expected proportion of eligible subjects with critical limb ischaemia (vs claudication) is 0.625. Therefore, we will need to calculate an overall expected event rate based on the relative proportion of each disease severity, in addition to their respective event rates. This calculation can be seen in table 1, and ultimately, the overall expected event rate is 14%. The Division of Vascular Surgery at The Ottawa Hospital is the sole vascular surgical provider for the region, therefore, the expected lost to follow-up is minimal and estimated at less than 5%. The anticipated rate of inclusion of bilateral legs of the same subject is less than 20%, and therefore, the expected loss of analytical power due to robust sandwich estimate cluster modelling is minimal and will be accounted for in our inflation adjustment of 10%. In light of an alpha of 0.05, beta of 0.20, buffer for lost to follow-up and cluster modelling of 10%, sampling distribution of 2.14:1, HR of 0.15, a total of 80 legs will be enrolled.

**Table 1** Sample size calculation

Variable	Value
Alpha	0.05
Power	0.80
Sampling distribution	2.14:1
Overall event probability	0.140
Critical limb ischaemia	0.205
Proportion of subjects with critical limb ischaemia	0.625
Claudication	0.032
Proportion of subjects with claudication	0.375
Calculation of overall event probability	$(0.205 \times 0.625) + (0.032 \times 0.375)$
HR	0.15
Inflation: loss to follow-up, cluster analysis	10%
<b>Total sample size</b>	<b>80 legs</b>

**Planned analyses**

The unit of analysis will be individual legs; one subject may contribute two eligible legs to the study. Therefore, all analyses will account for clusters of legs to each subject. Survival analysis of the primary outcome (MALE) as a function of the magnitude of improvement of perioperative TBI will be performed with Cox Proportional Hazards, using robust sandwich estimate cluster modelling, competing risk adjustment and adjusting for preoperative Rutherford's classification, anatomic level of disease and discrepant baseline characteristics. An unadjusted univariate log rank test will also be reported.

The following time-to-event secondary outcomes compared between those with positive limb pressure change and those without improvement or negative change will be analysed using Cox proportional hazards with generalised estimating equations for clustering, competing risk adjustment and adjustments for preoperative Rutherford's classification and anatomic level of disease: major and minor amputation, reintervention, target vessel patency, mortality and amputation-free survival. An unadjusted univariate log rank test will also be reported.

Logistic regression with generalised linear mixed model, clustering by patient and adjusted for preoperative Rutherford's classification and anatomic level of disease, will be used to analyse the binary outcome of any symptomatic improvement based on the postoperative Rutherford's classification. An unadjusted univariate logistic regression will also be reported.

Using ROC curves developed by models correlating MALE based on intraoperative change in toe and ankle pressures, the ideal threshold will be identified using Youden's method. This new threshold will then be used to replicate the primary analysis with binary toe and ankle pressure thresholds.

**Table 2** Schedule of assessments. see below for specific time point definitions

		Time point						Postoperative	
		Preoperative		Perioperative			Postoperative		
		Recruitment	Preprocedure	Preintervention	Postintervention	Postprocedure	1-month follow-up	0-12 months follow-up	
Clinical	Baseline characteristics	X							
	Rutherford's Score	X						X	
	Ipsilateral endovascular reintervention							X	
	Ipsilateral open reintervention							X	
	Minor amputation							X	
	Major amputation							X	
Mortality								X	
Pressures	Toe pressure		X	X	X	X	X		
	Ankle pressure		X	X	X	X	X		
	Arm pressure		X	X	X	X	X		
Radiographic	Severity of lesion stenosis	X				X			
	Society for Vascular Surgery (SVS) runoff score	X				X			
	Primary patency							X	
	Primary assisted patency							X	
	Secondary patency							X	
	Feasibility	X				X	X	X	

Time point definitions. Preprocedure: lying supine, on day of procedure, prior to arterial puncture. Preintervention: balloon deflated but while catheter across lesion. Postintervention: balloon deflated but while catheter across lesion. Postprocedure: lying supine, after all catheters/sheaths are removed, and after manual pressure applied to the puncture site has been released.

The correlation between immediate postoperative toe and ankle pressure measurements and follow-up pressure measurements will be assessed using Pearson's coefficient, Intraclass correlation and Bland-Altman plots. We will repeat these correlation analyses when comparing preprocedure and preintervention measurements, as well as a comparison of postintervention and postprocedure measurements (table 2). In addition, analysis of the variability in measurement of both preoperative and postoperative values will be performed. As these measurements are repeated three times during both of these time points, we will report both SD and SE of the mean.

Planned subgroup analyses include stratification for the three vascular levels (iliac, femoropopliteal and tibial), critical limb ischaemia versus claudication, stenting vs angioplasty alone and preoperative TASC II classification.

Feasibility outcomes, including enrolment, consent, intraoperative data capture and postoperative retention rates, will be reported as absolute values and fractions.

Qualitative descriptions of reported unexpected disruptions to patient flow will be described. Total operative times will be presented alongside the allocated timeframe for the procedures. No statistical analyses are planned for feasibility outcomes.

#### Missing and incomplete data

If no clinical contact is made with a subject following the index procedure, the subject will be considered lost to follow-up and will be excluded from analysis. Missing postoperative pressure measurements due to missed appointments will be addressed with mixed model repeated measures imputation. Missing postoperative pressure measurements due to amputation or mortality will be excluded from correlation analyses.

The primary outcome, MALE, is a composite outcome that accommodates potential intercurrent events such as reintervention and amputation, however, it does not include mortality. In the case of mortality, this will be

labelled as a competing risk and will be accommodated by the survival analyses models. The secondary outcomes will use a treatment policy strategy, where the variable will be included regardless of intercurrent events. However, specific intercurrent events of amputation, mortality or in certain outcomes intercurrent bypass surgery, will be included as competing risks in the survival analysis models.

## STUDY ADMINISTRATION

### Feasibility and study duration

Between the division of vascular surgery and the division of radiology, approximately six lower extremity endovascular revascularisation procedures per week are performed at the Civic Campus. Approximately half of these cases are expected to be eligible based on an audit of the prior year. With a target enrolment of 80 legs, enrolment could be achieved within 7 months if all cases are enrolled. The enrolment rate of eligible cases is expected to be moderate, given the non-invasive nature of this study. In total, 11 months have been allocated to study enrolment.

### Data sources

Baseline and postoperative follow-up clinical data will be collected through vOACIS-PROD (V.r7.3.0\_20130320). vOacis is the central electronic medical record system used by The Ottawa Hospital, and is where all vascular surgery clinical appointment and operative notes are documented. Perioperative data will be the only data collected in addition to standard medical care. This is the only data source that is a result of study member interaction with the study subjects.

### Data collection

After enrolment into the trial, the study administrator will collect baseline data based on relevant notes in vOacis as described above. Only the principal investigator and study coordinator will have access to the password and data collection forms.

Perioperative data collection will occur on the day of surgery. An automated non-invasive blood pressure cuff (NIBP) will be placed around the patient's arm, and additional ankle and toe blood pressure cuffs will be placed around the patient's leg and great toe with a distal photoplethysmography recorder. Because only femoral vascular access will be considered in this study, the blood pressure cuffs below the knees will be separate from the operative field and will be covered by standard draping procedure to maintain sterility.

The ankle blood pressure cuff size will be a universal Hokanson SC12 straight segmental cuff, 13 cm x 85 cm. Toe blood pressure cuff size will be chosen as the cuff width closest to 20% wider than the toe diameter. Available toe pressure cuffs are Hokanson UPC2.5 2.5 cm x 12 cm and Hokanson UPC3.3 3.3 cm x 12 cm. The FalconPro Viasonix machine will be used for NIBP measurements,

connected to a FalconQuad machine for Viasonix Disk PPG sensor input.

Prior to commencement of the procedure, the ankle and toe blood pressure of the affected limb(s) in addition to the blood pressure of the arms will be measured. If any regional anaesthetic such as epidural or spinal analgesia is to be administered, the preoperative measurement must be taken at minimum 15 min after anaesthetic administration to allow for onset of sympathetic blockade vasodilation. Preprocedure and postprocedure pressure measurements will be repeated three times at least 5 min apart to assess measurement variability.

After vascular access is obtained and the intra-arterial vascular sheath has been inserted, another set of blood pressure measurements will be obtained. This is because the physical presence of the intra-arterial instruments may affect distal leg and toe pressures. Following angioplasty, a repeat set of pressure measurements will be obtained prior to removal of intra-arterial instruments. The postintervention measurements will be repeated after repeated endovascular treatment on the same leg during the procedure, such as multilesion angioplasty, stent or atherectomy. Finally, after the completion of the procedure and removal of all intra-arterial instruments, a final set of postoperative measurements will be obtained.

If an ulcer or infection precludes great toe pressure measurement, an alternate toe will be used to measure toe pressure. If the baseline ABI or TBI is greater than 1.5, we will infer incompressible vessels and deem the measurement unreliable.

Postoperatively, patients will follow routine follow-up scheduled clinic and ultrasound appointments at 1–3 months, which will not involve any active study intervention. The angiograms will be de-identified and presented to a blinded investigator to determine procedural anatomic success. Data will be collected from these images and appointments, during which the observer collecting postoperative data will remain blinded to the intraoperative results. On completion of follow-up data collection, the datasets will be frozen and merged for analysis. The schedule of assessments is presented in [table 2](#).

Subject retention will be primarily promoted by the design of the study, which completes intraoperative measurements in a single and non-intrusive patient encounter during surgery. Postoperatively, the study leverages the Ottawa Division of Vascular Surgery as the only vascular surgical service in the public health region, to ensure complete data capture of postoperative outcomes. Because there is no further study-specific subject contact after surgery, we anticipate high postoperative retention rates. Subjects will be encouraged to attend all postoperative appointments at the time of enrolment, but will not be contacted by study personnel to promote postoperative appointment adherence.

### Blinding

The surgical operator, operating assistant, scrub nurse and any other member participating in the patient's

circle of care will be blinded from the intraoperative results of this study. The operators will rely on standard of care intraoperative feedback mechanisms such as intraoperative angiogram to guide the procedures. This blinding applied both to the intraoperative period as well as the postoperative period, such that the intraoperative pressure results will not factor into postoperative decision-making by members of the subject's circle of care.

As well as blinding clinicians involved in the administration of healthcare, all ultrasound technologists responsible for postoperative blood pressure measurements will be blinded from the intraoperative limb pressure results. Finally, the intraoperative pressure measurement data collection file will be 'frozen' and provided to our statistician before any postoperative clinical outcome data collection is performed. The study official who will then perform postoperative outcome data collection will be separate from the study members who performed intraoperative pressure measurements, and will be blinded from these results while performing postoperative outcome data collection.

#### Data monitoring and management

This is a single-centre study and all data will be stored locally. All intraoperative data collection will initially occur on hard copy datasheets, which will be stored in a locked container in a locked room within the study hospital, which is only accessible by the study member performing intraoperative data measurement. Each limb is assigned a 'study-specific identification number', which will be used to link data for analysis.

All intraoperative data will be transferred to a password-protected spreadsheet locally, which is held on The Ottawa Hospital server and will be updated until recruitment is complete, at which time the intraoperative dataset will be 'frozen' and sent to a statistician. Double data entry will be performed by a second study member will separately repeat data entry from the paper form to another password-protected spreadsheet, which will also be sent to the statistician to ensure accurate data coding between the two members.

Independent source verification will be performed by the statistician, by reviewing at random 20% of all paper case report forms. In addition, the intraoperative pressure data will be screened for outliers by flagging any pressure measurement value falling outside 2 SD of the baseline measurement for review. The statistician will have access to paper case report forms to ensure accuracy of data entry in these cases.

Postoperative outcome assessment will not start until recruitment is complete, and will be performed by two additional study members who will not have access to intraoperative results. Double data entry will be performed by each member into independently password-protected electronic datasets for all postoperative outcomes including the primary outcome of MALE. On completion of postoperative outcome measurements, the outcome datasets will also be available to the statistician

for final analysis and confirmation of accuracy between the double-entry files. At any point, discrepancy between double-entry files will be brought to the attention of the principal investigator for resolution.

The individual study members conducting intraoperative data collection will have separate password access to their individual files, in addition to the principal investigator and local ethics board who have access to all files as required by the ethics committee. This is designated as a minimal-risk study, and there will be no interim analysis for the purposes of safety monitoring. Due to the relatively short duration of the study, these passwords will remain constant during the study unless a security breach is suspected. All paper and electronic datasets will be retained for 10 years following completion of the study.

#### Access to data

The Ottawa Hospital Research Institute - Research Ethics Board (OHRI-REB) will have access to anonymised data at their discretion, as per REB policy. However, no third party investigators or corporate bodies will have access to study data prior to synthesis and dissemination.

#### Confidentiality

All data and records generated during this study will be kept confidential in accordance with institutional and OHRN-REB policies. The investigators will not use such data and records for any purpose other than conducting the study. Only necessary personal identification data will be collected, and deleted or destroyed at the earliest feasible time. Data will be collected and stored securely and anonymously in password protected files and on a hospital server, as described above.

#### Study timeline

Enrolment start date: October 2018.

Enrolment stop date: August 2019.

Data collection stop date: August 2020.

Submission for publication: September 2020.

#### ETHICS AND DISSEMINATION

##### Risk assessment

The only procedure affecting study subjects beyond the standard of care is a benign NIBP measurement of the lower extremities, which they already routinely receive serially in the same fashion before and after surgery at ultrasound appointments. On review of literature, there have been no reported adverse events resulting from blood pressure measurement of the lower extremity. However, cuff inflation at the ankle immediately following a lower tibial intervention such as angioplasty may theoretically encourage vessel thrombosis; the ankle cuff will not be inflated following any lower tibial interventions. The transiently inflated blood pressure cuff of the leg may be uncomfortable for the duration of inflation, similar to blood pressure measurement of the arm. This will be minimised by inflating the lower extremity blood

pressure cuffs to appropriate pressures standardised by the upper extremity inflations. The blood pressure cuffs will be applied several feet away from the operative field, addressing any potential compromise of surgical field sterility.

#### Reportable events

Any suspected (confirmed or unconfirmed) breach in confidentiality will be immediately reported to the OHRI-REB. This will include coordination with the review board for rapid notification of the patient(s) in question.

Any significant interruption in the flow of the operating theatre may be reported by any member of the operating theatre to the OHRI-REB. The study protocol, in addition to primary investigator, study coordinator and OHRI-REB contact information, will be posted and freely accessible in all vascular surgical operating theatres to ensure study transparency.

The study subjects will also be encouraged to report any irregular events to the study coordinator, principal investigator and/or OHRI-REB as described in the consent forms.

#### Consent

Consent for this study is necessary as there are measurements that will occur beyond the standard of care. These measurements, while they qualify as minimal risk, will be fully explained to the subjects prior to obtaining consent. The access to electronic health records will also be discussed. The coordinator obtaining consent will have no direct involvement in the medical care of the subject.

#### Protocol amendments

All protocol amendments will require REB approval, in addition to principal investigator and study coordinator consensus.

#### Patient and public involvement

There were no funds or time allocated for patient and public involvement, however, we have invited patients to help us develop our dissemination strategy.

#### Dissemination

Following completion of data analysis, the study will be synthesised and submitted for presentation at national and international vascular surgical society meetings, in addition to submission for publication in publicly accessible medical journals. All publicly presented and published data will describe the cohorts as a whole anonymously and will not include any direct identifiers.

#### Limitations

The eligibility criteria may unintentionally exclude subjects with a history of unrelated venous procedures such as great saphenous venous stripping, and include aortic stenting for occlusive disease, which is a relatively unique and rare procedure. Although these are anticipated to affect only a small subset of patients and will likely not have a differential effect, these eligibility

criteria were established at the time of enrolment and will not be changed during the course of the study to maintain integrity.

The original protocol guiding enrolment of the majority of subjects did not explicitly state that both arm blood pressures will be measured and that the highest systolic pressure will be used for calculations of pressure indices. This is the standard protocol for assessment of ABI and TBI, and this method of determining the arm laterality for use in calculations has been performed in all instances, but has not been explicitly described in the protocol until a revision on 21 June 2019.

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**Competing interests** None declared.

**Patient consent for publication** Not required.

**Ethics approval** This study has received OHRI-REB approval (Protocol 20180656-01H), which was most recently provided following an amendment on 10 January 2019.

**Provenance and peer review** Not commissioned; externally peer reviewed.

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