An Alternative Prophylaxis for Deep Vein Thrombosis Using Intermittent Electrical Stimulation

by

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Abstract

Deep vein thrombosis (DVT) is a blood clot that typically forms in the deep veins of the lower body and is the third most common cardiovascular disease, after myocardial infarction and stroke, in the world today. One of the causes of DVT, is the slow movement or stoppage of blood flow, known as venous stasis. Current methods of DVT prevention include anticoagulants and mechanical prophylaxis. Despite these methods having previously shown to lower the incidence of DVT, anticoagulant use is contraindicated in individuals with major bleeding risks and mechanical interventions often prove to be cumbersome and uncomfortable. The overall goal of my project was to investigate a novel method for DVT prevention, termed intermittent electrical stimulation (IES). The current study investigated the effects of IES on healthy typical, as well as post-stroke persons. The results showed that IES-induced contractions, lead to significant increases in venous flow compared to baseline, at relatively low levels of IES-induced contractions, and at comfortable levels of stimulation in typical and in post-stroke persons.

The results indicate that IES can sufficiently increase venous flow to prevent venous stasis and is comfortable for end users. Incorporation of IES into a clinical device, could serve to provide a feasible and effective alternative for DVT prophylaxis.

Preface

This thesis is an original work by Kahir A. Rahemtulla. The research project, of which this thesis is a part, received ethics approval from the University of Alberta Human Research Ethics Board, under the project name, “Prevention of deep vein thrombosis in immobile individuals using intermittent electrical stimulation,” No Pro00039421, October 24, 2017.

To my loving and joyful parents. I can never thank you enough for what you have given me.

Contents

Table of Figures

Table of Tables

1 Literature Review

1.1 Definition and Classification of Deep Vein Thrombosis

Deep vein thrombosis (DVT) is a blood clot, or thrombus, that forms in one or more of the deep veins, usually in the lower-body.[1] There are many risk factors that can increase the chances of developing a DVT, such as undergoing surgery, long periods of immobilization and having blood that is genetically predisposed to abnormal clot formation. DVTs can lead to further complications such as excessive swelling in the legs known as post thrombotic syndrome (PTS). Furthermore, DVTs become life-threatening when they dislodge from the venous wall, or embolize, and travel to the lungs where they can become lodged in the pulmonary vasculature, blocking the ability of blood flow to participate in necessary gaseous exchange. These clots are known as pulmonary emboli (PEs). Together, DVT and PE constitute the pathology known as venous thromboembolism (VTE).

1.2 Significance of DVT

VTE is one of the most prevalent cardiovascular diseases in the world today. With 10 million cases of VTE occurring each year, VTE is the 3rd leading vascular disease after acute myocardial infarction and stroke.[2] A systematic review performed by Raskob et al.,[2] which reviewed studies from Western Europe, North America, Australia and parts of Latin America, showed that the incidence for VTE ranged from 0.75 to 2.69 per 1 000 individuals. In Canada, the incidence of DVT, is 1-2 per 1 000 persons.[3]

To further add to its debilitating nature, VTE can be a chronic disease; it has been reported that 30% of all patients with a VTE, have a reoccurrence within 10 years.[4] Furthermore, PTS is a

chronic complication of DVT that causes leg redness and swelling, and can lead to leg ulcers, which are difficult to treat.[5] PTS develops in 20-50% of patients with DVT.[6]

The ubiquity of VTE and its chronicity can have significant impacts financially. In 2014, it was estimated that the yearly economic burden of VTE in the US was $7-10 billion USD.[7] However, perhaps the most severe attribute associated with a DVT is its link to developing a PE. It is estimated that 600 000 cases and an excess of 50 000 deaths can be attributed to PE in the United States annually.[8] PEs can have severe acute impacts on mortality; studies have shown that 12% of PEs have one-month mortality rates[9] and about 20% of patients with PE die before being diagnosed or shortly after.[10] Furthermore, 90% of all PEs result from DVTs,[11] suggesting that DVT prevention could have profound effects on negating the mortality and morbidity caused by PEs. Lastly, 70% of PEs have asymptomatic DVTs,[11] illustrating DVT's insidiousness and the need for prevention in those who are asymptomatic but are at a higher risk of developing DVT.

1.3 Hemostasis

1.3.1 Overview of Hemostasis

Although the formation of pathological clots can be harmful, the process by which clots are formed, or hemostasis, is a vital physiological process that minimizes the amount of blood lost following injury. Therefore, it is important to understand the normal progression of hemostasis before grasping the etiology of DVT.

During blood vessel injury, hemostasis prevents excessive bleeding, stabilizes the injury and provides the blood vessel time to heal. Hemostasis is comprised of two parts, primary hemostasis and secondary hemostasis. Primary hemostasis involves the formation of a "platelet-plug" to initially stop blood from leaking outside the vessel. However, it is not a sustainable

solution and requires the protein, fibrin, which is formed in secondary hemostasis, to maintain a longer duration of clot sustainability. This Chapter examines the biochemical mechanisms of primary and secondary hemostasis in greater detail. Furthermore, the process of anticoagulation and clot-breakdown is also addressed.

1.3.2 Primary Hemostasis

Primary hemostasis is the formation of the platelet-plug, which forms a temporary clot to prevent bleeding, and is comprised of four steps: vasoconstriction, platelet adhesion, platelet activation and degranulation and platelet aggregation (Figure 1-1). When damage to the endothelial wall of the blood vessel occurs, vasoconstriction is needed to limit the amount of blood throughput, and in turn blood loss. It achieves this through two main mechanisms. The first is via a nerve reflex, where the smooth muscles of the blood vessels contract. The second is through the peptide endothelin, which acts to contract the smooth muscle cells in blood vessels, resulting in vasoconstriction. Moreover, vasodilators, such as nitric oxide (NO) and prostacyclin, decrease in concentration, furthering blood vessel vasoconstriction.

The second step of primary hemostasis is platelet adhesion. Platelets are typically prevented from sticking to endothelial walls of blood vessels by NO and prostacyclin. During injury, the concentration of these vasodilators reduces, and platelets encroach upon the endothelial walls and the site of injury. For platelets to form a plug at the site of injury, they require adhesion to von Willebrand Factor (vWF), which is attached to the subendothelial collagen. vWF is normally present in the blood but is secreted in higher concentrations by the endothelial cells at the site of injury. Once bound to the subendothelial collagen, vWF can bind to the platelet surface membrane, through the glycoprotein Ib alpha chain surface receptor, also

known as the GPIb receptor.

Once platelets bind to vWF, the third step – platelet activation and degranulation – can occur. This binding causes a conformational change in the platelet and allows its GPIIb/IIIa receptor to bind to fibrinogen, a necessary step that occurs only if the platelet is activated, leading eventually to the formation of a network of platelets. Furthermore, when the platelets are activated, granule sacs are released from the platelets into the blood, further promoting clotting. These granule sacs contain alpha and dense granules. While alpha granules, release fibrinogen and vWF, dense granules, release serotonin, ADP and calcium, which promote vasoconstriction, platelet activation and aggregation and secondary hemostasis, respectively. Additionally, activated platelets secrete thromboxane A2, a vasoconstrictor that causes increased platelet activation and helps with the last step of primary hemostasis, aggregation. Platelet aggregation is the binding of fibrinogen to the GPIIb/IIIa receptor on activated platelets as mentioned earlier. These network of connections between platelets and fibrinogen, are known as the platelet-plug.

1.3.3 Secondary Hemostasis

Primary hemostasis is a transient solution and requires improvements to increase its structural integrity through the addition of fibrin protein molecules, which are involved in secondary hemostasis. The purpose of secondary hemostasis is to convert fibrinogen to fibrin, a protein that promotes a more stable clot than was produced in primary hemostasis, through a process known as the coagulation cascade (Figure 1-2).

Fibrinogen is present in the blood as a zymogen and must be catalyzed to form fibrin through a series of coagulation factors that move through two main pathways, the intrinsic and extrinsic pathways, that are activated by internal and external trauma, respectively. These

pathways involve a cascade of reactions and exist to improve the efficiency of fibrinogen-to-fibrin conversion.

The intrinsic pathway involves a series of coagulation factors (factors XII, XI, IV, VIII) that catalyze one another through a cascade, amplifying the concentration of the next factor to maximize the amount of the final product, factor X. Factor X, in combination with factor V, will catalyze prothrombin into thrombin, where thrombin will catalyze fibrin into fibrinogen in the common pathway. The extrinsic pathway similarly uses combinations of coagulation factors (tissue factor and factor VII) to produce high amounts of factor X. Similar to the intrinsic pathway, the extrinsic pathway converges with the common pathway at factor X. Furthermore, thrombin institutes positive feedback on many factors of the intrinsic and extrinsic pathway to further increase fibrin formation. When fibrin is formed, factor XIII catalyzes cross-linking between fibrin strands to ensure a consolidated and stable clot is formed.

1.3.4 Anticoagulation and Thrombolysis

It is apparent that hemostasis must have a control mechanism to prevent an infinite propagation of clot development. Indeed, anticoagulation and thrombolysis – a process that prevents clots from forming and a process that breaks down clots after they have been formed, respectively – are two processes to ensure thrombosis development is controlled.

Anticoagulation is the process by which the body prevents clots from forming. It achieves this by preventing both primary and secondary hemostasis. Primary hemostasis is prevented by two molecules secreted by endothelial cells, NO and prostacyclin. These molecules prevent platelets from sticking to the endothelial walls and cause vasodilation to ensure adequate blood flow through the vessel. In turn, this prevents the formation of a platelet-plug. Secondary

hemostasis is prevented by two other molecules secreted by endothelial cells, heparin-like molecule and thrombomodulin. Heparin-like molecule interacts with anti-thrombin III – already present in the blood – to inactivate thrombin. Recall, thrombin is responsible for transforming fibrinogen into fibrin to form a stable mesh. Furthermore, this interaction additionally inactivates factor X. Thrombomodulin also interacts with thrombin, altering its normal function. When a thrombomodulin/thrombin complex is formed, protein C, with activation from protein S, becomes activated and interacts with the thrombomodulin/thrombin complex. This interaction inhibits factors V and VIII from continuing the intrinsic pathway of the coagulation cascade.

Thrombolysis is the process by which the body breaks down previously formed clots. Endothelial cells play a vital role by releasing plasminogen activator, which transforms plasminogen, the zymogen normally present in the blood, into plasmin. Plasmin breaks down fibrin and fibrinogen at a clotting site, thus allowing breakdown of the clot.

1.4 Etiology of DVT

The body's natural equilibrium mechanisms allow for a balance between clotting and clot prevention to ensure that neither hemorrhage nor thrombosis outweighs the other. Excessive clotting leads to a pathological thrombosis. In 1856, Rudolf Ludwig Carl Virchow described three key conditions that contribute to thrombus formation that still hold true today.[9,11-13] This triad is composed of stasis, hypercoagulability and endothelial damage, known as *Virchow's Triad*. Furthermore, each triadic component can be associated with genetic and/or behavioral risk factors. These will be briefly addressed here and will be elaborated on more thoroughly in Section 1.6 Risk Factors.

Stasis is defined as the slow movement or stoppage of blood flow. It can be caused by pathology such as congestive heart failure and polycythemia (hyperviscosity due to overproduction of red blood cells). Stasis can also arise due to a reduction in mobility, which is a suspected mechanism for thrombosis in long-distance travellers[14] and in hospitalization[15]. In reduced mobility cases, stasis can lead to a DVT by increasing the contact time of coagulation factors with the endothelium.[11]

Another element of Virchow's Triad is vessel endothelial wall damage. Normal endothelium is antithrombotic and damage exposes subendothelial collagen, allowing for platelet binding and promotion of coagulation. Endothelial damage can be commonly induced through major surgery, trauma or a chronic indwelling of a venous catheter.

The last element of Virchow's triad is hypercoagulability – having blood that has a high proclivity to clot. Hypercoagulability can be either hereditary or acquired. Common hereditary hypercoagulability, or thrombophilia, include Factor V Leiden mutation, prothrombin gene mutations and deficiencies in antithrombotic factors, such as antithrombin and protein C.[11] Thrombophilia can be acquired through factors such as cancer, chemotherapy, oral contraceptives, pregnancy, central obesity and heparin-induced thrombocytopenia (HIT). Cancer, for example, can induce thrombophilia through producing procoagulant proteins or releasing microparticles that lead to hypercoagulable states;[16,17] oral contraceptives can result in hyperestrogenemia, which increases synthesis of procoagulant proteins and decreases synthesis of anticoagulant and fibrinolytic proteins.[18]

1.5 Pathophysiology of DVT

DVTs arise disproportionately in the lower extremities in comparison to the upper extremities; it has been shown that 96% of DVTs manifest in the lower extremities while 4% manifest in the upper extremities.[19] In the lower extremities, a majority of DVTs originate in the calf.[20] However, many of these are asymptomatic, as 88% of lower extremity DVTs that are symptomatic, involve more proximal vasculature of the leg.[20] Furthermore, DVTs that involve the proximal veins lead to a higher rate of recurrent VTEs.[21]

Within the veins themselves, a majority of DVTs form in the cusps of the valves.[22] This occurs because the avascular venous valve environment (lacking of blood vessels) promotes fibrin formation. Due to its avascular nature, coupled with reduced oxygenated blood flow in the veins, the valvular endothelium is predisposed to be hypoxemic. This hypoxemic environment causes the endothelium to express adhesion molecules that attract leukocytes, which transfer tissue factor to the endothelium.[23] As visited previously, tissue factor will bind with factor VIIa to begin the extrinsic pathway of the coagulation cascade, forming fibrin. If a clot is not resolved, it eventually becomes incorporated as part of the vessel wall and a layer of endothelial cells form over it through re-endothelization.[23] This incorporation, known as organization, allows for blood flow to resume but destroys the valves and causes scarring of the veins.[24] The resulting complication is PTS due to this scarring as well as venous reflux that results from the diminishment of valvular function.[24]

1.6 Risk Factors of Deep Vein Thrombosis

Risk factors for DVT have been well documented and encompass environmental and heritable factors.[9,25-27] Independent risk factors include high BMI,[28] trauma or fracture,[25] active

cancer with[25,29] or without[25] chemotherapy, major surgery,[25] hospitalization for an acute medical illness,[26] nursing home confinement,[26] neurological disease with leg paresis,[4] pregnancy or postpartum[27] and oral contraceptive use.[30] Other independent risk factors of DVT include central venous catheterization,[26] transvenous pacemaker,[26] prior superficial vein thrombosis,[25] increased baseline plasma fibrin D-dimer[31] and family history of VTE.[32] Furthermore, sex, age and ethnicity play a role in the incidence of DVT; male sex and age above 60 years,[33] as well African American individuals,[34] have been shown to have higher incidence rates. Conversely, some attributes have been shown to lower the risk of DVT. These include having chronic liver disease[25] and taking HMG-Coenzyme A reductase inhibitors,[35] although the mechanisms of their protective effects remain unclear.

Heritable traits are often risk factors for DVT. A study in European populations demonstrated that Factor V Leiden and prothrombin gene mutation, with a prevalence of 3-7% and 1-2%, respectively, are the most common heritable disorders.[36] Other significant heritable thrombophilia pathologies include antithrombin deficiency, protein C and protein S deficiency.[36]

Typically, multiple risk factors affect an individual, rather than a single isolated factor; however, high-VTE risk surgeries, cancer and immobilization are key risk factors that profoundly influence the societal toll of DVT and require further attention. Neurosurgery, knee or hip arthroplasty, abdominal pelvic surgery for cancer, renal transplantation and cardiovascular surgery, have all been deemed “high-risk” VTE inducing procedures.[37] In cancer patients, VTE is the second leading cause of death.[38] Furthermore, cancer patients contribute up to 20% of VTEs in the community.[26] Additionally, cancer patients have a two- to three-fold risk of a recurrent VTE, compared to patients who do not have cancer.[39]

In hospitals and nursing homes, the risk of VTE is 100 times greater than that of community residents.[40] The incidence of VTE in hospitals and nursing homes is almost 60%,[40] where immobilization is often a contributing factor.[15] Together with surgery, immobilization has been shown to account for 15% of VTEs.[41] Furthermore, the impacts of immobilization are not exclusively restricted to individuals in health care settings. Long-distance flights (eight or more hours) have a two- to four-fold increase in DVT risk, particularly when other risk factors are present.[42]

As knowledge regarding DVT risk factors has grown tremendously over the past few decades, better preventative measures can be taken to reduce the incidence of DVT. However, a third to a half of DVT cases still remain unlinked to a cause,[43] making DVT a rather insidious problem to treat. Furthermore, even in groups that have been identified as high risk, prevention measures are still suboptimal. In arthroplasty patients, with current VTE prophylaxis, 1 out of 100 patients with partial knee and 1 in 200 patients with hip arthroplasty develop a symptomatic VTE prior to hospital discharge.[44] Moreover, in cancer patients, the incidence of DVT is expected to increase as patients live longer and take on more treatment protocols, despite better preventative measures than in past.[45] DVT's subtlety, its increasing likelihood to increase in prevalence in high-risk groups and its ability to lead to potentially fatal PEs, affirm the need for new prophylactic interventions that are suitable to a variety of users.

1.7 Current Methods of Prophylaxis for DVT

1.7.1 Overview of Prophylactic Methods for DVT

Designing interventions for prophylaxis rather than reactionary approaches is imperative for reducing the incidence of DVT and the impact of its complications. This section provides an

overview of current methods of DVT prophylaxis including anticoagulants and mechanical prophylactic methods (including graduated compression stockings, intermittent pneumatic compression and neuromuscular electrical stimulation).

1.7.2 Anticoagulants for DVT Prophylaxis

Anticoagulants are a major pillar in DVT prophylaxis.[13] They serve to inhibit different aspects of the coagulation cascade depending on the type of anticoagulant, moving the balance of hemorrhage and thrombosis away from thrombosis and towards hemorrhage. In general, anticoagulants reduce the chances of clotting, but major bleeding risks are a significant limitation of this intervention. This section will discuss the most imperative anticoagulants, examining their mechanisms of action, indications and contraindications to use.

Warfarin, an orally administered anticoagulant, blocks the regeneration of vitamin K(1) epoxide, thus preventing synthesis of vitamin K-dependent clotting factors (factors II, VII, IX and X) and secondary hemostasis.[46] Warfarin is an effective method of DVT prophylaxis, resulting in a 21% lower incidence after major surgery compared to no prophylaxis.[47] Furthermore, warfarin reduces the incidence of DVT in those who have a central venous catheter compared to no prophylaxis.[48] Other warfarin indications include atrial fibrillation and valvular replacements.[49] However, warfarin therapy has a number of challenges. When first administered, warfarin requires overlap with heparin anticoagulants because it takes several days for it to impact coagulation. Furthermore, warfarin therapy requires constant monitoring to titrate its dosage to maintain blood coagulability between 2.0-3.0 (based on the international normalized ratio), which can be taxing to the patient and medical staff.[50] Lastly, warfarin can have interactions with many medications and foods.[51]

Heparins are an injectable class of anticoagulants, with sub-classes including unfractionated heparin (UFH), low-molecular-weight heparin (LMWH) and fondaparinux. UFH inhibits factor Xa and thrombin, while LMWH and fondaparinux preferentially inhibit factor X to prevent fibrin formation. UFH is administered intravenously, while LMWH and fondaparinux are administered subcutaneously. UFH requires dose adjustments and monitoring while LMWH does not require monitoring and can be administered at a constant dosage.[13]

Heparins are effective in reducing the incidence of VTE.[52-56] In a randomized controlled trial, Bergqvist et al.[57] reported that LMWH significantly reduced DVT incidence by 21%, compared to the placebo group in hip arthroplasty patients. Furthermore, a meta-analysis of randomized trials in general surgery showed a significant reduction in asymptomatic DVT with LMWH use compared to placebo and no treatment.[58] Turpie et al.[59] performed a meta-analysis of four randomized, double-blind studies, and showed that fondaparinux can be even more effective than LMWH in reducing the incidence of VTE in orthopedic patients. Although, LMWH has been shown to be a more efficacious and safe treatment than UFH,[60] UFH is indicated for patients undergoing thrombolysis and for severe renal impairment, due to its shorter half-life, ease of monitoring and ability to immediately reverse its effects with protamine.[13]

Despite the consistent demonstrated effectiveness of heparins, one of the major complications of these anticoagulants is heparin-induced thrombocytopenia (HIT). HIT is where IgG antibodies bind to heparin/platelet complexes and produce a potentially dangerous hypercoagulable state.[61] The absolute risk for HIT with UFH has been shown to be 2.6% and 0.2% with LMWH.[62] In such a scenario, fondaparinux or other non-heparin anticoagulants are recommended for prophylactic therapy.[63]

Direct oral anticoagulants (DOACs) were introduced over the past decade for treatment of VTE. This anticoagulant class most notably consists of thrombin inhibitors (e.g., dabigatran) and factor Xa inhibitors (e.g. rivaroxaban, apixaban and edoxaban). DOACs are administered at fixed doses without need for monitoring and have little interaction with medications or food, thus overcoming many of the hurdles presented by vitamin K antagonists like warfarin.[64] A number of large phase 3 trials have shown that DOACs are as effective as vitamin K antagonists in preventing VTEs and have relatively lower clinically relevant major bleeding risks compared to vitamin K antagonists.[65-70]

Despite the demonstrated effectiveness of anticoagulants in lowering the incidence of DVT, hemorrhagic complications can prevent individuals from using anticoagulants for prophylaxis. Randomized controlled trials that compared a variety of anticoagulants to placebo, have shown that major bleeding rates are between 0.2-5.6%, when administered for DVT prophylaxis.[71] Those of highest concern for major bleeding episodes include greater than 65 years of age, history of gastrointestinal bleeding, anemia, history of stroke, diabetes, renal insufficiency, hypertension, malignancy and previous VTE.[72-75] Risks of bleeding often challenge clinicians in determining the cost-benefit of these medications where bleeding risks are a concern, making them less ideal solutions in certain scenarios.[76] To summarize, anticoagulants are an established modality of DVT prophylaxis in many applications. Yet, their limiting factor is the risk of major bleeding, making their use impractical in certain patient populations, thus creating demand for other methods of DVT prophylaxis.

1.7.3 Mechanical Methods for DVT Prophylaxis

1.7.3.1 Graduated Compression Stockings for DVT Prophylaxis

Graduated compression stockings (GCS) are wearable garments, donned on the legs of users in efforts to prevent PTS, leg edema, chronic venous insufficiency (CVI) and DVT. Although the exact mechanism to prevent DVT and resulting complications by GCS is still unclear, it is thought that the application of a graded circumferential pressure gradient on the leg, distally to proximally, allows blood from the superficial venous system to reach the deep venous system through perforator veins, increasing the volume of flow and reducing stasis.[77]

Proponents of GCS use for DVT prophylaxis often relied on its ability to prevent PTS,[78,79] which is a sequalae of 50-60% of DVTs. Although prevention of DVT sequelae with GCS use is valid, GCS' ability to prevent DVT formation has demonstrated inconclusive incidence, as posited by a recent Cochrane Review.[80] This study[80] shows that GCS prevents DVT in general and orthopedic surgery settings, but is inconclusively effective in other settings and has not shown to reduce the risk of PEs.

The CLOTS trial 1, a multicenter, randomized controlled trial, which evaluated the risk of DVT development in stroke patients with GCS, further draws uncertainty surrounding the effectiveness of GCS use for DVT prophylaxis.[81] This study[81] reported a non-significant absolute reduction in DVT risk with GCS use. In fact, GCS use lead to more complications compared to non-use, such as skin breaks, ulcers, blister and skin necrosis. Furthermore, the CLOTS trial 2,[82] demonstrated that thigh-length GCS, while potentially a form of GCS with less compliance from patients, was superior to below-knee GCSs in reducing DVT incidence. Due to the lack of conclusive evidence of GCS in lowering the incidence of DVT and its potential for complications, a requirement for other mechanical interventions is needed.

1.7.3.2 Intermittent Pneumatic Compression for DVT Prophylaxis

Another commonplace mechanical method for DVT prophylaxis is intermittent pneumatic compression (IPC). IPC consists of inflatable pads that wrap around the leg, which inflate and deflate cyclically, to exert intermittently circumferential pressure on the leg and a pressure gradient from distal to proximal muscles.[83] Its mechanism of action to prevent DVT remains unclear,[84] but it is thought that the external compression increases blood flow in an attempt to prevent venous stasis.[83] Furthermore, an increase in fibrinolytic activity may play a role.[85]

The reduction of DVT incidence via IPC has been well documented.[86-90] Urbankov et al.[88] in a meta-analysis, demonstrated that IPC can reduce the risk of DVT by 60% compared to no prophylaxis including anticoagulants. In the CLOTS trial 3,[89] a multicenter randomized, controlled trial to assess IPC in people who have had stroke, IPC reduced the risk of DVT by 3.6% compared to no IPC. Other studies have shown IPC to be effective in DVT prevention in post-operative patients,[90] and when used synergistically with anticoagulants.[83,91]

However, a major drawback of IPC is that its effectiveness in DVT prevention is highly dependent on its user compliance.[92] IPC user compliance has been substandard in the past due to itchiness, excessive heat, sweating, lack of portability and excessive noise.[93-96] Some have investigated the potential of portable IPC devices in an effort to improve patient compliance,[96] but these systems are still in early development. Furthermore, IPC has limited effectiveness in specific high-risk populations, which include cancer, greater than 60 years of age and those with previous history of DVT.[97] Lastly, IPC can lead to severe complications such as peroneal nerve palsy and neurovascular compression, although rarely.[98,99]

1.7.3.3 Neuromuscular Electrical Stimulation for DVT Prophylaxis

Although anticoagulants and IPC have shown effectiveness in DVT prevention, hemorrhaging risks and low patient compliance remain consistent concerns. Therefore, an effective, patient compliant, non-hemorrhaging modality for DVT prophylaxis is needed. Neuromuscular electrical stimulation (NMES) may provide an alternative modality that could fulfill this requirement. NMES can be defined as the application of current to the skeletal muscle nerve branches via electrodes attached to the skin, to produce muscular contractions.[100]

NMES for rehabilitation is not new. Previous applications of NMES include prevention of deep tissue injury, a dangerous class of pressure ulcers,[101] restoration of motor loss in stroke populations,[102] prevention of muscle wasting in seniors[103] and increase of exercise tolerance in COPD,[104] among many other applications.

Utilizing NMES for DVT prophylaxis is also not a new phenomenon. Some of the first studies documented date back to 1964, and were performed by Doran et al.[105] who posited that NMES can prevent venous stasis in perioperative settings. However, its use was limited at that time due to the pain it induced in users.[105-107] Over the past two decades, significant strides have been made to develop miniaturized NMES devices, electrodes and stimulation paradigms that improve user comfort.[108] These will be explored further in this section. Other potential benefits of NMES when used for DVT prophylaxis, include reducing pain associated with intermittent claudication,[109] improving orthostatic limb edema,[110] preventing recurrent DVTs when used for PTS treatment,[111] improving microvascular circulation[112,113] and improving lymphatic function with associated lymphedema.[114]

1.7.3.3.1 Physiology of NMES for DVT Prophylaxis

To induce voluntary muscle contractions, the motor cortex sends commands to the spinal cord in the form of action potentials.[115] These in turn result in action potentials generated in the motor neurons innervating the muscles of interest. These action potentials propagate through the motor axons towards the neuromuscular junction, where they cause the release of acetylcholine. The release of acetylcholine generates action potentials that propagate along the muscle fiber membrane and cause the release of calcium from the sarcoplasmic reticulum. Calcium enables actin and myosin to bind and slide against one another, producing a contraction and generating force.

With surface electrical stimulation applied to peripheral nervous system, the electrical stimulus creates an electrochemical environment that produces an action potential in the axons of peripheral nerves, instead of in the cell bodies of motor neurons.[115] The action potentials then propagate to the neuromuscular junction producing the excitation-contraction coupling described above. Innervated muscles are more easily excited by activating their corresponding nerve. However, denervated muscle fibers can also be activated through electrical stimulation, but because nerves are more excitable than muscle fibers, much higher stimulation amplitudes are needed to activate muscle fibers directly. Pain becomes a limiting factor with higher currents and voltages; thus, direct muscle stimulation is not typically performed.

Muscular contractions of the calf – induced voluntarily or via electrical stimulation – act as a physiological pump that plays a vital role in enhancing venous return from the lower limbs to the heart.[116] It does this through generating up to 250 mmHg of intramuscular pressure, compared to 9-15 mmHg in a relaxed state.[116] These pressure gradients lead to rapid movement of blood flow from the deep veins of the calf, to the more proximal areas of the lower

extremities, preventing venous stasis and therefore DVT formation.

However, differences between voluntary and NMES-induced contractions exist. In voluntary contractions, muscle fibers are recruited in order of size – the size principle.[115] This principle states that muscle fibers will be recruited starting from the smallest motor units, followed by activation of the larger motor units [a motor unit is comprised of a motor neuron and the muscle fibers that it innervates]. In NMES-induced contractions, recruitment order is reversed as larger motor units are often preferentially recruited. These larger motor units are more susceptible to fatigue; therefore, making muscular fatigue a potential drawback with NMES if stimulation is delivered frequently. Furthermore, NMES-induced contractions are less asynchronous, another potential factor leading to more fatigue when compared with voluntary contractions.[115]

1.7.3.3.2 Muscles Targeted by NMES for DVT Prophylaxis

Prevention of DVT via NMES is thought to stem from its activation of the calf-muscle pump, causing an increase in venous flow and thus reducing venous stasis – one of the three components of Virchow's triad.[117] Stimulation that targets the posterior aspects of the leg, compared to anterior muscles demonstrated greater venous volume emptying of the popliteal vein, and increases in peak venous velocity from baseline in the femoral vein.[113,118] To better target these muscles, Lyons et al.[119] demonstrated that the optimal site for NMES electrode placement involves placing the cathode high on the calf, just distal to the end of the proximal muscle head, and placement of the anode "well above the Achilles tendon."[119] Electrodes should be bigger (around 81 cm^2 compared to smaller sizes of 9 or 36 cm^2) to reduce pain with use.[120] Other efforts have investigated stimulation of the nerve directly to improve venous flow and user

comfort instead of delivering stimulation to the skeletal nerve branches; however, the effect on venous flow and user comfort have been inconclusive.[121,122]

1.7.3.3.3 NMES Stimulation Parameters and their Effect on Hemodynamic Characteristics

NMES can induce either one of two types of contractions: tetanic or twitch contractions. Tetanic contractions are sustained muscle contractions that are evoked when the motor neurons conduct action potentials at a high frequency, while twitch contractions are generated by a single action potential and fire at a slow enough rate, such that, summation between action potential does not occur.[100] Tetanic contractions of the calf-muscles have demonstrated significantly higher increases in venous ejection volume[123] and in peak venous velocity,[124] compared to single-twitch contractions, making tetanic contractions more effective from a hemodynamics perspective.

Parameters related to the stimulation waveform can also be modified to ensure sufficient hemodynamic performance of NMES, while minimizing discomfort and muscle fatigue. To best achieve this, the following has been recommended from literature for NMES waveform design: biphasic, charge-balanced waveforms have been shown to be most comfortable for users;[100] a pulse-with of 300 μs has been shown to be the most suitable for increases in venous flow, without comprising comfort for users;[125] frequency of each bout of stimulation between 20-40 Hz maximizes the increases in venous flow while being cognizant that higher frequencies can fatigue the stimulated muscles faster;[119,125] an "OFF" time of at least four seconds between stimulations is recommended to allow for muscle recuperation, adequate venous refilling and to prevent muscle fatigue.[119,126]

One of the most critical, yet, least studied components of NMES parameters is the stimulation amplitude. Although a positive correlation between stimulation amplitude and

popliteal peak venous velocity,[127,128] as well as with the strength of induced muscular contractions,[129] have been demonstrated, a clear identification of the best stimulation amplitude levels to increase venous flow is lacking. Therefore, an opportunity exists to better direct future NMES interventions by quantifying the stimulation amplitude needed, a factor that was investigated in this work.

1.7.3.3.4 Reduction of DVT Incidence with NMES

The ability of NMES to lower the incidence of DVT has been studied in post-operative settings as early as 1967, showing a 12.7% absolute reduction in incidence and a 61% relative reduction in incidence compared to no prophylaxis.[106,107,130] When compared to heparin, NMES reduces the incidence of DVT in select types of surgeries.[131] Certain clinical scenarios, such as total knee arthroplasty with perioperative application,[132]and in neurosurgical patients when used post-operatively in conjunction with anticoagulants,[133] have demonstrated effectiveness of NMES. Effectiveness was also demonstrated with perioperative use in patients with malignancy.[123] However, in other cases, such as in trauma patients[134] and in patients undergoing major upper abdominal or thoraco-abdominal procedures,[135] NMES was ineffective.

To date, the potential of NMES to prevent DVT in large, diverse, populations have not been tested. Moreover, the inconsistency of NMES application between studies had made it difficult to ascertain the effectiveness of NMES in reducing the incidence of DVT.[117] Although, NMES is likely to lower the risk of DVT compared to no prophylaxis,[136] comparisons to other interventions cannot be made with the current level of evidence. Thus, calls have been made for adequately powered, high-quality, randomized, controlled trials to provide guidance on the potential effectiveness of NMES.[136]

1.7.3.3.5 An Example of Commercial NMES Devices for the Prevention of DVT

Recognizing the opportunity that NMES could be an effective prophylactic method for DVT and the downfalls of existing mechanical prophylaxis, commercial NMES devices have been developed. Most notable of these devices are the VEINOPLUS®[108] and the geko™.[137] The VEINOPLUS® delivers brief (50ms-long) trains of stimuli up to 120 times per minute, stimulating the gastrocnemius muscles,[108] while the geko™ delivers a single stimulus pulse, 60 times per minute, and stimulates the common peroneal nerve that innervates the tibialis anterior muscles.[137]

These devices have been shown to lead to significant increases in venous flow of the popliteal vein, at comfortable levels of stimulation, mainly in healthy persons.[108,138] Usage in patient populations have shown similar results, including usage in persons with leg casts[137] and chronic post-stroke (>6 months) persons.[139] Compared to other modes of mechanical prophylaxis, the geko™ can produce similar increases in popliteal peak venous velocity from baseline as IPC, at comfortable levels of stimulation for the user.[93,138] Furthermore, the geko™ has demonstrated that NMES is already capable of being an established method of DVT prophylaxis, as implemented in England.[140] In this setting, the geko™ has been recommended for "people for whom other methods of prophylaxis are impractical or contraindicated and have a high risk of VTE," [140] and has been shown to reduce the cost of a DVT by €170, compared to no prophylaxis.[140]

Despite the advances and promising performance of these technologies, the approach and the translational potential to everyday clinical settings of these devices, is flawed. Firstly, by stimulating every second in the case of the geko™, or up to 120 beats per minute in the case of the VEINOPLUS®, these devices focus on imitating a heartbeat rate. Not only is mimicking the

rate of a heartbeat an incorrect premise for the prevention of DVT,[106] stimulating too often in a clinical setting where 24 hours of use is required, would likely induce muscle fatigue. This is particularly true in the case of the VEINOPLUS® which uses pulse trains.[108] Secondly, because the geko™ not only uses twitch contractions, but also stimulates the tibialis anterior muscle, only 26% of the muscle mass in the leg is activated during stimulation, failing to empty the deep veins of the posterior compartment adequately, in contrast to what usually occurs when walking.[141] Lastly, because devices such as the VEINOPLUS® stimulate the gastrocnemius muscle repeatedly without keeping the foot in a neutral position after each induced contraction, an increase in spasticity and/or contractures could result especially in populations with neurological conditions such as stroke, which could limit user acceptance. Therefore, a new stimulation paradigm that can mitigate the limitations in current NMES devices and provide more effective and user-compliant systems is needed. Such systems could circumvent the problems associated with current anticoagulant and other mechanical interventions.

1.8 Intermittent Electrical Stimulation as an Alternative Form of DVT Prophylaxis

The Mushahwar Lab has been investigating a novel stimulation paradigm, intermittent electrical stimulation (IES), for the use of DVT prophylaxis. IES differs from previous stimulation paradigms by administering stimulation once every 3 minutes, with stimulation delivered to the gastrocnemius and the tibialis anterior muscles in a sequential fashion. By stimulating every 3 minutes, compared to other interventions which typically stimulate 60 – 120 times a minute, we hypothesize that IES is less likely to induce muscle fatigue. Furthermore, by stimulating the gastrocnemius and tibialis anterior muscles sequentially, IES will bring the foot back to a neutral position after each cycle of stimulation, stretching the gastrocnemius muscle to

avoid contractures and to possibly prevent spasticity in people who have neurological conditions.

1.9 Overview of Masters Work

1.9.1 Masters Scope

The focus of my thesis work was to investigate IES' effectiveness in increasing venous flow in neurologically intact and post-stroke persons. The main goal was to determine the strength of muscular contractions needed to elicit sufficient increases in venous flow in the popliteal and femoral veins in neurologically intact people and the popliteal vein in post-stroke people.

1.9.2 Stimulation Paradigm

The stimulation paradigm chosen included a 1s "ON" stimulation of the gastrocnemius muscle, followed by a 1s "ON" stimulation of the tibialis anterior muscle, repeated every 3 minutes. One second for each muscle was chosen to ensure enough time for an adequate tetanic contraction to form without inducing muscle cramping. Parameters of stimulation chosen were biphasic, 17.5 Hz frequency and 300 μs pulse width. The stimulation amplitude of the gastrocnemius muscle was modulated throughout the experiment to produce recruitment curves in each subject. A recruitment curve examines the relationship between stimulation amplitude and venous velocity, and force of contractions induced with stimulation and venous velocity. This was conducted to elucidate the amount of contraction needed to yield sufficient increases in venous flow with IES.

1.9.3 Hypothesis

I hypothesized that:

1) IES induces significant increases in peak venous velocity relative to rest-flow in the *popliteal* vein of typical healthy persons at low levels of muscular contraction.
2) IES induces significant increases in peak venous velocity relative to rest-flow in the *femoral* vein of typical healthy persons at low levels of muscular contraction.
3) In post-stroke patients with atrophied muscles, IES induces significant increases relative to rest-flow in popliteal peak venous velocity.
4) IES is comfortable for use by typical and post-stroke persons.

Null hypotheses:

1) IES does not produce sufficient increase in peak venous velocity for typical and post-stroke peoples.
2) The use of IES is uncomfortable.

Chapter 2 of my thesis describes the experiments I carried out to validate my hypotheses, and the results obtained, accompanied with their significance. Chapter 3 outlines the conclusions of my work, along with future directions for the clinical adoption of IES as a method for DVT prophylaxis.

1.10 Figures

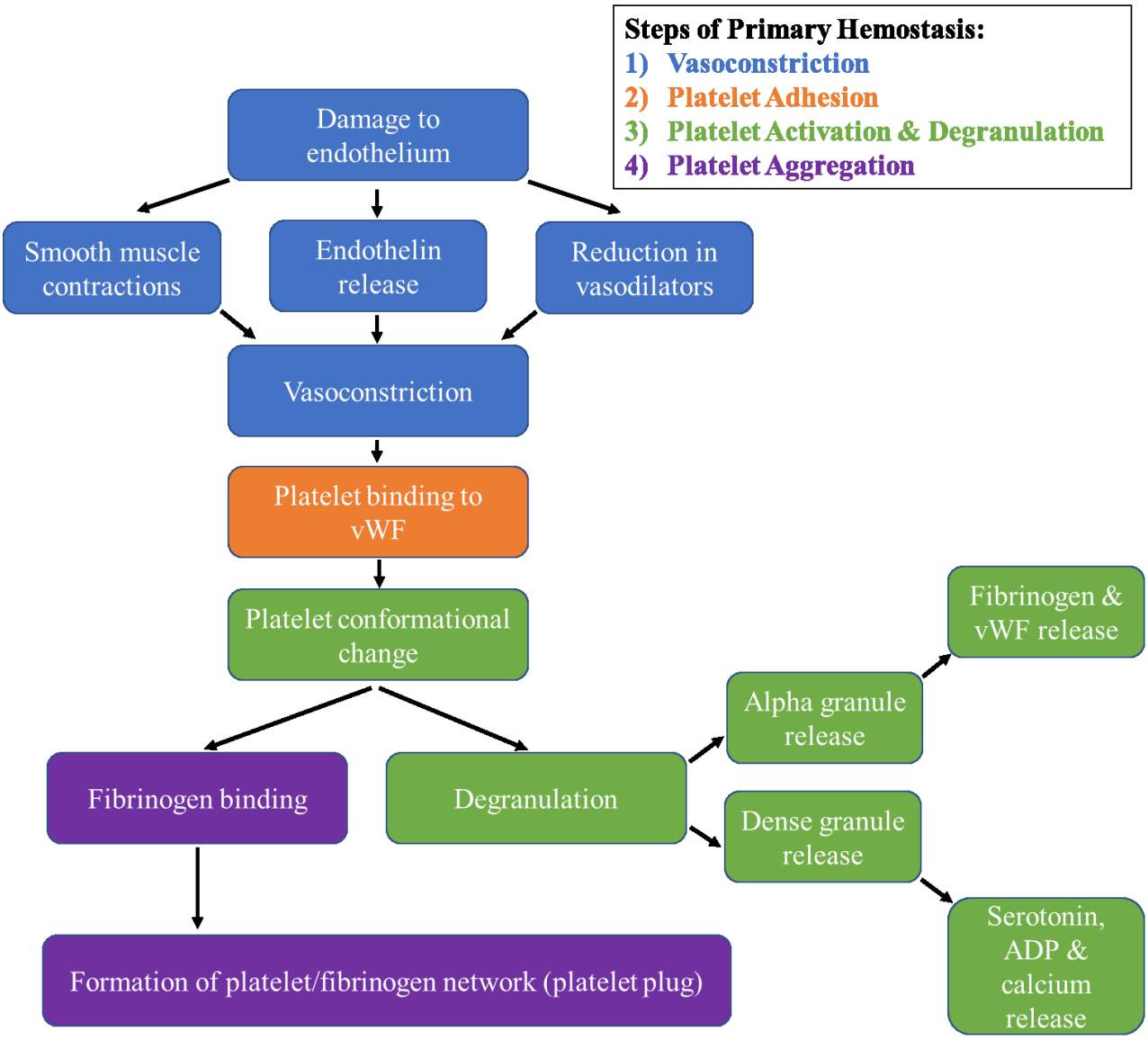

Figure 1-1: Overview of steps involved in primary hemostasis.

Primary stasis involves four steps (vasoconstriction, platelet adhesion, platelet activation and platelet aggregation) which enable formation of a platelet plug at the site of endothelial injury of the blood vessel.

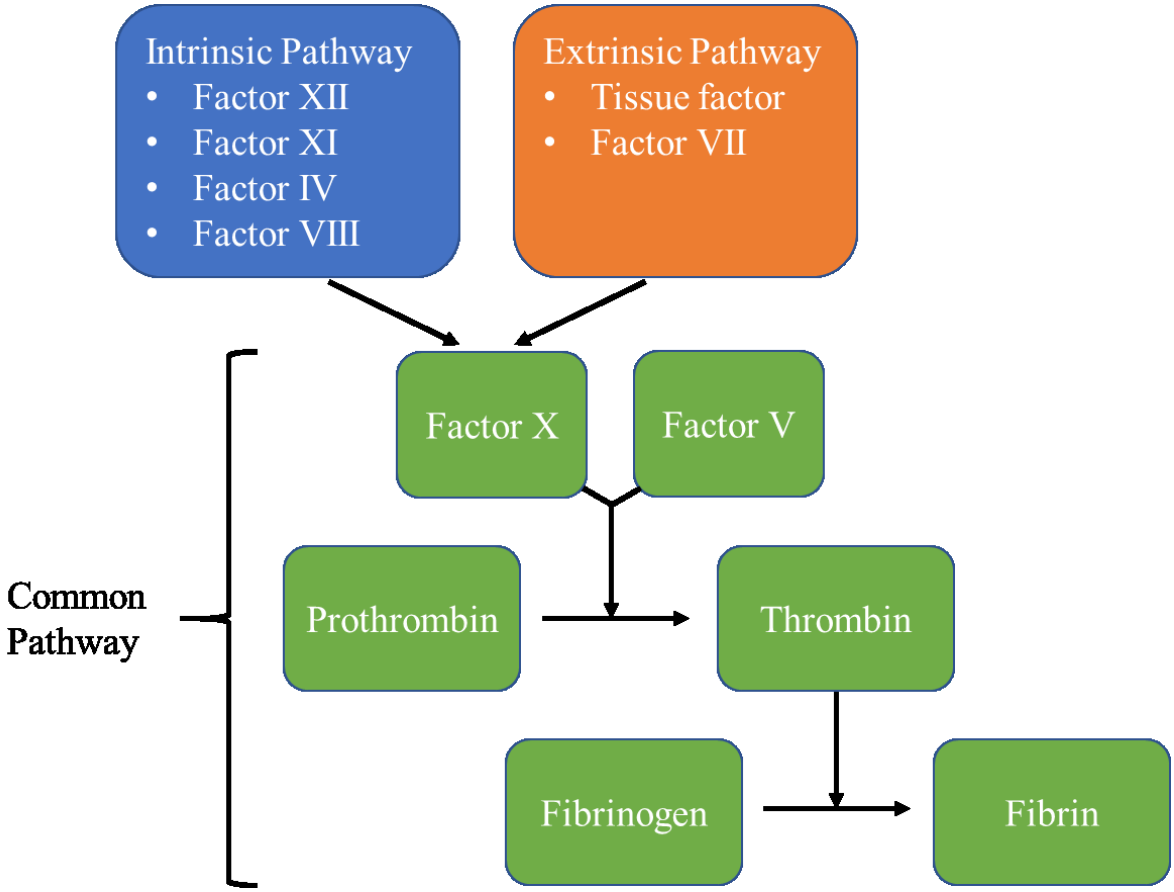

Figure 1-2: Overview of steps involved in secondary hemostasis, the coagulation cascade.

The coagulation cascade operates to transform fibrinogen into fibrin to reinforce the pre-existing platelet plug formed in primary hemostasis and form a stable clot.

1.11 References

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2 An Alternative Prophylaxis for Deep Vein Thrombosis Using Intermittent Electrical Stimulation[1]

2.1 Introduction

Deep vein thrombosis (DVT) is a common medical condition and is a major contributor to the global disease burden.[1] Etiologically, venous stasis is a common target of current, prophylactic, mechanical interventions in intra- and post-operative settings as well as non-operative settings. The mainstay of these mechanical interventions is intermittent pneumatic compression (IPC). IPC is effective in reducing the incidence of DVT;[2] however, poor patient compliance due to discomfort, itchiness, excessive heat, sweating, lack of portability as well as the potential to develop peroneal nerve palsy, ultimately limit its acceptance by users.[3-5] Furthermore, DVT prophylaxis often requires a 24-hour intervention regimen. Due to IPCs non-portable nature, its utility as a prophylactic method in non-hospital settings is unfavorable.

Electrical stimulation may present an attractive mechanical alternative for DVT prophylaxis due to its capacity to improve hemodynamic performance[6-11] and its general acceptability.[6,7,12] Electrical stimulation entails the application of electrical current through electrodes placed on the skin to produce contractions in the underlying muscle.[13] Much work has been performed to determine a stimulation pattern that maximizes hemodynamic performance. Specifically, tetanic versus twitch contractions,[14] and the muscle of choice to stimulate,[15] have been investigated. However, existing electrical stimulation systems have either been limited to short duration use (20-30 min, 2-3 times per day) due to rapid fatigue of the target muscle,[10] or use twitch contractions that are ineffective in mobilizing blood effectively in proximal veins.[16]

We proposed a new electrical stimulation paradigm, named intermittent electrical

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stimulation (IES), that utilizes brief tetanic, sequential contractions of the gastrocnemius and tibialis anterior muscles repeated every few minutes for the prevention of DVT formation due to venous stasis. IES has the potential to be translated into a clinically applicable intervention that is portable, has a high degree of patient compliance, and can be utilized up to 24 hours/day, thus avoiding some of the downfalls of IPC and existing electrical stimulation systems.

The present study focused on three specific goals that addressed the viability of IES as a mechanical prophylactic intervention for venous stasis. First, although specific parameters of electrical stimulation waveforms have been previously investigated,[15,17,18] this study investigated, for the first time, the level of IES-induced contractions required to generate a sufficient increase in venous velocity. Secondly, while most electrical stimulation studies measured the effects of the induced muscle contractions on the popliteal vein,[7,9,19] the present study systematically investigated, for the first time, the effect of IES on more proximal vasculature, such as the femoral vein, in which thrombi are more likely to lead to pulmonary emboli (PE).[20] Thirdly, in addition to testing in typical individuals with healthy muscles, this study identified, for the first time, the hemodynamic performance of IES when used in atrophied muscles secondary to acute stroke, where individuals are at high-risk of DVT development. Previous electrical stimulation studies were undertaken in intensive care unit patients,[21] post-operative hip and knee arthroplasty[6,12] and patients with chronic venous disease.[7,22] However, investigation in stroke patients in whom the prevalence of venous thromboembolism is 20-42%,[23-25] had not been investigated extensively in the past.

2.2 Materials and Methods

2.2.1 Participants

Thirty-two participants (8 females; 24 males) completed the study. Participants were informed of the experimental procedures and signed a written consent form. Protocols used in the experiments were approved by the University of Alberta Human Research Ethics Board.

Of the 32 participants in the study, 22 were typical healthy subjects recruited from the general Edmonton community, and 10 were in-patient post-stroke subjects recruited at the Glenrose Rehabilitation Hospital (GRH) in Edmonton. Exclusion criteria included having an implantable device, a need for translation to communicate, severe peripheral vascular disease, diabetes with amputations, pre-existing motor neuropathy, neuromuscular disease, an existing DVT or a recommendation to be excluded by a treating physician. Experiments involving the typical study participants were performed at the University of Alberta and those involving post-stroke in-patients were performed at GRH.

Table 2-1: Summary of participants in each study group.

Group	Sample Size	Description	Sex	Mean Age (yrs) (Min, Max)	Venous Diameter (cm) (Min, Max)
1	12	Typical subjects	8 male/ 4 female	48±14 (26, 64)	Popliteal: 0.99±0.18 (0.68, 1.32)
2	10	Typical subjects	9 male/ 1 female	38±17 (21, 60)	Popliteal: 0.90±0.15 (0.61, 1.10) Femoral: 0.92±0.11 (0.75, 1.10)
3	10	Post-stroke patients	7 male/ 3 female	65±14 (46, 89)	Popliteal: 0.57±0.12 (0.46, 0.86)

2.2.2 Experimental Protocol

2.2.2.1 Overview

The participants were divided into 3 groups (Table 2-1) and changes in venous velocity in the

popliteal and/or femoral veins were measured during IES-induced muscle contractions using Doppler ultrasound. The forces generated during the muscle contractions were also recorded using a custom-built force apparatus. Stimulation amplitude was modulated to evaluate the relationship between stimulation amplitude, force generation and changes in venous velocity. Potential discomfort associated with IES was evaluated during the testing sessions using a visual analog scale (VAS).

2.2.2.2 Application of Intermittent Electrical Stimulation

A two-channel stimulator (BioMedical Life Systems, Vista, California, USA) was used to administer IES (biphasic, cathodic-first, charge-balanced pulses, 300 μs pulse width, 17.5 Hz repetition rate). IES was delivered through pairs of 7.5 x 10 cm electrodes (Axelgaard Manufacturing CO., LTD, Fallbrook, California, USA) placed on the posterior and anterior sides of the leg. To induce a plantar flexion contraction, the cathode was placed over the motor point of the gastrocnemius muscle and the anode was placed proximally to the Achilles tendon (Figure 2-1A, left). To induce a dorsi flexion contraction, cathodic placement corresponded to the motor point of the tibialis anterior muscle, with anodic placement approximately five centimeters distal to the cathode (Figure 2-1A, right). Electrode size and location were chosen to maximize comfort.[26]

The IES stimulation paradigm consisted of a 1s "ON" of plantar flexion contraction, followed immediately by 1s "ON" of dorsi flexion contraction (Figure 2-1B) and an "OFF" period of 3 min. This novel pattern was intended to produce tetanic, non-fatiguing contractions in the muscles while also maintaining neutral position of the foot between IES cycles.

IES was applied to the right leg for Groups 1 and 2 (Table 2-1) and the more affected leg

with more atrophied muscles in Group 3. The maximal tolerable stimulation amplitudes for the gastrocnemius and tibialis anterior muscles were determined by gradually increasing the stimulation amplitude starting from the lowest stimulator setting. To generate recruitment curves that relate the strength of muscle contraction to changes in venous velocity, stimulation amplitude to the gastrocnemius muscle was modulated from the lowest stimulator setting to the maximal tolerable stimulation level. The stimulation amplitude to the tibialis anterior muscle remained constant throughout the experiment and was chosen to be below the maximal tolerable level, yet at a level that elicited a visible contraction.

2.2.2.3 Testing Setup

All subjects were seated in a semi recumbent position, with the tested leg in the custom-built force apparatus (Figure 2-1C). The subject's leg was positioned such that the plantar surface of the foot rested firmly on a force plate while maintaining approximately 60^{o} of flexion in the knee joint, allowing for adequate access of the ultrasound probe to the popliteal fossa. The ankle rested on a thick, padded strap and the thigh was also secured with a strap. For typical subjects (Groups 1 and 2), maximal voluntary contractions (MVCs) of the plantar flexor muscles were then obtained in triplicate and averaged. Care was taken to ensure that the subjects did not utilize their proximal leg muscles during MVC recordings. Group 3 post-stroke subjects were unable to perform voluntary contractions using their experimental (more affected) leg; therefore, the maximal recorded contraction with stimulation (MRCS) was used as a substitute.

IES was then applied in successively increasing stimulation amplitudes to the gastrocnemius muscle and the resulting plantar flexion force and changes in popliteal and/or femoral venous velocities were recorded for each stimulation level (Figures 2-2A and 2-2B).

This was repeated until the maximal tolerable stimulation amplitude to the gastrocnemius was reached. The stimulation was then reset to the lowest level and the process was repeated two additional times for Group 1, resulting in a total of three repetitions. This procedure was performed a total of two times for each vein (popliteal or femoral) in Group 2, and a total of two times in Group 3. Between repetitions, rest-venous velocities were recorded in triplicate, without stimulation, to monitor any changes in baseline venous velocity over the course of the experiment.

2.2.3 Venous Velocity and Force Measurements

Prior to initiating the application of IES, the diameter of the popliteal vein (and femoral vein in Group 2) was measured using B-mode ultrasound (Table 2-1). Doppler ultrasound was then used to monitor changes in venous velocity during the IES-induced muscle contractions. Two ultrasound systems were used for the measurements. For the experiments performed at the University of Alberta (Groups 1 and 2), an ACUSONS2000 ultrasound machine (Siemens, Mountain View, California, USA) was used along with a 40 mm, 4-8 MHz, linear probe. For the experiments performed at GRH (Group 3), a HD15 ultrasound machine (Philips, Markham, Ontario, Canada) was used with a 20 mm, 4-8 MHz, linear probe. The popliteal and femoral veins were examined using a longitudinal view in the popliteal and femoral fossae, respectively. The Doppler beam had an angle of 60^{o} and a gate size of 2 mm, placed at the center of the vein during measurements. Care was taken to ensure the angle of the doppler beam and vein were in parallel and that the quality of the B-mode image was appropriate before recording measurements.

Force generated during IES-induced muscle contractions was measured using a custom-

made apparatus that consisted of an LCPB-100 load cell (Omega Engineering INVC., St-Eustache, Quebec, Canada) secured in a "boot" where the subject's foot rested (Figure 2-1C). The force signals were digitized at a rate of 1000 Hz using an NI USB-6361 data acquisition system (National Instruments, Austin, Texas) (DAQ), and a custom-written MATLAB (version 2017b, MathWorks, Natick, Massachusetts, USA) program.

2.2.4 Evaluation of Participant Comfort During Stimulation

The VAS was used to determine and track the subjects' level of discomfort during IES using a 0-to-10 scale, where 10 represented the maximal imaginable level of pain, and 0 represented a complete absence of discomfort or pain. Mild, moderate and severe discomfort or pain were classified as ≤ 3, ≥ 3 and ≤ 7, and > 7, respectively. At the end of the testing session, each subject was asked whether they would feel comfortable having IES applied for several hours a day and if they thought they could sleep with it.

2.2.5 Data Analysis

Ultrasound DICOM images were exported to MATLAB for analysis using a custom-written program. Signals in the images were converted to a continuous curve using differences in pixel intensity to differentiate signal (defined as a pixel intensity greater than 3.5 standard deviations from complete non-signal) from noise. An example of the MATLAB generated continuous curve is shown as a red line in Figures 2-2A and 2-2B. Baseline and peak venous velocities were then identified, and peak venous velocity (PVV) for each test trial per subject was plotted against stimulation amplitude (PVV-IES amplitude recruitment curves) as well as against peak plantar flexion force (Figure 2-2C; PVV-force recruitment curves). Peak venous

flowrates were calculated by finding the product of PVV and the cross-sectional venous area.

The PVV-force recruitment curves were averaged for each subject. To compare across subjects within a group, the force produced by the plantar flexion contractions was expressed as %MVC in Groups 1 and 2 and binned in 10% MVC size bins. In Group 3, the plantar flexor force produced by IES at various stimulation amplitudes was expressed as %MRCS. In all groups, popliteal PVV for each subject was also plotted against the rate of force generation during the upstroke portion of the plantar flexor force trace.

2.2.6 Statistical Analysis

For normally distributed data, a one-way ANOVA and Holm-Sidak post-hoc analysis was performed (SigmaPlot 13.0, Systat Software Inc., San Jose, California, USA) to identify statistical changes in popliteal and femoral PVV as a function of %MVC or %MRCS. Where normality was not achieved, a Kruskal-Wallis ANOVA and Dunn's post-hoc analysis were used. Statistical significance was achieved for $p \leq 0.05$.

2.3 Results

2.3.1 Participants

A summary of the study participant demographics is shown in Table 2-1. Participants recruited in Group 1 had a similar age-range and mean to that of Group 2 ($p=0.75$). As expected, the age range of study participants in Group 3 was skewed to the right and the average age in this group was significantly higher than that in Group 2 ($p=0.007$) but not in Group 1 ($p=0.12$). Interestingly, Group 3 had a smaller average popliteal venous diameter compared to Groups 1 and 2 ($p<0.001$). This could possibly be due to lack of perfusion in the more affected side of the

post-stroke subjects.

2.3.2 Effect of Strength of IES-Induced Plantar Flexion on Increases in Popliteal Venous Velocity

Examples of three popliteal PVV-IES amplitude recruitment curves from one participant in Group 1 are shown in Figure 2-2D. Figure 2-3A shows the averaged popliteal PVV-force recruitment curves for each participant in Group 1, and Figure 2-3B shows the same recruitment curves with the forces expressed as %MVC. In most participants, there was a sharp increase in popliteal PVV at the low levels of %MVC but tended to plateau at higher %MVC, suggesting that large muscle contractions are not necessarily needed to produce large increases in PVV. To determine the %MVC required to increase popliteal PVV significantly above baseline, the PVV-force recruitment curves from all participants in Group 1 were averaged (Figure 2-3C). Across all subjects, IES-induced muscle contractions resulting in forces as small as 11-20 %MVC were adequate to produce significant increases in popliteal PVV relative to baseline (6.27±1.81 cm/s versus 55.27±25.89 cm/s, $p=0.014$). Contractions as small as 11-20 %MVC increased popliteal PVV 8 times above baseline.

2.3.3 Changes in Popliteal and Femoral Venous Velocity with Increasing Force Generation

Figure 2-2E shows the popliteal and femoral PVV-IES amplitude recruitment curves from one participant in Group 2. Similar increases in both popliteal and femoral PVV were seen with increasing stimulation amplitudes to the gastrocnemius muscles in this participant. Popliteal and femoral PVV-force recruitment curves from all participants in Group 2 are shown in Figures 2-4A and 2-4B, respectively. Similar to the results in Group 1, the PVV in both the popliteal and femoral veins sharply increased at weak IES-induced muscle contractions in most participants

and plateaued at stronger contractions. The popliteal and femoral PVV-force recruitment curves are plotted as %MVC in Figures 2-4C and 2-4D, respectively, and averaged across all participants in Group 2 in Figure 2-4E. Not surprisingly, the increases in the popliteal PVV as a function of increased IES-induced contraction strengths were significantly larger than the increases in the femoral PVV ($p=0.003$). Nonetheless, muscle contractions producing as low as 11-20 %MVC produced significantly large increases in both popliteal and femoral PVV relative to baseline [(popliteal: 6.60±1.35 cm/s versus 54.92±26.30 cm/s, $p=0.003$); (femoral: 7.89±2.58 cm/s versus 38.84±13.31 cm/s, $p=0.002$)]. This confirms that relatively small IES-induced contractions are adequate for increasing PVV significantly above baseline. At 11-20 %MVC, PVV increased by 8.3 times above baseline in the popliteal vein and by 4.9 times above baseline in the femoral vein.

A direct comparison between the increases in popliteal and femoral PVV is shown in Figure 2-4F. Interestingly, there is a close to unity linear relationship between popliteal PVV and femoral PVV for popliteal PVVs below 80 cm/s. The ratio of popliteal to femoral PVV as a result of IES-induced contractions was 1:0.73 ($R^2=0.99$) for popliteal PVVs below 80 cm/s. This demonstrates that, for the setup in this experiment, the increases in femoral PVV due to IES-induced contractions in the gastrocnemius muscle were similar in magnitude to those seen in the popliteal PVV. For popliteal PVVs >80 cm/s, the increases in femoral PVVs was substantially smaller. Collectively, this suggests that changes in femoral PVV caused by contractions in the gastrocnemius muscle can be directly estimated based on the changes in the popliteal PVV.

2.3.4 Changes in Popliteal Venous Velocity due to IES-inducted Contractions in Atrophied Muscles

Examples of popliteal PVV-IES amplitude recruitment curves from one post-stroke participant in Group 3 are shown in Figure 2-2F. Popliteal PVV-force recruitment curves for all participants are provided in Figure 2-5A, and the same curves expressed in %MRCS are shown in Figure 2-5B. Unlike the popliteal PVV-force recruitment curves in typical healthy participants in Groups 1 and 2 (Figures 2-3 and 2-4, respectively), there was a linear increase in popliteal PVV with increases in force generation in the post-stroke participants. Moreover, because of muscle atrophy in the post-stroke participants in Group 3, significantly lower IES-induced peak forces compared to typical subjects in Groups 1 and 2 (the maximal IES-induced force was 46±22 N in Group 3, compared to 193±91 N and 111±42 N in Groups 1 and 2, respectively; $p<0.001$). Furthermore, the typical population produced significantly higher average MVC forces (348±113 N and 321±124 N for Groups 1 and 2, respectively), compared to MRCS forces in the post-stroke group (46±22 N in Group 3; $p<0.001$).

Figure 2-5C shows the averaged popliteal PVV-force recruitment curve across all subjects. Muscle contraction strengths producing 51-60 %MRCS were needed to produce significant increases in popliteal PVV above baseline (8.93±1.98 cm/s versus 52.92±22.38 cm/s, $p=0.013$). IES-induced plantar flexor contractions at 51-60 %MRCS produced a 5.9 factor increase in popliteal PVV above baseline. Therefore, the lowest absolute force needed for each group to elicit a significant increase in popliteal venous velocity from baseline was between 38±12 N to 70±23 N (11-20% MVC) for Group 1, 35±14 N to 64±25 N (11-20% MVC) for Group 2 and 23±11N to 28±12 N (51-60% MRCS) for Group 3. These results suggested that in atrophied muscles with no prior conditioning with electrical stimulation, low to moderate contractions are needed to produce significant increases in popliteal PVV.

2.3.5 Changes in Peak Volumetric Flowrate due to IES-induced Contractions

A comparison of the peak volumetric flowrate-force recruitment curves for typical and post-stroke subjects is shown in (Figure 2-6A). The IES-induced muscle contraction forces were 3 times larger in the typical subjects than the post-stroke subjects. Moreover, because the diameter of the popliteal vein was significantly smaller in the post-stroke group, the peak flow rates are also smaller in this group relative to the typical groups (Groups 1, 2) for the same level of induced contraction forces. Nonetheless, at the maximal force levels produced across all groups, similar popliteal PVVs were achieved (Figures 2-3C, 2-4E, 2-5C; $p=0.58$).

2.3.6 Effect of Rate of Force Generation on Peak Popliteal Venous Velocity

The rate of force generation via IES-induced contraction of the gastrocnemius muscle was also compared between the typical and post-stroke study participants (Figure 2-6B). Interestingly, there was a positive relationship between the rate of force generation and popliteal PVV for all subjects. Furthermore, the post-stroke subjects achieved higher popliteal PVVs at lower rates of force generation, likely due to their smaller vessel diameter and possibly suggesting that less atrophied muscles do not need to contract as fast to generate a given increase in popliteal PVV.

2.3.7 Comfort and Acceptability of IES for DVT Prophylaxis

The VAS scores for all study groups are shown in Figure 2-6C. All participants felt relatively low levels of discomfort with IES use (Group 1 = 3.82±1.97; Group 2 = 1.97±2.40; Group 3 = 0.80±0.97). Interestingly, post-stroke subjects in Group 3 found IES to evoke the least discomfort compared to other groups. This was significant compared to the typical subjects in

Group 1 (p=0.001). Discrepancies between the typical groups (Group 1 and 2) could be due to the use of higher stimulation amplitudes in Group 1 which produced larger IES-induced forces (compare Fig. 2-3A and 2-4A) and/or the use of better adhering electrodes in Group 2, which collectively may have impacted subject discomfort in Group 1.

With respect to everyday use of IES, 68% of typical and 100% of post-stroke subjects said they would feel comfortable using IES for several hours a day. Moreover, 63% of typical and 50% of post-stroke subjects said they would be able to sleep with IES.

2.4 Discussion

2.4.1 Overview

The goal of this work was to investigate the hemodynamic performance of IES, a novel electrical stimulation paradigm for preventing venous stasis and DVT formation. The results demonstrate, for the first time, that IES produces significant increases in popliteal PVV at low plantar flexor contractions, both in typical and post-stroke subjects. The results also revealed, for the first time, a near linear unity relationship between the increases in popliteal and femoral PVVs as a result of IES (Figure 2-4F). This suggests that the IES-induced plantar flexor contractions are effective in improving the hemodynamics of proximal veins in which DVTs have a high risk of causing pulmonary emboli. The study also showed that increases in maximal PVV caused by IES-induced plantar flexion are similar between subjects with healthy muscles and veins and post-stroke patients with atrophied muscles and smaller diameter veins. This suggests that IES will likely be effective in a wide range of patient populations at risk of developing DVT. Importantly, no muscle fatigue was detected in any of the participants during the testing sessions, and all participants found IES comfortable. Collectively, the results suggest

that IES may be an effective and acceptable means for DVT prophylaxis.

2.4.2 Comparison of IES to Existing Mechanical Compression Systems

Compression stockings and IPC devices have been promoted as mechanical systems for the prevention of DVT.[27,28] While IPC devices are effective in reducing the incidence of DVT in acute care settings[29] the evidence for compression stockings as an effective means for preventing DVT is lacking.[30]

The effectiveness of IPC stems from its ability to mobilize venous blood dynamically by sequentially compressing the legs distally to proximally. IES also aims to mobilize the blood dynamically, but instead of passively compressing the legs, it accomplishes this by inducing periodical muscle contractions through a wearable sock-like device that actively engages the muscle pump. The IES system may mitigate the low degree of patient compliance and lack of portability associated with IPC. Moreover, unlike IPC, IES may be effective in retaining and increasing muscle mass and contractile strength in people with reduced mobility such as post-stroke patients, thus reducing muscle atrophy. Finally, this study demonstrated, for the first time, that the rate of muscle contraction positively affects the increase in PVV: the higher the rate of contraction, the greater the increase in PVV in both typical and post-stroke subjects (Figure 2-6B). This suggests that IES may be more effective than IPC in mobilizing venous blood due to the limitation of pneumatic devices to produce rapid compressions.

2.4.3 Comparison of IES to Existing Electrical Stimulation System for Preventing DVT

Other electrical stimulation devices, particularly the VEINOPLUS®[10] and geko™,[16] have also focused on preventing the formation of DVT. Nonetheless, IES fundamentally differs from

these systems with regards to its mechanism of action for DVT prevention. Both the VEINOPLUS® and geko™ utilize patterns of stimulation that reproduce a heartbeat, with the aim of increasing peak systolic velocity.[10,16] Specifically, the VEINOPLUS® delivers very brief (50ms-long) trains of stimuli up to 120 times per minute,[10] and the geko™ delivers a single stimulus pulse 60 times per minute.[16] Moreover, while the VEINOPLUS® applies the stimulation to the gastrocnemius muscle, the geko™ stimulates the common peroneal nerve that innervates the tibialis anterior muscle.

The principle of operation of IES is not based on augmenting the heart in mobilizing venous blood on a beat-by-beat basis. While irregular or weak cardiac contractions can indeed lead to clot formation, the health conditions that increase the risk of clot formation are much more pervasive and venous blood flow is more related to calf muscle contractions, compared to left ventricular pressure.[31] Instead of augmenting the action of the heart on a beat-by-beat basis, IES mimics the action of leg muscles in preventing venous stasis during standing, walking or leg movements while sitting or sleeping. Specifically, the IES pattern utilizes 1s-long trains of stimuli repeated every 3 min. This pattern of stimulation therefore does not require accurate synchronization with the heartbeat, does not risk the chance of counteracting the effect of a heartbeat and mimics the more natural pattern utilized by muscles to prevent venous stasis. Importantly, because the stimuli are delivered less frequently using the IES pattern than that in the VEINOPLUS® or geko™ systems, the chances of muscle fatigue are substantially reduced, allowing IES to be used effectively up to 24 hours per day. A variant of the IES pattern utilized in this study has already been demonstrated to be fatigue-resistant in an application focused on preventing pressure ulcers.[32,33]

2.4.4 Muscle Contraction Characteristics Most Suitable for the Prevention of DVT

In addition to the repetition rate of a stimulation pattern, the mode of muscle activation (i.e., tetanic vs. twitch contraction) and the muscle(s) chosen for stimulation play an important role in mobilizing venous blood. Janssen et al.[34] showed that tetanic contractions did not significantly increase popliteal PVV compared to twitch contractions. However, newer evidence demonstrated that twitch contractions, and especially those induced in the tibialis anterior muscle, may be inadequate for venous emptying.[14] Particularly, the geko™ system which only stimulates the common peroneal nerve, activates only 26% of the muscles in the leg, resulting in suboptimal venous emptying of deep veins in the posterior region of the leg.[14] While IES is capable of increasing popliteal PVV on average more than 8 times above baseline with small plantar flexor contractions, maximal stimulation amplitudes are needed by the geko™ to achieve similar results.[35]

Similar to IES in this study, VEINOPLUS® stimulates the gastrocnemius muscle to induce effective increases in popliteal PVV. The IES-induced plantar flexor contractions in this study produced large increases in both the popliteal and femoral PVV at low levels of contraction. However, unlike the VEINOPLUS®, IES was also applied to the tibialis anterior immediately after the its application to the gastrocnemius muscle. This was done to ensure that the ankle returned to a neutral position following the plantar flexor contractions. Continuous stimulation of the plantar flexors, as is the case with the VEINOPLUS®, has the risk of increasing spasticity and contractures in populations at high risk of developing DVT, such as people with stroke. This situation would be further exacerbated with stimulation patterns inducing contractions up to 120 times per minutes, as is done using VEINOPLUS®, without a means to return the ankle to a neutral position.

2.4.5 Conclusion

The work presented in this study elucidated the clinical viability of IES as a prophylactic approach to DVT. It demonstrated that IES is comfortable, hemodynamically effective even in post-stroke patients with atrophied muscles and does not cause appreciable muscle fatigue. Future work will assess the feasibility and effectiveness of IES for DVT prophylaxis in acute and non-acute care settings through clinical trials.

2.5 Figures

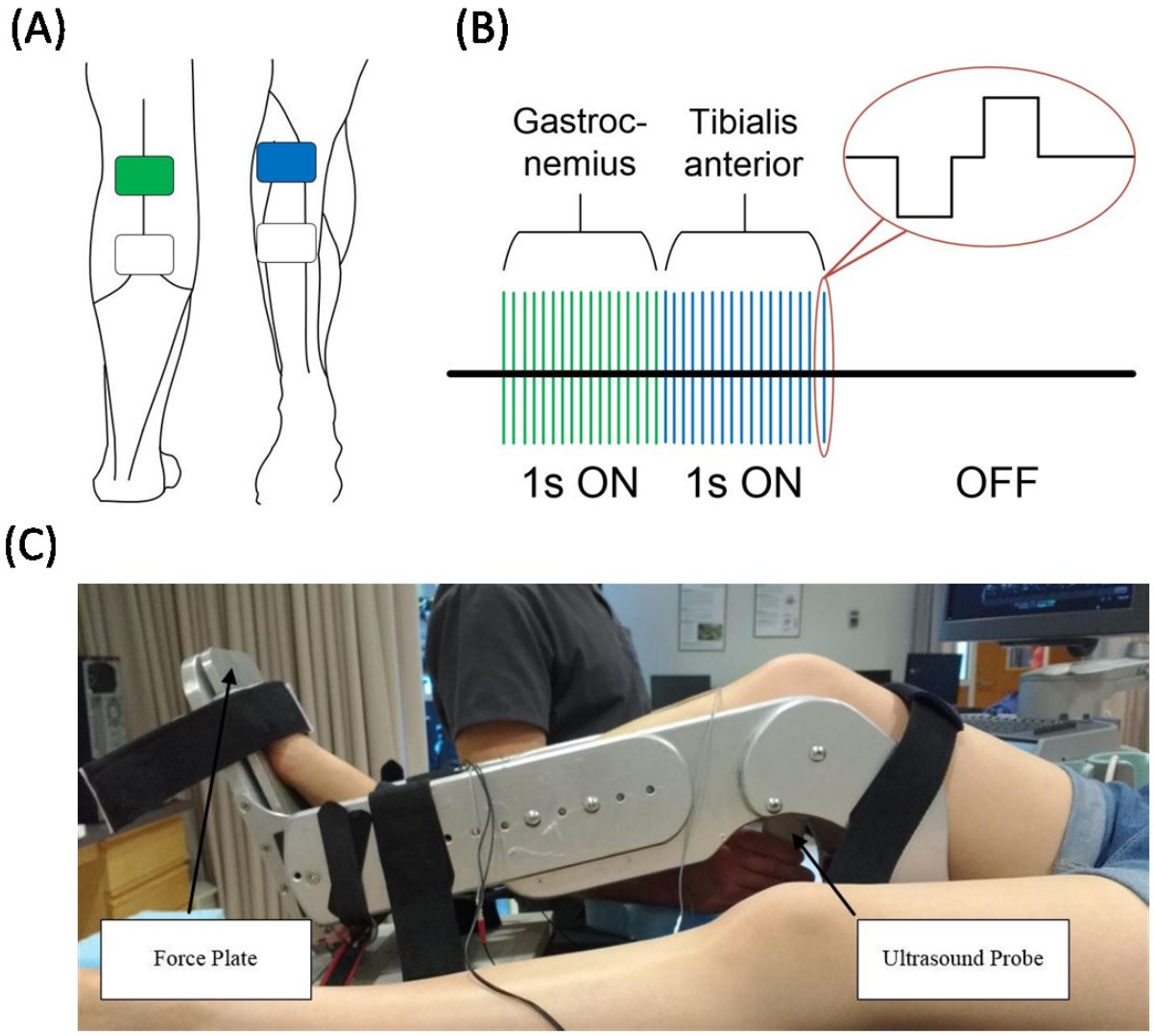
(A)
(B)
Gastroc-
nemius
Tibialis
anterior
1s ON
1s ON
OFF
(C)
Force Plate
Ultrasound Probe

Figure 2-1: Electrode placement, stimulation paradigm and experimental setup.

(A) Electrode placement for activating the gastrocnemius (left) and tibialis anterior (right) muscles. (B) IES paradigm which comprised of trains of biphasic pulses (17.5 Hz), stimulating the gastrocnemius muscle for 1s, followed immediately by stimulating the tibialis anterior muscle for 1s. Pulses had a pulse width of 300 μs and their amplitude was modulated during the experiment. (C) Custom-built apparatus for measuring the forces evoked by IES-induced contractions. The setup allowed access to popliteal and femoral veins for measuring venous velocity using Doppler ultrasound.

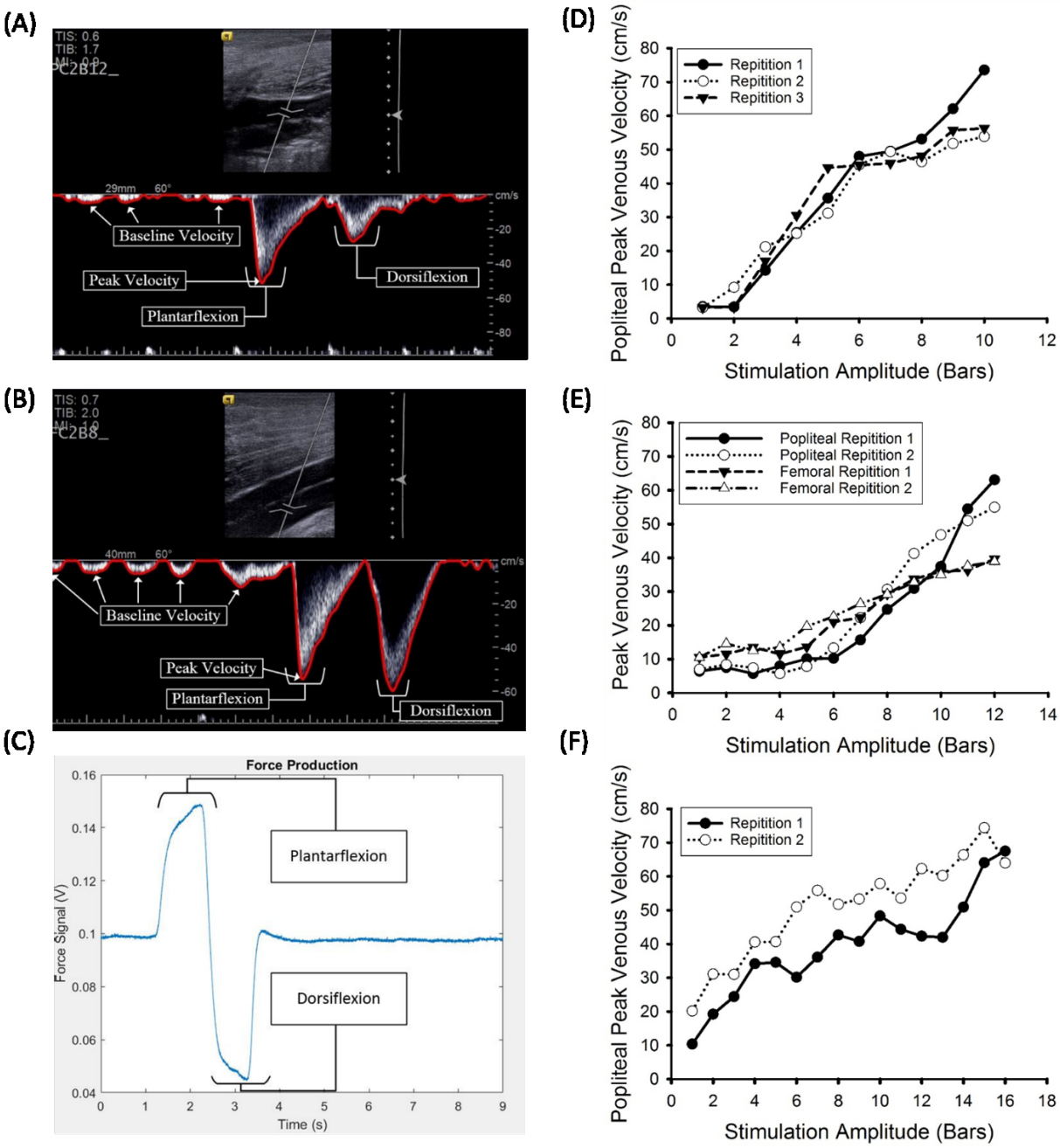
(A)
Baseline Velocity
Peak Velocity
Plantarflexion
Dorsiflexion
(B)
Baseline Velocity
Peak Velocity
Plantarflexion
Dorsiflexion
(C)
Force Production
Plantarflexion
Dorsiflexion
Force Signal (V)
Time (s)
(D)
Repitition 1
Repitition 2
Repitition 3
Popliteal Peak Venous Velocity (cm/s)
Stimulation Amplitude (Bars)
(E)
Popliteal Repitition 1
Popliteal Repitition 2
Femoral Repitition 1
Femoral Repitition 2
Peak Venous Velocity (cm/s)
Stimulation Amplitude (Bars)
(F)
Repitition 1
Repitition 2
Popliteal Peak Venous Velocity (cm/s)
Stimulation Amplitude (Bars)

Figure 2-2: Outcome measures of venous blood velocity and force, with recruitment curves from a single subject, in each of the three study groups shown.

(A) Doppler ultrasound trace of a single bout of IES on the popliteal vein, showing baseline venous velocity prior to the delivery of IES and peak venous velocities during IES-induced plantarflexion and dorsiflexion. The continuous curve used to calculate baseline and peak velocities, produced by MATLAB, is shown in red overlying the raw trace. (B) Doppler ultrasound trace of a single bout of IES on the femoral vein. Identical parameters are shown as described in (A). (C) Force trace produced during a single bout of IES, showing the isometric forces produced during plantarflexion and dorsiflexion. Recruitment curves from a single subject, in each of the three study groups. (D) Example IES amplitude-popliteal PVV recruitment curves from one subject in Group 1. Three recruitment curves were obtained for each subject in this group. (E) Example IES amplitude-popliteal and femoral PVV recruitment curves from one subject in Group 2. Two recruitment curves were obtained per vein, for each subject in this group. (F) Example IES amplitude-popliteal PVV recruitment curves from subject in Group 3. Two recruitment curves were obtained for each subject in this group.

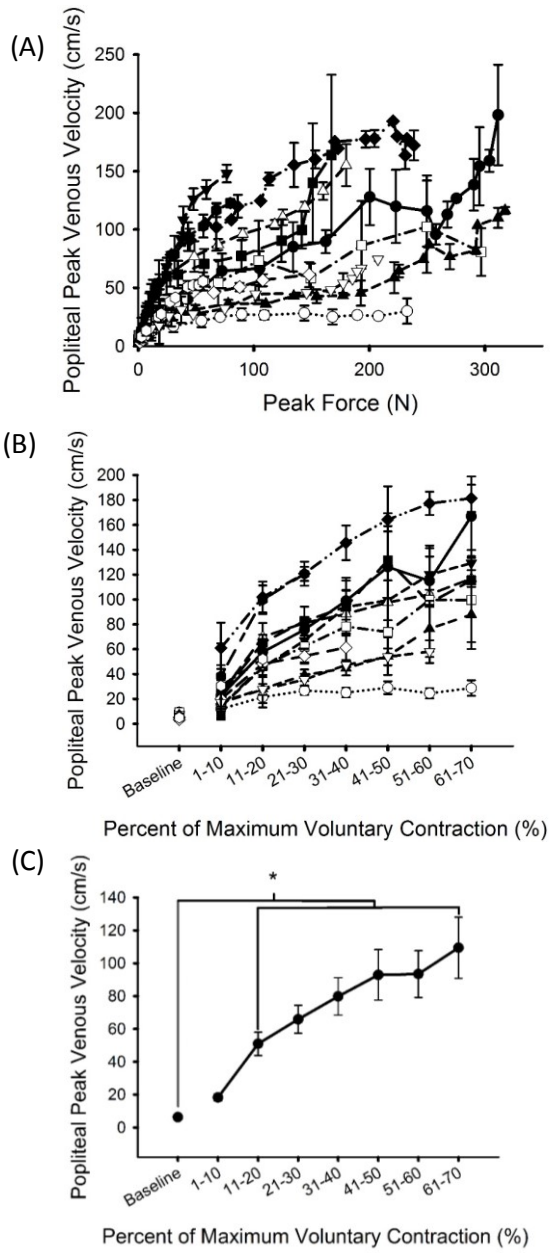

Figure 2-3: Group 1 typical population data.

(A) Popliteal peak venous velocity vs. peak force for all Group 1 subjects (mean ± standard deviation). (B) Popliteal peak venous velocity replotted against bins of percent MVC (mean ± standard deviation). Percent MVC was binned to compare across subjects. Baseline velocities (without stimulation) are also shown. (C) Averaged popliteal peak venous velocity across all subjects in Group 1 vs. percent MVC (mean ± standard error). *p=0.014.

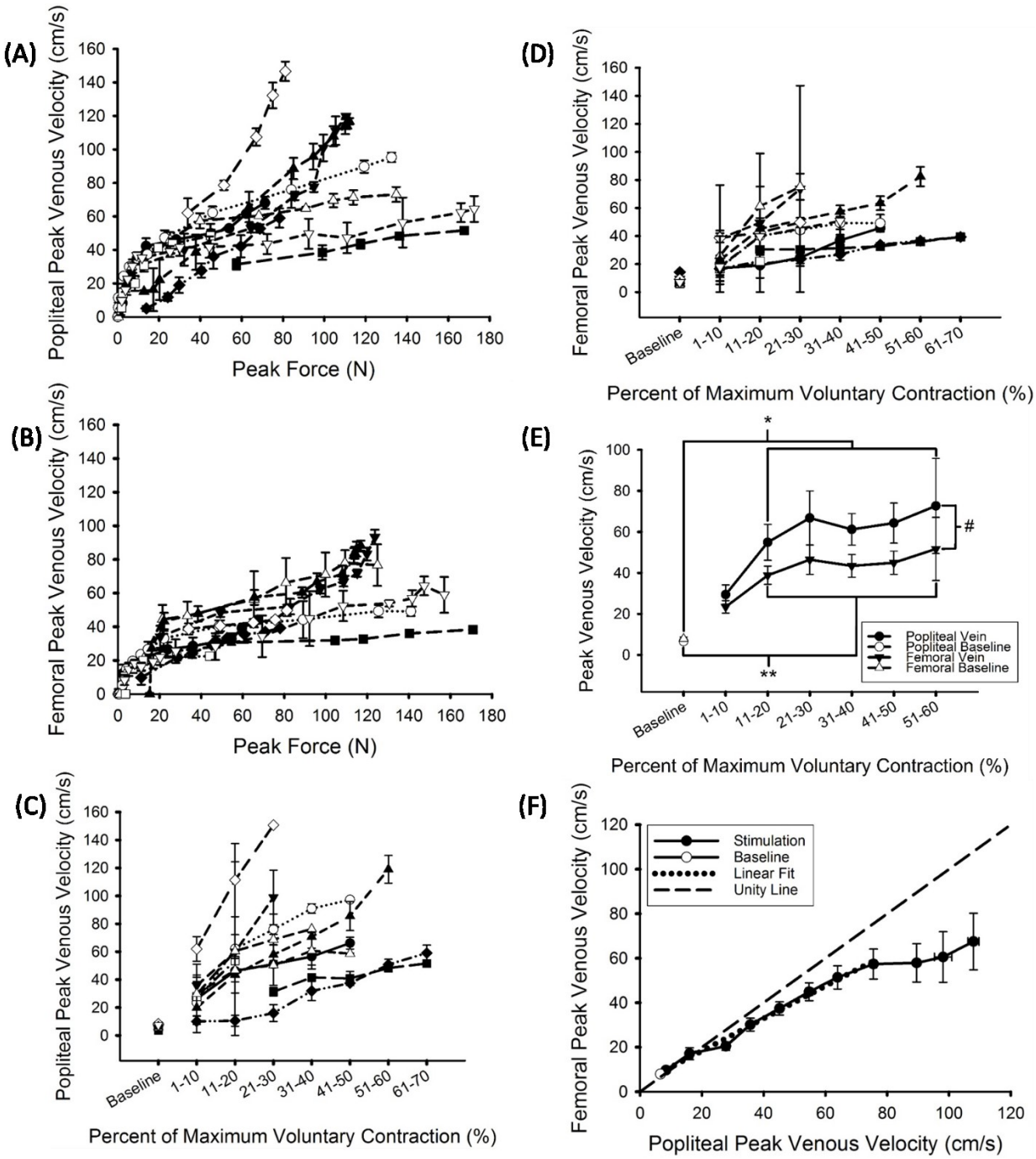
(A)
Popliteal Peak Venous Velocity (cm/s)
Peak Force (N)
(B)
Femoral Peak Venous Velocity (cm/s)
Peak Force (N)
(C)
Popliteal Peak Venous Velocity (cm/s)
Baseline
1-10
11-20
21-30
31-40
41-50
51-60
61-70
Percent of Maximum Voluntary Contraction (%)
(D)
Femoral Peak Venous Velocity (cm/s)
Percent of Maximum Voluntary Contraction (%)
(E)
Peak Venous Velocity (cm/s)
*
**
#
Popliteal Vein
Popliteal Baseline
Femoral Vein
Femoral Baseline
Percent of Maximum Voluntary Contraction (%)
(F)
Femoral Peak Venous Velocity (cm/s)
Stimulation
Baseline
Linear Fit
Unity Line
Popliteal Peak Venous Velocity (cm/s)

Figure 2-4: Group 2 typical population data of the popliteal and femoral veins.

(A) Peak force and popliteal peak venous velocity for all participants (mean ± standard deviation). (B) Peak Force and femoral peak venous velocity (mean ± standard deviation). (C) Popliteal peak venous velocity for all subjects binned as percent of MVC (mean ± standard deviation). Baseline venous velocity (without stimulation) is also shown for each subject. (D) Femoral peak venous velocity for all subjects binned as percent of MVC (mean ± standard deviation). Baseline (without stimulation) is also shown for each subject. (E) Averaged popliteal and femoral peak venous velocities (mean ± standard error). The popliteal and femoral velocities were significantly different (#p=0.003). All popliteal and femoral venous velocities for MVCs ≥11-20 with stimulation were significantly larger than venous velocities at baseline (*p=0.003; **p=0.002). (F) Relationship between popliteal peak venous velocity and femoral peak venous velocity. Popliteal venous velocities were binned in sizes of 10 cm/s, starting from zero, allowing popliteal and femoral velocities to be averaged within each bin. A linear fit was completed on the first eight points of the stimulation curve ($y=0.73x+3.50$; $R^2=0.99$). Baseline velocities of the popliteal and femoral veins were plotted. Vertical and horizontal error bars represent standard errors.

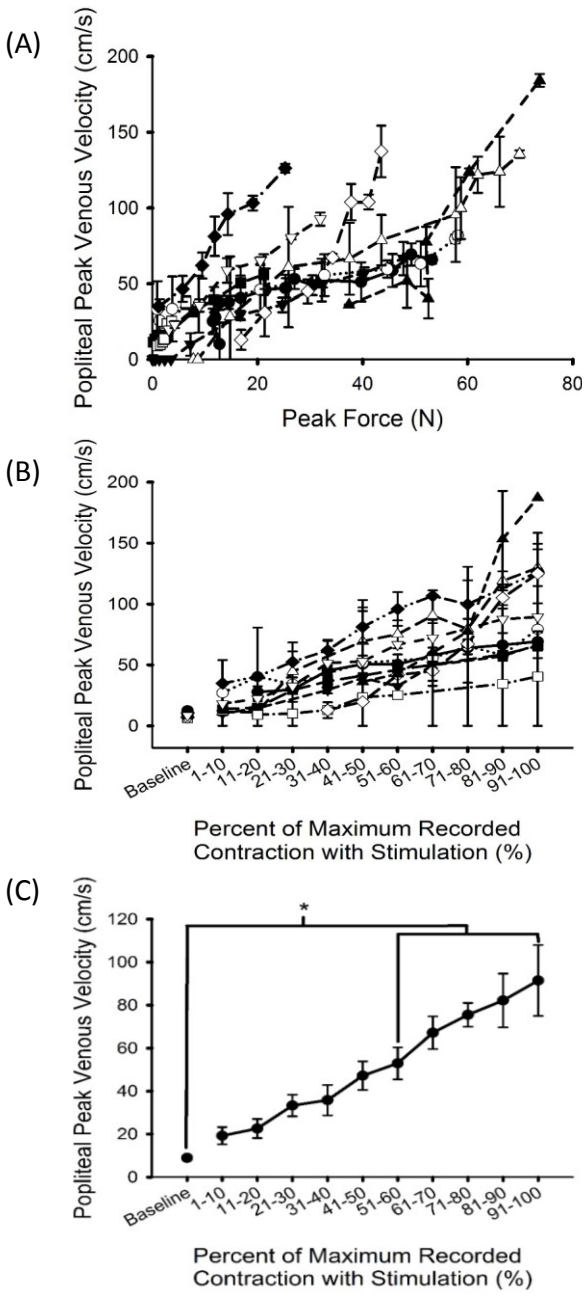

Figure 2-5: Group 3 post-stroke population data.

Group 3 post-stroke data. (A) Peak popliteal venous velocity vs. peak force for all Group 3 subjects (mean ± standard deviation). (B) Peak popliteal venous velocity plotted against binned percent of maximum recorded contractions with stimulation (mean ± standard deviation). Baseline popliteal venous velocity of all subjects is shown. (C) Averaged peak popliteal venous velocity at binned percent of maximum recorded contractions with stimulation are shown (mean ± standard error). *p=0.013.

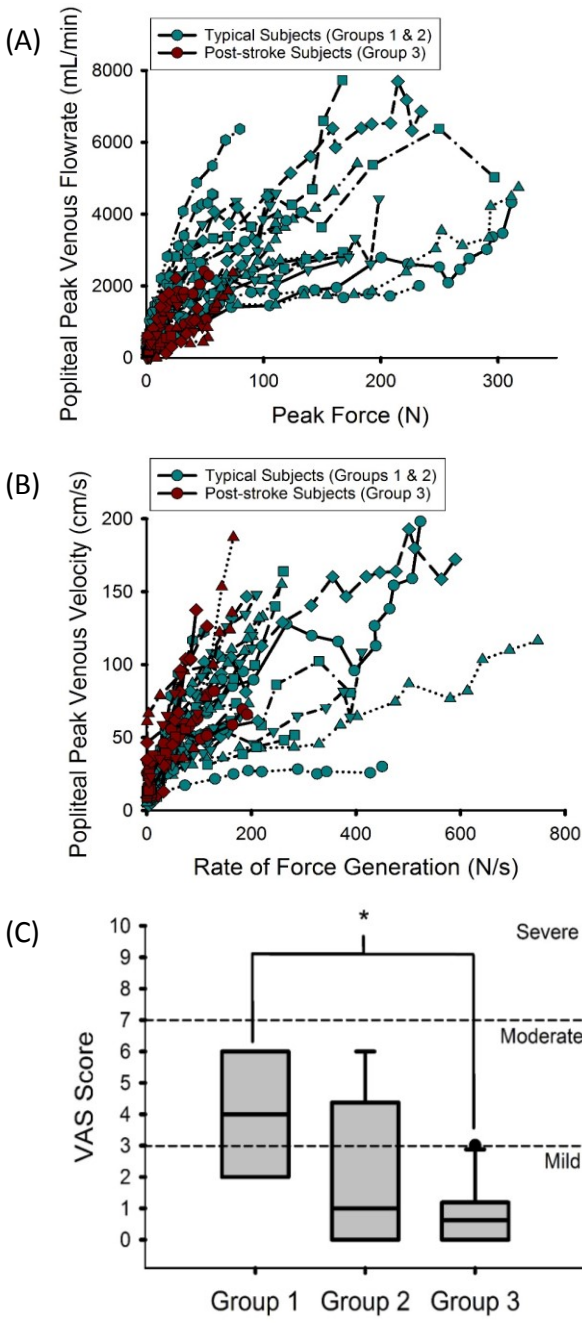

Figure 2-6: Comparison between Groups 1 & 2 (typical subjects) and 3 (post-stroke subjects) for select parameters, is shown.

Comparison between Groups 1 & 2 (typical subjects) and 3 (post-stroke subjects) for select parameters, is shown. (A) Popliteal peak venous flowrate, as a function of peak force, for both the typical and post-stroke groups are shown. (B) Popliteal peak venous velocity, as a function of rate of force generation, is shown for both typical (Group 1 & 2) and post-stroke groups (Group 3). (C) Box and Whisker plots of VAS scores for all study groups. The median is shown with the interquartile range. The maximal values are shown where they exceed the interquartile range. Group 3 had one outlier identified by the closed circle (*p=0.001).

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3 General Conclusions and Future Directions

The main goal of my thesis was to investigate the use of intermittent electrical stimulation (IES) as a prophylactic method for deep vein thrombosis (DVT). To accomplish this, recruitment curves were constructed to determine the relationship between stimulation amplitude, force of IES-induced gastrocnemius contractions and venous velocity of the popliteal and femoral veins, while also assessing subject comfort. In addition to typically healthy people, testing was also conducted in post-stroke people focusing on their more affected side with atrophied muscles.

For typical subjects, IES produced significant increases from baseline not only in popliteal, but also in femoral venous velocity at low levels of IES-induced muscular contractions (11-20% of maximum voluntary contraction (MVC)). Moreover, these levels of stimulation were deemed to be comfortable by the typical study participants, all of whom had fully intact sensation. Similarly, in the post-stroke study participants, IES was able to produce significant increases in popliteal venous velocity above baseline, at low to moderate levels of IES-induced muscular contractions (51-60% of maximum recorded contractions with stimulation (MRCS)), and levels of stimulation that were deemed comfortable. These results demonstrate that IES can improve blood hemodynamics in high-risk DVT prone areas in the lower extremities, even in people with atrophied muscles, and suggest that has the potential to be an effective and acceptable intervention for DVT prophylaxis.

3.1 Conclusions

My results indicate that IES may be able to prevent DVT formation by reducing venous stasis, one of the components of Virchow's etiological triad for DVT. As the proficiency of venous hemodynamics and comfortability levels did not wane in the post-stroke group, this

suggests that this approach may be effective in a wide range of conditions with increased risk for developing DVT including the elderly, people with neurological conditions, bone and joint disorders, cancer treatment, smokers, pregnant women undergoing post-partum or frequent flyers.

Based on these encouraging results, an IES device is currently under development to test IES' efficacy in the long-term prevention of DVT. This system is patent-pending and trademarked as the SOCC^{TM} (Figure 3-1). The system is composed of a "sock-like" garment with a miniature stimulator that are donned on the user to be used throughout the day. The hope is that the SOCC^{TM} could be used in populations at high-risk of developing a DVT, particularly where immobilization is a concern and anticoagulant use is contraindicated.

3.2 Limitations

Patients with certain pathologies could limit IES' effectiveness and safety. For example, concerns regarding IES interfering with electrical therapeutic devices, such as pacemakers and deep brain stimulation, should be acknowledged and accounted for until it is shown that local IES would not disrupt their function. Motor neuropathy and neuromuscular disease are other pathologies that could limit the effectiveness of IES use should these conditions lead to muscle denervation. Lastly, IES use could dislodge a pre-existing DVT and lead to a possible embolus.

3.3 Future Directions

The results from this thesis suggest that IES is a viable modality for DVT prevention. However, some limitations of the current study need to be addressed in future investigations:

1) IES was shown to have effective hemodynamic changes at comfortable stimulation levels for

healthy and post-stroke peoples. However, this was conducted through electrodes placed on the skin, attached to a hand-held stimulator, which is not the intended, final form of IES delivery for clinical application. Rather, the ability of the SOCC^{TM} to replicate hemodynamic performance and comfort shown in this study should be validated to establish its translational potential. Moreover, testing of IES in the present study was performed where muscular contractions were isometric. Further study with the SOCC^{TM} should determine if dynamic shortening contractions have an impact on venous hemodynamics and comfort.

2) Due to inherent limitations, IES was evaluated at only one session that lasted 2-3 hours on average. Current protocols for DVT prophylaxis, often require around 3 months of administration, depending on circumstance.[1] Therefore, evaluating the hemodynamics and comfort at multiple time points over a longer time course in healthy and higher-risk users would provide further confidence in the long-term feasibility of IES for DVT prevention.
3) Other electrical stimulation devices have been compared to and have shown promise against current mechanical prophylactic interventions of DVT, including intermittent pneumatic compression (IPC).[2-4] Therefore, IES should be evaluated against IPC to determine that its hemodynamic performance and comfortability is equivalent to, if not superior than IPC, to further advocate its cause as a front-runner among electrical stimulation applications.
4) Our current thought is that IES could prevent DVT by activating the calf-muscle pump, increasing venous flow, and preventing stasis – a component of Virchow's etiological triad for DVT. However, it is uncertain, from a morphological standpoint, how electrical stimulation impacts venous flow through muscular contractions. One way to elucidate this mechanism is to perform magnetic resonance imaging (MRI), or other form of imaging, with and without application of IES. The construction of a mathematical model that can predict

blood flow under IES-induced contractions may serve to better understand blood flow changes with muscular contractions of the leg. This could enable a better understanding of how electrically induced contractions could prevent stasis and DVT formation and provide avenues for potential refinement of the stimulation paradigm in the future.

5) To ultimately demonstrate IES' potential to prevent DVT, clinical trials are needed to compare the current standard of care for DVT prevention against IES prophylaxis to determine differences in acute, sub-acute and chronic incidence rates of DVT. Alternatively, another insightful comparison would consider the standard of care against the standard of care plus IES use. Efforts, such as these, would strive to elucidate the effectiveness of IES in a diversity of potential users, asserting IES as either a viable or non-viable means of DVT prophylaxis.

3.4 Figures

Figure 3-1: The SOCC.^{TM}

Smart ongoing circulatory compressions, or the SOCC,^{TM} is a device designed to deliver IES in a user-friendly fashion.

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Appendix

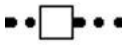
Group 1 Detailed Subject Characteristics

Subject	Sex	Age	Popliteal Venous Diameter (cm)
	Female	51	0.68
	Male	55	1.19
	Female	58	0.79
	Male	59	0.86
	Male	26	1.00
	Male	60	1.15
	Male	55	0.92
	Male	33	0.99
	Female	27	0.93
	Female	38	0.98
	Male	64	1.05
	Male	53	1.32

Group 2 Detailed Subject Characteristics

Subject	Sex	Age	Popliteal Venous Diameter (cm)	Femoral Venous Diameter (cm)
	Female	59	0.72	0.79
	Male	26	0.95	0.89
	Male	34	0.90	0.92
	Male	60	0.90	0.95
	Male	22	1.10	1.00
	Male	22	1.00	1.10
	Male	21	1.04	1.05
	Male	25	0.61	0.75
	Male	57	0.80	0.85
	Male	55	0.96	0.93

Group 3 Detailed Subject Characteristics

Subject	Sex	Age	Popliteal Venous Diameter (cm)
	Male	49	0.86
	Male	69	0.60
	Female	55	0.52
	Male	70	0.54
	Male	65	0.48
	Female	89	0.55
	Male	85	0.61
	Male	46	0.46
	Female	57	0.48
	Male	68	0.62