Neuromuscular Electrical Stimulation in the Management of Peripheral Arterial Disease and Muscle Recovery

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1st June 2018

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Inspiration

‘The journey of a thousand miles begins with one step’

- Lao Tzu

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ABSTRACT

Background and Aim

Peripheral arterial disease (PAD) has a significant global health and economic burden. Intermittent claudication (IC) is an early manifestation of PAD, causing significant functional disability and poor quality of life (QoL). Management includes lifestyle and atherosclerotic risk factor modification. A supervised exercise programme (SEP) is the recommended first line strategy, showing significant improvements in pain free walking distance. This is underutilised and inaccessible to the majority in the UK. Neuromuscular electrical stimulation (NMES) is an evolving novel technology showing potential for use in vascular disease. The aim of this study was to assess the utility of NMES in the management of PAD, as an adjunct to SEPs and in muscle recovery following fatigue.

Methods

Background research included assessment of the outcomes associated with a local SEP, a national online audit of access to SEPs in UK and Ireland and a literature review on current evidence of the utility of NMES in IC.

National ethics and regulatory approval was gained for NMES based research in PAD. Patients were recruited from the vascular outpatient clinic at Charing Cross Hospital. Two planned PAD studies were completed as follows:

1: NMES in the management of IC - a proof of concept study of the independent effect of 6 weeks intervention with NMES.

2: The adjuvant benefit of NMES to SEPs in the management of IC - a randomised controlled study to assess the adjunctive benefit of NMES to SEPs, comparing a control group receiving SEP only with another receiving SEP and footplate NMES, for 6 weeks.

Outcomes included treadmill walking distances, disease specific and generic QoL scores, haemodynamic measures of the superficial femoral artery (Duplex ultrasound) and skin microcirculation (Laser Doppler Flowmetry).

Ethics approval was gained for muscle recovery studies, recruiting healthy volunteers from Imperial College London and Kings College London. Two studies were undertaken:

1: Use of NMES in muscle recovery following high intensity exercise – a pilot randomised controlled study assessing the utility of NMES compared to passive rest in calf muscle recovery following high intensity exercise.
2: Use of NMES in the recovery of short and long term calf muscle fatigue – a randomised controlled trial assessing the utility of NMES compared to passive rest in muscle recovery following calf muscle fatigue over time.

Outcomes assessed muscle performance by vertical jump test and numeric rating scale (NRS) for pain.

Results

NMES showed significant improvements in functional ability and both disease specific and generic QoL following 6 weeks intervention. There was a significant adjuvant benefit of NMES compared to SEP in improving the initial claudication distance in patients with IC

following 6 weeks intervention as well as disease specific quality of life score. Blood flow and Time Averaged Mean Velocity increased significantly whilst the device was on. There were no significant improvements in calf muscle recovery following fatigue in healthy individuals.

Conclusions

Functional and QoL measures were improved by NMES intervention. These clinical trials provide a good foundation for further robust clarification of the utility of NMES in PAD. Exploration of the mechanisms by which this may occur, is also needed.

List of Abbreviations

ABPI	Ankle-Brachial Pressure Index
ACD	Absolute Claudication Distance
ACEi	Angiotensin Converting Enzyme inhibitor
ACh	Acetyl Choline
AU	Arbitrary Units
AWD	Absolute Walking Distance
BMT	Best Medical Therapy
CAD	Coronary Artery Disease
CCB	Calcium Channel Blocker
CKD	Chronic Kidney Disease
CLI	Critical Limb Ischaemia
CTA	Computed Tomography Angiography
CVD	Cerebrovascular Disease
DOMS	Delayed Onset Muscle Soreness
DU	Duplex Ultrasonography
ECQ	Edinburgh Claudication Questionnaire
eNOS	Endothelial Nitrous Oxide Synthase
EQ-5D	EuroQoL-5D
ESVS	European Society of Vascular Surgery
FES	Functional Electrical Stimulation
FI	Fatigue Index
GDP	Gross Domestic Product
HDL	High Density Lipoprotein
HSC	Health and Social Care Ireland
hsCRP	High Sensitive C-Reactive Protein
HVES	High Voltage Electrical Stimulation

Hz	Hertz
i.e.	Id Est (In other words)
IC	Intermittent Claudication
ICAM	Intracellular Adhesion Molecules
ICD	Initial Claudication Distance
ICQ	Intermittent Claudication Questionnaire
iL-6	Interleukin-6
ISVS	International Society of Vascular Surgeons
LDL	Low Density Lipoproteins
MCD	Maximum Claudication Distance
MCP-1	Monocyte Chemoattractant Molecule-1
MHRA	Medicine and Healthcare products Regulatory Agency
MI	Myocardial Infarction
mmHg	Millimetres of Mercury
MnSOD	Manganese Superoxide Dismutase
MRA	Magnetic Resonance Angiography
MWD	Maximum Walking Distance
NIRS	Near Infrared Spectroscopy
NMES	Neurmomuscular Electrical Stimulation
NMJ	Neuromuscular Junction
NO	Nitrous Oxide
NRES	National Research and Ethics Service
PAD	Peripheral Arterial Disease
PAOD	Peripheral Arterial Occlusive Disease
peABPI	Post exercise Ankle Brachial Pressure Index
PIS	Patient Information Sheet
PVD	Peripheral Vascular Disease
PVD	Peripheral Vascular Disease

ROS	Reactive Oxygen Species
RR	Relative Risk
RRR	Relative Risk Reduction
SBP	Systolic Blood Pressure
SEP	Supervised Exercise Programme
SET	Supervised Exercise Training
SF-36	Short-form 36
sICAM-1	serum Intracellular Adhesion Molecule-1
SMC	Smooth Muscle Cell
TAMV	Time Averaged Mean Velocity
TASC	Transatlantic Intersociety Consensus
TIA	Transient Ischaemic Attack
TOI	Tissue Oxygenation Index
VCAM	Vascular Cell Adhesion Molecule
VE	Voluntary Exercise
VSGBI	Vascular Society of Great Britain and Ireland
WD	Walking distance

Table of Contents

1. Background 26

1.1 Peripheral Arterial Disease 26

1.1.1 Definition of PAD and its clinical manifestations 26

1.1.2 Epidemiology and Economic Impact 28

1.1.2.1 Asymptomatic disease 28

1.1.2.2 Intermittent Claudication 29

1.1.2.3 Critical Limb Ischaemia 30

1.1.2.4 Economic impact of PAD 31

1.1.3 Pathophysiology of Peripheral Arterial Disease 32

1.1.3.1 Endothelial dysfunction 32

1.1.3.2 Arteriosclerosis 33

1.1.4 Risk Factors for PAD 37

1.1.4.1 Smoking 37

1.1.4.2 Ethnicity 38

1.1.4.3 Diabetes 38

1.1.4.4 Hypertension 39

1.1.4.5 Hypercholesterolaemia and Hyperlipidaemia 40

1.1.4.6 Inflammatory markers and cytokines 40

1.1.4.7 Genetic predisposition 41

1.1.5 Guidelines 42

1.1.6 Diagnosis 44

1.1.6.1 Clinical presentation and symptoms 44

1.1.6.2 Differential Diagnoses 45

1.1.6.3 Ankle Brachial Pressure Index 47

1.1.6.4 Duplex Ultrasound 49

1.1.6.5 Computed Tomography/Magnetic Resonance Angiography 50

1.1.6.6 Classification of PAD 51

1.1.7 Management Strategies 53

1.1.7.1 Best Medical Therapy and lifestyle modification 54

1.1.7.2 Exercise Therapy 59

1.1.8 Alternative therapies in the management of PAD 60

1.1.8.1 Intermittent Pneumatic Compression 60

1.1.8.2 Extracorporeal Shockwave Therapy 62

1.2 Muscle 63
1.2.1 Muscle morphology 63
1.2.1.1 Structure 63
1.2.1.2 Classification 66
1.2.2 Skeletal muscle contraction 67
1.2.2.1 Neuromuscular Junction 68
1.2.2.2 Sliding filament theory 69
1.2.3 Muscle fatigue and recovery 71
1.2.4 Muscle adaptations 73
1.2.4.1 Muscle in PAD 74
1.3 Neuromuscular Electrical Stimulation 79
1.3.1 Neuron morphology 79
1.3.2 Electrical therapy and evolution in medicine 81
1.3.3 Neuromuscular Electrical Stimulation 83
1.3.4 NMES stimulation parameters 83
1.3.4.1 Current 84
1.3.4.2 Pulse frequency 84
1.3.4.3 Pulse duration 85
1.3.4.4 Duty cycle 85
1.3.4.5 Amplitude 85
1.3.4.6 Output 86
1.3.4.7 Electrodes 86
1.3.5 Motor unit recruitment 86
1.3.6 NMES devices 87
1.3.6.1 Veinoplus® 87
1.3.6.2 Geko™ 90
1.3.6.3 Revitive™ IX 92
2 Foundation Research 94
2.1 Supervised Exercise Programmes in the UK: Are we meeting NICE recommendations? 94
2.1.1 Background 94
2.1.2 Methods 96
2.1.2.1 Survey Design 96

2.1.2.2 Survey Dissemination 98
2.1.2.3 Data collection and analysis 98
2.1.3 Results 99
2.1.4 Discussion 105
2.2 NMES in healthy subjects 108
2.2.1 Revitive™ IX NMES device use in Healthy subjects 108
2.2.2 Haemodynamic changes in Healthy Subjects with the Revitive™ IX NMES device 109
2.3 Literature review of NMES in PAD 112
2.3.1 Introduction 112
2.3.2 Methods 112
2.3.3 Results 115
2.3.3.1 Haemodynamic changes 115
2.3.3.2 Walking Distances 116
2.3.3.3 Fatigue Index 116
2.3.3.4 Skin Temperature 117
2.3.4 Conclusion 117
2.4 Mechanisms of NMES on lower limb blood flow and muscle 119
3 NMES in PAD Studies 121
3.1 Measures and Outcomes 121
3.1.1 Ankle Brachial Pressure Index (ABPI) 121
3.1.2 Treadmill walking distances 121
3.1.3 Adherence 123
3.1.4 Quality of Life questionnaires 123
3.1.4.1 Euro-QoL-5 Dimension Questionnaire (EQ-5D-5L with VAS) 124
3.1.4.2 RAND Short Form 36 Questionnaire (SF-36) 124
3.1.4.3 Intermittent Claudication Questionnaire (ICQ) 124
3.1.5 Ultrasound Haemodynamic Assessment 126
3.1.5.1 Ultrasound scan validation study 126
3.1.6 Tissue Oxygenation 131
3.1.6.1 Laser Doppler Flowmetry (LDF) 131
3.2 Supervised Exercise Programme 132

3.3 Statistical Analyses 133

3.4 NMES in the Management of Intermittent Claudication 135

3.4.1 Introduction 135

3.4.1.1 Aims 135

3.4.1.2 Null Hypothesis..... 135

3.4.2 Inclusion and Exclusion criteria 136

3.4.3 Ethical Approval and Registration..... 136

3.4.4 Methodology..... 137

3.4.4.1 Study Design..... 137

3.4.4.2 Sample size 137

3.4.4.3 Methods 137

3.4.4.4 Outcome measures 141

3.4.4.5 Data analysis 141

3.4.5 Results 142

3.4.5.1 Patient Flow 142

3.4.5.2 Demographics 144

3.4.5.3 Walking distances 146

3.4.5.4 Quality of Life Questionnaires..... 149

3.4.5.5 Haemodynamic measures 154

3.4.5.6 Compliance 161

3.4.6 Discussion and Conclusion 161

3.5 Adjunctive benefit of NMES to Supervised Exercise Programmes in patients with Intermittent Claudication 166

3.5.1 Introduction 166

3.5.2 Aims 166

3.5.3 Study Design 167

3.5.3.1 Sample size 167

3.5.4 Inclusion and Exclusion criteria 168

3.5.4.1 Ethical Approval and Registration 168

3.5.5 Methodology..... 169

3.5.5.1 The Device..... 173

3.5.5.2 Supervised Exercise Programme..... 173

3.5.6 Outcome measures..... 173

3.5.6.1 Data analysis 173

3.5.7 Results 174
3.5.7.1 Patient Flow 174
3.5.7.2 Demographics 176
3.5.7.3 Walking distances 178
3.5.7.4 Quality of Life Questionnaires 185
3.5.7.5 Haemodynamic measures 187
3.5.7.6 Compliance 191
3.5.8 Conclusions 192

4 Muscle Recovery Studies 197

4.1 Introduction 197

4.2 Calf muscle fatigue 199

4.2.1 Lunge fatigue exercise 199
4.2.2 Calf raise exercise 201

4.3 Endpoints and Outcome measures 202

4.3.1.1 Numeric Pain Rating Scale 202
4.3.1.2 Sargent's Jump Test 202
4.3.1.3 Video assisted Jump Test 203

4.4 NMES use in calf muscle recovery after high intensity exercise ..205

4.4.1 Introduction 205
4.4.2 Aim and hypothesis 206
4.4.3 Methods 206
4.4.3.1 Study Design 206
4.4.3.2 Sample size 206
4.4.3.3 Inclusion and Exclusion criteria 207
4.4.3.4 Ethical Approval 207
4.4.3.5 Outcome measures 207
4.4.3.6 Methodology 208
4.4.3.7 Data analysis 209
4.4.4 Results 211
4.4.4.1 Demographics 211
4.4.4.2 Sargent's Jump Test 211
4.4.4.3 NRS score 214
4.4.5 Conclusions 218

4.5 NMES in the recovery of short and long term calf muscle fatigue 220

4.5.1 Introduction 220
4.5.2 Methods 220
4.5.2.1 Study Design 220
4.5.2.2 Sample size 220
4.5.2.3 Inclusion and Exclusion criteria 221
4.5.2.4 Ethical Approval 221
4.5.2.5 Outcome measures 221
4.5.2.6 Methodology 222
4.5.2.7 Data analysis 223
4.5.3 Results 225
4.5.3.1 Demographics 225
4.5.3.2 Vertical "My Jump" jump test 226
4.5.3.3 NRS pain score 229
4.5.4 Conclusions 233

5 Summary and Conclusions 237

5.1 Current and Future trials 242

6 References 244

7 Appendices 270

7.1 Patient Information Sheets for NMES studies 270

7.1.1 NMES in Patients with IC Patient Information Sheet 270
7.1.2 Adjuvant benefit of NMES to SEP in the management of IC clinical trial .. 275
7.1.3 NMES in muscle recovery following high intensity exercise PIS 281
7.1.4 NMES in the recovery of short and long term calf muscle fatigue PIS..... 285

7.2 Consent forms for NMES studies 288

7.2.1 NMES in IC study 288
7.2.2 Adjuvant benefit of NMES to SEPs in patients with IC 289
7.2.3 NMES in muscle recovery following high intensity exercise PIS 290
7.2.4 NMES in recovery of short and long term calf muscle fatigue 291

7.3 Data tables for studies 292

7.3.1 Summary of studies for literature review NMES in the management of IC. 292
7.3.2 SF-36 score for Group A in the Adjuvant benefit of NMES to SEPs in IC study 295
7.3.3 SF-36 score for Group B in the Adjuvant benefit of NMES to SEPs in IC study 296
7.3.4 Raw data: NMES in muscle recovery following high intensity exercise study 298
7.3.5 Raw data: NMES in muscle recovery following high intensity exercise study 299
7.3.6 Raw data: NMES in muscle recovery following high intensity exercise 300
7.3.7 Raw data: NMES in muscle recovery following high intensity exercise study 301
7.3.8 Raw data for NMES in recovery of short and long term calf muscle fatigue 302
7.4 Questionnaires 304
7.4.1 Intermittent Claudication Questionnaire (ICQ)..... 304
7.4.2 Euro-QoL 5 Dimension 5 Level (EQ5D)..... 305
7.4.3 RAND Short Form Survey– 36 306
7.5 Outcomes of a supervised exercise programme for patients with IC poster 312
7.6 Academic achievements.....313
7.6.1 Journal Publications..... 313

List of Tables

Table 1: Differential diagnosis of PAD 46

Table 2: Fontaine Classification of PAD 51

Table 3: Rutherford classification for Acute Limb Ischaemia (ALI) 51

Table 4: Rutherford classification for Chronic Limb Ischaemia 52

Table 5: Availability of supervised exercise programs in selected European countries and healthcare expenditure per country 106

Table 6: Inclusion and Exclusion criteria 136

Table 7: Demographics of patients included in the NMES in the management of IC clinical trial 145

Table 8: Walking distances in patients at baseline and 6 weeks follow up 146

Table 9: Disease specific and generic quality of life questionnaire scores and EQ VAS health score from week 0 to week 6 following NMES intervention 150

Table 10: Changes in the RAND SF-36 scores by domain from week 0 to week 6 following NMES intervention 152

Table 11: ANOVA analysis of USS parameters (Diameter, Blood Flow, TAMV) 158

Table 12: Change in temperature and fluximetry by site from week 0 to week 6 after NMES intervention 160

Table 13: Change in temperature and blood flux according to site comparing measures with Device ON and Device OFF 161

Table 14: Inclusion and Exclusion criteria 168

Table 15: Demographics of patients included in the Adjuvant Benefit of NMES to SEP in the management of IC clinical trial 177

Table 16: Intra-group median change in ICD (m) and MCD (m) from week 0 to week 6 in Group A: SEP only and Group B: NMES & SEP 179
Table 17: Sensitivity analysis assuming no change in walking distance parameters at follow-up (Group A: n=21, Group B: n=19) 181
Table 18: Sensitivity analysis assuming a 10% increase in walking distance parameters at follow-up (Group A: n=21, Group B: n=19)..... 182
Table 19: Sensitivity analysis assuming a 10% decrease in walking distance parameters at follow-up (Group A: n=21, Group B: n=19)..... 183
Table 20: Change in ICD and MCD of week 6 Group A (SEP only) vs Group B (NMES & SEP) 184
Table 21: ICQ scores in Group A (n=20) and Group B (n=16) from week 0 to week 6..... 185
Table 22: EQ-5D scores in Group A (n=20) and Group B (n=16) from week 0 to week 6.. 186
Table 23: Intra-group and inter group analysis of change in USS parameters (Diameter, Blood Volume Flow, TAMV) from week 0 to week 6 (No device. At rest) 188
Table 24: ANOVA analysis of USS parameters (Diameter, Blood Flow, TAMV) of the Superficial Femoral artery according to device status in Group B at week 0 and week 6.... 188
Table 25: Group A Change in LDF parameters from week 0 to week 6 (Rest only)..... 189
Table 26: Group B Change in LDF parameters from week 0 to week 6 a. at rest and b. Device ON..... 190
Table 27: Group B % change in LDF parameters over 6 weeks according to Device off (rest) and Device ON period..... 191
Table 28: Demographic criteria of trial participants (n=20) 211
Table 29: Demographic data of NMES in short and long term muscle recovery 226

List of Figures

Figure 1: Schematic process of atherosclerotic plaque formation..... 35

Figure 2: Schematic process of developing atherosclerotic plaque, rupture and thrombosis . 36

Figure 3: Measurement of ankle systolic and arm systolic pressures to calculate ABPI..... 49

Figure 4: Structure of skeletal muscle..... 65

Figure 5: Structure of muscle fibre and its supporting structures to produce muscle contraction..... 69

Figure 6: Role of regulatory proteins for the interaction of myosin and actin for muscle contraction..... 70

Figure 7: Dysfunctional mitochondrial processing increasing ROS, causing further damage 76

Figure 8: Veinoplus® neuro-stimulation device 88

Figure 9: Arterial inflow in the stimulated and control limbs using Veinoplus device..... 89

Figure 10: Geko™ neuro-stimulation device..... 90

Figure 11: Revitive™ IX NMES device with footplates and optional IsoRocker® 92

Figure 12: Skip logic questions for national SEP access audit 97

Figure 13: Respondents according to belief in the benefit of SEPs (n=118)..... 100

Figure 14: Responses to 'Does your hospital or trust offer SEPs?'..... 100

Figure 15: Percentage of patients not adherent to the full SEP..... 102

Figure 16: Reasons for non-adherence to SEPs..... 103

Figure 17: Reasons for no availability of SEP 104

Figure 20: Change in blood flow (cm/sec) and time averaged mean velocity (cm/sec) in the superficial femoral vein and artery at baseline, 15 minutes with NMES stimulation and immediately post stimulation. 111

Figure 21: PRISMA diagram of literature search showing process of study inclusion and exclusion..... 114
Figure 22: Bland-Altman analysis of the intra-rater reliability of ultrasound haemodynamic measures of the Femoral artery 128
Figure 23: Bland-Altman analysis of Inter-rater reliability of Ultrasound haemodynamic measures (KW-AB) 129
Figure 24: Protocol flowchart of NMES in the management of IC study 140
Figure 25: Patient Flow for NMES in the management of IC study 143
Figure 26: Absolute changes in A. ICD (m) and B. MCD (m) in all patients from week 0 to week 6 147
Figure 27: Change in A. ICD (m) and B. MCD (m) from week 0 to week 6 of NMES intervention (Tukey plot) 148
Figure 28: Absolute change in ICQ scores from week 0 to week 6 after NMES intervention 150
Figure 29: Box and whiskers plot of EQ-5D-5L score from week 0 to week 6 (Tukey plot) 151
Figure 30: Change in EQ-Visual Analogue Score for pain from week 0 to week 6 after NMES intervention (Tukey plot)..... 151
Figure 31: RAND SF-36 domain changes from week 0 to week 6 after NMES intervention 153
Figure 32: Change in USS arterial diameter (cm) at week 0 and week 6 according to device status..... 156
Figure 33: : Change in USS arterial Volume Flow (cc/min) at week 0 and week 6 according to device status..... 156

Figure 34: Figure: Change in USS arterial TAMV (cm/s) at week 0 and week 6 according to device status..... 157
Figure 35: Study protocol for Adjuvant Benefit of NMES to SEP in the management of IC trial..... 172
Figure 36: CONSORT diagram of patient flow through the Randomised Controlled Trial of Adjuvant Benefit of NMES to SEP in patients with IC..... 175
Figure 37: Absolute changes in ICD (m) and MCD (m) over time by per protocol analysis 180
Figure 38: Change in **A.** MCD (m) and **B.** ICD (m) at week 6 in Group A (n=20) and Group B (n=17)..... 184
Figure 39: Change in SF-36 domain from week 0 to week 6 in Group A and Group B 186
Figure 40: Lower limb lunge exercise for calf muscle fatigue..... 200
Figure 41: Sargent's vertical jump test..... 203
Figure 42: Trial flowchart: NMES use in calf muscle recovery following high intensity training..... 210
Figure 43: Jump height (cm) levels in the passive recovery (A) and active recovery (B) groups over time..... 213
Figure 44: Sargent's jump height scores at various trial timepoints comparing passive (REST) and active (NMES) recovery..... 214
Figure 45: NRS pain scores in the passive (REST) group (A) and active (NMES) group (B) over time..... 216
Figure 46: NRS pain score at various trial timepoints comparing passive (REST) to active (NMES) recovery..... 217
Figure 47: Trial flowchart: NMES use in short and long term calf muscle recovery..... 224
Figure 48: CONSORT diagram mapping the patient flow through this randomised controlled trial..... 225

Figure 49: Change in jump height (cm) in A. Control (REST) and B. Active (NMES) groups over time..... 228
Figure 50: Change in Jump height (cm) between control (REST) and active (NMES) groups over time..... 229
Figure 51: Change in NRS Pain scores in A. Control (Rest) and B. Active (NMES) groups over time..... 231
Figure 52: Change in NRS pain scores in both control (REST) and active (NMES) groups over time..... 232

1. Background

1.1 Peripheral Arterial Disease

1.1.1 Definition of PAD and its clinical manifestations

Peripheral Arterial Disease (PAD) can be defined as a risk factor related disorder causing an impaired blood flow in the arterial circulation, excluding the heart and main aorta. Although this can include carotid, cerebrovascular, renal, upper limb and mesenteric arterial circulation, for the purposes of this research thesis, the definition will apply from the aorto-iliac bifurcation to the crural arteries supplying blood flow to the lower limbs and feet.

PAD is largely a result of an atherosclerotic disease process that can narrow or occlude one or more of the peripheral arteries causing deterioration in function and lifestyle with a potential threat to limb and life (Criqui and Aboyans 2015). Atherosclerosis may occur as an asymptomatic process or manifest clinically with Intermittent Claudication (IC) or, in more severe disease as Critical Limb Ischaemia (CLI), under the umbrella term of PAD. From a haemodynamic perspective, PAD can be defined as having an ankle brachial pressure index, a ratio of the blood pressure at the ankles compared to the right upper limb, below 0.9 (Norgren, Hiatt et al. 2007).

Intermittent Claudication describes the symptom of pain in the lower limbs on exertion, which is reversible following a short period of rest. At rest or low activity, blood supply is satisfactory to meet the metabolic needs of muscles and tissues of the lower limb. However, this balance tips with ongoing exercise, where increasing metabolic demand cannot be met appropriately with the blood flow supplied.

In more severe PAD, when the metabolic demands of the lower limb tissues cannot be met at rest, patients may present with Critical Limb Ischaemia. This refers to a severe level of insufficiency in arterial circulation to an extent inadequate to support the microcirculation or nutrient supply required for tissue viability at rest. Definitions of CLI were more specific with the emergence of haemodynamic assessment in the context of clinical signs and symptoms. The European Society of Vascular Surgeons (ESVS) recommended definition of CLI is the presence of ischaemic rest or night pain requiring adequate analgesia for at least 2 weeks duration, with or without tissue loss, and with an ankle systolic pressure less than 50 mmHg or a toe systolic pressure below 30 mmHG (Becker, Robert-Ebadi et al. 2011). This is a severe form of PAD.

1.1.2 Epidemiology and Economic Impact

Approximately 200 million people worldwide suffer with PAD, ranging from those without symptoms to those with severe manifestations of disease (Fowkes, Rudan et al. 2013). A large retrospective US population study suggests the mean annual prevalence of PAD to be 10.69% and the mean annual incidence to be 2.35% (Nehler, Duval et al. 2014). There are, however, variations in published prevalence rates for PAD, mainly due to the underlying definitions and stratifications used by each population-based study. The Transatlantic Intersociety Consensus for the management of PAD (TASCII) reports prevalence rate range, from various studies, at 3-10% rising to between 15-20% in those aged over 70 years (Norgren, Hiatt et al. 2007). Prevalence of PAD is also variable according to demographic characteristics and risk factors, as will be explored further in this chapter (Selvin and Erlinger 2004).

Although it may seem logical for a disease to progress stepwise through the severity of symptoms according to the degree of underlying disease, this is not the case in PAD. It is not necessary that a patient with CLI would have IC symptoms previously, as they may not undertake sufficient activity to illicit claudication pain (Matzke and Lepantalo 2001) whilst the disease is progressive.

1.1.2.1 Asymptomatic disease

Asymptomatic disease represents a population that may have underlying pathophysiological markers of disease, but not demonstrate any clinical symptoms associated to that disease at a specified time point. Obtaining an accurate figure for the incidence and prevalence of asymptomatic PAD in the population is difficult on account of no specific symptoms being present in this cohort. However, estimations can be made by population-based studies using

non-invasive measures that suggest the presence of an underlying disease process, but yet without its clinical manifestations. Due to its high sensitivity and specificity, the lower limb ankle-brachial pressure index (ABPI) being less than 0.9 is currently considered the most accepted measure of sub-optimal haemodynamic status (Bernstein and Fronek 1982, Criqui, Denenberg et al. 1996). The Edinburgh Artery Study involved a clinical examination of 1592 invited participants, within the 55-74 years age range, from ten general practice patient lists in Edinburgh, Scotland. Nine per cent of these participants were found to have ABPI defined asymptomatic PAD (Fowkes, Housley et al. 1991). The multicentre, prospective PARTNERS (PAD awareness, Risks and Treatment: New Resources for Survival) program in United States of America completed clinical screening of 6417 participants from 350 primary care centres, stratified as either being over 70 years old or between 50-69 years with a history of smoking and/or diabetes. In this cohort, there was a prevalence of 13% identified as having asymptomatic PAD on the basis of an ABPI <0.9 (Hirsch, Criqui et al. 2001).

The development of PAD symptoms is dependent upon the ability to supply the metabolic demand of exercising muscle and tissue; whether any collateral circulation is available and the anatomic site of arterial stenosis or occlusion (Hills, Shalhoub et al. 2009).

1.1.2.2 Intermittent Claudication

Intermittent Claudication, or pain in the lower limbs on exertion that settles with a period of rest, is a manifestation of symptomatic PAD. The absence of this symptom does not negate the underlying presence of PAD, as demonstrated by a significant estimated population prevalence of asymptomatic PAD. Results from the Edinburgh Artery Study suggest a prevalence of IC of 4.5% in the 50-74 years old age group (Fowkes, Housley et al. 1991).

The Rotterdam study, a Netherlands population based study of 7715 subjects over the age of 55 years, reported an overall prevalence of IC in 1.6% (Meijer, Hoes et al. 1998) as compared to a study in Limburg of 3171 participants between 40-74 years old suggesting an overall IC prevalence of 6.6% (Stoffers, Rinkens et al. 1996). The latter study is likely to overestimate the prevalence of disease due to a more inclusive definition of PAD including and ABPI measure <0.95. The extensive Framingham study suggests an all age annual incidence of 7.1 per 1000 in the male category. Although lower in females, at the younger age group, the annual incidence between both sexes is equivalent by 65 years (Kannel and McGee 1985).

Many patients with progressive disease may not exhibit IC on account that this symptom requires the sufferer to have an activity level to provoke it. Therefore, sedentary PAD patients with severe disease may present directly with symptoms of critical limb ischaemia.

1.1.2.3 Critical Limb Ischaemia

Few studies have looked at the prevalence and incidence of this end-stage form of PAD. The Inter-Society Consensus group (TASC) suggests an incidence between 220-1000 new cases per million of population based on previous European and American studies (1995, Norgren, Hiatt et al. 2007). Nehler et al undertook a retrospective cohort analysis of approximately 12 million insured adult patients treated for a PAD or CLI related event between 2003 and 2008. The overall mean annual prevalence of CLI was 1.33% and the mean annual incidence was 0.35%. CLI represented 11.08% of the PAD population on an annual basis (Nehler, Duval et al. 2014).

1.1.2.4 Economic impact of PAD

In 2013, Fowkes et al systematically reviewed and analysed published literature on the prevalence of PAD, defined as patients with an ABPI of less than or equal to 0.90, in order to provide an estimate of global prevalence. Their analyses suggested that 202 million people globally were suffering with PAD in 2010, with 31.3% in high income countries, as defined by the World Bank (Fowkes, Rudan et al. 2013). There has been a 29% increase in PAD prevalence in lower and middle income countries compared to a 13% increase in high income countries between 2000 and 2010 (Fowkes, Aboyans et al. 2017). Further, Hirsch et al analysed Medicare data and claims made in USA in 2001 to establish PAD related healthcare costs. Their study found that the economic burden to the US health service was US$4.37 billion of which 88% was spent on inpatient care alone (Hirsch, Hartman et al. 2008). The costs attributed to PAD related treatment increased with age by 4.5%, 7.5% and 11.8% in age groups of 65-74 years, 75-84 years and over 85 years old respectively (Hirsch, Hartman et al. 2008).

PAD has a significant global health and economic burden. Developing strategies to prevent PAD or identify and manage this in the earliest stages of the disease are necessary to reduce this burden.

1.1.3 Pathophysiology of Peripheral Arterial Disease

The underlying pathophysiology of PAD is a process called atherosclerosis. This is a chronic inflammatory condition, characterized by the formation of fibrous and lipid plaques within the arterial wall eventually causing narrowing or an occlusion resulting in impaired or no blood flow distally. The disease process is instigated and exacerbated by various risk factors including smoking, diabetes, dyslipidaemia, hypertension (Abdulhannan, Russell et al. 2012). These risk factors are explored further in the context of PAD in the next section.

Atherosclerosis involves a complex interplay of these risk factors that systematically allow the formation of sub-intimal plaques through a process of endothelial dysfunction, inflammation, reactive oxidative species injury, proliferation of vascular smooth muscle cells (SMC) and altered matrix metabolism (Faxon, Fuster et al. 2004). This process is summarised in Figure 1.

1.1.3.1 Endothelial dysfunction

The endothelial lining of arteries acts in an active manner to maintain vascular haemostasis in terms of vascular tone, modulation of inflammation, thrombosis and anticoagulation. It is able to do this chemically through the production of mediators including Nitrous Oxide (NO), prostaglandins, endothelin and angiotensin II; a balance of which regulate vasodilation and vasoconstriction (Faxon, Fuster et al. 2004). Of these, the most academically understood mediator is NO, stimulated to be produced by endothelial NO synthase (eNOS), normally causing a significant vasodilatory effect (Rees, Palmer et al. 1989). However, atherosclerosis reduces the production of endothelial NO, leading to an imbalance of vasodilatory mediators, favouring vasoconstriction. Together with an already narrowed vessel, this provides an ideal environment for turbulent blood flow, especially at bifurcating sites within the arterial

circulation causing intimal injury and arterial thrombosis of vulnerable plaques. Moreover, the reduced expression of NO promotes platelet activation, adhesion and aggregation, promoting atherosclerosis and further thrombosis (Loscalzo 2001).

The endothelial lining also produces chemokines, cytokines and transcription factors that assist in flagging sites of vascular injury to leukocytes and assisting their function through chemotaxis, adhesion and diapedesis into the subendothelial layers (Berk, Abe et al. 2001).

1.1.3.2 Arteriosclerosis

Early arteriosclerosis manifests as fatty streaks within the arterial wall. This process is usually triggered by an atherogenic diet, which promotes the expression of adhesion molecules (intracellular adhesion molecules, ICAMs; vascular cell adhesion molecules (VCAMs) from the endothelial cells. ICAM expression also promotes connective tissue proteoglycan production, which bonds with low density lipoproteins, which are modified by an oxidative process and enter the subintimal layer. Turbulent blood flow, mainly at bifurcating areas of the arterial tree, causes endothelial shear stress and further upregulates the expression of the adhesion molecules that act as receptors for leucocytes like monocytes and lymphocyte T cells (Kaperonis, Liapis et al. 2006). Leucocyte adhesion triggers chemoattractant molecules, like monocyte chemoattractant molecule-1 (MCP-1), to aid passage of these cells into the subintimal area where they convert to lipid engorging macrophages through the action of macrophage-colony stimulating factor (M-CSF). The engorged macrophages are known as foam cells, which collect under the endothelial layer forming the classic fatty streak (Figure 2A). Ongoing inflammatory cycles ensure proliferation of the fatty streaks into fibro lipid plaques, made up of necrotic foam cells (lipid core), proliferative vascular smooth muscle cells and fibroblasts forming a fibrous cap on repetitive remodelling (Figure 2B) (Libby, Ridker et al. 2002, Faxon, Fuster et al. 2004).

Although this lesion initially grows towards the adventitial layer, upon further growth, it threatens the patency of the vessel lumen. This can progress to form a vulnerable plaque, which can undergo complications based on further stressors applied to it. Fibrous cap rupture or bleeding into the plaque from plaque infiltrating small blood vessels from the medial layer can cause platelet activation, aggregation and thrombosis, which can lead to further lumen stenosis or complete occlusion (Lusis 2000) and therefore clinical symptomatic manifestations of arterial disease (Figure 2C). Further complications can cause detachment of a thrombotic segment which can lodge distally in the arterial tree causing acute occlusion and therefore acute limb ischaemia (ALI).

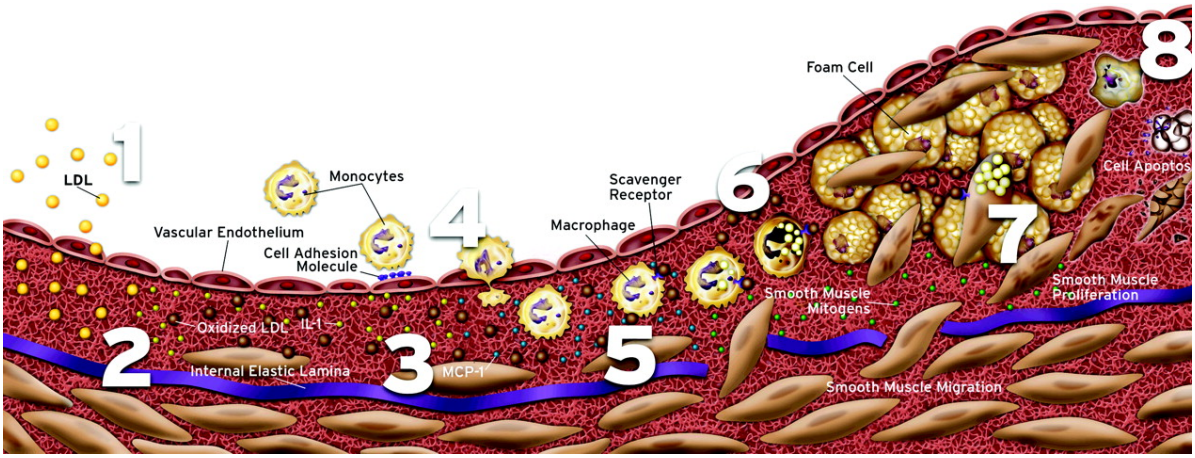


Figure 1: Schematic process of atherosclerotic plaque formation

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Low Density Lipoprotein (LDL) enters the subendothelial layer (1) where it is oxidised by the macrophages and smooth muscle cells (2). The dysfunctional endothelium releases cytokines attracting further monocytes into the subendothelial layer (3 and 4). These engorge on the lipids to form foam cells, which together with smooth muscle cell proliferation, cause plaque growth to progress (5-8).

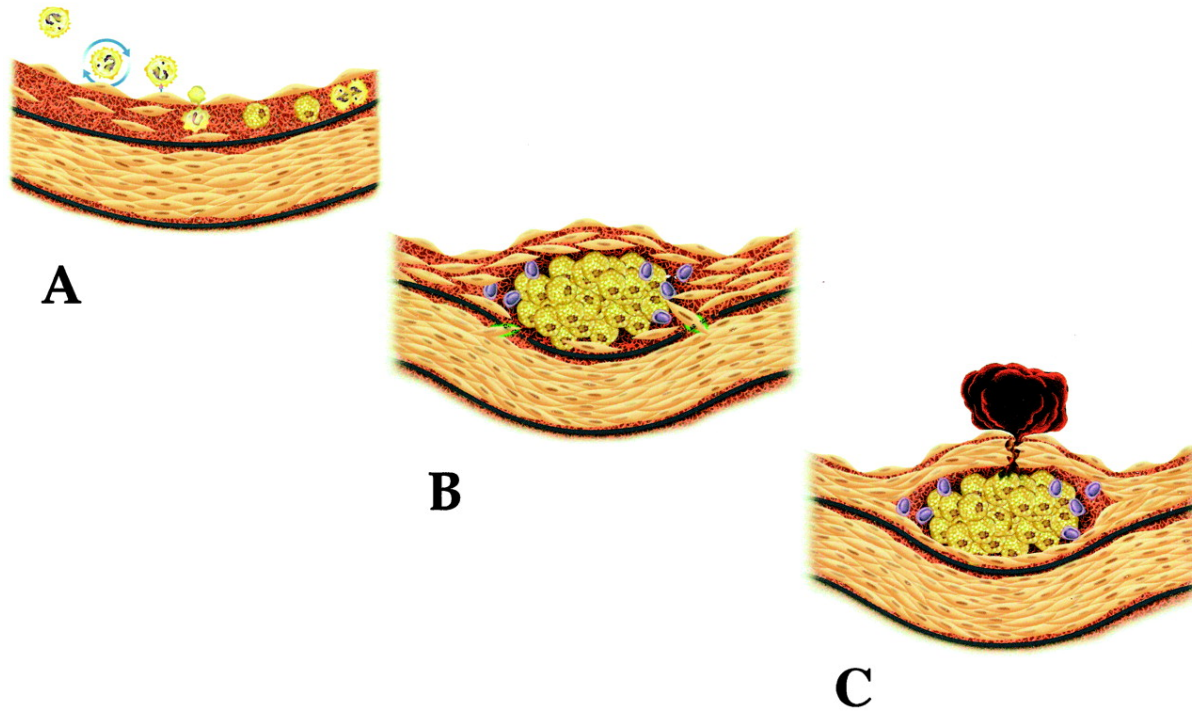


Figure 2: Schematic process of developing atherosclerotic plaque, rupture and thrombosis

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1.1.4 Risk Factors for PAD

Risk factors for developing PAD are similar to those for developing atherosclerosis and other atherosclerotic diseases. It is estimated that patients with PAD have a 3 times increased risk of developing and dying of other major cardiovascular diseases including coronary and cerebrovascular disease compared to the population not suffering from PAD (Kannel and McGee 1985, Fowkes, Rudan et al. 2013).

1.1.4.1 Smoking

Active smoking is the most significant risk factor for PAD, more so than for developing coronary arterial disease (Agrawal and Eberhardt 2015). An association between smoking and Intermittent Claudication compared to non-smokers, has been known about since the early part of the 20th century, as described by Wilhelm Erb in 1911(Erb 1911). A US based study assessing PAD prevalence and risk factors by analysing the results from the National Health and Nutrition Examination Survey (NHANES) from 1999 to 2000, found current smoking to have a strong association to symptomatic PAD (OR 4.46, 95% CI 2.25 to 8.84) in those aged 40 years and older (n=2174) (Selvin and Erlinger 2004). Willigendael et al carried out a systematic review of studies looking at smoking association with PAD, finding a mean odds ratio from ten included studies was 2.3 (range 1.7-4.6), where all studies showed a significant link associating this risk factor to developing PAD (Willigendael, Teijink et al. 2004). Compared to non-smokers, smokers have up to 5.6 times increased risk of PAD development (Fowkes, Housley et al.), with IC being 8-10 times more common as a symptom. The Framingham study attributed 78% of patients suffering IC to being current smokers and suggests the risk of developing PAD associated to smoking is double that of developing coronary artery disease (Kannel and McGee 1985). The risk of developing PAD

extends to passive smoking in a dose related response as found in a study on Chinese women by He et al (He, Lam et al. 2008).

Underlying mechanism suggested for increased risk of cardiovascular disease include the effects of nicotine and carbon monoxide in smoke causing hypertension, tachycardia, vasoconstriction and further constituents of smoke causing endothelial cell damage, affecting its integrity as a barrier, promoting the atherosclerosis disease process (Krupski 1991). Further, smoking is considered to increase inflammatory markers, especially CRP, which has been implicated as one of the main biomarkers in the pathophysiology of atherosclerosis development (Libby, Ridker et al. 2002, Libby and Ridker 2004). A 5-year period of smoking cessation is suggested to bring inflammatory markers such as CRP to baseline levels and this confers with an improved risk of cardiovascular events in this time period (Bakhru and Erlinger 2005).

1.1.4.2 Ethnicity

The NHANES study suggested that the African-American ethnic group was 7.9% more prevalent in suffering PAD; approximately 3 fold higher than in the Caucasian ethnic group, with a significant odds ratio (OR2.39, 95% CI 1.11 to 5.12) remaining even after adjusting for all other risk factors (Selvin and Erlinger 2004, Ostchega, Paulose-Ram et al. 2007). The underlying reason for this is unexplained, but clearly highlights the need for astute vigilance in the ethnic minority groups for the development and therefore timely management of PAD.

1.1.4.3 Diabetes

Diabetes has a strong association with the development of PAD (Selvin and Erlinger 2004). The presence of diabetes increases the risk of developing PAD and seems to have more of a

progressive course in terms of disease and outcome than in non-diabetics (Norgren, Hiatt et al. 2007). A meta-analysis by Selvin et al in 2004 suggested that for each 1% increase in glycosylated haemoglobin, there is a pooled relative risk of 1.26 of developing PAD (Selvin, Marinopoulos et al. 2004). Ramos et al from Spain showed an odds ratio of 1.59 for development of PAD in the 35-79 years age group in a population-based study of 6262 participants (Ramos, Quesada et al. 2009). Insulin resistance is thought to be a significant factor in developing PAD, even amongst non-diabetics, by up to 50% (Norgren, Hiatt et al. 2007).

The nature of arterial disease in diabetics is more likely to be distal and result in higher rates of amputation than non-diabetic counterparts. However, with a multi-disciplinary team approach to the management of diabetic foot complications of PAD, improvements in amputation rates and morbidity have been reported (Moxey, Gogalniceanu et al. 2011).

1.1.4.4 Hypertension

Hypertension is a known risk factor for the development of atherosclerosis and therefore contributing to risk of suffering from cardiovascular disease and PAD (Selvin and Erlinger 2004). A cohort study reviewing the electronic health records of 4.2 million patients showed that a 20 mmHG increase in systolic blood pressure than usual blood pressure correlated with a 63% higher risk of developing PAD. Also, a 10 mmHg increase in usual diastolic blood pressure was associated with a 35% increased risk of PAD prevalence (Emdin, Anderson et al. 2015). Men with hypertension have a 2-fold increased risk, and women a 4-fold increased risk of suffering from IC (Kannel and McGee 1985).

1.1.4.5 Hypercholesterolaemia and Hyperlipidaemia

Hypercholesterolaemia is associated with the risk of developing PAD with an odds ratio of 1.68 (95% CI 1.09 to 2.57) (Selvin and Erlinger 2004). Lipids are an integral part of the process of developing atherosclerosis, where by migration of LDL into the arterial wall follows linkage to proteoglycans. It is hypothesised that modified lipoproteins undergo oxidative alteration, inducing the production of chemokines, cytokines and adhesion molecules promoting an inflammatory process. The modified LDL is ultimately sequestered by monocyte and macrophage cells, which become lipid laden foam cells, forming the basis of the lipid core of an atherosclerotic plaque (Faxon, Fuster et al. 2004). HDL is considered to act as an antioxidant and prevents LDL uptake thereby conforming atheroprotective tendencies (Libby, Ridker et al. 2002).

The Framingham study suggests that HDL as a ratio of total cholesterol is strongly linked to the prevalence of PAD and that a fasting serum cholesterol level over 7 mmol/L is associated with a 2 fold increase in suffering from IC (Murabito, D'Agostino et al. 1997, Norgren, Hiatt et al. 2007). Statin treatment, which reduces LDL cholesterol, is also linked to the reduction of developing atherosclerosis by reducing vascular inflammation (Bustos, Hernandez-Presa et al. 1998).

1.1.4.6 Inflammatory markers and cytokines

Inflammatory processes have been implicated in the development of atherosclerosis, the underlying pathology to developing cardiovascular disease and PAD. Large population based studies have shown that measuring certain biomarkers in healthy individuals, may provide accurate risk stratification for developing future incidents of vascular aetiology (Libby, Ridker et al. 2002). These include the acute phase proteins CRP and Fibrinogen, increased

levels of which have been associated with PAD prevalence (Libby and Ridker 2004, Selvin and Erlinger 2004). Ridiker et al conducted a prospective study of 28, 263 post-menopausal women with 3 year follow up of, measuring baseline cytokine and inflammatory markers with the ability to predict cardiovascular events. High-sensitivity CRP (hsCRP) was strongly associated to increased risk of cardiovascular events with a relative risk of 4.4 seen in those with baseline levels in the highest quartile compared to the lowest quartile. Serum Amyloid A was also a significant predictive marker (RR 3.0) as was sICAM (RR 2.6) and IL-6 (RR 2.2) (Ridker, Hennekens et al. 2000).

1.1.4.7 Genetic predisposition

Genetic factors are significant in the development of atherosclerosis. Studies have suggested that a family history of Coronary Heart Disease (CHD) is an independent factor to developing CHD compared to all other risk factors (Goldbourt and Neufeld 1986). The risk associated with genetic factors is approximately 50% in some studies (Faxon, Fuster et al. 2004). The development of proteomic and genomic profiling technologies, as well as metabonomic studies will assist to profile genes, and the proteins they produce, that are mainly implicated in the development vascular disease.

Risk factors for PAD are multifactorial including the traditional cardiovascular risk factors of hypertension, hypercholesterolaemia, smoking and diabetes. Further population based studies are revealing more risk factors, identification and measures of which could help predict and prognosticate the prevalence of PAD. These include genetic and inflammatory markers. Within the latter, CRP seems to be a target inflammatory marker for further research (Libby and Ridker 2004).

1.1.5 Guidelines

A number of national and international guidelines have been produced to provide best evidence based recommendations on diagnosis and management of PAD. One of the earliest documents guiding diagnosis and management of PAD was formed by consensus and collaboration of 16 international vascular surgery societies and organisations under the umbrella title of the Trans-Atlantic Inter-Society working group (Norgren, Hiatt et al. 2007). Recommendations are graded according to the US Agency for Healthcare Research and Quality ratings based on the level of available evidence. This document has undergone a number of revisions, initially published in 2000 (Dormandy and Rutherford 2000), with an updated TASC II document published in 2007 (Norgren, Hiatt et al. 2007) and a supplement to this published by the TASC steering committee in 2015 to reflect the advances made in endovascular management strategies for revascularisation (Jaff, White et al. 2015).

This consensus recommendation report has been useful in establishing national guidelines to support local healthcare providers and patients in the context of their healthcare system. In the US, the American Heart Association and American College of Cardiology issue guidelines on the management of lower limb peripheral arterial disease, last updated in 2017 (Hirsch, Haskal et al. 2006, Writing Committee, Gerhard-Herman et al. 2017). European guidelines are also available from the European Society of Cardiology and European Society of Vascular Surgery, last updated in 2017 (Aboyans, Ricco et al. 2018).

In the UK, practice guidelines for the diagnosis and management of lower limb arterial disease is provided by the National Institute for Health and Care Excellence (NICE) (NICE147 2012). This guidance was produced in 2012, with an update of 2 recommendations

provided in 2018 reflecting new evidence based practice of diagnosing PAD in people with diabetes.

A quality standard was subsequently issued in 2014 highlighting the expectations of providers to ensure quality improvements with best evidence care in the management of PAD (QS52 January 2014). This quality standard was issued to prioritise the prevention of premature deaths related to PAD and improve quality of life.

1.1.6 Diagnosis

1.1.6.1 Clinical presentation and symptoms

Patients can present with varying types of symptoms that need further clarification and assessment for the diagnosis of PAD. Essentially, PAD symptoms and signs present due to impaired blood flow, unable to provide for the metabolic demands of muscles and tissues distal to the site of impairment. PAD symptoms may manifest as IC, or reversible pain in the lower limbs on exertion, relieved by rest; or rest pain, where discomfort due to ischaemia is present without exertion; or night pain, which is exacerbated due to the gravitational position of the limb and the increased metabolic demands of a warm limb under the bed covers (Abdulhannan, Russell et al. 2012). With the latter, pain relief typically occurs on getting up and walking, especially on a cooler floor surface, or alternatively not being able to lie flat at all due to the excruciating symptoms. This usually implies chronic CLI.

Acute limb ischaemia (ALI) can present with sudden symptoms, of less than 2 weeks duration, of pain, paraesthesia and loss of function. Signs of ALI include a cold, pale and pulseless limb or foot, depending on the arterial site of occlusion (Abdulhannan, Russell et al. 2012).

An assessment of associated risk factors helps in guiding the diagnosis, especially identifying co-morbid disease including hypertension, diabetes, previous stroke or TIA; and personal habits including diet, smoking and level of activity (Criqui and Aboyans 2015).

A full cardiovascular examination should be undertaken to include the upper limbs, neck, chest, abdomen, lower limbs and feet. Inspection can detect changes in colour, evidence of hair loss, shiny skin and tissue loss or ulceration. Palpation can assess temperature and all

pulses including radial, brachial, axillary, carotid, femoral, popliteal, posterior tibial and dorsalis pedis. Palpation may also be used to examine for common arterial aneurysm sites including abdominal aortic or popliteal artery. Auscultation can be used to listen for bruits in the carotid and femoral vessels, and to listen for cardiac murmurs. Buerger's test is a more focal test to assess arterial insufficiency by raising the horizontal lower limb to a 45° angle observant of skin pallor and lowering the limb to assess for erythematous changes suggesting arterial circulation compromise (Abdulhannan, Russell et al. 2012).

1.1.6.2 Differential Diagnoses

Differential diagnoses to be aware of include neurogenic claudication, popliteal entrapment syndrome, diabetic neuropathy and chronic compartment syndromes (Norgren, Hiatt et al. 2007, Abdulhannan, Russell et al. 2012). These can present in similar ways to intermittent claudication, but can usually be distinguished by careful history taking and examination. Differential diagnoses can include non-vascular as well as vascular causes (Table 1).

Table 1: Differential diagnosis of PAD

Nonvascular Causes of PAD-like Symptoms	Vascular Causes
Orthopedic causes (joint disease, Baker cyst, bursitis)	Peripheral atherosclerosis
Compartment syndrome (from fracture or crush injury)	Thromboembolism (cardiogenic, related to aortoiliac aneurysm, or in situ thrombosis)
Peripheral neuropathy	Connective tissue disorders (Marfan syndrome or Ehlers-Danlos [type IV] syndrome)
Venous claudication (after iliofemoral DVT, such as in May-Thurner syndrome)	Fibromuscular dysplasia
Spinal stenosis or cauda equina pseudoclaudication	Buerger disease
	Heritable thrombophilias (Factor V Leiden, prothrombin gene mutation, antithrombin III deficiency, and protein C and S deficiency)
	Vasculitides (giant cell arteritis, polyarteritis nodosa, systemic lupus erythematosus)
	Entrapment syndromes (popliteal)

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1.1.6.3 Ankle Brachial Pressure Index

Ankle Brachial Pressure Index, or the ratio of the systolic blood pressure at the ankle compared to the arm, is accepted as a simple, baseline, non-invasive test for diagnosing PAD.

Blood pressure is usually higher in peripheral arteries compared to central arteries due to a phenomenon known as pulse wave propagation, driven by a combination of stroke volume ejection, branching changes in the arterial tree, arterial elasticity and arteriolar resistance (Vosse and Stergiopulos 2011). Therefore, in healthy subjects, the systolic blood pressure at the ankle is slightly higher than in the arm. Literature suggests this increase can sometimes be as much as 20mmHG in the femoral vessels and up to 55 mmHG in the dorsalis pedis when compared to the systolic blood pressure at the axillary artery (Nielsen, Barras et al. 1974). Atherosclerotic plaques cause obstruction to the normal flow within the artery, causing a high pressure gradient across the lesion resulting in low pressure in the post stenotic segment.

Normal ABPI measures in healthy subjects are stated as a range from 0.9 to 1.03, where 0.7-0.9 signify mild PAD, 0.4-0.7 signify moderate disease and less than 0.4 signify severe disease. An ABPI ratio above 1.3 suggests an incompressible vessel likely due to calcification (Association 2003).

ABPI as a technique is reported to have 97% sensitivity and 100% specificity when comparing pressures in patients with angiographic evidence of atheroma in the distal arterial tree with healthy subjects used as controls (Yao, Hobbs et al. 1969, Bernstein and Fronek 1982). This was one of the earliest studies demonstrating the use of doppler ultrasound technology in establishing the ABPI. However, the reliability of ABPI in its accuracy at identifying either asymptomatic or mild forms of PAD does appear to be more moderate than

the previous study. Allen et al studied the utility of ABPI measures in non-diabetic patients with PAD, comparing to colour duplex ultrasonography as a gold standard. Using an ABPI threshold of 0.8, this had an 83% accuracy at detecting PAD patients. Post exercise measures of ABPI in the same patients had an 85% accuracy compared to the colour duplex ultrasound. Accuracy decreased further to 76% in detecting arterial disease in patients with ABPIs more than or equal to 0.90 and interestingly, there was a 100% accuracy at detecting PAD in those with ABPI less than 0.6 (Allen, Oates et al. 1996). This suggests that ABPI is reliable in detecting severe PAD but less reliable in mild or asymptomatic disease. Moreover, ABPI is unreliable in evaluating progressive atherosclerotic disease (41% sensitivity, 84% specificity, 68% overall accuracy), compared to angiography and ultrasound imaging techniques as gold standard (McLafferty, Moneta et al. 1997).

As a baseline screening test, ABPI remains an appropriate non-invasive tool with good overall sensitivity and specificity for detecting PAD. Indeed, the cut-off of 0.90 and below is used within the definition of PAD diagnosis in all major guidelines. Change in ABPI post exercise can also be used in some patients to identify PAD, but this may be limited by ability to exercise due to co-morbid disease (Norgren, Hiatt et al. 2007, NICE147 2012). ABPI has been proven to accurately risk stratify patients with likelihood of having a cardiovascular event or mortality in a ten year period and adds significantly to this risk estimation in those with diabetes or chronic kidney disease (Aboyans, Ricco et al. 2018). However, it is appreciated that good training is required to accurately measure the ABPI.

The ABPI is measured with the patient in the supine position who has been at rest for at least 10 minutes. Systolic blood pressure is then measured with the cuff around the arm using the doppler ultrasound to detect the systolic signal. The same measure is then taken from the

posterior tibial and dorsalis pedis arteries with the pressure cuff around the ankle. The ABPI is measured as the ratio between the highest systolic pressure measurement between the posterior tibial or dorsalis pedis artery and highest systolic pressure of the arms.

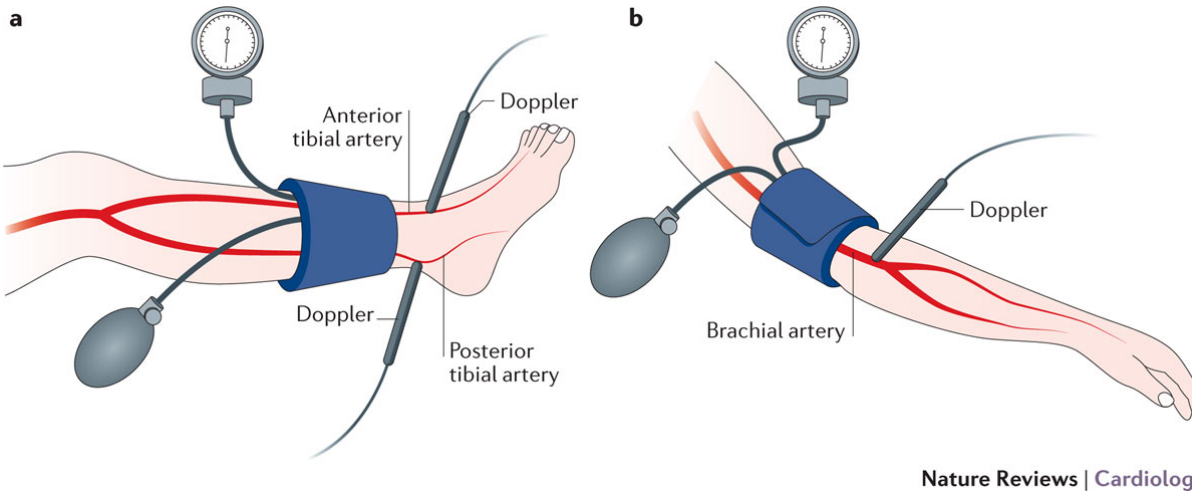


Figure 3: Measurement of ankle systolic and arm systolic pressures to calculate ABPI

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1.1.6.4 Duplex Ultrasound

Duplex ultrasonography (DU) should be undertaken in all PAD patients in whom revascularisation is being considered. This non-invasive imaging modality is a useful first line assessment, being able to accurately detect, localise and quantify atherosclerotic lesions in the lower limb arterial tree. The various doppler modalities allow blood flow velocity assessment which provides further detail on the effect of the lesion detected. For lesions causing over 50% stenosis, colour DU has over 90% sensitivity and specificity (Mathew and Kramer 2018). However, great skill is required to make an accurate assessment and the

reliability of this modality remains highly operator dependent. (NICE147 2012, Aboyans, Ricco et al. 2018).

1.1.6.5 Computed Tomography/Magnetic Resonance Angiography

Computed Tomography Angiography (CTA) or Magnetic Resonance Angiography (MRA) are next line investigations after DU and especially useful for supra-inguinal disease where DU can be functionally limited due to body habitus. Either of these modalities, and occasionally both, are required for planning endovascular or surgical revascularisation treatments.

CTA is useful for characterising arterial lesions and identifying narrowed vessels. However, the limitations of CTA include artefacts that develop from metal prostheses and with heavily calcified vessels, which can be common especially in the smaller vessels in PAD (Tanaka, Yoshioka et al. 2018). The contrast used can also be nephrotoxic and caution needs to be taken in patients with acute or chronic kidney disease.

MRA is considered as having better sensitivity and specificity for detecting atherosclerotic lesions causing stenosis of more than 50% than the above modalities. However, there are limitations to this technique, including toxicity from the gadolinium based contrast causing nephrogenic systemic fibrosis in patients with chronic kidney disease (CKD). In addition, there can be movement artefact, especially if non-contrast MRA techniques are used, which have a longer acquisition time (Mathew and Kramer 2018). Additionally, MRA can be contra-indicated in patients with pacemakers.

1.1.6.6 Classification of PAD

Classification for PAD was initially developed according to symptoms by Fontaine in 1954 (Norgren, Hiatt et al. 2007) (Fontaine, Kim et al. 1954)(Table 2). In 1997, these were further developed upon with the benefit of haemodynamic criteria by Rutherford et al (Rutherford RB 1997). The latter stratification varies according to presentation by acute limb ischaemia or chronic limb ischaemia, which is more in keeping with the original Fontaine classification (Table 3, Table 4).

Table 2: Fontaine Classification of PAD

Stage	Symptom
I	Asymptomatic
IIa	Mild Claudication
Iib	Moderate to severe claudication
III	Ischaemic rest pain
IV	Ulceration or gangrene

Table 3: Rutherford classification for Acute Limb Ischaemia (ALI)

		Findings		*Doppler signals*	
Category	*Description/prognosis*	*Sensory loss*	*Muscle weakness*	*Arterial*	*Venous*
I. Viable	Not immediately threatened	None	None	Audible	Audible
II. Threatened					
a. Marginally	Salvageable if promptly treated	Minimal (toes) or none	None	Inaudible	Audible
b. Immediately	Salvageable with immediate revascularization	More than toes, associated with rest pain	Mild, moderate	Inaudible	Audible
III. Irreversible	Major tissue loss or permanent nerve damage inevitables	Profound, anesthetic	Profound, paralysis (rigor)	Inaudible	Inaudible

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Table 4: Rutherford classification for Chronic Limb Ischaemia

Grade	*Category*	*Clinical description*	*Objective criteria*
0	0	Asymptomatic—no hemodynamically significant occlusive disease	Normal treadmill or reactive hyperemia test
	1	Mild claudication	Completes treadmill exercise†; AP after exercise >50 mm Hg but at least 20 mm Hg lower than resting value
I	2	Moderate claudication	Between categories 1 and 3
	3	Severe claudication	Cannot complete standard treadmill exercise† *and* AP after exercise <50 mm Hg
II*	4	Ischemic rest pain	Resting AP <40 mm Hg, flat or barely pulsatile ankle or metatarsal PVR; TP <30 mm Hg
III*	5	Minor tissue loss—nonhealing ulcer, focal gangrene with diffuse pedal ischemia	Resting AP <60 mm Hg, ankle or metatarsal PVR flat or barely pulsatile; TP <40 mm Hg
	6	Major tissue loss—extending above TM level, functional foot no longer salvageable	Same as category 5

AP, Ankle pressure; *PVR,* pulse volume recording; *TP,* toe pressure; *TM,* transmetatarsal.
*Grades II and III, categories 4, 5, and 6, are embraced by the term chronic *critical* ischemia.
†Five minutes at 2 mph on a 12% incline.

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1.1.7 Management Strategies

Management strategies in PAD concentrate on relieving symptoms, preventing disease progression and improving function. Reduced functional capacity limits activities and has a negative effect on quality of life (Norgren, Hiatt et al. 2007).

The onset of PAD, its clinical course and severity are linked to the risk factors that contribute to the development of atherosclerosis, which is the main pathophysiological process in the development of coronary artery disease and cerebrovascular disease. The UK Heart Protection Study, which included 20,536 patients between the ages of 40 and 80 years, found that diabetes mellitus, current smoking, hyperlipidaemia and hypertension accounted for over 75% of patient related risk of development of PAD (Study 2002).

Patients with PAD are high risk candidates for associated cardiovascular disease morbidity and mortality. The opposite is also true, PAD is an independent predictor of cardiovascular risk related morbidity and mortality. Therefore, the focus of non-invasive modalities is to address cardiovascular risk by managing modifiable factors for atherosclerosis.

Population studies suggest that claudication remains stable in 70-80% of patients, worsening in 10-20%, progressing to CLI in 5-10%. The rate of major amputation for IC in 5 years is approximately 1-3.3%. Deterioration is most rapid in the first year after diagnosis at a rate of 7-9%, reducing to 2-3% annually thereafter (Norgren, Hiatt et al. 2007). This highlights the importance of early diagnosis and management of PAD and its co-morbidities.

Failing adequate management with the strategies explored below, invasive intervention in the form of percutaneous angioplasty or surgical revascularisation may be necessary. A recent

study in Australia has shown that early revascularisation for IC compared to conservative management had a significantly increased risk of major amputation within 5 years (6.2% vs 0.7% (P=0.003) respectively) (Golledge, Moxon et al. 2018).

1.1.7.1 Best Medical Therapy and lifestyle modification

Risk factor modification of atherosclerosis contributes to the prevention of developing other related conditions including stroke and myocardial infarction. Invasive management should only be considered on failure of all lifestyle modification and medical management strategies.

1.1.7.1.1 Smoking cessation

This is considered the most important lifestyle modifiable factor for all forms of cardiovascular disease. Smoking is also associated with failure of graft related revascularisation surgery and risk of amputation (Flu, Tamsma et al. 2010). Risk of cardiovascular morbidity and mortality are reduced by half after 12 months of smoking cessation. The risk is equivalent to a non-smoker after 5 years (Norgren, Hiatt et al. 2007, NICE147 2012).

Suggested strategies for smoking cessation include counselling and subsequent pharmacological therapies including nicotine replacement. Providing this as a planned and structured intervention produces significant levels of abstinence (Agrawal and Eberhardt 2015). NICE guidance evidence suggests a combination of smoking cessation advice with nicotine replacement improves abstinence by 30% (NICE147 2012).

1.1.7.1.2 Statin Treatment

Statin medications inhibit HMG Co-A-reductase, a liver based enzyme important in the conversion of precursors through a metabolic pathway into cholesterol, thereby reducing serum cholesterol and triglycerides. Statins also promote high density lipoprotein (HDL) and reduce production of Low Density Lipoprotein (LDL), implicated in the atherosclerosis process.

The Heart Protection Study randomised over 20,500 patients with established diagnosis of either coronary artery disease, any other arterial occlusive disease (non-coronary) and /or diabetes, to use of simvastatin 40mg once daily and placebo. Total cholesterol levels were over 3.5 mmol/l. The study findings showed that statins significantly reduced overall mortality, with a 24% risk reduction in developing a major cardiovascular event in patients with PAD (Study 2002).

The Scandinavian Simvastatin Survival Study randomised 4,444 patients with elevated total plasma cholesterol levels (5.5-8.0 mmol/l) and coronary heart disease to receive simvastatin or placebo. Overall mortality rate was reduced by 30% and mortality from coronary events was reduced by 42% in the simvastatin group. The study concluded that simvastatin would be beneficial and should be offered to patients with a total cholesterol over 5.2 mmol/l (Larsen 1995).

The JUPITER trial was a multi-centre, international randomised controlled study assessing the use of rosuvastatin in primary prevention of first time cardiovascular events compared with placebo in patients with below statin treatment threshold levels of LDL cholesterol (<130 mg/dL), but at risk of cardiovascular disease due to increased serum levels of CRP.

The study showed 44% reduction in the above end point (P<0.00001), with 54% reduction (P<0.001) in heart attacks, 48% reduction (P=0.002) in strokes and 46% reduction (P<0.001) in arterial revascularisation procedures. The study was stopped early, just short of 2 years follow up due to the significant differences with medical intervention (Ridker 2009).

As well as reducing the cholesterol burden contributing to atherosclerosis, statins are considered to have independent mechanism of reducing progression of this disease (Ridker, Hennekens et al. 2000). The cholesterol precursor that statins prevent from forming, melavonate, has multiple end products after further processing, with several other functions. The production of these is halted by inhibiting melavonate production, and therefore statins are considered to improve endothelial function, reduce the proliferation of vascular smooth muscle cells, reduce inflammatory cytokines and chemokines (Interleukin-6) and matrix metalloproteinases (Ikeda and Shimada 2001). Further research is ongoing to confirm the mechanisms by which these effects of statins occur.

The British Joint societies guidelines for prevention of cardiovascular disease suggest rigorous control of blood total cholesterol, with a target of less than 4 mmol/l and LDL cholesterol less than 2 mmol/l (disease 2014).

1.1.7.1.3 Anti-platelet therapy

Aspirin has not shown any benefits in reducing cardiovascular events in asymptomatic PAD patients with moderate to low ABPI ratios (ABPI < or = 0.95) compared with placebo (Fowkes, Price et al. 2010). The CAPRIE study, a randomised blinded international trial, compared the use of 75mg clopidogrel to 325 mg aspirin daily in reducing ischaemic stroke, MI or vascular death in a subgroup of at least 6300 patients with symptomatic PAD. Other

groups included recent MI or recent stroke, with over 19,100 patients in total. Overall there was a relative risk reduction (RRR) of 8.7% (95% CI 0.3-16.5) in the 3 outcomes in favour of clopidogrel (Annual risk of ischaemic stroke, MI or vascular death 5.32% for clopidogrel versus 5.83% for aspirin). Focussing on the PAD subgroup, there was a 23.8% RRR in favour of clopidogrel (CAPRIE 1996). Dual therapy did not convey any additional benefit, but there was a slightly increased risk of bleeding reported.

NICE guidelines advise aspirin as first line anti-platelet in those with an MI within the last 12 months following the findings of the Antithrombotic Trialists' Association showing significantly reduced rates of non-fatal MI, ischaemic stroke and vascular deaths in patients with symptomatic PAD (Collaboration 2002).

1.1.7.1.4 Anti-hypertensives

Hypertension follows smoking and diabetes in relative risk of PAD (Agrawal and Eberhardt 2015). Hypertension is a risk factor for atherosclerosis and even small increases above the acceptable limit of 140/90 increases risk of mortality by coronary artery disease or stroke. NICE guidelines suggest each 2 mmHg increase in systolic blood pressure (SBP) is associated with a 7% increase in CAD mortality and 10% increased risk of stroke related mortality (He and Whelton 1999, NICECG127 2011). The prospective multicentre cohort UKPDS study assessed all-cause mortality as a primary endpoint, and lower limb amputation or death due to peripheral vascular disease (PVD) as part of the secondary outcomes in diabetic patients. The study found a 12% reduction in the primary outcome with 10mmHg decrease in mean systolic blood pressure (SBP). It showed a 16% decrease per 10mmHg SBP decrease for lower limb amputation and/or death due to PVD (Adler, Stratton et al. 2000).

The aim of treating hypertension is to prevent cardiovascular morbidity and mortality. Hypertension management in the UK is guided by NICE recommendations, formed in collaboration with the British and Irish Heart Society (NICECG127 2011). The HOPE study evaluated the use of Ramipril, an angiotensin converting enzyme inhibitor, in reducing complications from atherosclerotic disease and mortality in patients with atherosclerosis or diabetes and at least one cardiovascular risk factor. The study found a 25% reduction in cardiac events in this cohort (Hoogwerf and Young 2000).

Within a primary care setting, current NICE guidance advises a calcium channel blocker (CCB) as first line management of hypertension in those over 55 years of age or of black or afro-Caribbean descent. Second line treatment is with an ACE-i followed by an Angiotensin II receptor blocker (ARB) . Betablockers have been used in hypertensive patients with recent MIs and known to have reduced mortality by up to 15% when used within 12 hours of a cardiac event (Hjalmarson 1997). Although Beta blockers can reduce cardiac output, Paravastu et al found no relation to use of beta blockers and walking distance in a Cochrane review and therefore suggested continued use in PAD patients (Paravastu, Mendonca et al. 2009). This is fourth line treatment in the guidelines for the management of hypertension in adults.

1.1.7.1.5 Pharmacotherapy for PAD

Certain pharmacotherapy can reduce the progress of peripheral arterial disease. In the US only cilostazol and pentoxyfilline are licenced for use in PAD. Naftidrofuryl is licenced for use in the UK (Conte, Pomposelli et al. 2015).

Cilostazol is a vasodilator and platelet aggregation inhibitor functioning as a phosphodiesterase inhibitor. This has shown to improve pain free walking distances in IC. Pentoxyfylline reduces platelet aggregation, improves blood flow to end organs by reducing viscosity of blood, and increases fibrinogen levels (Conte, Pomposelli et al. 2015).

Natidrofuryl Oxalate is a serotonin receptor antagonist, working by increasing the efficiency of oxygen consumption and energy use in end organs. Naftidrofuryl affects vascular smooth muscle by inhibiting vasoconstriction and decreasing cell proliferation. A systematic review of 11 trials comparing cilostazol, pentoxifylline and Naftidrofuryl Oxalate found the latter produced the most benefit, especially in walking ability, followed by cilostazol then pentoxifylline. Naftidrofuryl increased the maximum walking distance by 60% and initial claudication distance (pain-free distance) by 49% compared to placebo (Stevens, Simpson et al. 2012). Natidrofuryl Oxalate was also found to be more cost-effective than the other drugs, costing £6070 per quality adjusted life year (QALY) gained (Meng, Squires et al. 2014).

1.1.7.2 Exercise Therapy

Exercise therapy for PAD patients has historically shown positive benefits both from a symptom management and general health perspective.

Extensive high level evidence exists supporting Supervised exercise therapy as the most effective non-invasive modality in improving functional ability in terms of walking distance in patients with PAD (Bendermacher, Willigendael et al. 2006, Watson, Ellis et al. 2008, Fokkenrood, Bendermacher et al. 2013, Lane, Ellis et al. 2014, Lane, Harwood et al. 2017). This is the first line non-invasive treatment recommended by NICE guidance for PAD to be administered in concordance with lifestyle modification and best medical therapy (NICE147

2012). There are many issues with accessibility to these programs and patient compliance in completing them (Shalhoub, Hamish et al. 2009, Makris, Lattimer et al. 2012, Babber A 2015). The mode of supervised exercise has not been found to influence the beneficial effects of this therapy, however the superiority of supervised over unsupervised and any other form of exercise is suggested (Parmenter, Raymond et al. 2013).

Alternative exercise therapies are being researched to improve accessibility and utilisation with home-based exercise and the use of wearable sensor technology to set targets and motivate completion of these (Savage, Ricci et al. 2001, Normahani, Kwasnicki et al. 2017). Further research is needed in both these fields to correlate utility of these in functional improvement in the same way as exists for SEPs.

1.1.8 Alternative therapies in the management of PAD

1.1.8.1 Intermittent Pneumatic Compression

Intermittent pneumatic compression has shown some benefit in the treatment of patients with PAD ranging from IC to CLI (Labropoulos, Leon Jr et al. 2005, Kalodiki and Giannoukas 2007). Morgan et al showed the first documented increase in duplex measured lower limb arterial blood flow in 10 patients with a mean ABPI of 0.62 (0.33-0.74) after 5 minutes use of an IPC device at a 45 degree foot down position (Morgan, Carolan et al. 1991). Subsequent studies by Van Bemellen et al (van Bemmelen, Mattos et al. 1994) and Delis et al (Delis, Labropoulos et al. 2000, Delis, Nicolaides et al. 2000, Delis, Nicolaides et al. 2000, Delis, Husmann et al. 2001, Delis and Knaggs 2005, Delis and Nicolaides 2005) suggested a 3 to 4 fold increase in arterial blood flow in the dependent limb of patients with lower limb arterial disease. Claudication distances have been shown to improve significantly and are comparable

to supervised exercise in PAD patients (Kakkos, Geroulakos et al. 2005) over a 6 month active treatment phase.

Three mechanisms for the improvement in lower limb arterial inflow following compressive therapy have been suggested.

Firstly, the post compression state decreases venous pressure in the lower limb, there-by increasing the arterio-venous pressure gradient and under the influence of hydrostatic pressure, the arterial inflow increases (Delis and Knaggs 2005).

Secondly, sympathetic autoregulation in the form of the veno-arteriolar response (VAR) exists to maintain a homeostatic blood flow to the lower limb capillaries. A postural change from horizontal to sitting or standing position causes a sympathetic axon reflex resulting in pre-capillary arteriolar vasoconstriction. This affects the total peripheral resistance to blood flow to maintain safe capillary flow homeostasis. This VAR is disrupted in severe arterial disease, such that a conversely increased blood flow to the lower limb is seen upon dependency or standing position (Morgan, Psaila et al. , Delis, Lennox et al. 2001, Delis, Nicolaides et al. 2001). Delis et al suggest that upon successful revascularization, the VAR can return to normal (Delis, Lennox et al. 2001).

Lastly, compression therapy is thought to increase shear stress and increase release of vasodilatory nitric oxide from the arterial endothelium, which reduces peripheral arterial resistance to flow (Delis and Knaggs 2005).

IPC for the management of PAD has not established itself as yet in clinical practice. One reason may be a lack of large-scale studies, from diverse centres, in current literature. However, results from the above studies do provide scope for further research. Limitations to the use of IPC are mainly poor patient compliance due to immobility, pain, heat and risk of peroneal nerve palsy (de Haro, Acin et al. 2010, Hajibandeh, Hajibandeh et al. 2017).

1.1.8.2 Extracorporeal Shockwave Therapy

Extracorporeal shockwave therapy is well established in the treatment of urinary stones by fragmentation. This is a form of mechanical energy that may have angiogenesis properties through mechano-transduction effects promoting the release of angiogenetic factors like VEGF and NO producing enzymes. Studies showing some utility of this therapy, within a hospital setting, are emerging with promise in improving walking distances (Green, Harwood et al. 2018, Harwood, Green et al. 2018).

1.2 Muscle

1.2.1 Muscle morphology

1.2.1.1 Structure

Skeletal muscle is an important and adaptable contractile tissue that functions by converting biochemical pathways into kinetic energy to support the mechanical functions of the human body. Mechanically, muscle contraction and relaxation are constant systematic processes that maintain the form of the body, at the same time demonstrating plasticity in conforming to the stresses and activity needed in order to be efficient. From a biochemical standpoint, skeletal muscle is a store for glycogen, produces proteins and participates in energy conversion to heat to maintain body temperature(Frontera and Ochala 2015).

The ability of skeletal muscle to function optimally is influenced by a number of factors including nutrition, physical activity, injury and disease. The latter will be explored further in this section.

Skeletal muscle contributes approximately 40 % to total body weight and is composed almost 75% of water. The remaining proportions include protein (20%) and carbohydrates with other inorganic compounds (5%) (Frontera and Ochala 2015).

The structure of skeletal muscle is shown in Figure 4 below. A whole skeletal muscle is enclosed within a connective tissue epimysium and is made up of a number of bundles of muscle fibres. These bundles are encapsulated within a layer of perimysium holding a number of muscle fibres together. Each muscle fibre cell in turn is surrounded by the sarcolemma, which interacts with the internal elements of the muscle fibre by transmission of neural activity to produce muscle contraction.

Muscle fibres are made up of smaller fibre units known as myofibrils. These contain numerous contractile elements of the muscle called myofilaments, which are composed of proteins involved in the process of muscle contraction and relaxation. These proteins include myosin, also known as the 'motor' protein as it forms the mobile component of the myofilament, and actin, making up the thin, fixed filament component of a single myofilament. The myofilaments are surrounded by sarcoplasm and the interaction of these components, along with other supportive or regulatory proteins (troponin I, C and T), allows neural excitation, transmitted from the sarcolemma, to effect ion exchange allowing contraction which generates force. The sarcoplasm contains an intricate network of tubules known as the transverse tubular system (T tubules) which run perpendicular to the myofibrils and open to the sarcolemma of the muscle cell. This system is responsible for distributing the neural excitation equally along the fibre. This system is closely supported by the sarcoplasmic reticulum network which is responsible for calcium storage, ready for release for muscle activation and then reuptake on relaxation. The homeostasis of calcium within this network is maintained by 2 ATPase proteins. The sarcoplasm also contains mitochondria, which are involved in protein and oxidative energy production to meet the demand of the muscle action required. The positioning of these mitochondria is important according to the function of the muscle. The closer the mitochondria are to the surface of the muscle fibre, the closer the proximity to capillary circulation allowing short distance, efficient diffusion of oxygen into the mitochondria for energy production to support muscle function (Frontera and Ochala 2015).

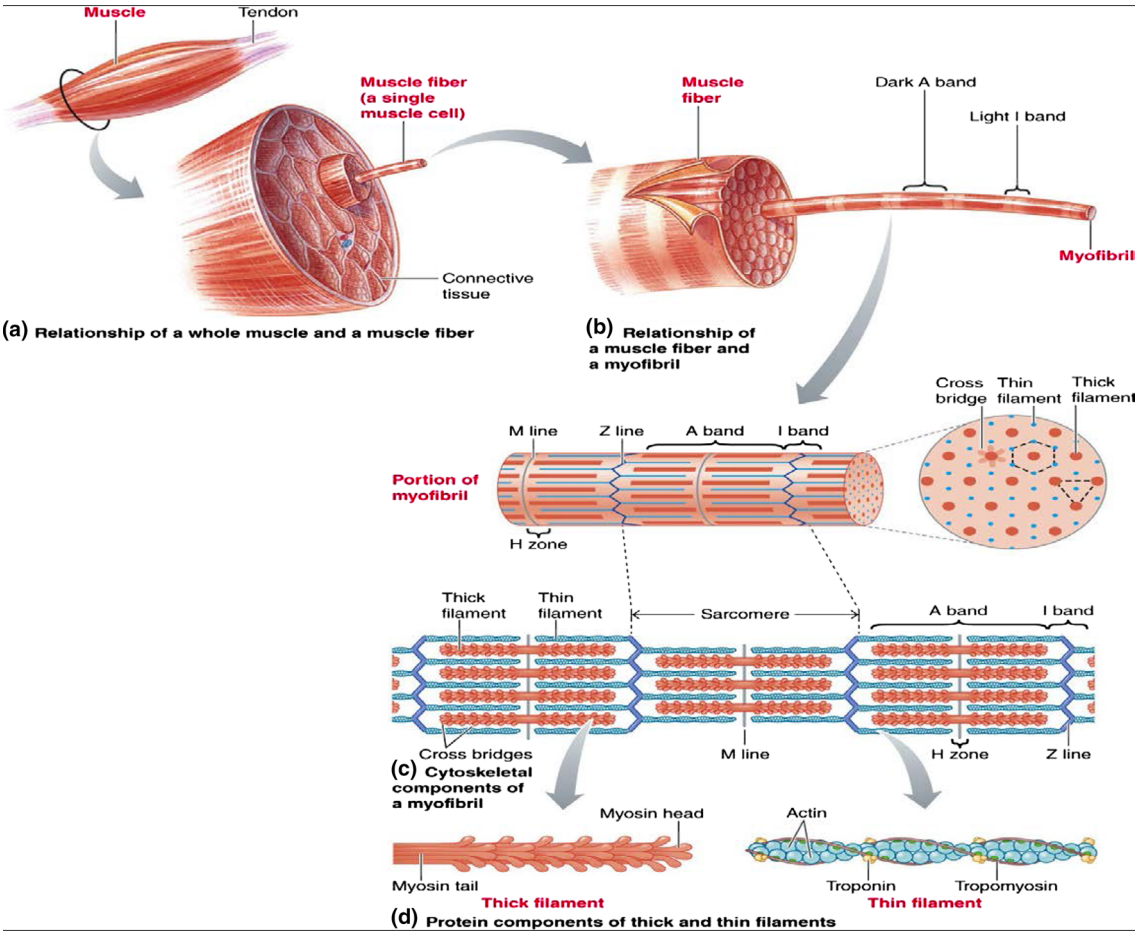


Figure 4: Structure of skeletal muscle

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1.2.1.2 Classification

There are multiple classification systems for skeletal muscle that can vary according to colour, speed, predominance of metabolic function and contractile elements. However, the most widespread classification of muscle is by fibre phenotype of which there are 3: type I, type IIA and type IIx.

Muscle fibre phenotype is characterised by 2 processes: a. the speed of muscle contraction, which correlates to the development of the sarcoplasmic reticulum and b. resistance to fatigue, which is linked to the mitochondrial content and oxidative ability and capacity of the muscle (Schiaffino and Reggiani 2011).

Type 1 fibres are slow contractors, functioning with energy production via the oxidative metabolic pathway and resistant to fatigue. These tonic muscle fibres are of use in endurance activities like marathon running. Type IIA fibres are fast contractors, primarily oxidative but may also utilise the non-oxidative glycolytic pathway if needed and hence are less fatigue resistant than type I. These are likely to be used for fast action like sprinting. Type IIx fibres are fast contractors primarily functioning with the glycolytic pathway and are fatigable (Scott, Stevens et al. 2001, Gohil, Lane et al. 2013).

Skeletal muscles are heterogenous in their composition of muscle fibre types, allowing flexibility of function according to activity demand. In addition, skeletal muscle displays great plasticity or malleability, with fibre phenotype composition influenced by activity, ageing and disease (Schiaffino and Reggiani 2011).

1.2.2 Skeletal muscle contraction

Skeletal muscles are innervated by efferent lower motor neurons, controlled by the motor cortex, brainstem or spinal cord. The cell bodies of the neurons are in the ventral horn of the spinal cord, from where they extend axons directly to the skeletal muscles as part of the peripheral nerves as α-motor neurons. The motor neuron, which is a myelinated axon extending peripherally to skeletal muscle, branches within the muscle to supply a vast number of dispersed muscle fibres with terminal branches. Each muscle fibre is supplied by a single branch of the motor neuron. This organisation of a single α-motor neuron and the muscle fibres it supplies is called a motor unit, a term coined by the British Neurologist C Sherrington (Sherrington 1894). Motor units can be large or small according to the action of the muscle and muscle fibre phenotype. For example, the soleus muscle is a muscle mainly required for sustained posture (endurance type fibres) so each motor neuron will supply approximately 180 muscle fibres. However, in contrast the gastrocnemius muscle, required for activity such as walking or running will have large motor units where each motor neuron will supply 1000-2000 muscle fibres per motor neuron (fatigable muscle type) (Purves D 2004).

Recruitment of motor units according to the force required to conduct an activity or move a load is demonstrated by Henneman's size principle. This is a stepwise increase in recruitment of initially small motor units with slow, fatigue resistant, durable muscle fibres, which have a lower threshold for activation, followed by larger motor units with fast, less fatigue resistant fibres, which have a higher threshold for activation (Henneman, Somjen et al. 1965). This process is energy efficient, using just enough effort to complete the necessary activity.

Muscle contraction occurs when electrical energy is converted into chemical energy that encourages the proteins of the myofilament to link and create force. The interface of electrical energy transmission from the motor end plate of the neuron to the muscle tissue is called the Neuro-muscular Junction (NMJ).

1.2.2.1 Neuromuscular Junction

Branches of the α-motor neuron terminate close to junctional folds of a muscle fibre, where a specialised synapse is formed called the neuromuscular junction (NMJ). Electrical energy is transmitted from nerve to muscle via neurotransmitter chemicals at the junction that chemically bridge the synaptic cleft or space between the neuron and junctional fold. Acetylcholine (ACh) is stored in presynaptic vesicles at the terminal end of the neuron. A depolarising electrical current in the form of an action potential promotes voltage gated calcium channels to allow an influx of calcium which bind to the synaptic vesicles containing ACh. This promotes the fusion of synapses to the axon terminal and release of ACh into the synaptic cleft by exocytosis. The junctional folds have an abundance of ACh receptors which the ACh binds to. This ligand gated receptor changes conformation allowing an influx of sodium ions into the sarcolemma, depolarising the muscle fibre. Sufficient depolarisation (Post synaptic voltage change from -70mV to 30mV) causes the action potential to be generated in the sarcolemma spreading across the muscle fibre internally through the T tubule system (Figure 5).

Depolarisation at the T tubule system stimulates voltage gated calcium channels to open in the adjacent sarcoplasmic reticulum releasing calcium ions into the sarcoplasm which surrounds the myofilaments. The depolarising electrical current is translated to a chemical

response, which allows interaction of the myosin and actin proteins to cause contraction. This interaction is called the sliding filament theory (Huxley and Niedergerke 1954).

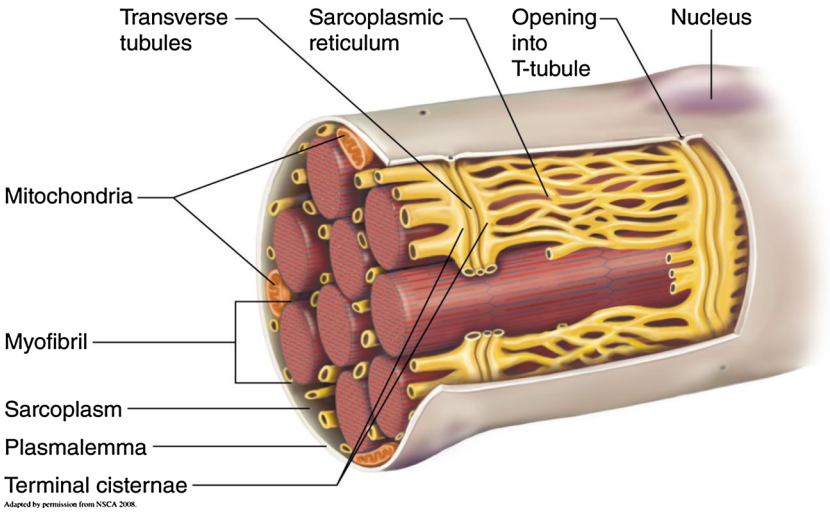


Figure 5: Structure of muscle fibre and its supporting structures to produce muscle contraction

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1.2.2.2 Sliding filament theory

The sliding filament theory of muscle contraction was defined by Huxley in 1954 (Huxley and Niedergerke 1954). This theory described actin and myosin proteins are in their unbound state at rest due to troponin and tropomyosin proteins conformed in a way as to block their respective binding sites from linking. With the influx of calcium from the sarcoplasmic reticulum as a result of the depolarising current transmitted through the T tubule system as described above, the regulatory proteins change conformation, exposing the actin and myosin binding sites that proceed to link forming cross bridges (Figure 6). Strong cross linking occurs by the release of energy upon the breakdown of ATP to ADP and Pi (inorganic phosphate), which is known as the ‘power stroke’ (Goody 2003). The process of linking and unlinking the actin and myosin is ATP synthesis dependent, provided by stored resource

(minimal), anaerobic breakdown of glycogen or aerobic synthesis by glycogen or fat breakdown. This process occurs over the whole motor unit supplied by the initial depolarising motor neuron and collectively forms a muscle contraction. Muscle contraction will continue as long as there is enough ATP and calcium present in the sarcoplasm.

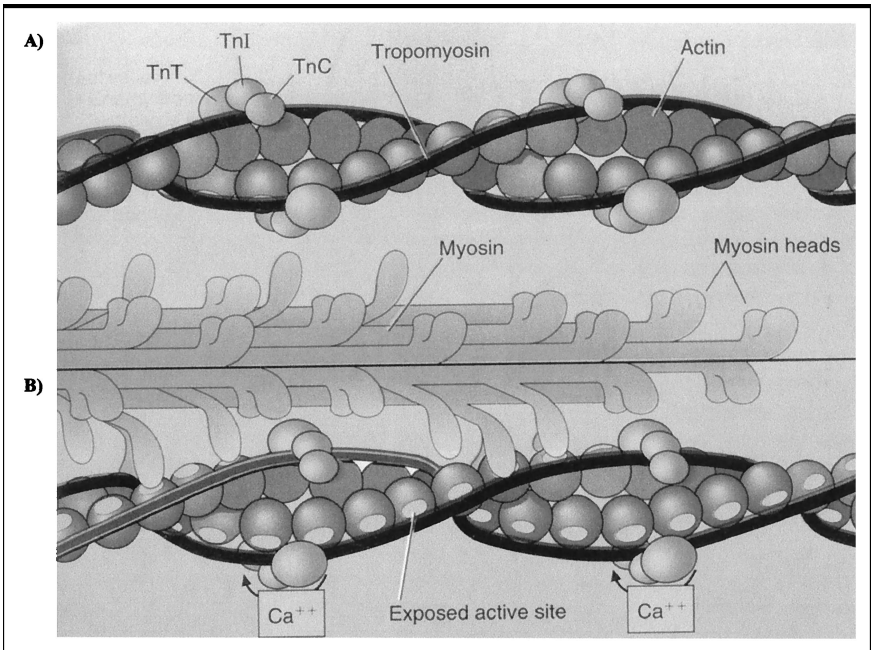


Figure 6: Role of regulatory proteins for the interaction of myosin and actin for muscle contraction

Regulatory protein conformation of troponin (Troponin T, TnT; Troponin I, TnI; Troponin C, TnC) and tropomyosin changes with calcium (Ca++) binding to expose the active site on the actin filament for myosin to bind to in an energy dependent way allowing muscle contraction by the sliding filament theory.
Reprint permission granted by Oxford University Press (Scott, Stevens et al. 2001)

1.2.3 Muscle fatigue and recovery

Optimal muscle contraction is a reflection of its performance. Sustained muscle contraction can cause muscle fatigue and therefore reduced performance. Fatigue can be defined as the reversible deterioration of performance or maximal voluntary force of a muscle; the reversible component, or muscle recovery occurs with rest (Allen, Lamb et al. 2008). The recovery time required varies according to the activity and intensity of training (Malone, Blake et al. 2014).

Understanding the underlying mechanisms of muscle fatigue is evolving with ongoing research, especially in the sports science arena, where further understanding assists in developing targets for efficient recovery management and rapid return to optimal performance. Fatigue may be controlled at the central nervous system with neurotransmitter decreases in the brain, usually serotonin (Davis and Bailey 1997), or peripherally at the level of the muscle (Bishop, Jones et al. 2008). At a peripheral level, muscle fatigue is dependent on the composition of muscle fibre phenotype as discussed above in section 1.2.1.2 above. Metabolic changes are likely to play a large role in muscle fatigue with muscle function at a fibre level being sensitive to levels of ATP, its breakdown products of ADP and inorganic phosphate (Pi) and lactic acid build up secondary to anaerobic processes. Inorganic phosphate build up affects force production at a muscle fibre level , reducing sarcoplasmic reticulum release and sensitivity to Calcium ions (Westerblad, Allen et al. 2002). A build-up of lactic acid from anaerobic respiration with resulting decrease in pH levels due to hydrogen ions can also reduce the maximal force production of a muscle fibre (Allen, Lannergren et al. 1995).

Within healthy athletes, sports training associated muscle fatigue is a common occurrence affecting performance. Strategies for reversal of fatigue are at the forefront of sports science

research to allow muscle recovery effectively and efficiently for the return to optimal performance. Within the highly competitive world of sports, the smallest of differences in performance could render an athlete victorious or eliminated from a competition. Muscle fatigue is the rate limiting step between further training, training at higher intensity and preparation for better performance. Hence, the stakes are high for optimal recovery from exercise, which can be classified as immediate, or in between muscle contraction; short term, between exercises within a session or training recovery, occurring between sessions (Bishop, Jones et al. 2008). High intensity use of muscle without adequate recovery may increase the risk of injury. Therefore, extensive research and commercial development of modalities to enhance muscle recovery are currently in place, of which neuromuscular electrical stimulation is proving an effective strategy for improved power and strength (Barnett 2006). This will be explored further in studies conducted on the utility of NMES in muscle recovery in section 4 below.

In PAD, lower limb muscles undergo exercise induced ischaemia causing fatigue or reduced muscle performance, followed by a period of rest and reperfusion before being able to function optimally again. This cycle is thought to alter morphological and metabolic features of muscle in the PAD cohort resulting in a phenomenon being described as 'Myopathy of peripheral arterial disease' (Pipinos, Judge et al. 2007, Pipinos, Judge et al. 2008). On an ongoing and repetitive basis, these changes can affect optimal muscle strength and performance. This is explored more in the next section 'Muscle adaptations'.

There are parallels to be gained from the understanding of the underlying mechanisms of muscle fatigue and recovery in healthy individuals and patients with PAD. Assessing modalities for efficient muscle recovery in healthy subjects experiencing muscle fatigue may

improve our understanding and ability to non-invasively manage patients with PAD. Muscle recovery studies in healthy participants forms a part of this clinical thesis.

1.2.4 Muscle adaptations

Muscle tissue is adaptive in response to neural inputs, activity, nutrients and disease. This plasticity attempts to provide efficiency of muscle use in the case of exercise training, or reflect a pathological disease state like PAD.

Exercise training conforms morphological and metabolic changes to the skeletal muscle tissue that is specific to the activity being undertaken. Exercise has health proven benefits, especially the endurance kind, by preventing risk factors and disease development like obesity, diabetes and cardiovascular disease. Exercise therapy has proven benefits in the management of PAD and is the current gold standard first line, non-invasive tool in PAD treatment (Norgren, Hiatt et al. 2007, NICE147 2012). The beneficial effects and improvements in endurance activities like walking distances in this cohort may be due to the adaptations displayed by muscle tissue with increased frequency and intensity of exercise.

Endurance training conforms muscle tissue that is able to sustain forces for a prolonged period of time without fatigue. This tissue is able to use substrates of ATP more efficiently and has a superior oxidative capacity, where by oxygen delivery to muscle fibres via the capillary network is increased with abundant mitochondria in close proximity to the network allowing rapid diffusion of oxygen for further energy production. There is an upregulation of genes to produce proteins that support the oxidative process, like those involved in the Kreb's cycle of ATP synthesis. Muscle fibre phenotype, switch, from type II to tonic type I may occur due to altered expression of Myosin Heavy Chain (MHS) type I to fatigue resistant type

fibres to improve the efficiency and support the optimised metabolic changes (Röckl, Hirshman et al. 2007).

Muscle adaptations in the form of loss of lean mass in ageing (sarcopenia) and inactivity have been widely researched (Frontera and Ochala 2015). There is a phenotype switch from type I to type II fibres along with lean mass reduction (Lane, Barrett et al. 1998). This reduces the maximal voluntary force and power provided by muscle tissue and increases the risk of falls and injury (Keevil and Romero-Ortuno 2015).

1.2.4.1 Muscle in PAD

The adaptation of skeletal muscle tissue in PAD, especially intermittent claudication, has been extensively researched (McGuigan, Bronks et al. , Regensteiner, Wolfel et al. 1993, Hiatt, Regensteiner et al. 1996, Askew, Green et al. 2005, Gohil, Lane et al. 2013). The descriptive term used to describe the global muscle adaptations seen in this cohort is 'Myopathy in PAD'.

Myopathy in PAD is a multi-factorial phenomenon. Reduced blood flow is a part of this but by no means the only or major component of symptomatic PAD. A study by Hiatt et al randomly assigned 19 patients with IC to receive a total of 12 weeks of supervised exercise treatment for 1 hr/day and 3 days/week or control with no intervention. Peak exercise performance was assessed by treadmill test to the maximal point of tolerated exercise before stopping. Plethysmography of calf blood flow was also assessed. Results suggested a significant ($P<0.05$) improvement of 130% in peak walking time, 30% in peak oxygen consumption and 165% in maximum walking distance. Although there was small non - significant increase in blood flow to the calf muscles, this did not correlate to the functional

improvements seen, suggesting that improved exercise tolerance in these patients includes factors beyond blood flow change, most likely to represent a change in intrinsic muscle morphological and metabolic factors (Hiatt, Regensteiner et al. 1990, Brass, Hiatt et al. 2004). The non-isolated association of blood flow changes and changes in symptomatic PAD are demonstrated by further studies (Larsen and Lassen 1966, Pernow, Saltin et al. 1975).

The skeletal muscle intrinsic factors that likely play an important role in the progression of PAD include impaired metabolic processing of oxygen by dysfunctional mitochondrial units that develop hypertrophy, hyperplasia and disorientation; impaired mitochondrial processing of carbohydrates for energy; impaired acylcarnitine mitochondrial metabolism, which if elevated is a marker of incomplete, and therefore impaired, oxidative phosphorylation. At a molecular level, these dysfunctional mitochondrial adaptations cause impaired oxidative processing for energy production, translating as sub-optimal muscle contraction (Pipinos, Judge et al. 2007).

Dysfunctional mitochondrial processes can increase the amounts of reactive oxygen species (ROS) which in turn can damage the mitochondria further and affecting other lipids and proteins. This accentuates further ROS development in a cyclical fashion (Figure 7 below). Manganese superoxide dismutase (MnSOD) is an anti-oxidant mechanisms neutralising the effect of ROS. There is a lack of expression of this mechanism in PAD skeletal muscle, as well as other antioxidants including glutathione, which contributes to the deleterious effects of ROS (Pipinos, Judge et al. 2008).

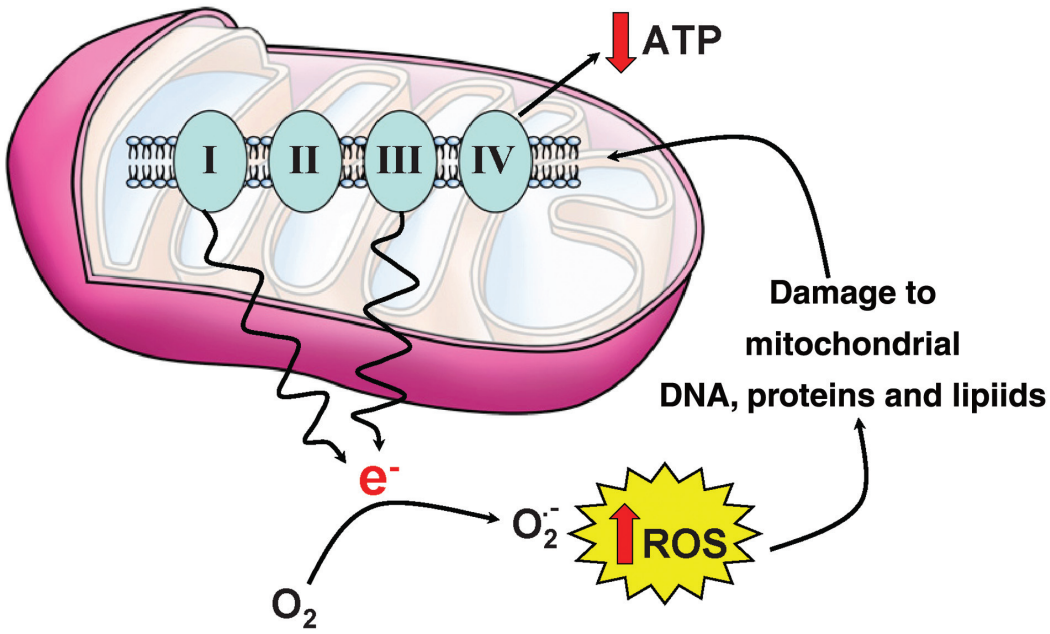


Figure 7: Dysfunctional mitochondrial processing increasing ROS, causing further damage

Gratis permission for reprinting granted by Sage Journals (Pipinos, Judge et al. 2008)

Change in muscle fibre phenotype as a structural adaptation to PAD is also noted. However, there is heterogeneity in study findings as described below.

Askew et al studied skeletal muscle phenotype in 16 patients with stable IC compared to 13 healthy matched control participants with gastrocnemius muscle biopsy sampling and histological methods after a treadmill test. Samples were taken from the medial aspect of the gastrocnemius of the most symptomatic limb and from any lower limb in the controls. Results suggested the PAD group had significantly less type I muscle fibres by 48% ($P<0.05$), more type IIa fibres, and a lower capillary to fibre ratio by 20% ($P=0.08$) (Askew, Green et al. 2005).

McGuigan et al conducted a histological study of needle biopsies from the gastrocnemius muscle of 14 PAD patients with IC compared to 8 activity matched controls. Findings suggested a significant decrease in MHC 1 protein expression in those with IC (type I fibres) (McGuigan, Bronks et al.). There was a significant increase in muscle capillarisation and a significantly increased capillary to fibre ratio (23%, $P<0.05$), with more capillary to fibre contacts in the PAD group compared to control. Fibre phenotype IIA was unchanged in this study, but there was an increased capillary supply to these fibres seen in PAD patients (Pernow, Saltin et al. 1975).

Regensteiner et al studied the histological appearance of skeletal muscle in 26 PAD patients compared to 6 healthy matched controls finding significantly increased denervation to muscle fibres and decreased type II cross sectional area in the gastrocnemius muscle biopsy in PAD vs control. In addition, PAD patients demonstrated less muscle force or strength compared to control and this was correlated to the decreased cross sectional area of type II fibres (Regensteiner, Wolfel et al. 1993).

Gasparini et al assessed the difference in muscle strength in the gastrocnemius muscle after electrical stimulation to fatigue in 17 PAD patients and 17 healthy controls. Findings suggested quicker contraction of the skeletal muscle with earlier fatigue in the PAD group compared to control. There was a suggestion that this may be due to a muscle fibre phenotype shift from type I to type II fibres in the PAD cohort (Gasparini, Sabovic et al. 2012).

The variability in findings of these studies may suggest a heterogeneity of study methods and parameter measures in histological sampling of skeletal muscle in PAD patients compared to healthy controls. Further research is necessary for clarification in order to better understand

underlying mechanisms and therefore develop ideal targets for managing this disease (Harwood, King et al. 2017). However, there is evidence that PAD as a disease does have skeletal muscle adaptation, which may explain the poor exercise tolerance, pain and impaired exercise ability of this cohort. The above studies have also suggested that muscle strength, or force is reduced in the PAD population, which may be correlated to the histological muscle phenotype abundance within the skeletal muscle or the result of a combination with the adaptation of intrinsic factors leading to 'Myopathy of PAD'.

1.3 Neuromuscular Electrical Stimulation

1.3.1 Neuron morphology

Neurons, the basic functional units of the nervous system, are able to create electrical signals and transmit these long distances to sense, move or regulate a variety of body functions through electrical and chemical neurotransmitters. In order to achieve this, neurons are able to form networks to connect the central nervous system (brain and spinal cord) to the peripheral nervous system and are usually connected to one another by specialised junctions called synapses. There are 3 classes of neurons; sensory controlling perception stimuli such as sound, light and pain; motor controlling muscular function and interneurons that are able to connect neural networks together.

From a structural point of view a motor neuron has a cell body (containing the nucleus involved in protein synthesis) which lies in the brain, brainstem or spinal cord, locally advancing neural branch like projections called dendrites and an axon, which is the main nerve fibre carrying electrical impulses in the form of an action potential away from the cell body to the effector organ like skeletal muscle. The axon is able to transmit the propagating action potential through neurotransmitters at specialised junctions with skeletal muscle called neuromuscular junctions in order to cause muscle contraction. This transmission forms the excitation process of the excitation contraction coupling required for muscle contraction. Neuromuscular junctions and muscle contraction are explored in more detail in section 1.2.2, above.

All nervous and skeletal muscle tissue are able to generate and propagate an electric current made up of the intrinsic ionic differences across intracellular and extracellular portions of the neuron cell membrane. Active cell membrane ion pumps, like the sodium – potassium ATP

pump, ensure a resting membrane potential of -70 mV across axons and -90 mv for skeletal muscular tissue. The skeletal muscle motor unit comprises the motor neuron from the central nervous system (CNS), its corresponding axon and dendrites, the motor end plate and the muscle fibres that contract as a result of unit activation. The motor end plate is a type of synapse at the skeletal muscle interface (Watson 2008).

At the CNS, propagation of an action potential along the corresponding motor neuron is dependent on the balance of excitatory and inhibitory post-synaptic potentials at its dendrites and cell body, caused by synaptic chemical release in response to afferent neuronal activation. If the excitatory potential is sufficient enough to chemically alter ionic composition across the post-synaptic neuron, membrane depolarising this above its threshold, an action potential is generated which propagates along this neuron as an all or nothing basis.

For efficiency of propagation of the electrical signal, the axon is covered by a myelin sheath called Schwann cells. These cells are separated by tiny spaces of unsheathed axon called nodes of Ranvier, which has a high concentration of ion channels. Action potentials are able to propagate efficiently and quickly at these nodal points by a process called saltatory conduction. There is no myelin sheath at the axon terminal, which instead has a hood protecting the NMJ. Action potentials travel in one direction as the membrane preceding the depolarised section undergoes a refractory period of re-establishing the resting membrane potential.

This action potential reaches the neuromuscular junction, releasing a chemical transmitter, acetylcholine. At this point, neurotransmission of the action potential causes calcium ionic changes within the sarcolemma and sarcoplasmic structures of the muscle fibre causing it to

contract as per the sliding filament theory proposed by Huxley et al in 1971 (Huxley and Simmons 1971) and described in more detail in section 1.2.2, above.

1.3.2 Electrical therapy and evolution in medicine

Intrigue into the use of electrical therapy in the management of various medical ailments has been ongoing for over 2000 years. In his medical compositions, Scribonius Largus, a 1st Century AD Roman physician, appreciated the role of the 'torpedo' fish in treating gout after hearing the experience of a local minister's symptoms improving after stepping on a live torpedo fish. Even at this time, the torpedo fish (*Torpedo occidentalis*) was long known to stun its prey by an electric discharge, but this was the first documentation of the medical use of electrical therapy (Tsoucalas G 2014).

Research into electricity made major advances in the 18th century with the development of storage vessels called Leyden jars and electrostatic generating machines. These advancements were capitalised by researchers like Luigi Galvani (1737-1798) and Benjamin Franklin (1706-1790) who were both instrumental in developing 'medical electricity' as electrical therapy for medicinal use. The former contributed to the understanding of nervous control of muscular contractions in frog models, dispelling the concept of 'animal spirits' and the latter used electrical therapy to some success in treating patients with paralysis (Bresadola 1998, Hirschmann 2005).

Further progress in the field of electricity led to the development of the battery, negating the requirement for an electromagnetic generator, whereby stored electrical energy was readily available for use. In the 19th Century, Guillaume De Duchenne De Boulogne, the famous neurologist and suggested father of electrotherapy, used faradic and galvanic currents on the

skin to map out the effects of various muscles of the body. He was able to use this electrical energy as a means of electro-diagnosis, describing a number of conditions including Duchenne muscular dystrophy and Duchenne Erb palsy (Silver and Weiner 2013).

The 20th Century saw a further understanding of the parameters of electrical energy and their application to the human body for various ailments, mainly due to trial and error. This understanding has allowed the development of various electrical devices to deliver energy to tissues by percutaneous, transcutaneous or implantable methods for the treatment of symptoms including pain and for managing psychiatric (Allan and Ebmeier 2011), cardiac (Galtes and Lamas 2004, Schuler and Leon 2005), urological(Schreiner, dos Santos et al. 2013), and colorectal disease (Cowley, Waudby et al. 2014). In addition, from the 1960's, there has been a surge of electrotherapy in sports and rehabilitation medicine (Lake 1992).

1.3.3 Neuromuscular Electrical Stimulation

Neuromuscular Electrical Stimulation (NMES) is the use of externally applied electrical energy, usually through superficial electrodes, that is sufficient to cause depolarization of the peripheral nerves and muscles causing contraction.

The usual setup of an NMES device includes an anode, or positive electrode, and a cathode, the negative electrode. Current flows from the anode to the cathode. In order for underlying nerve depolarisation to occur, a reversal of the cell membrane resting potential is required as described in section 1.3.1, above. Upon the flow of electric current from anode to cathode, there is an extracellular build-up of negative charge under the cathode and a subsequent intracellular positive charge, which slowly depolarises the neuron cell membrane. Once this depolarization reaches the threshold level, an action potential is generated and propagated along the motor neuron. Within this circuitry, the cathode is termed the 'active' electrode (Watson 2008).

1.3.4 NMES stimulation parameters

Excitation and subsequent contraction of muscle can only occur if the stimulation parameters are sufficient. In order to translate an electrical stimulation to a therapeutic response, these parameters need to be optimal. Classes of neuron respond differently to a combination of stimulation parameters that must be ideal for optimal depolarisation of the specific neuron, be it sensory, motor or nociceptive. There is a preferential pattern of neuron stimulation directly related to the stimulation parameters applied. Appropriate documentation of stimulation parameters is key in enabling clinical studies to be replicated in a standardised fashion. However, there is a major lack of standardisation found across clinical trials using NMES promoting the ad hoc use of stimulation parameters and preventing robust understanding of

the effects of optimal stimulation (Hosker, Cody et al. 2007, Watson 2008). Important NMES parameters include the current, pulse frequency, pulse duration, duty cycle, amplitude and electrodes (Watson 2008, Glaviano and Saliba 2016).

1.3.4.1 Current

Current is the flow of electricity or electric charge measured in amperes (amps or A). This flow can be direct, also known as DC current, with continuous unidirectional flow; alternating or AC with continuous bidirectional flow; and pulsed where the flow of current, which can be in either direct or alternating directions, is interrupted intermittently. Current travels in waveform patterns that can be monophasic or biphasic in relation to the negative or positive current. The 'power' pushing forward the current due to differences in the electrodes (one positive and one negative) is called the voltage and this drives the current. The current amplitude is the intensity of the electric charge. Voltage drives the current depending on the impedance or resistance faced. This relationship is known as Ohm's law, which is V=IR, where V is voltage, I is current and R is resistance. This is important as stimulation parameters have to be sufficient to allow a current to pass through the impedance of the skin and subcutaneous tissues in order to deliver the current appropriately to the motor units.

1.3.4.2 Pulse frequency

For a pulsed current, the frequency is the number of pulses of current delivered in one second and this is measured in hertz (Hz). This frequency has a direct relationship to muscle force production or torque and increasing frequency can also cause muscle fatigue. Muscle fatigue is discussed in section 1.2.3, above. Higher frequency and therefore higher muscle force increases the metabolic demands of the muscle, increasing anaerobic metabolite production and can lead to muscle damage (Glaviano and Saliba 2016).

1.3.4.3 Pulse duration

The pulse duration is also known as the pulse width and is measured in milliseconds or microseconds. Motor neuron stimulation, without stimulation of nociceptive fibres can occur ideally between 20 and 200 microseconds pulse duration (Alon, Allin et al. 1983). Further research has shown that for a therapeutic effect of stimulation, a pulse duration of approximately 400 microseconds is optimal. The higher the pulse duration the more muscle torque produced. There is a balance between optimal muscle contraction and pain production. Too high a duration could result in more pain and more muscle force, whereas too low could prevent NMES from having any therapeutic benefit.

1.3.4.4 Duty cycle

The duty cycle refers to the ratio of the current being on and off. The ideal ratio would prevent over stimulation and therefore muscle fatigue. There is no ideal duty cycle, but the shorter the total cycle is, the less time the muscle has to recover and therefore is prone to fatigue (Glaviano and Saliba 2016).

1.3.4.5 Amplitude

Amplitude is the intensity of the current and is measured in milliamps (mA). This is related to the motor unit recruitment and therefore the area on which a stimulation acts and the force produced by the effector muscle. The more the amplitude, the more chance of muscle fatigue and pain. However, ineffective amplitude will prevent any therapeutic effect of the stimulation.

1.3.4.6 Output

The output refers to the pulse delivery pattern, which may be continuous, burst or modulated. Burst output is the delivery of a 'train' of pulses with silent periods between the bursts.

1.3.4.7 Electrodes

The current is usually transmitted via electrodes or pads placed on the skin. The size, shape and position of these effects the current transmission and therefore the therapeutic effect of the stimulation. In terms of size, the density of current transmission is inversely proportional to the contact surface area of the electrode or pad. Therefore the bigger the electrode, the shallower the current density which can be uncomfortable (Glaviano and Saliba 2016).

1.3.5 Motor unit recruitment

Preferential activation of smaller motor neurons that supply motor units of slow acting, more fatigue resistant muscles (e.g. soleus) occurs during a voluntary muscle contraction compared to the large motor neurons supplying fast acting, highly fatigable muscles (e.g. gastrocnemius) (Brown 1929, Milner-Brown, Stein et al. 1973). The frequency required to activate motor neurons supplying human skeletal muscle is approximately 6-40 Hz (Watson 2008).

External electrical stimulation tends to recruit motor units in the opposite fashion to voluntary activation. The current applied preferentially recruits the lower threshold, large motor neurons which are more superficial in the muscle tissue. This also bypasses the central nervous system control of muscular contraction because if the stimulation intensity is sufficient, it will cause an action potential to generate in the peripheral nerves propagating directly to the motor end plate, causing muscle contraction (Watson 2008).

1.3.6 NMES devices

The evolution in better understanding stimulation parameters and the interaction of electricity with the human body and disease has manifested in the commercial production of a number of NMES devices. The clinical applications of these devices can vary according to their parameters, design and region of clinical interest. From a vascular perspective, the following NMES devices have been developed for the management of ailments of the lower limb.

1.3.6.1 Veinoplus®

This portable battery powered electro-stimulation device (Ad Rem Technology, France) was developed in 2004 to treat symptoms of venous insufficiency including lower limb pain and swelling. It comprises electrodes, which are placed on the posterior calf surface and connected to the portable device, which allows modification of various stimulation parameters. The device produces burst output stimulation in a square waveform pattern of 50 ms pulse duration with a pulse width of 240 μs and adjustable voltage from 1-5 volts. The frequency of current stimulus is from 1-250 Hz producing 60 to 100 calf contractions per minute. With these contractions, the calf muscle pump is activated to increase venous return from the lower limbs. (Image 1)



Figure 8: Veinoplus® neuro-stimulation device

(http://www.veinoplus.com/fr/images_db/flyer_veinoplus_light_en.pdf)

Griffin et al (Griffin, Nicolaides et al. 2010) undertook a pilot test of this device and showed that the peak systolic velocity in the popliteal vein could be increased 10 fold reaching 95-106 cm/s. The venous flow increased from 20 ml/min to 240 ml/min, a 12 fold increase with the device. The proposed mechanism was due to augmentation of the calf muscle pump.

This device is CE marked and FDA approved for use in non-healing venous ulceration of the lower limb and post-thrombotic syndrome.

Abraham et al investigated the use of the Veinoplus® device in altering arterial heamodynamics to the lower limbs of patients suffering stable (Fontaine 2) intermittent claudication. The intervention arm was use of the NMES device, at various stimulation intensities, on the most symptomatic leg, using the contralateral limb as control. Study findings included a significant increase in lower limb arterial flow in the intervention arm, that was not reciprocated in the control. This increase ranged from 27 to over 700% amongst the patient cohort with no pain secondary to device use or ischaemia reported. There was no latent similar effect to arterial inflow post intervention (Figure 8).

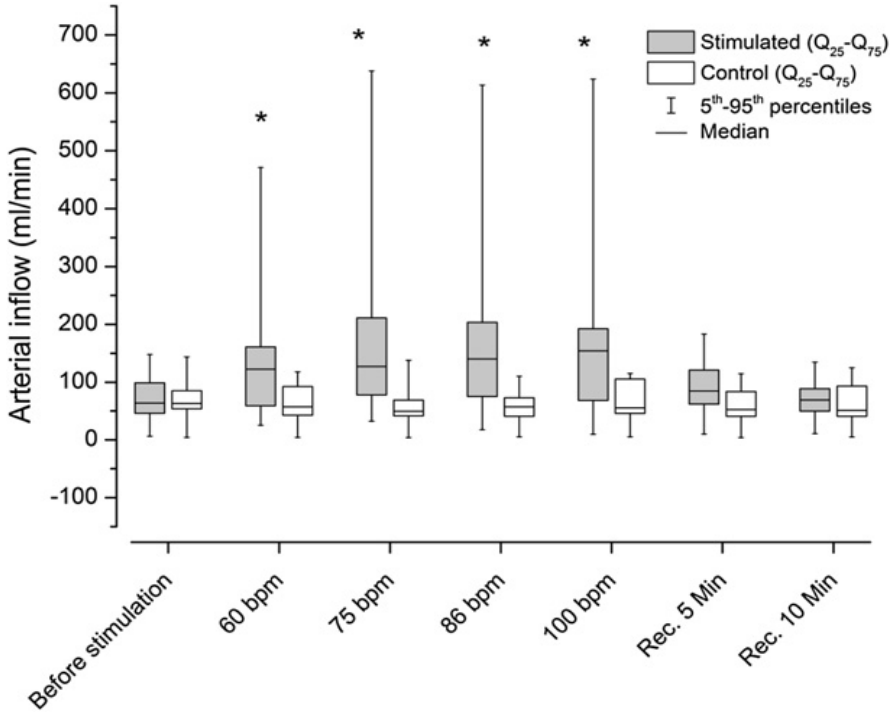


Figure 9: Arterial inflow in the stimulated and control limbs using Veinoplus device

Median and interquartile ranges shown over time of stimulation and post cessation (Rec 5 min and Rec 10 min)

Reprinted with permission from The Society of Vascular Surgery and Elsevier (Abraham, Mateus et al. 2013)

1.3.6.2 Geko™

This Geko™ device (Firstkind Ltd, UK) is a self-adhesive, portable, disposable NMES device powered by a cell battery, which can last up to 30 hours of use. It is placed over the head of the fibula to stimulate the common peroneal nerve. Stimulation is pre-set at 7 different intensities, according to pulse width, which are set for use by the individual according to the level required for contraction of the tibialis anterior, lateral gastrocnemius and peroneus longus muscles. This activates the calf muscle pump, which as described above, increases venous return from the lower limb, thereby providing the claimed therapeutic benefits. These include reduced lower limb swelling, ulcer and wound healing, recovery from strains and sprains and preventing deep venous thrombosis (DVT). This device can be used whilst ambulatory and functional with little restriction (Figure 10).



Figure 10: Geko™ neuro-stimulation device

Williams et al (Williams, Moore et al. 2014) compared lower limb haemodynamics in 10 healthy individuals comparing the Geko™ neuro-stimulation device with IPC. This was a randomized crossover study, which showed significant improvement in lower limb venous and arterial blood flow parameters following use of the NMES device. Although IPC showed a significant increase in venous peak velocity, venous flow was not significantly improved and there was no significant change to arterial inflow either.

This device has a good evidence base for improvement of lower limb haemodynamics and is the only electrostimulation device to be recommended by NICE for the mechanical prevention of venous thromboembolism (Jawad, Bain et al. 2014, NICE-MTG19 2014, Griffin, Bond et al. 2016).

1.3.6.3 Revitive™ IX

The Revitive™ IX (Actegy Ltd, UK) NMES device, differs from the previous 2 in that it's electrodes consist of 2 electro-carbon conductive foot plates with an optional rocker device (IsoRocker®) to replicate heel-toe raises along with calf muscle contraction. The inbuilt circuitry goes through a pre-programmed cycle of 15 stimulation patterns lasting approximately 1 minute each. The stimulation parameters for this device include a frequency of 1-50Hz with a maximum output current of 15mA applied in quasi-symmetrical biphasic waveforms that are shaped rectangular or bipolar. Each pulse duration is 370µs or 940µs, with 11-256 pulses per burst; 0.1-0.3 bursts per second; and a burst duration of 1.9-8.4 seconds depending on the programme. The device display shows the countdown duration of use, which can be set at minute intervals; the intensity level from 0-99, which is altered according to the user's comfort; and a display of intensity for the optional body electrodes included (Figure 11).



Figure 11: Revitive™ IX NMES device with footplates and optional IsoRocker®

(http://www.revitive.com/revitive-ix)

Similar to the previous devices, this device also claims improvement in lower limb swelling and pain symptoms and is currently CE marked for use in healthy individuals.

Varatharajan et al (Varatharajan, Williams et al. 2014) assessed the lower limb haemodynamic effects of this NMES device in healthy volunteers. In 2 separate studies of healthy participants who experienced a 30 minute stimulation cycle of the device with the IsoRocker® activated, duplex ultrasound measurements of the femoral vein (n=10) and artery (n=20) were taken at baseline, 15 minutes into the cycle and immediately post stimulation cessation. The results of this study showed a significant improvement in blood flow and mean velocity in both the artery and vein whilst using the NMES device compared to baseline. The effects were not sustained post stimulation.

A number of studies have been done to ascertain the efficacy of this device in improving lower limb venous blood flow and swelling in patients with chronic venous disease according to CEAP classification (Ravikumar, Williams et al. 2017). Twenty-two consecutive patients with CEAP class 2-4, were randomised to receive 6 weeks treatment with the Revitive IX NMES device or sham. Significant differences between the device and sham were seen whilst the device was on at week 0 with TAMV 102.4% vs -9.1% ($P<0.06$), volume flow 107.9% vs -3.7% ($P<0.0001$) and peak velocity 377.7% vs -6.7% ($P<0.0001$) respectively.

The above studies suggest some impact of this NMES device to lower limb haemodynamics in healthy participants and support further research in clinical populations including those with lower limb venous disease and PAD.

2 Foundation Research

2.1 Supervised Exercise Programmes in the UK: Are we meeting NICE recommendations?

2.1.1 Background

Peripheral arterial disease (PAD) is a chronic risk factor related disease with a global prevalence increasing from 5% to 19% with advancing age from 45 to 89 years old, respectively (Fowkes, Rudan et al. 2013). Intermittent claudication, a common manifestation of lower limb arterial disease, may be experienced by up to 50% of those with symptomatic PAD (Norgren, Hiatt et al. 2007). Concurrent to modifying risk factors associated with arterial disease, exercise therapy has been historically known to improve IC symptoms as first described in a single patient case study by Wilhelm Erb, a German neurologist in 1898 (Erb 1898) and later by Larsen et al in the first randomized control trial comparing exercise therapy to best medical treatment in 1966 (Larsen and Lassen 1966). In 2014, Lane et al (Lane, Ellis et al. 2014) reinforced the beneficial effect of exercise therapy for intermittent claudication in an updated Cochrane systematic review including 30 trials and 1816 patients in total. Overall there was a mean improvement in maximum walking distance of 108.99 metres and mean improvement of 4.51 minutes in maximum walking time, with these beneficial effects lasting up to 2 years. This review added 11 studies to the original review in 2008 by Watson et al (Watson, Ellis et al. 2008), which suggested similar positive effects of exercise rehabilitation on IC.

From the mounting evidence supporting exercise therapy in intermittent claudication, in particular, supervised exercise programmes (SEP) have emerged as providing the most beneficial non-invasive improvement in symptom control and pain-free walking distance

(Bendermacher, Willigendael et al. 2006). Level I evidence in the form of randomised controlled trials (Regensteiner, Steiner et al. , Hiatt, Wolfel et al. 1994, Cheetham, Burgess et al. 2004) have contributed to Cochrane Reviews (Bendermacher, Willigendael et al. 2006, Fokkenrood, Bendermacher et al. 2013, Lauret, Fakhry et al. 2014) and provided grounds for strong recommendations in favour of SEPs by the Trans-Atlantic Inter-Society Consensus Group (TASC II) guidelines (Norgren, Hiatt et al. 2007) and the Scottish Intercollegiate Guidelines Network (SIGN) (SIGN89 2006). More recently, the National Institute of Health and Care Excellence (NICE) have made similar strong recommendations for SEPS as an initial management strategy in all patients with early symptomatic PAD (NICE147 2012). A NICE quality standard (QS52 January 2014) has also been issued prioritising the availability of SEPs for these patients, highlighting quality improvement expectations for patients, providers and those commissioning funds to SEPs.

Since the publication of NICE guidelines in 2012 (NICE147 2012) and the quality standard in 2014 (QS52 January 2014), no study has shown the national status of accessibility to SEPs for the treatment of PAD. Subsequently, this is the first survey of referrers and providers to ascertain access to SEPs, types of SEPs and explore reasons affecting the accessibility to this effective, yet underutilised, management strategy.

2.1.2 Methods

This audit was done in collaboration with two 3rd year medical students at Imperial College London, Lauren D'Sa and Yuegi Ge as part of a national academic competition called AcaMedics. Overall supervision was provided by Professor Alun Davies. Personal involvement was proactive with daily project oversight and responsibility for project conception, survey design, implementation, data analysis, presentation and dissemination.

2.1.2.1 Survey Design

The survey questions were initially formulated following a review of current literature through PubMed and Ovid Medline, with IC patient and provider input following structured interviews and feedback from two SEP patients and consultation with Mrs Laura Burgess, Clinical Specialist Physiotherapist at Imperial College Healthcare NHS Trust, respectively.

A closed questioning style (pre-conceived option selection) was followed for the most pertinent aspects of this audit for ease of data acquisition and analysis. Some questions allowed multiple choice selection and others permitted free text opinions to be expressed by the respondent. The survey questions were reviewed and finally approved by A Babber and A Davies (Figure 12).

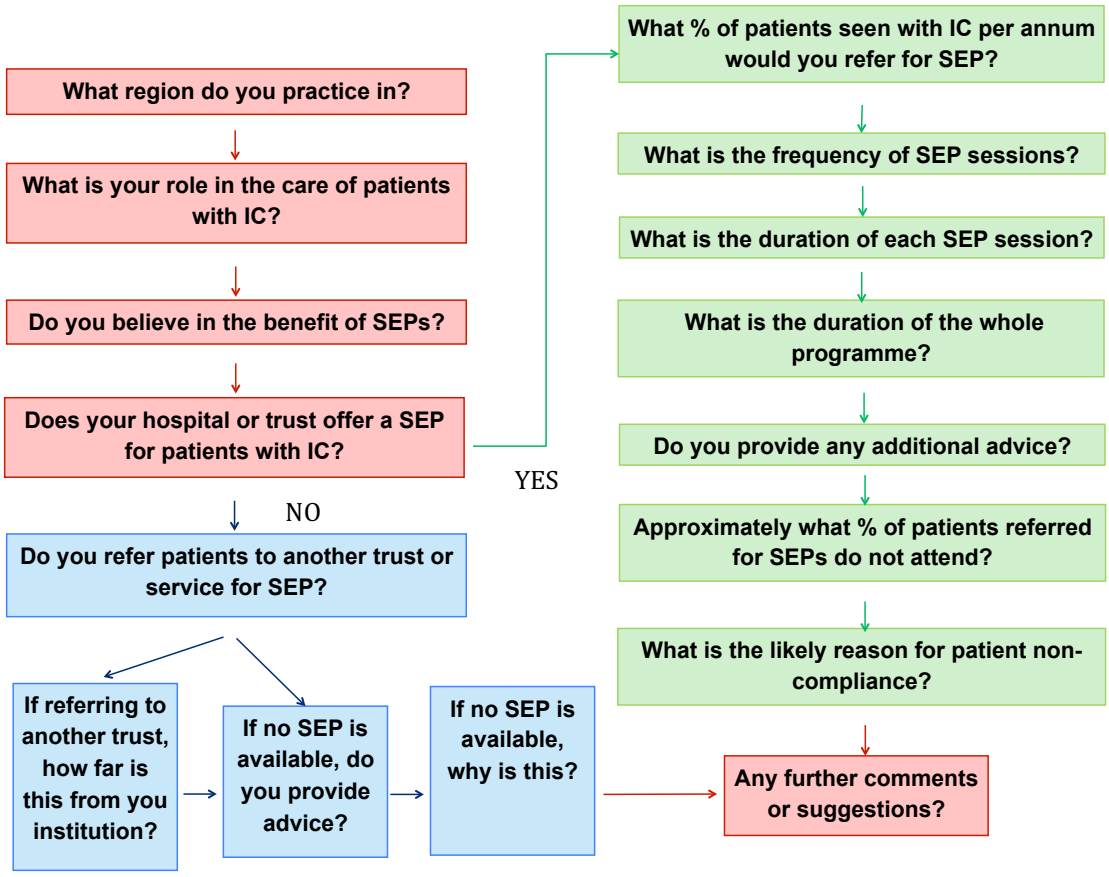


Figure 12: Skip logic questions for national SEP access audit

2.1.2.2 Survey Dissemination

The final survey was uploaded to a web-based survey provider www.surveymonkey.com. Using this platform, the survey was disseminated to the main referrers and providers of SEPs including members on the most recently available electronic mailing list of the Vascular Society of Great Britain and Ireland (VSGBI), and a link posted on the discussion forum of the British Association of Chartered Physiotherapists and Amputee Rehabilitation (BACPAR).

The audit was registered with the Imperial College NHS Trust (Registration No. 1771).

2.1.2.3 Data collection and analysis

All responses were collected and collated by the online survey platform, through which basic analysis was performed and presented as percentages in Microsoft Excel format. The authors also scrutinised the free text responses.

2.1.3 Results

A total of 118 responses were received, with widespread national representation from NHS England, NHS Scotland, NHS Wales and HSC Ireland. Respondents included 88 Vascular Consultants (75%), 23 physiotherapists (20%) and 6 trainee surgeons (5%).

One hundred and ten respondents (93.2%) believed in the benefit of SEPs as a management strategy for patients suffering IC (Figure 13). Open comments suggested that a lack of belief was due to 'benefits offset by poor compliance from those that need it most', and 'studies small…not well replicated in clinical practice'.

Only 35% respondents had access to SEPs, with 10% respondents previously offering a SEP, which was now closed. The total number of respondents without access to SEPs was 76 (65%) with one physiotherapist unsure of the local availability (Figure 14).

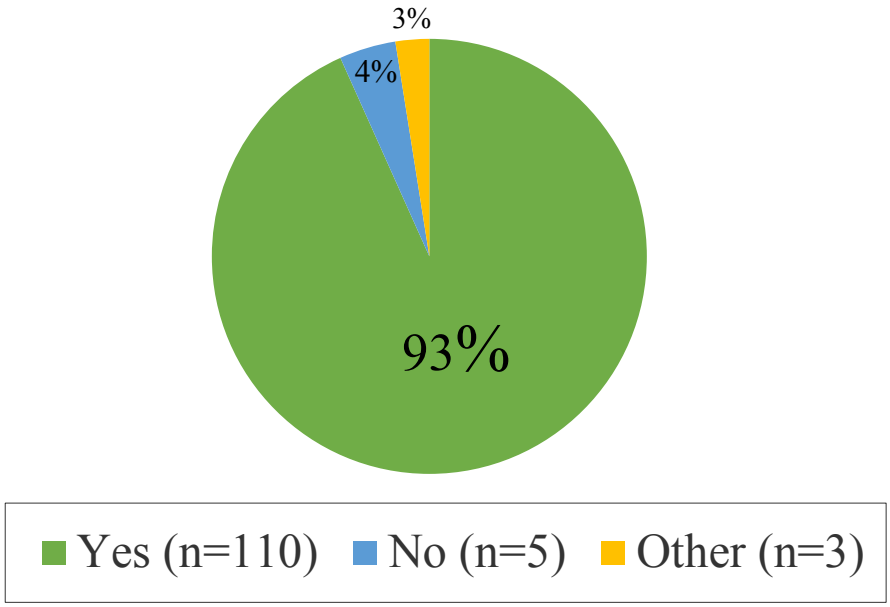


Figure 13: Respondents according to belief in the benefit of SEPs (n=118)

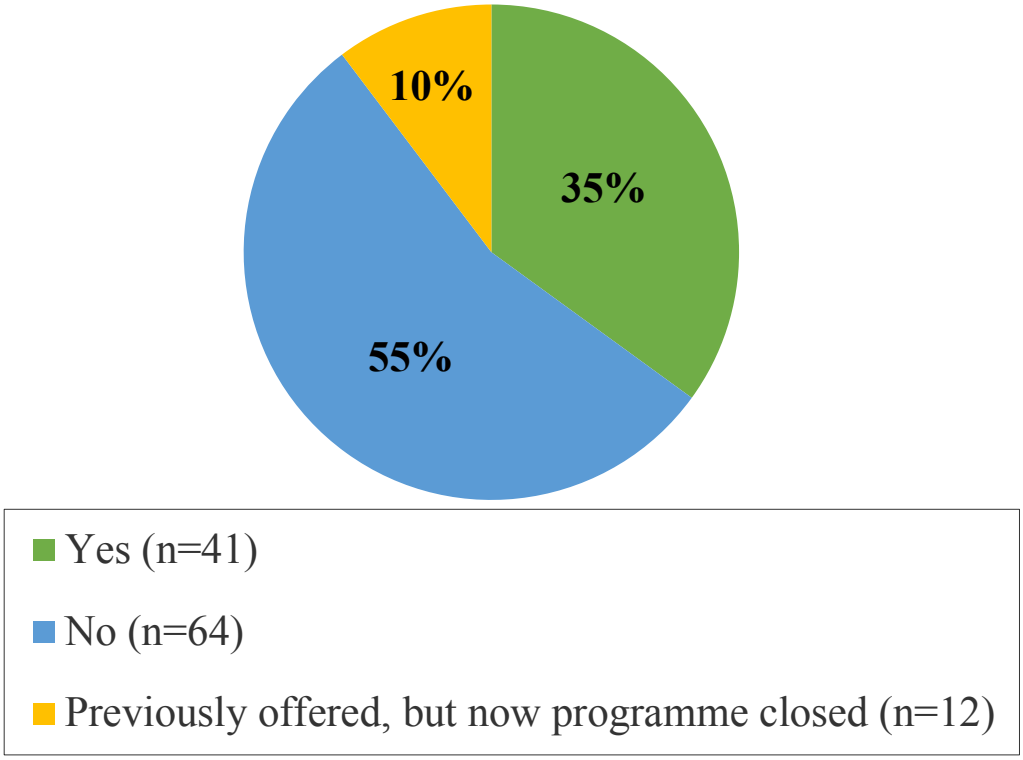


Figure 14: Responses to 'Does your hospital or trust offer SEPs?'

For those with access to a SEP (n=41), only 5% referred all IC patients for this therapy, with 29% referring up to a quarter of patients and a further 12 referring up to half of all the patients suffering IC seen by them per annum. Fifteen respondents (37%) referred up to 99% of their patients.

Of the 41 respondents with access to a SEP, these sessions were mainly provided by physiotherapists (85%), a specialist vascular nurse (37%), nurse (12%) and/or supported by fitness instructors (10%) or technicians (10%). One respondent (2%) suggested the regular presence of a doctor at the SEP.

The most common frequency, session duration and programme duration was 1 session per week (57%), for 1 hour (66%) for a total period of 3 months (37%).

Non-adherence rates to the SEPs are shown in figure 4 and in the majority are suggested as 10% or less (17 respondents) or between 10% and 20% (10 respondents). Eight respondents (20%) suggested a non-compliance rate of over 30% (Figure 15). The main reasons for this were the distance of the SEP (55%), a lack of travel convenience (48%), lack of patient motivation to attend (48%) and personal expense (30%) in accessing the exercise classes (Figure 16).

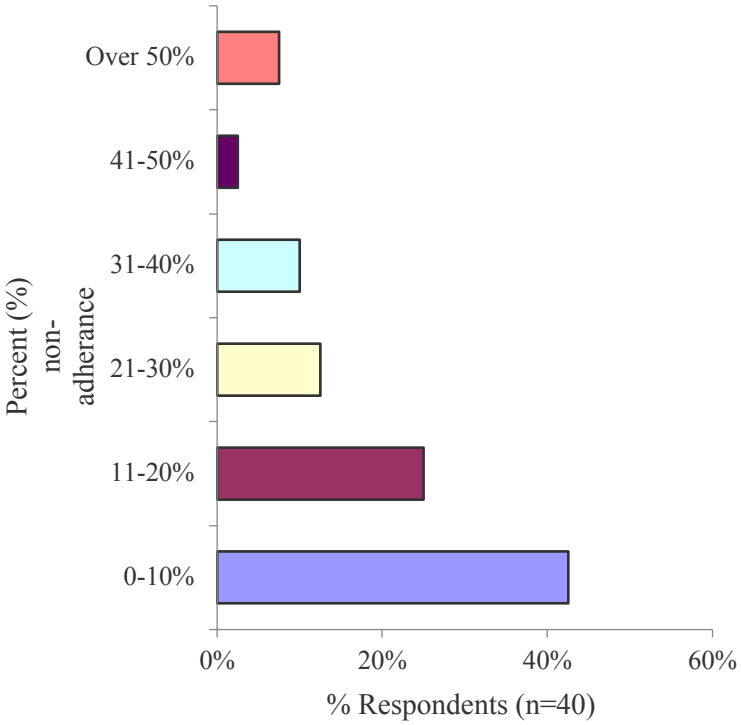


Figure 15: Percentage of patients not adherent to the full SEP

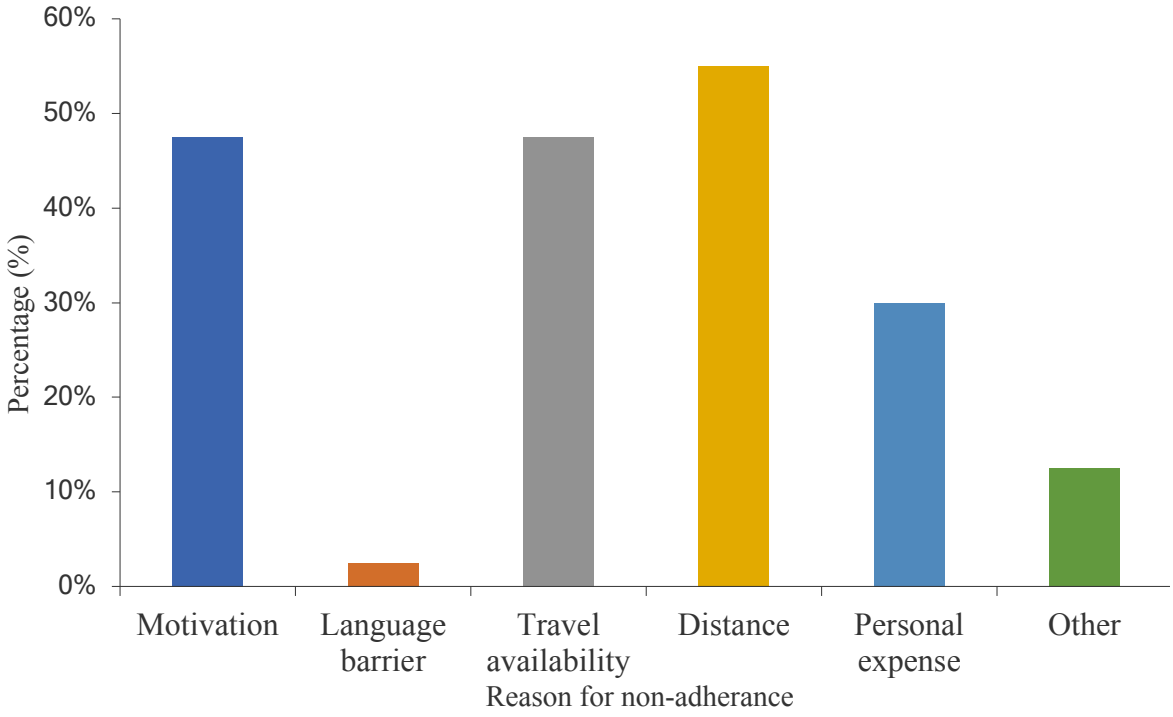


Figure 16: Reasons for non-adherence to SEPs

Of those without access to SEPs, from 76 responses, only 6 (8%) had the facility to refer their patients to other trusts or services for a SEP. For 4 respondents, these SEPs were within 5 miles from the referring institution and the remaining 2 respondents suggested a journey over 15 miles to attend a SEP.

Sixty-six (88%) of 75 total respondents stated that lack of funding was the reason why no SEP was available to them. Lack of suitable staff (44%) was cited as the next main reason for SEP inaccessibility, followed by a lack of suitable resources (24%) (Figure 17). Fourteen respondents suggested other reasons and those that elaborated in the free text suggested these were 'considered to be a primary care responsibility' whilst at the same time suggesting that the 'CCG has refused to fund', with another respondent having set up a SEP but 'awaiting CCG funding'.

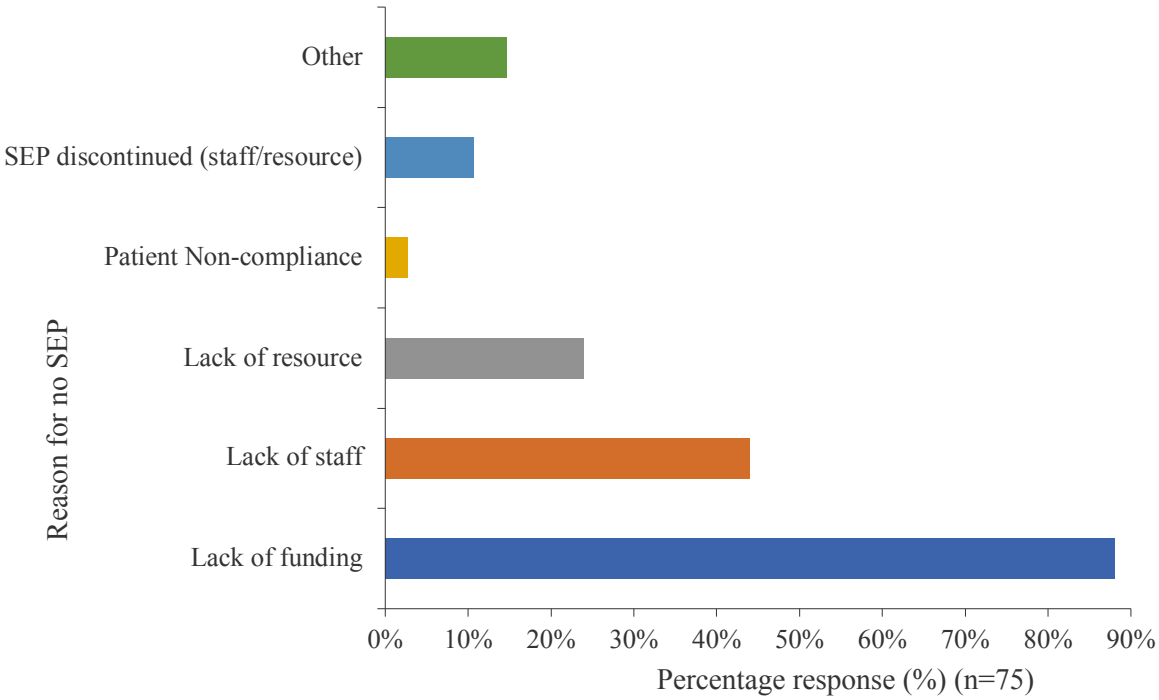


Figure 17: Reasons for no availability of SEP

Alternative advice was provided to patients in this group, mainly verbally (88%) and by leaflet (41%) with the rest referring to online media (4%) or other methods (5%) including input via primary care. Of those respondents with access to a SEP (n=41), 81% provided verbal advice, 76% provided advice by leaflet with 7% referring to online media and the rest using other techniques (7%) including expert led talks at exercise classes, face to face group discussions and community care input.

2.1.4 Discussion

In 2009, Shalhoub et al (Shalhoub, Hamish et al. 2009) carried out a survey audit disseminated by post to the 186 members of the Vascular Society of Great Britain and Ireland (VSGBI) and ascertained that approximately a quarter of 84 respondents had access to a SEP. Of this cohort, only 14% referred all eligible patients for a SEP.

Although there is a significant evidence base for the use of SEPs as a first line management strategy in all able patients presenting with IC, this underutilisation of SEPs seems to be a global problem. Makris et al (Makris, Lattimer et al. 2012) disseminated an online survey in the UK to members of the VSGBI and RSM vascular section; within Europe through the ESVS and the Hellenic Vascular Society; and further internationally through the membership electronic mailing list of the International Society of Vascular Surgery. A total of 378 responses were received from 43 countries with 95% from Europe of which 34% were from UK. In the UK, 36.4% of 129 respondents had access to a SEP. Access to SEPs varied widely from 10% in Greece to 100% in Netherlands (Table 5). The healthcare expenditure as a percentage of Gross Domestic Product (GDP) was included by the author, possibly to identify a link between this and SEP access rates. This ranged from 9.3-11.4% within the countries displayed, however this data cannot reliably be used to provide any correlation with SEP access, unless the apportioned amount for this service per country is known.

Table 5: Availability of supervised exercise programs in selected European countries and healthcare expenditure per country

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((Makris, Lattimer et al. 2012)(*https://doi.org/10.1016/j.ejvs.2012.09.009*)

Countrya	Number of participants in the survey	Access (%) to SEPs per country	Healthcare expenditure by %GDPb
Netherlands	18	100	11.1
France	9	66.7	11.2
Germany	15	46.7	11.3
Italy	21	38.1	8.9
UK	129	36.4	9.3
Switzerland	14	35.7	11.4
Spain	19	10.5	9.3
Greece	40	10	9.7

aOnly countries with at least 9 participants in the survey were included in the above table.
bOECD health data 2009 (http://stats.oecd.org/index.aspx); GDP: Gross domestic product; SEPs: Supervised exercise programmes.

The above studies were conducted prior to the publication of NICE guidance in 2012 recommending SEPs for all patients presenting with IC and published quality standards in 2014 for quality improvement in prioritising SEP as a first line management modality (NICE147 2012, QS52 January 2014). Considering the well-published data on significant functional benefits of supervised exercise, this study is timely in reflecting the shortfall in providing the best level of care for patients with IC and should act as a guide to assist commissioning bodies to channel necessary funding to improve access to SEPSs nationwide (Bendermacher, Willigendael et al. 2006, Fokkenrood, Bendermacher et al. 2013, Lane, Ellis et al. 2014). A re-audit of the availability and access to SEPs should be undertaken prior to the next review of the NICE guidance in 2022, assessing the impact of the quality standards and adopting further strategies to provide patients with evidence based treatment for this early manifestation of PAD. Alternatively, other non-invasive treatment modalities, which

are being developed and researched widely, should be appraised and encouraged if response to these is equivocal or better than SEPs (Abraham, Mateus et al. , Harwood, Green et al. 2018).

2.2 NMES in healthy subjects

2.2.1 Revitive™ IX NMES device use in Healthy subjects

The NMES device of interest for the purposes of this research is the Revitive™ IX NMES device, described in detail above. In addition to being industry sponsored for further research into identifying appropriate vascular clinical indications, this device is regarded as most ideal for assessing efficacy in PAD due to the direct and indirect actions from the most distal aspect of the lower limbs. Precluding any clinical trials, this device has been used to assess circulatory effects on the lower limbs of healthy volunteers.

In 2012, Mileva et al (Mileva 2012) measured foot and calf tissue perfusion and skin temperature with laser Doppler flowmetry (LDF) and tissue oxygenation by near infra-red spectroscopy (NIRS) in healthy participants whilst using the Revitive™ IX NMES device. Sixteen healthy volunteers (11 male, 5 female; 28.31+/-1.96 years old, age range 19-48 years) acted as their own controls in this crossover study where the same cohort had repeated measurements taken following voluntary exercise (VE), at least one day later, using the IsoRocker® activated only, with the NMES device turned off, for the same 30 minute cycle duration. The blood flux, measured by LDF was significantly increased in the ES group compared to baseline, increasing 10 fold in the foot (1088.39+/-168.14%, $P<0.001$) and 7 fold in the calf (696.11+/-82.2%, $P<0.001$) (Figure). The VE group also showed increases in blood flux compared to baseline, but to a much lower degree in both the foot (316.75+/-38.29%, $P<0.05$) and the calf (235.03+/-26.06%, $P<0.05$) respectively.

The tissue oxygenation, measured by a reduction in deoxyhaemoglobin levels, was significantly improved in both groups with no significant intergroup difference ascertained in both the foot and calf.

Although there were no retention effects on blood flux in both foot and calf following ES or VE, there was a significant retention effect of oxygen saturation in the foot in the ES group (8.3+/-5.08%; $P<0.05$), which was not seen in the calf.

This was a key study, showing a beneficial micro-circulatory effect of one 30 minute cycle of the Revitive™ IX device in healthy volunteers.

2.2.2 Haemodynamic changes in Healthy Subjects with the Revitive™ IX NMES device

Varatharajan et al (Varatharajan, Williams et al. 2014) assessed the lower limb haemodynamic effects of the Revitive™ IX (Actegy Ltd, UK) NMES device in healthy volunteers. Those with good general health, over the age of 18 years and with an ABPI over 0.9 were included in the study. In 10 healthy participants who experienced a 30 minute stimulation cycle of the device with the IsoRocker® activated, duplex ultrasound measurements of the femoral vein were taken at baseline, 15 minutes into the cycle and immediately post cycle. Similarly, in a separate cohort of 20 healthy individuals, undergoing the same stimulation parameters and cycle, arterial inflow haemodynamics over the superficial femoral artery were measured. Lower limb haemodynamic assessment was made using a Philips iU22 Doppler ultrasound scanner with an L12-5 vascular probe and standard flow volume measure protocols. These measured blood flow (cc/minute) and time averaged mean velocity (cm/second) over the superficial femoral artery and vein respectively. Measures were taken at baseline, 15 minutes post stimulation and immediately after

completion of one cycle of stimulation. An average of 3 readings taken at each time point was calculated and data was analysed by Wilcoxon matched-pairs signed rank test on GraphPad Prism 6 with a significance level set at 95%.

In 10 healthy volunteers (6 males, 4 females; average age 34 years, age range 21-63 years) the venous blood flow increased significantly at 15 minutes into the NMES stimulation compared to baseline (88 cc/min, 31% increase; $P<0.05$) (Figure 18).

In 20 healthy volunteers (10 males, 10 females; average age 41 years, age range 23-64 years), compared to baseline, there was a significant increase in superficial femoral artery blood flow (39 cc/min, 53% increase; $P<0.0001$) and TAMV (2.2 cm/sec, 62% increase; $P<0.001$) (Figure 18).

There was no retention effect of either blood flow or TAMV seen in either the superficial femoral vein or artery.

Interestingly, the beneficial micro-circulatory effects from the study by Mileva et al (Mileva 2012) were replicated in the haemodynamic measurements of the superficial femoral vessels.

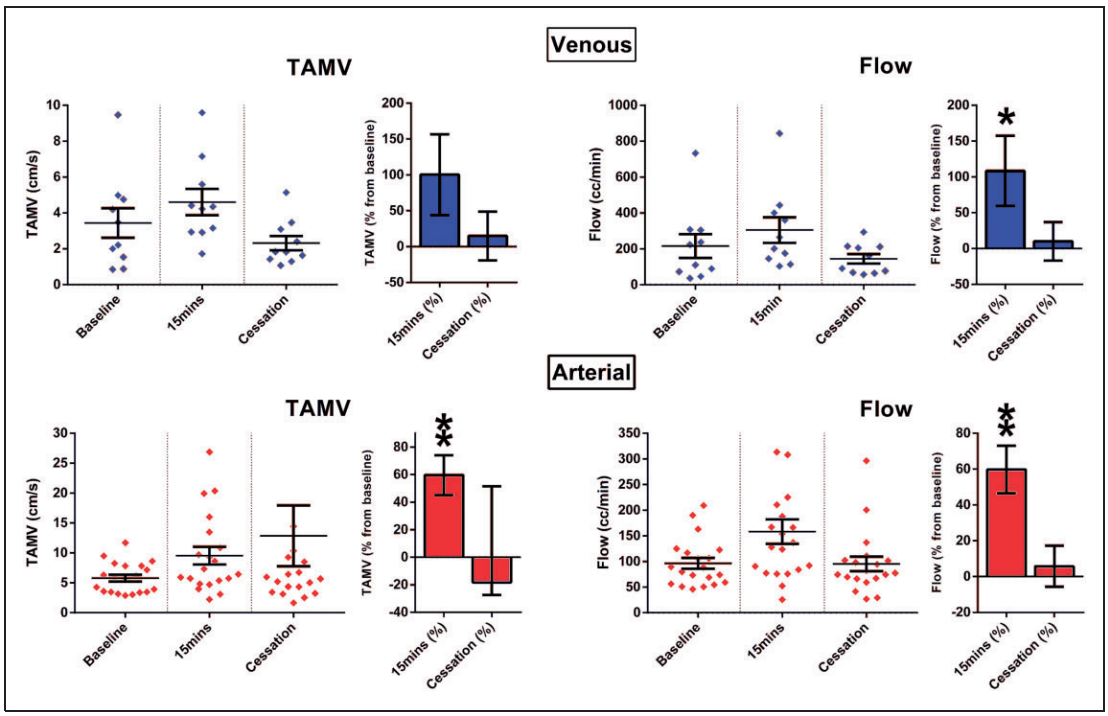


Figure 18: Change in blood flow (cm/sec) and time averaged mean velocity (cm/sec) in the superficial femoral vein and artery at baseline, 15 minutes with NMES stimulation and immediately post stimulation.

Permission granted as gratis reuse by Phlebology Journal, Sage publishing (Varatharajan, Williams et al. 2014)

Improvements in lower limb circulation as highlighted by the above studies provide a good basis for further research into the clinical applications of the Revitive™ IX NMES device.

2.3 Literature review of NMES in PAD

2.3.1 Introduction

Supervised exercise therapy, the current gold standard non-invasive management strategy for the early manifestation of PAD and proven to improve functional and quality of life outcomes, is an underutilised resource and largely inaccessible to referrers (Shalhoub, Hamish et al. 2009, Makris, Lattimer et al. 2012, NICE147 2012, Fokkenrood, Bendermacher et al. 2013, Hageman, Fokkenrood et al. 2018). The development of medical devices that are more accessible, clinically efficacious and cost effective is required to support exercise therapy. Intermittent pneumatic compression has shown promise in the amplification of lower limb arterial circulation (Delis and Nicolaides 2005) as reviewed in section 1.1.7.4, above. However, this technology has limitations of use, including long therapeutic sessions, costly, discomfort and restriction (de Haro, Acin et al. 2010).

A prior literature review was conducted and published with colleagues, looking at the utility of medical devices including IPC and electrical stimulation devices (NMES, FES, Galvanic, TENS) in PAD (Williams, Babber et al. 2017). The scope of this review was widespread and therefore repeated for the purposes of this thesis, to concentrate on NMES devices and current knowledge base on their utility in the management of PAD, specifically intermittent claudication.

2.3.2 Methods

Ovid Medline (1946 to March 2018) and Embase (1947 to May 2018) databases were scrutinised using the following search strategy:

["Neuromuscular Electrical Stimulation" OR "Electri* device" OR "Electric* Stimul*"] AND ["Lower limb" OR Lower Extrem*" OR "Limb" OR "Leg"] AND ["Peripheral Arterial Disease" OR "Peripheral Vascular Disease" OR "Lower limb occlusion" OR "Intermittent Claudication" OR "claudication"]

The initial search was deduplicated and followed by limitation to English language and clinical trials of any kind. The subsequent exclusion process of title review, abstract review and full text review was carried out in line with criteria requirements for this review. Papers were included if an intervention involved electrical stimulation with visible muscle contraction (NMES), was a clinical trial of any kind, with walking distance or haemodynamic measures as outcomes in a population with stable claudication. Exclusions included any other devices including spinal cord stimulation devices or invasive stimulation devices, treatment of severe PAD including CLI and those without objective outcomes. A further search of papers was conducted through the search engine 'Google'. This search strategy was updated on 23rd May 2018.

The PRISMA diagram for the above search strategy is shown in Figure 19 below.

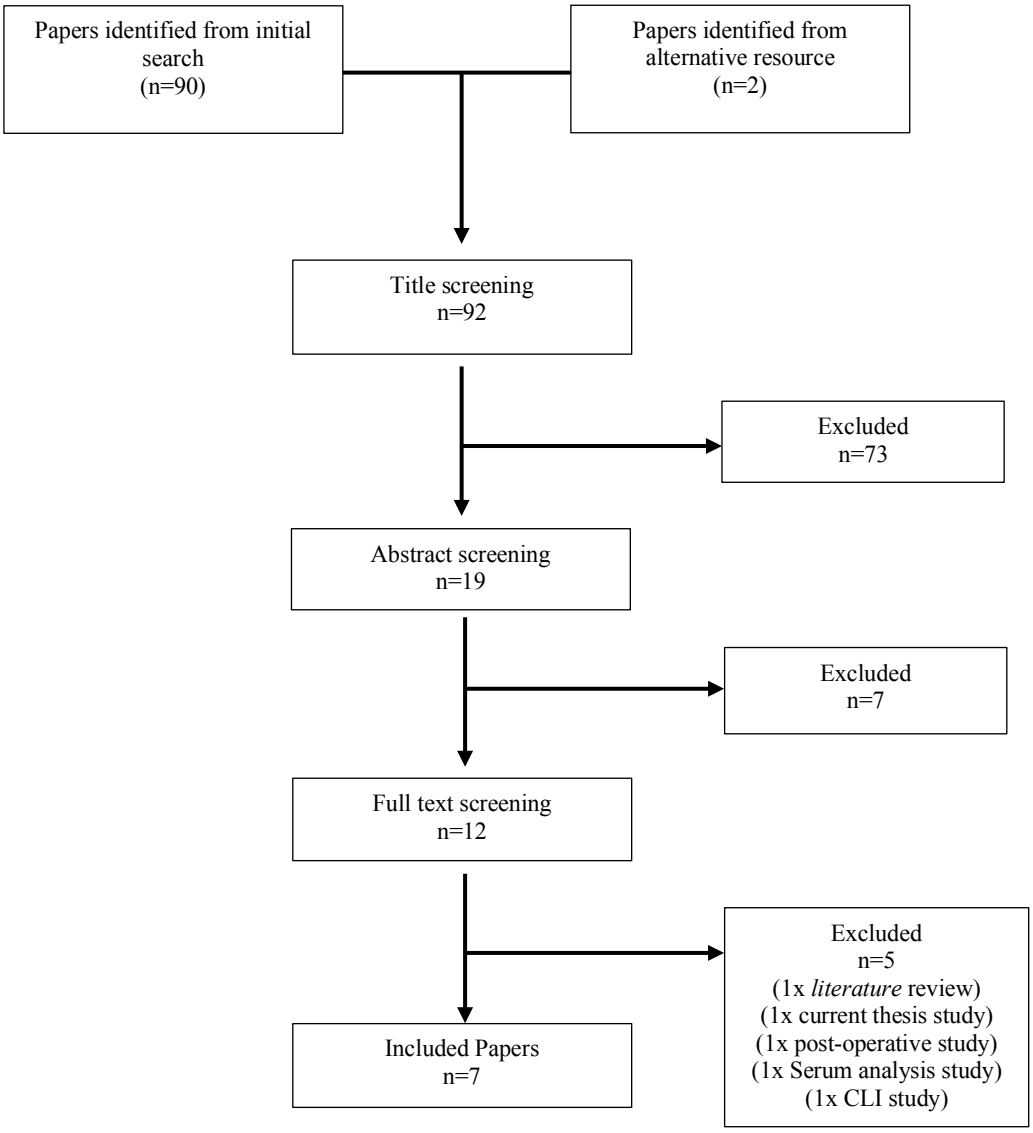


Figure 19: PRISMA diagram of literature search showing process of study inclusion and exclusion

2.3.3 Results

Seven papers matched the criteria for inclusion into this literature review of NMES in the management of IC. A summary of the included studies can be found in Appendix 7.3.1.

A meta-analysis of the studies could not be carried out due to the significant heterogeneity of the studies in terms of intervention used, the intervention protocols and outcomes.

From an NMES perspective, this updated literature review added 2 further studies to the previous review which searched the literature to July 2013.

Studies were analysed according to outcome changes as follows.

2.3.3.1 Haemodynamic changes

Ellul et al studied the use of the Veinoplus™ (Adrem Tech, France) device in a pre-test, post-test study of 40 patients over 12 weeks and found a significant increase in post-test ABPI measures ($P<0.001$) at rest (Ellul, Formosa et al. 2017). The remaining studies did not show a significant change in ABPI with their respective protocols post intervention.

Two studies formally assessed duplex ultrasound measured blood flow in the femoral artery. Abraham et al studied the Veinoplus™ device in an observational study of stable claudication patients during 1 session of 20 minutes stimulation and found a 240% increase in blood flow when the device was providing stimulation at the rate of 100 bursts a minute (Abraham, Mateus et al. 2013). However, using a different device and protocol, Guirro et al, in a crossover study also including the use of continuous shockwave diathermy and physical exercises as separate intervention protocols with 7 day washout periods in between, showed

no change to femoral, popliteal or posterior tibial blood flow before or after the intervention period in any group (Guirro, Guirro et al. 2015).

2.3.3.2 Walking Distances

Studies assessed both initial claudication distance, defined as the distance walked before onset of symptoms and maximum claudication distance, defined as the distance at which the patient stopped due to IC symptoms. This was given various nomenclatures including absolute claudication distance (ACD), absolute walking distance (AWD), maximum walking distance (MWD and maximum claudication distance (MCD). This outcome was assessed by a variation of fixed (Hudlicka 1994, Tsang, Green et al. 1994, Anderson, Whatling et al. 2004) and graded treadmill test (Ellul, Formosa et al. 2017). All studies showed an NMES related significant increase in initial and maximum claudication distances ($P<0.05$). The largest change seen was an improvement in ACD by 141% ($P<0.0001$) (Ellul, Formosa et al. 2017) and ICD of 133% ($P<0.004$) (Tsang, Green et al. 1994).

2.3.3.3 Fatigue Index

This is a measure of the functional ability of a muscle group over time. This index is measured by resting the foot flat on a plate with strain gauges attached that measure the torque (force) of plantarflexion during calf muscle contraction. The foot is kept flat on the plate by means of a knee strap to prevent the foot lifting off the plate during muscle contraction. Contraction occurred by continuous stimulation of plantar flexors (6 Hz and 350 μs pulse width) over a 5 minute duration. Measures of the plantar flexion torque were then taken every minute and presented as a ratio of the baseline torque (Tsang, Green et al. 1994). The higher the ratio the more normal and healthier the contraction.

This FI was reported as being significantly higher after NMES stimulation than control intervention with TENS by up to 200% ($P<0.05$) (Hudlicka 1994). This index however, returned to baseline 4 weeks after intervention cessation (Tsang, Green et al. 1994).

2.3.3.4 Skin Temperature

Skin temperature was reported by 2 studies conflicting in their findings. Loubser et al noted no significant change in pedal temperature after 1 session of NMES over 60 minutes of the common peroneal nerve and dorsum of the foot (Loubser, Cardus et al. 1988). However, in a study looking at the Veinoplus™ device, there is a statistically significant increase of 2° C ($P<0.05$) in thermographic assessment of pedal sole temperature measured using a special thermal sensitive camera (Ellul, Formosa et al. 2017). The inference is that increased temperature is a reflection of increased blood flow in the region of interest.

2.3.4 Conclusion

This updated literature review includes 2 further studies of NMES in the management of patients with IC (Guirro, Guirro et al. 2015, Ellul, Formosa et al. 2017), both published after the search date of the previous review (Williams, Babber et al. 2016).

Walking distances remain the main endpoint of choice of most of the recent studies as this outcome is suggested as a valid and reliable assessment of functional ability (Kruidenier, Nicolaï et al. 2009). Interestingly, none of the included studies assessed quality of life as part of their outcomes.

This literature review shows that there is ongoing paucity of robust studies in the field of NMES use in IC. The studies are small in sample size with a wide degree of variation on

devices used, intervention protocols, NMES dosages, outcomes assessed and method of outcome assessment. This makes it difficult for a statistically robust comparison between the studies precluding a meta-analysis.

However, the literature does confirm that NMES as a novel technology, which is improving in knowledge and technique over time, does have a positive effect on the functional and haemodynamic limitations of IC. These findings support further research to add to the evidence base of NMES in the management of PAD and further attempt to assess the mechanism by which this may help functional parameters.

2.4 Mechanisms of NMES on lower limb blood flow and muscle

Mechanistic suggestions of the benefit of NMES in lower limb arterial disease may be similar to those for IPC, discussed in section 1.1.8.1. These include improved blood flow due to augmentation of the calf muscle pump in creating a pressure gradient, sympathetic autoregulation to cause vasodilation of arterioles and shear stress induced vasoactive factor release to promote muscle angiogenesis (Delis, Nicolaides et al. 2000, Delis, Nicolaides et al. 2001, Delis and Nicolaides 2005).

Studies conducted with healthy participants and those with venous disease using NMES have shown enhancement of the venous blood flow in the lower limb (Griffin, Nicolaides et al. 2010, Varatharajan, Williams et al. 2015, Ravikumar, Williams et al. 2017). A study by Nådland et al on 20 healthy volunteers undergoing calf muscle contraction by plantarflexion exercise suggested the femoral artery blood flow measured by duplex ultrasound, significantly increases within 15 seconds of exercise in the tilted position (0.5L/min, $P<0.05$). After 80 seconds of calf muscle exercise, this increase in femoral artery flow had plateaued to 0.39L/min. The study proposes that the calf muscle pump may be linked directly to improved muscle perfusion by increasing arterial haemodynamics to the lower limb in the short term. However, in the longer term, this is maintained by metabolic vasodilation processes (Nadland, Walloe et al. 2009).

Increased blood flow is considered to assist a fatigued muscle recover by the rapid removal of anaerobic metabolic by-products like lactic acid and enhance the oxygen supply to the target muscle (Babault, Cometti et al. 2011).

Studies assessing the utility of extracorporeal shockwave therapy suggest mechano-transduction is a stimulus for angiogenesis promoting the release of angiogenic factors like vascular endothelial growth factor in the muscle tissue thereby increasing the oxidative capacity of the muscle (Green, Harwood et al. 2018, Harwood, Green et al. 2018). Whether this mechanism could be related to NMES use is unknown, but may seem like a valid theoretical suggestion and further research would be recommended.

NMES may also alter metabolic and structural elements of the skeletal muscle including the oxidative capacity, or mitochondrial ability to process the delivered oxygen efficiently for energy purposes; and muscle fibre type (Sillen, Franssen et al. 2013). However, studies are heterogenous in devices used, methodologies and protocols such that a meta-analysis is not possible. Further research is required in this area, as progressive understanding of the mechanistic processes for NMES causing effective change in muscle type can assist in identifying targets for management of easily fatigued muscle as seen in PAD.

3 NMES in PAD Studies

3.1 Measures and Outcomes

3.1.1 Ankle Brachial Pressure Index (ABPI)

Following extensive review, TASC II guidance suggests measuring ABPI in all patients with symptoms suggestive of PAD (Norgren, Hiatt et al. 2007). A more extensive review and technique of measurement is provided in the Diagnosis (page 47) section of Chapter 1 ‘Background' of this thesis and Figure 3.

3.1.2 Treadmill walking distances

Treadmill testing has been used extensively in measuring objective data in patients with PAD and this is recommended by TASC II guidelines for an objective measure of improvement in claudication secondary to an intervention (Laing and Greenhalgh 1986, Norgren, Hiatt et al. 2007).

Studies report a mixture of treadmill protocols including graded tests, whereby a fixed speed is pre-set (usually 2km/h) with the inclination of the treadmill increasing from the flat (0%) by 2 % every 2 minutes (Gardner, Skinner et al. 1991); and fixed load tests, where a constant speed is paired with a constant inclination for the whole of the test (Cheetham, Burgess et al. 2004). There are mixed views on the superiority of any particular treadmill protocol in reliability and reproducibility in measuring walking distances in patients with IC. Labs et al assessed the utility of a repeated graded treadmill test and compared the reliability to a constant (fixed) load treadmill test in a cohort of 330 patients undergoing assessment for the utility of an oral prostacycline in the management of IC. There was a 2 week study run-in

period with weekly graded treadmill test (2mph, 0% gradient increasing by 2% every 2 mins) performed, followed by graded and constant load treadmill (2mph, 12%) test at the entry into the study and a repeat of these measures at 3 months. Using reliability coefficient (RC) and relative precision (RP) calculations based on test process and between patient variances, the study found that the graded test was highly reliable (RC 0.952, RP 21.9%) in the study run in phase for assessment of the ACD. During the whole study phase the reliability of the graded test was 0.902 (RP 31.3%) and for the constant load test was 0.876 (RP 35.2%). The reliability for ICD using either test was lower. The study found that, for non-severe forms of IC, the graded and constant load treadmill tests are comparable. In severe IC the graded test is more preferable (Labs, Nehler et al. 1999). The reliability of the constant load test is related to the inclination with a higher inclination providing a more reliable test (10%: 0.89, 95% CI 0.86-0.91; 12%: 0.91 95% CI 0.88-0.92) (Nicolaï, Viechtbauer et al. 2009). The latter study recommended the use of the graded test for ACD measurement as superior to constant load treadmill test. Constant load treadmill tests also remain a reproducible and valid method of walking distance assessment with good reproducibility in IC patients (Falkensammer, Gasteiger et al. 2012).

For the initial and absolute claudication distance measurement, a fixed load treadmill test was carried out at 3.5 km/h with a 10% gradient. The initial claudication distance (ICD) is the distance walked until the onset of pain and the absolute claudication distance (ACD) is the distance walked before the participant is forced to stop due to typical pain. The choice of this test was based on its reproducibility, accepted reliability, local walking distance assessments for supervised exercise therapy and limitations of the treadmill testing equipment available.

The treadmill equipment available for walking distance analysis within the department is not digitally automated, requiring manual changes to be made according to a needle dial indicator for speed and angle of inclination. These parameters are easier and more accurately set before the start of the treadmill machine, which commences at the inclination angle required with a short build-up of speed to the pre-selected value. A handrail is present for safety reasons and patients are allowed to momentarily use this for initial balance purposes.

3.1.3 Adherence

A diary card of when the device will be used will be kept. This acts as a compliance measurement tool. Participants will be trained in the usage of the device, which has been manufactured with home users in mind. They will be provided with the NMES device. Participants will be asked to use the device for one 30 minute session daily for 6 weeks and will be shown how to complete the patient use diary. Patients are instructed to complete the diary card on a daily basis, noting the stimulation intensity used and time. If the device was not used, patients were asked to mark this in the diary and provide a reason if willing to.

3.1.4 Quality of Life questionnaires

Recommendation 13 of the TASC II guidelines includes the use of validated disease specific and generic health related questionnaires for assessing efficacy of treatment in patients with PAD (Norgren, Hiatt et al. 2007).

For the purpose of the clinical trials, the validated disease specific questionnaire that will be used is the Intermittent Claudication Questionnaire. The RAND Short Form-36 (SF-36) and EuroQoL 5 Dimension 5 Level (EQ-5D-5L) will be the generic quality of life questionnaires to be used in these trials.

3.1.4.1 Euro-QoL-5 Dimension Questionnaire (EQ-5D-5L with VAS)

This is a commonly used quality of life health survey looking at with scoring based on replies to questions about pain, anxiety/depression, mobility, usual activities and self-care. This is a valid and reliable measure of generic QoL in patients with cardiovascular diseases (Dyer, Goldsmith et al. 2010) also allowing economic analysis in the form of quality adjusted life years (QALYs) to be calculated (Whitehead and Ali 2010). The EQ-5D correlates well with the disease specific Intermittent Claudication Questionnaire (ICQ) (Chong, Garratt et al. 2002).

3.1.4.2 RAND Short Form 36 Questionnaire (SF-36)

The short form 36 health questionnaire is based on 36 general health and emotion related questions that can be divided into 8 domains for scoring purposes. This is a widely used generic quality of life survey with good validity and reliability with strong recommendations for use with vascular patients (Regensteiner, Steiner et al. , McHorney, Ware et al. 1993, Regensteiner, Hiatt et al. 2008). The domains measured by this questionnaire include Physical function, Role limited by Physical Health, Pain, Role limited by Emotional and mental health, General health, Vitality and Social function.

3.1.4.3 Intermittent Claudication Questionnaire (ICQ)

This disease specific questionnaire was developed by Chong et al in 2002 as an instrument to measure quality of life in patients suffering IC. It is a 16 item health related questionnaire assessed for reliability and validity amongst other outcome measures. The Cronbach's α score for reliability was 0.94, measuring consistency between the items making up the questionnaire. Validity analysis suggested good correlation between the ICQ and EQ-5D

(*r*=0.58) and 7 of the domains from the SF-36 (*r=0.33-0.68)* questionnaire (Chong, Garratt et al. 2002).

3.1.5 Ultrasound Haemodynamic Assessment

The use of high frequency sound waves from a transducer can be used to pass through areas of the body with reflecting echoes picked up by the same transducer, converted to form images and waveforms according to intensities received. These can be analysed to provide further information relevant to the anatomy that is being assessed.

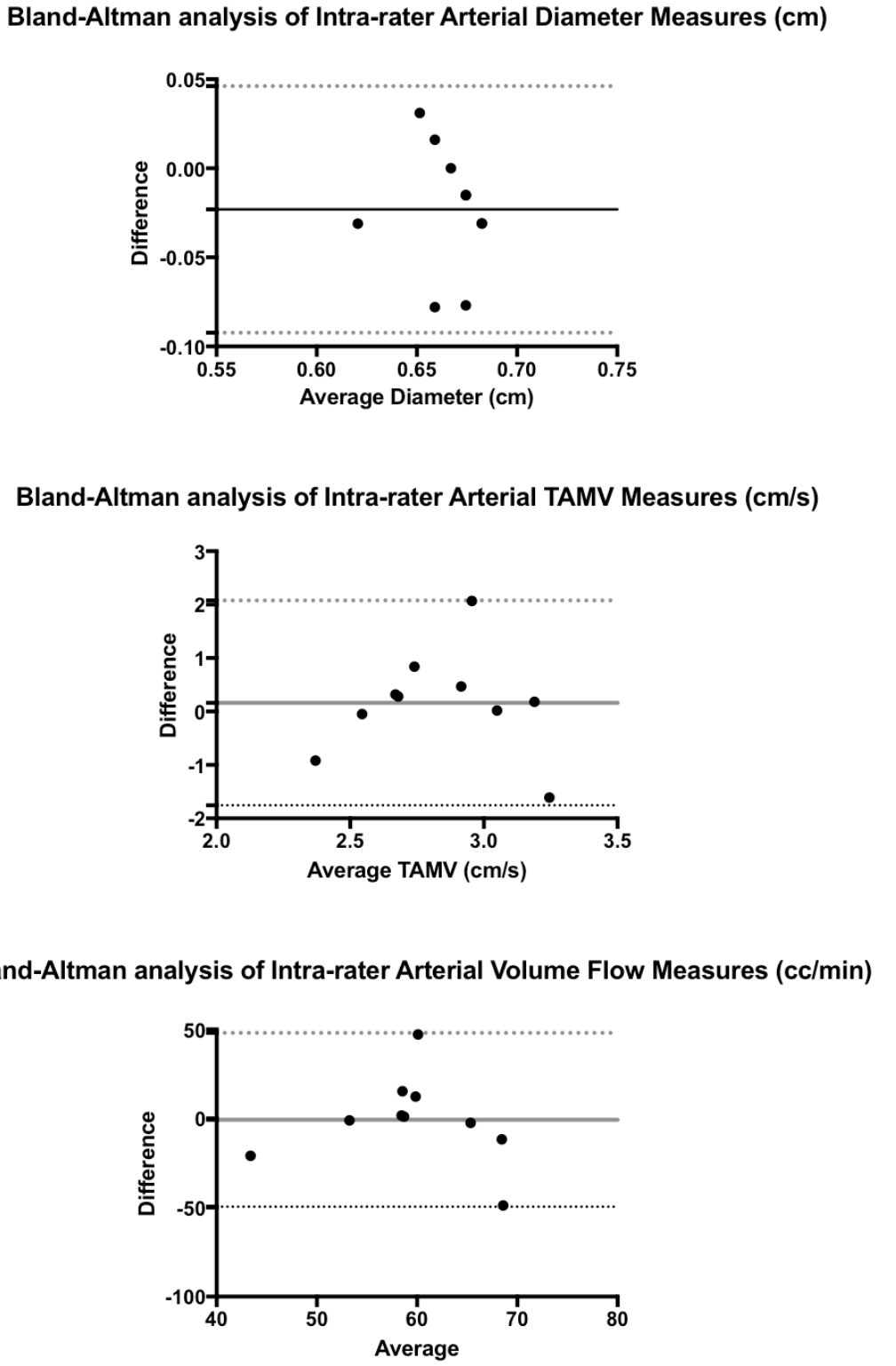
A Phillips iU22 Ultrasound machine, with a L12-5 transducer probe and vascular flow measurement protocol, was used to assess arterial diameter, time adjusted mean velocity (cm/s) (TAMV) and blood flow (cc/min) in the superficial femoral artery. Standard pre-set flow volume measurement protocols will be used. Haemodynamic flow measures will be taken approximately 10-15 cm below the mid inguinal point over the superficial femoral artery in longitudinal orientation. The optimal position for transducer placement will be marked using a marker pen on the skin, such that the longitudinal view of the SFA encompasses the maximal inner to inner arterial diameter. In keeping with accepted standards for blood flow assessment in the femoral artery, an angle correction of 60° will be adopted.

Reliability of duplex ultrasound measurements of haemodynamic parameters are user dependent with inter-observer variation of volumetric blood flow assessment at the SFA reported as up to 20% (Hussain, Smith et al. 1996). A validation study, detailed below, was undertaken.

3.1.5.1 Ultrasound scan validation study

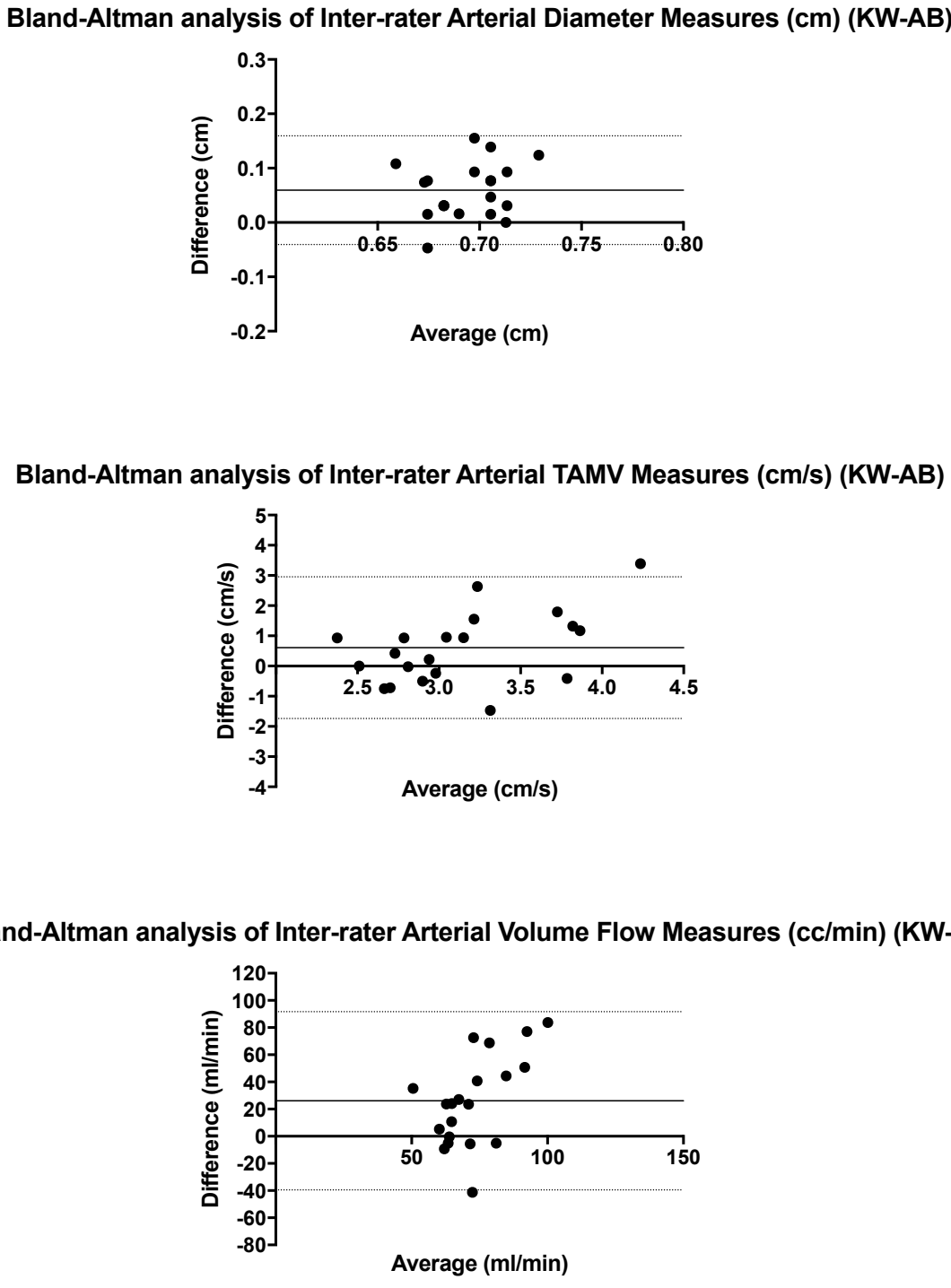
A validation study to assess the accuracy and reproducibility of ultrasound measures was completed. Measures were completed by 2 individuals (AB and KW).

A single healthy subject sitting in a chair with knees flexed at 90° underwent a sequence of 10 arterial duplex measurements of the right superficial femoral artery over 15 seconds measuring blood flow (cm/sec), TAMV (cc/min) and vessel diameter (cm). Following a short break of 45 minutes, another 10 measurements were repeated. Bland-Altman analysis and coefficient of variance were undertaken using Prism 5 software (GraphPad Software Inc). A significance level of 0.05 was used.



(solid line: bias; dotted line: 95% confidence intervals)

Figure 20: Bland-Altman analysis of the intra-rater reliability of ultrasound haemodynamic measures of the Femoral artery



(solid line: bias; dotted line: 95% confidence intervals)

Figure 21: Bland-Altman analysis of Inter-rater reliability of Ultrasound haemodynamic measures (KW-AB)

Intra-rater reliability analysis shows all measures to fall within the 95 % confidence intervals (Figure 20). The coefficient of variation measured for arterial diameter, TAMV and arterial volume flow were 3.85%, 19.9% and 24.3% respectively (AB). The same coefficient measurements for KW were 5.0%, 23.1% and 24.9% respectively.

The inter-rater reliability measures also suggest accuracy and reproducibility lying within the 95% confidence interval sufficient (Figure 21). The average bias for arterial diameter, TAMV and volume flow between AB and KW were 0.059, 0.61 and 26 respectively.

In agreement with published data, the intra-observer variation is far less than inter-observer variation. (Hussain, Smith et al. 1996). Ultrasound haemodynamic assessment will be taken and repeated by the author for all studies requiring this outcome measure

3.1.6 Tissue Oxygenation

3.1.6.1 Laser Doppler Flowmetry (LDF)

This device uses laser wavelength technology through optical probes to assess the temperature and skin microcirculation (Arbitrary units or au), called blood flux. Laser doppler flowmetry is a measure of the skin microcirculation or perfusion. The probe emits a laser set at a wavelength at 780nm, which is absorbed by the superficial skin and is able to assess the microcirculation with respect to the movement of red blood cells. This measure is sensitive to ambient temperature and movement, which creates signal artefact making this a poorly reproducible measure. Due to this, it is an appropriate assessment of the microcirculation within a particular patient, at the time of measurement, but difficult to form accurate comparisons between timepoints and cohorts.

A dual channel moorVMS-LDF (Moor instruments, UK) was used in this cohort of patients. Optical probes on fibre optic leads attached to the LDF monitor, were placed on the back of the hand and back of the foot using a probe specific adhesive tape after cleaning the skin. Patients had rested for at least 15 minutes prior to using the LDF instrument.

3.2 Supervised Exercise Programme

The SEP was conducted within the same trust that patients were screened at for the inclusion into this study, specifically at Charing Cross Hospital, part of the Imperial College Healthcare NHS Foundation Trust. Patients were normally appointed between 2-3 weeks after vascular outpatient referral and attended the baseline appointment for this clinical trial within a week of their SEP start date.

The SEP was specific for IC patients and took place in an open gym facility in the physiotherapy department. The programme included a 1 hour session weekly for a total 6 month duration and involved a circuit of lower limb muscle specific exercises including walking, steps, treadmill, exercise bike, obstacle walk and passive stretching. As well as being specific for IC, these exercises are complimentary to general cardiovascular health. Supervision was provided by a physiotherapist who provided motivation during the circuit training as well as ensuring the correct techniques were applied to gain maximum efficiency of the exercises in accordance to patients abilities. Class size was normally kept up to 8 participants to provide everyone with sufficient access to all the gym equipment.

An audit of the outcomes of this SEP was conducted and presented as a poster at the Society of Academic Research in Surgery meeting in January 2015 (Babber A 2015). Over a 6 month time period, 56 patients approximately doubled their ICD ($P<0.0001$) and 63 patients significantly improved MCD by 57 metres ($P<0.0001$) at the same time (Appendix 7.5).

3.3 Statistical Analyses

All raw and scored data for the outcome measures was transcribed into a database on Microsoft Excel (MS Office software, version 2016). Further basic analysis, including percentages and means, were completed using the MS Excel software with any formulated statistical analysis completed using GraphPad Prism software (GraphPad Software, Inc. Version 5.0-7.0, USA).

Where appropriate, the data underwent normality testing using both the D'Agostino & Pearson test and Shapiro-Wilk test. Probability analysis for paired normal data (repeated measures of same patient) involved parametric analysis by paired t test; non-normal data underwent the non-parametric paired Wilcoxon matched-pairs signed rank test; and unpaired, non-normal data underwent the non-parametric Mann-Whitney test. If normality testing suggested a mixture of normal and non-normal datasets, in keeping with accepted statistical principles, further probability analysis was by non-parametric test.

Ultrasound repeated measures were collected over 3 timepoints including at rest, device 'ON' (15 minutes into stimulation cycle) and device 'OFF' (immediately post cessation of stimulation cycle). This data was subject to a one way Analysis of Variance (ANOVA) with further post hoc analysis conducted with Bonferroni correction to assess the probability of each compared grouping.

LDF data was analysed using the licensed instrument specific Moor VMS software and transcribed appropriately into MS Excel and GraphPad for further analysis as above.

Probability values were considered significant if less than 0.05, suggesting a less than 5% chance of the result occurring due to chance. This level is deemed acceptable to control for type I errors.

3.4 NMES in the Management of Intermittent Claudication

3.4.1 Introduction

Following on from the positive effects on lower limb haemodynamics seen in the healthy volunteer studies undertaken by Mileva et al (Mileva 2012) and Varatharajan et al (Varatharajan, Williams et al. 2014) it was deemed ideal to undertake a proof of concept pilot study in patients with IC as the primary clinical study of the effect of NMES in patients suffering PAD. Referral to a supervised exercise programme, although recommended by all major clinical guidelines (Norgren, Hiatt et al. 2007, Singer, Imfeld et al. 2012) as primary management of all IC patients, is not always possible and this is a heavily underutilised management strategy worldwide (Shalhoub, Hamish et al. 2009, Makris, Lattimer et al. 2012). Patient factors are a large part of the non-adherence to SEPs. These include distance and travel inconvenience to the hospital site undertaking the SEP and lack of motivation (Babber A 2015). Therefore, these patients were more likely to receive best medical therapy to control risk factors for PAD and advice to exercise in their own time. These patients were most suitable for this pilot study to assess the effect of NMES intervention.

3.4.1.1 Aims

The aim of this study was to investigate the efficacy and functional change of neuromuscular electrical stimulation in patients with Intermittent Claudication.

3.4.1.2 Null Hypothesis

The null hypothesis (H_0) states that there will be no improvement in walking distance with neuromuscular electrical stimulation in patients suffering with intermittent claudication.

3.4.2 Inclusion and Exclusion criteria

The main inclusion and exclusion criteria for recruitment into this study are as shown in Table 6 below.

Table 6: Inclusion and Exclusion criteria

Inclusion criteria	Exclusion Criteria
Age >18 years All ethnic groups BP <160/100 No tissue loss	Any unstable condion deemed unreliable or incapable of complying with protocol (Psychiatric disorder, substance abuse) Diabetes ABPI >0.9 Pacemaker or implanted defibrillator device Recent lower limb injury or low back pain

3.4.3 Ethical Approval and Registration

Ethical approval was gained from the NRES Committee East of England – Cambridge Central (REC Reference: 14/EE/0086). Approval was also gained from the MHRA. In accordance to the conditions of ethical approval, this study was registered on the clinicaltrials.gov database under registration number NCT02436200.

3.4.4 Methodology

3.4.4.1 Study Design

This is proof of concept trial is a prospective, observational cohort study in patients with intermittent arterial claudication of the lower limbs.

3.4.4.2 Sample size

The target study sample size was 20 patients. In view of little previous research in this area, it has not been possible to calculate a target sample size using power calculations. The chosen target provides a plausible, realistic sample size within the clinical setting in order to achieve the study aims for the proof of concept study, forming the basis for planning ongoing NMES in PAD studies.

3.4.4.3 Methods

Eligible patients, meeting the above inclusion criteria, were identified from the vascular outpatients clinic at Charing Cross Hospital. They were provided with a patient information leaflet (Appendix 7.1.1) detailing the study aims and patient involvement in this trial. Patients willing to participate were recruited either immediately to attend an initial appointment or contacted within a few days of clinic attendance to confirm participation and attend an initial appointment.

During the baseline appointment, patients underwent a fully informed consent procedure (Appendix 7.2.1) before demographic and anthropometric data including age, date of birth, smoking status, blood pressure, height, weight and pulse. A full medical history followed by peripheral arterial examination and baseline ABPI measures was then undertaken (Figure 3). All patients underwent a fixed load treadmill test at 3.5 km/h at 10% gradient to measure the

initial claudication distance (ICD), or distance at onset of IC pain; and maximum claudication distance (MCD) or the maximum distance before stopping the treadmill test due to lower limb pain. Following the treadmill test, patients were required to rest for at least a 15 minute period during which the relevant quality of life questionnaires were completed including Intermittent Claudication Questionnaire (ICQ) (Appendix 7.4.1 below), EuroQoL-5D (EQ-5D) (Appendix 7.4.2 below) and Short-form 36 (SF 36) (Appendix 7.4.3 below).

An induction of the NMES device (the Revitive IX device 1.3.6.3 above) was undertaken to identify the patients with the device and also establish the necessary stimulation intensities required to use the device appropriately.

Baseline sensory and motor thresholds were established and noted. The sensory (perception) and motor thresholds were established by systematically varying the stimulation intensity with steps of ±1% maximal output whilst the participant provided verbal feedback indicating whether a tingling sensation had been felt or not. The minimal intensity, which the participant is able to clearly feel, was recorded as the perception threshold, and that producing visible muscle twitches – as the motor threshold. The stimulation intensity for the main interventions were adjusted to produce visible but non-painful contraction of the lower limb calf muscles based on the individual motor threshold (suprathreshold).

These patients were then instructed to complete the test intervention, where a 30 minute neuromuscular electrical foot stimulation session with the device at motor threshold intensity sufficient to evoke lower limb muscle contractions, would be undertaken.

Before starting the test intervention, one laser Doppler flow meter probe was attached to the back of a hand and the other to the dorsum of a foot, allowing the measurement of blood flux and temperature. Using an L5/S probe on the duplex ultrasound machine, baseline haemodynamic parameters were recorded from the superficial femoral artery approximately 10-15 cm below the inguinal ligament, usually on the most affected limb. If this was occluded or poorly visible, the contralateral superficial femoral artery was used.

Haemodynamic data were collected before device use, then at 15 minutes whilst the device was on, and then within 1 minute after stimulation had stopped, i.e. when the device was off.

Patients were supplied with a device to take home and encouraged to complete the patient compliance diary on a daily basis until for the 6 week intervention period. Patients were instructed to use the device for one 30-minute session daily. Telephone support was available 24 hours a day. Support in the form of a 24/7 accessible mobile number was provided. Patients then attended a 6-week follow up appointment where all above measures were repeated. The appointment marked the end of patient participation within the trial (Figure 22).

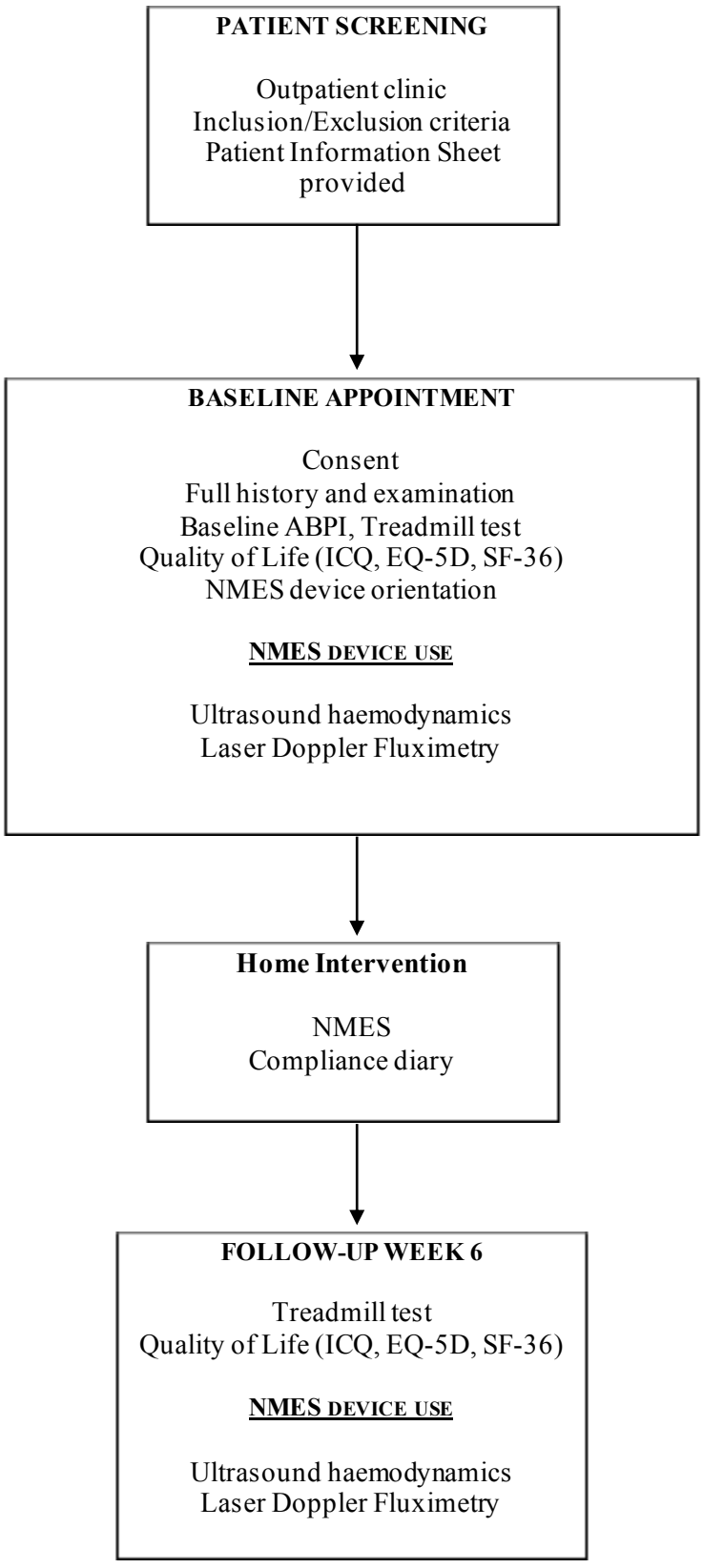


Figure 22: Protocol flowchart of NMES in the management of IC study

3.4.4.4 Outcome measures

The primary outcome of this study is to investigate the efficacy of this neuromuscular electrical stimulator device to improve maximum claudication distance (MCD) in patients with claudication.

The secondary outcome measures include:

Initial Claudication Distance (ICD) – treadmill test

Duplex Ultrasound femoral artery heamodynamics

Blood flux – Laser Doppler Fluximetry

Disease specific questionnaire: Intermittent Claudication Questionnaire (ICQ)

Generic Quality of Life questionnaires: SF-36 and EQ-5D

Patient compliance diary

3.4.4.5 Data analysis

A master database was setup in Microsoft Excel. Data was analysed with the GraphPad Prism software, version 6.0 and above (GraphPad Software Inc.). Statistical analyses were undertaken in the format as described in section 3.3 ‘Statistical Analyses’ above.

3.4.5 Results

3.4.5.1 Patient Flow

Twenty-five patients were deemed eligible from the vascular outpatients clinic and invited to attend the baseline appointment. Due to an inability to complete the treadmill test and therefore attain the primary outcome measure, 4 patients were excluded at this point. An additional patient was a significant outlier with respect to his follow-up treadmill walking distance. This was identified by the ROUT outlier statistical method and therefore excluded from data analysis for risk of data skewness and outcome bias. Therefore, 20 patients were included in the data analysis, meeting the target sample size for this pilot study (Figure 23).

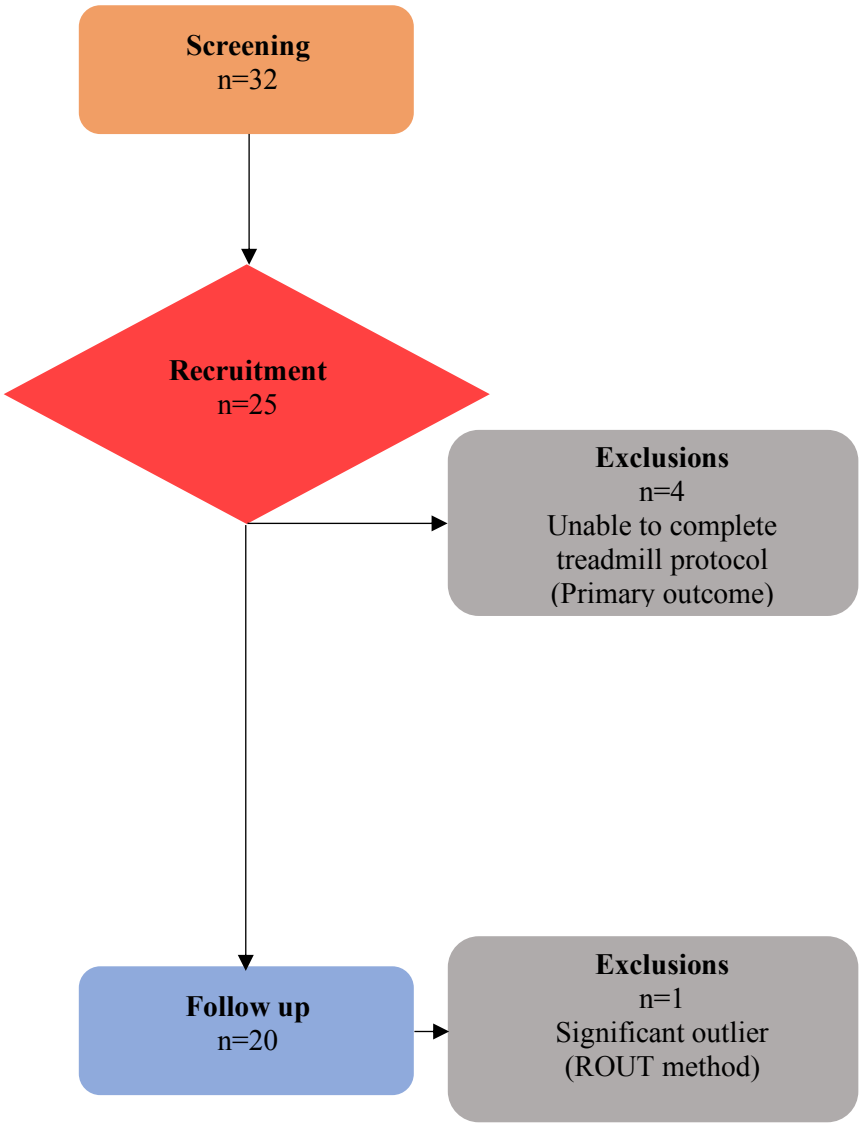


Figure 23: Patient Flow for NMES in the management of IC study

3.4.5.2 Demographics

Twenty patients completed the clinical trial successfully including 16 males. The average age was 70 years with average BMI of 27.4. Eighty percent of patients were ex-smokers with 15% current smokers, all trying to reduce this habit with the aid of their doctor, understanding its link to their debilitating symptoms. In terms of co-morbid disease, 80% were being treated for hypertension, 90% for hypercholesterolaemia management and 20% had previously suffered a TIA or stroke (not functionally debilitating).

Over half of the patients had femoral artery disease (55%) with the remainder having predominantly iliac disease (20%) or crural disease (25%). The average baseline ABPI measures were 0.71 in the right and 0.69 in the left. (Table 7).

Table 7: Demographics of patients included in the NMES in the management of IC clinical trial

		Patient Cohort
n		20
Mean Age (Years) [SD]		70 [11.7]
Males (%)		80
Smoker(%)	Current	15
	Ex	80
	Never	5
BMI (Mean) [SD]		27.4 [4.5]
Hypertension (%)		80
Stroke (%)		20
MI (%)		40
Hypercholesterolaemia (%)		90
Angina (%)		10
ABPI (Mean) [SD]	Right	0.71 [0.17]
	Left	0.69 [0.17]
Disease (%)	Iliac	20
	Femoral	55
	Below Knee	25

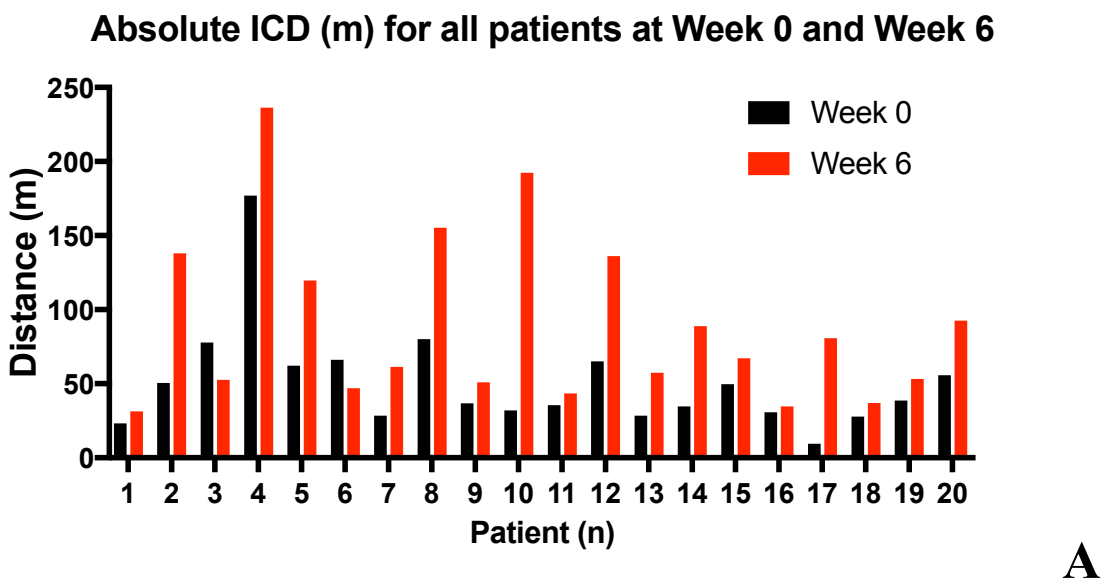
3.4.5.3 Walking distances

The MCD, as the study primary outcome, had a highly significant median increase of 40.7 m (46%, P<0.0001) following 6 weeks of NMES intervention (Figure 25). During the same period, the median ICD improved significantly almost 27 m (71%, P<0.0004). Median walking distances are shown in Table 8. Figure 24 shows the absolute scores of ICD (Figure 24 A) and MCD (Figure 24 B) for the study cohort.

Table 8: Walking distances in patients at baseline and 6 weeks follow up

Claudication Distance	Week 0 (n=20) Median [IQ Range]	Week 6 (n=20) Median [IQ Range]	P Value
ICD (m)	37.7 [29 - 64.45]	64.3 [48 - 132]	0.0004*
MCD (m)	89.3 [57.8 - 138.1]	130 [85.9 - 281.2]	<0.0001*

ICD – Initial Claudication Distance, MCD – Maximum Claudication Distance
**statistically significant result (p<0.05)*
Data statistics: Wilcoxon signed rank test



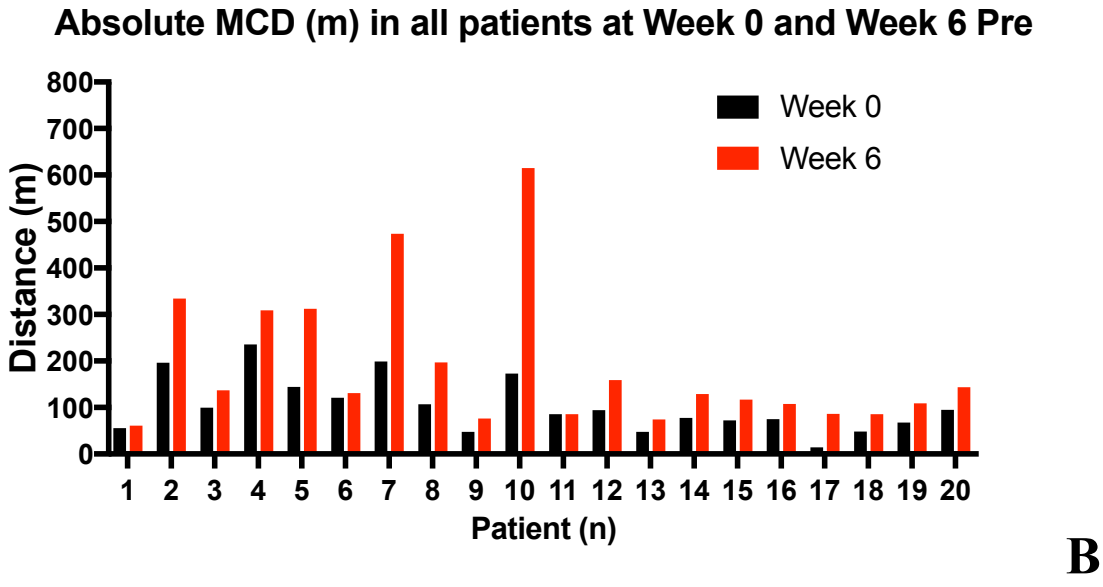


Figure 24: Absolute changes in A. ICD (m) and B. MCD (m) in all patients from week 0 to week 6

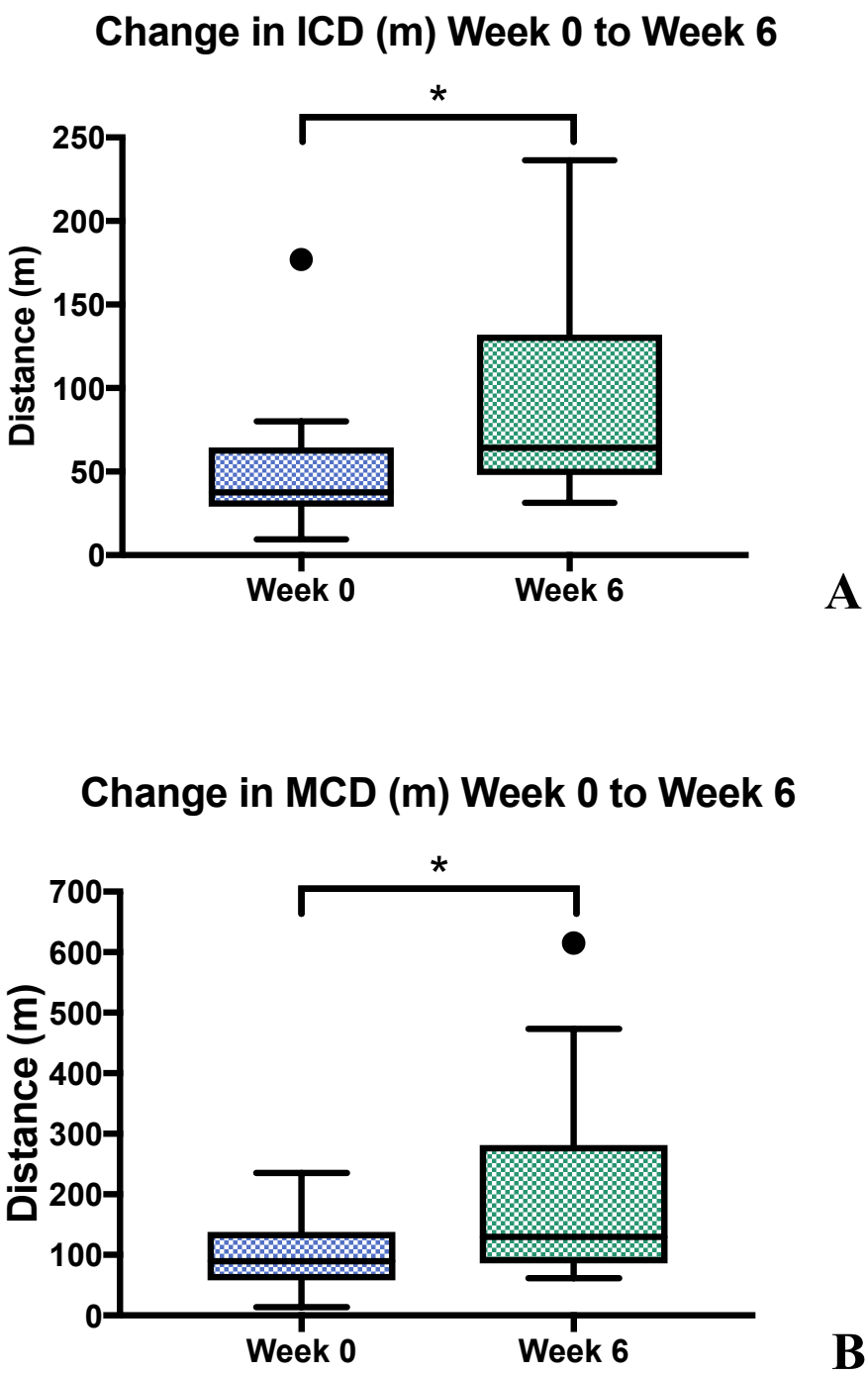


Figure 25: Change in A. ICD (m) and B. MCD (m) from week 0 to week 6 of NMES intervention (Tukey plot)

**statistically significant result ($p<0.05$)*
Data statistics: Wilcoxon signed rank test
Lines denote: Median, IQ range, furthest points (3/2 of IQR), outlier (dot)

3.4.5.4 Quality of Life Questionnaires

The disease specific quality of life questionnaire scores for ICQ decreased by approximately 9 points (20%, P=0.009) denoting a significant improvement following 6 weeks use of NMES (Table 9). Absolute scores of the ICQ for the study participants is shown graphically in Figure 26.

The generic EuroQoL-5 Dimension–5 level quality of life score improved significantly by almost 12% (P=0.007) after 6 weeks NMES intervention (Figure 27). Over the same period, the associated generic health score, EQVAS had a mean decrease of 3%, which was non-significant (P=0.905) (Figure 28).

The SF-36 quality of life questionnaire, which provides scores based on 8 health related domains largely affecting the patient within the previous 4 weeks, is shown in Table 10and graphically in Figure 29. All but two health domains were non-significant following 6 weeks intervention with NMES (P>0.05). Study findings suggested a decrease in the 'Emotional well-being' score by 20% (P=0.013), but an overall 'General health' score improvement of 10% (P=0.012) over the same time period (Figure 29).

Table 9: Disease specific and generic quality of life questionnaire scores and EQ VAS health score from week 0 to week 6 following NMES intervention

ICQ-Intermittent Claudication Questionnaire, EQ-5D-5L – EuroQoL-5 Dimensions – 5 Levels, EQVAS – EuroQoL Visual Analogue Score

QoL Questionnaire n=20	Week 0	Week 6	P Value
ICQ Score	44.0 [22.3]^	35.2 [22.9]	0.009[A]*
EQ-5D-5L Score	0.629 [0.38-0.73] $	0.703 [0-0.21]	0.007[B]*
EQVAS Score	75 [60-88.75] $	72.5 [50-87.5]	0.905[B]

^ (mean) [SD]
$ (median) [IQR]
[A] Paired t - test
[B] Wilcoxon signed rank test
* Statistically significant result (P<0.05)

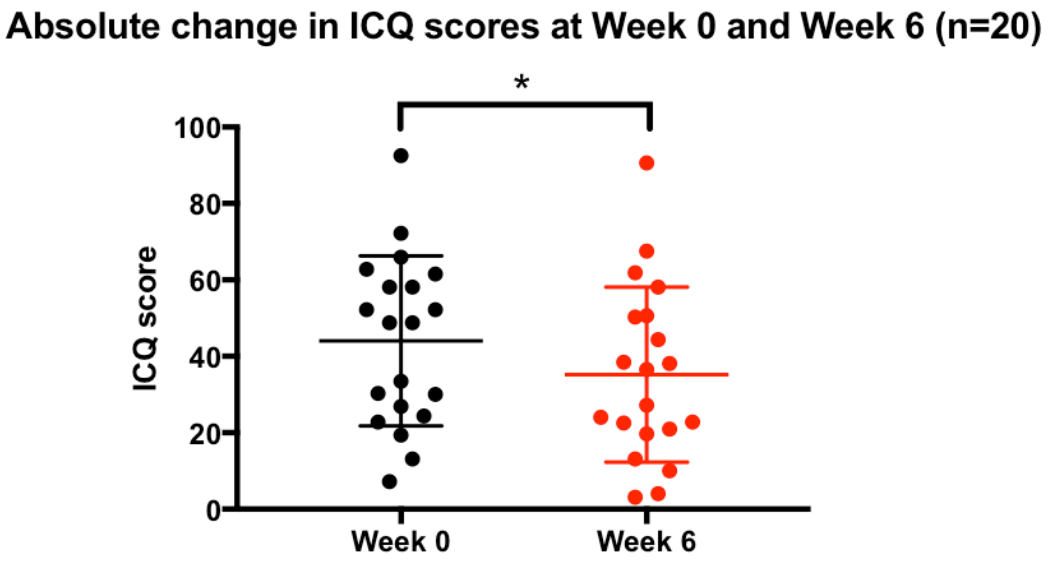


Figure 26: Absolute change in ICQ scores from week 0 to week 6 after NMES intervention

(Lines denote: Mean and standard deviation)

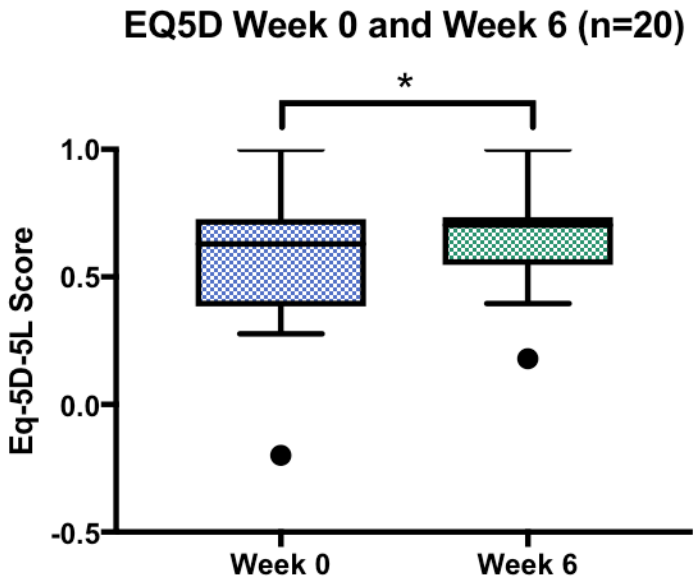


Figure 27: Box and whiskers plot of EQ-5D-5L score from week 0 to week 6 (Tukey plot)

Data statistics: Wilcoxon signed rank test
Lines denote: Median, IQ range, furthest points (3/2 of IQR), outlier (dot)

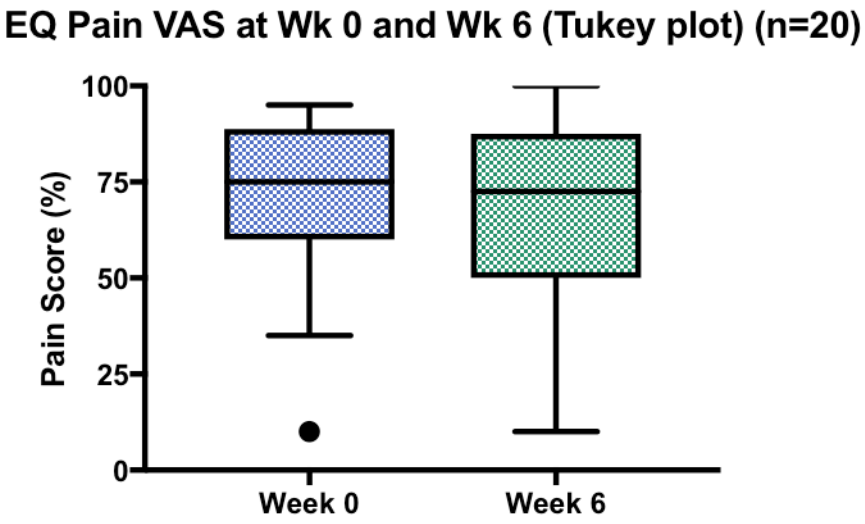


Figure 28: Change in EQ-Visual Analogue Score for pain from week 0 to week 6 after NMES intervention (Tukey plot)

Data statistics: Wilcoxon signed rank test
Lines denote: Median, IQ range, furthest points (3/2 of IQR), outlier (dot)

Table 10: Changes in the RAND SF-36 scores by domain from week 0 to week 6 following NMES intervention

SF-36 Domain n=19	Week 0 (median) [IQR]	Week 6 (median) [IQR]	Wilcoxon Signed Rank Test (P Value)
Physical functioning	40 [25-70]	50 [25-80]	0.2554
Role functioning/physical	50 [0-100]	50 [0-100]	0.6328
Role functioning/emotional	100 [0-100]	100 [33.3-100]	0.375
Energy/fatigue	55 [50-65]	65 [50-75]	0.184
Emotional well-being	80 [60-88]	64 [52-84]	0.0131*
Social functioning	62.5 [50-100]	87.5 [50-100]	0.2283
Pain	45 [32.5-77.5]	55 [45-77.5]	0.176
General health	50 [45-70]	55 [40-75]	0.0119*

Data statistics: Non-parametric Wilcoxon signed rank test
*Statistically significant result (P<0.05)

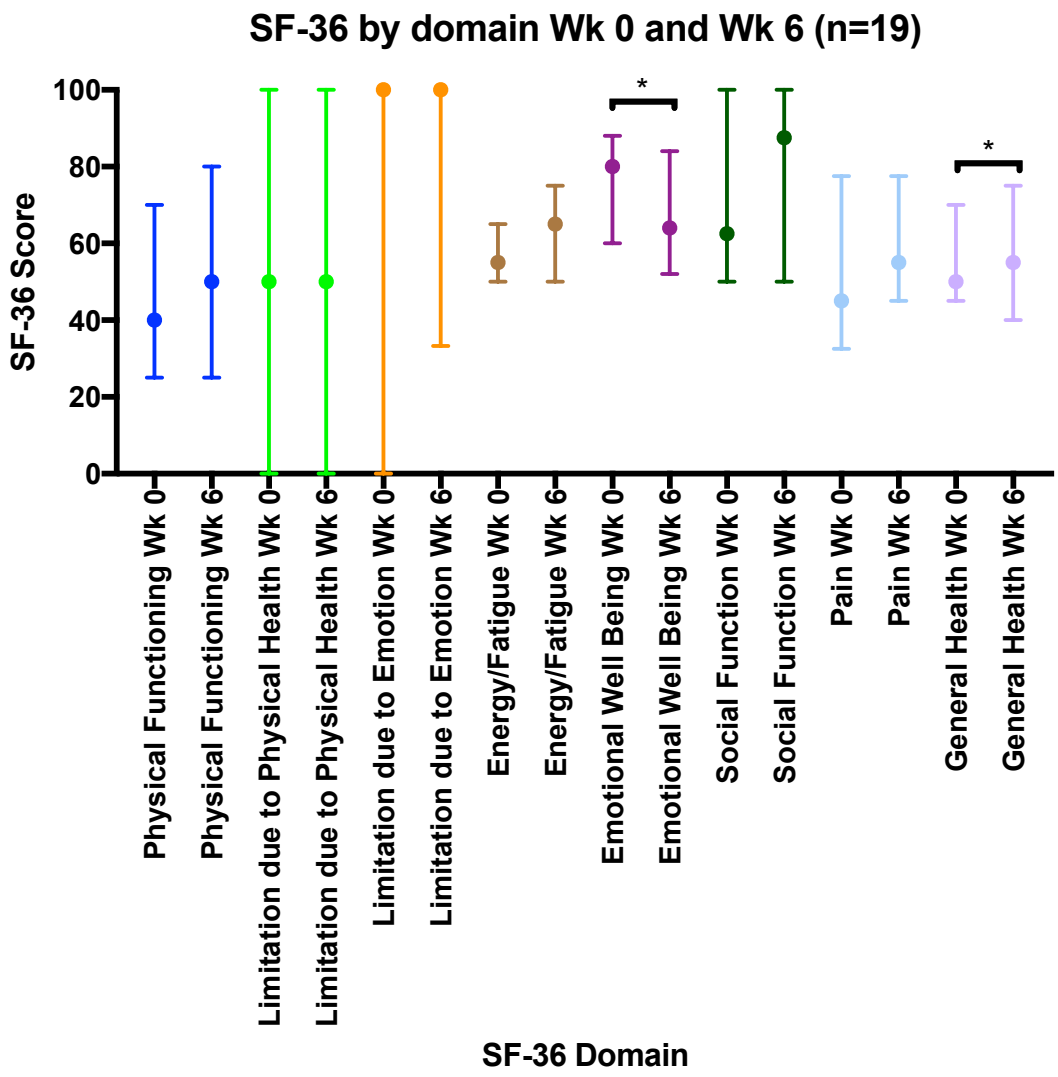


Figure 29: RAND SF-36 domain changes from week 0 to week 6 after NMES intervention

**statistically significant result ($p<0.05$), Data statistics: Wilcoxon ranked signed test*
Lines denote: Median, IQ range. This survey was reprinted with permission from the RAND Corporation. Copyright © the RAND Corporation. RAND's permission to reproduce the survey is not an endorsement of the products, services, or other uses in which the survey appears or is applied.

3.4.5.5 Haemodynamic measures

Ultrasound haemodynamic measures of the diameter (cm), blood volume flow (cc/min) and TAMV (cm/s) at the superficial femoral artery (SFA) are shown in Figure 30, Figure 31 and Figure 32, respectively. These measures were taken at the baseline appointment at week 0 and following 6 weeks of NMES intervention at 3 timepoints. These timepoints were according to device status, which was at rest (control), 15 minutes into the stimulation cycle of the NMES device (Device ON) and immediately after the total 30 minute stimulation cycle completed (Device OFF).

These data underwent statistical ANOVA with the results according to device status at week 0 and week 6 for all 3 ultrasound parameters summarised in Table 11.

There was no significant change in SFA diameter according to device status at week 0 ($F=2.63$, $P=0.160$) or at week 6 ($F=0.286$, $P=0.642$) after NMES use (Figure 30, Table 11).

Blood volume flow (cc/min) showed a significant change at week 0 according to device status ($F=9.24$, $P=0.0007$). Further post hoc analysis with Bonferroni correction revealed a significant increase in flow from rest to device ON ($P=0.013$) and decrease in flow from device ON to device OFF post stimulation cycle ($P=0.0014$). There was no significant difference between control (rest) and device OFF ($P>0.999$). Further, there was no significant difference in the change in the volume flow between week 0 device ON and control vs week 6 device ON and control.

At week 6, the ANOVA for blood volume flow suggested significant change ($F=6.625$, $P=0.01$) according to device status. Further Bonferroni analysis showed this change due to a

significant decrease in blood flow from device ON to device OFF (P=0.007) back to resting levels. Therefore, there was no significant change between control (rest) and device OFF following stimulation cessation (P=0.617).

There were significant changes over device status for TAMV at both week 0 (F=8.35, P=0.001) and week 6 (F=12.57, P=0.001). Post ANOVA analysis by Bonferroni correction showed a significant increase between control (rest) and device ON at week 0 (P=0.011) and week 6 (P=0.021). There was a significant decrease in TAMV between device ON and device OFF after stimulation cessation at week 0 (P=0.004) and week 0 (P=0.0001). There was no significant difference between control and device OFF at either week 0 or week 6 (P>0.05).

Unpaired t test analysis showed no significant differences in any of the ultrasound haemodynamic parameters between week 0 and week 6 for individual device status points (i.e. week 0 control vs week 6 control, week 0 device ON vs week 6 device ON and week 0 device OFF vs week 6 device OFF). Further, there was no significant difference in the change in the TAMV between week 0 device ON and control vs week 6 device ON and control.

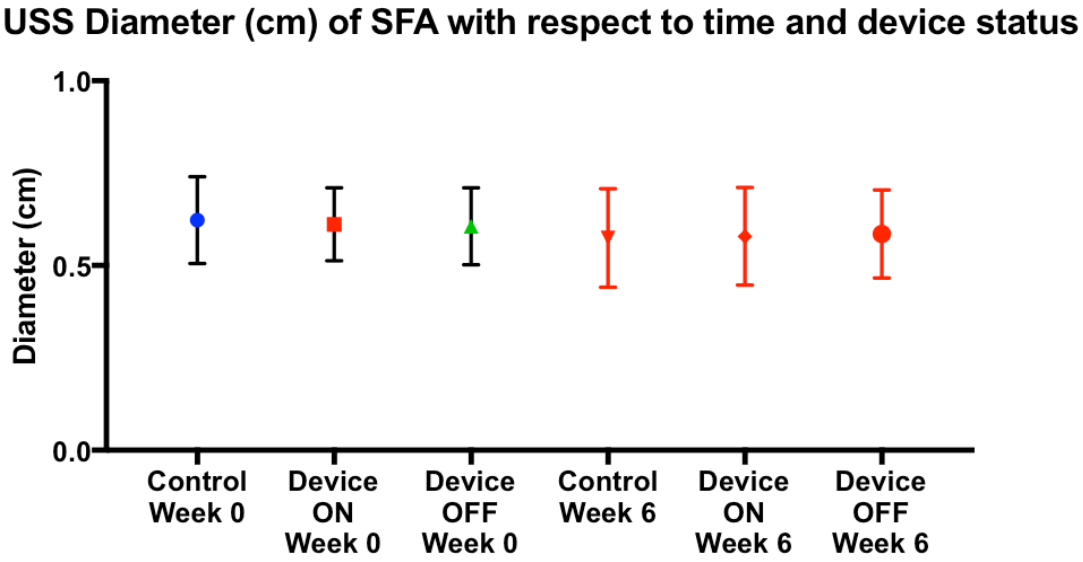


Figure 30: Change in USS arterial diameter (cm) at week 0 and week 6 according to device status

Lines denote: Mean, SD

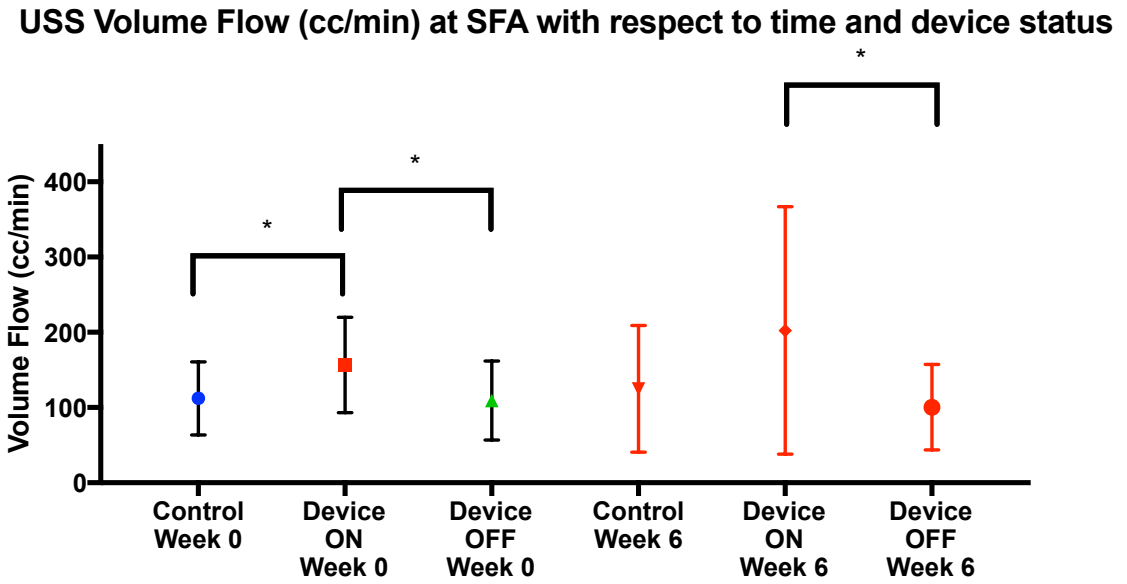


Figure 31: : Change in USS arterial Volume Flow (cc/min) at week 0 and week 6 according to device status

Lines denote: Mean, SD
**Statistically significant result (P<0.05)*

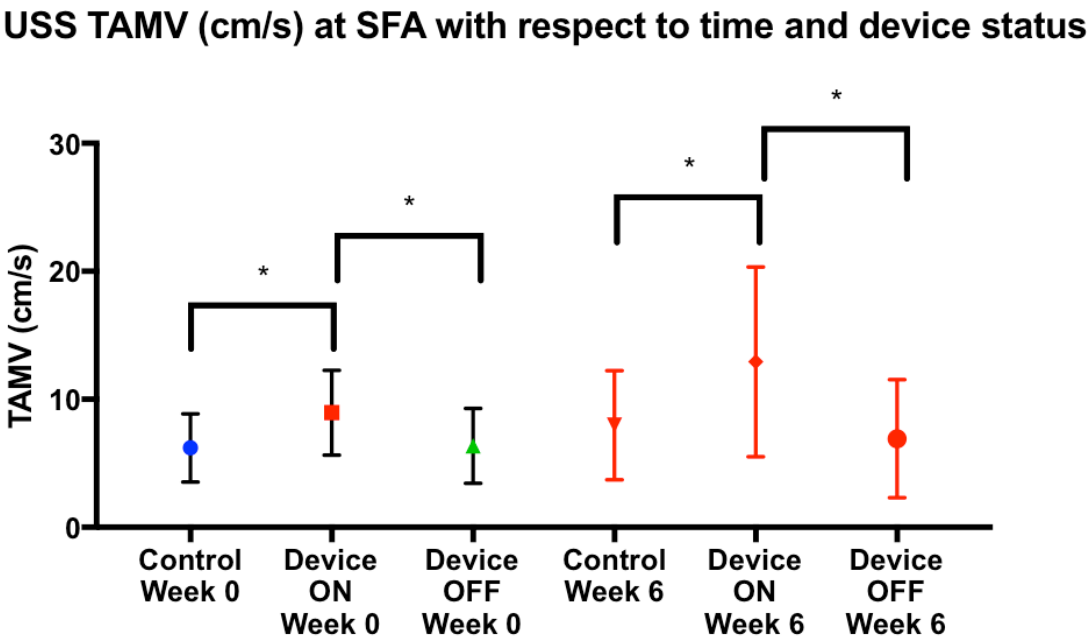


Figure 32: Figure: Change in USS arterial TAMV (cm/s) at week 0 and week 6 according to device status

Lines denote: Mean, SD
**Statistically significant result (P<0.05)*

Table 11: ANOVA analysis of USS parameters (Diameter, Blood Flow, TAMV)

Measured at the SFA, according to device status at week 0 and week 6

USS Parameter	Device status	Week 0 Mean change	P Value	Week 6 Mean change	P Value
Diameter (cm)	Control Vs Device ON	0.012	0.850	-0.004	>0.999
	Control Vs Device OFF	0.017	0.265	-0.011	>0.999
	Device ON Vs Device OFF	0.005	0.222	-0.007	0.971
	ANOVA	F=2.63	0.160	F=0.2858	0.642
Blood Volume Flow (cc/min)	**Control Vs Device ON**	-44.270	**0.013***	-77.640	0.151
	Control Vs Device OFF	2.835	>0.999	24.300	0.617
	Device ON Vs Device OFF	47.100	**0.0014***	101.900	**0.007***
	ANOVA	F=9.244	**0.0007***	F=6.625	**0.010***
TAMV (cm/s)	**Control Vs Device ON**	-2.750	**0.011***	-4.953	**0.021***
	Control Vs Device OFF	-0.159	>0.999	1.064	0.865
	Device ON Vs Device OFF	2.591	**0.004***	6.017	**0.0001***
	ANOVA	F=8.35	**0.001***	F=12.57	**0.001***

ANOVA analysis of USS parameters

Post hoc analysis with Bonferroni correction

**statistically significant result (<0.05)*

Laser doppler flow measures of mean temperature and blood flux of the hand and foot at week 0 and week 6 are shown in Table 12, with the % change in the same time period shown in Table 13.

There were no significant differences observed for either the temperature or blood flux in the hand or foot at week 0 or week 6 measured at either device OFF (rest) or device ON. Moreover, significant differences between the % change in LDF parameters from week 0 to week 6, between device OFF and device ON were not apparent in this cohort of PAD patients.

Table 12: Change in temperature and fluximetry by site from week 0 to week 6 after NMES intervention

Device OFF (REST) LDF Parameter [Site]	Week 0 Median [IQR]	Week 6 Meidan [IQR]	Median Difference [IQR]	P Value
Temperature (ºC) - [Hand]	30.10 [29.23-30.65]	30.05 [28.25-30.6]	-0.15 [-0.575-0.3]	0.25
Temperature (ºC) - [Foot]	28.65 [27.8-29.8]	28.35 [26.63-29.4]	-0.35 [-0.875-0.475]	0.15
Flux (au) - [Hand]	62.10 [29.05-87.68]	63.70 [39.93-87.5]	10.75 [-23.18-36.1]	0.47
Flux (au) - [Foot]	19.10 [13.58-42.63]	15.45 [12.93-26.05]	-3.35 [-21.5-5.425]	0.11

*statistically significant result (P<0.05)
Data statistics: Wilcoxon signed rank test

Device ON LDF Parameter [Site]	Week 0 Median [IQR]	Week 6 Meidan [IQR]	Median Difference [IQR]	P Value
Temperature (ºC) - [Hand]	30.65 [29.63-31.4]	30.50 [29.85-30.95]	-0.50 [-0.9-0.375]	0.30
Temperature (ºC) - [Foot]	28.6 [28.1-31.4]	28.2 [27.6-29.15]	-0.5 [-1.1-0.45]	0.10
Flux (au) - [Hand]	60.75 [33.28-83.3]	55.10 [45.05-90.4]	8.25 [-26.05-31.78]	0.74
Flux (au) - [Foot]	33.15 [19.03-46.8]	42.95 [23.98-68.48]	11.70 [-7.825-31.65]	0.11

*statistically significant result (P<0.05)
Data statistics: Wilcoxon signed rank test

Table 13: Change in temperature and blood flux according to site comparing measures with Device ON and Device OFF

LDF Parameter [Site]	Device OFF Median [IQR] (% Change)	Device ON Meidan [IQR] (% Change)	Median Difference (Change %)	P Value
Temperature (ºC) - [Hand]	-0.49 [-1.92-0.98]	-1.615 [-2.87-1.21]	-1.125	0.77
Temperature (ºC) - [Foot]	-0.7 [-2.19-1.87]	-1.43 [-2.66-2.31]	-0.73	0.77
Flux (au) - [Hand]	31.1 [-33.67-82.27]	15.37 [-4.3-56.81]	-15.73	0.6
Flux (au) - [Foot]	-16.49 [-61.26-36]	44.48 [-22.58-95.47]	60.96	0.082

*statistically significant result (P<0.05)
Data statistics: Mann-Whitney U test

3.4.5.6 Compliance

Further analysis of the compliance diaries showed there was a 97% compliance (range: 81-100%) to use of the Revitive™ IX NMES device over the 6 week intervention period. No patient contacted the investigators for additional support and most reported good tolerability of device use which could be satisfactorily incorporated within their daily routine.

3.4.6 Discussion and Conclusion

This pilot observational cohort study suggests a significant improvement in both functional and quality of life measures following the 6 weeks use of NMES.

From a functional perspective, treadmill testing showed significant improvements in walking distances before limitation with IC, similar to those shown in supervised exercise clinical efficacy trials (Bendermacher, Willigendael et al. 2007, Fokkenrood, Bendermacher et al. 2013). Supervised exercise is the current gold standard, first line, non-invasive management strategy for the treatment of IC, but this is underutilised by patients and largely inaccessible

to referrers due to resources and funding (Shalhoub, Hamish et al. 2009, Makris, Lattimer et al. 2012, Babber A 2015).

Over the last 3 decades there has been an emerging evidence base of the functional benefits of NMES technology in patients with symptomatic lower limb arterial disease (Abraham, Mateus et al. , Loubser, Cardus et al. 1988, Hudlicka 1994, Tsang, Green et al. 1994, Anderson, Whatling et al. 2004, Guirro, Guirro et al. 2015, Ellul, Formosa et al. 2017). These studies have been assessed as part of a literature review on NMES in the management of IC, which can be found in section 2.3 'Literature review of NMES in PAD', with a summary of data from these studies in appendix 7.3.1. There have been reported significant improvements of absolute claudication distance of 141% ($P<0.0001$) (Ellul, Formosa et al. 2017) and initial claudication distance of 133% ($P<0.01$)(Tsang, Green et al. 1994) after using NMES in patients with IC. Unfortunately, there is a lack of standardisation, small sample sizes and significant heterogeneity between NMES studies in PAD to date, including devices used, frequency of use, stimulation parameters, duration of use and outcome assessment technique. Therefore, a meta-analysis of the combined effect of these studies cannot be undertaken.

The direct effects of IC on patients health, emotion and function was assessed by the disease specific ICQ survey. This significantly improved from baseline to follow up after 6 weeks of NMES device use. This questionnaire has a strong correlation (Chong, Garratt et al. 2002) with the EuroQoL-5D generic quality of life questionnaire, which also showed a significant improvement in score. Within the limits of a search strategy in Ovid Medline and Embase, there were no similar NMES studies reporting change in quality of life measures, whether disease specific or generic, in the PAD population. One study by Embrey et al assessed the effects of a wearable functional electrical stimulation (FES) unit on disease specific quality of

life measures in patients with varying degrees of IC. This unit was placed over the nerves controlling plantar flexors and dorsiflexors bilaterally with inbuilt motion sensors detecting when patients had started to walk. The electrical stimulation would then commence automatically, providing calf muscle contractions as an adjunct to walking exercise. These stimulations ceased on stopping exercise. This was a single blind, randomised controlled study which compared Intermittent Claudication Questionnaire scores as a secondary measure between a FES plus walk group (n=13) and walk only group (n=14). The FES device was used 6 days a week for an hour daily and a duration of 8 weeks. After this intervention period, no device intervention was used and patients were followed up again 8 weeks later (week 16). The FES plus walk group showed significant improvement in ICQ scores from baseline to completion of intervention at week 8 (10.8 points, 95% CI: 3.7-17,8, P=0.0003) and baseline to follow up at week 16 (14 points, 95% CI: 5.6-2.4, P=0.002). A significant change was not reported in the walk only group or a significant difference between the 2 groups at baseline and week 8. However, there was a significant difference in ICQ scores at week 16 follow up between the groups, in favour of FES (13.1 points, 95% CI: 0.3-2.5, P=0.01) (Embrey, Alon et al. 2017). This device and its application are completely different to the NMES device used in the study above, but this was the only QoL related electrostimulation study in PAD patients found.

Haemodynamic assessment by duplex ultrasound showed a significantly improved median blood flow and velocity in the arterial segment measured whilst the device is ‘ON’ compared to control (rest), but returning to baseline levels at stimulation cessation. In keeping with the outcomes observed in the impact of the same NMES device in healthy individuals (Varatharajan, Williams et al. 2015), the volume flow and TAMV measures returned to near baseline levels immediately after stimulation cessation. This implies that, whilst using the

device, there is an increased amount and more rapid flow of blood in the arterial circulation to the lower limbs over time. From this pilot observational cohort study data alone, it is difficult to predict a mechanistic cause and effect of this increased blood flow and volume in improving outcome measures. Although the ANOVA shows significant improvements of volume flow and TAMV separately at week 0 and week 6 according to device status, there is no such significant difference found between the same device status at week 0 and week 6. In addition, there was no significant device status related difference found in the skin microcirculation by assessing temperature and blood flux at week 0 and week 6. This would warrant further investigation with a larger sample size.

Lower limb haemodynamic change with NMES device use in patients with PAD has been contentious. In one of the earliest studies, Loubser et al found a significant change in plethysmograph waveform analysis at the great toe and increased skin temperature, eluding to improved haemodynamics, in 8 IC patients compared to 8 control subjects (Loubser, Cardus et al. 1988). However, subsequent studies in varying small sample sizes of IC patients using a variation of NMES devices and protocols have not found any significant improvement of ABPI (Hudlicka 1994, Tsang, Green et al. 1994), duplex ultrasound lower limb arterial blood flow (Guirro, Guirro et al. 2015) and lower limb spectral waveform analysis (Ellul, Formosa et al. 2017). In addition, tissue oxygenation assessment, a surrogate measure of improved local blood flow measured by near infrared spectroscope (NIRS) did not show any significant improvement in 15 IC patients using the Veinoplus NMES device on the calf during an observational cohort study (Abraham, Mateus et al. 2013).

In terms of application and tolerability, subjective patients reported benefits included a comfortable and user friendly device, easy to incorporate into a daily routine.

This proof of concept pilot study shows promise for the use of NMES in the non-invasive management of IC. Further robust research is warranted to explore the parameters assessed in this study in a larger sample size to ascertain firmer correlations.

3.5 Adjunctive benefit of NMES to Supervised Exercise Programmes in patients with Intermittent Claudication

3.5.1 Introduction

Current literature supports SEPs in improving walking outcomes in patients with IC and hence this is recommended as a gold standard management strategy for all PAD patients by international and national guidelines (Norgren, Hiatt et al. 2007, Carthy 2013). However, the underutilisation and lack of access to this modality is well known and evidenced in repeated snapshot surveys both nationally and internationally (Bendermacher, Willigendael et al. 2006, Shalhoub, Hamish et al. 2009, Makris, Lattimer et al. 2012, NICE147 2012, Fokkenrood, Bendermacher et al. 2013, Babber A 2015). This justifies further research in the utility of alternative non-invasive management strategies, for example, neuromuscular electrical stimulation in the management of intermittent claudication. The proof of concept pilot study described above, suggests significant improvement in walking distances before the onset of pain (ICD) and before stopping due to pain (MCD). Therefore, if NMES does improve outcomes, comparative to SEP only trials, in patients with IC, does this modality confer an adjunctive benefit?

3.5.2 Aims

The aims of this study are to assess the adjunctive benefit of NMES as a non-invasive modality, to SEPs in the management of IC. This study will compare NMES in addition to SEPs to a control condition involving a supervised exercise programme alone and no NMES device over a 6 week intervention period. The null hypothesis (H_0) states that NMES does not provide an adjunctive benefit to SEPs in the management of IC.

3.5.3 Study Design

This is a prospective, randomised, controlled, clinical study in patients with intermittent claudication.

3.5.3.1 Sample size

This is a randomised controlled trial measuring the adjunctive benefit of NMES to SE in patients with IC. Considering the changes in primary outcome in previous studies, the total sample size calculated for this study is 45 patients. This sample size represents a 60 m change in walking distance, assuming a standard deviation of 120 m, with a 90% power and 5% significance level (Greenhalgh, Belch et al.). For 2 groups, this sample size would be rounded up to 46, suggesting 23 patients required in each group. Sample size was calculated with an online software tool from the Massachusetts General Hospital Biostatistics Center (http://hedwig.mgh.harvard.edu/biostatistics/)

3.5.4 Inclusion and Exclusion criteria

Inclusion and exclusion criteria for this study are shown in Table 14.

Table 14: Inclusion and Exclusion criteria

Inclusion criteria	Exclusion Criteria
Age >18 years All ethnic groups BP <160/100 No tissue loss	Any unstable condion deemed unreliable or incapable of complying with protocol (Psychiatric disorder, substance abuse) Pregnancy Diabetes Concurrent exercise therapy or invasive intervention Pacemaker or implanted defibrillator device Recent lower limb injury or low back pain

Due to a large number of screened patients being excluded from this study with diabetes, limited study time, anticipated difficulty in meeting the recruitment target and reconsideration of the likely co-morbidity profile of the target population, a request for substantial amendment to the NRES committee to include this co-morbidity in the clinical trial was submitted. This was approved by the NRES and then submitted and approved by the MHRA (July 2016) as having no objections.

3.5.4.1 Ethical Approval and Registration

Ethical approval was gained from the Cambridge central committee of the National Research and Ethics Service (NRES) with reference number 14/EE/0193. Approval was also gained from the Medicine and Health products Regulatory Agency (MHRA) and the clinical trial was registered on a public trials registry site (clinicaltrials.gov, NCT02429310) as per the ethical approval requirements.

3.5.5 Methodology

Eligible patients, meeting the above inclusion criteria, were identified from the vascular outpatients clinic at Imperial College Healthcare NHS Trust. They were provided with a patient information leaflet (Appendix 7.1.2) detailing the study aims and patient involvement in this trial. Patients willing to participate were recruited either immediately to attend an initial appointment or contacted within a few days of clinic attendance to confirm participation and accordingly attend a baseline appointment.

During the baseline appointment, patients completed an informed consent form (Appendix 7.2.2) before demographic and anthropometric data were collected. A full medical history was followed by peripheral arterial examination and ABPI assessment. Patients then underwent an online randomisation process (www.sealedenvelope.com) and grouped into either 'Group A' receiving best medical therapy and a SEP alone or 'Group B' where they were to receive NMES & SEP. All patients underwent a fixed load treadmill test at 3.5 km/h at 10% gradient to measure the initial claudication distance (ICD), or distance at onset of IC pain; and maximum claudication distance (MCD) or the maximum distance before stopping the treadmill test due to lower limb pain. Following the treadmill test patients were required to rest for at least 15 minute during which the relevant quality of life questionnaires were completed including the Intermittent Claudication Questionnaire (ICQ), EuroQoL-5D (EQ-5D) and RAND Short-Form 36 survey (SF-36) (Appendices 7.4.1, 7.4.2 and 7.4.3).

For those in Group B, an induction of the NMES device, the Revitive™ IX, was undertaken to familiarise them and establish the necessary stimulation intensities required to use the device appropriately (Figure 33).

The Revitive™ IX (Actegy Ltd, UK) NMES device has 2 electrodes consisting of electro-carbon conductive foot plates with an optional rocker device (IsoRocker®) to replicate heel-toe raises along with calf muscle contraction. The inbuilt circuitry goes through a pre-programmed cycle of 15 stimulation patterns lasting approximately 1 minute each. The stimulation parameters for this device include a frequency of 1-50Hz with a maximum output current of 15mA applied in quasi-symmetrical biphasic waveforms that are shaped rectangular or bipolar. Each pulse duration is 370μs or 940μs, with 11-256 pulses per burst; 0.1-0.3 bursts per second; and a burst duration of 1.9-8.4 seconds depending on the programme. The device display shows the countdown duration of use, which can be set at minute intervals and the intensity level from 0-99, which is altered according to the user's comfort.

Baseline sensory and motor thresholds were established and noted. The sensory (perception) and motor thresholds were established by systematically varying the stimulation intensity with increments of ±1% maximal output whilst the participant provides verbal sensory feedback. The minimal intensity, which the participant is able to clearly feel, was recorded as the perception threshold, and that producing visible muscle twitches – as the motor threshold. The stimulation intensity for the main interventions was adjusted to produce visible but non-painful contraction of the lower limb calf muscles based on the individual motor threshold (suprathreshold).

These patients were then instructed to complete the test intervention:

Test condition (ES) – One 30 minute electrical foot stimulation session with the device at suprathreshold (approximately 2 x motor threshold) intensity sufficient to evoke lower limb muscle contractions.

Patients in Group B were supplied with a device to take home. They were instructed to use the device for one 30-minute session daily for the next 6 weeks.

All patients, from group A and B were informed to continue their best medical therapy and SE programme, provided locally as standard care.

All patients were appointed to a 6-week follow up visit where the above measures were repeated. The 6-week follow-up visit marked the end of patient participation within the trial (Figure 33). At this point, those that were in Group A were given the option of trialling the device.

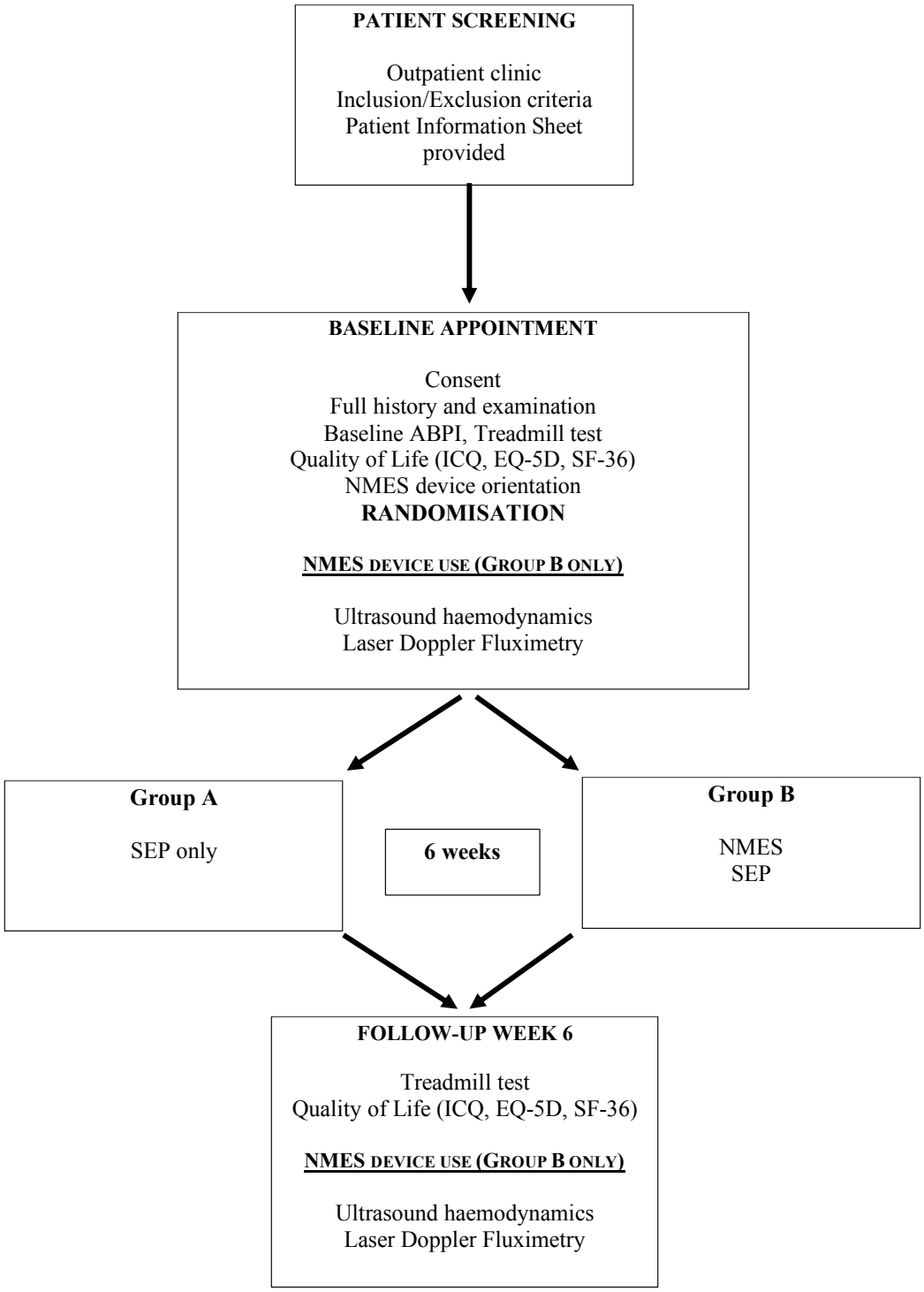


Figure 33: Study protocol for Adjuvant Benefit of NMES to SEP in the management of IC trial

3.5.5.1 The Device

The device used to provide neuromuscular electrical stimulation (NMES) was the Revitive™ IX (Actegy Ltd, UK) – see section 1.3.6.3.

3.5.5.2 Supervised Exercise Programme

The SEP attended was within Charing Cross Hospital part of the Imperial College Healthcare NHS Foundation Trust. Details of this programme are provided in section 3.2, above.

3.5.6 Outcome measures

The primary outcome of this study is maximum claudication distance (treadmill testing).

The secondary outcome measures include:

Initial Claudication Distance (metres)

Duplex Ultrasound femoral artery heamodynamics

Blood flux

Disease specific questionnaire – Intermittent Claudication Questionnaire

Change in patients quality of life scores – SF-36 and EQ-5D

Patient use diary

3.5.6.1 Data analysis

A master database was setup in Microsoft Excel. Data was analysed with the GraphPad Prism software, version 6.0 and above (GraphPad Software Inc.). Statistical analyses were undertaken in the format as described in section 3.3 ‘Statistical Analyses’ above.

3.5.7 Results

3.5.7.1 Patient Flow

Seventy-five patients were identified from the vascular outpatient clinic and sent patient information sheets inviting them to participate in the clinical trial. Within the study time period, 42 patients were recruited, attending the baseline appointment and undergoing a randomisation process. Twenty-two patients were randomised to Group A and 20 to Group B. At the baseline appointment, 1 patient was excluded from each group due to inability to carry out the treadmill test (Primary outcome measure). On a separate occasion a patient declined to continue with the protocol from the baseline appointment, following randomisation to Group B and not feeling comfortable with the device. There was an unintended protocol violation in automatic re-allocation of this randomisation to the next recruited patient. This error was never repeated.

Baseline measures were taken for 21 patients in Group A and 19 patients in Group B. At the 6 week follow up appointment a further patient was excluded from Group A for not attending follow up, and 2 patients excluded from Group B. In the latter, 1 patient did not attend follow up and the other suffered a motorbike accident resulting in a fractured ankle rendering the patient unable to continue.

Follow-up repeated measures were taken from 20 patients in Group A. Although 17 patients attended the follow up appointment in Group B, 1 patient was only able to attend for the primary outcome measure of the treadmill test, and therefore did not complete any other follow up measures. Although analyses were undertaken with the intention to treat principle, formally on study completion there were 17 treadmill distance measures and 16 measures for all other outcomes in this group .

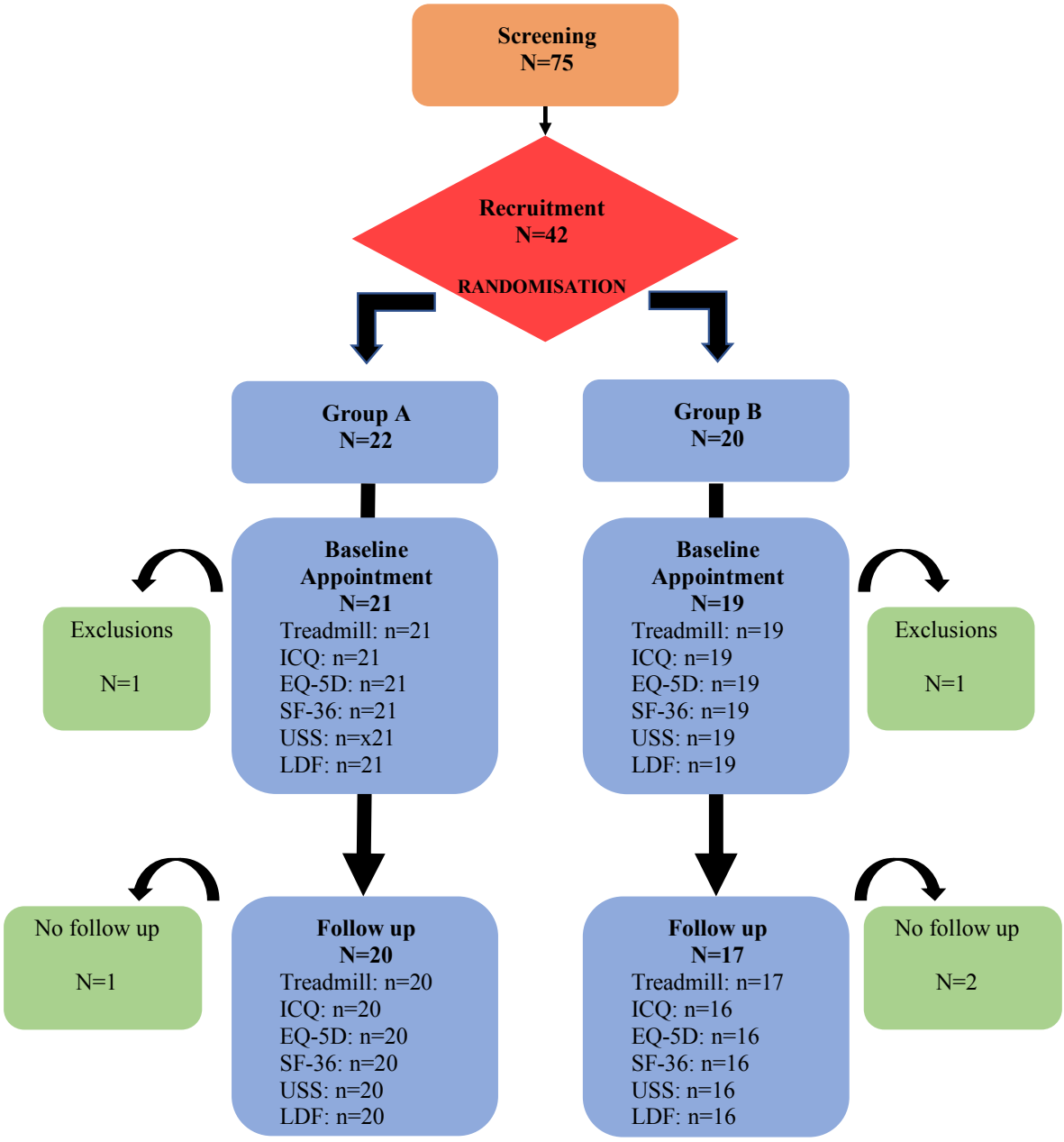


Figure 34: CONSORT diagram of patient flow through the Randomised Controlled Trial of Adjuvant Benefit of NMES to SEP in patients with IC

3.5.7.2 Demographics

The demographic parameters for patients included in the study can be seen in Table 15. There were no significant differences between the groups found for any demographical parameter. The majority of patients in both groups had underlying femoral artery disease (57% group A vs 63% group B). Although ABPI measures are important in the diagnosis of symptomatic PAD, further mapping of disease localisation is not undertaken in all patients, especially where invasive intervention is not planned. Therefore, 29% in group A and 26% in group B had 'unknown' localisation of disease, having never had imaging for mapping.

Table 15: Demographics of patients included in the Adjuvant Benefit of NMES to SEP in the management of IC clinical trial

		Group A SEP Only	Group B NMES & SEP	P Value
n		21	19	
Mean Age (Years) [SD]		68 [11]	66 [8]	0.524 ^
Males (%)		71	74	0.873 $
Smoker(%)	Current	10	0	0.078 $
	Ex	14	42	
	Never	76	58	
BMI (Mean) [SD]		27 [4]	27 [5]	0.654 ^
Hypertension (%)		71	75	0.873 $
Stroke (%)		14	5	0.344 $
MI (%)		14	5	0.344 $
Hypercholesterolaemia (%)		90	84	0.550 $
Angina (%)		14	11	0.720 $
[Diabetes (%)]		{10]	{16]	0.547 $
Aspirin (%)		71	68	0.836 $
Clopidogrel (%)		33	21	0.835 $
Warfarin (%)		5	5	0.942 $
DOAC (%)		5	0	0.335 $
Statin (%)		90	100	0.168 $
ABPI (Mean) [SD]	Right	0.75 [0.14]	0.72 [18]	0.461 ^
	Left	0.70 [0.12]	0.68 [0.14]	0.702 ^
Disease (%)	Iliac	5	11	0.675 $
	Femoral	57	63	
	Below Knee	5	0	
	Mixed	5	0	
	Unknown	29	26	

^ Mann-Whitney U test
$ Chi-square test

3.5.7.3 Walking distances

Within group changes in ICD and MCD from week 0 to week 6 in are shown in Table 16, below. Absolute changes per patient, with median and interquartile range, in each group is shown as a scatter plot in Figure 35.

There is a significant increase in MCD by approximately 64% (P=0.0002) and ICD by approximately 41% (P=0.006) over the 6 weeks of SEP only in group A (n=20). Significant changes are also seen in the NMES plus SEP group B (n=17) with an increase in MCD of approximately 40% (P=0.0006) and ICD of approximately 41% (P=0.0001). This is a per protocol analysis with follow up non-attenders excluded from analysis.

For a comprehensive analysis of primary outcome data, subsequent sensitivity analysis was carried out to observe any effect change with the inclusion of follow-up non-attenders. This analysis included within group data with a. no change to walking distance parameters at follow up (Table 17), b. 10% increase in walking distance parameters at follow up (Table 18) and c. 10% decrease in walking distance parameters at follow up (Table 19). Within group analyses showed significant increases in MCD and ICD in both group A (n=21) and group B (n=19) if assumptions as above are made for these walking distance parameters at follow-up for non-attenders.

Between group analysis showed no significant change in MCD at 6 weeks (14%, P=0.283). However, there was a significant increase of approximately 46% (P=0.014) in ICD at 6 weeks in favour of group B, NMES plus SEP (Table 20, Figure 36).

Table 16: Intra-group median change in ICD (m) and MCD (m) from week 0 to week 6 in Group A: SEP only and Group B: NMES & SEP
**statistically significant result (P<0.05)*

Table: Per protocol analysis of Group A (n=20)

Walking Distance	Group A Week 0 (m) Median [IQR]	Group A Week 6 (m) Median [IQR]	% Change	P Value
ICD	46.65 [32.6-77.8]	65.60 [33.98-93.88]	40.62	0.0056*
MCD	89.45 [52.48-147.3]	146.70 [7.53-214.3]	64.00	0.0002*

* Statistically significant result (P<0.05)

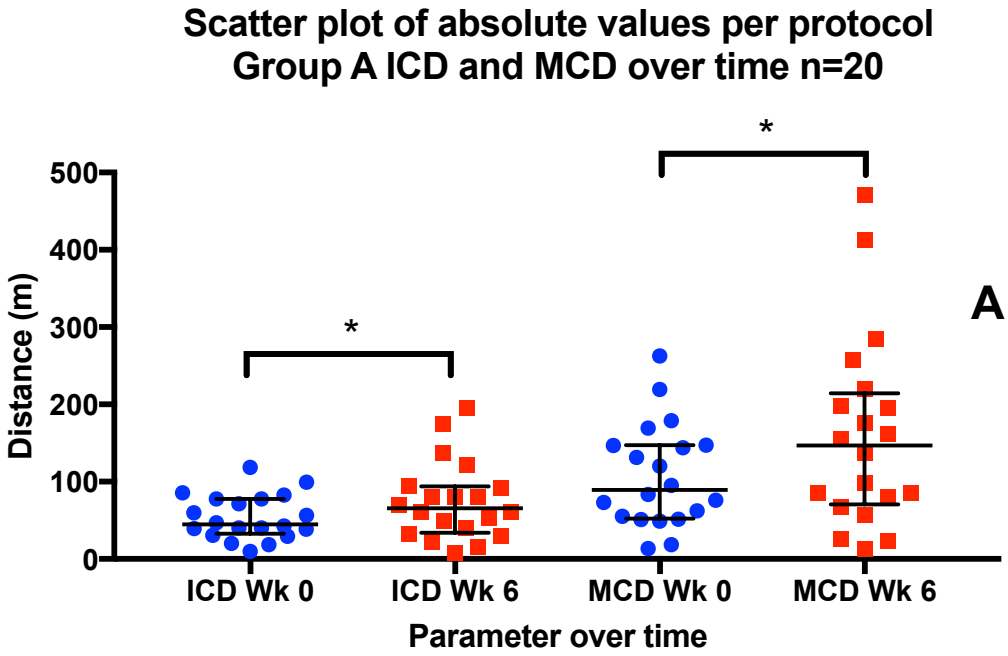
Wilcoxon matched pairs signed rank test

Table: Per protocol analysis of Group B (n=17)

Walking Distance	Group B Week 0 (m) Median [IQR]	Group B Week 6 (m) Median [IQR]	% Change	P Value
ICD n=19	65.10 [31-101.4]	91.70 [72.9-132.6]	40.86	0.0001*
MCD (n=19)	120.00 [74-189]	167.40 [92.5-232.4]	39.50	0.0006*

* Statistically significant result (P<0.05)

Wilcoxon matched pairs signed rank test



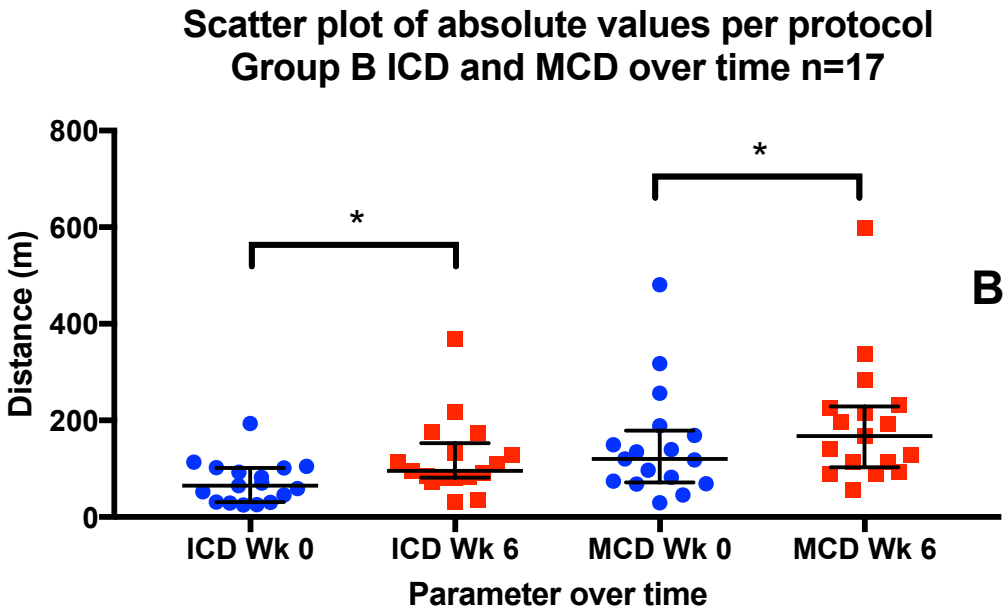


Figure 35: Absolute changes in ICD (m) and MCD (m) over time by per protocol analysis

A. Group A (n=20) B. Group B (n=17)

**statistically significant result (P<0.05)*

Table 17: Sensitivity analysis assuming no change in walking distance parameters at follow-up (Group A: n=21, Group B: n=19)

**statistically significant result (P<0.05)*

Table: Senitivity analysis assuming no change to follow up measures for non-attenders (n=21)

Walking Distance	Group A Week 0 (m) Median [IQR]	Group A Week 6 (m) Median [IQR]	% Change	P Value
ICD	46.70 [34.6-80.2]	69.80 36.15-93.05]	49.46	0.0056*
MCD	95.30 [53.45-147.2]	137.80 [73.65-208.8]	44.60	0.0002*

* Statistically significant result (P<0.05)

Wilcoxon matched pairs signed rank test

Table: Sensitivity Analysis assuming no change to follow up of non-attenders (n=19)

Walking Distance	Group B Week 0 (m) Median [IQR]	Group B Week 6 (m) Median [IQR]	% Change	P Value
ICD n=19	65.10 [31-101.4]	91.70 [72.9-132.6]	40.86	0.0001*
MCD (n=19)	120.00 [74-189]	167.40 [92.5-232.4]	39.50	0.0006*

* Statistically significant result (P<0.05)

Wilcoxon matched pairs signed rank test

Table 18: Sensitivity analysis assuming a 10% increase in walking distance parameters at follow-up (Group A: n=21, Group B: n=19)

**statistically significant result (P<0.05)*

Table: Sensitivity analysis assuming 10% Increase in follow up measures of non-attenders (n=2

Walking Distance	Group A Week 0 (m) Median [IQR]	Group A Week 6 (m) Median [IQR]	% Change	P Value
ICD	46.70 [34.6-80.2]	69.80 [36.15-97.4]	49.46	0.003*
MCD	95.30 [53.45-147.2]	147.60 [73.65-208.8]	54.88	0.0001*

* Statistically significant result (P<0.05)

Wilcoxon matched pairs signed rank test

Table: Sensitivity analysis assuming 10% Increase in f/up non-attenders (n=19)

Walking Distance	Group B Week 0 (m) Median [IQR]	Group B Week 6 (m) Median [IQR]	% Change	P Value
ICD	65.10 [31-101.4]	91.70 [80.21-132.6]	40.86	<0.0001*
MCD	120.00 [74-189]	167.40 [96.19-232.4]	39.50	0.0003*

* Statistically significant result (P<0.05)

Wilcoxon matched pairs signed rank test

Table 19: Sensitivity analysis assuming a 10% decrease in walking distance parameters at follow-up (Group A: n=21, Group B: n=19)

**statistically significant result (P<0.05)*

Walking Distance	Group A Week 0 (m) Median [IQR]	Group A Week 6 (m) Median [IQR]	% Change	P Value
ICD	46.70 [34.6-80.2]	69.80 [36.15-93.05]	49.46	0.013*
MCD	95.30 [53.45-147.2]	137.80 [73.65-208.8]	44.60	0.0007*

* Statistically significant result (P<0.05)

Walking Distance	Group B Week 0 (m) Median [IQR]	Group B Week 6 (m) Median [IQR]	% Change	P Value
ICD	65.10 [31-101.4]	91.70 [71.4-132.6]	40.86	0.0002*
MCD	120.00 [74-189]	167.40 [92.5-232.4]	39.50	0.0016*

* Statistically significant result (P<0.05)

Table 20: Change in ICD and MCD of week 6 Group A (SEP only) vs Group B (NMES & SEP)

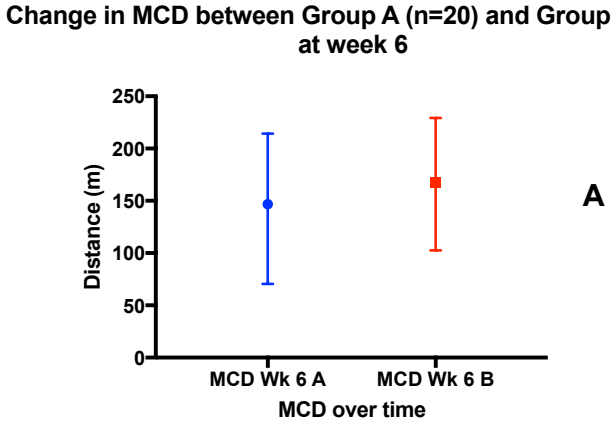
**statistically significant result (P<0.05)*

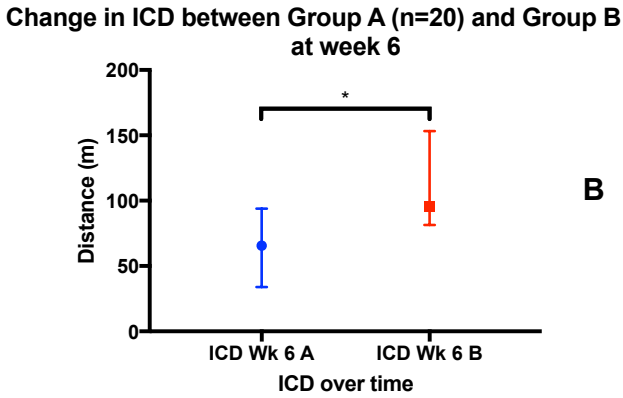
Table: Per protocol analysis of the Adjunctive benefit of NMES (Group B, n=17) to SEPs (Group A, n=20)

Walking Distance	Group A Week 6 (m) Median [IQR]	Group B Week 6 (m) Median [IQR]	% Change	P Value
ICD	65.60 [33.98-93.88]	95.50 [81.4-153.3]	45.58	0.0138*
MCD	146.70 [70.53-214.3]	167.40 [102.7-229.2]	14.11	0.283

* Statistically significant result (P<0.05)

Mann Whitney test





**statistically significant result(P<0.05)*

Figure 36: Change in **A.** MCD (m) and **B.** ICD (m) at week 6 in Group A (n=20) and Group B (n=17)

3.5.7.4 Quality of Life Questionnaires

Within group analysis showed a significant improvement in disease specific ICQ score from week 0 to week 6 in Group B as shown in Table 21. Further analysis of the change in the ICQ score over 6 weeks within Group A ($\overline{x}$ = 4.175, σ = 6.83) and group B ($\overline{x}$ = 11.17, σ = 12.24) showed a significant change in favour of Group B (P=0.036).

Within group analysis of the generic EQ-5D QoL survey score showed only group A to have a significant increase (P=0.048) from week 0 to week 6 (Table 22). There was no significant change in group B over the same time period. Between group analysis also showed no significant change in scores for each timepoint and there was no significant difference in the change of score within each group over 6 weeks (P=0.244).

The SF-36 generic quality of life survey did not show any significant change over 6 weeks in any of the 8 health domains between group A (SEP only) and B (NMES plus SEP) (Figure 37). Within group analyses of SF-36 scores can be seen in Appendix 7.3.2 and 7.3.3.

Table 21: ICQ scores in Group A (n=20) and Group B (n=16) from week 0 to week 6

Time	ICQ Group A Mean [SD]	Group B Mean [SD]	P Value
Week 0	47.91 [16.4]	48.3 [15.41]	0.942
Week 6	43.74 [15.47]	37.13 [12.33]	0.174
P Value	0.413	0.031*	

** Statistically significant result (P<0.05)*

Data analysis: Paired t test within groups, Unpaired t test between groups

Table 22: EQ-5D scores in Group A (n=20) and Group B (n=16) from week 0 to week 6

Time	EQ-5D Group A Mean [SD]	Group B Mean [SD]	P Value
Week 0	0.56 [0.16]	0.56 [0.19]	0.92
Week 6	0.64 [0.14]	0.62 [0.11]	0.258
P Value	0.048*	0.298	

** Statistically significant result (P<0.05)*

Data analysis: Paired t test within groups, Unpaired t test between groups

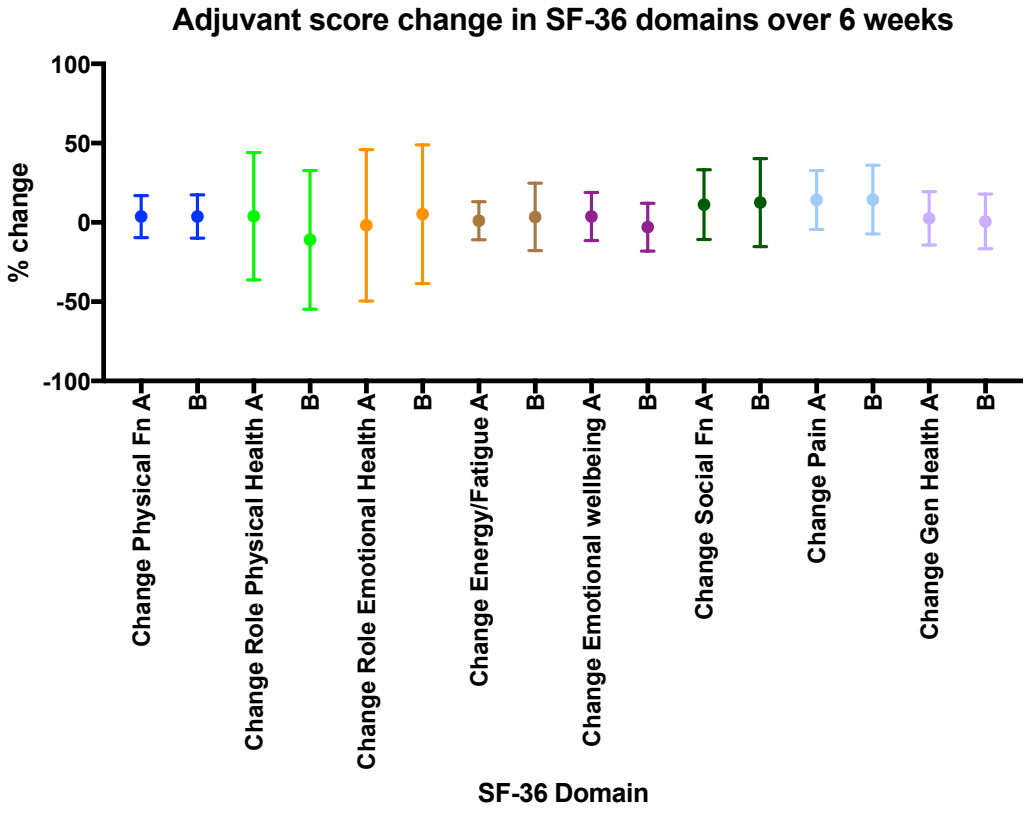


Figure 37: Change in SF-36 domain from week 0 to week 6 in Group A and Group B

3.5.7.5 Haemodynamic measures

Changes in ultrasound haemodynamic parameters including superficial femoral artery diameter, blood volume flow and TAMV are shown in Table 23. Within group analysis only shows a significant increase in TAMV in Group A (P=0.025) from week 0 to week 6. There were no significant changes in these parameters in Group B in the same time period at rest. A significant decrease in the change in TAMV over 6 weeks at rest is seen between group A (SEP only) and group B (NMES plus SEP) (P=0.022).

The device was only used by group B and therefore further ANOVA analysis of the effect of device use on haemodynamic parameters was undertaken (Table 24). Similar to the previous study, control denoted measurement at rest, device ON denoted measurement at 15 minutes into the stimulation cycle and device OFF denoted immediately after stimulation cessation at 30 minutes.

There was no significant change in USS diameter at week 0 or week 6 depending on device status (Table 24).

Blood volume flow showed a significant increase from control to device ON at week 6 of 58% (P=0.002) and a subsequent significant decrease to near baseline levels between device ON and device OFF (P=0.014). This was not replicated at week 0 (Table 24).

There was no significant change in TAMV at week 0 according to device status. However, there was a significant increase of 63% (P=0.0008) in TAMV from control to device ON at week 6. There was a subsequent significant decrease in TAMV towards baseline levels from device ON to device OFF at week 6 (Table 24).

Table 23: Intra-group and inter group analysis of change in USS parameters (Diameter, Blood Volume Flow, TAMV) from week 0 to week 6 (No device. At rest)

USS Parameter	Group A Mean change	P Value $	Group B Mean Change	P Value $	Group B Vs Group A Mean Change	P Value^
Diameter (cm)	-0.021	0.427	-0.004	0.908	-0.018	0.615
Blood Volume Flow (cc/min)	22.910	0.199	-27.960	0.274	-58.82	0.052
TAMV (cm/s)	1.843	0.025*	-1.282	0.374	-3.768	0.022*

**statistically significant result (<0.05)*

$ Paired t test

^ Unpaired t test

Table 24: ANOVA analysis of USS parameters (Diameter, Blood Flow, TAMV) of the Superficial Femoral artery according to device status in Group B at week 0 and week 6

USS Parameter	Device status	Week 0 Mean change	P Value	Week 6 Mean change	P Value
Diameter (cm)	Control Vs Device ON	-0.001	>0.999	0.009	0.730
	Control Vs Device OFF	0.0001	>0.999	0.006	>0.999
	Device ON Vs Device OFF	0.001	>0.999	-0.003	>0.999
	ANOVA	F=0.9603	0.960	F=0.743	0.467
Blood Volume Flow (cc/min)	**Control Vs Device ON**	-5.723	0.999	**-77.300**	**0.0024***
	Control Vs Device OFF	20.280	0.513	-13.980	>0.999
	Device ON Vs Device OFF	26.010	0.245	**63.320**	**0.0139***
	ANOVA	F=1.771	0.189	**F=7.926**	**0.006***
TAMV (cm/s)	**Control Vs Device ON**	-0.642	>0.999	**-4.518**	**0.0008***
	Control Vs Device OFF	1.088	0.375	-1.270	0.768
	Device ON Vs Device OFF	1.731	0.208	**3.248**	**0.0178***
	ANOVA	F=2.455	0.106	**F=9.024**	**0.0038***

ANOVA analysis of USS parameters

Post hoc analysis with Bonferroni correction

**statistically significant result (<0.05)*

Looking at LDF parameters of limb specific temperature and blood flux, within group A, there was a significant increase noted in blood flux of the hand (P=0.02) and foot (P=0.02) from week 0 to week 6 at rest (Table 25).

Within group B there was no significant change noted for any LDF parameter at rest from week 0 to week 6. However, a significant increase in blood flux at the foot of 84% (P=0.02) was noted at week 6 during the device ON period (Table 26). There was no significant change in LDF parameters over 6 weeks between the rest period and device on period (Table 27).

Table 25: Group A Change in LDF parameters from week 0 to week 6 (Rest only)

Group A LDF Parameter [Site]	Week 0 Median [IQR]	Week 6 Meidan [IQR]	Median Difference [IQR]	P Value
Temperature (ºC) - [Hand]	29.90 [29.45-30.8]	29.50 [29-31.08]	-0.25 [-1.475-1]	0.39
Temperature (ºC) - [Foot]	30.05 [28.35-31.45]	30.3 [28.4-31.3]	-0.25 [-1.275-1.1]	0.92
Flux (au) - [Hand]	35.60 [24.23-56.3]	64.45 [28.85-84.7]	21.30 [-2.675-54.13]	0.024*
Flux (au) - [Foot]	14.65 [12.63-21.65]	27.80 [19.48-32.33]	10.60 [1.05-15.75]	0.02*

*statistically significant result (P<0.05)
Data statistics: Wilcoxon signed rank test

Table 26: Group B Change in LDF parameters from week 0 to week 6 a. at rest and b. Device ON

Group B Device OFF (REST) LDF Parameter [Site]	Week 0 Median [IQR]	Week 6 Meidan [IQR]	Median Difference [IQR]	P Value
Temperature (ºC) - [Hand]	30.10 [30-30.9]	29.95 [28.63-31]	-0.75 [-1.5-0.55]	0.25
Temperature (ºC) - [Foot]	29.95 [27.95-31.25]	29.7 [28.25-31.25]	-0.3 [-0.75-0.675]	0.67
Flux (au) - [Hand]	45.65 [26.48-77.98]	47.30 [[35.15-108.5]	-2.20 [-20.3-35.7]	0.75
Flux (au) - [Foot]	22.70 [14-41.8]	38.10 [15.3-67.8]	10.40 [0.8-24.1]	0.07

*statistically significant result (P<0.05)
Data statistics: Wilcoxon signed rank test

Group B Device ON LDF Parameter [Site]	Week 0 Median [IQR]	Week 6 Meidan [IQR]	Median Difference [IQR]	P Value
Temperature (ºC) - [Hand]	30.35 [29.58-31.35]	30.05 [29.6-31.23]	-0.40 [-0.875-0.55]	0.38
Temperature (ºC) - [Foot]	29.5 [28.3-31.2]	29.2 [28.3-31.8]	0.1 [-0.4-1.1]	0.31
Flux (au) - [Hand]	55.90 [33.18-100.6]	64.35 [34.05-118.6]	7.65 [-5.75-42.23]	0.21
Flux (au) - [Foot]	51.10 [31.8-74.7]	94.30 [55.1-109.9]	45.70 [-0.6-53.7]	0.02*

*statistically significant result (P<0.05)
Data statistics: Wilcoxon signed rank test

Table 27: Group B % change in LDF parameters over 6 weeks according to Device off (rest) and Device ON period

LDF Parameter [Site]	Device OFF Median [IQR] (% Change)	Device ON Meidan [IQR] (% Change)	Median Difference (Change %)	P Value
Temperature (ºC) - [Hand]	-2.495 [-4.82-1.83]	-1.34 [-2.81-1.89]	1.16	0.3807
Temperature (ºC) - [Foot]	-0.68 [-2.2-2.24]	0.39 [-1.44-3.61]	1.07	0.4608
Flux (au) - [Hand]	-5.53 [-26.61-111.1]	24.21 [-11.53-115]	29.4	0.8381
Flux (au) - [Foot]	25.41 [6.15-99.61]	81.88 [-2.86-128.4]	56.47	0.5949

*statistically significant result (P<0.05)
Data statistics: Mann-Whitney U test

3.5.7.6 Compliance

Further analysis of the compliance diaries of those completing the trial in group B (n=17) showed there was a 96% compliance (range: 90-100%) in use of the Revitive™ IX NMES device over the 6 week intervention period. No patient contacted the investigators for additional support and most reported good tolerability of device use which could be satisfactorily incorporated within their daily routine.

3.5.8 Conclusions

Walking distance is an important and reliable objective measure of the effect of IC symptoms on the functional ability of patients (Kruidenier, Nicolaï et al. 2009). Supervised exercise therapy has shown to significantly improve the distance before onset of IC symptoms and the absolute walking distance, being the limit of exertion due to IC (Bendermacher, Willigendael et al. 2007, Fokkenrood, Bendermacher et al. 2013, Lane, Harwood et al. 2017). It is no surprise, therefore, that SEPs are a first line recommendation for the non-invasive management of early symptomatic PAD in national and international guidelines on the management of lower limb arterial disease (Norgren, Hiatt et al. 2007, NICE147 2012, Aboyans, Ricco et al. 2018). This improvement was reflected by the significant increase in both the ICD and MCD within group A, solely undertaking a SEP, and within group B using an NMES device as well as attending an SEP. There was no significant difference in the increase in maximum claudication distance at week 6 between these 2 groups suggesting that NMES does not provide any adjunctive benefit to SEPs in increasing the symptomatic limitation of IC. Although the MCD measure was not significantly different between the groups at week 6, it should be noted that there was approximately a 12 % increase in this parameter in Group B compared to Group A. However, the ICD between these groups at week 6 was significantly different in favour of adjunctive NMES use (P=0.0138).

Disease specific ICQ scores were significantly better in Group B only (P=0.031) over 6 weeks. When the change in scores within each group over 6 weeks were compared, this showed a significant improvement in favour of the NMES group, suggesting an adjunctive benefit of this intervention. Although the EQ-5D score was significantly better in Group A only (P=0.048), there was no significant adjunctive benefit of NMES comparing the change

in scores over 6 weeks in each group. The SF-36 did not show any differences in 8 health related domains between the groups. However, there were some increased changes to pain and social functioning in group A and pain in group B. It is anticipated that in line with the very generic format of the health survey, that patients considered all aspects of their health in the replies as these findings for the pain domain are out-with the significant improvements in disease specific ICQ and generic EQ-5D quality of life measures. Definitive quality of life improvements, whether measured by disease specific or generic methods have not been shown in relation to exercise therapy in the current evidence base. Studies are largely small trials with heterogenous methodology and QoL surveys, making meta-analysis of grouped studies difficult to undertake.

There were no significant changes seen in the haemodynamic ultrasound measures taken at rest for group A at week 0 and week 6 except for TAMV which was significantly increased in this time period. The corresponding blood volume flow was not significantly different. The same was not observed in group B, in fact statistically seems significantly better in group A than B. This result cannot be logically explained as being attributable to SEP in Group A as both groups had SEP and at least the same effect would be expected in group B. Further analysis of the haemodynamic measures within Group B show significant increase in blood flow (cc/min) and TAMV (cm/s) in the arterial circulation supplying the lower limb when the device is ON compared to rest and after stimulation is complete (device OFF). This is in keeping with results shown in the previous proof of concept pilot study described and also other healthy participant studies using this specific NMES device (Varatharajan, Williams et al. 2015). Of course, further research is required to better understand mechanisms by which blood flow improvement may confer functional improvement in patients with IC, but augmentation of the calf muscle pump has been suggested to increase cardiac output and

therefore total blood flow (Grunovas, Silinskas et al. 2007) suggesting a possibility of more efficient nutrient and oxygen supply to working muscles in the lower limbs. Lower limb arterial blood flow has been noted to increase, in some cases by up to 4 fold, secondary to intermittent pneumatic compression therapy in various trials (Morgan, Carolan et al. 1991, van Bemmelen, Mattos et al. 1994, Delis, Nicolaides et al. 2000, Delis and Knaggs 2005, Delis and Nicolaides 2005). Mechanisms suggested for these improvements include compression related change in the arterio-venous pressure gradient promoting an increase in arterial flow (Delis and Knaggs 2005), or sympathetic autoregulation processes (Delis, Nicolaides et al. 2001) described further in section 1.1.8.1, and shear stress induced vasoactive transmitter release (e.g. NO) allowing vasodilatation and reduction of peripheral vascular resistance (Delis and Knaggs 2005). These explanations for the improved arterial blood flow to lower limbs with IPC remain theoretical and further research is not only required to ascertain a correlation, but also to establish whether these processes correlate with NMES mechanisms of haemodynamic improvement.

At device stimulation cessation, haemodynamic parameters of blood flow and TAMV returned to baseline, which is in keeping with studies of this device in healthy individuals (Varatharajan, Williams et al. 2015). Skin microcirculation seemed to improve significantly at rest within group A with blood flux increase in the foot and hand. The same was not observed in Group B at rest, but there was a significant improvement in blood flux, as a reflection of skin microcirculation with the device ‘on’ after 6 weeks intervention.

There is no consensus on the haemodynamic improvement of lower limb blood flow amongst the NMES in PAD studies as discussed in the previous study and literature review in section

Further robust research in this area is required, within a standardised fashion, to elicit any such correlation.

This study was designed as a randomised controlled trial to provide robust information about the clinical efficacy of NMES as an adjunct to SE in the management of patients with IC. There were limitations noted in this clinical trial, most importantly the inability to recruit the full sample size. A large number of those screened were initially excluded due to having diabetes. A substantial amendment to protocol was formally requested from the ethics committee to include this co-morbidity and granted 3 months prior to completion resulting in 4 further patients included in the study. Unfortunately, 2 patients were excluded after baseline appointment and randomisation due to the inability to complete the treadmill test, and a further 3 did not attend the follow up assessment. This reduced the total patients included to 37 for complete data analysis. From a primary outcome perspective, the findings of this study accept the null hypothesis that NMES does not provide an adjuvant benefit to SEPs in the management of IC. However, in the context of the above limitations to recruitment, this may represent a type II error. There is an adjuvant benefit of NMES to SEPs in the improvement of pain free walking distance or ICD. Further research with a larger sample size is certainly warranted as comparison between groups did not suggest a decline in function or health deterioration due to NMES.

With the gold standard non-invasive treatment modality of SEPs being significantly underutilised and having problems with patient adherence, the development of novel technologies like NMES have an immense implication for the ongoing first line management of intermittent claudication. The total cost of 2 hours of supervised exercise per week for 3 months is approximately £288 (£232-£345) per patient (Bermingham, Sparrow et al. 2013). A

more cost effective and immediately accessible treatment modality, allowing the patient to be independent and actively involved within their treatment regime would be the most ideal solution.

Although further dosing studies are required, from patient feedback received during the clinical trials, NMES is easy to use and its accessibility allowed incorporation of the device into a daily routine. Hence the compliance of use in the follow up patients of Group B in 6 weeks was 96%.

This clinical trial provides some important inferences between the use of NMES and functional improvement in patients suffering with IC, that firmly support further robust research to contribute to the evidence base and knowledge.

4 Muscle Recovery Studies

4.1 Introduction

As explored in chapter 1, there are some parallels between the underlying metabolic changes within skeletal muscle observed in healthy athletes and patients with PAD during muscle fatigue. Although exercise induced muscle fatigue in the PAD population is accelerated, most likely due to the underlying impaired blood flow, compared to healthy individuals, both require an adequate period of rest and reperfusion to the skeletal muscle to wash out metabolic products of anaerobic metabolism including lactic acid and inorganic phosphates for adequate muscle recovery. The skeletal muscle is then ready for exertion again. There has been extensive research to understand these principles, largely within the sports science arena, in order to identify targets for the development of modalities to provide effective muscle recovery. Neuromuscular electrical stimulation is one such tool that is being assessed in its utility for muscle recovery (Babault, Cometti et al. 2011, Gondin, Brocca et al. 2011, Maffiuletti, Minetto et al. 2011, Maffiuletti, Vivodtzev et al. 2014, Veldman, Gondin et al. 2016).

The underlying morphological changes to muscle fibre phenotype and metabolic changes in skeletal muscle as an adaptation to NMES are similar to adaptations seen following endurance training (Hawley 2002, Gondin, Brocca et al. 2011).

There is a significant paucity of calf muscle based fatigue and recovery studies in the current literature and therefore the aim of the following studies was to assess the utility of NMES in muscle recovery in calf muscle based fatigue in healthy individuals and further attempt to draw parallels with the PAD population. Initially a pilot study was conducted, with various outcome parameters, that was repeated as a randomised controlled trial.

These studies were completed in collaboration with Professor Alison McGregor (Professor of MSK biodynamics, Imperial College London), supervised physiotherapy and biomedical students (see 'Acknowledgements') with an interest in biomechanical research. The latter were instrumental in data collection and interpretation. The thesis author had responsibility for conceptualisation of all the studies, methodology, provision of NMES devices, oversight of regulatory approvals, information provision to participants, data interpretation and analysis, and presentation of the results within this thesis. Overall supervision was by Professor Alun Davies.

Prior to conducting the studies, the calf muscle fatigue protocols were established followed by outcome parameters that would be useful, effective and straightforward to assess with limited resources. A literature review on outcomes measures in muscle fatigue and recovery was completed in the previous chapter.

4.2 Calf muscle fatigue

As the commonest site of exercise induced ischemic pain amongst patients with IC is the calf muscle group and the action of the study NMES device is on calf muscle contraction over a stimulation cycle, it was considered appropriate to undertake a fatiguing protocol based on this muscle group. The majority of muscle fatigue related research uses the quadriceps muscle group and so conventional standardised protocols for calf muscle fatigue were not available.

Along with muscle fatigue, a concept known as Delayed Onset Muscle Soreness (DOMS) can also develop and is characterised by delayed pain 24 to 48 hours after especially unusual intense exercise (Newham 1988) lasting approximately 5 days.

4.2.1 Lunge fatigue exercise

An initial randomised controlled pilot study was conducted to assess muscle recovery following high intensity fatigue inducing exercise in a group using active NMES recovery compared to a passive recovery group. The calf fatigue protocol included alternate lower limb lunge exercises. Eccentric muscle exercises were deemed to provide maximal fatigue and soreness (Newham, Mills et al. 1983). The exercise involved lunging towards markers placed on the floor to allow for hip and knee flexion at a 90° angle (Figure 38). After a 5 minute standard warm up, this fatigue exercise was performed for 10 minutes at a consistent intensity level of 6 on a rate of perceived exertion scale (Borg 1982). This scale is a reliable way of guiding exercise to maintain a similar intensity based on the individuals capacity throughout a testing protocol. Following the lunge exercise protocol, participants had 5 minutes to stretch.

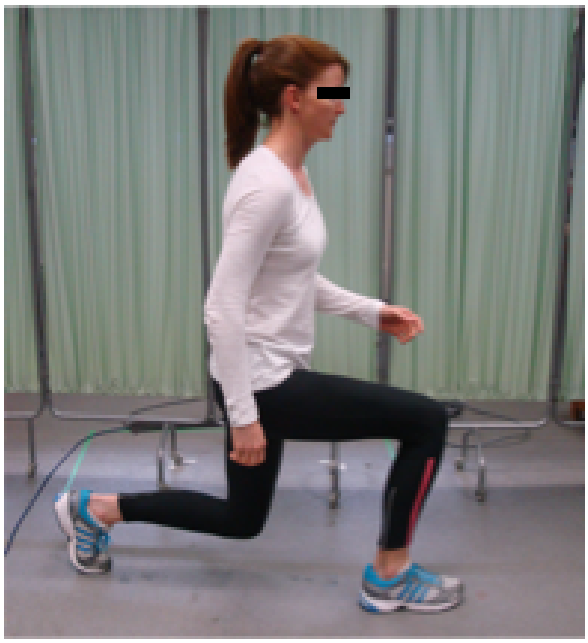


Figure 38: Lower limb lunge exercise for calf muscle fatigue

4.2.2 Calf raise exercise

For a repeat randomised controlled trial assessing the utility of NMES as a tool for recovery following muscle fatigue compared to passive recovery, an alternative calf muscle fatigue protocol was used. This involved calf muscle fatigue by heel raise exercises. This exercise has been shown to specific and effective at causing localised fatigue in the calf muscle group including the targeted area for research interest, the gastrocnemius medialis, gastrocnemius lateralis and the soleus (Hebert-Losier, Schneiders et al. 2012).

The exercise protocol includes placing the feet flat on the ground and raising the heels synchronously to a tip-toe position and then back to resting state. This was repeated continuously until failure, defined as the inability to continue limited by pain and muscle fatigue. The exercise and therefore onset of fatigue, could be augmented by placing the forefoot on the edge of a platform placing the calf muscle under constant contraction throughout the exercise.

4.3 Endpoints and Outcome measures

4.3.1.1 Numeric Pain Rating Scale

The numeric pain rating scale (NRS) is a visual scale from 0 to 10 denoting a spectrum of pain where 0 is no pain and 10 is the worst pain possible. This is a valid scale with good test-retest reliability and sensitivity for detecting differences in pain scores (Summers 2001, Ferreira-Valente, Pais-Ribeiro et al. 2011).

4.3.1.2 Sargent's Jump Test

This is a vertical jump performance test to assess power of the lower limb muscles. This has excellent reliability (R>0.97) and validity (R>0.95), with low variability when assessed with other similar tests (Aragón 2000, Markovic, Dizdar et al. 2004).

This test, first described as by Sargent in 1921, instructs a vertical jump to the highest possible height after bending at the knees and using the upper limbs for propulsive momentum. This test is done beside a wall on which a mark is placed with the nearest arm reaching upwards as high as possible, whilst at rest in the standing position. The participant then has chalk applied to the index finger of the arm nearest the wall and places this as a marker during the jump test, at the highest perceived point . The difference calculated between the maximum height jumped and the resting height constitutes the jump height measurement. The Sargent's jump test was repeated 3 times with a 20 second break in between, with the maximal difference recorded as the jump height.

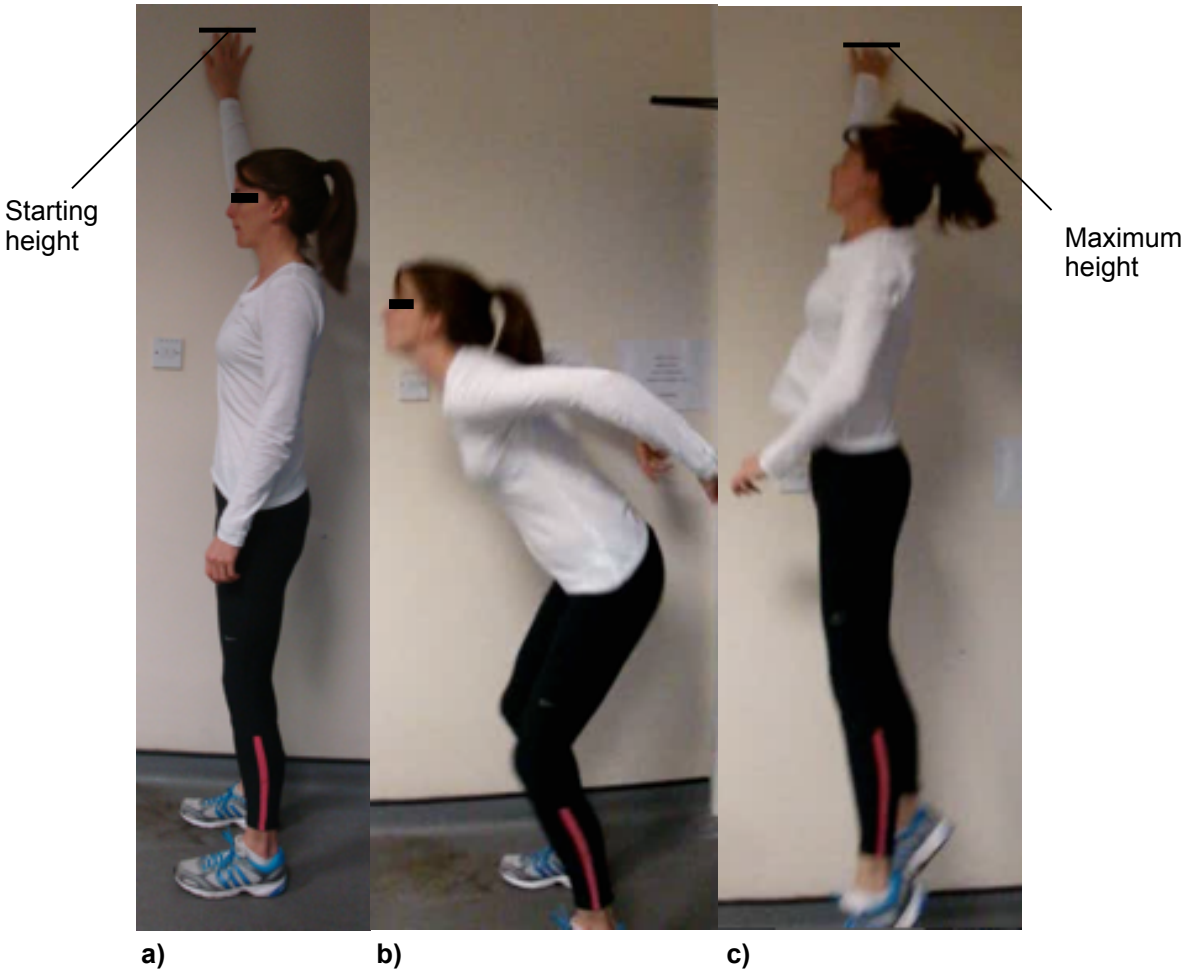


Figure 39: Sargent's vertical jump test

a) A resting mark is placed on the wall with an outstretched hand b) the arms are used for propulsion within the jump action to achieve maximal height c) a chalk mark from the index finger of the hand closest to the wall is placed as the maximal jump height level.

4.3.1.3 Video assisted Jump Test

For the follow up randomised controlled trial, the vertical jump assessment was measured using an iPhone 5 application called 'My Jump'. This application uses the iPhone 5 in-built high speed camera to capture the flight time between feet leaving the ground and landing again. The application algorithm then calculates the jump height. This application has had validity and reliability testing against the traditional countermovement force platform jump test, which records the time in the air after the feet leave the platform to land again. Intraclass

correlation co-efficient was 0.977 ($P<0.001$) with an excellent validity for height measurement ($r=0.995$, $P<0.001$). This is a readily available application with ease of use and highly reliable. The best value of jump height from 3 was recorded according to the timepoint of measurement for this study.

4.4 NMES use in calf muscle recovery after high intensity exercise

4.4.1 Introduction

Exercise induced ischemia with the build-up of anaerobic metabolites in the lower limb muscles is one proposed mechanism for intermittent claudication in symptomatic PAD (Pipinos, Judge et al. 2007). Similarly, muscle fatigue in healthy individuals occurs when the oxygen and nutrient demand of the working skeletal muscle is not sufficiently supplied by oxygenated blood thereby causing a build-up of metabolites of anaerobic respiration. Similar to IC patients, this can cause pain and reduces the performance of the skeletal muscle, which is reversible by rest. Overtraining a muscle can also lead to delayed onset muscle soreness, of which the exact underlying mechanisms are unknown. This manifests approximately 48 hours after the fatiguing exercise and can last up to 1 week (Newham 1988).

Bishop et al suggested that there are 3 important timepoints for muscle recovery in the athlete, which is immediate, or between muscle contractions; short term, or between exercises; and training recovery which is between training sessions (Bishop, Jones et al. 2008). Within the context of IC patients, short-term recovery, between bouts of walking and having to stop due to exercise induced ischemic muscle fatigue seems the most similar.

Strategies for muscle recovery include passive, which simply includes resting, most likely to allow reperfusion and metabolite wash out, and active, which can include massage therapy, submaximal intensity training, stretching (Rey, Lago-Penas et al. 2012) as well as novel techniques of cold water baths, cryotherapy and compression, however there is lack of clear evidence to support any of these as being effective (Babault, Cometti et al. 2011).

4.4.2 Aim and hypothesis

The aim of this study was to assess the utility of a footplate NMES device in muscle recovery in a calf fatigue model of healthy participants as an active recovery strategy compared to passive recovery, by assessing calf muscle function in the short and long term. The hypothesis is that NMES will allow muscle recovery more rapidly both short and long term reflecting in calf muscle performance closer to baseline and faster relief from DOMS than the controlled group (passive recovery).

4.4.3 Methods

4.4.3.1 Study Design

This study was designed as a pilot randomised controlled trial using random allocation via an online platform (www.sealedenvelope.com) to an active experimental (NMES) or control recovery group.

4.4.3.2 Sample size

There is a lack of sufficient data to power this study adequately with a calculated sample size. A sample size of 20 patients in total (10 per group) was considered sufficient to provide a proof of concept for ongoing research.

4.4.3.3 Inclusion and Exclusion criteria

Participants were included into the study if the met the following criteria:

- Age >18 years
- Physically active, participating in at least 3 hours of moderate physical exercise weekly

Patients were not recruited to the trial if they met any of the following exclusion criteria:

- Current or chronic lower limb or back musculoskeletal problems
- Pre-existing conditions precluding exercise activity
- Currently taking analgesic or anti-inflammatory medication
- Neurological or vascular conditions or Diabetes Mellitus
- Had a pacemaker or implantable defibrillator device
- Pregnancy
- Open wounds or tissue loss at the feet

4.4.3.4 Ethical Approval

Ethical approval for this clinical trial was granted by the Imperial College Research Ethics Committee (ICREC Reference: 14IC2143).

4.4.3.5 Outcome measures

The primary outcome measure was a countermovement jump test to assess muscle performance by means of jump height, called the 'Sargent's jump test'. The methodology for this is explained in section 4.3.1.2 above.

The secondary outcome measure was the numeric rating scale for pain, also described in section 4.3.1.2 above.

4.4.3.6 Methodology

Participants were recruited from the staff and student body of Imperial College London and Kings College London. They were provided with written participation information sheets (Appendix 7.1.3) and underwent a consent procedure for inclusion to the clinical trial (Appendix 7.2.3).

The clinical trial flow chart is shown in Figure 40. On day 1 the participants were randomised into either the active recovery group, who would go on to use the NMES device; or the passive recovery control group, who would use rest as a means to recovery. Outcome measures were taken at baseline followed by 5 minutes of standardised simple static and dynamic warm up exercises. This followed by 10 minutes of calf muscle fatigue using lunge exercises as described in section 4.2.1, above. Following 5 minutes of stretching, outcome measures were repeated as post fatigue measures. The control group were requested to rest by sitting for a further 30 minutes whilst the active group, received a 30 minute pre-programmed cycle of NMES with the Revitive™ IX device at supra-threshold level of visible but non painful calf contractions. This has been described in previous PAD related studies within this thesis.

Outcome measures were repeated for both groups again. The participants in the active arm of the trial took a device home with them and were instructed to use the device for a further 30 minute pre-programmed cycle the next day, whilst the control arm had no device and were advised to refrain from strenuous activities and undertake rest as per passive recovery.

On Day 2, the participants were telephoned to provide a 24 hour NRS pain score.

Participants from both groups returned on day 3, where 30 minutes NMES recovery in the active arm and rest in the control group was followed by final outcome measures being repeated. This marked the end of the participation in the trial.

4.4.3.7 Data analysis

Data was transcribed to a trial database on Microsoft Excel 2016 and further analysis was completed using GraphPad Prism software for Mac (USA). Repeated measures within groups were analysed by one way ANOVA with inter group analyses at specific time points carried out by unpaired t test. If the ANOVA result suggested significance ($P<0.05$), further column analysis was undertaken with post hoc Bonferroni correction. Statistical significance was noted if the probability of the result occurring by chance was less than 5% ($P<0.05$).

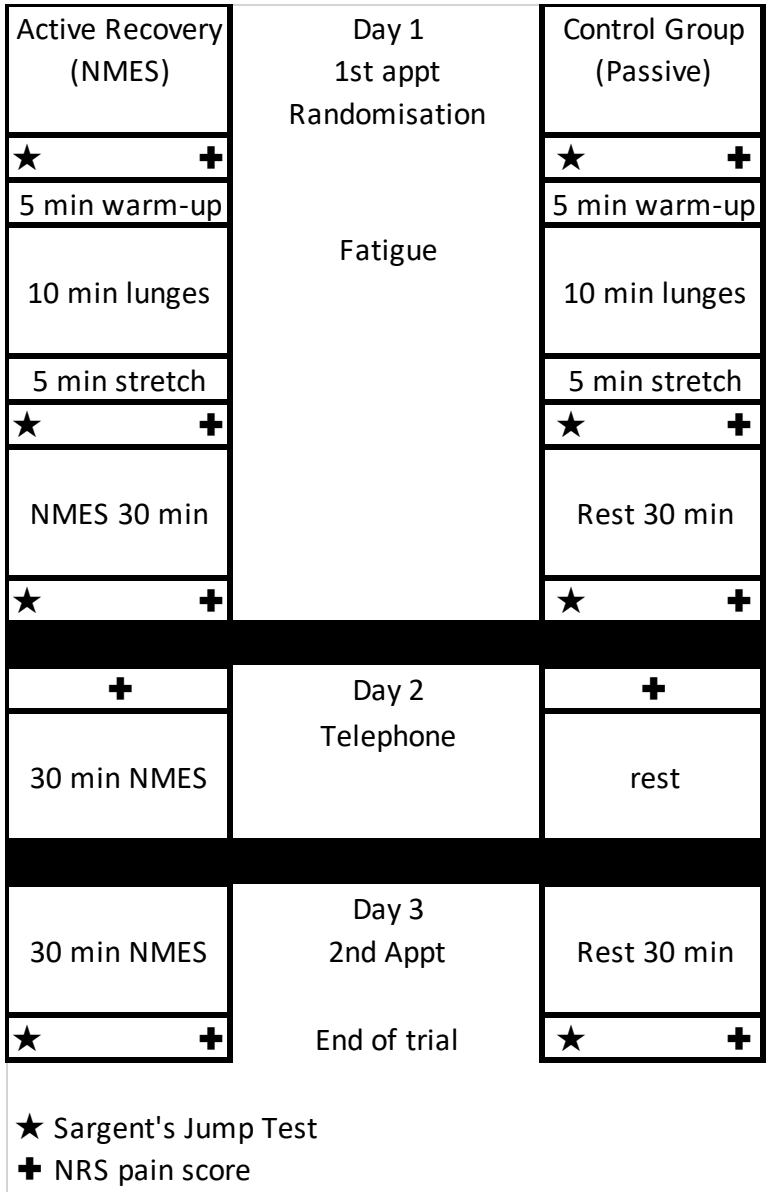


Figure 40: Trial flowchart: NMES use in calf muscle recovery following high intensity training

4.4.4 Results

4.4.4.1 Demographics

Twenty healthy participants were recruited to the trial (70% female) with demographic criteria shown in Table 28. The groups were well matched with no significant differences between the groups (P>0.05).

Table 28: Demographic criteria of trial participants (n=20)

(P>0.05 for all criteria)

	Control	ActiveNMES
n	10	10
Mean Age (yrs) [SD]	25 [2.61]	26 [3.39]
Female (%)	60	80
Mean Height (cm) [SD]	170 [11.41]	168.45 [10.41]
Mean Hrs of exercise/week [SD]	5.18 [2.45]	6.46 [5.55]

4.4.4.2 Sargent's Jump Test

The evolution of jump height scores (cm) according to the trial timepoints of measure are shown in Figure 42 comparing passive (REST) recovery to active (NMES) recovery following high intensity muscle fatiguing exercise. The D'Agostino & Pearson normality test showed data to be normal for both groups.

Analysis within groups using the one-way ANOVA suggested a significant change of jump height in the passive recovery control group over time (F 9.114, P=0.0033) (Figure 41). Further post hoc analysis with Bonferroni correction showed the significantly reduced jump height from baseline to be at the post rest (recovery) period on day 1 (P=0.0007) and post rest (passive recovery) period on day 3 (P=0.021) (Figure 41A).

There was no significant change in the one-way ANOVA for jump height in the active (NMES) recovery group (F 3.28, P=0.061). However, further analysis between timepoints suggested a small but significant decrease in jump height post NMES (recovery) on day 1 compared to baseline (P=0.047) (Figure 41B).

Between group analysis showed there was no significant difference in jump height, a marker of muscle performance, between the passive (REST) and active (NMES) arms of the trial over time (Figure 42).

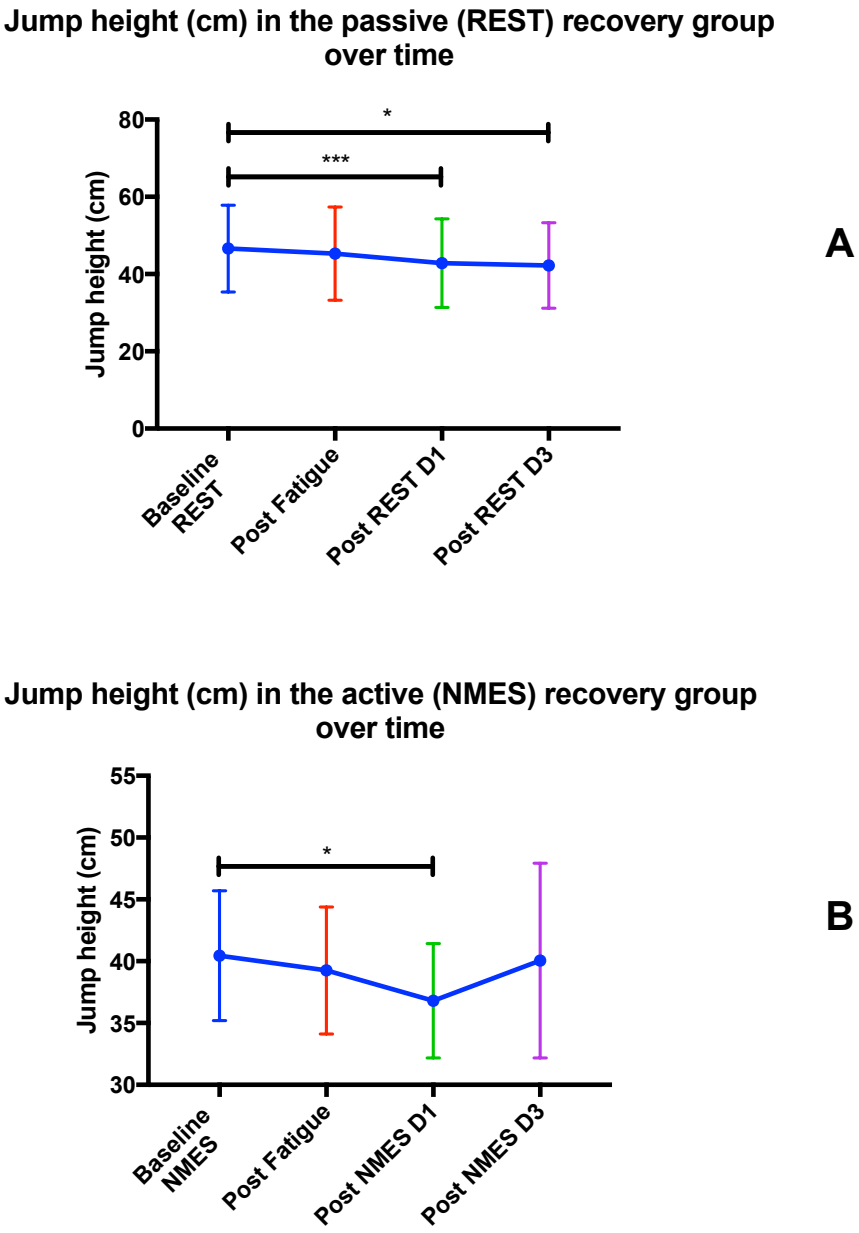


Figure 41: Jump height (cm) levels in the passive recovery (A) and active recovery (B) groups over time

denotes P<0.05, * denotes P<0.001*

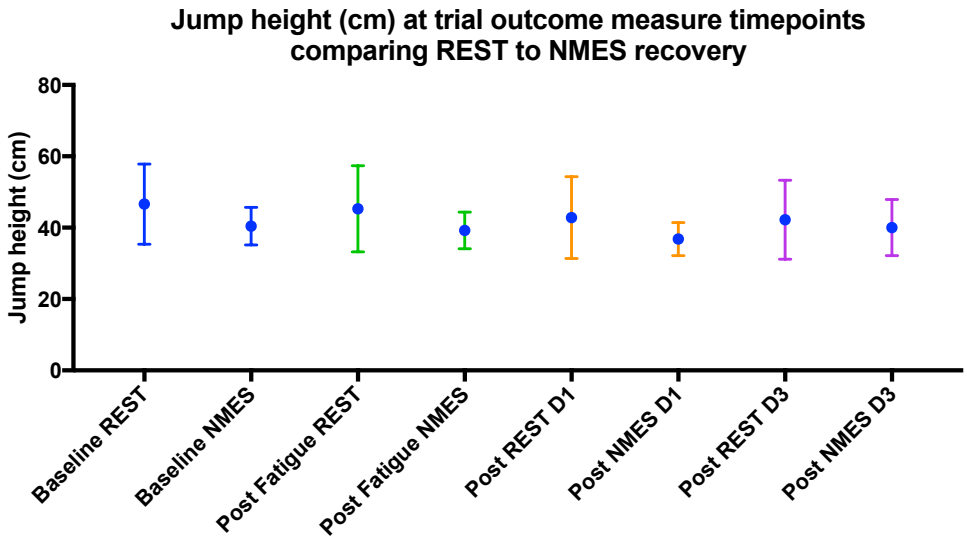


Figure 42: Sargent's jump height scores at various trial timepoints comparing passive (REST) and active (NMES) recovery

No significant differences found (P>0.05)

4.4.4.3 NRS score

The D'Agostino & Pearson normality test showed data to be normal for both groups except at the baseline for the active (NMES) group (P=0.007). This violation of normality was noted, but did not influence any change in statistical analyses by either parametric or non-parametric analysis. For continuity of comparison between groups, all data was assessed by parametric analyses.

Analysis within groups using the one-way ANOVA suggested a significant change of NRS scores in the passive recovery control group over time (F 7.349, P=0.007) (Figure 41). Further post hoc analysis with Bonferroni correction showed a significantly increased pain score from baseline immediately post fatigue exercise (P=0.028) and on day 2 (P=0.019) (Figure 43A).

There was also a significant change in the one-way ANOVA for NRS pain score in the active (NMES) recovery group (F 5.094, P=0.028). Post hoc analysis with Bonferroni correction showed a significant increase in pain scores compared to baseline immediately post fatigue exercise (P=0.008) and at day 2 (P=0.0035) (Figure 43B).

Between group analysis showed there was no significant difference in NRS pain score, between the control passive (REST) and active (NMES) arms of the trial over time (Figure 44).

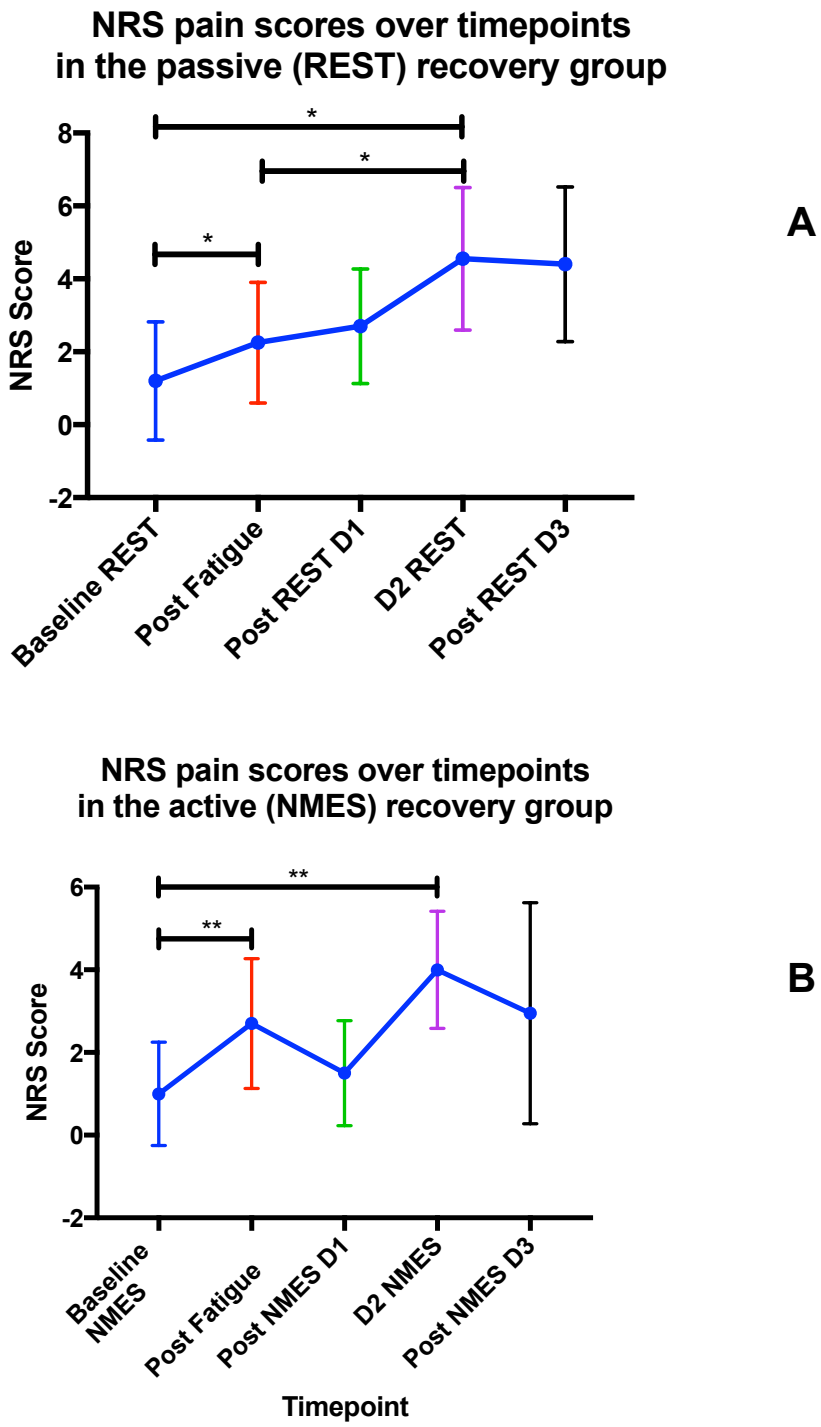


Figure 43: NRS pain scores in the passive (REST) group (A) and active (NMES) group (B) over time

**denotes P<0.05, ** denotes P<0.01*

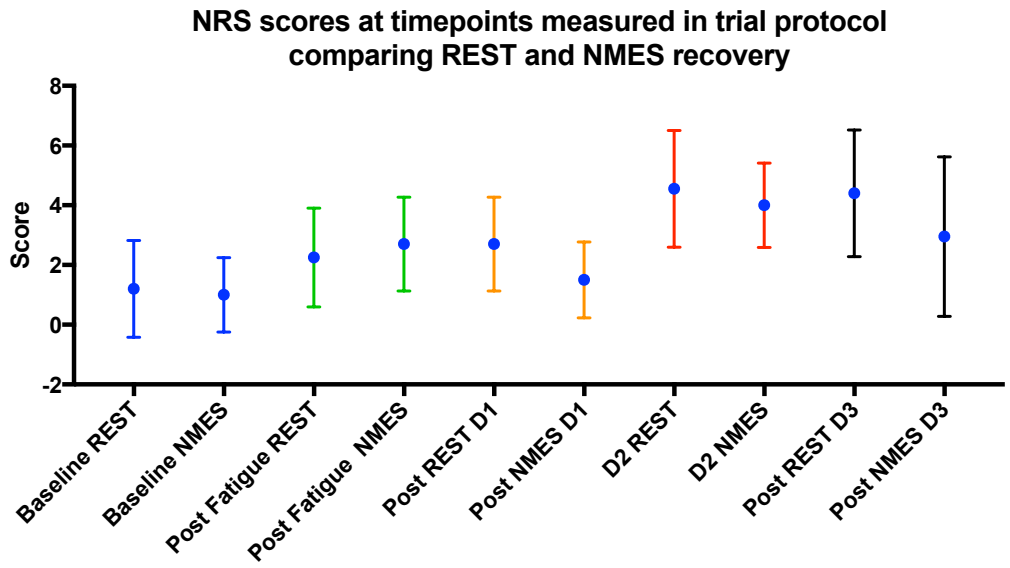


Figure 44: NRS pain score at various trial timepoints comparing passive (REST) to active (NMES) recovery

4.4.5 Conclusions

This small randomised controlled trial reveals that muscle performance, measured as best jump height, does not significantly improve with the active recovery method of NMES after high intensity exercise compared to passive recovery. This is true of all time points, short and long term (Figure 42).

Muscle performance, as measured by the Sargent's jump test, seems to return to baseline levels on day 3 in the active (NMES) group (Figure 41), hence no significant difference between these 2 timepoints. The change in jump height at day 3 is only 1% below that of baseline in the active (NMES) group. The same cannot be inferred in the passive recovery control group. There is a significantly poorer muscle performance observed at day 3 compared to baseline (-9.4%). Although this is not statistically different between active and passive recovery groups, the data err towards the NMES modality providing better muscle recovery over 48 hours. The lack of significant difference in this result may be due to some of the study limitations including a small sample size. Both groups show a significant reduction in muscle performance immediately post recovery method, either 30 minutes rest (control) or 30 minutes NMES (active), on day 1. This suggests that the fatiguing exercise was sufficient for the trial.

Change in pain scores are significantly worse at the same 2 timepoints in both groups. This is immediately post fatigue and at day 2. This credits the fatiguing exercise with being appropriate to the trial and also supports the perception of DOMS (Newham 1988). In fact, further paired parametric analysis of the pain score at day 2 compared to post fatigue exercise shows a significant decrease in the control group ($P=0.02$) but this is not replicated in the active (NMES) recovery group. The day 2 pain scores between both groups are not, however,

significantly different, so although there may be a trend towards significance, further robust research is necessary to ascertain the utility of NMES in active recovery to reduced DOMS.

A global observation suggests that participants using the active (NMES) modality of muscle recovery have a quicker return to baseline of muscle performance and pain experience. Although these changes are not significantly different, there is a motive for further improved and robust research to establish clearer correlations between passive and active recovery methods.

The limitations within this study include a small sample size and short time period of data collection. A small sample size does not allow us to make concrete inferences about the results due to the large possibility of error. A post hoc power calculation based on jump height data immediately after recovery at day 1, suggests that this study had a power of only 34.4%. A minimum of 80% would be needed to make accurate inferences between active and passive muscle recovery methods.

The short period of follow up time is important, especially in the active (NMES) recovery group, who have been provided with a new piece of equipment that they have not been used to functioning, possibly having an impact on results due to their technique and lack of experience with the device. These limitations can be rectified with a longer term study to assess these outcome measures as well as an appropriately powered sample size.

4.5 NMES in the recovery of short and long term calf muscle fatigue

4.5.1 Introduction

This study was carried out to address some of the limitations in the previous study including sample size and study length. The aim of this study is to be able to show more robust inferences between control passive (REST) and active (NMES) recovery of muscle fatigue.

The null hypothesis states that NMES as an active muscle recovery modality, will not significantly improve muscle performance and reduce DOMS in a calf muscle fatigue model compared to passive (rest) recovery.

4.5.2 Methods

4.5.2.1 Study Design

This study was designed as a randomised controlled trial using blocked (2,4,2) random allocation via an online platform (www.sealedenvelope.com) to an active experimental (NMES) or control passive (REST) recovery group.

4.5.2.2 Sample size

The previous study was significantly underpowered. Post hoc power calculations suggested the above study to have a power of 34.4%. Using short term recovery jump height data from this study, a standard sample size calculation was conducted online (http://clincalc.com/stats/SampleSize.aspx). With anticipated means of 43 (SD:11) in the control group and 37 in the intervention groups, at 80% power with alpha at 0.05, a minimum of 53 patients would be required per group to have sufficient statistical power to detect a treatment effect.

4.5.2.3 Inclusion and Exclusion criteria

Participants were included into the study if the met the following criteria:

- Age >18 years
- Physically active, participating in at least 3 hours of moderate physical exercise weekly

Patients were not recruited to the trial if they met any of the following exclusion criteria:

- Current or chronic lower limb or back musculoskeletal problems
- Pre-existing conditions precluding exercise activity
- Currently taking analgesic or anti-inflammatory medication
- Neurological or vascular conditions or Diabetes Mellitus
- Had a pacemaker or implantable defibrillator device
- Pregnancy
- Open wounds or tissue loss at the feet

4.5.2.4 Ethical Approval

Ethical approval for this clinical trial was granted by the Imperial College Research Ethics Committee following an amendment of the previous study protocol (ICREC Reference: 14IC2143).

4.5.2.5 Outcome measures

The primary outcome measure was a countermovement jump test to assess muscle performance by means of jump height, using the video assisted application 'My Jump'. The methodology for this is explained in section 4.3.1.2 above.

The secondary outcome measure was the numeric rating scale for pain, also described in section 4.3.1.2 above.

4.5.2.6 Methodology

Participants were recruited from the staff and student body of Imperial College London by word of mouth and advertisement. They were provided with written participation information sheets (Appendix 7.1.4) and underwent a consent procedure for inclusion to the clinical trial (Appendix 7.2.4).

The overall methodology used in the previous trial was repeated during this trial. A further timepoint of outcome assessment at day 7 and jump height measurement by a phone application 'My Jump' instead of the Sargent's Jump Test, were different in this trial compared to the last. Also, the calf fatiguing exercise was modified from lunges in the last trial to calf raises. This form of muscle fatigue exercise and the video assisted jump height measurement is explained earlier in this chapter.

The clinical trial flow chart is shown in Figure 45. On day 1 the participants were randomised into either the active recovery group, who would go on to use the NMES device; or the passive recovery control group, who would use rest as a means to recovery. Outcome measures were taken at baseline followed by 5 minutes of standardised simple static and dynamic warm up exercises. This followed by 10 minutes of calf muscle fatigue using calf raise exercises as described in section 4.2.1, above.

Following 5 minutes of stretching, outcome measures were repeated as post fatigue measures. The control group were requested to rest by sitting for a further 30 minutes whilst the active group, received a 30 minute pre-programmed cycle of NMES with the Revitive™ IX device

at supra-threshold level of visible but non painful calf contractions. This has been described in previous PAD related studies within this thesis.

Outcome measures were repeated for both groups again. The participants in the active arm of the trial took a device home with them and were instructed to use the device for a further 30 minute pre-programmed cycle daily for 7 days, whilst the control arm had no device and were advised to refrain from strenuous activities and undertake rest as per passive recovery.

On Day 2, the participants were telephoned to provide a 24 hour NRS pain score.

Participants from both groups returned on day 3, where 30 minutes NMES recovery in the active group and rest in the control group was followed by a repeat assessment of outcome measures.

Participants continued with their respective daily recovery methods and were appointed for review at day 7, where post recovery outcomes were assessed for the final time. This marked the end of the participation in the trial.

4.5.2.7 Data analysis

Data was transcribed to a trial database on Microsoft Excel 2016 and further analysis was completed using GraphPad Prism software for Mac (USA). Repeated measures within groups were analysed by one-way ANOVA with inter group analyses at specific time points carried out by unpaired t test. If the ANOVA result suggested significance ($P<0.05$), further column analysis was undertaken with post hoc Bonferroni correction. Statistical significance was noted if the probability of the result occurring by chance was less than 5% ($P<0.05$).

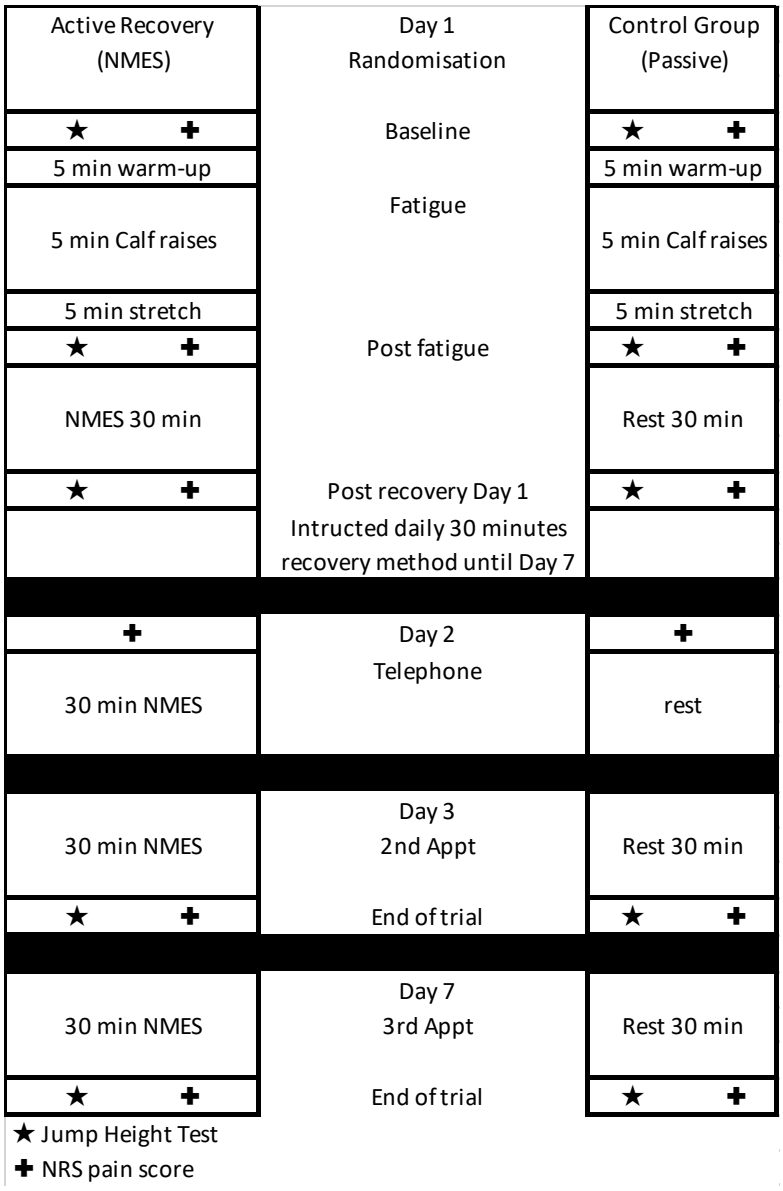


Figure 45: Trial flowchart: NMES use in short and long term calf muscle recovery

4.5.3 Results

The CONSORT diagram of patient flow is shown in Figure 46, below.

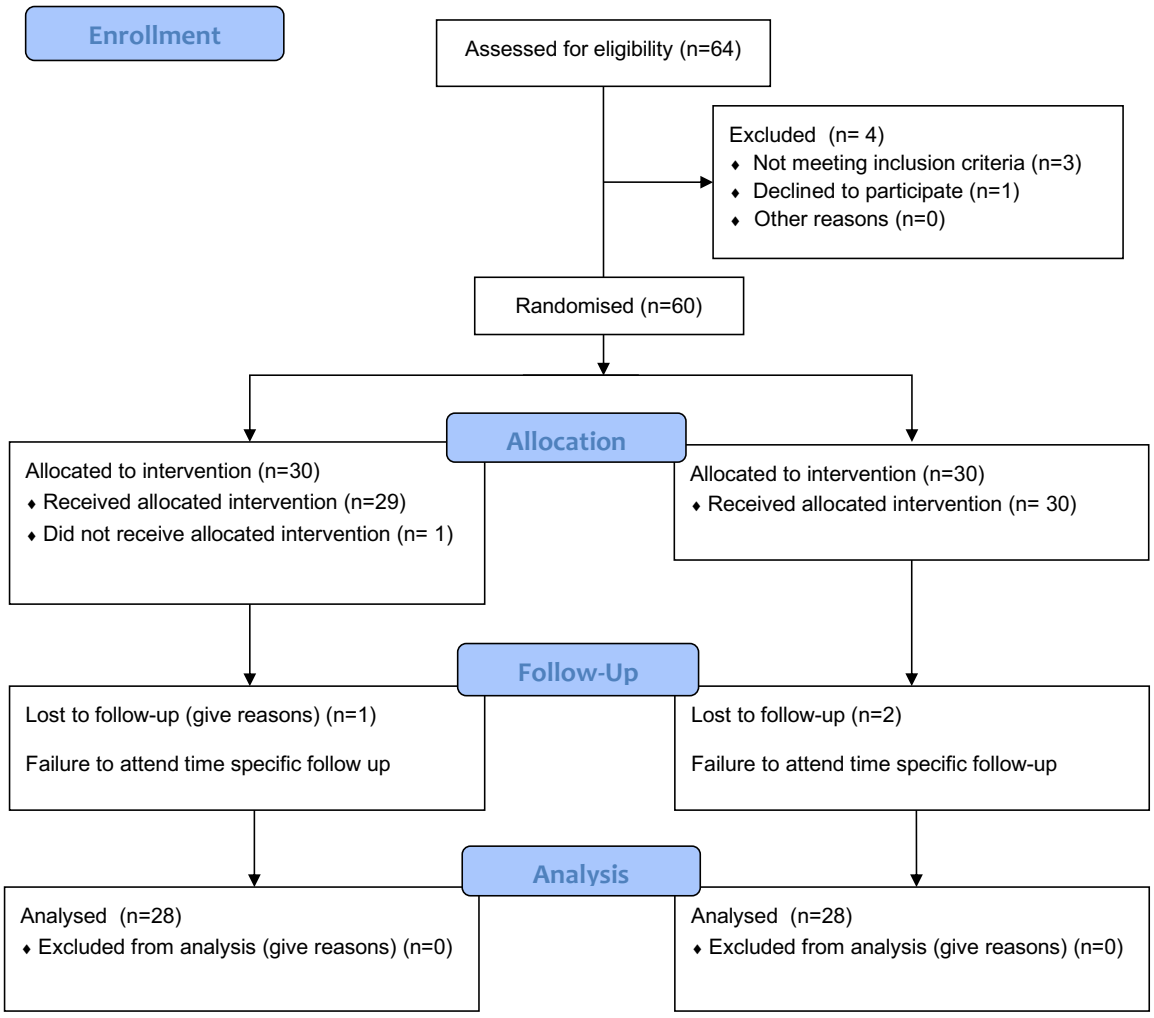


Figure 46: CONSORT diagram mapping the patient flow through this randomised controlled trial

4.5.3.1 Demographics

Fifty six participants were recruited to the trial (48% female) with demographic criteria shown in Table 29. The groups were well matched with no significant differences between the groups (P>0.05).

Table 29: Demographic data of NMES in short and long term muscle recovery

	Control Rest	Active NMES	t test (P value)
n	28	28	
Mean Age (yrs) [SD]	21.5 [1.9]	21.1 [1.8]	0.39
Female (%)	50	46	
Mean height (cm) [SD]	170.7 [14.1]	173.6 [11.2]	0.41
Mean Hrs exercise/week [SD]	1.4 [1]	1.4 [1.1]	0.9

No significant difference in groups (P>0.05)

4.5.3.2 Vertical "My Jump" jump test

Jump height measurements for each group taken over time are shown in Figure 47. Within group ANOVA analysis shows a highly significant difference in both the passive control group (F 81.62, P<0.0001) and active NMES group (F 33.64, P<0.0001).

Both sets of data underwent post ANOVA analysis using Bonferroni correction, comparing all the timepoints with the mean baseline jump height for each respective group. Both groups showed highly significant (P<0.001) deterioration patterns in jump height from baseline to post fatigue, post recovery day 1 and post recovery day 3. There was no significant difference compared to baseline in the mean jump height for both groups at day 7 (P>0.05).

To assess significant jump height differences between each timepoint within each group, the ANOVA test was modified to compare each timepoint mean to the other, with further analysis after Bonferroni correction. Within the control group, all subsequent timepoints from

baseline showed significant decreases ($P<0.01$) in jump height to the previous timepoint other than a significant increase in jump height from post recovery day 2 to post recovery day 7. Within the active NMES group, significant decrease in mean jump height was observed from baseline to post fatigue ($P=0.0004$), but there was no significant drop in jump height for subsequent timepoints. AS with the control group, there was a significant increase ($P<0.0001$) in mean jump height between post recovery day 3 and post recovery day 7, where the jump height was back to baseline level.

Analysis between the groups was carried out by unpaired t test and a graph of the mean jump heights at trial outcome assessment timepoints is shown in Figure 48.

There was no significant difference of jump height between either group at any of the trial outcome timepoints ($P>0.05$).

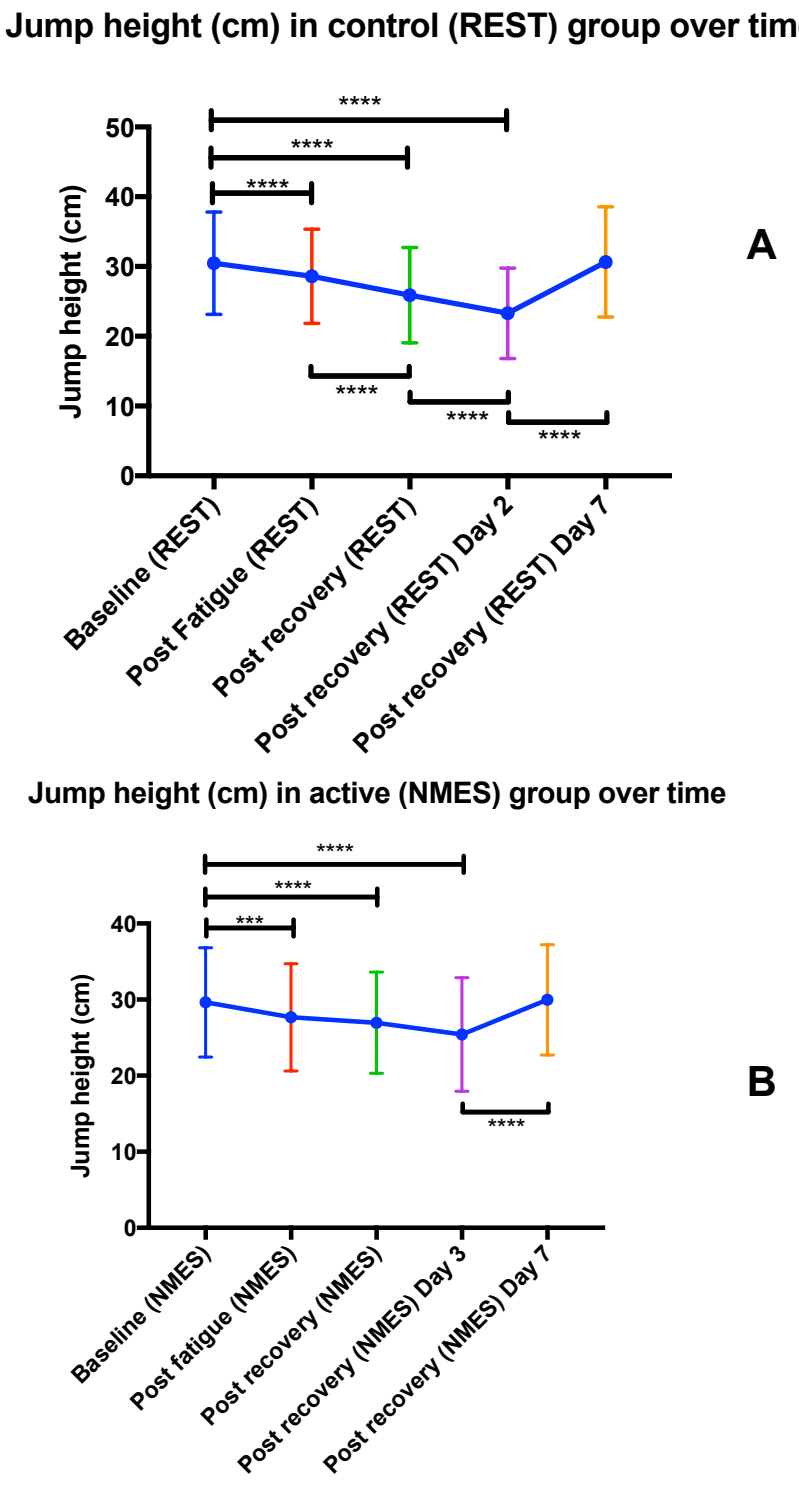


Figure 47: Change in jump height (cm) in A. Control (REST) and B. Active (NMES) groups over time

**** denotes P<0.001, **** denotes P<0.0001*

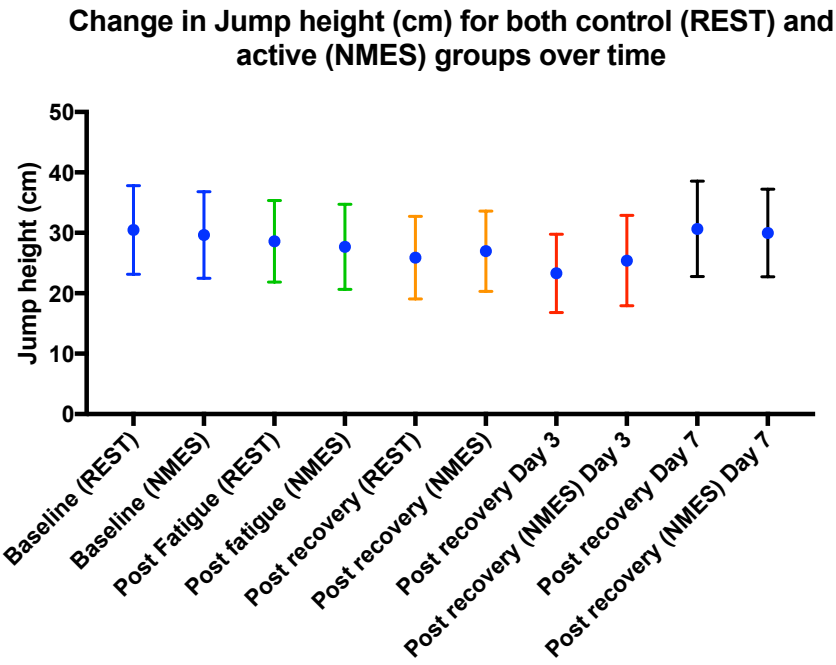


Figure 48: Change in Jump height (cm) between control (REST) and active (NMES) groups over time

4.5.3.3 NRS pain score

The change in NRS pain scores for each group over time are shown in Figure 49. Within group ANOVA analysis shows a highly significant difference in pain score in both the passive control group (F 103.8, P<0.0001) and the active NMES group (F 79.02, P<0.0001).

Further post ANOVA analysis comparing the various timepoints with mean baseline pain score show significant increases until post recovery day 3 (P<0.0001). After this timepoint, at post recovery day 7, NRS pain scores are back to baseline levels in both groups (P>0.05).

To assess significant NRS pain score differences between each timepoint within the group, the ANOVA test was modified to compare each timepoint mean to the next, with further

analysis after Bonferroni correction. Within the control group, following an initial highly significant increase in pain score from baseline to post fatigue ($P<0.0001$), there is and significant drop in pain score at post recovery day 1 ($P<0.0001$). There is no significant change in pain score between the latter and day 2 ($P>0.05$). The pain score then significantly increases between day 2 and post recovery day 3 ($P=0.009$) but then significantly increases back to baseline levels by post recovery day 7 ($P<0.0001$).

A similar pattern of significant changes was observed in the active NMES group of this study. The only difference was that there was no significant increase in pain score from day 2 to post recovery day 3 ($P>0.9999$).

all subsequent timepoints from baseline showed significant decreases ($P<0.01$) in jump height to the previous timepoint other than a significant increase in jump height from post recovery day 2 to post recovery day 7. Within the active NMES group, significant decrease in mean jump height was observed from baseline to post fatigue ($P=0.0004$), but there was no significant drop in jump height for subsequent timepoints. AS with the control group, there was a significant increase ($P<0.0001$) in mean jump height between post recovery day 3 and post recovery day 7, where the jump height was back to baseline level.

Analysis between the groups was carried out by unpaired t test and a graph of the mean jump heights at trial outcome assessment timepoints is shown in Figure 50.

There was no significant difference of jump height between the same trial outcome timepoints of either group ($P>0.05$).

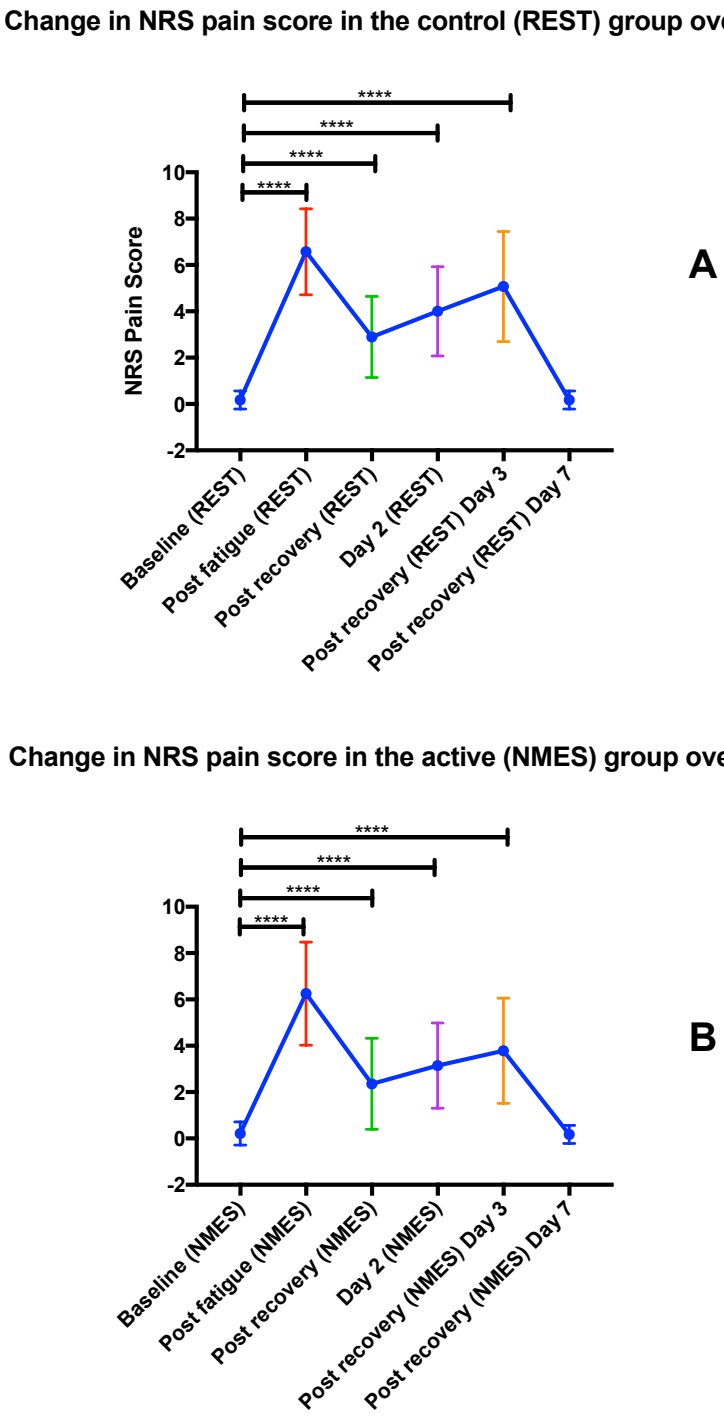


Figure 49: Change in NRS Pain scores in A. Control (Rest) and B. Active (NMES) groups over time

**** denotes P<0.001, **** denotes P<0.0001*

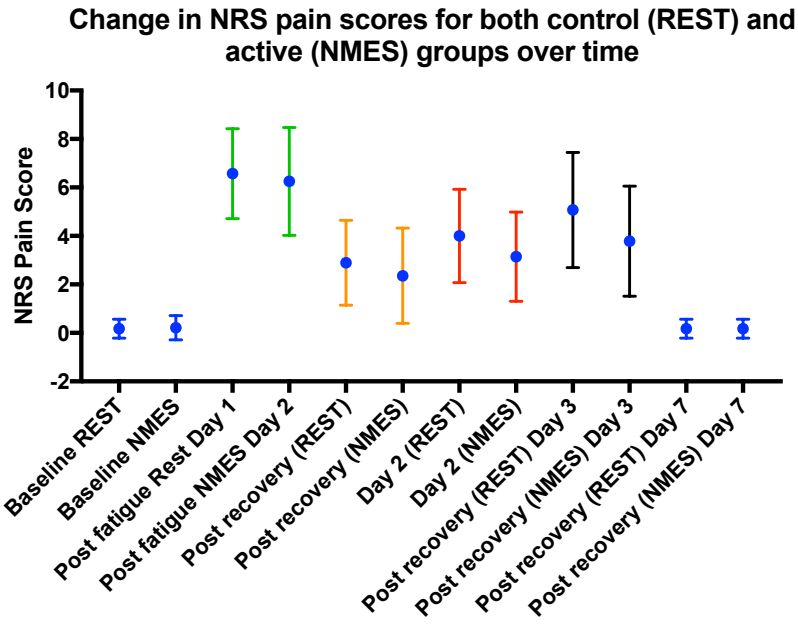


Figure 50: Change in NRS pain scores in both control (REST) and active (NMES) groups over time

4.5.4 Conclusions

The purpose of this larger study was to be able to gain better inference between muscle performance and pain improvement according to the type of recovery modality used, including passive (REST) recovery and active NMES recovery methods in groups of healthy individuals. By undertaking this trial, the aim was for a better understanding of the utility of the Revitive IX NMES footplate device in short and long term muscle recovery following muscle fatigue.

This study did not meet its sample size target to make significant inferences about the utility of the NMES device in active calf muscle recovery after muscle fatigue. However, there were almost 3 times the number of patients in each randomised group analysed, compared to the previous pilot study, providing some further clarity.

Muscle performance seemed to significantly deteriorate in a step wise fashion over the measured timepoints for both the control and active NMES groups. Both groups had recovered baseline calf muscle performance by day 7 follow up. This finding and further between group analysis showed no significant differences in muscle performance according to timepoint, suggesting NMES does not infer any advantage as an active modality for calf muscle recovery post fatigue.

The same was true for pain associated with calf muscle fatigue, where a very similar pattern response to calf muscle fatigue was observed between the passive and active recovery groups. Although within each group there were significant increases in pain score, as per the

expected delayed onset muscle soreness following muscle fatigue, there were no significant differences between the groups at any of the outcome timepoints.

This study suggests NMES is not effective as an active modality for calf muscle recovery following calf muscle fatigue. Bieuzen et al studied the utility of a locally applied NMES (Veinoplus) device to calf muscles of 13 male football players following a muscle fatigue protocol to assess if increasing the total blood flow by increasing venous return would enhance muscle recovery and therefore performance compared to passive recovery. This study did not find a significant difference in the vertical jump test or visual analogue pain scores in either group, however the capacity to carry out explosive anaerobic exercise (rowing) for 30 seconds, was significantly better in the NMES group suggesting an improvement in oxidative capacity of the muscle (Bieuzen, Pournot et al. 2012). Lattier et al studied 3 forms of muscle recovery including passive (rest), active by exercising at 50% normal intensity and electrical muscle stimulation post muscle fatigue from uphill running. Electrical stimulation was not found to have any significant advantage over the other modalities in muscle recovery (Lattier, Millet et al. 2004).

Employing subjective tools of performance perception does suggest at least a psychological effect of NMES on personal performance (Cortis, Tessitore et al. 2010).

Exercise induced muscle fatigue and pain is considered to be due to increased metabolic electrolytes as by-products of anaerobic respiration for energy production. Rest as a form of passive recovery is considered to allow blood flow reperfusion sufficiently enough to washout the anaerobic metabolites and replenish nutrients and oxygen for muscle recovery and performance. The use of adjunctive modalities to enhance this process have been

employed mainly in the sports population due to the importance of optimal recovery strategies to maintain and accelerate performance for added competitive edge (Lattier, Millet et al. 2004). One of these modalities is neuromuscular electrical stimulation. The intended benefit of this modality is to improve blood flow either systemically via the calf muscle pump, which may increase cardiac output, or locally at the muscle level prioritising blood flow to a sub maximally active muscle in order to wash out anaerobic metabolites and enhance muscle recovery. In addition, there is an expectation of reduced muscle soreness and pain, through unknown mechanisms (Butterfield, Draper et al. 1997). However, current literature is heterogenous in study size, type of device, frequency of use, stimulation parameters, population parameters and outcomes assessed, making it difficult to formulate a consensus on the utility of NMES in muscle recovery and post fatigue pain relief (Babault, Cometti et al. 2011).

Considering the suggested mechanisms of muscle fatigue and expectations of modality specific improvement in muscle recovery and performance, it is natural to have parallel expectations of NMES in disease states like PAD. The Revitive IX NMES device is known to increase resting venous and arterial blood flow in healthy individuals (Varatharajan, Williams et al. 2015) and so it would be expected to enhance muscle recovery and reduce associated pain following calf muscle fatigue. Within the context of this study, the parallel between the use of NMES in a healthy population calf muscle fatigue model and PAD patients is that the underlying exercise provoked ischemia, inducing the build-up of anaerobic metabolites leading to lower limb muscle fatigue in patients with claudication (Pipinos, Judge et al. 2007, Pipinos, Judge et al. 2008), appears to be similar to the healthy population. However, it appears that findings from this study, and the preceding study on the use of NMES in muscle recovery have added to the heterogeneity and unknown utility of this modality.

On a different note, this study shows that NMES as a modality did not confer any negative impact to muscle recovery, performance and DOMS compared to passive recovery strategies. As with the heterogenous findings in other NMES related studies, a lack of standardisation and multiple unknowns need further exploration to fully and robustly assess the utility of NMES in post fatigue muscle recovery.

5 Summary and Conclusions

Peripheral arterial disease is a debilitating condition with a significant global health and economic burden (Hirsch, Hartman et al. 2008, Fowkes, Rudan et al. 2013). Early symptomatic PAD can manifest as intermittent claudication, which limits functional ability and can have a negative impact on quality of life (Norgren, Hiatt et al. 2007). Narrowed or blocked arteries are the basis of insufficient blood circulation to active muscles during exertion, causing an ischaemia induced muscle fatigue and pain, limiting further function, until adequate circulation is restored to allow repeated exertion.

National and international guidelines provide graded evidence based recommendations for the diagnosis and management of lower limb arterial disease (Norgren, Hiatt et al. 2007, NICE147 2012, Aboyans, Ricco et al. 2018). First line management strategies are conservative, including lifestyle modifications and control of risk factors including smoking, hypertension, diabetes, hyperlipidaemia and obesity. Exercise therapy as a first line treatment option for early symptomatic disease can improve functional ability. Level 1A evidence informs the strong guideline recommendations for all patients with IC to be referred for a supervised exercise programme. Despite the known significant functional benefit of SEPs, there is a national underutilisation of this modality largely due to lack of access. Where programmes are available, lack of patient compliance hinders the effectiveness of this treatment option. This has encouraged the development of novel non-invasive technologies to circumvent the limitations of supervised exercise therapy and attempt to provide the same functional benefits. Neuromuscular electrical stimulation is one such technology which has seen a rapid evolution over the last 30 years, in understanding of electrical parameters and their application for clinical benefit. However, this understanding is currently limited for utility in the management of peripheral arterial disease.

Therefore, the focus of this research was to assess the utility of NMES in the management of early symptomatic PAD and its effectiveness in muscle recovery after fatigue.

Foundation research included an audit of the outcomes of the local SEP over a 6 month period confirming significant functional improvements typically associated with supervised exercise (Appendix 7.5) as reported in a number of Cochrane reviews (Bendermacher, Willigendael et al. 2007, Fokkenrood, Bendermacher et al. 2013, Lane, Ellis et al. 2014).

This was followed by an audit which established the national lack of access and underutilisation of SEPs. Only 35% of referrers had access to a SEP, largely due to lack of funding and resources to establish a programme. Patient compliance was also a problem due to the distant locations, disruptive routine and lack of motivation.

A focussed literature review was then undertaken, on the current application of NMES for the treatment of early symptomatic PAD. This included 7 studies, which largely showed significant improvements in walking distances assessed by treadmill testing and lower limb blood flow parameters. However, a variety of different devices used, small sample sizes, different stimulation parameter protocols, outcome measures and study protocols prevent these from undergoing a meta-analysis. The findings of these studies showed the need for further research into the use of NMES in PAD.

An initial pilot study was conducted, using a footplate NMES device called the Revitive IX, to ascertain its utility in the management of patients with IC. This observational cohort study included 20 patients with IC, already on best medical therapy for risk factor control,

instructed to use the NMES intervention for 6 weeks. Significant improvements were seen in both the MCD and ICD accompanied by significant improvements in disease specific ICQ and generic EQ-5D quality of life measures. These changes may have been attributed to the significantly increased blood flow and TAMV seen whilst the device was on compared to control. However, this increase reverted to control levels on stimulation cessation. All these patients had been offered a SEP and had either declined or were due to start after the 6 week trial period. Therefore, the results of NMES intervention were not influenced by other formal exercise therapies. The pilot study provided sufficient proof of concept to carry out a follow up study to assess the adjunctive benefit of this NMES device to supervised exercise in the management of patients with IC. One limitation of this study was the absence of a sham device comparator. It was considered very difficult to measure a placebo response by applying a sham device as patients would be able to notice absence of calf muscle contractions. A sham device providing sensation only but no contraction could have been feasible to increase the robustness of this trial.

The follow up study was a randomised controlled trial aiming for a total sample size of 46 patients. Total recruitment included 42 patients, assigned to either group A, SEP only (n=22) or group B, NMES plus SEP (n=20). The intervention period was 6 weeks and outcomes were assessed at baseline and week 6. By the end of the trial, 20 patients in group A and 17 patients in group B had sufficiently completed the trial protocol and provided measures for the primary outcome of MCD. Although this study showed within group analysis to have significant improvements in MCD and ICD walking parameters, there was no adjunctive benefit of the NMES device seen for the MCD over the 6 week intervention period. However, there was a significant adjunctive benefit shown in the ICD, suggesting that NMES use could significantly delay the onset of IC symptoms during exertion compared to SEP alone. There

were no further positive correlations attributable to NMES compared to SEP only when analysing quality of life scores or haemodynamic measures.

Limitations of this study included an inability to complete recruitment to calculated sample size, which was attributed to a large number of screened patients initially excluded due to diabetes mellitus. A substantial amendment to include these patients was subsequently made, but delays in approvals meant too short a remaining recruitment period to fulfil requirement for a powered study. Dosing of NMES may be another potential limitation of this study, whereby patients only used the device once daily for 30 minutes. Further clarification is needed whether altering stimulation parameters or dosing parameters has a size effect on outcome measures for PAD patients.

Keeping this in context, this study does suggest an independent correlation of NMES to the improvement in functional ability in the form of the ICD and certainly does not cause any negative impact on the parameters assessed when used together with the SEP. Further robust research into the adjunctive role of NMES to SEPs in the management of PAD and as an independent modality on the functional and quality of life is suggested.

Intermittent claudication involves exercise and ischemia induced muscle fatigue requiring a period of rest to allow muscle recovery before further use. Using NMES in healthy models of exercise induced muscle fatigue was considered to improve understanding of its utility in muscle recovery and performance. An initial randomised pilot trial of NMES versus rest recovery in healthy individuals after a lunge fatigue protocol suggested a trend towards improved performance in the NMES group, but no significant results prevailed. The study

was repeated in a larger randomised controlled trial, but no significant differences were found between NMES and passive rest recovery in muscle performance or pain.

Limitations of this study included an inability to recruit sufficient volunteers to meet a sufficient sample size to make significant inferences. This may contribute to a type II error and further research with measures to correct for this are advised. In addition, there is a paucity of calf specific muscle fatigue protocols and validated outcome measures to assess calf muscle performance in relation to an intervention. Potentially a more robust method of measuring muscle strength would be by assessing maximal force of calf raises against a strain gauge apparatus.

A common limitation to all studies may be the dosing or stimulation parameters of the NMES device. Within the studies an arbitrary use of NMES on the basis of the department of health recommendations of 30 minutes exercise daily for healthy living were applied. There is scope to assess change in dosing and stimulation parameters of NMES in the management of early symptomatic PAD and muscle recovery in order to firstly assess for utility and subsequently identify optimal dosing and stimulation necessary for improvement.

In conclusion, independent use of a footplate NMES device for 6 weeks has shown improvement in functional and quality of life parameters in patients with early symptomatic PAD. There does not seem to be any adjunctive benefit of NMES over supervised exercise in the study presented, however with the absence of detrimental effects of NMES and in view of the limitations encountered possibly contributing to a false-negative conclusion, there is scope for further research. Blood flow and TAMV during device use have shown a significant improvement, but this is not sustained and its correlation to functional benefits is

not clear. Further research would be recommended to clarify this correlation and provide further insight into the effect of NMES on lower limb arterial haemodynamics.

5.1 Current and Future trials

Neuromuscular electrical stimulation using various devices, has recently been used in a number of trials in vascular disease, showing valid potential (Abraham, Mateus et al. 2013, Guirro, Guirro et al. 2015, Ellul, Formosa et al. 2017, Ravikumar, Williams et al. 2017).

Following on from the above studies, a successful application to the National Institute for Health Research, as part of their efficacy and mechanistic evaluation (EME) grant stream was made. This stream is currently funding a multicentre trial to assesses the utility of the NMES in effecting functional changes in patients with IC in comparison to local standard care, which is SEP in 4 centres and no SEP in the remaining 4 centres. The primary outcome is absolute walking distance with secondary outcomes including ICD and further haemodynamic duplex and LDF assessment to provide a further understanding on any potential mechanisms.

Further studies are also planned for the utility of NMES in the management of diabetic neuropathy, with yet unpublished pilot data suggesting improvements in lower limb neural health and electro myograph measures. This benefit may be due to direct neural mechanisms and/or improvement in circulation. This is a significant trial, which could benefit diabetic patients promoting good foot care and preventing or delaying the development neuropathic disease.

Critical limb ischaemia is an end stage manifestation of PAD requiring either limb preserving surgical revascularisation or amputation in non-reconstructable disease. A pilot trial for the

use of NMES in the management of CLI would be interesting to assess utility in pain relief and preservation of the limb by assessing prevention of major amputations. This cohort usually has limited other treatment options.

As mentioned above, dosing and stimulation parameter studies, initially in healthy individuals progressing to vascular disease patients, would provide essential evidence that could influence the validity of NMES trials and support optimal NMES protocols to be used.

There is good scope for the development of NMES as a key modality in the non-invasive management of PAD. As findings from this thesis show, more robust, standardised, and adequately powered trials are needed to assess the utility of these devices independently or as adjuncts with current modalities in the effective management of peripheral arterial disease.

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7 Appendices

7.1 Patient Information Sheets for NMES studies

7.1.1 NMES in Patients with IC Patient Information Sheet

Imperial College London

Information Sheet for Research Participants

You will be given a copy of this information sheet to keep

Neuromuscular Electrical Stimulation (NMES) in Patients with Intermittent Claudication

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.

Please ask if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part. Thank you for your time.

What is the purpose of the study?

Patients with claudication are known to have poor circulation in their legs and feet leading to complications such as painful legs while walking or resting. A new therapy option has become available to improve circulation in the legs, and the aim of this study is to look at its effect on people with limited walking distance.

Why have I been chosen?

You have been chosen because you are a patient with intermittent claudication and have a problem with blood circulation in your legs.

Do I have to take part?

Participation in this trial is voluntary. Even if you start the trial and change your mind, you are free to withdraw at any point without giving a reason. Your medical care and legal rights will not be affected. By taking part in this study you are helping us to develop an exciting treatment for people with claudication.

Tell me some more about the device

The device is called Revitive™ and is made by Actegy™ health LTD. Revitive activates your leg muscles by applying proven Electrical Muscle Stimulation (EMS) to the soles of your feet through two large foot pads. This EMS makes the foot and calf muscles contract and relax to create a pumping action. The IsoRocker allows the Revitive IX to gently 'rock' back and forth creating involuntary ankle movement to replicate heel toe raises. Consequently the blood immediately moves through the arteries in your legs and back to your heart, improving circulation.

Imperial College London







Imperial College London

What will happen to me if I take part?

You will be required to attend Charing Cross Hospital, Northwick Park or Addenbrooke's Hospital to meet with a member of the research team. Your visit will last approximately 1.5 hours. You will have some measurements taken and receive training on how to use of the device, following which you will use the device for 30 minutes. Further assessments will be undertaken, as detailed in the next paragraph. At the end of this visit, you will be advised to use the device daily for 30 minutes for a total period of 6 weeks thereafter. Following this 6 week study period, you will be invited for a last session of measurements similar to the first session. The latter visit will also last 1.5 hours and will conclude your study participation.

In more detail, for the initial session, you will have a medical history and examination taken by a doctor. You will also have your blood pressure, heart rate and oxygen levels measured. Other measurements that will be recorded include height, weight and blood pressure measurements at the wrist and ankle. A blood sample and urine sample will be taken. The urine sample will be tested to ensure that female participants are not pregnant. A syringe will be used to collect a one tablespoon (10mls) sample of blood. Both the blood sample and urine sample will be used for further analysis related to your condition. A baseline treadmill test will be done to establish the distance at which you experience the onset of your symptoms. An ultrasound scan of your upper leg blood circulation will be undertaken. You will then be asked to place both your feet on the footpads of the device through which electrical muscle stimulation will be delivered at intensity sufficient to evoke lower limb muscle contractions. During this time and for a few minutes afterwards, ultrasound measurement of the circulation in your legs will be taken.

Following training on use of the device, you will take one to use at home daily for 30 minutes for a total of 6 weeks. We will then invite you back to the hospital for repeated measures of the above tests.

At the end of the study period, you will be offered a device for free if you would like one.

What are the possible risks of taking part?

We do not anticipate any risk. The device has been through the national testing process and has a CE mark for healthy individuals. This new therapy option has become available to improve circulation in the legs, and the aim of this study is to look at its effect on people with Intermittent Claudication. We do not anticipate any additional risks for the patient group.

Activation of the device causes small impulses to travel through the skin to make your foot and calf twitch. It may be an odd sensation but should not hurt. There are 99 levels of intensity which can be adjusted for your comfort.

Imperial College London

What are the possible benefits of taking part?

We know from previous studies that the Revitive™ device increases blood flow in healthy people. We expect it to do the same for patients with intermittent claudication. If you have claudication we expect there to be a direct benefit to you. You will not get paid for participating in this study.

What if something goes wrong?

You should not join the study if you have an implantable pacemaker or defibrillator device. You may be withdrawn from the study if the doctors feel it is best for you not to participate 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 any discomfort or distress during the study you must say so immediately and we will stop straight away. If for any reason during the study and you do not wish to continue, than we will stop the tests immediately.

All of the previous work using the Revitive™ device has demonstrated it to be safe. When the Revitive™ device is applying an electrical stimulation, you will feel some muscle twitching and maybe tingling in your lower legs but this will soon pass unnoticed. There are very few risks or dangers involved in using this type of equipment.

Imperial College has insurance policies which apply to this study. If you experience serious and enduring harm or injury as a result of taking part, you may be eligible to claim compensation without having to prove that Imperial College is at fault. This does not affect your legal rights to seek compensation.

If you are harmed due to someone's negligence, then you may have grounds for a legal action. Regardless of this, if you wish to complain, or have any concerns about any aspect of the way you have been treated during the course of this study then you should immediately inform the research team (see below). The normal National Health Service complaints mechanisms are also available to you.

Will my taking part in this study be kept confidential?

All information that is collected about you during the course of the study will be kept strictly confidential. If you join the study, some parts of your medical records and the data collected for the study will be looked at by the research team. They may also be looked at by representatives of regulatory authorities to check that the study is being carried out to the highest professional and ethical standards.

Upon your consent, we will notify your General Practitioner of your involvement in this study.

If an abnormality is found, which does not relate to your claudication, a referral to an appropriate specialist will be made, with your permission, and your General Practitioner will be informed.

The company that make the device (Actegy health Ltd) will have access to your anonymised records.

What will happen to the results of the study?

We will publish the overall results of the study, whatever the findings, to allow doctors to learn from our findings. The study will form part of a PhD. As a participant, you will not be personally identifiable in any publication.

Who is organising and funding the research?

The project is organised by the Vascular Surgery research team at Imperial College London and funded by Actegy Ltd.

Further information

We are happy to provide you with any other information, now or later on. You can think about the study and come back to us at any time.

Please contact:

Professor Alun Davies (Professor of Vascular Surgery) or Mr Adarsh Babber (Clinical Research Fellow)

Academic Section of Vascular Surgery,

4 North, Charing Cross Hospital,

London

W6 8RF

Email: a.babber@imperial.ac.uk

Tel: 07946 646 855

7.1.2 Adjuvant benefit of NMES to SEP in the management of IC clinical trial

Imperial College London

Information Sheet for Research Participants

You will be given a copy of this information sheet to keep

Adjuvant Benefit of Neuromuscular Electrical Stimulation (NMES) to Supervised Exercise in Claudicants

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.

Please ask if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part. Thank you for your time.

What is the purpose of the study?

Patients with claudication are known to have poor circulation in their legs and feet leading to complications such as painful legs while walking or resting. A new therapy option of electrical stimulation of the lower limbs, has recently become available to improve circulation in the legs, and the aim of this study is to look at its effect on people with limited walking distance. We are comparing two groups of people with intermittent claudication, both of which will be on a supervised exercise programme. One group will also use the device providing electrical stimulation and the other will only be on the supervised exercise programme.

Why have I been chosen?

You have been chosen because you are a patient with intermittent claudication and have a problem with blood circulation in your legs.

Do I have to take part?

Participation in this trial is voluntary. Even if you start the trial and change your mind, you are free to withdraw at any point without giving a reason.

Tell me some more about the device

The device is called Revitive™ IX and is made by Actegy LTD. Revitive activates your leg muscles by applying Electrical Muscle Stimulation (EMS) to the soles of your feet through two large foot pads. This EMS makes the foot and calf muscles contract and relax to create a pumping action. The IsoRocker allows the Revitive IX to gently 'rock' back and forth allowing natural ankle movement to replicate heel toe raises.

Consequently the blood immediately moves through the arteries in your legs and back to your heart, improving circulation.







What will happen to me if I take part? (See flowchart in Figure 1)

You will be required to attend Charing Cross Hospital, Northwick Park Hospital or Addenbrooke's Hospital to meet with a member of the research team. You will be randomly allocated to either a supervised exercise programme (SEP) with using the device or continuing with supervised exercise only, without the device. Your visit will last approximately 1.5 hours. You will have some measurements taken and for those allocated use of the device, will receive training on how to use the device, following which you will use the device for 30 minutes. Further assessments will be undertaken, as detailed in the next paragraph. At the end of this visit, you will be advised to use the device daily for 30 minutes for a total period of 6 weeks thereafter. Following this 6 week study period both groups including those who used the device and those who did not, will be invited for a last session of measurements similar to the first session. The latter visit will also last approximately 1.5 hours and will conclude your study participation.

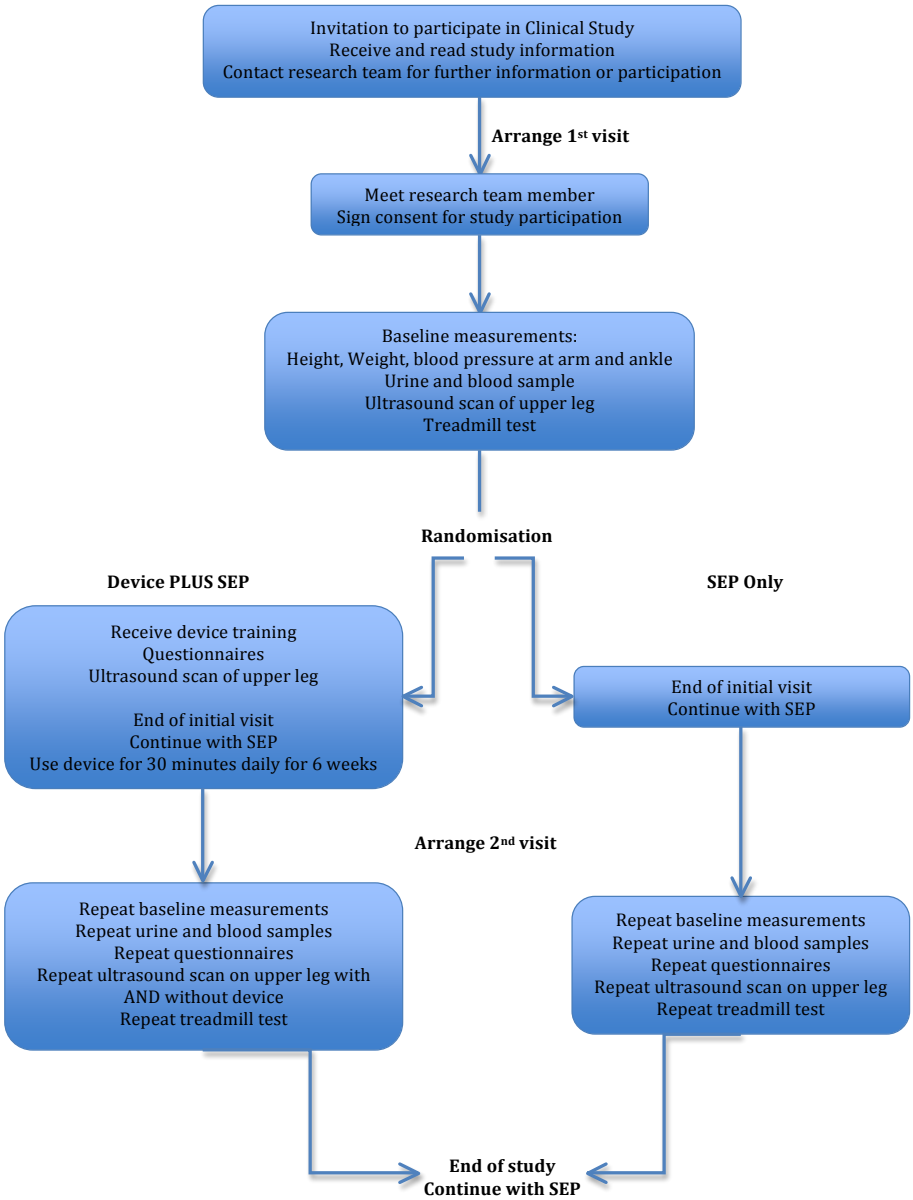
In more detail, for the initial session, you will have a medical history and examination taken by a doctor. You will also have your blood pressure, heart rate and oxygen levels measured. Other measurements that will be recorded include height, weight and blood pressure measurements at the wrist and ankle. A blood sample and urine sample will be taken. The urine sample will be tested to ensure that female participants are not pregnant. A syringe will be used to collect a one tablespoon (10mls) sample of blood. Both the blood sample and urine sample will be used for further analysis related to your condition. A baseline treadmill test will be done to establish the distance at which you experience the onset of your symptoms. An ultrasound scan of your upper leg blood circulation will be undertaken. According to a randomisation process, you will either continue on the supervised exercise programme only or have the additional use of the device. If in the latter group, you will then be asked to place both your feet on the footpads of the device through which electrical muscle stimulation will be delivered at an intensity sufficient to evoke lower limb muscle contractions. During this time and for a few minutes afterwards, ultrasound measurement of the circulation in your legs will be taken. Following training on use of the device, the test group will take one to use at home daily for 30 minutes for a total of 6 weeks. For both groups, questionnaires related to your symptoms and quality of life will be completed.

The supervised exercise programme will involve a total of 30 minutes of physical activity made up of rotating through various low impact exercises (treadmill walking, steps, stretching etc) under the supervision of the programme leader. This programme will occur once per week, however patients will be advised to continue 30 minutes of daily exercise to similar intensity between these sessions.

You will be asked to complete a diary card of your use of the device including dates and times with any further comments you may have. We will then invite you back to the hospital for repeated measures of the above tests.

At your follow up visit at 6 weeks, a treadmill test will be repeated and you will be asked to complete the questionnaires again, like the ones you completed on your first visit. Repeat blood and urine samples will be taken as above.

Figure 1: Study participation flow chart
(SEP: Supervised Exercise Programme)



If you were allocated to the device group, at the end of the study period, you will be offered a device for free if you would like one. If you are in the group that did not receive a device, you will be offered a trial use of this.

What are the possible risks of taking part?

We do not anticipate any risk. The device has been through the national testing process and has a CE mark for healthy individuals. We do not anticipate any additional risks for the patient group.

Activation of the device causes small impulses to travel through the skin to make your foot and calf twitch. The intensity of the impulses is user controlled and can be increased from 0 to 99 in single units. We will be aiming to reach a certain intensity threshold, which will be specific to you, keeping your comfort and tolerance into consideration. Very high intensities may be uncomfortable and are not advised when using the device. This will be clarified during the first meeting with a member of the research team. Further information prior to this meeting can be provided by contacting Mr Adarsh Babber, below.

What are the possible benefits of taking part?

We know from previous studies that the Revitive™ device increases blood flow in healthy people. We expect it to do the same for you. If you have claudication we expect there to be a direct benefit to you. You will not get paid for participating in this study.

What if something goes wrong?

You should not join the study if you are pregnant, have an implantable pacemaker or defibrillator device. You may be withdrawn from the study if the doctors feel it is best for you not to participate 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 any discomfort or distress during the study you must say so immediately and we will stop straight away. If 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 Revitive™ device has demonstrated it to be safe. When the Revitive™ device is applying an electrical stimulation, you will feel some muscle twitching and maybe tingling in your lower legs but this will soon pass unnoticed. There are very few risks or dangers involved in using this type of equipment.

Imperial College London holds insurance policies which apply to this study. If you experience serious and enduring harm or injury as a result of taking part in this study, you may be eligible to claim compensation without having to prove that Imperial College is at fault. This does not affect your legal rights to seek compensation.

If you are harmed due to someone's negligence, then you may have grounds for a legal action. Regardless of this, if you wish to complain, or have any concerns about any aspect of the way you have been treated during the course of this study then you should immediately inform the Investigator (see contact details below). The normal National Health Service complaints mechanisms are also available to you. If you are still not satisfied with the response, you may contact the Imperial AHSC Joint Research Compliance Office.

Will my taking part in this study be kept confidential?

All information that is collected about you during the course of the study will be kept strictly confidential. If you join the study, some parts of your medical records and the data collected for the study will be looked at by the research team. They may also be looked at by representatives of regulatory authorities to check that the study is being carried out to the highest professional and ethical standards.

If an abnormality is found, which does not relate to your claudication, a referral to an appropriate specialist will be made, with your permission, and your General Practitioner will be informed.

The company that make the device (Actegy health Ltd) will have access to your anonymised records.

What will happen to the results of the study?

We will publish the overall results of the study, whatever the findings, to allow doctors to learn from our findings. As a participant, you will not be personally identifiable in any publication.

Who is organising and funding the research?

The project is organised by the Vascular Surgery research team at Imperial College London and funded by Actegy Ltd.

Further information

We are happy to provide you with any other information, now or later on. You can think about the study and come back to us at any time.

Please contact:

Professor Alun Davies (Professor of Vascular Surgery) or Mr Adarsh Babber (Clinical Research Fellow)
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7.1.3 NMES in muscle recovery following high intensity exercise PIS

Imperial College London

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Chief Investigator: Professor Alison McGregor

Co-Investigator(s): Alison Baldwin, Catherine Cornwell, Adarsh Babber, Professor Alun Davies

Participant Information Sheet (version 2, 01/07/14)

Recovery following high intensity exercise using the Revitive IX device

This sheet describes the purpose of the study, and explains what is involved. Please read the information below before deciding whether or not you would like to take part.

Purpose of research

The aim of this project is to investigate whether the Revitive IX (a neuro-muscular electrical stimulation device) aids recovery from high intensity exercise, which will in turn potentially enhance sports performance. To date, research has provided limited evidence for the role of neuromuscular electrical stimulation in recovery from exercise and this study aims to address this. We propose that the Revitive IX device, a new devicecan enhance recovery following high intensity exercise, resulting in enhanced sport performance by enabling users to train more frequently at higher intensity.

Why have I been chosen?

We are asking you to think about joining this study because you take part in regular exercise. We are aiming to recruit a total of 20 participants to our study.

You are eligible to take part in this study if you:

- Participate in moderate intensity physical activity (that you would describe as 'hard' or as a 6-out-of-10, where 1 is very light activity and 10 is maximum effort activity) for a minimum of 3 hours per week
- Are aged 18 or over
- Read and speak good English

You are not eligible for this study if you have any of the following:

- Medical history of neurological or vascular impairments or Diabetes Mellitus
- Current or chronic lower limb or back musculoskeletal injury

- Medical conditions aggravated by exercise
- Are pregnant or could possibly be pregnant
- Fitted with a pace maker or defibrillator device
- Open wounds or infections of the feet
- Currently taking analgesia or anti-inflammatory medication
- Are participating in another trial during the time of intervention

Tell me some more about the device that is being tested

The device is called Revitive IX and is made by Actegy™ health LTD. Revitive IX activates your leg muscles by applying proven Electrical Muscle Stimulation (EMS) to the soles of your feet through two large foot pads. This EMS makes the foot and calf muscles contract and relax to create a pumping action. The IsoRocker allows the Revitive IX to gently 'rock' back and forth creating involuntary ankle movement to replicate heel toe raises.







What will happen to me if I take part?

Once you have decided to take part in this study, you will be invited to the Biodynamics laboratory at Charing Cross Hosptial (7th Floor East Wing), where a member of the research team will discuss the study with you, and answer any questions you may have. If you are still happy to take part, we will ask you to sign the consent form.

On Consent you will be asked to complete a medical questionnaire and answer subjective questions. You will be required to attend two sessions at the Biodyanmics Lab; the first session will last no longer than two hours and the second session will last one hour 15minutes.

You will then take part in a 5 minute standardised warm up and complete high intensity exercise in the form of 10 minutes of lunges. At the end of the exercise, you will be given the opportunity to stretch for 5 minutes before completing the jump test. You will be assigned to one of two groups – a treatment group or a control group. If you are in the treatment group you will receive an additional 30 minutes of neuromuscular electrical stimulation using the Revitive IX device. When you use this device you will feel a light prickling sensation in your feet or leg muscles that are being activated by the device at the start of the treatment. The intensity will be increased within your comfort levels and you will see a visible but non-painful contraction of your leg muscles. The stimulation will only be used at a comfortable level up to and including a pre-determined threshold calculated from when you first see a visible contraction of your muscles. The device will run through a series of programmes at random so you will feel different patterns and rhythms of muscle contractions throughout the 30 minutes of treatment. You will have control of the intensity of the device via a hand-held remote-control.

After the 30-minutes of treatment you will then complete a further jump test and subjective questions. You will be asked to stay in the lab for a further 30 minutes before the final jump test. If you are in the treatment group you will take the Revitive IX device home to use as prescribed over the next 48 hours. You will receive a follow up telephone call at a pre-determined time 24 hours after exercise to ask subjective questions and 48 hours after you will have to return to the laboratory for follow-up testing. In this session you will repeat the same protocol as on day 0, minus the exercise protocol; you will also return the device at the end of this session. If you are part of the control group the above procedure will apply, however you will not receive neuromuscular electrical stimulation and will not be issued with the Revitive IX device to use at home. You will need to rest for 30 minutes prior to two retests, including a further 30minutes rest between the tests.

During the 48 hour period after exercise you will be unable to participate in any other form of sporting or recreational activity aside from your normal commute to work and activities of daily living. We also request that you refrain from taking any pain relief, anti-inflammatories or post-exercise recovery supplements (if you have any questions please ask one of the investigators)

Do I have to take part?

No, it is entirely up to you. If you would like to take part and have these additional measures performed, you will be asked to sign a consent form. Even after you have signed this consent form and agreed to the study, you are free to withdraw from the study at any time. A decision to withdraw at any time, or a decision not to take part, will not affect your education/employment.

Are there any risks or benefits?

The assessment techniques are entirely safe and non-invasive and there are no known risks from having these test performed. All tests will be performed within your own limits. Should you find the testing tiring, please inform the researcher and if you need to rest or want to stop you can do so at any time. The exercise protocol is designed to be high-intensity activity for 10-minutes. You are likely to experience more than moderate levels of muscle ache after the exercise protocol; however, this may not present itself until 24- or 48-hours after the exercise. Any discomfort will usually ease within the following 24-hours. Muscle ache post-exercise is common and there is minimal risk of injury from further exercise during this period. To further negate this risk, we ask you to refrain from taking part in any sporting or recreational activities as mentioned above.

Revitive IX device has regulatory authority approval for use in healthy individuals and is safe to use following manual instructions. There will be no financial benefits for your participation in this study.

What will I need to bring with me?

You will need to wear active sportswear and being a pair of good trainers to complete the testing and exercise protocol. We also recommend that you bring a book or some work with you as there will be some waiting during the recovery periods.

Will my taking part in this study be kept confidential?

Any information you give us will be kept confidential. If the findings of this study are published in a scientific journal, no individual will be identified in any way. The data will be held in accordance with the Data Protection Act, which means that we keep it safely and cannot reveal it to other people, without your permission. Your personal details will be stored in a locked filling cabinet which belongs to Imperial College London.

Who has reviewed the study?

This study has been reviewed by the Imperial College Research Ethics Committee.

How to contact us:

If you are unsure about this study and would like to consider further before you make your decision, please take your time to do so. Please contact Alison Baldwin (alison.baldwin@kcl.ac.uk) or Catherine Cornwell (catherine.cornwell@kcl.ac.uk) for further information or call 07732 782923.

Thank you for taking time in reading this document and for your co-operation.

Imperial College London

7th Floor Biodynamic
Laborator
Charing Cross Hospita
Fulham Palace Roa
London W6 8R
dm2113@ic.ac.u
07718 20186

Measuring the effect of Electrical Stimulation on muscle recovery following intense exercise – Information Sheet

Principal Investigator: Alison McGregor

Co-Investigators: Adarsh Babber, Alun Davies, Dominic Murray

Thank you for considering to take part in this trial, every participant is a huge help. All information gathered will be kept strictly confidential as in accordance with the data protection act, no personal details shall be kept on computer, but will be kept in a locked filing cabinet at Charing Cross Hospital.

What is this study all about?

In this study I will be examining the effect of the Revitive IX NMES device on improving recovery in the calf muscle. This project is building on a similar BSc project done last year, which looked at the effect on the leg over all. Muscle fatigue is an everyday part of many people's lives, from the fatigue we feel from walking upstairs, to the fatigue felt by elite athletes after a training session. The Revitive IX device is an example of Electrical Muscular Stimulation (EMS) device that aims to combat the problems of fatigue and delayed onset of muscular soreness (DOMS). This device works on the legs, by firing electrical pulses into the feet, creating a circuit using both legs. The device aims to increase muscular contraction of the calf, therefore increasing blood flow and increasing the clearance rate of substances that are believed to be responsible for muscular soreness.

What will you be doing?

You will be taking part in the research, lasting a week. You will be first spoken to and asked to sign a consent form confirming your desire to take part in the trial. You will also have to fill out a pre-trial and medical questionnaire that confirm that you are eligible for the study. You will then be asked to visit for the testing at Charing Cross Hospital at a chosen time.

You will be asked to undertake the fatiguing protocol, which will be heel raises, until you feel as though you can do no more. We will ask you to perform three standing jump tests before and after this exercise, where we will record your best results. After this, you will use the Revitive IX machine for 30 minutes, or sit and rest fort 30 minutes, depending on which group you will be randomly assigned to.

After this you will be asked to undertake the jump test once again, to determine the effects of the exercise and recovery on your ability to perform.

We will then give you a device to use for 30 minutes a day, instructions on how to use it yourself and instructions to avoid any physical activity, over normal functions of daily life. After 24 hours, we will call you to ask a few questions and ask how your calves are feeling. After 48 hours you will be asked to come to the hospital, where the jump tests will be repeated.

After 1 week, you will make your final trip to the hospital, where we will do the jump tests again and you will return the device. If are randomly assigned to the control group, the protocol will be the same, except instead of getting and using the Revitive IX device, you will instead sit and rest for half an hour each day.

You will be able to opt out of the study at any time with no consequence.

Are you eligible to take part?

We are aiming to gather 60 participants for this study, who will be randomly assigned to either the active or control group. We would like to gather a range of ages and fitness types, although at least moderate fitness is required to perform the fatiguing protocol.

To be eligible for this study you must –

- Be 18 years old or over
- Be able to perform heel raises from a raised surface (e.g step)
- *Read and speak good English*

You are not eligible if you –

- Are taking part in any other study during the week long period
- Are pregnant or possibly could be pregnant
- Have a medical history of neurological or vascular impairments or Diabetes Mellitus
- Have current or chronic lower limb or back musculoskeletal injury
- Have a medical condition exacerbated by physical activity
- Are fitted with a pace maker or defibrillator device
- Have open wounds or infections of the feet
- Currently taking analgesia or anti-inflammatory medication
- Are unable to avoid physical activity for the week period, over normal daily activity.

The Revitive IX Device

The Revitive IX Device is an electrical stimulation device designed and manufactured by the Actegy Health™ Company. It is marketed primarily towards those with problems with circulation in their legs as a 'circulation booster.' The Revitive IX is the second most recent model of the product produced by

the company. They are interested in finding out the effect of the device when used as a method for muscle recovery, which is why this study is being done.

How does the Revitive IX device work?

The device works by sending electrical impulses through the footpads into the feet, the legs then create a circuit for the electricity to travel through. The device at its lowest intensity levels cause a slight tingling sensation, then start to produce visible muscle contraction of the calves as the intensity is increased, and at a therapeutic level will cause a muscle contraction strong enough to cause movement of the feet. The intensity levels will be slowly increased to make sure that you are comfortable, while trying to attain a level of contraction that will have therapeutic benefit. The Revitive IX device also includes an 'IsoRocker™' system, which allows the feet to flex up to 20° as the calves contract. The programme lasts half an hour, and will go through 15 different stimulation patterns twice, to prevent muscle habituation and to ensure that the entire muscle is targeted.

Are there any risks?

The device has regulatory approval to be used in healthy participants, and there are no known risks or complications that are associated with using the device as instructed. Overuse of the device may cause symptoms similar to muscle fatigue, however this should be avoided if used as instructed. The exercise is likely to cause moderate to high muscle ache, however you will be able to judge when you feel you can do no more heel raises, you will be not asked to continue with the exercise if you do not feel comfortable with doing so. There will always be a researcher on hand to talk to if you have any worries, questions or concerns about the study.

What will you need to bring?

You should wear clothes you feel comfortable to exercise in, including shoes you will be able to do heel raises in. You can expect to be in the testing rooms for around 90 minutes, with a great deal of this being recovery time, therefore feel free to bring something to read or work to do while you are recovering.

How can you contact us?

If you would like to participate in the trial or have any further questions, please email Dominic Murray at **dm2113@ic.ac.uk** or call 07718 201865, as he will be able to answer any questions and arrange a date to come into to the hospital to begin the participation process. All participants have the option to participate in the 'heel raise leader board' where the Male and Female who does the heel raises for the longest will win a prize.

7.2 Consent forms for NMES studies

7.2.1 NMES in IC study

Informed Consent Form

Subject Number: ☐☐☐ Subject initials: ☐☐☐

Title of study: Neuromuscular Electrical Stimulation (NMES) in Intermitter Claudication

Please initial the boxes if you agree with the following statements:

I can confirm that I have read and understood the information sheet (version 1.1 21/02/2014) for this study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily. I have received enough information to make up my mind ☐

I understand that I am free to withdraw from this study, without giving a reason, at any time without my medical care or legal rights being affected ☐

I agree to:

Use the neuromuscular stimulation device on my legs after being fully informed of all potential hazards ☐

Carry out an ultrasound examination on 2 visits to the hospital ☐

Complete questionnaires on the same 2 hospital visits ☐

Give blood and urine samples as specified in the patient information sheet. I give permission for storage of these samples and analysis for the purposes of this project ☐

For my personal identifiable data to be stored on a secure Imperial College London computer (for Charing Cross Hospital and Northwick Park Hospital patients) or a secure computer at Addenbrooke's Hospital (for Addenbrooke's Hospital patients) ☐

I give permission for responsible individuals to access my research notes and/or data (i.e. Imperial College, NHS Trust or regulatory authorities) to check that the research is being conducted correctly ☐

I give permission for responsible individuals from Actegy Health Ltd to access my anonymised research data for device monitoring purposes. ☐

I agree to my general practitioner being informed of my participation in the study. ☐

I agree to take part in the above study ☐

Signature..... Print Name: …….. Date: ……

Consent by: Signature …… Print Name:…….…… Date:……..

7.2.2 Adjuvant benefit of NMES to SEPs in patients with IC

Imperial College London

Informed Consent Form

Subject Number: ☐☐☐ Subject initials: ☐☐☐

Title of study: Neuromuscular Electrical Stimulation (NMES) in Intermittent Claudication

Please initial the boxes if you agree with the following statements:

I can confirm that I have read and understood the information sheet (version 1.1 21/02/2014) for this study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily. I have received enough information to make up my mind ☐

I understand that I am free to withdraw from this study, without giving a reason, at any time without my medical care or legal rights being affected ☐

I agree to:

Use the neuromuscular stimulation device on my legs after being fully informed of all potential hazards ☐

Carry out an ultrasound examination on 2 visits to the hospital ☐

Complete questionnaires on the same 2 hospital visits ☐

Give blood and urine samples as specified in the patient information sheet.
I give permission for storage of these samples and analysis for the purposes of this project ☐

For my personal identifiable data to be stored on a secure Imperial College London computer (for Charing Cross Hospital and Northwick Park Hospital patients) or a secure computer at Addenbrooke's Hospital (for Addenbrooke's Hospital patients) ☐

I give permission for responsible individuals to access my research notes and/or data (i.e. Imperial College, NHS Trust or regulatory authorities) to check that the research is being conducted correctly ☐

I give permission for responsible individuals from Actegy Health Ltd to access my anonymised research data for device monitoring purposes. ☐

I agree to my general practitioner being informed of my participation in the study. ☐

I agree to take part in the above study ☐

Signature..... Print Name: ..... Date: .....

Consent by: Signature ..... Print Name:..... Date:.....

Please tick this box if you would like to be informed of the trial results ☐

7.2.3 NMES in muscle recovery following high intensity exercise PIS

Imperial College London

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Department of Surgery and Cancer
Imperial College London
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Chief Investigator: Professor Alison McGregor
Co-Investigator: Alison Baldwin, Catherine Cornwell, Adarsh Babber, Professor Alun Davies
Participant Identification Number:

CONSENT FORM

Recovery following high intensity exercise using the Revitive IX

Participant Identification Number for this study: ☐

Please initial box

1. I confirm that I have read and understood the Participant Information Sheet dated Version 2 dated 01/07/14 for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily. ☐
2. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, and without legal rights being affected. ☐
3. I understand that during the 48 hour study period I will not be able to participate in any other sporting or recreational activity other than my normal commute to work and activities of daily living. ☐
4. I agree to use the neuromuscular electrical stimulation device on my legs after being fully informed of all potential hazards. ☐
5. I agree to my data, which will be fully anonymised, being stored on Imperial College London computer systems. ☐
6. I agree to take part in the above study. ☐

_____	_____	_____
Name of participant	Date	Signature
_____	_____	_____
Name of person taking consent (if different from researcher)	Date	Signature
_____	_____	_____
Researcher	Date	Signature

7.2.4 NMES in recovery of short and long term calf muscle fatigue

Imperial College London

7th Floor Biodynamics Laboratory
Charing Cross Hospital
Fulham Palace Road
London W6 8RF
dm2113@ic.ac.uk
07718 201865

Supervisors: Dr Adarsh Babber, Dr Alison McGregor, Dr Alun Davies

Student researcher: Dominic Murray

Participant ID.....

Consent Form

The purpose of this form is to confirm that you wish to take part in this study, and to ensure that you comprehensively understand what will happen and what will be expected of you for the week long period, including any relevant risks.

	Please Initial
I have read through the information sheet and been given time to ask any questions I have about the study.	☐
I meet all eligibility criteria as explained in the information sheet.	☐
I am not taking part in another medical study while participating in this one	☐
I have read and understood the medical questionnaire and noted any conditions I believe may interfere with participating in this study.	☐
I have been told I am allowed to withdraw from taking part at any time without any consequence.	☐
I will not participate in any physical activity above normal daily activity while I participate.	☐
I agree to the use of the Revitive IX electrical stimulation device after proper instruction, and have been made aware of any potential risks.	☐
I agree to my anonymised data being stored by Imperial College Union, and used as part of the study and in any publications that may result from it.	☐
I agree to participate in the study.	☐

7.3 Data tables for studies

7.3.1 Summary of studies for literature review NMES in the management of IC

Author	Design	Population	Intervention	N	Timepoints	Outcomes	Findings
(Loubser, Cardus et al. 1988)	Observational cohort controlled study	Stable Claudicants Vs Healthy controls	Unilateral, low frequency (2Hz), stimulation over common peroneal nerve and dorsum foot. 60 minutes stim.	8/8	Baseline 30 minutes intervals of stim. 30 minutes after stim cessation.	BP, HR, B/L gt toe plethysmography B/L pedal skin temperature	No significant changes in BP and HR in either group Significant change in great toe plethysmograph waveform and skin temp in IC group Vs control No significant changes noted in either group 30 minutes post stimulation
(Tsang, Green et al. 1994)	Single blind placebo RCT	Stable Claudicants for 6 months ABPI<0.9 MWD<500m Post exercise ABPI drop 30mmHg	NMES (Medicompex) Vs Placebo (TENS) Popliteal and Anterior Tibial Nerve stim (8Hz, 350 μs V) 20mins 3 times daily. 4 weeks.	13/13	Baseline. Intervention 4 weeks later for 4 weeks duration. F/up week 10 and 12 after baseline.	Treadmill (fixed) ICD/MWD ABPI recovery Fatigue Index (FI)– ankle flexion force ratio to baseline Compliance	No demographic differences between groups. 100% compliance device use 126% (P<0.003) increase ICD with NMES Vs 122% placebo at 8 weeks 133% (P<0.004) increase MWD Vs 127% placebo at 8 weeks No significant difference 4 weeks post intervention cessation No change in ABPI over study period Fatigue index increased in both groups by week 8, but returned to normal 4 weeks after intervention cessation No significant changes in walking distances or FI in placebo group.

(Hudlicka 1994)	Single blind placebo RCT	Stable claudicants	NMES (Medicompex) Vs Placebo (no contraction) Popliteal and Anterior Tibial Nerve stim (8Hz, 350 μs V) 20mins 3 times daily.8 weeks.	12/12	Baseline Weekly for 4 weeks of intervention	MWD ABPI FI	No significant changes in MWD or FI in control group. In NMES group 161% increase in MWD (P<0.05). FI increased 200% (P<0.05). No changes in ABPI in either group seen.
(Anderson, Whatling et al. 2004)	Single blind RCT	Stable claudicants for 3+ months peABPI <0.8 WD 50-350m	NMES (Medicompex) Vs Placebo (TENS) Popliteal and Ant Tibial nerve stim (8Hz 350 μs V) 20mins, 3xdaily, 4 wks.	15/15	Baseline 2 weeks 4 weeks 2 weeks post stim cessation	Blood leucocytes Urine albumin:creatinine ratio ICD/MWD Calf muscle function Compliance	No demographic differences between groups ICD improved by 108% (P<0.01) and MWD by 50% (P<0.05) in NMES group No significant change in ICD/MWD in control group No significant changes to activated leucocytes and microvascular permeability seen after NMES or control.
(Abraham, Mateus et al. 2013)	Observational cohort study	Stable claudicants 1+ months ABPI<0.9 Patent femoral artery b/l mid-thigh No fem-pop bypass Worse leg used for stim Other leg control	Veinoplus NMES (1-250Hz, max 250 μs pulse width, 0.1-0.5V) Gastrocnemius/Soleus 60 - 100 bpm increasing every 5 mins for 20mins total	15	Baseline, stimulation and 10 minutes post stim cessation	Blood flow Duplex SFA Tissue oxygenation NIRS	240% increase blood flow during stimulation at 100 bursts per minute)P<0.01) No change in tissue oxygenation on stimulation Stimulation well tolerated.

(Guirro, Guirro et al. 2015)	Crossover study Random initial allocation 3 intervention protocols 7 day washout	Diabetics Stable claudication by APBI 0.4-0.9	High Voltage Electrical stim (HVES) (IBRAMED) Shortwave diathermy Exercise	15	Baseline 0, 20, 40, 60 minutes intervention	Duplex blood flow at femoral, popliteal and posterior tibial artery	No significant changes to maximum blood flow seen in any artery over intervention period in any group.
(Ellul, Formosa et al. 2017)	Prospective, pretest-posttest study	Diabetics with ABPI<0.9 Reproducible calf claudication	Veinoplus arterial model (1-250 Hz, low energy rectangular pulses (<25 μC) , low voltage (50V) 60 minute session	40	Baseline 12 weeks post test	Resting ABPI Spectral Doppler waveforms analysis Temperature change Absolute Claudication Distance (ACD) – graded treadmill test	Significant increase in ABPI post-test (P=0.001) No changes in spectral waveform analysis 137m (141%) improvement in ACD (P<0.0001) Statistically significant increase in resting temperature of 2 degrees Celsius noted on foot sole at hallux. medial and lateral foot and heel.

7.3.2 SF-36 score for Group A in the Adjuvant benefit of NMES to SEPs in IC study

SF-36 Domain Group A	Week 0 Mean [SD]	Week 6 Mean [SD]	Change in Score Mean [SD]	P Value
Physical functioning	41.32 [15.35]	45 [18.63]	3.684 [13.21]	0.24
Role functioning/physical	27.63 [34.25]	31.58 [35.2]	3.947 [40.19]	0.674
Role functioning/emotional	71.93 [38.91]	70.17 [36.68]	-1.758 [47.76]	0.873
Energy/fatigue	46.05 [15.33]	47.17 [14.77]	1.121 [11.97]	0.688
Emotional well-being	71.58 [15.31]	75.37 [10.35]	3.789 [15.17]	0.291
Social functioning	63.16 [25.84	74.34 [23.74	11.18 [22.01]	0.039*
Pain	41.05 [17.66]	55.26 [3.32]	14.21 [18.62]	0.004*
General health	46.05 [16.29]	46.68 [19.64]	2.632 [16.86]	0.505

Stats analysis: Paired t test

**Signifies significance (P<0.05)*

7.3.3 SF-36 score for Group B in the Adjuvant benefit of NMES to SEPs in IC study

SF-36 Domain Group B	Week 0 Mean [SD]	Week 6 Mean [SD]	Change in score Mean [SD]	P Value
Physical functioning	41.88 [20.81]	45.63 [15.37]	3.75 [13.72]	0.292
Role functioning/physical	42.19 [41.55]	31.25 [39.26]	-10.94 [43.75]	0.332
Role functioning/emotional	47.93 [38.44]	53.13 [43.56]	5.2 [43.78]	0.642
Energy/fatigue	48.75 [20.45]	52.19 [12.11]	3.438 [21.27	0.528
Emotional well-being	73 [13.58]	70 [19.97]	-3 [15.14]	0.441
Social functioning	66.41 [23.15]	78.91 [18.1]	12.5 [27.76]	0.092
Pain	42.66 [22.59]	57.03 [12.88]	14.38 [21.69]	0.018*
General health	51.88 [20.32]	52.5 [17.42]	0.625 [17.21]	0.886

Stats analysis: Paired t test

**Signifies significance (P<0.05)*

7.3.4 Raw data: NMES in muscle recovery following high intensity exercise study

Jump Heght (cm)							
	Baseline	Post Fatigue	% Change	Post REST	% Change	Post REST	% Change
	REST		from baseline	D1	from baseline	D3	from baseline
1	54.5	53.5	-1.8	48.0	-11.9	42.0	-22.9
2	46.0	45.5	-1.1	45.0	-2.2	43.0	-6.5
3	31.5	25.5	-19.0	28.5	-9.5	28.0	-11.1
4	40.5	38.0	-6.2	33.5	-17.3	33.5	-17.3
5	38.0	37.5	-1.3	33.5	-11.8	32.5	-14.5
6	58.0	57.5	-0.9	52.5	-9.5	53.0	-8.6
7	51.5	50.5	-1.9	49.5	-3.9	50.0	-2.9
8	40.0	40.5	1.3	37.0	-7.5	43.0	7.5
9	38.0	37.5	-1.3	35.0	-7.9	33.5	-11.8
10	68.0	67.0	-1.5	66.0	-2.9	64.0	-5.9
Mean	46.6	45.3	-3.4	42.9	-8.4	42.3	-9.4
SD	10.6	11.4	5.5	10.9	4.4	10.5	7.9

7.3.5 Raw data: NMES in muscle recovery following high intensity exercise study

Jump height (cm)						
Baseline	Post Fatigue	% Change	Post NMES	% Change	Post NMES	% Change
NMES		from baseline	D1	from baseline	D3	from baseline
40.0	37.0	-7.5	38.0	-5.0	38.5	-3.8
47.0	39.0	-17.0	33.5	-28.7	39.5	-16.0
44.0	46.5	5.7	42.0	-4.5	52.0	18.2
39.5	39.5	0.0	37.0	-6.3	38.0	-3.8
39.5	39.0	-1.3	39.0	-1.3	40.5	2.5
37.0	37.0	0.0	34.0	-8.1	34.5	-6.8
33.5	31.0	-7.5	32.5	-3.0	35.5	6.0
33.0	36.0	9.1	31.0	-6.1	34.0	3.0
49.0	49.0	0.0	46.0	-6.1	56.0	14.3
42.0	38.5	-8.3	35.0	-16.7	32.0	-23.8
40.5	39.3	-2.7	36.8	-8.6	40.1	-1.0
5.0	4.9	7.2	4.4	7.8	7.5	12.1

7.3.6 Raw data: NMES in muscle recovery following high intensity exercise

NRS pain score CONTROL (REST)									
	Baseline	Post Fatigue	Change	Post REST	Change		Change	Post REST	Change
	REST		from baseline	D1	from baseline	D2	from baseline	D3	from baseline
1	1	3	2	4	3	4.5	3.5	4	3
2	0	1	1	2	2	7	7	7	7
3	1	4	3	4	3	5	4	5	4
4	0	1.5	1.5	3	3	4	4	5	5
5	0	1	1	2	2	6	6	7	7
6	4	5	1	6	2	7	3	2	-2
7	0	1	1	1	1	5	5	5	5
8	2	2	0	2	0	1	-1	0	-2
9	0	0	0	1	1	4	4	4	4
10	4	4	0	2	-2	2	-2	5	1

7.3.7 Raw data: NMES in muscle recovery following high intensity exercise study

NRS pain score ACTIVE (NMES)								
Baseline	Post Fatigue	Change	Post NMES	Change		Change	Post NMES	Change
NMES		from baseline	D1	from baseline	D2	from baseline	D3	from baseline
1	4	3	2	1	1	0	0.5	-0.5
1	4	3	3	2	5	4	4	3
0	3	3	0	0	5	5	4	4
0	3	3	0	0	3	3	4	4
1	3	2	2	1	5	4	6	5
2	3	1	3	1	3	1	1	-1
0	0	0	1	1	4	4	1	1
4	5	1	3	-1	4	0	0	-4
0	1	1	1	1	4	4	1	1
1	1	0	0	-1	6	5	8	7

7.3.8 Raw data for NMES in recovery of short and long term calf muscle fatigue

Patient Code.	Jump Score (cm) CONTROL (REST)				
	Baseline	Post Fatigue	Post recovery (REST)	Post recovery Day 2	Post recovery Day 7
BP8	38.6	33.5	28.6	30.2	37.7
BY0	27.2	27.3	24.2	19.9	28.7
BZ4	32.7	32.7	33.3	28.4	33.6
BZ6	31.6	30.9	27.6	24.2	30.4
CD5	41.3	39.3	36.2	40.8	42.1
CE5	16.3	16.8	12.2	11.6	15.3
CT0	34.7	33.8	28.3	25.1	36.0
ET5	40.0	36.5	33.3	23.5	40.5
GC6	17.2	16.0	13.3	12.0	13.3
HL9	23.0	20.9	20.4	18.5	22.0
HV6	28.4	26.3	24.2	21.0	27.9
JM9	30.7	30.7	24.4	23.2	29.3
KK0	22.7	21.3	20.8	20.4	23.0
MU4	30.3	28.3	24.2	22.1	33.6
NL4	28.6	24.3	21.6	21.2	28.4
NO4	24.2	23.8	21.6	16.8	24.0
NU3	28.1	24.2	21.6	23.6	30.4
OM1	24.9	22.3	20.1	18.2	25.5
QB3	28.7	29.7	25.3	20.1	28.7
QK8	19.3	17.9	15.1	12.2	19.2
SI4	37.9	34.3	31.2	30.3	37.9
SJ4	23.6	23.1	23.8	19.8	24.0
UG6	36.5	34.2	30.1	25.4	37.5
WN4	39.1	37.2	36.1	28.4	41.3
XI1	40.5	36.5	37.7	31.2	41.0
XI9	36.4	35.2	33.2	29.1	37.5
YI8	39.8	36.7	33.2	28.4	38.2
ZV1	31.3	27.4	23.5	26.7	31.6

Raw data for NMES in recovery of short and long term calf muscle fatigue

Patient Code.	Jump Test Score (cm) ACTIVE (NMES)				
	Baseline	Post fatigue	Post recovery (NMES)	Post recovery (NMES)Day 3	Post recovery (NMES) Day 7
AH4	32.6	30.2	27.4	23.1	28.7
AK6	32.3	27.7	28.2	24.9	29.3
AU5	37.9	38.5	36.1	33.1	37.6
BH2	23.5	22.2	21.3	17.5	28.2
CP4	24.7	23.3	20.8	20.1	25.2
DN1	33.6	31.7	30.2	30.9	34.2
EO4	26.6	25.4	25.3	25.4	26.3
HX7	27.4	25.3	25.2	25.3	27.6
IW6	31.2	27.6	26.3	22.6	32.1
JD0	34.9	31.2	30.1	29.0	35.2
LC0	16.9	14.0	16.9	14.5	18.2
LV6	23.8	23.6	22.4	23.9	24.6
MP5	16.1	15.7	14.5	15.0	14.8
MP7	22.9	28.6	25.4	21.3	27.6
OJ6	28.3	26.4	25.1	25.7	28.3
OU2	40.3	36.8	36.7	36.5	41.0
RK3	14.1	11.7	11.1	8.5	13.7
SD4	29.7	28.4	26.3	26.7	30.1
SM2	33.3	32.4	35.8	31.0	33.4
TK4	27.6	26.2	24.8	21.6	26.2
TY6	34.4	28.9	30.1	31.8	35.2
VX0	35.4	33.3	34.9	33.9	37.0
WC9	31.1	27.1	25.2	20.6	34.4
WK9	36.6	34.2	33.7	31.3	36.0
XB9	32.3	27.7	28.2	24.9	32.5
XQ1	24.9	21.2	22.6	20.7	23.6
XX1	32.2	31.2	32.2	26.2	32.3
ZZ6	45.2	44.6	38.2	45.5	46.1

7.4 Questionnaires

7.4.1 Intermittent Claudication Questionnaire (ICQ)

Appendix A: The Intermittent Claudication Questionnaire (ICQ)

Pains, Cramps, Numbness or Discomfort in Your Calves, Thighs or Buttocks

The questions below ask about the problems of pains, cramps, and numbness or discomfort that patients with arterial disease get in their calves, thighs or buttocks when walking. The term "leg pains" has been used to describe all of these problems. Please answer every question with a tick. If you are unsure about how to answer a question, please give the best answer you can. When answering each question think about any pains, cramps, numbness or discomfort that you may get in your calves, thighs or buttocks when walking. Tick only one box per question.

1. During the past 2 weeks, how severe were your leg pains?

☐ None, I had no leg pain	☐ Very mild	☐ Mild	☐ Moderate	☐ Severe	☐ Very severe

The following questions ask about activities you might do during a typical day. Do your leg pains limit you in these activities? If so, how much?

		Totally limited	Very limited	Moderately limited	A little limited	Not limited at all
2.	Crossing the Road	☐	☐	☐	☐	☐
3.	Using the bus train or tube	☐	☐	☐	☐	☐
4.	Climbing several flights of Stairs	☐	☐	☐	☐	☐
5.	Climbing one flight of stairs	☐	☐	☐	☐	☐
6.	Walking more than a mile	☐	☐	☐	☐	☐
7.	Walking 100 Yards	☐	☐	☐	☐	☐
8.	Going out of the the house	☐	☐	☐	☐	☐

9. During the past 2 weeks, how often have you had to stop walking and rest because of the pains in your leg?

☐ More than 3 times a day	☐ 2 to 3 times a day	☐ Once a day	☐ Less than once a week	☐ Not at all

10. During the past 2 weeks, how much of the time have spent thinking about your leg pains?

☐ All of the time	☐ Most of the time	☐ Some of the time	☐ A little of the time	☐ None of the time

11. During the past 2 weeks, how much of the time have you felt downhearted and low because of your leg pains?

☐ All of the time	☐ Most of the time	☐ Some of the time	☐ A little of the time	☐ None of the time

12. During the past 2 weeks, how much of the time have you been worried that your leg pains will get worse?

☐ All of the time	☐ Most of the time	☐ Some of the time	☐ A little of the time	☐ None of the time

13. During the past 2 weeks, how much did your leg pains interfere with your normal work (including work both outside the home and housework)?

☐ Not at all	☐ A little bit	☐ Moderately	☐ Quite a bit	☐ Extremely

14. During the past 2 weeks, how much did your leg pains interfere with your hobbies or pastimes?

☐ Not at all	☐ A little bit	☐ Moderately	☐ Quite a bit	☐ Extremely

15. During the past 2 weeks, how much of the time have your leg pains interfered with social activities (like visiting with friends and relatives, etc.)?

☐ All of the time	☐ Most of the time	☐ Some of the time	☐ A little of the time	☐ None of the time

16. During the past 2 weeks, how much of the time have your leg pains interfered with doing errands (like shopping, going to the post office or bank, etc.)?

☐ All of the time	☐ Most of the time	☐ Some of the time	☐ A little of the time	☐ None of the time

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7.4.2 Euro-QoL 5 Dimension 5 Level (EQ5D)

EQ-5D

Under each heading, please tick the ONE box that best describes your health TODAY

MOBILITY

I have no problems in walking about ☐
I have slight problems in walking about ☐
I have moderate problems in walking about ☐
I have severe problems in walking about ☐
I am unable to walk about ☐

SELF-CARE

I have no problems washing or dressing myself ☐
I have slight problems washing or dressing myself ☐
I have moderate problems washing or dressing myself ☐
I have severe problems washing or dressing myself ☐
I am unable to wash or dress myself ☐

USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*

I have no problems doing my usual activities ☐
I have slight problems doing my usual activities ☐
I have moderate problems doing my usual activities ☐
I have severe problems doing my usual activities ☐
I am unable to do my usual activities ☐

PAIN / DISCOMFORT

I have no pain or discomfort ☐
I have slight pain or discomfort ☐
I have moderate pain or discomfort ☐
I have severe pain or discomfort ☐
I have extreme pain or discomfort ☐

ANXIETY / DEPRESSION

I am not anxious or depressed ☐
I am slightly anxious or depressed ☐
I am moderately anxious or depressed ☐
I am severely anxious or depressed ☐
I am extremely anxious or depressed ☐

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7.4.3 RAND Short Form Survey– 36



RAND > RAND Health > Surveys > RAND Medical Outcomes Study > 36-Item Short Form Survey (SF-36) >

36-Item Short Form Survey Instrument (SF-36)

RAND 36-Item Health Survey 1.0 Questionnaire Items

Choose one option for each questionnaire item.

1. In general, would you say your health is:

- 1 - Excellent
- 2 - Very good
- 3 - Good
- 4 - Fair
- 5 - Poor

2. **Compared to one year ago**, how would you rate your health in general **now**?

- 1 - Much better now than one year ago
- 2 - Somewhat better now than one year ago
- 3 - About the same
- 4 - Somewhat worse now than one year ago
- 5 - Much worse now than one year ago

The following items are about activities you might do during a typical day. Does **your health now limit you** in these activities? If so, how much?

	Yes, limited a lot	Yes, limited a little	No, not limited at all
3. **Vigorous activities**, such as running, lifting heavy objects, participating in strenuous sports	○ 1	○ 2	○ 3
4. **Moderate activities**, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	○ 1	○ 2	○ 3
5. Lifting or carrying groceries	○ 1	○ 2	○ 3
6. Climbing **several** flights of stairs	○ 1	○ 2	○ 3
7. Climbing **one** flight of stairs	○ 1	○ 2	○ 3
8. Bending, kneeling, or stooping	○ 1	○ 2	○ 3
9. Walking **more than a mile**	○ 1	○ 2	○ 3
10. Walking **several blocks**	○ 1	○ 2	○ 3
11. Walking **one block**	○ 1	○ 2	○ 3
12. Bathing or dressing yourself	○ 1	○ 2	○ 3

During the **past 4 weeks**, have you had any of the following problems with your work or other regular daily activities **as a result of your physical health**?

	Yes	No
13. Cut down the **amount of time** you spent on work or other activities	○ 1	○ 2
14. **Accomplished less** than you would like	○ 1	○ 2
15. Were limited in the **kind** of work or other activities	○ 1	○ 2
16. Had **difficulty** performing the work or other activities (for example, it took extra effort)	○ 1	○ 2

During the **past 4 weeks**, have you had any of the following problems with your work or other regular daily activities **as a result of any emotional problems** (such as feeling depressed or anxious)?

	Yes	No
17. Cut down the **amount of time** you spent on work or other activities	○ 1	○ 2
18. **Accomplished less** than you would like	○ 1	○ 2
19. Didn't do work or other activities as **carefully** as usual	○ 1	○ 2

20. During the **past 4 weeks**, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbors, or groups?

- ○ 1 - Not at all
- ○ 2 - Slightly
- ○ 3 - Moderately
- ○ 4 - Quite a bit
- ○ 5 - Extremely

21. How much **bodily** pain have you had during the **past 4 weeks**?

- 1 - None
- 2 - Very mild
- 3 - Mild
- 4 - Moderate
- 5 - Severe
- 6 - Very severe

22. During the **past 4 weeks**, how much did **pain** interfere with your normal work (including both work outside the home and housework)?

- 1 - Not at all
- 2 - A little bit
- 3 - Moderately
- 4 - Quite a bit
- 5 - Extremely

These questions are about how you feel and how things have been with you **during the past 4 weeks**. For each question, please give the one answer that comes closest to the way you have been feeling.

How much of the time during the **past 4 weeks**...

	All of the time	Most of the time	A good bit of the time	Some of the time	A little of the time	None of the time
23. Did you feel full of pep?	○ 1	○ 2	○ 3	○ 4	○ 5	○ 6
24. Have you been a very nervous person?	○ 1	○ 2	○ 3	○ 4	○ 5	○ 6
25. Have you felt so down in the dumps that nothing could cheer you up?	○ 1	○ 2	○ 3	○ 4	○ 5	○ 6
26. Have you felt calm and peaceful?	○ 1	○ 2	○ 3	○ 4	○ 5	○ 6
27. Did you have a lot of energy?	○ 1	○ 2	○ 3	○ 4	○ 5	○ 6
28. Have you felt downhearted and blue?	○ 1	○ 2	○ 3	○ 4	○ 5	○ 6
29. Did you feel worn out?	○ 1	○ 2	○ 3	○ 4	○ 5	○ 6
30. Have you been a happy person?	○ 1	○ 2	○ 3	○ 4	○ 5	○ 6
31. Did you feel tired?	○ 1	○ 2	○ 3	○ 4	○ 5	○ 6

32. During the **past 4 weeks**, how much of the time has **your physical health or emotional problems** interfered with your social activities (like visiting with friends, relatives, etc.)?

- ○ 1 - All of the time
- ○ 2 - Most of the time
- ○ 3 - Some of the time
- ○ 4 - A little of the time
- ○ 5 - None of the time

How TRUE or FALSE is **each** of the following statements for you.

	Definitely true	Mostly true	Don't know	Mostly false	Definitely false
33. I seem to get sick a little easier than other people	○ 1	○ 2	○ 3	○ 4	○ 5
34. I am as healthy as anybody I know	○ 1	○ 2	○ 3	○ 4	○ 5
35. I expect my health to get worse	○ 1	○ 2	○ 3	○ 4	○ 5
36. My health is excellent	○ 1	○ 2	○ 3	○ 4	○ 5

ABOUT

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7.5 Outcomes of a supervised exercise programme for patients with IC poster

Imperial College London

Outcomes of a Supervised Exercise Programme for Patients with Intermittent Claudication

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Introduction and Aims

Peripheral arterial disease (PAD) is a risk factor related chronic disease affecting the arterial circulation to the lower limbs. There is a global prevalence of approximately 20% of those aged over 80 years suffering from PAD[1]. Intermittent Claudication (IC), an exertional induced pain in the lower limbs, is an early stage symptom. Although 20% of patients suffering PAD will have IC, 1-2% of these will have significant disease progression requiring a lower limb amputation in 5 years[2].

Exercise Therapy, in the form of a Supervised Exercise Programme (SEP), is one measure of risk factor control that can improve quality of life and walking distances before onset of IC[3].

Trans-Atlantic Inter-Society Guidelines (TASC)[2], the Scottish Intercollegiate Guidance Network (SIGN)[4] and the National Institute of Clinical Excellence (NICE)[5] suggest all patients with IC should be referred for a SEP. However, this recommendation is under-utilised.

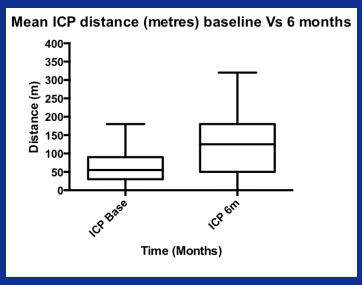
Our institution provides SEPs for patients with IC. Our aim is to present objective and subjective data collected for these patients.

Methods

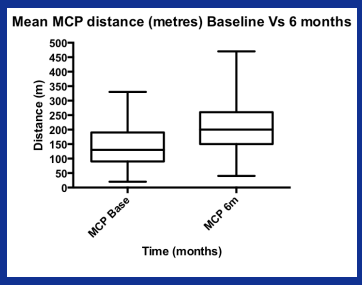
A retrospective analysis of prospectively collected data including initial claudication distance (ICD), maximal claudication distance (MCD) and IC questionnaire scores (CXQ) was carried out of patients with IC that had completed a SEP at our local institution, from January 2012 to August 2014.

Each SEP lasted 6 months in duration, consisting of 1 hour of supervised circuit exercise training per week. Fixed load treadmill measures and Charing Cross Questionnaire responses were taken at baseline and 6 months. Only patients with completed data sets for either outcome were included. Data was analysed on Prism 6 (© GraphPad software Inc) using the paired t test.

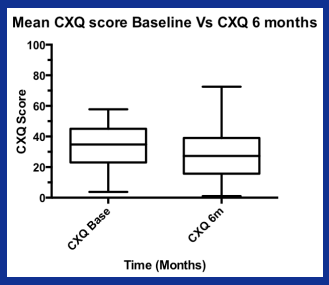
Results



Graph 1: Initial claudication distance was collected for 56 patients, showing a significant improvement (p<0.0001) from 63 metres (95% CI 50-73, baseline) to 125 metres (95% CI 100-147, 6 months).



Graph 2: A similar improvement was seen in 63 patients with MCD data, improving (p<0.0001) from 145 metres (95% CI 125-164, baseline) to 202 metres (95% CI 182-221, 6 months).



Graph 3: In the 70 patients with IC questionnaire scores, these improved (p<0.001) from 34 (95% CI 31-37, baseline) to 28 (95% CI 25-32, 6 months).

Conclusions

Distance outcome parameters and quality of life indicators showed a significant improvement following a SEP. This not only adds weight to an effective SEP, but also adds evidence to follow the recommendations of national and international guidelines in the management of early PAD.

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7.6 Academic achievements

7.6.1 Journal Publications

"Neuromuscular Electrical Stimulation for the Prevention of Venous Thromboembolism". Ravikumar R, Williams KJ, Babber A, Moore HM, Lane TRA, Shalhoub J, Davies AH. Phlebology. 2018; 33(6): 367-378.

"Randomised Controlled Trial: Potential Benefit of a Footplate Neuromuscular Electrical Stimulation Device in Patients with Chronic Venous Disease". Ravikumar R, Williams KJ, Babber A, Lane TRA, Moore HM, Davies AH. Eur J Vasc Endovasc Surg. 2017 Jan;53(1):114-121

"Non-Invasive Management of Peripheral Arterial Disease". Williams KJ, Babber A, Ravikumar R, Davies AH. Adv Exp Med Biol. 2017;906:387-406.

"A Review of the Evidence to Support Neuromuscular Electrical Stimulation in the Prevention and Management of Venous Disease". Williams KJ, Ravikumar R, Gaweesh AS, Moore HM, Lifsitz AD, Lane TR, Shalhoub J, Babber A, Davies AH. Adv Exp Med Biol. 2017;906:377-386.

Abstract publications:

“Neuromuscular Electrical Stimulation in the Management of Intermittent Claudication: A ‘Stimulating’ Prospect”. Babber A, Ravikumar R, Williams KJ, Davies AH. Journal of Vascular Surgery 2016;63(6):16S-17S

“Can Neuromuscular Stimulation Relieve Symptoms of Chronic Venous Disease, and Improve Quality of Life?” Williams KJ, Ravikumar R, Babber A, Davies AH. BJS 2015;102(S5):9

“Outcomes of a Supervised Exercise Programme for Patients with Intermittent Claudication”. Babber A, D’Sa L, Ge Y, Sizer K, Burgess L, Davies AH. BJS 2015;102(S5):48

“Electrical Stimulation of the Foot Pump: A Pilot Randomised Controlled Trial in Patients with Chronic Venous Insufficiency”. Ravikumar R, Williams KJ, Babber A, Davies AH. BJS 2015;102(S5):6

“Availability of Supervised Exercise Programmes for Patients with Peripheral Arterial Disease”. Babber A, D’Sa L, Ge Y, Davies AH. BJS 2015;102(S5):46

"Pilot Randomised Control Trial: Neuromuscular Electrical Stimulation in Treating Venous Disease." Ravikumar R, Williams KJ, Babber A, Lane TRA, Moore HM, Davies AH. European Society for Vascular Surgery (ESVS) annual meeting, Porto, Portugal. September 2015

- "Neuromuscular Electrical Stimulation for prevention of venous thromboembolism" Ravikumar R, Williams KJ, Babber A, Lane TRA, Moore HM, Davies AH. European Venous Forum, St Petersburg, Russia. July 2015. Oral

- "Prevention and management of vascular disease with neuromuscular stimulation" Williams KJ, Ravikumar R, Babber A, Davies AH CX Venous Workshop. 37th Charing Cross International Vascular Symposium 2015, London, UK, April 2015.

"A pilot trial of neuromuscular stimulation in the management of patients with chronic venous disease". KJ Williams, A Babber, R Ravikumar, AH Davies. Annual Meeting of American Venous Forum, Palm Springs, CA, USA, Feb 2015

- "Potential clinical applications for Electrical Muscle Stimulation in venous disease" (poster presentation) Ravikumar R, Williams KJ, Babber A, Davies AH. Annual Meeting of American Venous Forum, Palm Springs, CA, USA, Feb 2015

- "Electrical stimulation of the foot pump: A pilot randomised control trial in patients with chronic venous insufficiency" (poster presentation) Ravikumar R, Williams KJ, Babber A, Davies AH. Annual Meeting of American Venous Forum, Palm Springs, CA, USA, Feb 2015

"Thromboprophylaxis With Neuromuscular Electrical Stimulation (NMES): A Meta-Analysis of Imaging Proven Venous Thromboembolism". Ravikumar R, Williams KJ, Babber A, Lane TRA, Moore HM, Shalhoub J, Davies AH. Venous Forum, Royal Society of Medicine, London. May 2015 . Oral

- "Neuromuscular Electrical Stimulation in Treating Venous Disease: A Pilot Randomised Control Trial." Ravikumar R, Williams KJ, Babber A, Lane TRA, Moore HM, Davies AH. Venous Forum, Royal Society of Medicine, London. May 2015. Poster presentation

"Can neuromuscular stimulation relieve the symptoms of chronic venous disease, and improve quality of life?". KJ Williams, R Ravikumar, A Babber, AH Davies SARS Annual Meeting, Durham, Jan 2015

"Electrical stimulation of the foot pump: A pilot randomised control trial in patients with chronic venous insufficiency" **(Patey Prize Session).** R Ravikumar, KJ Williams, A Babber, AH Davies
SARS Annual Meeting, Jan 2015

- "Pilot trial of neuromuscular stimulation in the management of chronic venous disease". KJ Williams, A Babber, R Ravikumar, M Ellis, AH Davies. Vascular Society Annual Scientific Meeting, Glasgow, UK. Nov 2014

"A pilot trial using neuromuscular leg stimulation in the management of chronic venous disease" **(Prize winner).** KJ Williams, R Ravikumar, A Babber, M Ellis, AH Davies. RSM President's Day, MIA Trainee Session, Nov 2014

Grants

National Institute for Health Research – Efficacy and Mechanistic Evaluation Grant

Co-Applicant

A multicentre randomised controlled study: Does Neuromuscular Electrical Stimulation improve the absolute walking distance in patients with Intermittent Claudication compared to best available treatment? (NESIC) [ISRCTN 18242823]