MPhil

The Haemodynamic effect of the Geko ™ Device

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This thesis is submitted for the Master of Philosophy at Queen Mary University of London

Statement of originality

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Abstract

Intermittent electrical stimulation of the common peroneal nerve by the Geko device ™ has an effect on haemodynamics. The Geko ™ is a device, which prevents the formation of venous thromboembolism (VTE). The Geko ™ works to stimulate the foot and calf muscle pumps in the leg to increase venous return. VTE carries a significant morbidity and mortality for patients, and so it is a valid scientific question to ascertain whether the Geko ™ can also have a beneficial secondary effect, on the haemodynamics, which could be used clinically, to improve patient outcomes.

Increasing the venous return to the heart should theoretically increase cardiac output and possibly arterial blood pressure. Firstly, we examined whether there could be any arterial blood pressure increases caused by the Geko ™, which could then be used to stabilize the blood pressure changes that occur after an anaesthetic induction. We did not find any significant change in blood pressure in 13 patients using a cross-over design pilot study.

Secondly, we examined the haemodynamic changes produced by the Geko ™ in healthy volunteers (n=21) using non-invasive cardiac output monitoring. We found that the cardiac output increased by 12% at the ten-minute stimulation period (p= 0.02), this effect ceased after the Geko ™ was switched off for ten minutes. We also found that this effect of increased cardiac output by the Geko ™ was not sustained if the device was left on for longer periods of up to 45 minutes, n=10.

Thirdly we sought to examine this finding of increased cardiac output using invasive cardiac monitoring. Although we did find a slight increase in cardiac output, when using the Geko for a ten-minute stimulation, (2.5%), p= 0.17, N-=5, the finding is not statistically significant.

In conclusion, this thesis points to some mild central haemodynamic changes from the Geko ™ device that needs more investigation. The haemodynamic changes are small and unlikely to be beneficial clinically. This thesis also highlights the lack of knowledge, research and measuring equipment for the venous circulatory system.

Abbreviations

AE	Adverse event
AI	Augmentation Index
ASA	American Society of Anesthesiologists
Bpm	Beats per minute
CI	Confidence interval
CIx	Cardiac Index
CVP	Central venous pressure
DVT	Deep vein thrombosis
IPC	Intermittent pneumatic compression
IPC	Intermittent pneumatic compression
ITT	Intention-to-treat
ITU	Intensive Therapy Unit
IV	Intravenous
LMA	Laryngeal Mask Airway
LMWH	Low molecular weight heparin
LVOT VTI	Left ventricular outflow tract velocity time integral
MAP	Mean arterial pressure
MSE	Mean squared error
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health research
NMES	Neuromuscular electrical stimulation
PAC	Pulmonary Artery Catheter
PE	Pulmonary embolism
PPG	Photoplethysmography
PSV	Peak systolic velocities
PTS	Post-thrombotic syndrome
PWV	Pulse wave velocity

RCT	Randomised control trial
SD	Standard deviation
SE	Standard error
SR	Systematic review
SV	Stroke volume
TAMV	Time-averaged maximum velocity
TIVA	Total intra venous anaesthetic
TT	Transit time
TVF	Total volume flow per minute
UFH	Unfractionated heparin
VTE	Venous thromboembolism

Glossary of terms

Term	Definition
Augmentation Index	The Augmentation Index is a ratio calculated from the blood pressure waveform. The Augmentation Index is commonly accepted as a measure of the enhancement of central aortic pressure by a reflected pulse wave. This enhancement provides a measure of arterial stiffness. The augmented pressure is calculated as the systolic pressure minus the inflection or shoulder point of the wave, which is in turn calculated by calculus derivatives. The Augmentation Index is defined as the ratio of augmented pressure to pulse pressure.
Myocytes	A type of cell found in muscle.
OnPulse Technology	The hardware and software used in the Geko ™ to deliver an electric current limited to 27mA at fixed intervals. The technology also allows variable pulse width settings.
Peroneal nerve	Nerve controlling contraction of the foot, shin, and calf muscles
Pulse Pressure	The difference between systolic and diastolic pressure
Pulse wave	When the heart pumps blood into the aorta, it also generates a pressure wave that travels along the arteries ahead of the pumped blood.
Transit Time	This is the time taken for a pulse wave to travel through a length of the arterial circulation that is defined.
Threshold setting	Minimum setting to elicit a minor muscular contraction in both the calf and the foot

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Chapter 1: Introduction

1.1 Context of the Geko ™ within the realm of Venous Thromboembolic Disease prevention

The main hypothesis of this thesis is that intermittent electrical stimulation of the common peroneal nerve by the Geko device ™ has an effect on haemodynamics. It is also hypothesised that the physiological processes involved are numerous and potentially beneficial in the critical care environment. This thesis will investigate the hypothesis and examine the mechanisms behind any changes. The background section will explain why the question is important and relevant clinically.

The Geko ™ was first devised in 2010 to prevent the formation of Deep Vein Thrombosis (DVT). It works to activate the muscle pumps in the lower leg to enhance the return of blood back to the heart, thereby preventing the stasis that can occur in the deep veins of the legs, which can lead to DVTs. The device is a novel neuromuscular electrical stimulation (NMES) device featuring OnPulse technology. This technology delivers safe reliable electrical impulses limited to 27mA at 1Hz, which has been determined from experiments for optimal comfort and venous return. The question arises as to whether this augmented blood flow from the legs back to the heart is potentially utilisable in patients in whom blood flow is compromised. This is not known, and is an important novel scientific question. It is the scope of this thesis to ask further questions about the Geko ™'s physiological effects, particularly on the vascular system. The importance of DVT prevention is outlined below. If the Geko™ has additional benefits it may be a potentially significant cost saving device in some settings such as the critical care environment.

Venous Thromboembolic (VTE) disease is a well-known complication of surgery. It is routine and mandatory to consider this diagnosis for all NHS hospital patients and manage it preventatively via National Institute of Clinical Excellence (NICE) guidelines[1]. VTE develops when blood clots inappropriately, and can manifest as a spectrum from asymptomatic deep vein thrombosis (DVT) to a lethal pulmonary embolism (PE).

A thrombus (clot) forms in the vein, formed by platelets and fibrin, and then obstructs the flow of blood. As early as 1856, a German pathologist, Virchow, realized that it was the divergence of normal blood flow that caused the clot to develop. He described a triad of causation: venous stasis, hypercoagulability, and blood vessel abnormalities. An embolus occurs when the clot (or part of the clot) migrates in the blood stream. The clot will travel via the venous system to the heart and in most people will lodge in the pulmonary arterial tree. The clot is known as a pulmonary embolus. This can

lead to a variety of pathological insults, depending on how much of the respiratory and circulatory system has been compromised. Mortality rates for acute pulmonary embolus have been found to be as high as 17.4%[2].

VTE is a leading cause of mortality and morbidity in hospitalized patients. In a study looking at seven million patients discharged from 944 North American acute care hospitals, VTE was the second highest occurring medical complication, the second most common cause of delayed discharge, and the third most common cause of excess mortality and costs[3]. The incidence of DVTs is about one in a thousand people annually. The risk is increased in surgical patients and specifically the risk is actually different in the different surgical groups[4] , for example, 47-51% of multiple trauma patients will develop DVT if no prophylaxis is given compared with 9-32% of urology patients . Men and women have equal risk of their first episode of VTE, however men have a higher risk of getting VTE recurrently.[5]

DVTs can be divided into two types: distal (located in the calf) and proximal (located in the popliteal, femoral or iliac vein). Proximal DVTs have a much higher risk of mortality because there is a higher risk of embolising as a PE; 90% of acute PE are due to proximal DVTs. [6]

Complications of VTE include DVT, PE, post thrombotic syndrome (chronic pain and swelling in the affected leg), venous ulcers and chronic thromboembolic pulmonary hypertension.

Despite its importance there is a relative lack of data concerning VTE in critically ill patients. Most ICU patients will have at least one major risk factor for VTE, many will have multiple factors. See figure 1.1. One review[7] highlighted the risks as being between 13% and 31% in patients receiving no prophylaxis. PE has been reported in 7 to 27% (mean 13%) of postmortem examinations in ICU patients[8]. This deserves consideration because a small PE can have large physiological impact on a critically ill patient.

There is inconsistent prophylactic treatment of VTE in hospital patients, despite PE being recognized as the most common preventable cause of hospital death, and preventing VTE being regarded as the number one risk management strategy of improving patient safety in hospitals[9]. A 2005 study in the UK showed that in patients assessed to be medium or high risk of DVT, a staggering 71% did not receive any form of prophylaxis[9]. In the UK in 2005, VTE was reported as being the underlying cause of death in hospitalized patients in over 25 000 cases. In terms of health economics, it is estimated that the UK spends £640 million (direct and indirect costs) on managing VTE.

It is recommended by NICE Clinical guideline 92, that all patients who are admitted to hospital should have an assessment of their risk of VTE and bleeding risk and an that an individualized plan for prophylaxis be established. [1] Therefore one can see that DVT prevention is an important consideration for all patients, especially immobile ITU patients. If the Geko ™ was shown to have an enhancing effect on circulation and cardiac output, this would be a significant side benefit of the device, which would promote its use over the established forms of prevention. The other established methods of prevention do have side effects and potential complications, e.g., bleeding with anticoagulation or skin damage or breakdown with compression stockings.

NICE recommend basing the choice of the prophylaxis on the clinical condition of the patient, the surgical procedure and the preference of the patient. The choices are mechanical prophylaxis and pharmacological means[10].

The mechanical means of VTE prevention are anti-embolism stockings (thigh or knee length), foot impulse devices and intermittent pneumatic compression devices (IPC). A number of contraindications exist which limit the usage of the mechanical VTE prevention, see figure 1.1 below.

Figure 1.1 - Contra-indications for antithrombotic stockings and Intermittent pneumatic compression

Contra-indications	Antithrombotic stockings	IPC
	Dermatitis	Dermatitis
	Post-op vein ligation	Allergy to the material in the device
	Gangrene skin	Gangrene skin
	Recent skin graft	Recent skin graft/vein ligation
	Proven severe ischaemic vascular disease	Suspected/confirmed DVT
	Severe lower extremity oedema	Severe ischaemic vascular disease
	Significant leg deformity	Severe heart failure
	Skin ulceration	Skin ulceration
	Suspected / confirmed DVT	Fragile skin
	Peripheral neuropathy	Severe oedema
	Fragile skin	Peripheral neuropathy

The patient compliance with the mechanical devices can be highly variable. For example, the plastic sleeves of the compression devices can cause sweating, which make them uncomfortable to wear. The size, weight and requirement for an external electrical source also adversely effects the compliance[11].

All patients at risk of VTE, must be assessed for the risks of bleeding before starting pharmacological methods of prophylaxis, which includes the use of fondaparinux sodium, rivaroxaban, apixaban, dabigatran, low molecular weight heparin (LMWH) and unfractionated heparin (UFH) largely for patients with renal failure, but also when the risks of bleeding need to be tightly managed. UFH's anticoagulation effects can be reversed by protamine.

A multicenter study from North America of 1935 medical and surgical patients for the concordance with DVT prophylaxis guidelines each day, showed for 3167 patient-days (24.8%) no pharmacological prevention was given. The reasons for this included high risk of bleeding, active bleeding, invasive procedure or surgery, nighttime admission/discharge, limiting life support, perceived unnecessary, suspected / proven heparin induced thrombocytopenia, no reason evident, severe anaemia, mildly abnormal laboratory results, pharmacy error, ward omission, patient decline and ambulation[12].

A new licensed method, the Geko ™ device is recommended by NICE for use in preventing DVTs when other forms of prophylaxis are contraindicated[13]. This is largely because the other forms of prevention are firmly established and cost effective, as well as the fact that this is a relatively new device, which has the need for further research and clinical experience. The information above outlines the importance of VTE within clinical practice, it is paramount to consider for hospital patients. If the Geko ™ device can be shown to improve a haemodynamic profile as a secondary or dual effect, this could potentially be a huge cost saving device with a potential for reducing long-term morbidity and possibly with a sequential improvement in quality-of-life indicators.

Early studies of a similar technique but different technology [14] have shown the drop in venous volume flow (of 46% in this study after 4 hours) that is seen by bed rest is reversed by the direct neurostimulation of the calf muscles. Early studies have looked at this technique to preventing DVT but as the stimulation is directly on the muscle (as opposed to the nerve with Geko ™) it has been limited to anaesthetized patients due to the currents required and the pain of the stimulation[15-17]. Recent less painful technology with a new device called Veinoplus™ (Ad Rem Technology, Paris, France) has been used to activate the calf muscle pump and achieve good results in improving blood flow; this will be expanded on below.

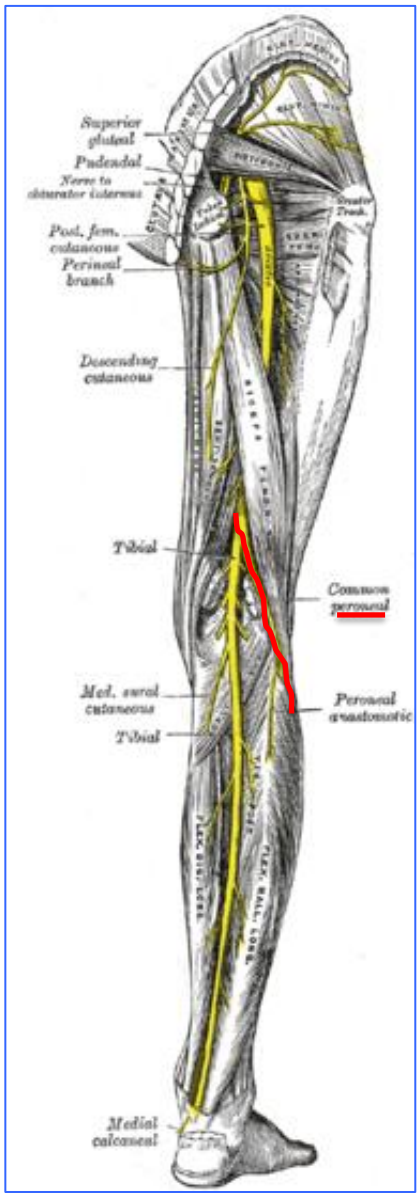
The studies of this relatively new technology are slowly expanding, and are detailed below. They involve looking at various components, including the haemodynamic changes, the relation to oedema and venous ulceration, comparisons with intermittent pneumonic compression, the relationship with bladder incompetence, looking at coagulation blood markers, coronary perfusion.

Initial work has shown improvement in various parameters that suggest alterations in the haemodynamics. If shown to be present the implications would be potentially significant in the short term and long term for patients. Clinical outcomes, which one could postulate in ITU, are reduced mortality, reduced inotrope requirement, reduced hospital stay, reduced renal impairment, renal supportive treatment, and reduced critical care neuropathy. Furthermore, clinical outcomes may be enhanced in patients with raised abdominal pressures, where a mechanically aided venous return may improve blood return to the heart and hence cardiac output. Pregnant women, who also have raised abdominal pressures, as well as relatively vasodilated systems compared with non-pregnant individuals and increased risks of DVT, are another group who may experience improved clinical outcomes if the Geko ™ is found to alter physiology in a beneficial way.

1.2 Anatomy

The anatomy section will explain the biomechanics of how the Geko ™ works. The simple device stimulates one nerve, this leads to a muscular pump action in the calf, which in turn aids blood flow from the leg to the heart. The nerve that is stimulated is called the common peroneal nerve.

Figure 1.2: Picture of the common peroneal nerve from posterior view



Adapted from 1918 Grays Anatomy (Public Domain), the common peroneal nerve is highlighted.

Common Peroneal Nerve

The common peroneal nerve is formed from the fourth and fifth lumbar nerve roots and the first and second sacral nerves. It is a lateral branch of the sciatic nerve, which divides into the tibial nerve and the common peroneal nerve. The sciatic nerve is the largest nerve in the lower limbs.

The common peroneal nerve starts in the superior part of the popliteal fossa passes down the leg alongside the medial margin of Biceps Femoris muscle curve around the fibula head. At this part in its journey, it is only covered by skin and subcutaneous tissue and so is amenable to electric stimulation by the Geko ™ device. The nerve travels behind the peroneus longus muscle (also known as the fibular tunnel) into the anterior compartment of the leg. It is here that the nerve divides into the superficial peroneal nerve and the deep peroneal nerve. Before the division it gives off articular and lateral sural cutaneous nerves. There are some variances here which may explain why there are some patients who may have asymmetry in Geko ™ response or have no response[18].

The lateral sural cutaneous nerve supplies the skin on the posterior and lateral surfaces of the leg. The motor branches of the common peroneal are the superficial and deep peroneal nerves.

The superficial peroneal nerve supplies the muscles in the lateral compartment of the leg; videlicet peroneus longus and peroneous brevis. These muscles contract to cause eversion and planter flexion of the foot.

Figure 1.3: Simple drawing to show Foot Eversion

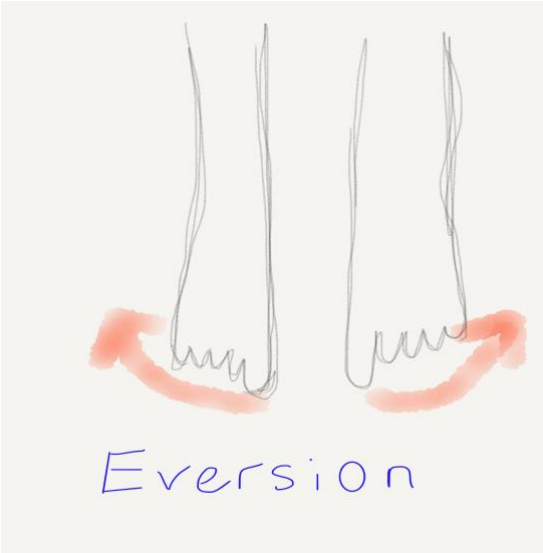
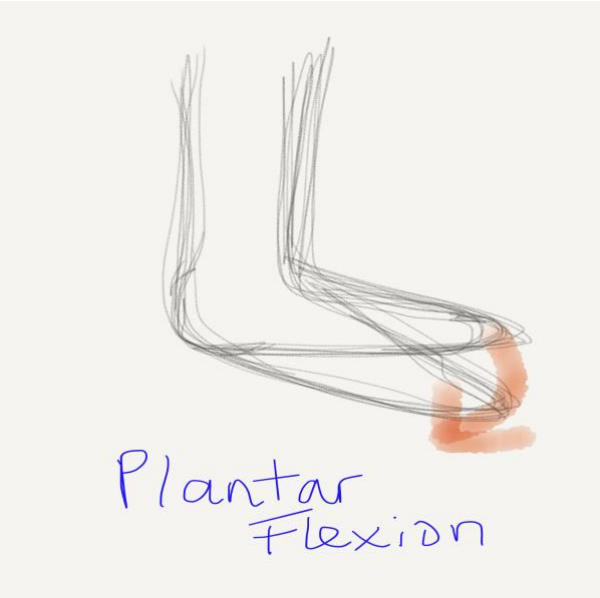


Figure 1.4: Simple drawing to show Plantar Flexion



The deep peroneal nerve supplies the muscles in the anterior compartment of the leg; tibialis anterior, extensor hallucis longus, extensor digitorum longus and peroneus tertius. These muscles are the main dorsiflexors of the foot and extensors of the toes.

Understanding the anatomy is important; because the device is activating muscles and nerves that are a small component of the in-situ calf pump achieved by walking. The main resulting movement from the device is dorsiflexion of the foot with some foot eversion and extension of the toes.

Peripheral Venous System

The peripheral venous system is the route in which de-oxygenated blood returns back to the heart. It also acts as a reservoir to hold extra blood. As compared with the arterial system, the veins are 30 times more compliant than arteries[19]. The compliance is a measure of the ability of a vessel to distend and increase its internal volume when there is an increase in the transmural pressure. The veins have this property because of their histological structure. Veins have thinner walls compared to the lumen of arterial vessels. The walls still have the same three components as found in arterial vessel walls: namely tunica adventitia, tunica media and tunica intima. However, the elastic and muscle elements of the wall are less prevalent. The result of this is that the venous vessel has the ability to stretch more and thus accommodate more blood. Veins therefore also transmit more external pressure increases, such as calf muscles contracting, to the blood inside the veins, than arteries do.

The veins are also the main capacitance vessels in the circulation, due to their compliance, their larger internal diameter and they are more numerous. The veins hold approximately 70% of the total blood volume; the arteries hold 18% and the terminal arteries and arterioles hold 3%. Capacitance is the volume of blood at a given internal pressure. In terms of the venous capacitance function, there are two functional compartments. The very compliant peripheral venous compartment (which is mainly veins in the splanchnic region) stores the majority of blood in the circulation (about 60%) and a less compliant central venous compartment that holds about 10% of the total circulation but is important to cardiac output[20].

The shape of the venous tube varies depending on the flow, pressure and the volume. When the vein is empty, and thus the pressure low, the veins collapse and the walls coapt. The normal pressure range is about 5 to 25 mmHg, which can represent a wide variety of flows.

Other differences, which further highlight the function of the venous system, are the presence of valves, which prevent backflow of blood in a lower pressure system.
To some extent the venous circulation is a more complex system than the arterial, and there is a relative paucity of understanding regarding the physiology and the pathophysiology.

The anatomy of the venous system in the lower limbs

The venous system in the legs is divided into a superficial and a deep venous system, and in addition perforator veins which connect the two networks. It is mainly the deep venous system and the perforator veins that are squeezed by the calf pump[21].
The primary collecting veins of the lower limbs are suprafascial and belong to the superficial venous system. These vessels are thin-walled and can distend to accommodate significant volumes without significant increases in intraluminal and transluminal pressure. This is also due to the fact that easily compressible and moveable soft tissues such as fatty tissue surround them.

The network of veins here is intricate, variable and unique for individuals; many of the veins are unnamed for this reason. The main named superficial veins of the lower leg are the *small saphenous vein*, running from the ankle to the knee and the *great saphenous vein*, running from the ankle to the groin.

The Small Saphenous Vein (SSV)

It is not a classic superficial vein as it runs between the main crural fascia and a membranous layer of the superficial fascia[22].

This vein starts in the lateral side of the foot and then travels inferiorly and posteriorly to pass along the posterior part of the leg in the midline. As the vein then approaches the upper calf, it enters the popliteal space between the two heads of the gastrocnemius muscle in the majority of people. This vein has about 2-10 valves throughout its length[22].

The Great Saphenous Vein (GSV)

The GSV originates in the medial side of the foot. It then ascends up the leg by the medial tibia. At the knee it travels over the medial epicondyle of the femur. Above the knee the GSV passes up the anterior part of the leg, superior to the deep fascia. It passes through the foramen ovale, an opening in the fascia lata, to join the femoral vein at the Saphenofemoral junction (SFJ).

Perforating veins

This is a network of veins whereby the superficial veins pass through the deep fascia to join with the deep veins of the calves or thigh. These veins are also valved, and some have a constant location.

Deep veins

All the blood in the leg eventually drains into the deep system. Most people have five main deep veins, two above the knee and three below. In the lower leg these are the anterior tibial vein (ATV), which channels the blood from the dorsum of the foot, the posterior tibial vein (PTV) which channels the medial aspect of the foot and the peroneal vein which drains the lateral aspect of the foot. The deep veins then unite behind the knee to become a large single popliteal vein. The popliteal vein then travels up the thigh anteromedially in the adductor canal, which it then becomes renamed the femoral vein. The femoral vein and deep femoral vein then combine to form the common femoral vein (CFV), which travels cranially, and superior to the groin crease to become the iliac vein[23].

1.3 Physiology

Cardiac Output

The cardiac output (CO), of about 5-10 litres per minute for the average adult male of 70 kg, is the blood pumped out by the left ventricle into the aorta each minute. It is determined by the product of heart rate (HR) (beats per minute) and stroke volume (SV) (ml of ejected blood per heart beat). The equation representing this is CO = HR x SV. The blood eventually returns back to the heart; starting with arteries leading to arterioles, which feed capillary networks. The capillary networks drain into the end-capillary venules, which feed into the venules and then on into veins. Veins eventually coalesce into central veins, which lead into the right atrium of the heart.

The blood ejected from the right side of the heart always equals the volume ejected from the left side of the heart, except on occasion for a few beats during circulatory adjustments. The cardiac contractions create a volume wave that moves through the vasculature. An important determinate of the flow is elastic recoil force that is generated by stretching the vascular walls, [24]the increased pressure generated is moved on to the next vascular segment which has a lower pressure. The elastic recoil potential energy stored in the vascular walls has both a static and pulsatile component (pulsatile because of the pulsatile flow generated by the heart)[24].

Another equation to help understand cardiac output is Ohm's law; Flow equals pressure gradient divided by resistance. Hence,

$$CO = \frac{\text{Mean arterial pressure} - \text{Right atrial pressure}}{\text{Total peripheral resistance}}$$

The right heart has low pressure in early diastole, allowing a pressure gradient to be created, and the elastic recoil pressure in the veins to drain the veins and venules back to the heart.

This equation is important because in most clinical situations we can only measure certain cardiac parameters. We are able to measure blood pressure and hence derive the mean arterial pressure (MAP). Although MAP is an important physiological measure, as it is the driving pressure for organ perfusion, it does not tell us about the quantity of blood that moves per second i.e., the flow. The flow is important because one function of the cardiovascular system is to continuously provide essential chemicals e.g., oxygenated haemoglobin and glucose and simultaneously remove waste products.

Organ perfusion relies heavily on the pressure of the blood within blood vessels but an adequate flow is also important.

Venous Return

The venous return is the blood volume delivered to the right atrium each minute. The venous flow at rest is accomplished by the pressure difference between the venules and the right atrium of about 15 mm Hg, and is termed vis a tergo. At rest, respiration also plays a part in venous return. When we inhale, the blood flow to the heart is increased by a reduction in intra-thoracic pressure.

Determinants of venous return

$$VR = \frac{P_{msf} - P_{RA}}{VaR_{TP}}$$

VR = venous return. P_{msf} = Mean systemic filling pressure. P_{RA} = Pressure in the right atrium. VaR_{TP} = Total venous vascular resistance.

Flow is a determined by Ohm's law, and equals the pressure difference divided by the resistance to flow. When the flow is venous return, the pressure gradient is the mean circulatory filling pressure minus right atrial pressure, and the resistance is the total peripheral vascular resistance. The P_{msf} is defined as the mean vascular pressure that exists after a stop in cardiac output and redistribution of blood.

Regulation of venous physiology

As highlighted above the venous system acts as a reservoir of blood. The highly compliant properties of veins can maintain filling pressures for the right heart by releasing volume from the peripheral venous compartment into the central venous compartment. It is the splanchnic and cutaneous veins that represent the largest store of blood volume; they are also the most compliant. These veins also have a high prevalence of α_1 and α_2 adrenergic receptors compared to skeletal muscle veins. The cutaneous veins are mainly controlled by temperature. The release of blood volume is mainly achieved by sympathetically mediated constriction of the smooth muscle tone of splanchnic veins.

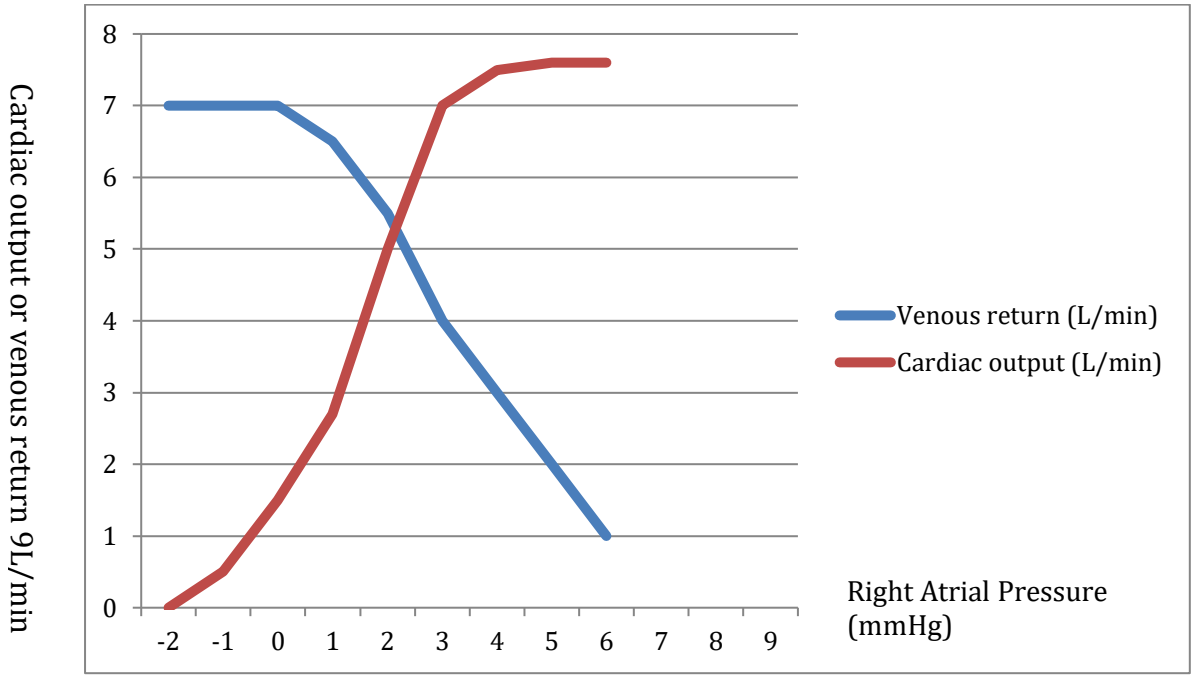
Other mechanisms that alter vascular capacitance are the baroreflex response, renal mechanisms, hormonal effects and local counter-regulatory responses by local mediators, e.g., nitric oxide.

Relationship between venous return and cardiac output

The circulation is a closed circuit, which means the cardiac output must equal the venous return. Guyton felt that the cardiac output was influenced largely by three factors: the pump function of the heart, the resistance to flow and the degree of filling. Experiments which involved Guyton varying the heart rate in electrically paced dogs, concluded that the heart rate didn't have a great effect on cardiac output, until the preload was increased (increased right atrial pressure)[25].

The relationship between venous return, right atrial pressure and cardiac output was well described by Guyton and coworkers in the 1950s[26,27], see below. Their experiment showed an approximately linear relationship between right atrial pressure and cardiac output. The linearity of this relationship is confirmed with other experiments including those of Maas[28]. Guyton concluded that the heart is somewhat passive and responsive to the blood it receives in a steady state[29]. The interpretation of this was that the right atrial pressure is the independent variable in the experiments. However more recent interpretation [26] argue that the cardiac output is the main driver of the right atrial pressure, and that redistribution of blood occurs from the venous system to increase the atrial pressure when the cardiac output decreases[30,31].

Figure 1.5: Guyton's venous return and cardiac output curves



What determines mean systemic filling pressure?

A key variable in venous return and therefore cardiac output is the mean circulatory filling pressure (MSFP). Guyton believed that the resistance of organs and muscles were the main determinants of this. Rothe[32] in his review, explains that MSFP is dependent on blood volume, various vascular compliances and stressed volume. Unstressed volume is the blood volume contained in a vessel at a distending pressure of zero. The stressed volume is the additional volume that generates the intravascular pressure and elastic recoil that is important in generating flow. In a circulation with minimal sympathetic tone, approximately 30% of the total blood volume is stressed, 70% is unstressed[24].

$$\text{MSFP} = \frac{\text{stressed volume}}{\text{Venous compliance}}$$

The cardiac output can be changed without changes in stressed volume by changes in arterial and venous resistances, which lead to a redistribution of blood, and a change in pressure gradients throughout the vasculature. Changing vascular capacitance can also increase the stressed volume, by recruiting unstressed volume into stressed volume. This would also lead to a change in cardiac output.

What will Geko ™ do to Venous Return, Mean Systemic Filling Pressure, and Cardiac Output?

In theory, when considering the pure venous effects of the Geko ™, the external squeezing of the leg veins should increase MSFP, by recruiting unstressed volume into stressed volume, thereby increase VR and thus increase CO.

There may also be changes to the sympathetic nervous system caused by the Geko ™, which will lead to changes in the haemodynamics. The series of experiments will attempt to establish the effects of the device.

If CO is increased, we can theorise this is caused by increased VR, but we would not prove increased VR or MSFP. We should also be able to explain if this effect is in part due to decreased afterload and vascular resistance by a vasodilation of the arterial system, perhaps caused by local metabolites.

1.4 Calf Muscle Pump

The calf muscle pump is an important mechanism for returning blood from the legs to the heart. Another mechanism is the foot pump, which is active during walking and is reported to prime or boost the calf pump.

During exercise; the gastrocnemius and soleus contract and compress the intramuscular and deep veins, which facilitates the venous return to the heart by raising venous pressures during contraction and allowing for refill during relaxation. Thus, a peripheral pump mechanism is created. Functioning one-way valves restrict backflow. The pump, also known as the peripheral heart leads to vertical streaming flow and also horizontal streaming, via the perforating veins.

The pump mechanism involves decreasing the high hydrostatic pressure in the lower legs during ambulation[33]. The hydrostatic pressure in the upright position is due to gravity, and creates the venous hypertension that can become pathological in some individuals. The hydrostatic pressure augments by 0.8 mm Hg / centimeter below the right atrium, and so depending on the height of the individual can be in range of 80-100 mm Hg[34]. This pressure is equal in the deep and superficial venous system[35]. The venous pressure in the lower legs and feet is reduced to 30 mm Hg after a few steps. The thigh veins however stay at the same pressure level [35] (despite some fluctuations during the calf pump activity). An ambulatory pressure gradient (ankle-thigh) of about 37.4 +/- 6.4 mm Hg is accomplished by walking [36]. The skeletal pump can be very efficient at emptying the veins. A study by

Stewart in 2004 found that as much as 40% of the blood volume within the muscle can be emptied by one single tip-toe maneuver (from standing position stand on tiptoe) [37].

The calf pump vertical ejection of blood involves two components. Calf contraction generates centripetal flow and calf relaxation generates centrifugal flow[38]. During calf contraction the pressure in the veins increases up to 140 mm Hg, due to the external compression. This subsequently expels venous blood into the popliteal and femoral vein. There is a difference between the pressure of the popliteal vein (above pump) to popliteal tibial vein (below pump) on average about 50 mm Hg[35]. The centrifugal component of flow then occurs during muscle relaxation, and last approximately 200 – 300 milliseconds.

The horizontal flow is bidirectional and occurs through the valved perforating veins. During calf contraction the pressure build up in the deep vein system leads to flow into the superficial system; the average difference between the Popliteal Tibial Vein (deep venous system) and the Great Saphenous vein (superficial venous system) was on average 13 mm Hg. During muscle relaxation, the pressure difference is turned around and the great saphenous vein has a higher pressure, and therefore the blood flow reverses. Two studies have shown this, a duplex ultrasonographic study in healthy volunteers[39] and an electromagnetic flow measurements in patients with varicose veins[40].
The predominate direction of horizontal flow occurs from superficial to deep, during the calf pump activation, and this is augmented if saphenous reflux is present.

The foot pump venous anatomy has been described[41] using cadavers and consists of a structure called the plantar venous plexus. This in turn features the lateral plantar vein, medial plantar vein and the deep plantar venous arch. Initial studies using video-phlebography, suggested that it was the weight bearing that emptied the deep plantar veins, rather than muscle contractions during toe curls or ankle flexing[42]. Later studies using Doppler suggested that both weight bearing and toe curls have equivalent venous emptying, and thus physiologically both have a role[43]. During Geko ™ usage in a supine subject only emptying achieved by muscular contraction would occur. A further study by Kaplan [44] showed that NMES stimulation of the plantar muscles had a venous emptying effect. This finding is important as the Geko ™ causes muscle contractions of ankle flexion and eversion in addition to the anterior compartment contraction, and thus the complex pattern of contraction may enhance the venous flow as a synergistic phenomenon as opposed to the individual muscle groups that have been previously examined by NMES.

The efficiency of the venous pump is defined as the ability to keep the venous outflow from the lower leg equal to the arterial flow whilst in exercise, which in turn limits the venous dilation of the veins, and keeps the pressure in the ankle low[45].

Effect of breathing on calf pump and venous return

A study in 2005, assessed whether respiratory mechanics have an impact on the venous return of the calf pump in the semi-recumbent position, and this found no effect on net flow, although there were marked changes within each breath of the femoral blood flow at rest and with calf contractions[46]. These changes were also dependent on the type of breath (predominately diaphragmatic vs. predominately ribcage and accessory muscle) and the phase of the breath (inspiratory vs. expiratory).

There have not been any studies looking at the effect of the calf pump in subjects ventilated with positive pressure. It is well known that increases in intrathoracic pressure decrease venous return and decrease cardiac output by decreasing the cardiac compliance and increasing the afterload[47]. It is also been shown that an increase in abdominal pressure of as little as 5cmH_2O can completely halt the venous return from the legs. Therefore, it is likely that positive pressure ventilation will diminish any improved venous return from the Geko ™ device.

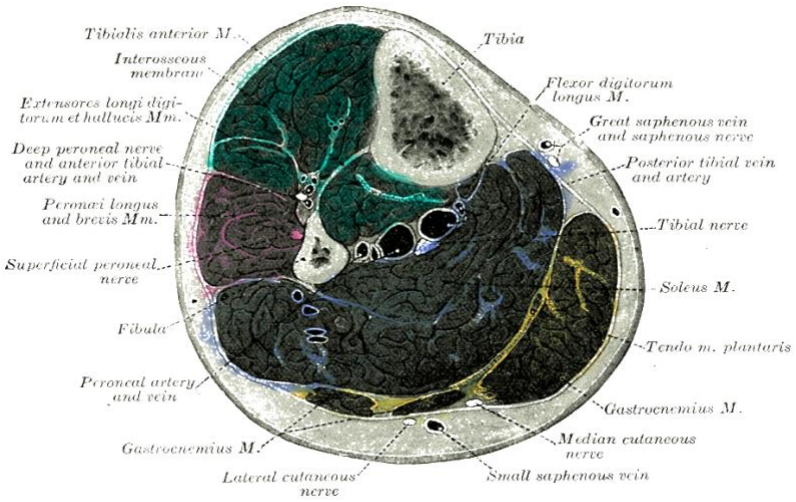
Which muscle group or groups are important?

The lower leg is divided into four compartments (see Figure 1.6 below, the colour coding also relates to Figure 1.7). The interosseous membrane between the tibia and the fibula, as well as the transverse intramuscular septum and the posterior intramuscular septum delineate the compartments. The compartments are the anterior compartment, the lateral compartment, the deep posterior compartment and the superficial posterior compartment.

Figure 1.6: Table of the fascial muscle compartments in the lower leg

Compartment	Muscles	Neurovascular structures
Anterior compartment of the leg	Tibialis anterior, Extensor hallucis longus, extensor digitorum longus, peroneus tertius	Deep peroneal nerve, anterior tibial vessels
Lateral compartment of the leg	Peroneus longus, peroneus brevis	Superficial peroneal nerve
Deep posterior compartment of the leg	Tibialis posterior, Flexor hallucis longus, Flexor digitorum longus, popliteus	Tibial nerve, posterior tibial vessels
Superficial posterior compartment of the leg	Gastrocnemius, Soleus, Plantaris	Medial sural cutaneous nerve

Figure 1.7:: Cross sectional representation of the leg (colour relates to Figure 1.6)



Adapted from 1918 Gray's Anatomy (public domain). The colours indicate the muscle compartments described in Figure 1.6

The traditional view of the calf pump is that it is mainly driven by gastrocnemius and soleus muscle. The Geko TM™ does not stimulate either of these muscles. The Geko ™ stimulates the muscles in the anterior and lateral compartments and yet venous blood flow created is significant, a fourfold increase in superficial femoral vein blood flow compared with rest[48]. One potential explanation is that additional muscle groups may be involved in the calf pump mechanism. Another explanation is that additional physiological processes are involved, e.g., local metabolites causing regional vascular changes.

A device called Veinplus™ also stimulates the calf pump, however it uses electrodes placed over the gastrocnemius muscles to directly stimulate them with electrical impulses. In a study of 24 semi-recumbent volunteers with the Veinoplus™ using popliteal vein ultrasound[49], the peak systolic velocities (PSV) and ejected volume per individual stimulus (popliteal stroke volume SV) and ejected total volume flow per minute (TVF) were examined using varying stimulation rates. The mean baseline popliteal PSV was 10 cm/s. This value increased tenfold for stimulation rates between 2 and 8 beats per minute to a PSV of 96-105 cm/s.

Another interesting finding from the Veinplus™ study is the concept of the flow generated by the calf pump action being non-linearly related to the rate of contraction. A rate that is too fast does not allow the veins enough time to fill with blood. The stimulation rate had the opposite effect on PSV compared to TVF. Low rates of stimulation (2-8 bpm) had a greater effect on PSV than TVF, whilst high rates of stimulation had a lower effect on PSV than TVF. This was reasoned to be due to correlation between time between muscle contractions and venous refilling. The TVF was reported to increase up to 7-fold. This is larger effect than shown for the Geko ™ and may be due to the presence of gastrocnemius contraction. Unfortunately, the VeinplusTM study did not look at cardiac output.

A similar study using direct muscle stimulation from a different device (BMR NeuroTech NT2000™), also utilized the gastrocnemius and revealed significant increase in blood velocity of the popliteal vein[50].

A study looking at which muscle actions cause the most calf muscle movement by EMG of the gastrocnemius muscle in four healthy male subjects showed that rhythmic toe rise foot movements and foot rotation have minimal effect[51]. Whereas rhythmic heel rise foot movements and knee extension with plantar flexion have the most effect. This study has many limitations, including low volunteer numbers and the positioning of the EMG electrode solely at the gastrocnemius muscle to register calf pump movement.

A key study in 1994[52] looked at the relationship between muscle and venous pressure in 9 healthy young women. This study placed three intra-muscular catheters and two venous catheters into a leg, attached to a pressure transducer. The muscle catheters were placed into three muscle compartments of the leg: the deep posterior compartment (DPC), the superior posterior compartment (SPC) and the anterior tibial compartment (ATC). The two venous catheters were placed in the popliteal vein (PV) and greater saphenous vein (GSV). Pressures were measured in decubitus, seated, standing, squatting positions, foot flexion, foot extension, and also a continuous recording during five minutes of walking.

The results showed that during foot flexion, the main muscular compartment involved was the ATC (with a 472% rise in the decubitus position and an 1861% rise in the seated position and a 456% rise in the standing position). The DPC had a lesser rise in pressure (154% in the decubitus position, 1610% in the sitting position and 143% in the standing position).

The results for foot extension reveal that the DPC is the only compartment with a significant rise in pressure (318% in the decubitus position, 3440% in the seated position and 377% in the standing position). No important action was attributed to the SPC.

The GSV and PV pressure rose during foot flexion in the decubitus position, (50% and 25%) mainly secondary to ATC increases.

The Geko ™ causes foot flexion, and therefore we can postulate pressure increases in the ATC, with subsequent venous flow enhancement. The neurological effect of the Geko ™ does not mirror the actual physiological calf pump, for example no effect on gastrocnemius. Furthermore, we are investigating the effect in the supine position, because this is the position that most patients will be in within a critical illness clinical context. The hydrostatic venous pressure in the ankles is lower in the supine position, and so the pump effect of the Geko ™ will be lower. We cannot make like-for-like comparisons to the physiological calf pump.

Foot veins are an important component of the physiological pump. The Geko ™ does work to plantar flex and evert the foot. The plantar venous plexus comprises multiple valved large veins that travel the arch of the foot. A study by White et al.[53] showed that mechanical compression of the plantar venous plexus increased the peak velocity within the posterior tibial vein, which would occur with force during ambulation. But perhaps more relevant to the Geko ™ in supine patients, other studies by Gardner and Fox[15] revealed that because the venous plexus is attached to the arch, even stretching of the arch without weight bearing would work to forcibly empty the veins. This finding and theory is also demonstrated by a study in Japan on 20 patients on bed rest in an intensive care unit which demonstrated that passive foot exercises with a nurse for 5 minutes was equivalent if not superior to a compression foot pump[15]. The ratio of the diameter of the venous plexus veins to the posterior tibial veins is about 1.9:1 and also suggests a bellows like effect.

A study looking at whether compression of foot and calf compression separately or simultaneously augments arterial flow, found simultaneous contraction to be better[54].

Is there evidence for a graded response?

A study using neuromuscular electrical stimulation on the gastrocnemius muscle found that increasing the rate of stimulation led to increased arterial inflow of the femoral artery[55].

Studies with the Geko ™ show that both the current and frequency of the stimulation have a dose response effect on the venous flow volume[48].

1.5 The device

Name: Geko ™, OnPulse Technology

Manufacturer: Sky Medical Technology Ltd

Webpage: www.Gekodevices.com

Sky Medical Technology Ltd and Firstkind Limited are certified to ISO 13485:2003.

The device is CE marked as a Class IIa medical device in October 2010 to increase blood circulation and prevent venous thrombosis formation. In 2012 the scope of the CE mark was widened to treating and preventing oedema, treating venous insufficiency, and promoting wound healing.

The Geko ™ device is certified to EN 60601-1-2:2007 regarding Electromagnetic Compatibility. Medical Electrical Equipment needs special precautions regarding EMC and needs to be installed and serviced according to the EMC information provided at http://www.Gekodevices.com/media/33907/EMCDeclaration.pdf

Description and use

A single use, self-contained, internal battery supplied, electro-stimulation device that can be worn by patients. Adhesive pads adhere distal to the posterior knee crease on one or both legs, as prescribed by the doctor. The Geko ™ is placed using a location indicator aligned with the laterally located head of fibula. A non-replaceable, lithium battery powers the device. The device can be used for twenty-four hours before needing to be replaced. The device sends an electrical impulse to the common peroneal nerve, which as stated above contracts the calf muscles. This in turn squeezes and empties the veins of the leg, and thus increases the return of blood from the legs to the heart. The device is lightweight (16 grams) and small in size (149mm by 42 mm by 11 mm) and so is designed to allow the muscles to contract without impeding their movement.

Figure 1.8: The Geko ™ device. Permissions obtained from Geko First Kind

Figure 1.9: Picture to show where the device is applied. Permissions obtained from Geko FirstKind

It has seven stimulation modes, which are selected by depressing the button. The different modes are incremental pulse widths 70, 100, 140, 200, 280, 400, and 560 microseconds, with a 5% error margin. They are activated sequentially by serial presses. There is no display on the device to tell the user which pulse width is currently selected. The stimulation frequency is 1 hertz, and the device has battery charge for 24 hours and then needs to be replaced with a new device. The shelf life is 2 years.

1.6 Studies looking at clinical evidence of the use of the Geko ™ device

Four studies were evaluated to assess the physiological changes caused by the Geko TM in healthy volunteers.

The study by Jawad looks at the Geko ™ in relation to cardiac output and is part of a PHD thesis from Queen Mary's University of London.
This single arm, single centre UK trial looked at 9 healthy volunteers, with the Geko ™ fitted bilaterally and using two different pulse width settings (400μs and 600μs). In both settings the frequency was 3 hertz and the duration of stimulation was 30mins. The recruits were supine, with their head slightly tilted; a period of 30 minutes of rest was timed before a baseline recording was taken.

The measurements of cardiac output were obtained using echocardiography and colour flow duplex ultrasound measurements obtained at baseline and during different stimulation settings with the device still active and 5 minutes before the completion of each stimulation period.

The conclusions drawn from this study are that neuromuscular stimulation with the Geko ™ device was effective in increasing cardiac output and vascular flow. Of all of the cardiac parameters assessed, the only significant change was seen in cardiac output. In comparison with baseline, 6% and 4% augmentation in cardiac output was seen using pulse width 400 μs and 600 μs, respectively.
The reasons for this are unclear, as heart rate was not monitored.

Analysis of diastolic function (echocardiography measurements of LV diastolic volume, E and A Wave diastolic velocity measured at the mitral valve that reflect early and late diastolic filling, in addition to deceleration time in to the LV and the E/E ratio, which is an assessment of LV filling diastolic pressure) suggests that electrical stimulation does not alter the filling pattern of the left ventricle. Data from the right heart was not analysed and so limits the conclusions that can be drawn regarding venous return.

A statistically significant augmentation was observed in femoral vascular flow parameters both at the arterial and microvascular level. Femoral arterial volume flow increased by more than 50% following electrical stimulation and femoral arterial peak velocity increased by 24%. Microvascular velocity increased by 1,186% following pulse width 400μs and 1,552% following pulse width 600μs, measured by laser Doppler flowmetry assessments of the lower leg. These increases may be due to the increased vessel flow provided by the venous valve system when active. This may provide direct

auxiliary assistance to the heart by reducing the pressure difference between inflow and outflow to the ventricle. Alternatively, a substantial up-regulation of the use of smaller vessels in the skin and possibly other organs may provide a large increase in the total available cross-sectional area and therefore a drop in vascular resistance.

In a series of studies in the UK by Rachel Barnes[56] as part of an MD looking at the various arterial, venous and microcirculatory effects of the Geko ™ device no change in blood pressure (systolic / diastolic / mean) or heart rate was found in a total of 36 patients with arterial and venous disease. Also, no change in cardiac output, pulse wave velocity, or augmentation index was found in 19 inpatients with infra-inguinal bypass for peripheral arterial occlusive disease (using the Vicorder device to obtain the data). This may have something to do with the diseased vasculature in this patient group, but it is difficult to draw any firm conclusions.

The study by Tucker et al.[48] examined 30 seated healthy volunteers with a Geko ™ applied to one leg and the other leg used as a control. The volunteers had a stimulation sequence that consisted of 5-minute episodes of stimulation and ten minutes rest, this was repeated 15 times. This study measured photoplethysmography (PPG Medsonics Ltd), strain gauge plethysmography (SPG Hokanson), laser Doppler fluxmetry (Laser Doppler Perfusion and Temperature Monitor DRT4 Moor Instruments), transcutaneous oxygen tension (TCM4 Tina Radimeter Ltd), pulse oximetery (Datex omeda) and superficial femoral vein blood flow and diameter (Phillips IU22 ultrasound) at various stimulation programme sequences. The results showed that photoplethysmography signal increased from baseline in all programme sequences. This increase was at least 50% of a full dorsiflexion motion in all sequences, and higher current settings produced more venous emptying. The strain gauge plethysmography, which measured the cyclic change in calf circumference during a stimulation sequence, was most significantly affected by the stimulation frequency. The laser Doppler fluxmetry demonstrated 25 fold increase in the stimulated leg compared with the un-stimulated leg, indicating an increase in the microcirculatory flow[57]. There was a bilateral decrease in tissue oxygenation of the legs during the experiment, although pulse oximetry and heart rate had no significant change. Importantly, there was a significant increase in mean venous flow and peak venous flow compared to baseline for all stimulation programme sequences.

Figure 1.10: Ultrasonography measurements showing venous volume flow at 15 different stimulation programmes versus baseline. Data presented as mean ± standard error of the difference. Adapted from Tucker et al. [48] by highlighting 1Hz. (Permission obtained)

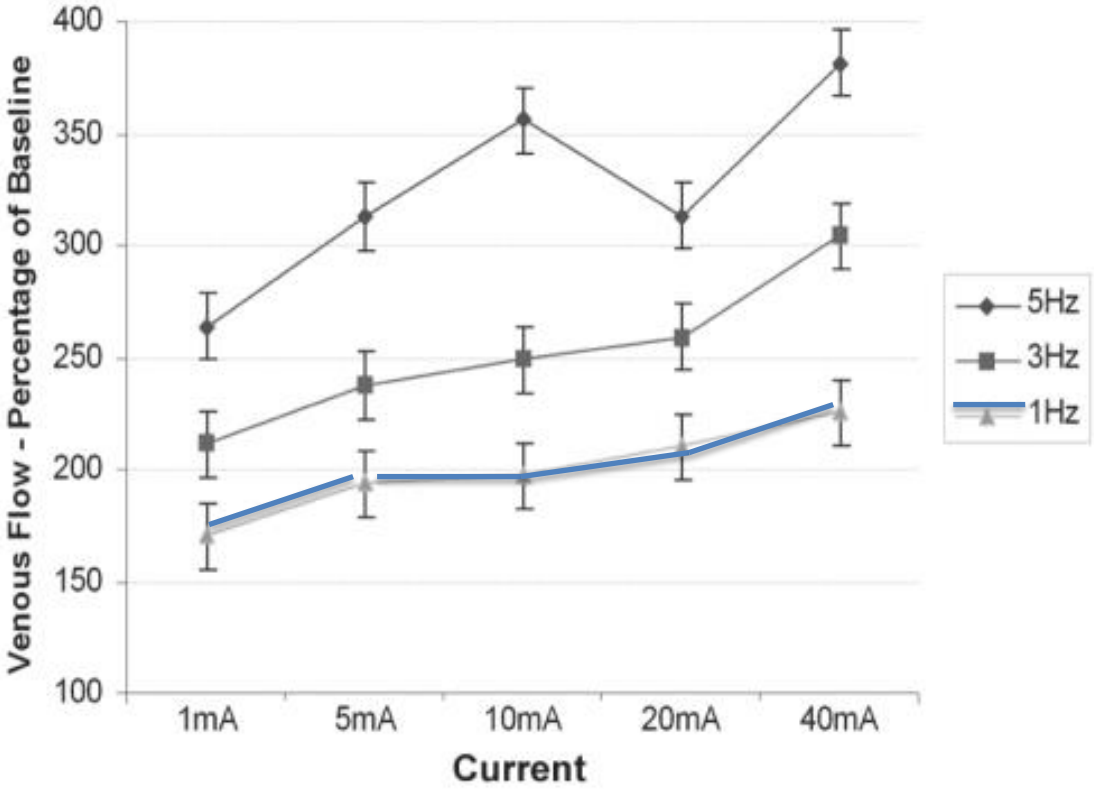
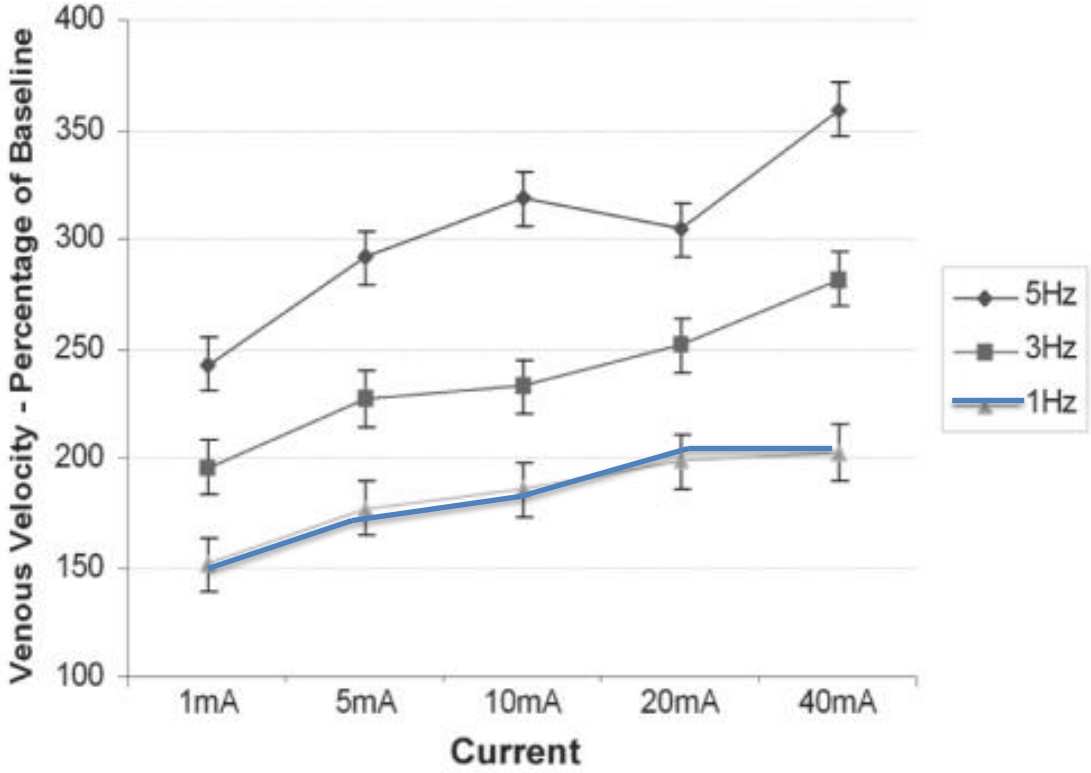


Figure 1.11: Mean peak venous velocity at 15 different stimulation programmes versus baseline. Data presented as mean ± standard error of the difference. Adapted from Tucker et al.[48] by highlighting 1 Hz. (Permissions obtained)



In summary, this experiment demonstrates an enhanced venous emptying and reduced peripheral resistance of the stimulated leg by the Geko ™ device.

A small study by Williams et al. [58] in ten healthy volunteers compared the Geko ™ to intermittent pneumatic compression. The study demonstrated increases in venous and arterial flow (peak velocity, time-averaged maximum velocity, and volume flow) with the Geko ™, whereas the IPC only demonstrated modest increases in venous flow. The improved arterial inflow may be due to increased cardiac output or locally reduced peripheral resistance.

Additional Clinical benefits of the Geko TM™

Aside from the postulated benefit of risk reduction in DVT formation. The Geko ™ has been reported to have some additional clinical benefits, which are outlined below. The studies are largely case reports and simple audits, which feature on the Geko ™ Firstkind webpage[59]. This reflects the relatively recent availability of the device and the need for further research.

There has been some evidence of reductions in oedema post ankle sprain; a clinical audit of 8 people in 2013 by a group of physiotherapists[60].
There have been a number of case studies identifying the potential benefit of wearing the Geko ™ after foot surgery in reducing oedema. Other areas of potential benefit have been highlighted as bladder and bowel incontinence, fracture healing and wound healing[61], and arterial and venous ulcer healing[62]

An important study to this thesis has recently reported improved coronary flow in 10 patients using the Geko[63]. The flow was measured invasively using Doppler flow wire after Geko stimulation of 4 minutes. Average peak velocity was increased in a non-stenotic vessel (20.3 +/- 7.7cm/s to 23.5 +/- 10cm/s; p= 0.03) compared to a stenotic vessel which had a non-significant increase in flow. Endothelial function was also assessed by peripheral artery tonometry at baseline and one hour after Geko stimulation, this was found to increase. Reactive hyperaemia-peripheral arterial tonometry (Rh-PAT) increased from 2.28 +/- 0.39 to 2.67 +/- 0.6 p = 0.045.

These studies all point to an increased circulation, especially to the leg, involving the venous and arterial system.

Post market surveillance

Post market surveillance of 213 patient questionnaire responses has been assessed by the company Firstkind about post wear feedback on the ergonomics and comfort of the device.

Results from this surveillance show that:

- 81.6% of patients found the Geko ™ device easy or very easy to apply
- 83.1% of patients found the Geko ™ device easy or very easy to start/stop
- 85.0% of patients found the Geko ™ device comfortable or very comfortable to wear once applied
- 91.7% of patients reported that their quality of sleep was normal; 5.8% reported worse sleep and 2.5% reported better sleep.

This feedback from patients shows that the Geko ™ device is considered easy to use (for both application and manipulation) and comfortable to wear.

Adverse event analysis

The only known adverse event is skin irritation or inflammation, which has previously been reported for other NMES devices using hydrogel electrodes. Firstkind has received four complaints of possible skin irritation with over 4,000 devices used, giving a frequency of 0.1%.

Failure to function rate

The Geko ™ does not produce any discernible muscle contractions in a small subsection of people. This rate was as high as 59% in studies on vascular patients in studies by Barnes. The presence of oedema, diabetes, neuropathy, increasing age were found to have negative effect on the ability of the Geko ™ to produce a twitch.

1.7 Does intermittent pneumatic compression increase cardiac output?

Intermittent pneumatic compression (IPC) is a medical device, which utilizes an air pump and leg sleeves that wrap around the legs. The device intermittently inflates the sleeves to squeeze the legs and hence pressurizes the tissues. This in turn leads to blood and lymph in the tissues being forced cranially as competent valves promote a proximal displacement.

Intermittent sequential pneumatic compression (ISPC) devices work in a similar way but these devices have multiple chambers, which employ waves of compression to enhance venous flow.

A study has suggested that that ISPC improves cardiovascular parameters during laparoscopic procedures that involve positive pressure pneumoperitoneum (PP)[64]. The effect of PP on the haemodynamics is to reduce venous return, stroke volume, cardiac output and increase systemic vascular resistance. The study involving 16 patients showed that PP reduced cardiac output by 20%, which was then improved by 27% after the ISPC was activated. The cardiac output was measured by transesophageal doppler. The haemodynamic effects of ISPC has also been shown in healthy volunteers[65], the MAP increased although the cardiac output reduced. 19 patients with chronic heart failure[66] showed an increased cardiac output (4.26 to 4.83 L/min p = 0.008) and stroke volume (56.1 to 63.5 ml p = 0.29) whilst SVR decreased (from 1520 to 1216 dyne-s/cm p= 0.0005) with ISPC. The studies suggest that in ISPC improves cardiac output when there is an element of pre-existing impairment (cardiac failure, PP), maybe acting as an auxiliary pump. This auxiliary pump is not as apparent when the cardiac function is normal.

This effect has not been shown in none sequential constant inflation pressure devices such as antishock garments[67,68]. Also, IPC has not been shown to increase cardiac output measured by the thermodilution technique in surgical intensive care[69,70].

The physiological reason behind this maybe the enhanced 'milking effect' of the ISPC to increase venous return. The decrease in SVR maybe due to increased nitric oxide release from the vascular endothelium. However this may not be a true phenomenon, as a case report found erroneous cardiac output measurements with ISPC[71].

The Geko ™ may demonstrate a similar result as the ISPC. The magnitude of this effect is difficult to predict as no previous work has been done on this. The mechanism of venous "milking" by the Geko ™ is different, involving circumferential muscular squeeze on veins, as opposed a more generalized squeeze on all leg tissues including the arterial system.

1.8 Monitoring Cardiac Output: methods and accuracy

There are many devices available to measure cardiac output. Some devices are invasive e.g., Pulmonary arterial (PA) catheter. Other devices are minimally invasive such as the Oesophageal Doppler, LiDCo and PiCCO (which require arterial catheters and central access). There are also non-invasive methods which utilize various techniques; pulse wave analysis (such as the Vicorder), bioreactance (such as Nicom) and bioimpedance such as (NICaS)[72].

No standard or reference measurement against which all these methods can be compared exists. The PA catheter and thermodilution technique is often regarded as the gold standard[73], though this also has a accuracy of +/- 10-20%. Critchley and Critchley reviewed comparative studies of cardiac output monitors and recommended that new methods only be accepted if when using Bland and Altman's[74] technique of comparing the two methods, the limits of agreement were +/- 30%.

We have used non-invasive methods of cardiac output monitoring in studies involving healthy volunteers to minimize unethical risks of harm, despite the lower levels of accuracy associated with these methods. We have also used the LiDCO in one experiment involving cardiac patients.

Pulse Contour Method

Cardiac output can be derived from morphological analysis of the pressure wave. There are a number of machines that can do this. Some need manual calibrating, others are self-calibrating, some are invasive, and others are not.

For example:

PiCCO = Fourier's transformation of the systolic portion of the curve.
LiDCO = calculates stroke volume from the pulse power after calibration with a lithium solution.

The Pulse contour method (PCM) is measured beat-to-beat which is different from more established methods of cardiac output, such as thermodilution, which is calculated over a time period. However, most devices also can then average the calculations over the measured time index chosen by the operator, e.g., the Vicorder.

PCM is based on the rise in pressure that occurs during systole is because of the ejection of the stroke volume into the aorta and thus subsequently into the large arteries.

There are a few mathematical models that have been used to calculate this.
The model most used measures the cross-sectional area under the systolic curve and derives a value using data from in vitro experiments on the human thoracic aorta. The PCM method is good at monitoring changes, which is what our experiments will look at. In order to get accurate cardiac output numbers, calibration is important to align the results with absolute figures. This is not possible during our experiments as the calibrating requires invasive techniques (e.g., thermodilution) or unwieldy equipment (inert gas breathing).

The Vicorder used in our experiments for measures of cardiac output utilizes the pressure recording analytical method (PRAM[75]). The theoretical background of this technique is based on the mathematical and physical theory called perturbation theory. This theory finds an approximate solution to a problem that cannot be solved exactly (A) by firstly finding a related variable (A_1) that can be easily found. To this variable a series of small parameters (A_3 etc.) or deviations can be considered that help reach an approximation of the original unsolvable problem.

$A \approx A_1 + \varepsilon A_2 + \varepsilon A_3 + \varepsilon A_4$ …….

PRAM analyses the whole arterial pressure wave (both systolic and diastolic) of each pulse and samples data at 1000Hz. The CO is calculated as a ratio of the area under curve in systole to the systemic impedance, which is based on a proprietary algorithm. The device does not require calibration and so is more useful for cardiac output trends rather than absolute numbers.

There have been a number of positive studies recommending this technique[75-78], although some studies have not found good correlation with PAC thermodilution in cardiac patients[79] and also critically unwell paediatric cases[80].

The Vicorder

The Vicorder records the pulsatile pressure change in the brachial artery for calculating the cardiac output. The device utilizes a pressure transducer and inflates a cuff to measure the blood pressure; it then deflates and subsequently re-inflates to the diastolic pressure. The inflation is then kept constant and the pulsatile waveform is analyzed and an algorithm correlating to central blood pressure[81] and cardiac output is applied to obtain the cardiac output. An average of 6-9 waveforms are used for the computation. A study in Cambridge has shown good correlation with the inert gas breathing method of cardiac output[82]. The Vicorder system can also utilise two cuffs that are placed over additional

peripheral arterial pulse locations in the body: carotid, femoral or ankle for the pulse wave analysis[83-85]. The device is easy to use, requires no skilled users or expensive consumables, it is also non-invasive and painless. There is validation data for measuring the pulse wave velocity with the Vicorder in comparison with other non-invasive devices [86,87].

The LiDCO™plus

The LiDCO™ is a continuous cardiac output monitor based on lithium dilution. A small dose of lithium is injected via a central or peripheral venous line, as the bolus indicator. A lithium sensor measures the arterial lithium concentration time curve and thus Fick's law derives the cardiac output. This then calibrates the system and the PusleCO™ system uses an algorithm to derive the cardiac output beat to beat from the arterial blood pressure trace[88].

In a study looking at the reliability of the minimally invasive devices LiDCO™ plus performed the best[89], and provided readings within the set limits of acceptance of +/- 30%[73,90,91] , which is based on the precision of the reference method (thermodilution) of +/- 20%. However more recently a meta-analysis review has suggested that a more realistic benchmark is +/- 45% for acceptable error with minimally invasive cardiac output devices. This is a very large error margin [92].

Pulse wave velocity

Pulse wave velocity shows a positive correlation with arterial stiffness. This measure has gained attention within the clinical community as it has prognostic significance with cardiovascular disease[93,94].

The pulse wave gets reflected back from the periphery and thus an early wave reflection boots the systolic pressure. This also puts extra pressure on the left ventricle to contract, i.e., increasing afterload. As the reflected wave is less in diastole it also reduces the coronary artery perfusion pressure.

Increased arterial stiffness leads to a greater risk of angina and heart attack, stroke and heart failure. Arterial stiffness can be increased by the following mechanisms

- An impairment in the elastic structure in the arterial walls.
- Damage to the endothelium/smooth muscle mechanism

- Increase in mean arterial pressure

It is possible to measure the moment of arrival of the reflected wave by studying the wave. This analysis can be done by wave intensity analysis, which uses time, or by using Fourier analysis and computations of impedance using frequency as a domain. Both techniques are accurate in analyzing the reflected wave composition.

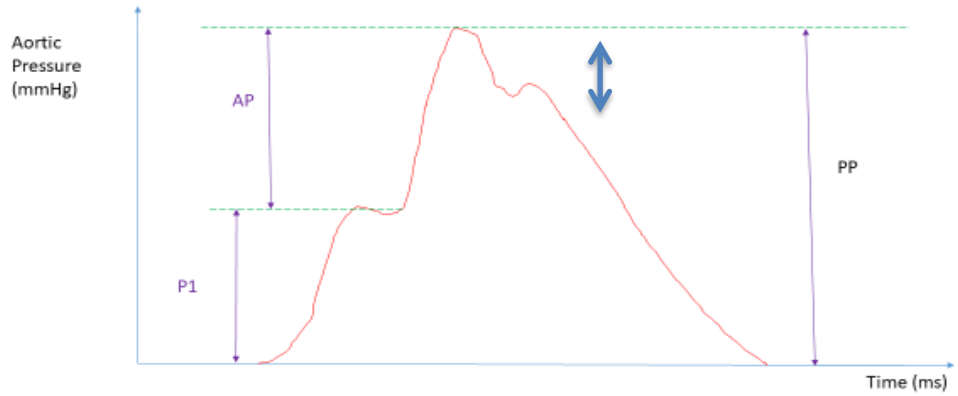
Vasodilators decrease the pulse wave velocity and augmentation index[95].

The augmentation index

The augmentation index (AI) is a ratio that is calculated from the blood pressure waveform, Figure 1.12. It is related to the wave reflection and tells us about systemic arterial stiffness. There are two types, central and peripheral, named after whether measured in the central or peripheral vasculature. The central AI (cAI) has been shown to be a predictor of adverse cardiovascular events[96].

Using the measured pressure wave, it is possible to find a specific point on the wave that corresponds to where the forward and backward waves interact. Although the definition of this point is equivocal and some authors use an inflection point determined by second order derivatives and others use a shoulder point as determined by higher order derivatives. Once this point is determined, the augmented pressure (AP) can be calculated as the systolic pressure minus the inflection/shoulder point. The augmentation index (Aix) is defined as the ratio of AP to Pulse Pressure (PP). P1 is the Pulse Pressure (PP) minus the AP.

Figure: 1.12 Demonstrating Augmentation Pressure (AP), measured from the inflection point to the peak systolic pressure.



1.9 Importance of cardiac function in intensive care

Cardiac output monitoring in intensive care is an established practice, to ensure tissue oxygenation and end organ perfusion. It can be difficult to make clinical decisions on whether a patient needs volume, vasopressors, inotropes or diuresis whilst critically ill[97]. Inappropriate management can exacerbate deranged physiology and excessive fluid overloading. Haemodynamic monitoring can play a key part in guiding management decisions, if accurate and interpreted correctly[98], although this occurs in clinical with considerable variability [99].

Clinical indices of the adequacy of tissue/organ perfusion[100]:

- Mean arterial pressure
- Urine output
- Mentation
- Capillary refill
- Skin perfusion/mottling
- Cold extremities
- Blood lactate
- Arterial pH, BE, and HCO_3
- Mixed venous oxygen saturation $SmvO_2$
- Mixed venous pCO_2
- Tissue pCO_2
- Skeletal muscle tissue oxygenation

As early as the 1970s, Shoemaker found that a cardiac index (CIx) of ≥4.5L/min/m^2 and an increased oxygen delivery ($D0_2$) of ≥600ml/min/m^2 predicted survival in trauma patients[101]. $D0_2$ is the product of cardiac output and arterial oxygen content. Normal range of CIx is 2.5 to 3.5 L/min/m^2. Subsequent studies in high-risk surgical patients suggested an improved survival by aiming for these "supranormal" levels[102,103]. However other studies have shown no difference in mixed groups of critically ill patients [104,105] and patients with sepsis[106]. An important study looking at increased oxygen delivery with dobutamine, an inotrope that increased cardiac output, showed worse outcome [107], the oxygen consumption was the same in the control and the treatment group.

A landmark study by Rivers[108] showed improved outcomes by looking at and treating markers of cardiac adequacy early in sepsis and showed improved mortality. Rather than looking at cardiac output, he used CVP (8-12 mmHg) for cardiac filling and central vein oxyhaemoglobin saturation ($Scv0_2$ >70%) and serum lactate for indication of perfusion adequacy. The treatment delivered was named Early Goal Directed Therapy (EGDT).

Three subsequent large studies did not show this benefit, but it may be partly due to the fact that they were conducted over 10 years later, when some of the learning from the initial Rivers paper would have been part of standard care.

The ProCESS study in 2014[109], conducted a multicenter, randomized protocolized care for early septic shock in 1341 patients in the United States. The protocol-based care arms had a higher use of central venous catherisation, intravenous fluids, vasoactive drugs, and blood transfusions. However, there were no significant differences in mortality, incidence and duration of cardiovascular failure or respiratory failure, and no significant differences in length of hospital stay.

The ARISE study in 2014[110], in Australia and New Zealand, examined 1600 patients presenting to emergency departments with early septic shock and found no difference in mortality with EGDT.

A UK based study called PROMISE[111], also looking at EGDT (a 6-hour resuscitation protocol) in 2015, did not show an improvement in mortality in 1260 patients.

Unfortunately, there have been relatively few studies that directly show cardiac output monitoring to directly improve outcomes in intensive care. In fact the key monitoring device the pulmonary artery catheter (PAC), the gold standard in monitoring, was found by a large randomized control trial (RCT), involving 1014 critically ill patients, to have no clear benefit or harm[112]. Though some small studies have suggested minimally invasive monitoring cardiac monitoring combined with goal directed fluid

administration did improve perioperative outcomes in high-risk surgical patients. The OPTIMISE trial was conducted in 17 acute care hospitals in the UK, and was a randomized controlled trial of 734 high risk patients undergoing major gastrointestinal surgery in 2014 to evaluate the clinical effectiveness of peri-operative cardiac output guided haemodynamic therapy algorithms versus usual care. The study did not find that the composite of outcome complications, defined by the study, or 30-day mortality was reduced[113]. The exact benefit of cardiac output monitoring is not clear and defined, as an interesting debate by Rupert Pearse and CG Morris points out[114].

Although central venous pressure (CVP) has been used for decades as an indirect measure of right ventricular afterload, unfortunately the relationship between them is highly unreliable, and CVP measurements do not correlate well with volume responsiveness[115].

In the last ten years, new dynamic measures of how stroke volume varies with respiration or passive leg raise are used for measures of fluid responsiveness and they are more accurate than static measures like CVP[100].

Chapter 2: Anaesthetic induced hypotension is unchanged by the Geko ™ Device. A Pilot Randomised Cross-over Design Study

2.1 Introduction

Induction of general anaesthesia can cause a sudden drop in blood pressure and cardiac output. This phenomenon occurs largely because the anaesthetic agents cause vasodilatation, reduced systemic venous return and consequent fall in blood pressure. In turn, this may or may not then lead to a compensatory tachycardia to re-establish cardiac output. This scenario is well recognised within anaesthetics, and is dependent on many factors including: speed of induction, anaesthetic agent used, and patient factors e.g., age, hypertensive disease, and concurrent sepsis. A study in Japan demonstrated that a 2mg/kg bolus dose of propofol, a standard intravenous anaesthetic agent at a standard dose can cause a -25.9% (+/- 4.0%) drop in systolic blood pressure and a -28% (+/- 8.7%) drop in diastolic blood pressure[116]. A paper by Sato[117] revealed a depression of the cardiovagal baroreflex at a target controlled infusion of propofol at a concentration of 5μg ml^{-1}.

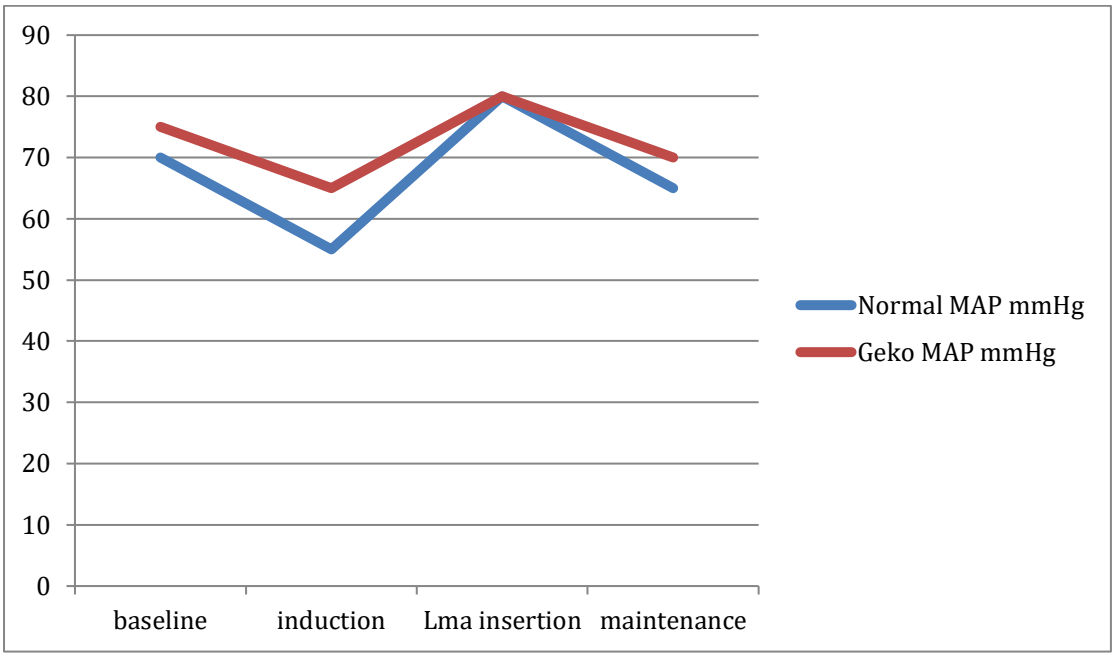
Blood pressure is usually maintained to provide adequate flow to the vital organs of the brain, heart and kidneys by auto-regulation. This level is usually maintained at systolic pressures above 70 – 80 mmHg. In hypertensive patients the level is higher. Untreated hypotension may lead to inadequate organ perfusion and so anaesthetists are trained to treat this with initially a fluid bolus to optimise preload and then a range of drugs to increase cardiac contractility and provide vasoconstriction.

In theory if the Geko ™ device increases venous return to the heart, the effect may be like a fluid bolus, i.e., optimise preload, and thus the increased cardiac output may be revealed in patients by the occurrence of diminished hypotension, see Graph 5.

Total intravenous anaesthesia is a technique used to administer anaesthesia in the continuous intravenous form, mainly propofol, as opposed to the inhalational anaesthetics. Better knowledge and understanding of the pharmacodynamics and pharmacokinetics of the drugs has allowed the development of computerised syringe drivers that can compute and deliver to the blood or target site concentration of anaesthetic set by the anaesthetist. This system allows a smooth induction, which is reliable and titratable. The anaesthetic is weight and age adjusted and the level can be standardized more easily as well as recorded.

The Geko ™ relies on muscle contraction to achieve its haemodynamic effect, and so the time period of the anaesthetic induction before muscle paralytic drugs were given was used for the data collection.

Figure 2.1: Hypothesis of how Geko ™ could affect the blood pressure during anaesthetic induction



2.2 Objectives

The objective was to examine the haemodynamic relationship between the Geko™ device and intravenous anaesthetic induction in terms of standard monitoring: heart rate, blood pressure, capnograph, oxygen saturations and capillary refill.

The null hypothesis was that no change in blood pressure or haemodynamic parameters from baseline would be seen.

There have been limited definitions of anaesthetic hypotension, however some studies suggest 30% as a definition[118,119]. Without prior studies to compare what effect the Geko ™ may have on the vasodilated patients we have been unable to perform a power calculation. Collecting data from 20 subjects was decided to be a reasonable aim within a 3-month study period. Success of the study is to show significant reduction in the expected BP drop at induction, which is approximately 25%. A reduction in BP drop, which would have a clinical benefit would be to reduce the BP drop completely. This is not a realistic effect size as the vasodilating effect of the anaesthetic is profound and systemic.

Augmenting the cardiac output by the Geko ™ may not improve the blood pressure, or it may be hypothesised to have a modest effect of minimising the drop in BP to a drop of 10%.

2.3 Study Approval

The study was sponsored by Bart's Health NHS Trust and funded by a National Institute for Health Research (NIHR) i4i grant. National Research Ethics Service (NRES), Dulwich NRES Committee, reference 13/LO/0295 approved the study on the 19th April 2013.

2.4 Material and Methods

2.4.1 Volunteers

20 adult participants were identified from theatres lists known to be suited for a TIVA anaesthetic, ENT surgery, large plastics cases, spinal surgery at the two hospitals: The Royal London, Whitechapel London and St Bartholomew's Hospital. The subjects were approached by the anaesthetic team and provided with information sheets (appendix 1) on the day of surgery. Written informed consent was obtained prior to the study for all volunteers. The demographic data of the volunteers is displayed Figure 2.4.

2.4.1.1 Inclusion criteria

Figure 2.2 Criteria that volunteers must fulfil for inclusion

Scheduled for elective surgery in theatres at The Royal London or St Bartholomew's Hospital
Adults aged 18 - 85
Planned TIVA anaesthetic
Fully informed written consent
Assent of anaesthetist, ODP and surgical team
American Society of Anesthesiologists (ASA) 1-3
Patient suitable for positive pressure ventilation via laryngeal mask airway

2.4.1.2 Exclusion criteria

Figure 2.3 Criteria that it volunteers have means exclusion from the study

History of ischaemic cardiac disease
Participating in any other study within 6 weeks
Patients who have had a serious complication during previous general anaesthesia, or where the clinically responsible anaesthetist and surgeon (at any stage) deem the patient unsuitable for any prolongation of anaesthesia or for the study
Any anticipated airway/mechanical ventilation problem
Any patient with serious peripheral vascular disease
Any patient at the highest risk of DVT, in whom calf/foot compression is required before the patient enters the operating theatre
History of calf pain / DVT
Skin lesion / infection at the site
History of allergy to propofol
Prolonged starvation / Nil by mouth (<12 hours without IV fluids) Or likelihood of moderate to severe dehydration
Neuromuscular relaxant required during anaesthetic induction

2.4.2 Equipment

Anaesthetic machine: Draeger Fabius Tiro

TCI pump: Asena PK Syringe pump

Geko ™ devices

2.5 Study Procedure

2.5.1 Screening Evaluation

After explaining the study protocol and obtaining informed consent a baseline questionnaire and physical examination was performed for each subject. The baseline questionnaire was designed to assess the general health of the subject, the presence of pre-existing hypertension or DVT. The physical examination included a cardiovascular examination, heart rate and blood pressure, weight and height, and a physical check of the legs.

2.5.2 Overall trial design

This was a pilot study as there is not enough published data on the GEKO ™ device at anaesthetic induction to know how many cases are required to power the study. We utilised a cross-over design to allow the subjects to be their own control.

We planned to study 20 patients, in two randomised groups:
The groups differed in terms of the sequence of timing for the device being on and off.

Group A: 10 patients with Geko ™ placed but not initially turned on,
5 minutes after LMA insertion, switched Geko ™ "on" for 5 minutes then "off" for 5 minutes

Group B: 10 patients with Geko ™ switched "on" before induction
5 minutes after LMA insertion, switched Geko ™ "off" for 5 minutes, then "on" for 5 minutes

The anaesthetist was solely responsible for the safe routine conduction of the anaesthetic with the operating department practitioner as his routine assistance. The anaesthetist was allocated by the Rota coordinator at the hospital and was not part of the research team. Investigator A knew the randomisation code, placed the device and switched the device on and off as appropriate. Investigator B was blinded to the group allocation and was solely responsible for obtaining the data. The anaesthetist and ODP and surgical team were also blinded.

Standard Anaesthetic Association of Great Britain and Ireland cardiovascular system measurements were recorded every two minutes.

The study was conducted in compliance with the protocol, ethics and GCP requirements.

2.5.2.1 Recruitment

20 cases were identified from surgical lists prior to surgery, using the inclusion criteria, at The Royal London Hospital and St Bartholomew's Hospital over a 6-month period of April 2013 to September 2013. After exclusion criteria were applied 13 patients remained (2 due to the presence of ischaemic heart disease, 3 due to needing a muscle relaxant for the anaesthetic and 2 declined to participate). It was necessary to obtain assessment from the Anaesthetist and Surgeon scheduled to perform the list, before the cases were identified.

2.5.2.2 Study setting

The study was conducted at St Bartholomew's Hospital, in London. The data was collected in the anaesthetic rooms for the theatres in the main theatre suite.

2.5.2.3 Interventions

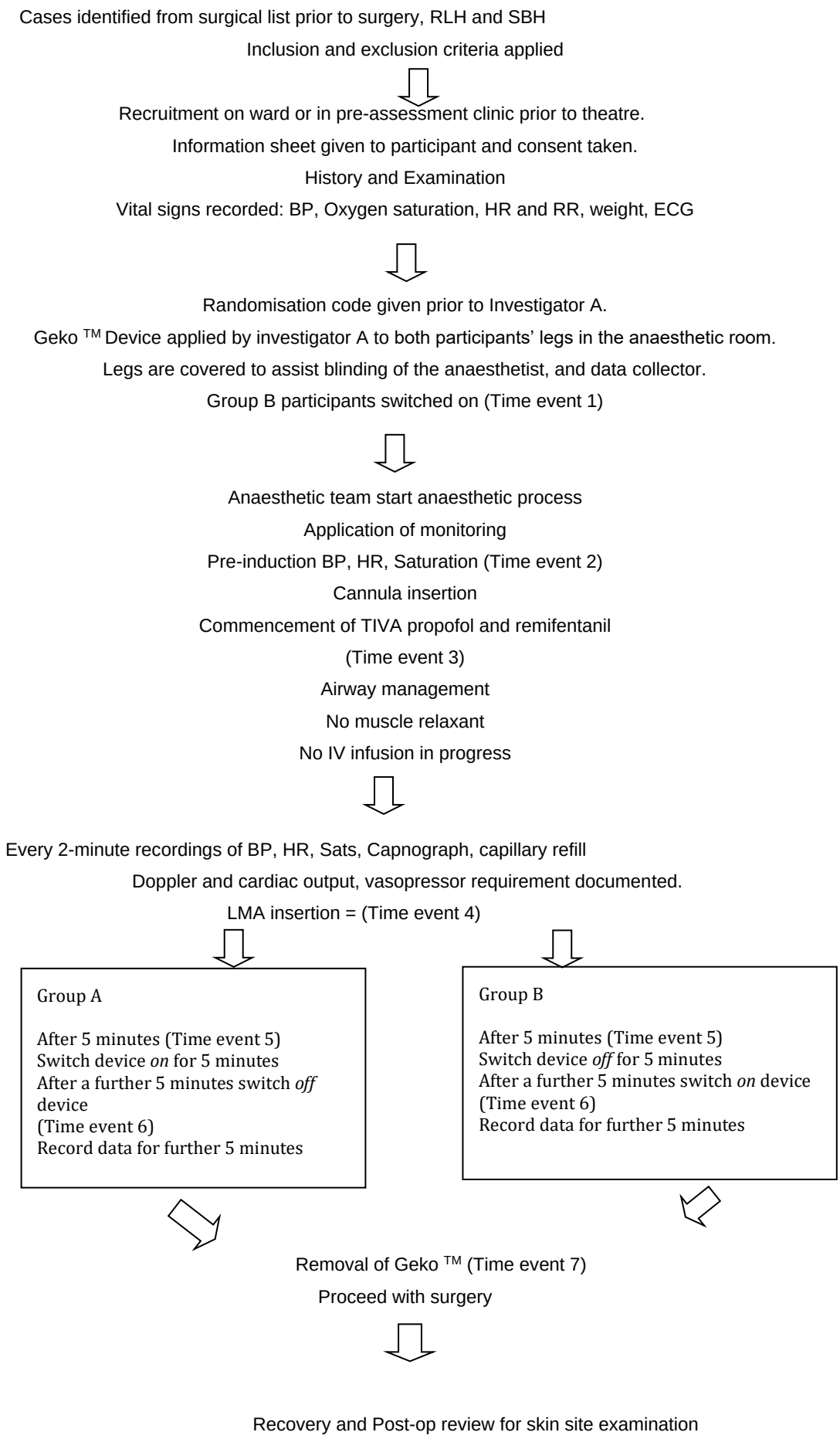
The invention in both groups was the application and activation of the Geko ™ device on both legs, this is described in more detail in the following Geko ™ application section. The Geko ™ was turned on to the setting which gave the maximal muscular response. The intervention was turned off and on in both groups, but the timings and sequence of this were different in both groups.

2.5.2.4 Outcomes

The dependent outcomes elicited in this study were blood pressure, heart rate, oxygen saturations and the calculated plasma settings of the drug Propofol as determined by the Target Controlled Infusion pumps used to deliver the anaesthetic drug. The independent variable was whether the Geko ™ was switched on or not.

2.5.3 Schema

Figure 2.4: Showing the plan of actions for the study procedures



2.5.4 Treatment procedures

2.5.4.1 Geko ™ application

The Geko ™ device is easy to fit, and can be fitted in sixty seconds. It is a one-size-fits-all device that weighs 16 grams. We removed the Ted stockings on both legs. We applied the device to both legs. We positioned the patient (lying laterally or standing) so that we could access the knee area. With a straight knee, we first identified the outer lateral tendon and the centre crease of the knee. Next, we used the grey gentle abrasive pad to gently rub the skin (without breaking the skin surface) over the area the Geko ™ was to be applied. Next, we wiped the skin with the alcohol device and left to dry for 30 seconds. This allowed good electrical contact and adhesion.

We then removed the backing film off the device and placed it at the back of the knee just above the skin crease, and the control button placed laterally, so that the arrow indicators on the device were aligned with the lateral tendon.

One firm quick click of the button turns on the device; a green LED flashes every 1.5 seconds, to signal it is operating correctly at the lowest level. The calf muscle twitches slightly if the level is adequate. There are 7 intensity levels which can be achieved by further one clicks of the button. Investigator A increased the intensity until the calf muscle is seen to twitch maximally.

To reduce the level the button is held down for two seconds. To turn the device off the button is held down for three seconds.

The device was then easily removed after the study by carefully and gently lifting off the control head.

We replaced any removed TED stockings.

2.5.4.2 Anaesthetic induction

The induction was, as most UK anaesthetists would regard as standard procedure. We ensured WHO checklist was completed first. The patient was supine on the anaesthetic trolley. A cannula was placed on the non-dominant dorsum of the hand. A ‘mini’ biers block was performed with venous occlusion

of the forearm with a hand whilst two mls of lignocaine 2% was injected into the cannula. This common procedure is a safe way of numbing the vein so that the induction dose of propofol is not painful. Pain may affect the results by altering the sympathetic nervous system.

Standard AAGBI monitoring was applied

The induction dose of propofol 8mcg/ ml was commenced via the TCI pump, after a 1-2mg/kg dose of fentanyl.

As standard for an anaesthetic, the anaesthetist gave oxygen and the airway was controlled by bag valve mask once the patient was anaesthetised. Once the induction was achieved the effect site target range for propofol was reduced to 4-6 mcg/ml.

The anaesthetist with bag, value, and mask managed the airway until a laryngeal mask airway was placed.

Routine monitoring was continued. Investigator B collected data. After completing the data collection, the device was removed by Investigator A. The patient proceeded to surgery as planned.

2.5.4.3 Randomisation

Randomisation was processed on a computer package random generator; the volunteers were assigned to one of two groups. The randomisation code read A1, A2, A3 B1, and B2 etc. up to A20 and B20. The website used was https://www.random.org/lists/. I generated the sequence and kept the code to assign the enrolled participants.
After creating the randomisation list, the patients were recruited to each group based on the order they were recruited. For example, if the first patient was assigned B5, they were placed in Group B.

2.5.4.4 Blinding

Investigator B was planned to be blinded from the allocation of the group status. However, it began apparent during the data collection stage that it was very obvious whether the Geko ™ was on or not. The movements of the legs were very visible and we were unable to adequately blind Investigator B from this.

2.6 Statistical Analysis

The baseline characteristic of the populations was assessed. The two- way ANOVA with repeated measures was used to analysis the relationship between the MAP, the systolic pressure, and diastolic pressures and whether the Geko ™ device was on or off in the time sequence of an induction. The two-way ANOVA with repeated measures is a type of mixed ANOVA. The software package used was SSPS, and Graphpad for the linear regression.

A mixed ANOVA compares the mean differences between groups that have been separated on two "factors", where one factor is a "within-subjects" factor and the other factor is a "between-subjects" factor. These factors are also known as independent variables. The dependent variable is the MAP, systolic and diastolic pressures. The "within-subjects" independent variable is time. The "between subjects" independent variable is Geko "on' or "off"

2.7 Results

Figure 2.5 Participant Flow for the Gain trial

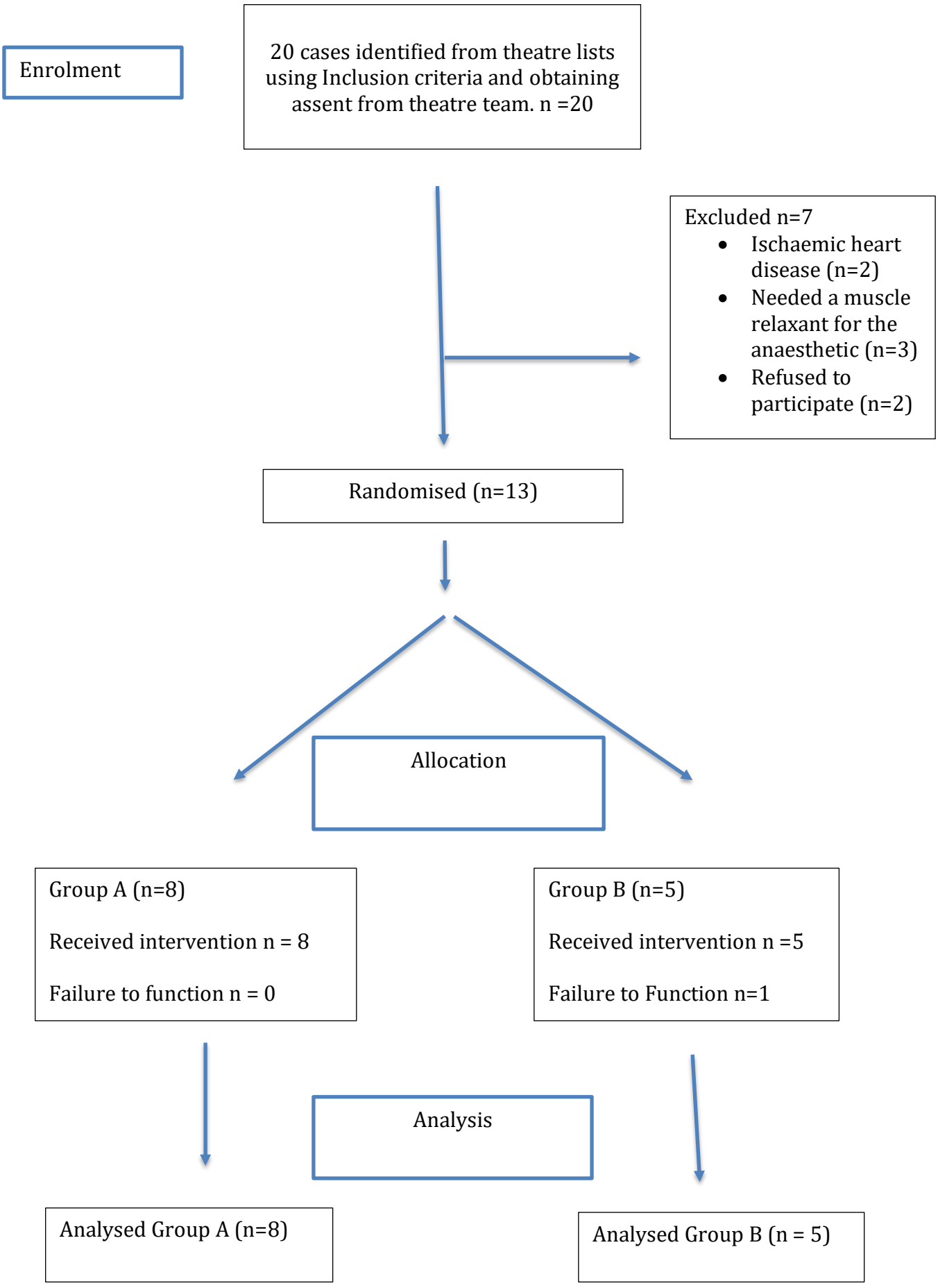


Figure 2.6: The baseline characteristics of the 13 subjects are in the following table

Variable	Mean (s.d)	Percentage % and Count (n=x)	Group A (n=8)	Group B (n=5)
Age (years)	46 (8.34)		45.8	46.3
Race		White 69.2% (9)	5	4
		Oriental 7.7% (1)	1	
		Asian 15.4% (2)	1	1
		African 7.7% (1)	1	
Sex		Female 100%	8	5
Smoker		Non-smoker 84.6% (11)		
		Smoker 15.4% (2)	1	1
Alcohol		Drink Alcohol 53.8% (7)	5	2
		Teetotal 46.2% (6)	3	3
Exercise		No exercise 7.7% (1)		1
		Once a week 46.2% (6)	4	2
		Twice a week 23.1% (3)	3	
		More than 3 times a week 23.1% (3)	1	2
Anxiety		No anxiety 15.4% (2)	1	1
		Mild anxiety 46.2% (6)	3	3
		Moderate anxiety 38.5% (5)	4	1
Pre-Med		Pre –med 7.7% (1)	1	
		No pre-med 92.3% (12)	7	5
Hypertension		No hypertension 100% (13)	8	5
Height (cms)	162 (6.8)		163 (5.9)	160 (4.8)
Weight (kg)	70.6 (21.5)		69.2 (13.2)	72.9 (21.6)
Baseline Systolic (mmHg)	114 (14.8)		114 (13.4)	114 (12.4)
Baseline Diastolic (mmHg)	67 (8.7)		66.9 (7.1)	67.2 (8.2)
Baseline MAP (mmHg)	82.7 (9.4)		82.5 (8.3)	83 (8.5)
Baseline HR (bt/min)	70 (14.5)			

Figure 2.7: Linear regression of the mean BP for Group A and B. p = 0.049

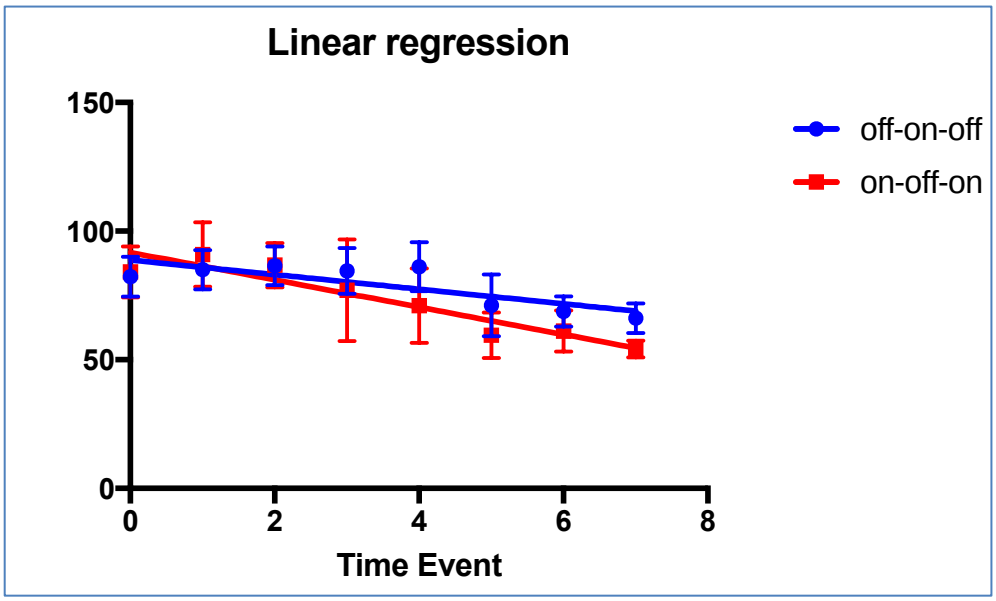


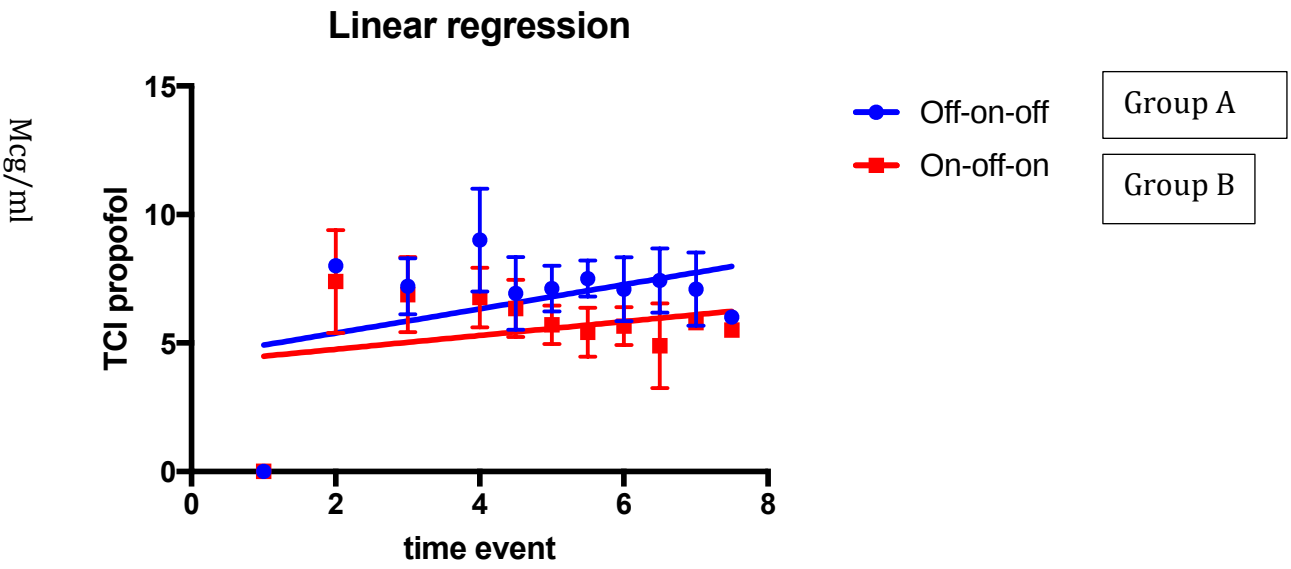
Figure 2.8 Table showing the explanation of each Time event in the Gain trial

Time Event	
1	Group B Geko ™ turned on
2	Pre-induction BP
3	Commencement of TIVA anaesthetic
4	LMA insertion
5	5 minutes after LMA insertion Group A Geko ™ turned on and Group B Geko ™ turned off
6	5 minutes later Group A turned off and Group B turned on
7	5 minutes later Group B turned off Remove device

The slopes are significantly different by a p value of 0.049, suggesting that there is a difference in the two groups, although it is close to the non-significant p value of 0.05. However, when using the mixed linear statistical analysis, the following graph is seen, which suggests the two groups are not statistically different. The results differ from the expected graph shown in figure 2.1, which had a more sigmoidal shape due to the prediction that the LMA insertion may increase the BP. This graph is not showing the same occurrence as the predicted graph which is demonstrating a case versus control scenario. This graph is showing the cross-

over design we have employed in our study.

Figure 2.9: Linear regression of Propofol TCI for both groups over the time periods p= 0.662 and table explaining the Time Event.



Time Event	
1	Group B Geko ™ turned on
2	Pre-induction BP
3	Commencement of TIVA anaesthetic
4	LMA insertion
5	5 minutes after LMA insertion Group A Geko ™ turned on and Group B Geko ™ turned off
6	5 minutes later Group A turned off and Group B turned on
7	5 minutes later Group B turned off Remove device

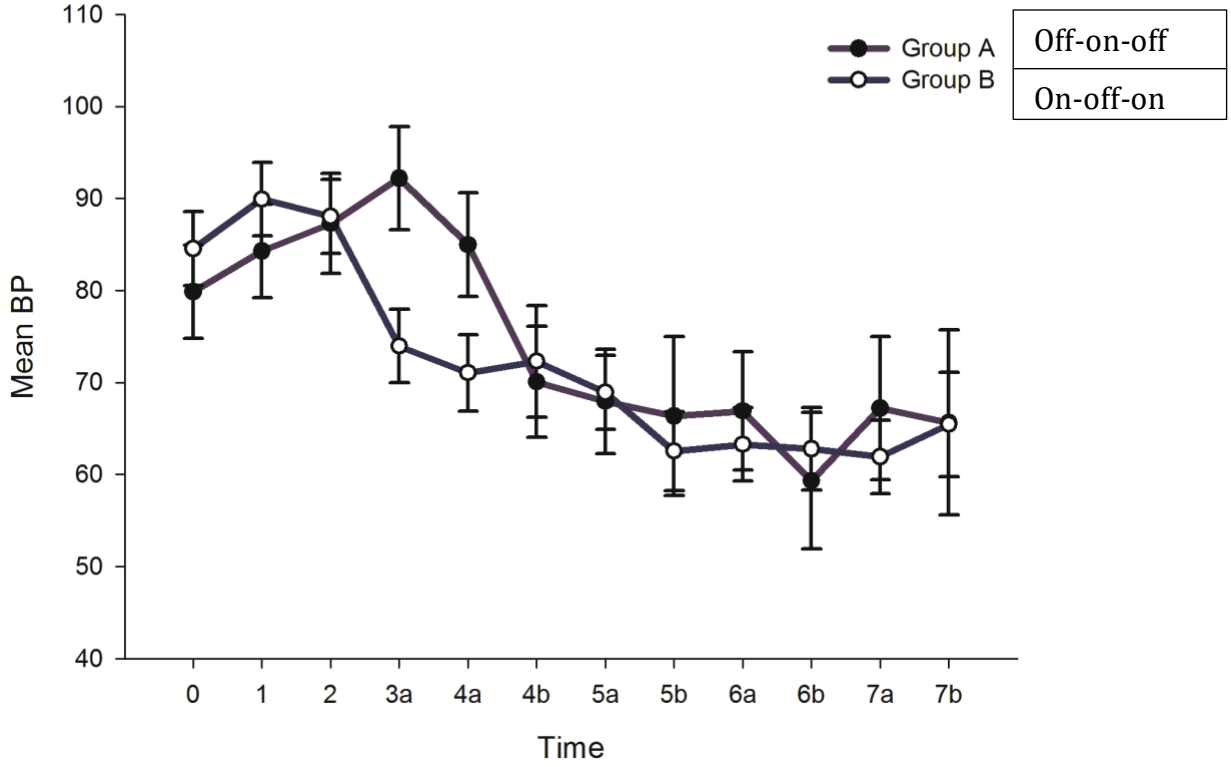
Are the slopes equal?

F = 0.197. DFn = 1, DFd = 18

P=0.662

The difference between the slopes is not significant.

Figure 2.10: Mixed Linear Method: Plot of Mean BP at the different Time Points for Group A and B and table explaining the Time Event



Time Event	
1	Group B Geko ™ turned on
2	Pre-induction BP
3a	Commencement of TIVA anaesthetic
4a	LMA insertion
4b	2 minutes after 4a
5a	5 minutes after LMA insertion Group A Geko ™ turned on and Group B Geko ™ turned off
5b	2 minutes after 5a
6a	5 minutes later Group A turned off and Group B turned on
6b	2 minutes after 6a
7a	5 minutes later Group B turned off Remove device
7b	2 minutes after 7a

In this case, linear mixed model was used to analyze outcomes of interest and first-order autoregressive covariance structure was used for repeated measures. A linear mixed model was used here because there were missing values in the MAP measurements during the study period. This is because different time windows occurred for different subjects as they flowed through the schema. For example, some patients had more time, and hence more blood pressure readings between induction of anaesthesia and insertion of LMA airway device. For a data table, it appears there are missing data, but actually it was not missing it just did not occur in time. For mixed ANOVA, it is difficult to deal with missing values since subjects with a missing value at any point should be excluded from further analysis and this would result in considerable loss of sample size and study power. In contrast, missing values are not a critical issue in the linear mixed model analysis because these models estimate between- and within-subject effects based on the covariance structures of repeated measures (MAP at distinct time points in your case). Accordingly, we had to determine the covariance structure before estimating the effects of interest. Among the miscellaneous covariance patterns, the first-order autoregressive covariance structure is commonly selected for repeated measures like this study. This covariance structure has homogeneous variances, while the correlation between any two elements gets smaller the further apart, they are separated. This model is best when all time events are equally spaced, which was not the case in our study.

Figure 2.11: The Evaluation of Fixed Effects from the Mixed Linear Model

Source	Numerator df	Denominator df	F	Sig.
Intercept	1	20.954	1287.170	.000
Group AB	1	20.954	.311	.583
Time	11	71.697	3.142	.002
Group AB * Time	11	71.697	1.640	.106

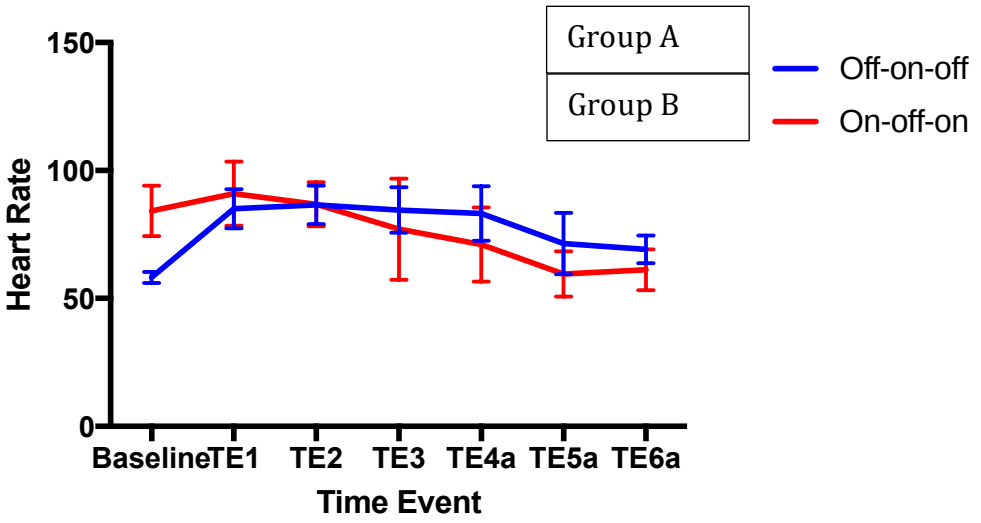
a. Dependent Variable: baseline mean abp.

Based on the analytical results, the patient group did not affect the mean BP ($p = 0.58$) in the study. Note that mean BP did significantly change over time ($p = 0.002$) but the pattern of change in mean BP over time was not significantly different between the two Geko ™ group ($p = 0.11$). Figure 2.7 illustrates the variation in mean BP of the two groups at distinct time points. Although Figure 2.7

appears to show a different time vs Mean BP pattern for Group A and B, the mixed ANOVA results are not significant.

Looking at HR changes with the Geko ™ groups

Figure 2.12: Two-way ANOVA with repeated measures for Heart Rate at the different time points



The variation between the two groups is non-significant p= 0.8

2.8 Discussion

This study did not establish a significant change in mean blood pressure by the Geko ™ device in female patients' post-anaesthetic induction. This could be due to limitations with the study methodology or because the effect of the Geko ™ on BP is negligible.

There were many limitations to this study, which make definitive conclusions impossible.

Study Design limitations

This study used a cross over design to establish whether there was a difference in blood pressure with the GEKO ™. A control group arm would have been helpful to establish a baseline change in blood pressure.

The study did not have preceding research to help guide a power calculation. The study had originally aimed to collect data on 20 volunteers, this was not achieved due to time constraints and low

numbers of patients suitable for a TIVA anaesthetic, and so data on 13 volunteers may not be enough patients to establish a significant difference. It was difficult to obtain assent from the scheduled anaesthetists and surgeons. The study would add additional time in the anaesthetic room for the patients. This would have a knock-on effect of timings for the management of the operating lists, which were already busy

All volunteers used in the study are women. The reason for this was largely because the gynaecology surgical list was appropriate for TIVA anaesthetic, and the other patients recruited from a plastic surgery list happened to be female also. This is a limitation because it is possible that the Geko ™ has a larger effect on the vasculature in males with larger calf muscles. Larger calf muscles may contract the venous vessels in the leg with more force and thus may have a larger effect on the effective ejection of blood over time.

Another limitation is the fact that the muscle contraction stimulated by the Geko ™ was not uniform across the volunteers. The methodology did try to standardize this to some effect by recording data at the maximal stimulation setting. However, this still caused a wide variation in muscle response, which was just observed and not quantified. It was not appreciated prior to the study that the muscular response would be so varied. There are many reasons for this. The muscle bulk of the patients were different and so different responses could be expected. The placement of the Geko ™ although standardized, cannot guarantee exactly identical proximity to the common peroneal nerve due to normal variations in anatomy. The electrical impedance of the subcutaneous tissue was different for each patient, due to subcutaneous fat and oedema and so the amount of current reaching the common peroneal nerve would also have varied.

Knowing the extent of calf pump action would have enabled us to analyse whether Geko ™ has a dose-response curve with regards to blood pressure. Which would strengthen the conclusion regarding association.

These are patients that are lying down, and so the ankle hydrostatic pressures would be lower, which may impair the Geko ™ ability to empty the venous veins. It would have been hard to incorporate this into our study on anaesthetized patients.

The patients would also have been mechanically or manually ventilated in the induction phase of the anesthetic and so this may have had marked effect on the ability of the Geko ™ to augment venous return.

Propofol vasodilates the arteriolar and venous blood vessels and so the effect of Geko ™ on blood pressure may be masked by the stronger effect of the drugs on the circulation. Furthermore, an anaesthetic induction is a very unstable time haemodynamically and so picking up a small signal of blood pressure change caused by the Geko ™ may be difficult despite the crossover design.

Looking at the shape of the mixed linear model graph, it is possible that one explanation of this is that Group B, starting with the Geko ™ on, needed more milligrams of propofol to anaesthetize the patient, due to the stimulation of the device, hence the more profound drop in BP after induction. Although the target concentrations set on the propofol syringe driver were recorded for the experiment, any extra bolus doses at the beginning of induction were not recorded and were given at the discretion of the anaesthetist.

Interpretation

Although the results show no significant change in BP this does not tell us whether there were any changes in the circulation, for instance venous flow. More investigations are required to look at other components of the cardiovascular system. This finding matches the findings of other studies looking at the effects of the Geko ™ on blood pressure in different populations not receiving an anesthetic.

Harms

No adverse effects of the Geko ™ were found during the study.

Failure to function rate is 8%

Chapter 3: Experimental studies in the haemodynamic effect of the Geko ™ in healthy volunteers.

3.1 Introduction

It was unclear whether the haemodynamically unstable time of an anaesthetic induction was masking the effect of the Geko ™. As mentioned previously, the hypotension caused anaesthetic induction, the positive pressure ventilation, the relative dehydration of a fasted elective patient may be diminishing the haemodynamic effect of the Geko ™. It was therefore decided to amend the study and test in healthy volunteers without an anaesthetic.

3.2 Objectives

- To observe if the Geko ™ device changes the mean arterial blood pressure
- To observe if there are any heart rates changes
- To observe if the non-invasive cardiac output is measured to change during the Geko ™ stimulation
- To observe if the stroke volume is measured to change
- To observe if the arterial system demonstrates any changes in its pulse wave velocity and augmentation index
- To examine a control group to demonstrate
- To investigate if the time interval of Geko ™ stimulation has a varied effect on the haemodynamics

3.3 Study Approval

The study was sponsored by Bart's Health NHS Trust and funded by a National Institute for Health Research (NIHR) i4i grant. National Research Ethics Service (NRES), Dulwich NRES Committee, reference 13/LO/0295 approved the study amendment on the 7th April 2014.

3.4 Trial design

The study was designed to test whether the Geko ™ increases the Blood pressure, heart rate and cardiac output in a group of healthy volunteers. The study was again not powered due to lack of

previous data. The study took baseline haemodynamic data and then kept recording during Geko ™ stimulation and then for a time period afterwards.

3.4.1 Changes to the trial design

It became apparent after starting the study in healthy volunteers that we should also investigate a control arm and investigate varying the Geko ™ stimulation time period. Ideally this would have been part of the initial trial design, because we could have randomised the treatment arms.

3.5 Methods and Materials

3.5.1 Volunteers

36 adult volunteers were identified from staff at The Royal London, Whitechapel London and St Bartholomew's Hospital. The subjects were recruited by posters and from word of mouth. Written informed consent was obtained prior to the study for all volunteers.

3.5.1.1 Inclusion criteria

Figure 3.1 Table showing the inclusion criteria for Geko ™ in healthy volunteer study

Be in good general health and fitness.
Aged between 18 and 85 years.
Free of significant abnormal findings as determined by medical history (specifically an absence of DVT or haematological disorders or indications), screening physical examination, vital signs (sitting blood pressure, sitting pulse rate, sitting respiratory rate and body temperature) and duplex ultrasound within 48 hours prior to commencement of each study phase.
BMI between 18 and 34
No history or signs of drug abuse (including alcohol abuse greater than recommended weekly consumption)
Agrees to not to use any medications during the course of the study without informing the Research Team.
Able to understand the Volunteer Information Sheet and signed the written Informed Consent Forms.
Able and willing to follow the Protocol requirements.

3.5.1.2 Exclusion Criteria

Figure 3.2 Table showing the exclusion criteria for the recruitment process of the Geko ™ in Healthy Volunteer study

Volunteers will not be admitted to the study if they meet any of the following exclusion criteria:
Any evidence of organ dysfunction, or any clinically significant deviation from normal in the physical determinations.
History or signs of haematological disorders (especially in relation to clotting or coagulation or previous deep or superficial vein thrombosis/pulmonary embolism).
Peripheral arterial disease (ABPI < 0.9), varicose veins or lower limb ulceration.
Musculoskeletal disorders (such as pain during exercise of lower limb).
Recent trauma to lower limb.
Pregnancy.
Any Medication judged to be significant by the Principal Investigator (such as anticoagulants, agents with significant vasoactive activity, Oestrogen pill, 'morning-after pill' or HRT).
Participation in any clinical study during the 8 weeks preceding the dosing period of the study
Donation of blood during the eight (8) weeks preceding the screening period of the study or during the investigation.
Any significant illness during the four (4) weeks preceding the screening period of the study.
History of disorders of the gastrointestinal, hepatic, renal, cardiovascular, endocrine, neurological, dermatological, rheumatologic, metabolic (including diabetes), psychiatric, haematological (especially in relation to clotting or coagulation), or systemic disease judged to be significant.
No use of any medications (prescribed or over-the-counter including herbal remedies) judged to be significant by the Principal Investigator during the thirty (30) days preceding the study

3.5.2 Study setting

The study was conducted at St Bartholomew's Hospital, in London. The data was collected in the research suite for Pain and Anaesthesia Research Centre. The 3 study subgroups were recruited and analysed from April 2014 till June 2014

3.5.3 Study Equipment

Vicorder, Vascular model by SMT Medical
This device uses a blood pressure cuff placed both on an arm and leg to measure the pulse wave and derive the cardiac output. Other indices measured are heart rate (HR), stroke volume (SV), mean arterial pressure (MAP), augmentation index (AI), total peripheral resistance (TPR) and the pulse transit time (TT).
Geko ™ devices
Ambient sound and light monitor
Thermometer

3.6 Study Procedure

3.6.1 Volunteer Screening

The volunteers were screened in an identical fashion to our first study. After explaining the study protocol and obtaining informed consent a baseline questionnaire and physical examination was performed for each subject. The baseline questionnaire was designed to assess the general health of the subject, the presence of pre-existing hypertension or DVT. The physical examination included a cardiovascular examination, heart rate and blood pressure, weight and height, and a physical check of the legs.

3.6.2 Study design

There were three groups in this study. The groups were run one after the other. A power calculation was not performed due to insufficient data of haemodynamic variables in Geko ™ usage. We did not know the means or standard deviations in each haemodynamic parameter within each population

group. Each group had an acclimatation period of at least 5 minutes, with the participant lying down without any stimulation, monitoring or conversation.

The first group was the “short time period group”. The group had the Geko ™ applied and the Vicorder monitoring applied. They were also asked to lie down on the examination couch and comfort was ascertained and improved if possible.
The data-recording period was started and a set of measurements was recorded (HR, MAP, CO, AI, SV, TPR, TT). The Geko ™ was turned on and then after 5 minutes the haemodynamics were recorded again, this was repeated after a further 5 minutes (the Geko ™ was on for 10 minutes). The Geko TM was turned off and a set of measurements was recorded after ten minutes and then after an additional five minutes (the Geko ™ was then off for 15 minutes in total). The data recording was then stopped. The number examined was n=21.

The second group was a control group. This group had the Geko ™ applied but not turned on. The volunteers had the Vicorder monitoring applied and then were asked to lie down on an examination couch. The volunteers were asked if they were comfortable, the response was recorded, and the reason why not comfortable was ascertained and rectified if possible. For example, if the volunteer needed an extra pillow. Once comfortable the data recording time period started.

The measurements of heart rate (HR), mean arterial blood pressure (MAP, cardiac output (CO), augmentation index (AI), stroke volume (SV), total peripheral resistance (TPR) and pulse transit time (TT) were recorded at the start of the data recording period and then at five minutes, and then ten minutes then twenty and twenty-five minutes. The data recording was then stopped. The control group had n=5.

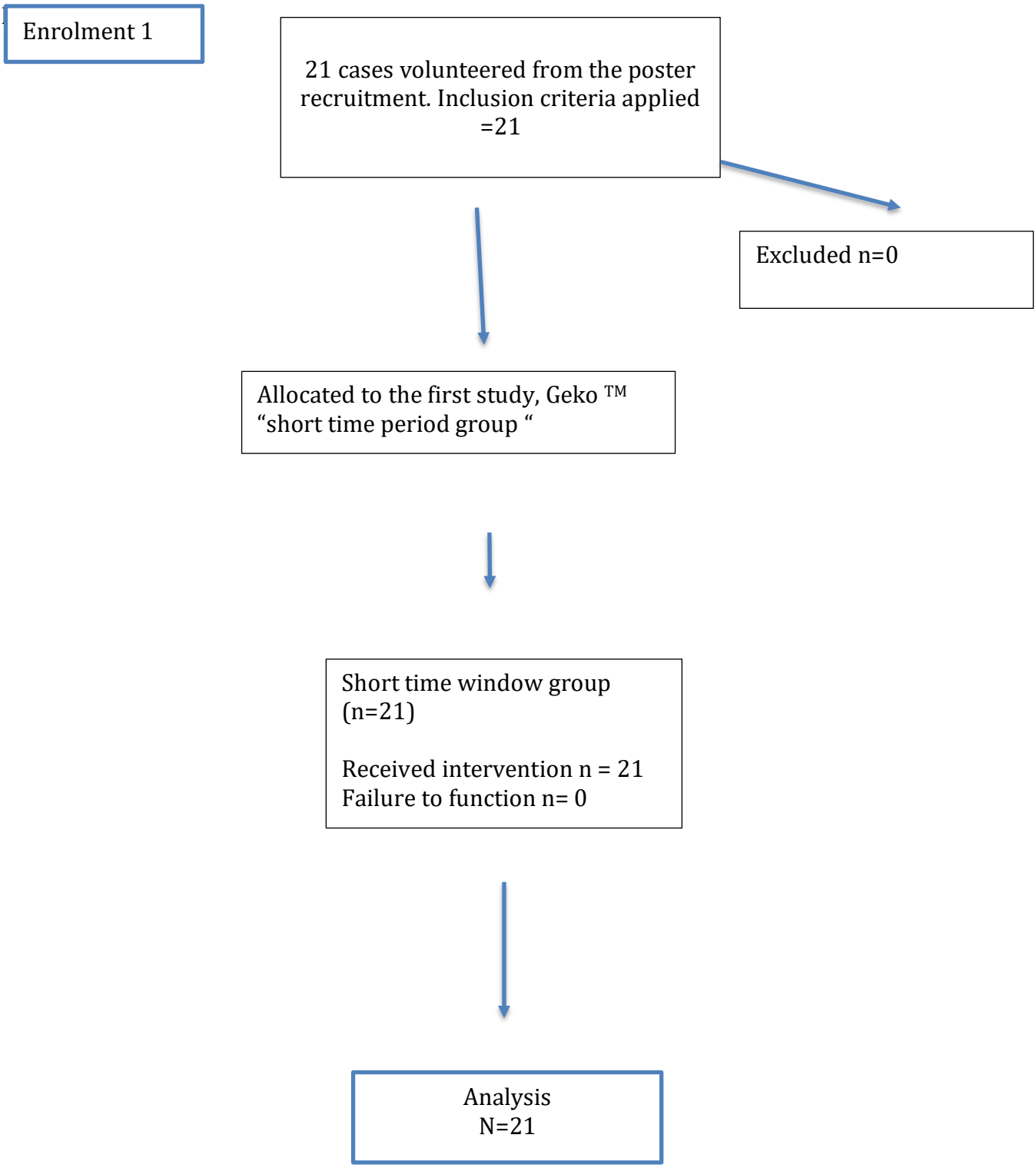
The third group was the “long time period group”. This group also had the Geko ™ applied and the Vicorder monitoring applied. They were also asked to lie down on the examination couch and comfort was ascertained and improved if possible.
The data recording period was started and a set of measurements was recorded (HR, MAP, CO, AI, SV, TPR, TT). The Geko ™ was turned on and a set of measurements at ten, twenty, thirty and forty-five minutes, and then the Geko ™ was turned off and the data recording stopped. The number examined was n=10.

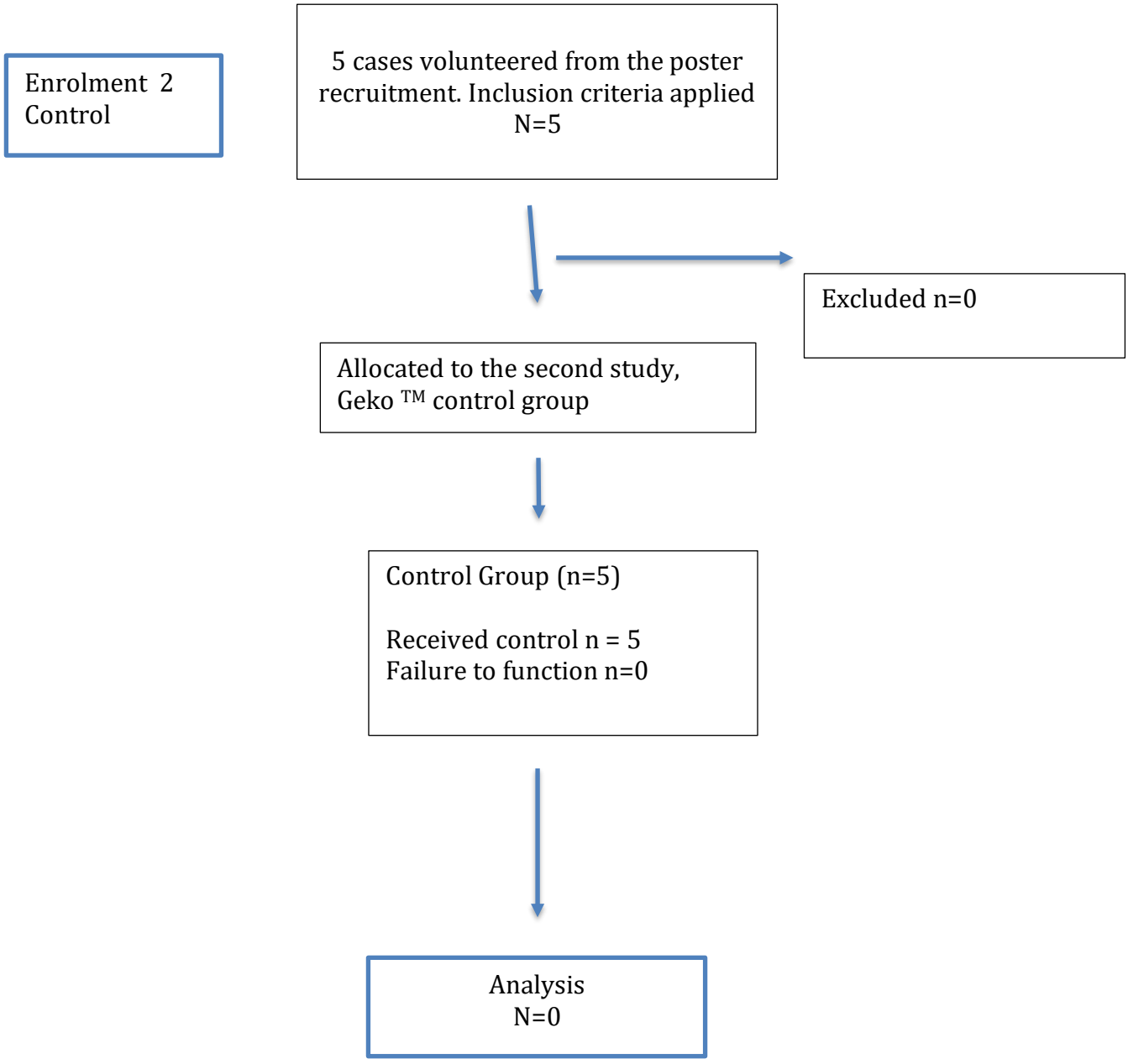
3.6.3 Outcomes

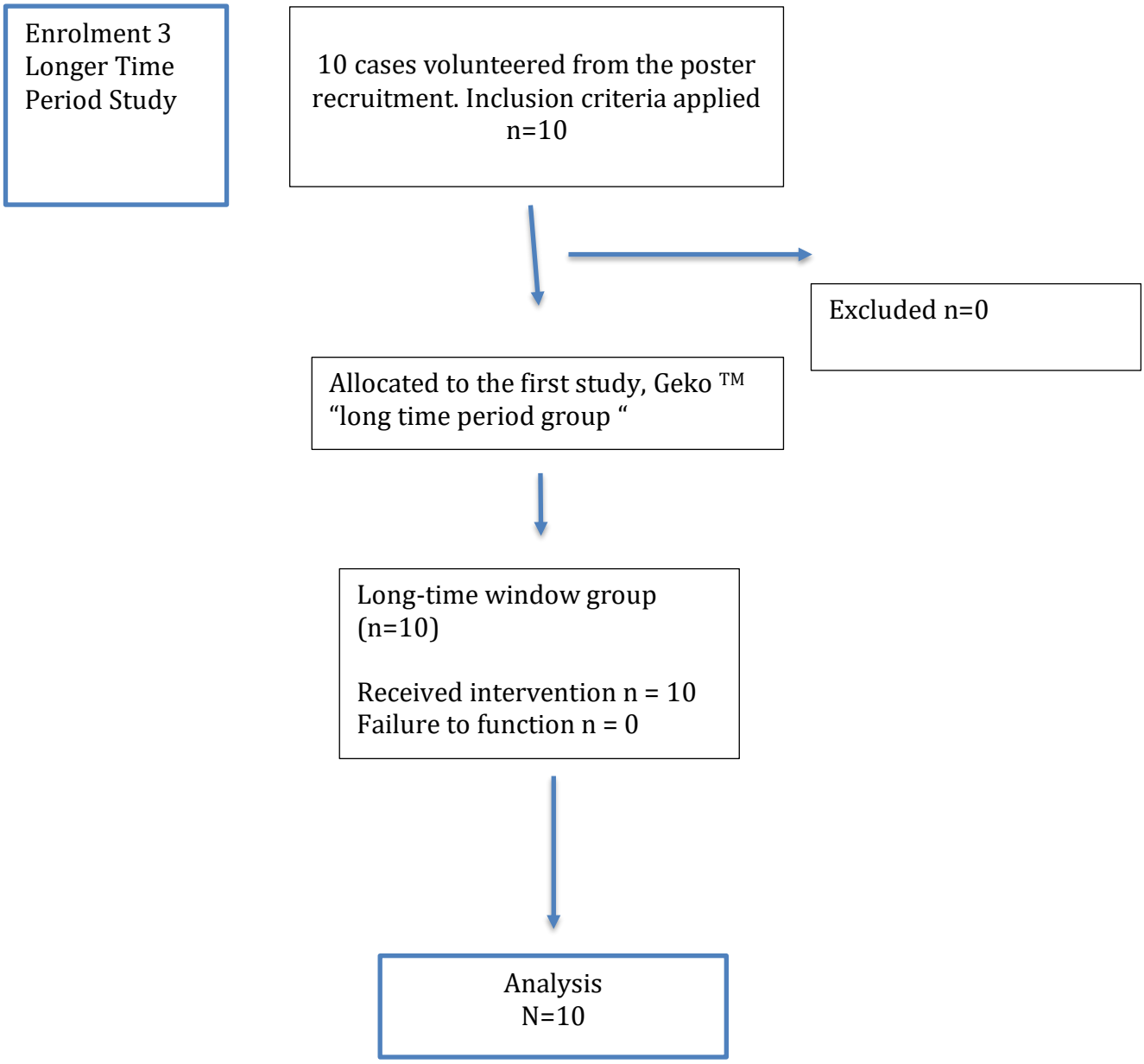
The dependent outcomes measured in the study are the heart rate, mean arterial pressure, non-invasive cardiac output, augmentation index, stroke volume, total peripheral resistance and transit time. The independent variable was the Geko ™ stimulation.

3.6.4 Participant Flow

Figure 3.3 Participant Flow for the Geko™ Study in healthy volunteers




Enrolment 2
Control
5 cases volunteered from the poster recruitment. Inclusion criteria applied
N=5
Excluded n=0
Allocated to the second study, Geko ™ control group
Control Group (n=5)
Received control n = 5
Failure to function n=0
Analysis
N=0


Enrolment 3
Longer Time
Period Study
10 cases volunteered from the poster recruitment. Inclusion criteria applied n=10
Excluded n=0
Allocated to the first study, Geko ™ "long time period group "
Long-time window group (n=10)
Received intervention n = 10
Failure to function n = 0
Analysis
N=10

3.7 Statistical analysis

One-way multivariate analysis of variance (MANOVA) was used to evaluate the group effects on the HR, MAP, CO, AI, SV, TPR and TT on SSPS software package. A two-way ANOVA with repeated measures was not used because it did not meet the assumption of sphericity using Mauchly's test of sphericity. Sphericity occurs when the variances of the differences between all paired "within subject" conditions are the same. Manova does not require an assumption of sphericity. Pillais trace test was also used as it is the most powerful and robust statistic for general use, especially when there are departures from assumption of sphericity.

3.8 Results

No trends or significant changes in any measurements were found in the healthy volunteer control group (n=5) whereby the Geko ™ device was placed but not activated. This result is as to be expected.

No harm was detected in any of the volunteers (n=36).

Figure 3.4 : Table showing Manova test of GEKO ™ in healthy volunteers "short time period"

Effect		Value	F	Hypothesis df	Error df	P
CO	**Pillai's Trace**	**.50**	**4.00**	**4.00**	**16.00**	**.02**
HR	Pillai's Trace	.16	.77	4.00	16.00	.56
SV	Pillai's Trace	.27	1.46	4.00	16.00	.26
MAP	Pillai's Trace	.22	1.14	4.00	16.00	.37
AI	Pillai's Trace	.23	1.18	4.00	16.00	.36
TPR	Pillai's Trace	.38	2.40	4.00	16.00	.09
TT	Pillai's Trace	.29	1.66	4.00	16.00	.21

The "short time period group" showed some significant changes, particularly after ten minutes of the Geko ™ being turned on. We found significant increases in Cardiac output (12%, p= 0.02) after a 10-minute stimulation window with the GEKO ™ device. There were very large confidence intervals in the cardiac output changes at 5 minutes, making the results non-significant at 5 minutes (see Figure 3.4). The graph shows that the increase in cardiac output also return to baseline after the device was switched off for 10-15 minutes

Figure 3.5: Mean values of outcomes at different time points for the short time period results

	Mean	**MSE**	**Lower Bound**	**Upper Bound**
relax CO	5.59	.28	4.99	6.18
5 mins CO	6.52	.61	5.25	7.79
10 mins CO	6.27	.32	5.60	6.95
10 mins post CO	5.69	.33	5.00	6.39
15 mins post CO	5.53	.33	4.83	6.22
relax HR	65.40	2.54	60.08	70.72
5mins HR	65.75	2.90	59.69	71.81
10 mins HR	68.55	3.33	61.57	75.53
10 mins post Hr.	65.95	2.89	59.89	72.01
15 mins post HR	60.66	3.99	52.30	69.02
relax SV	86.60	5.16	75.81	97.39
5 mins SV	102.15	10.11	80.99	123.31
10 mins SV	93.75	4.99	83.31	104.19
10 mins post SV	88.45	5.58	76.78	100.12
15 mins post SV	87.50	5.47	76.05	98.95
relax MAP	89.75	2.01	85.55	93.95
5 mins MAP	92.00	2.36	87.05	96.95
10 mins MAP	93.70	2.38	88.72	98.68
10 mins post MAP	89.90	2.09	85.52	94.28

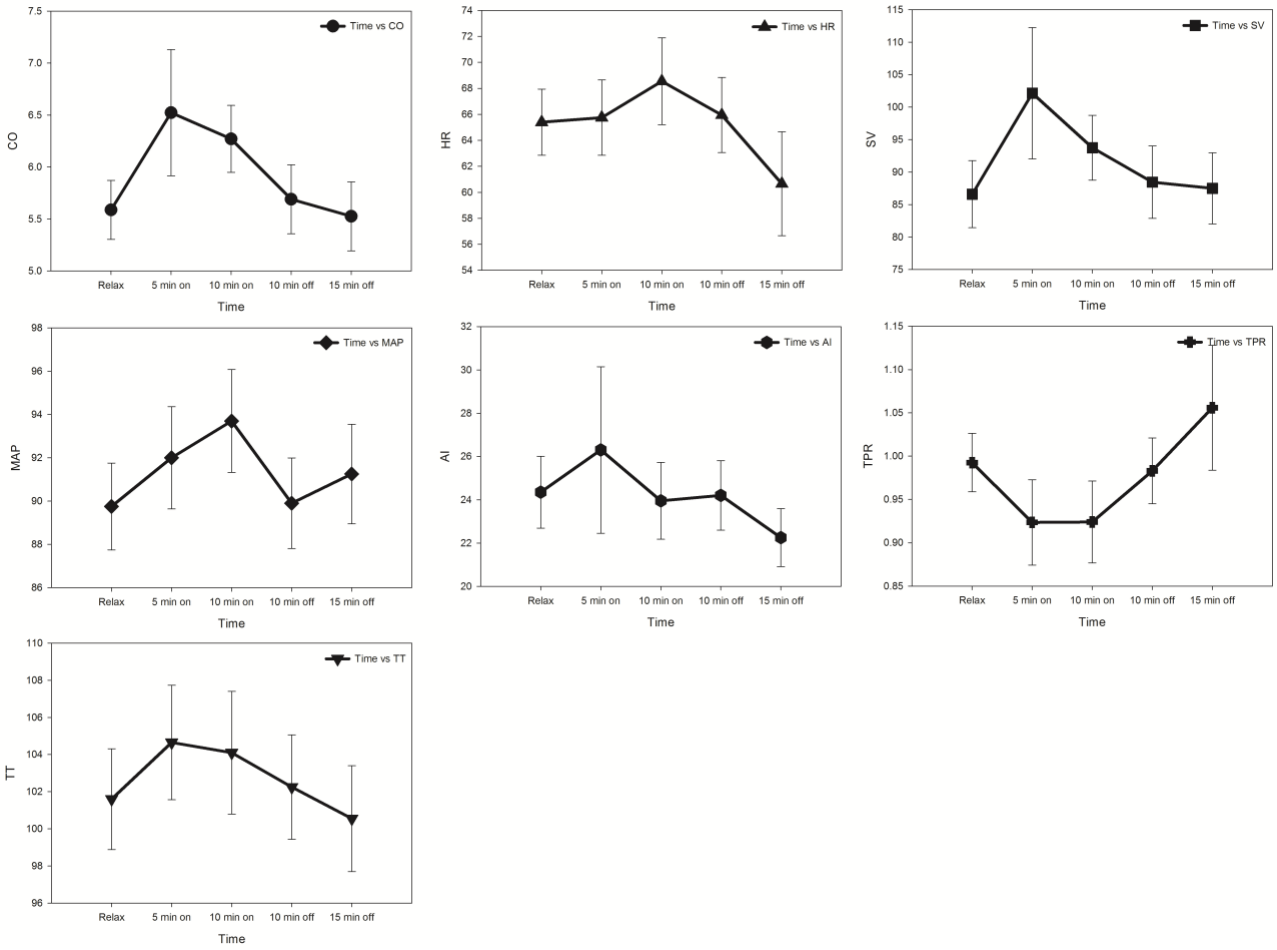
15 mins post MAP	91.25	2.30	86.44	96.06
relax AI	24.35	1.66	20.87	27.83
5 mins AI	26.30	3.85	18.24	34.36
10 mins AI	23.95	1.78	20.24	27.67
10 mins post AI	24.20	1.61	20.84	27.56
15 mins post AI	22.25	1.34	19.44	25.06
relax TPR	.99	.03	.92	1.06
5mins TPR	.92	.05	.82	1.03
10 mins TPR	.92	.05	.83	1.02
10mins post TPR	.98	.04	.90	1.06
15 mins post TPR	1.06	.07	.91	1.21
relax TT	101.60	2.72	95.91	107.29
5mins TT	104.65	3.09	98.19	111.11
10mins TT	104.10	3.30	97.19	111.01
10mins post TT	102.20	2.81	96.36	108.14
15 mins post TT	100.55	2.85	94.58	106.52

Figure 3.6: Post Hoc analysis showing mean CO at different time points. “Short time period”

(I) CO	(J) CO	Mean Difference (I-J)	SE	p	Lower Bound	Upper Bound
rest	5 minutes	-0.94	0.55	0.11	-2.10	0.22
	10 minutes	-0.68	0.28	0.02	-1.26	-0.11
	10 minutes post	-0.10	0.20	0.61	-.515	0.31
	15 minutes post	0.06	0.23	0.79	-.410	.53
5 mins	10 minutes	0.25	0.61	0.68	-1.03	1.53
	10 minutes post	0.83	0.65	0.22	-0.53	2.20
	15 minutes post	0.99	0.61	0.12	-0.28	2.28
10 minutes	10 minutes post	0.58	0.31	0.07	-0.06	1.22
	15 minutes post	0.74	0.22	0.01	0.28	1.21
10 minutes Post	15 minutes post	0.16	0.20	0.42	-0.26	0.58

Since there were only significant differences in CO between some time points, a post hoc analysis was done and the results are presented in table 10. Significant differences in mean CO were only noted between relax and 10 min on, and between 10 min on and 15 min post.

Figure 3.7: Physiological changes during Geko ™ stimulation in healthy volunteers "Short time period"



Finally, we tested the effect of potential confounding factors (BMI, movement scale, pwv) on CO. The results are presented as table 11. Note that only BMI had a significant effect on CO. CO is known to be larger in people with higher BMI's. A high BMI may also have been a negative confounder on the Geko ™ device as more subcutaneous tissue increases the electrical impedance. The pwv was not related to CO. Table 12 shows the BMI effect on cardiac output at distinct time points. Note that the BMI was positively correlated with CO, as expected, except at time point 10 mins on (non-significant).

Figure 3.8: Tests for effects of miscellaneous variables on CO at all the time points

Source	Type III Sum of Squares	df	Mean Square	F	Sig.
Height	3.07	1	3.07	1.98	.17
Weight	3.92	1	3.92	2.61	.12
BMI	12.57	1	12.56	12.30	.01
pwv	.73	1	.73	.93	.35

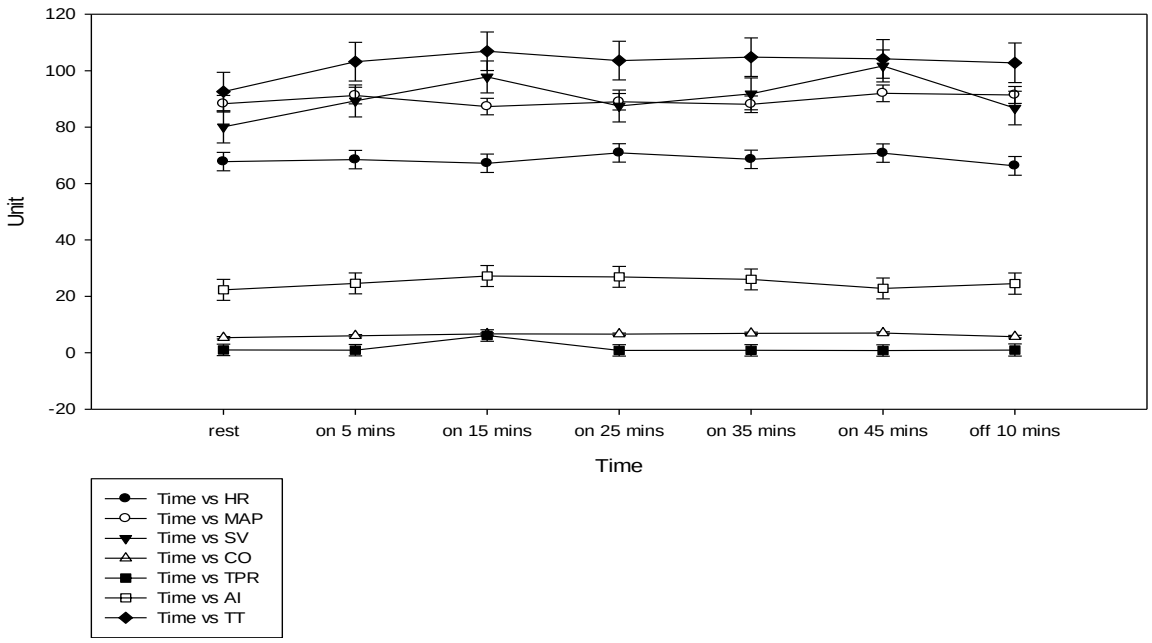
Figure 3.9: Parameter estimates of the BMI effect on CO at different time points

Time	Parameter	B	SE	t	Sig.
relax CO	BMI	.18	.05	3.75	.01
5 mins CO	BMI	.27	.12	2.23	.04
10mins CO	BMI	.09	.07	1.32	.21
10mins post CO	BMI	.182	.061	2.977	.008
15mins post CO	BMI	.146	.066	2.215	.040

The next study looking at the "long time period group "found that after the initial increase the BP and CO at 10 minutes (not significant) that there was no significant difference in outcomes of interest at the different time points.

Figure 3.10:

Showing the haemodynamic variables at different time points during the "long time period group with the Geko ™. There was no significant differences or findings from this subsection of the study.



3.9 Discussion

3.9.1 Limitations

A post hoc power calculation of difference in CO from rest (5.59 MSE .28) vs at 10 minutes (6.27 MSE .32) with the Geko ™ in 21 subjects, with an alpha type 1 error of 0.05 is 100% power. However there is a lot of controversy about the utility of post-hoc power calculations as the concept of probability and randomness are lost after a study had been performed[120].

The studies were run in sequence, which increases the risk of measurement bias. The studies would have had more statistical significance if we had planned to randomize the allocation into the different subsections.

The non-invasive cardiac output is an imprecise measurement device. The Vicorder, as does most non-invasive cardiac output devices, has a high error margin on it of plus or minus 20%. This again erodes the validity of our results. The technology of cardiac output monitoring is unfortunately not currently sophisticated enough to be applicable in research settings on healthy volunteers.

The Geko ™ device had variable responses in the volunteers. Some had large muscular contractions, some had very weak or no responses. This variability in response was not measured unfortunately. I did have plans to record video footage of the contractions and using a computer software package to quantify and compare the contractions. Unfortunately, we did not gain the ethical approval for this to be part of the amendment to the study. As time was a large limiting factor in my thesis, I was unable to incorporate this. The quantification of contraction would have been hugely useful to demonstrate a dose-effect response. Statistically this would have been a powerful tool.

The healthy volunteer group could not be blinded to the Geko ™ stimulation as they would feel the sensation and know whether the device was on or off. It could be that the volunteers are just demonstrating a neural sympathetic response to the sensation of electrical stimulation, which has nothing to do with mechanics of the calf pump.

3.9.2 Interpretation

The main finding of significantly raised cardiac output at 10 minutes of Geko ™ stimulation does fit with the graphs also showing the heart rate and stroke volume also increase with Geko ™ stimulation and then decrease to baseline once the Geko ™ is switched off. The graph showing the total peripheral resistance seems to suggest that this decreases with the Geko ™ stimulation. This would fit the findings of previous work which suggest an increase in microcirculation in the leg using Laser Doppler flowmetry[48].
The device may be increasing the venous return from the legs to the heart and thus increasing cardiac output. However, it is not a consistent effect, as we did not find this after a longer time period (e.g., 45 minutes). This suggests that maybe the finding is spurious or perhaps the physiological processes in the body adapt to the new equilibrium set up by the Geko ™ device by slowing the cardiac output down somehow. We cannot also conclude whether the increase in CO at 10 minutes was due to a sympathetic response to pain or due the mechanical venous pump.

The pulse wave velocity did not appear to alter with the Geko ™ device.

3.9.3 Generalisability

This is work in a group of healthy volunteers so the applicability of the results to the patient population is limited. The failure to function in this study of n=36 was 0%. Any haemodynamic effect in a patient group with more presence of oedema, diabetes and neuropathy would be reduced by a higher failure to twitch rate.

3.9.4 Future considerations

Ideally, we would have a venous circulation-monitoring device that would demonstrate exactly what happens to the compressed venous blood as it leaves the leg. For instance, does the augmented leg venous blood displace or reduce returning venous blood from other organs e.g. splanchnic venous blood. This would explain the relatively small and modest rise in cardiac output, because it would imply venous return presented to the heart would be mostly the same, but just comprising of more leg venous blood compared to other organs.

For future work I would have liked to also look at whether blood volume and degrees of dehydration had any effect on the Geko ™'s ability to increase cardiac output.

I would undertake a randomised allocation for Geko or control if I were to repeat the experiment. I would also have been interested in continuing the readings after the device was turned off to establish how long it took for readings to return to baseline. This would have given us some data about the washout period for the device.

Chapter 4.0 A Cross-over design study looking at invasive cardiac output changes with the Geko ™ device in post cardiac surgery patients

4.1 Introduction

The studies on healthy volunteers pointed to a change in cardiac output being the biggest change in the haemodynamics with the active Geko ™ device. Thus, we decided to measure the cardiac output invasively for a more accurate monitor.
Minimally invasive cardiac output monitors are more scientifically accurate than non-invasive methods[121], however there are potential side effects and harm for patients. We used pulse contour analysis using LiDCo, because this is what was available in our department routinely. LiDCo also has[122] good correlation with the gold standard cardiac output monitor, the pulmonary arterial catheter.

LiDCo requires an arterial line, which can cause haemotoma, infection, and arterial damage to the hand. LiDco also requires regular lithium calibration and so there is a potential theoretical risk of accidental lithium toxicity. Furthermore arrhythmias, aortic regurgitation and a change in systemic vascular resistance have all been shown to limit the accuracy of the pulse contour technique[123]. We needed our previous studies to direct us and justify using the Geko ™ with invasive monitoring.

4.2 Objectives

- To see if the cardiac output will be increased by the Geko TM device in post-operative patients
- To validate the findings of improved cardiac output by more accurate and validated monitoring

4.3 Study approval

The study was sponsored by Bart's Health NHS Trust and funded by a National Institute for Health Research (NIHR) i4i grant. National Research Ethics Service (NRES), Dulwich NRES Committee, reference 13/LO/0295 approved the study amendment on the 22nd July 2014.

4.4 Method and Materials

4.4.1. Setting

The study was carried out in the Cardiac Intensive Care Unit in St Bartholomew's Hospital in London from July 2014 till September 2014.

4.4.2 Volunteers

5 adult patients were identified from cardiac theatres lists known to be listed for a valve replacement or repair at St Bartholomew's Hospital. The subjects were approached by the anaesthetic team and provided with information sheets (appendix 1) on the day of surgery. Written informed consent was obtained prior to the study for all volunteers.

4.4.2.1 Inclusion criteria

Figure 4.1 Inclusion criteria for the volunteers in the Geko™ in Cardiac patients' study described in the below table.

Aged 18 – 85
BMI between 18-34
Able to understand the Patient Information Sheet and sign the informed consent form
Free of current or recent (6 months) DVT
Assent of anaesthetist, nurses and surgical team
Listed for cardiac valve replacement/repair
LiDCo planned as part of normal care

4.4.2.2 Exclusion criteria

Figure 4.2 Exclusion criteria for volunteers to the Geko ™ in Cardiac patients are described below in the following table.

Emergency cases
Participation in any clinical study during the 8 weeks preceding the dosing period of the study
Pregnancy
Recent surgery / trauma on the lower limb
Musculoskeletal disorders of the lower limbs
Peripheral arterial disease, varicose veins or lower limb ulceration
ASA 4/5
Lithium Toxicity
Contraindication to invasive monitoring with LiDCo

4.5 Study Procedure

4.5.1 Screening

The volunteers were screened in an identical fashion to our first study. After explaining the study protocol and obtaining informed consent a baseline questionnaire and physical examination was performed for each subject. The baseline questionnaire was designed to assess the general health of the subject, the presence of pre-existing hypertension or DVT. The physical examination included a cardiovascular examination, heart rate and blood pressure, weight and height, and a physical check of the legs. The patients were next seen after their operation in the intensive care.

4.5.2 Study design

The study was not powered, though this was a gross limitation of the study. We did have some data on a likely size of effect from the previous study in healthy volunteers. We were limited by time and the infrequency of the type of cardiac surgical patient, which we could conduct the study on.

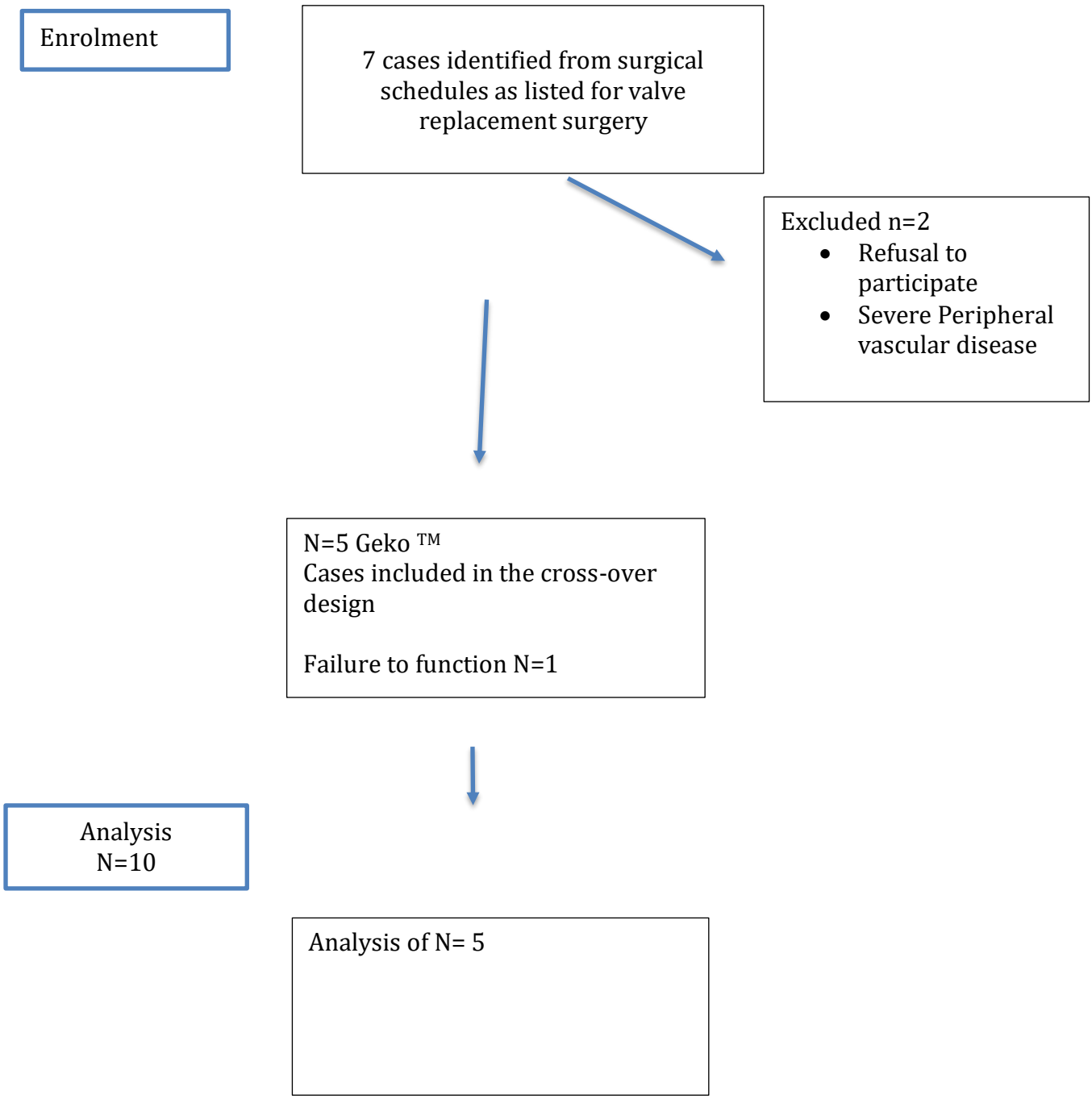
We looked at 5 post cardiac surgery patients to analyse the effect of Geko ™ on cardiac output by the Lidco device. The patients were intubated and ventilated and were on anaesthetic drugs in the cardiac intensive care environment immediately post operatively.
We waited for a period of stabilization before we conducted the data collection. The patients were observed and monitored until a steady haemodynamic rate was achieved (< 25% change in haemodynamic parameters, <10 % change in sedation/analgesia).
After the stabilization period, the Geko ™ device was applied to each leg. A series of haemodynamic measurements was taken initially: heart rate (HR), mean arterial blood pressure (BP), stroke volume (SV), cardiac output (CO), systemic vascular resistance (SVR) and central venous pressures (CVP).
The Geko ™ was then switched on for ten minutes and a set of data variables was recorded again. The Geko ™ was switched off for ten minutes and a set of variables was recorded again. The Geko ™ was turned on again for a second time and a set of variables recorded again. The Geko ™ was then turned off for a second time and a last set of measurements were recorded.

4.5.3 Outcomes

The dependent outcomes measured were heart rate, mean arterial pressure, stroke volume, invasive cardiac output, systemic vascular resistance and central venous pressure. The independent variable was Geko ™ stimulation.

4.5.3 Participant flow

Figure 4.3 Diagram showing the participant flow for the Geko ™ in cardiac patients study



4.6 Statistical analysis

Linear mixed models with first-order autoregressive covariance structure were used to evaluate within-subject effects of repeated measures of outcome variables. Post hoc comparisons were conducted using least significant difference tests. A p value less than 0.05 was considered statistically significant.

4.7 Results

Despite a slight increase in cardiac output 2.5% the result is not significant.
Also on average, patients had higher HR, CO and SV, and lower SVR when the Geko ™ was on, this result is not significant. There was no significant difference in mean CO, SV and SVR on distinct time points. However, significant differences in HR were noted among distinct time points. Post hoc analysis revealed that baseline HR was significantly lower than 1st Geko ™ on, also between 1st Geko ™ off and 2nd Geko ™ on, but the difference in HR between baseline and 2nd Geko ™ off was non-significant.

There was one patient who had no muscular twitches from the Geko ™ device (20% of the N=5) who included in the analysis as intention to treat.

There was no harm received to any of the patients on the trial.

Figure 4.4 : Statistical values of haemodynamic measurements with Geko ™ stimulation in post cardiac patients N=5

	Geko ™ OFF		Geko ™ ON		
	Mean	SE	Mean	SE	p
HR (bpm)	91.8	5.0	94.1	5.1	0.07
CO (L/min)	3.94	0.33	4.04	0.33	0.17
SV (ml)	44.2	6.1	44.9	6.1	0.36
SVR (mmHg/min/ml)	2449	419	2357	422	0.11

Figure 4.5 : 4 Graphs showing the haemodynamic changes with the Geko ™ device in 5 post cardiac patients (heart rate, cardiac output, stroke volume, systemic vascular resistance

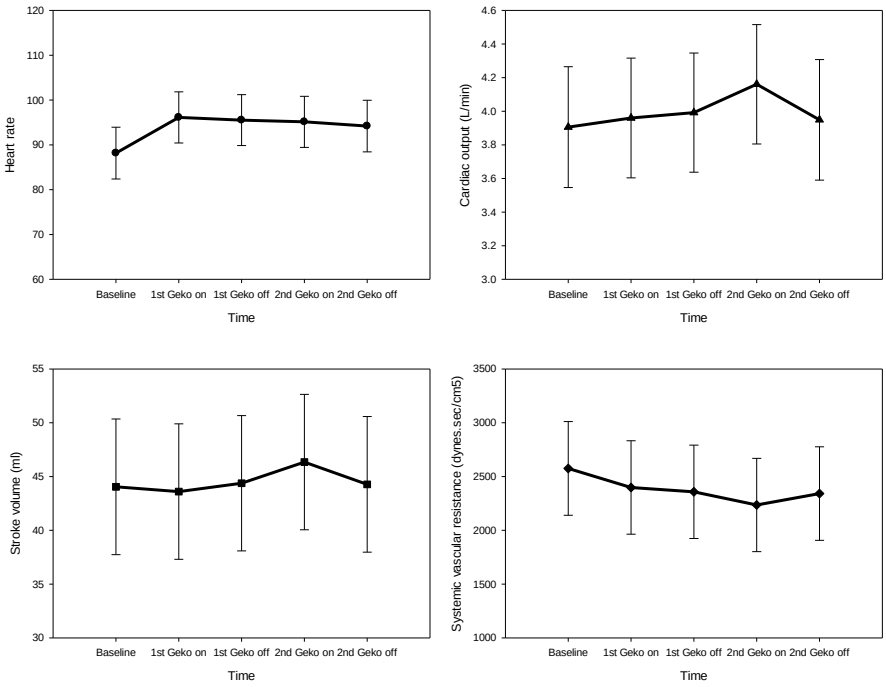
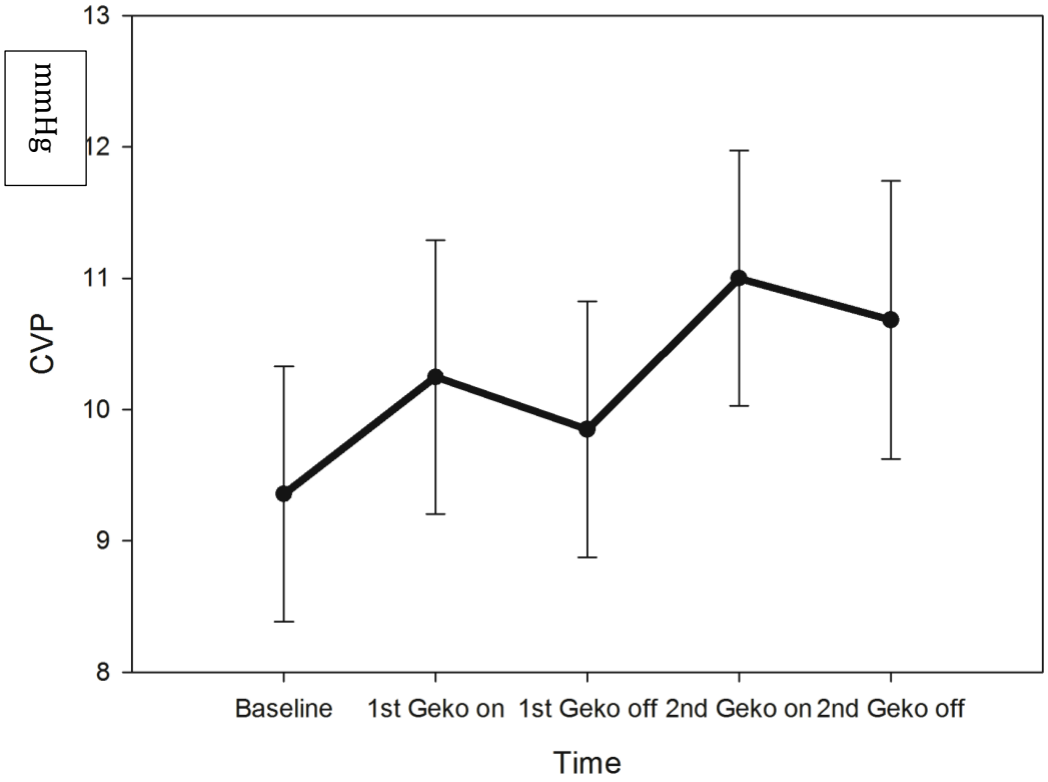


Figure 4.6 : Graph to show CVP readings in the 5 post cardiac patients with the Geko ™



4.8 Discussion

4.8.1 Limitations

5 patients are not enough to draw any firm conclusions, despite the "on off" experiment design, which does add statistical strength to any findings. Ideally, we would have performed an a priori power calculation to decide sample size. Using our previous study on healthy volunteers an increase in CO of 12% with a Standard Error of 0.3, an α (type 1 error) of 0.05 and a standard power of 0.8, the sample size would be 3 in each group.

We were limited to only use post-operative cardiac patients that were having valve replacement surgery. We decided on the post-operative period to take our experiments because it is a more stable haemodynamic time than an anaesthetic induction. We could only use cardiac patients because we did not manage to obtain approval from the main ITU at the hospital trust. Cardiac patients would already have the LiDCo as normal part of their care. We were limited to only recruiting valve replacement patients, because most cardiac bypass patients would have leg veins grafted for the bypass. A Geko ™ may potentially cause undue stress to newly sutured veins.

Post-operative cardiac valve patients will inevitably be haemodynamically labile, especially in the immediate recovery period in ITU. This is not the ideal situation to measure a small change in CO, as any positive correlation will be hard to pick up by small numbers of experimental data.

The buildup of CVP shown by graph 13 is interesting and does point to the Geko ™ increasing venous return. I cannot draw any conclusions due to the insignificance of the results however.

One of the patients had no muscular contractions but was included in the results. The failure to function rate being higher in patients compared to healthy volunteers is a limiting factor.

I was unable to recruit more patients to the study as I had to return to my anaesthetic trainee post.

4.8.3 Interpretation

The results do not allow us to draw any firm conclusions. More work is needed to establish if there is a relationship.

4.8.4 Future Work

It would have been helpful to also collect Vicorder recordings in these cardiac patients to further support our findings from the previous study in healthy volunteers. It would help to validate the Vicorder cardiac output measurements against the LiDCo. Unfortunately, it became clear that the nursing staff did not want me to attach more blood pressure cuffs on the patients, as they already had some as standard care on the ITU.

It would have been helpful to measure lactate at the different time points. Lactate is a useful biomarker of impaired global perfusion, although there are other reasons for the lactate to be raised, e.g., metabolic reasons. If the Geko ™ was shown the decrease the lactate, this would have suggested an improved circulatory system. A decreased lactate is something that would have clinical utility.

Further numbers are needed to establish if there is any relationship.

5.0 General discussion

Augmenting the cardiac output as a secondary benefit whilst preventing Deep Vein Thrombosis would have been clinically useful, especially in septic patients. This series of experiments have not found a significant change in the haemodynamics.

More numbers of patients would be needed to definitively find a positive correlation between Geko ™ and cardiac output, however these experiments do show that if there is an effect the magnitude is small and so probably not of importance clinically. Our experiments seem to suggest that having anaesthetic or sedative drugs on board diminish the haemodynamic effect of Geko ™. This could be because of a reduction in a sympathetic response driven by a painful/uncomfortable Geko ™ stimulation. Or it could be because a vasodilated patient would have a lower stressed venous volume, and so the mean systemic filling pressure is lower, and thus increasing flow in a compliant venous system may not increase right heart pressures.

Cardiac output monitoring is very inaccurate, with large error margins. Invasive monitors have a better accuracy however the potential complications are much higher and so this had to be balanced with the ethics of the studies. A significant proportion of the cardiac patients did not have a large muscular response from the Geko ™, either due to oedema, or subcutaneous fat impeding the electrical stimulation (20%) this limits the physiological conclusion, but is relevant to any clinical application.

The initial hypothesis of the calf pump augmenting venous return may not be as large as first hypothesized because the venous system is a capacitance system and thus may just absorb the extra blood delivered to it without increasing cardiac output. There is a paucity of knowledge, research and more importantly measuring equipment for the venous circulatory system. Ideally a venous imaging modality would show us exactly what happened to the venous blood from the legs and the abdomen, whilst the Geko™ was on. There is also not a practical way to measure the mean systemic filling pressure, which would have been a useful measure of understanding the changes, if any, to the haemodynamics. A further avenue of enquiry and investigation would have been to mathematically model the effect of a secondary pump on the circulation using computer models. I was unable to collaborate with people in this field on this project.

The Geko ™ does not stimulate the posterior calf muscles, in the same way that the physiological calf pump does whilst walking. It is surprising that the Geko ™ does have such an effect to improve the leg venous return by only using the foot pump and the anterior leg compartment.

There is a number of people who do not have any muscular response to the Geko, due to factors such as variable anatomy, obesity, oedema, faulty device, muscle paralysis. This failure to function was a high as 58% in the vascular patient group in work done by Rachel Barnes[56]. Our studies found one in 13 patients in the first study during the anaesthetic induction (8%) had no response and one in five of the cardiac patients (20%) had no response. All volunteers in the healthy volunteer study had a response. The ability of the Geko to work in all patients has a bearing on how useful it will be a clinical setting.

6.0 Future considerations and avenues for research

Collecting more data using invasive monitoring, and expanding the studies to the general intensive care would increase the data and potentially the understanding of the relationship that the Geko™ has with the haemodynamics. If the Geko ™ was found to increase cardiac output, it would then also be necessary to establish if this led on to improved patient outcomes such as reduced hospital stay and reduced mortality.

Despite a lack of evidence of a large change in cardiac output in post cardiac surgery patients immediately after surgery in the intensive care. The complete understanding of the central and peripheral haemodynamic changes has not been reached. The Geko™ may have some benefit in different patient groups with different pathologies, and looking at patient outcomes may be a more relevant question. For example, in sepsis, the Geko™ may improve circulation in the legs, toes and feet and thus prevent the ischemia which sometimes results after microemboli have disrupted blood supply. Post sepsis amputation is a traumatic and disabling event for a sepsis survivor, one study showed a 0.8% limb amputation rate after sepsis[124].

I would also have used video recording to numerically quantify the Geko ™ pump effect for each leg and for each patient, this would allow for a "dose dependent relationship" to be explored. I did obtain the access to some software that could analyse a marker point in a video and quantify the movement of the marker point. I would have placed the marker (e.g., blue adhesive sticker) on a standardised part of the anatomy for the volunteers, e.g., the tip of the hallux.

I would have also like to involve other experts in venous physiology and used their mathematical models of the circulation, to calculate what a theoretical Geko ™ calf pump would do to the circulation. It would be interesting to see if the mathematical algorithms matched our findings.

Interesting future work could also look at the circulation in the digestive system, perhaps using flow oximetry, to see if the microcirculation is altered by the Geko™.

Further work could also look at the haemodynamics in pregnant women, they have a vasodilated systemic circulation as well as higher abdominal pressures. The Geko ™ may be effective in this group of patients to reduce oedema and varicose veins.

Future work would aim to use the newer Geko ™ devices which have been engineered to be more effective in patients; the devices have a more conductive gel electrode; the electrode configuration and pulse width are also altered.

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APPENDIX

1) Consent form for Diminished anaesthetic hypotension by the Geko™ in Amaesthetic Indiction GAIN trial
2) Patient information sheet for the GAIN trail
3) Healthy Volunteer information sheet

1)

Consent to participate in:

A pilot study to assess the effect of neuromuscular electrical stimulation of the common peroneal nerve, using the geko ™, on the hypotension encountered during anaesthetic induction.

Diminished anaesthetic hypotension by the geko ™ in Anaesthetic Induction. (GAIN trial)

Please affix
Pt. Details sticker

	Participants Initials
I confirm that I have been given adequate time to read and understand the entire Patient Information Sheet version 2.0; Dated 14nd March 2013 relating to the trial. I have had the opportunity to ask any questions and have understood the responses.	
I understand that relevant sections of any of my medical notes and data collected during the study may be looked at by individuals from regulatory authorities or from the NHS Trust, where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records	
I understand that participation in the trial is entirely voluntary and that I have the right to withdraw at any time without giving my reasons.	
I agree to take part in the trial	
I consent to have details stored by the research team and understand that my details will not be available to anyone other than the research staff or database administrator.	
I understand that the results of the study may be presented at medical conferences and published in medical literature in an anonymous form. No identifiable details will be released to anyone outside of the research team.	

Participant Name: _____ date__/__/__

Signature: _____

Researcher Name: _____ date__/__/__ Signature

_____

2)

Haemodynamic changes by the Geko™ device.
GAIN Trial (Geko™ and Anaesthetic Induction)

Patient information sheet

Part 1

Invitation

You are being invited to take part in a research study. Before you decide, it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and talk to others about the study if you wish.

- Part 1 tells you the purpose of this study and what will happen to you if you take part
- Part 2 gives you more detailed information about the conduct of the study

What is the purpose of the study?

You have been invited to take part in a clinical trial to see if using a device called the geko™ can TEMPORARILY improve the blood flow in your body.

To help you decide if you would like to take part, please read this information sheet. It gives you details of what will be involved if you decide to take part and also who to contact if you would like to discuss the study or ask any questions.

What is this device? And how does it work?

A simple, small and light, self-adhesive device that is applied to the back of each knee, the disposable, one-size-fits-all geko™ device was originally designed to prevent the occurance of deep vein thrombosis (DVT), or blood clots in your veins deep inside your legs.

Small, painless, electrical impulses gently stimulate a nerve behind the knee to activate the calf muscle pumps of the lower leg that return blood towards the heart. The process is similar to that normally achieved by walking but without the patient having to move or exert energy and without uncomfortable muscle movements.

Do I have to take part?

No. It is up to you to decide whether or not to take part. If you do, you will be given this information sheet to keep and be asked to sign a consent form. You are still free to withdraw at any time and without giving a reason. Your non-participation or dropping out of the study will not affect you in any way.

Before you can begin the study

The recruiting investigator will tell you about any potential adverse events that could occur in the study. You will be told exactly what the study entails and what will be required of you. You are encouraged to ask questions until you are satisfied that you fully understand the nature of the study and the requirements.

What happens in the study?

If you think you might be interested in taking part in the study, you will have a short interview with one of the researchers so we can collect some details from you and make sure there is no reason not to include you in the trial. Once you are enrolled in the trial we will perform a simple routine examination, e.g. listen to your heart and lungs before taking some routine measurements from you, e.g. heart rate, blood pressure, height, weight etc.

This study is designed to be as minimally disruptive to you as possible; all the measurements we take will be, simple and routine. We will conduct the study in the intensive care area after your operation. You may or may not be sedated when we carry out the recordings. The device is not painful, and aside from placing it on, we will not be doing anything that will vary from your routine care.

We will wait for you to be settled and stable before we start. Next the geko will be turned on for ten minutes while we collect data, and then off for ten minutes, again while we collect data. The total data collecting time will be roughly 30 minutes.

We will be recording measurements like your blood pressure, heart rate, and heart function, to see if the geko improves your circulation. We will not be placing any invasive monitoring that is not already in situ, as part of your care. We will also use a Doppler machine to check blood supply in your leg, this is non-invasive and painless. We have not found any cases of worsened blood circulation with the geko; the worst we would expect is no change at all.

The device is removed after we have completed the data recording.

Are there any risks to participating in the study?

From the studies to date, there are no risks to participating in this study.

What are the potential benefits of taking part?

The study will not benefit you directly, however if the device is shown to improve the blood flow, it may be a useful treatment option in the future.

Could I come to any harm if I take part in the study?

You may be withdrawn from the study if the doctor/research team feel it is best for you or if you do not comply with the requirements of the study.

If you feel unacceptable discomfort, or for any reason during the study you do not wish to continue, than we will stop the tests immediately.

All of the previous work using the system was found to be safe. When the device is applying an electrical stimulation, you will feel some muscle twitching and maybe tingling in your lower legs. That is how the device works and is intended in this study,

There are very few risks involved in using this type of equipment and the device is commonly used for therapeutic purposes to exercise muscles under the supervision of a Physiotherapist, as well as by members of the public for “toning” purposes in their own homes, as well as preventing deep vein thrombosis.

What happens when the research study stops?

When the study is complete, you will be continuing your postoperative recovery as normal.

What if there is a problem?

Any complaint or concerns about the way you have been dealt with during the study or potential harm you might suffer will be addressed. The detailed information on this is given in part 2.
If you have a complaint please contact the following in the first instance:

Dr Preea Gill (see below)

If you feel any discomfort or distress during the investigations, you must say so and we will stop the tests immediately at any time. Any complaint about the way you have been dealt with during the study or any possible harm you might suffer will be addressed. The detailed information on this is given in Part 2. A contact number for complaints will be given.

Will my taking part in the study be kept confidential?

Yes. All the information about your participation in this study will be kept confidential. The details are included in Part 2.

Contact Details:

If you require any further information please contact Research team contact;

Dr Preea Gill
Pain and Anaesthesia Research Centre
1st Floor Dominion House
59 Bartholomew Close
West Smithfield
London
EC1A 7BE
Phone: 020 3416 5000 ext. 57238
Email: preeagill@bartshealth.nhs.uk

This completes Part 1 of the Information Sheet.

If the information in Part 1 has interested you and you are considering participation, please continue to read the additional information in Part 2 before making any decision.

Part 2

What if relevant new information becomes available?

Sometimes during the course of a research project, new information becomes available about the treatment/drug that is being studied. If this happens, your research doctor will tell you about it and discuss whether you want to or should continue in the study. If you decide not to carry on, your research doctor will make arrangements for your care to continue. If you decide to continue in the study you will be asked to sign an updated consent form.

Also, on receiving new information your research doctor might consider it to be in your best interests to withdraw you from the study. He/she will explain the reasons and arrange for your care to continue. If the study is stopped for any other reason, you will be told why and your continuing care will be arranged.

What will happen if I don't want to carry on with the study?

If you withdraw from the study we will need to use the data collected up to your withdrawal.

What if there is a problem?

If you have a concern about any aspect of this trial, you should first ask to speak to the researchers who will do their best to answer your questions. If you remain unhappy and wish to complain, you can do this via the NHS Complaints Procedure.

Details can be obtained from;
Patients advice and Liaison Service on **020 359 42040 42050 or email PALS@bartshealth.nhs.uk**

In the event that something does go wrong and you are harmed during the research and this is due to someone's negligence then you may have grounds for a legal action for compensation against Barts Health NHS Trust but you may have to pay your legal costs. The normal National Health Service complaints mechanisms will still be available to you. In the highly unlikely event that you suffer from
injury or illness as a result of participation in this study, indemnity will be provided by Barts Health NHS Trust. Compensation will be by the usual NHS procedures.

Will my taking part in this study be kept confidential?

All the information obtained about you in the course of the study is confidential and will be kept in a secure locked room. The investigators performing the study and a study Monitor will have access to the data collected in this study. They may also be looked at by representatives of regulatory authorities and by authorised people from Barts Health to check that the study is being carried out correctly. All will have a duty of confidentiality to you as a research participant and nothing that could reveal your identity will be disclosed outside the research site.

What will happen to the results of the research study?

The results of this study may be published or presented at meetings. You will not be identified in any report / publication or presentation. We would be happy to supply you with a copy of the results on request.

Who is organising and funding the study?

This study is organised and funded through the Pain and Anaesthesia Research Centre at St Bartholomew's Hospital and the National Institute of Health Research.

Who has reviewed this study?

The ethics behind this study have been reviewed and supported by the London Ethics Committee 13/LO/0295

Further information/independent advice

Independent advice regarding this study or any other aspect of your care can be obtained from the Patients Advisory Liaison Service (PALS) using the details below;

PALS OFFICE Second floor, Central Tower.

The Royal London Hospital. Whitechapel Road, London. E1 1BB

Tel. **020 359 42040 / 42050**
Email: **PALS@bartshealth.nhs.uk**

You can also look for more information / independent advice at http://www.invo.org.uk
INVOLVE is a national advisory group that supports greater public involvement in NHS, public health and social care research. INVOLVE is funded by and part of the **National Institute of Health Research** (NIHR).

What happens next?

Please discuss this information with your family, friends or GP if you wish. Any questions can be answered then or please do not hesitate to contact the research team on the number below. Thank you very much for taking the time to read this information sheet and considering taking part in our research.

Pain and Anaesthesia Research Centre
1st Floor Dominion House
59 Bartholomew Close
West Smithfield
London
EC1A 7BE
Phone: 020 3416 5000 ext. 57238

3)

Haemodynamic changes by the Geko™ device.
GAIN Trial (Geko™ and Anaesthetic Induction)

Healthy Volunteer information sheet

Part 1

Invitation

You are being invited to take part in a research study. Before you decide, it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and talk to others about the study if you wish.

- Part 1 tells you the purpose of this study and what will happen to you if you take part
- Part 2 gives you more detailed information about the conduct of the study

What is the purpose of the study?

You have been invited to take part in a clinical trial to see if using a device called the geko™ can TEMPORARILY improve the blood flow in your body.

To help you decide if you would like to take part, please read this information sheet. It gives you details of what will be involved if you decide to take part and also who to contact if you would like to discuss the study or ask any questions.

What is this device? And how does it work?

A simple, small and light, self-adhesive device that is applied to the back of each knee, the disposable, one-size-fits-all geko™ device was originally designed to prevent the occurance of deep vein thrombosis (DVT), or blood clots in your veins deep inside your legs.

Small, painless, electrical impulses gently stimulate a nerve behind the knee to activate the calf muscle pumps of the lower leg that return blood towards the heart. The process is similar to that normally achieved by walking but without the patient having to move or exert energy and without uncomfortable muscle movements.

Do I have to take part?

No. It is up to you to decide whether or not to take part. If you do, you will be given this information sheet to keep and be asked to sign a consent form. You are still free to withdraw at any time and

without giving a reason. Your non-participation or dropping out of the study will not affect you in any way.

Before you can begin the study

The recruiting investigator will tell you about any potential adverse events that could occur in the study. You will be told exactly what the study entails and what will be required of you. You are encouraged to ask questions until you are satisfied that you fully understand the nature of the study and the requirements.

What happens in the study?

This study is designed to be as minimally disruptive to you as possible; all the measurements we take will be non-invasive, simple and routine.

If you think you might be interested in taking part in the study, you will have a short interview with one of the researchers so we can collect some details from you and make sure there is no reason not to include you in the trial. Once you are enrolled in the trial we will perform a simple routine examination, e.g. listen to your heart and lungs before taking some routine measurements from you, e.g. heart rate, blood pressure, height, weight etc.

At the start of the study period you will have the geko device placed by one of the research team. You will either be placed in the seated or lying down position during the tests randomly decided to help our analysis.

You will be randomly placed in one of two groups. If you are in Group B, the geko™ device will be applied to your leg and switched on. You will experience the muscles in your leg and/or foot gently contracting/ twitching. A bed sheet, as standard, will cover your legs. The doctor collecting the data will not know which group you are in so that the results of the experiment will be fairer. If you are in Group A the device will be applied to your leg but will not be activated initially. Instead in Group A, the geko will be turned on after ten minutes. The totally data collecting time will be about 30 minutes.

We will be recording basic measurements like your blood pressure, heart rate, and heart function, to see if the geko improves your circulation. We will also use a Doppler machine to check blood supply in your leg, this is non-invasive and painless. We have not found any cases of worsened blood circulation with the geko; the worst we would expect is no change at all.

The device is removed after about thirty minutes; we will confirm you are ok. After this we will invite you to have a drink of water whilst we conduct a short questionnaire to find out how you found the experience.

Are there any risks to participating in the study?

From the studies to date, there are no risks to participating in this study.

What are the potential benefits of taking part?

The study will not benefit you directly, however if the device is shown to improve the blood flow, it may be a useful treatment option in the future.

Could I come to any harm if I take part in the study?

You may be withdrawn from the study if the doctor/research team feel it is best for you or if you do not comply with the requirements of the study.

If during the health screening tests any abnormal results are found, you will be immediately referred for clinical review as appropriate.

If you feel unacceptable discomfort, or for any reason during the study you do not wish to continue, than we will stop the tests immediately.

The blood flow measurements and ultrasound are non-invasive, painless and known to be entirely safe.

All of the previous work using the system was found to be safe. When the device is applying an electrical stimulation, you will feel some muscle twitching and maybe tingling in your lower legs. That is how the device works and is intended in this study,

There are very few risks involved in using this type of equipment and the device is commonly used for therapeutic purposes to exercise muscles under the supervision of a Physiotherapist, as well as by members of the public for “toning” purposes in their own homes.

What happens when the research study stops?

When the study is complete, you will be free to go.

What if there is a problem?

Any complaint or concerns about the way you have been dealt with during the study or potential harm you might suffer will be addressed. The detailed information on this is given in part 2.
If you have a complaint please contact the following in the first instance:

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If you feel any discomfort or distress during the investigations, you must say so and we will stop the tests immediately at any time. Any complaint about the way you have been dealt with during the study or any possible harm you might suffer will be addressed. The detailed information on this is given in Part 2. A contact number for complaints will be given.

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This study is organised and funded through the Pain and Anaesthesia Research Centre at St Bartholomew's Hospital and the National Institute of Health Research.

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The ethics behind this study have been reviewed and supported by the London Ethics Committee XXXXXXXX

Further information/independent advice

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INVOLVE is a national advisory group that supports greater public involvement in NHS, public health and social care research. INVOLVE is funded by and part of the **National Institute of Health Research** (NIHR).

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