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Proactive Management of Acute Oedema Following Hand and Minor Burn Injury

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PROACTIVE MANAGEMENT OF ACUTE OEDEMA FOLLOWING HAND AND MINOR BURN INJURY

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Declaration

To the best of the candidate's knowledge, this thesis contains no material previously published by another person, except where due acknowledgement has been made.

This thesis is the candidate's own work and contains no material which has been accepted for the award of any other degree or diploma in any institution.

Human Ethics

The research presented and reported in this thesis was conducted in accordance with the National Health and Medical Research Council National Statement on Ethical Conduct in Human Research (2007, updated 2018). The proposed research study received human research ethics approval from the University of Notre Dame Australia Human Research Ethics Committee (EC00418), Approval Numbers 015158F, 016128F and 019048F.

This research was conducted within the State Adult Burns Unit at Fiona Stanley Hospital, and received human research ethics approval from the South Metropolitan Health Service Human Research Ethics Committee (EC00265), Approval Numbers 14-101 and 16-143.

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ABSTRACT

Burn injury is a unique trauma. The inflammatory process initiated with burn injury adversely influences all of the Starling equation variables, resulting in increased transvascular fluid filtration, so that oedema as a product of burn injury is more readily formed than in other forms of trauma. Localised wound oedema forms due to minor burn injury, with increasing systemic oedema associated with increased size of burn. It is now recognised that a marked inflammatory and immune response is created with non-severe burn injury, indicating a systemic component with all burns. The effect of oedema formation on the course of the burn healing is well described in the literature, due to its impact on the zone of stasis in the wound and its potential to result in progressive tissue loss or conversion if poorly managed. Burn conversion leads to an increase in the area and depth of the burn wound, necessitating surgical intervention, which increases the risk of scarring. Burn scarring may lead to altered function and poor aesthetic outcomes, which have the potential to adversely affect patient psychological well-being. Despite the influence of oedema on the healing of the burn wound and therefore the scar worn for life, there is little evidence to guide clinicians who aim to proactively manage this oedema, with only two published, controlled trials investigating methods to improve peripheral oedema in burn injury.

The aim of the series of studies described in this thesis is to provide a holistic approach to the management of oedema following acute burn injury. To be able to effectively treat oedema, the clinician needs to be able to accurately assess the affected limb and wound for oedema. Oedema management in burn injury is often based on the clinicians' preference of intervention, without good understanding of the optimal parameters of application or efficacy. Therefore, evidence is required for optimising the management of oedema in the acute burn injured patient.

Furthermore, the hand's unique anatomical structure that produces functional dexterity adds complexity to the assessment and management of oedema formation in the hand. Burn injury to the hand is common, as hands provide interaction with the world, and are generally vulnerable during activities of daily living. In the event of major accidents, the hands are reflexively used to protect the face and body, further predisposing them to significant injury.

The ability to accurately measure oedema guides clinicians in their treatment of acute burn wound oedema. Current objective measures of oedema often lack sensitivity, increase pain, introduce a risk of infection from equipment contact with open wounds, or are cumbersome for repeated use in the clinical environment. They are also influenced by the cooperation of the patient, and burn injury often results in significant pain, impaired movement, and may require the use of medications that modify behaviour. As a result, oedema is usually assessed visually or through palpation of the tissue, noting the loss of skin creases or pitting of soft tissue. These assessments are subjective based on the clinician's experience and do not provide objective measures that can be repeated between testers or between sessions. Demonstrating the effectiveness of proactive oedema management following acute burn injury is therefore dependent on the ability to accurately assess the oedema using a valid, reliable and sensitive objective measure.

There is a lack of high-quality prospective studies investigating oedema management techniques in burn injury populations. In a 2011 systematic review, there was only one published randomised control trial, which investigated the use of electrical stimulation in addition to standard interventions for managing hand burn oedema, while a second conference presentation was reported as part of the review. There have been no further published studies in this space, providing clinicians with little guidance as to the optimal parameters to manage oedema in this challenging injury cohort. Measuring oedema in this patient group is similarly challenging.

The study series in this thesis addresses the challenge of measuring hand burn oedema and wound healing.

Bioimpedance spectroscopy (BIS) is a technology that has demonstrated reliability and validity for measuring whole body and limb oedema in burns patients during fluid resuscitation, and is sufficiently sensitive to measure oedema change with wound healing. Another BIS variable, Phase Angle, is validated to be a measure of cell health, as it measures the flow of current across the cell with respect to the voltage. Increased lag in the current is the result of increased cell mass and cell wall integrity (a healthier cell), resulting in an increased Phase Angle. This has been demonstrated to increase with healing in chronic wound populations, but has not been

validated in acute burn injury.

The first study in this thesis is a method validation study, investigating the measurement of hand volumes using a novel application of BIS. A technique to measure hand volumes using BIS has been described previously, however the burn injured hand is compromised by wounds. The guidelines for the use of BIS require that electrodes are placed on intact skin. The study compared different electrode configurations on the hand and arm to the previously described configuration in a non-injured population, to determine if different electrode configurations are valid for measuring hand volumes. The key findings of this study were that, when compared to previously described electrode positions on the dorsum of the hand and forearm, alternative electrode combinations on the volar surface of the hand and forearm, and an electrode array on the palm of the hand and the dorsum of the forearm, were both valid for measuring hand oedema volumes in an uninjured population. These outcomes provide novel evidence to guide electrode placements to measure hand volume using BIS where wounds precluded the use of standard electrode arrays.

The second study in this series is a validation study, informed by and used the electrode positions assessed in the first study, to determine the validity and reliability of BIS for measuring hand (oedema) volumes in a burn injured population. Repeated hand volume measures were obtained in 100 patients presenting with hand burn injury with BIS, and with water displacement volumetry as a gold standard comparison. The results of this study demonstrated that the electrode positions assessed as valid for measuring hand volumes in an uninjured population in the first study, were valid, reliable and sensitive for measuring oedema in the hand following burn injury, showing high correlation with the gold standard comparator. This technique was used to assess the primary outcome – oedema volume change – in the third study of this series.

The following studies in this thesis are intervention research, investigating techniques designed to proactively manage oedema in acute burn injury.

The third study described in this thesis is the first randomised controlled trial to investigate different methods of applying compression to the hand to manage acute

burn oedema. Compression is a commonly used technique to control oedema, reported to be applied based on clinician preference, which is dependent on the way each clinician was taught. In this study, 100 patients (the largest of its kind to the best of my knowledge), presenting with burn injury involving a portion of the hand were randomised to receive one of three commonly used methods of applying compression, to provide evidence as to which is the most effective at controlling acute burn wound oedema in the hand. In this study, the two most common methods of fabricating a custom compression glove using cohesive bandage were shown to be both equally effective at reducing post burn oedema in the hand, and both were more effective for reducing hand burn oedema than the control condition being an off the shelf compression glove. The patients in this study were also provided education regarding exercise to maintain function and promote oedema reduction, oedema management advice including elevation of the hand above the level of the heart at rest, and ensuring normal use of the hand while respecting the wound environment to minimise the risk of infection. These interventions resulted in significantly greater hand range of movement between test sessions, and a significant improvement in the QuickDASH (Disability of Arm, Shoulder and Hand) patient reported outcome measure.

The effect of a low energy, long duration electrical stimulation on the acute burn wound was investigated in study four. Electrical stimulation has been demonstrated to improve the rate of healing of chronic wounds, and aid the reduction of oedema in a number of populations, including patients with hand burn injury when used in addition to standard physiotherapy. The novel application of electrical stimulation in this study utilised a small patient applied stimulation device for more than 20 hours per day for a period of up to 14 days, with the current applied across the wound with electrodes placed either side of the injured tissue on intact skin. This was designed as a within-patient control, randomised trial. Patients with similar size and similar depth burns to multiple limbs participated in this study. Electrical stimulation was applied to one wound, with the contralateral wound serving as the control wound. The outcomes investigated were change in oedema, as measured by the BIS variable R0, measuring the impedance of the extra-cellular fluid; and wound healing, measured by the BIS variable Phase Angle, and compared to clinical photography of the wounds, which were assessed by a consultant burns surgeon to determine wound re-epithelialisation, or healing. Phase Angle and wound impedance were demonstrated

to be associated with wound healing. Electrical stimulation applied to a minor burn was shown to increase the rate of oedema reduction in the wound compared to the control wound, and increased Phase Angle at a faster rate than in the control wound, indicating an increase in cell and tissue health.

This thesis presents a study series whereby the first two studies validated a new method of measuring hand burn oedema quickly, with minimal imposition on the patient. This method was demonstrated as viable and applicable in acute burn patients, in both research and clinical practice contexts, and informed the ensuing studies in this series. The final two studies presented in this thesis are randomised controlled trials investigating the proactive management of oedema in acute burn injury, and contribute significant new knowledge to the literature, providing guidance to the burn clinician who manages acute oedema to prevent conversion of the burn wound and deterioration in function.

When presented with a hand burn injury, the clinician will be able to appropriately manage the ensuing oedema with a custom compression glove fabricated using a cohesive bandage with either of the most common methods therapists are taught. In addition, in minor burn wounds, the use of a small, easy to use, low energy long duration electrical stimulation device as an adjunct to standard burn wound care, will increase oedema reduction and improve the rate of wound healing compared to standard wound care alone.

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While my name is on the cover of this thesis, it is the product of collaboration and I could definitely not have done it alone. Please indulge me as I thank the people who have helped me along this PhD journey.

The opportunity to undertake a PhD was first presented to me by my principal supervisor, Associate Professor Dale Edgar (D1) in September 2014. I was the rotating P1 physiotherapist in the Burns Unit at Royal Perth Hospital, and was preparing for the challenges of transferring to the newly commissioned Fiona Stanley Hospital in early 2015. I had previously worked with D1 in Plastic Surgery and Hand Therapy, and I was one of his students in the Burns Unit back in 2007, so he understood that I had an interest in hands as well as burn injury. He asked if I was interested in research, and mentioned something along the lines of 'Burns and hands' and left the rest up to me. Without Dale's guidance, knowledge and belief, I would not have found burns or plastics as a passion, and definitely not been able to undertake a PhD, so thank you for being the biggest influence on my career D1. I hope that I am thinking what you are thinking.

The State Adult Burns Unit, as part of the Burns Service of Western Australia, is on the front of the wave in terms of research and patient care, and this is due to the vision of Winthrop Professor Fiona Wood. Thank you for being such a role model, and for the support through the Fiona Wood Foundation in making my research possible.

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The data in this research required special statistical analysis skills, and for that I owe Dr Dana Hince a debt of gratitude. We were on a journey together trying to understand the nuances of bioimpedance, but thank you so much for your sharing your knowledge to guide me, your patience and your time.

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PUBLICATIONS

Publications included in this thesis:

Edwick, D. O., Hince, D. A., Rawlins, J. M., Wood, F. M., & Edgar, D. W. (2020). Alternate electrode positions for the measurement of hand volumes using bioimpedance spectroscopy. *Lymphatic Research and Biology, 18(6),* 560-571. doi:10.1089/lrb.2019.0078

Edwick, D. O., Hince, D. A., Rawlins, J. M., Wood, F. M., & Edgar, D. W. (2020). Bioimpedance spectroscopy is a valid and reliable measure of edema in hand burn injury (Part 1 – Method Validation). *Journal of Burn Care & Research, 41(4),* 780-787. doi:10.1093/jbcr/iraa071

Edwick, D. O., Hince, D. A., Rawlins, J. M., Wood, F. M., & Edgar, D. W. (2020). Randomised control trial of compression interventions for managing hand burn edema, as measured by bioimpedance spectroscopy. *Journal of Burn Care & Research, 41(5),* 992-999. doi:10.1093/jbcr/iraa104

Edwick, D. O., Hince, D. A., Rawlins, J. M., Wood, F. M., & Edgar, D. W. (2022). Does electrical stimulation improve healing in acute minor burn injury, as measured by bioimpedance spectroscopy? A single centre, randomised, controlled trial. *Burns Open, 6(1),* 42-50. doi:10.1016/j.burnso.2021.11.001

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Edwick, D. O., Hince, D. A., Rawlins, J. M., Wood, F. M., & Edgar, D. W. (2020). 78 Optimising Compression for the Management of Acute Hand Burn Edema. *Journal of Burn Care & Research, 41* (Supplement_1), S50-S51. doi:10.1093/jbcr/iraa024.082

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Conference presentations during candidature:

Edwick, D.O., Hince, D.A., Rawlins, J.M., Wood, F.M. and Edgar, D.W. Validation of alternative electrodes positions for the measurement of hand volume in a non-injured population. Australia and New Zealand Burn Association Annual Scientific Meeting; 2016 Oct 11-14; Auckland, New Zealand (Poster).

Edwick, D.O., Hince, D.A., Rawlins, J.M., Wood, F.M. and Edgar, D.W. Validation of alternate electrode positions for the measurement of hand volumes in a healthy population. Australia and New Zealand Burn Association Annual Scientific Meeting; 2017 Oct 24-27; Adelaide, South Australia.

Edwick, D.O., Hince, D.A., Grisbrook, T.L., Murphy, R., Rawlins, J.M., Wood, F.M. and Edgar, D.W. Does electrical stimulation improve healing in acute burns, as measured by bioimpedance? 19th Congress of the International Society for Burn Injuries; 2018 Nov 30 – Dec 4; New Delhi, India.[1]

Edwick, D.O., Hince, D.A., Rawlins, J.M., Wood, F.M. and Edgar, D.W. Electrical stimulation improves healing in acute minor burn injury, as measured by bioimpedance spectroscopy: A single centre, randomised, controlled trial. Australia and New Zealand Burn Association Annual Scientific Meeting; 2019 Oct 14-17; Hobart, Tasmania.

Edwick, D.O., Hince, D.A., Rawlins, J.M., Wood, F.M. and Edgar, D.W. Comparison of different methods of compression for managing oedema following hand burn injury. Australia and New Zealand Burn Association Annual Scientific Meeting; 2019 Oct 14-17; Hobart, Tasmania (Poster) [2]

Edwick, D.O., Hince, D.A., Rawlins, J.M., Wood, F.M. and Edgar, D.W. Optimising Compression for the Management of Acute Hand Burn Edema. American Burn Association; 2020 March 17-20; Orlando, Florida, USA – Conference cancelled due to Covid-19.

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[1] Awarded Andre Zagamé Rehabilitation Specialist Prize.
[2] Awarded Best Research ePoster.

Edwick, D.O., Hince, D.A., Rawlins, J.M., Wood, F.M. and Edgar, D.W. Bioimpedance Spectroscopy Is a Valid and Reliable Measure of Edema in Hand Burn Injury. American Burn Association; 2020 March 17-20; Orlando, Florida, USA – Conference cancelled due to Covid-19.

Edwick, D. O., Hince, D. A., Rawlins, J. M., Wood, F. M., & Edgar, D. W. Bioimpedance spectroscopy is a valid and reliable measure of oedema in hand burn injury. Australia and New Zealand Burn Association Annual Scientific Meeting; 2021 October 13-15; Perth, Western Australia.

Edwick, D. O., Hince, D. A., Rawlins, J. M., Wood, F. M., & Edgar, D. W. Randomised control trial of compression interventions for managing hand burn oedema, as measured by bioimpedance spectroscopy. Australia and New Zealand Burn Association Annual Scientific Meeting; 2021 October 13-15; Perth, Western Australia.

Gow, E., Spilsbury, K., Edwick, D., Grisbrook, T., Wood, F. & Edgar, D. Hand burn influence on length of stay: A 20-year review of adult upper limb burn injury in Western Australia. Australia and New Zealand Burn Association Annual Scientific Meeting; 2021 October 13-15; Perth, Western Australia (Poster).

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Bioimpedance Spectroscopy	BIS	A measure of body composition performed by measuring the impedance of different tissues in the body to a small electric current across a frequency range of 4-1000Hz. Impedance of fluid volumes in different body compartments calculated using Cole-Cole modelling (Kyle et al., 2004a).
Electrical stimulation	ES	A low level electric current delivered into the tissue via a cutaneous coupling using surface electrodes (Houghton et al., 2010). Current can be delivered at differing frequencies, voltages and waveforms to achieve different treatment effects (Gardner et al., 1999).
Extracellular water / fluid	ECW / ECF	The fluid outside the cells. Accounts for 40% of TBF (17L in males, 14L in females). Made up of interstitial fluid (75%), plasma (20%) and transcellular fluid (5%). Rich in Na^+ and Cl^- (Aronson et al., 2017).
Impedance of extracellular water	R_0	Impedance measured at very low frequency derived from Cole modelling. High cell membrane capacitance limits conduction to the extracellular space (Earthman et al., 2007)
Impedance of intracellular water	R_i	The impedance of the intracellular fluid. Calculated as $(1/R_\infty - 1/R_0)^{-1}$ (Matthie, 2008)
Impedance of total body water	R_∞	At infinitely high frequency (derived from the Cole model), the cell membrane charges and discharges so quickly so as to become insignificant, allowing complete measurement of the impedance of total body fluid (Earthman et al., 2007; Matthie, 2008).
Intracellular water / fluid	ICW / ICF	The fluid inside the cell membranes. Makes up 60% of TBW (25L in males, 21L in females). Rich in K^+ and maintains intracellular ion balance through Na-K (Aronson et al., 2017).
Membrane capacitance	Cm	Capacitative resistance of the cell membrane, measured in nF. Determined by cell volume and cell membrane integrity (Matthie, 2008)
Oedema		Abnormal accumulation of excess fluid, primarily in the extra-cellular space, as a result of the body's response to injury due to increased vascular permeability (Demling, 2005)
Phase Angle	PhA	Calculated as the arc-tangent of Xc / R (measured in degrees) and is a measure of the current lag with respect to the voltage due to the cell membrane structure and function (Lukaski & Singer, 2011)
QuickDASH		The shortened version of Disability of Arm, Shoulder and Hand is a self-reported questionnaire designed to measure disability in the upper extremity (Wu et al., 2007).
Reactance	Xc	Resistive component of the cell, related to Cm and is dependent on the current frequency (Matthie, 2008)
Total Body Surface Area	TBSA	The area of skin damaged in burn injury, expressed as a percentage. Measured using the Rule of Nines in adults, and a nominal 1% attributed to the palmar area of the hand (Diver, 2008; Jose et al., 2004)
Total body water / fluid	TBW / TBF	Accounts for 60% of body weight (42L) in adult male and 50% body weight (35L) in females (Aronson et al., 2017).
Water Displacement Volumetry	WDV	A measure of volume of an object using Archimedes principle of water displacement. Recognised as the gold standard for measuring the volume of the hand for clinical and research purposes (Boland & Adams, 1996).

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CHAPTER 1 **INTRODUCTION**

1.1 Introduction

"Every intervention, from the time of the burn injury, has an impact on the scar worn for life" (Wood, 2013).

The impacts of the agent of the burn injury, time in contact with the source of the burn, quality of the first aid administered, time of referral to a burns centre and timing to surgery, all influence the outcome for the patient with a burn injury (Kao & Garner, 2000; Wood et al., 2016). There is a localised and systemic inflammatory response to burn injury, with a release of inflammatory mediators including vasoactive prostaglandins, histamines and bradykinins that increase vascular permeability, resulting in tissue oedema (Demling & LaLonde, 1990; Kao & Garner, 2000; Toliver-Kinsky, Kobayashi, Suzuki, & Sherwood, 2018).

Local tissue oedema formation occurs rapidly following burn injury, as part of the body's natural response to injury, and water content in the burn wound can double within an hour of injury (Demling, 2005). Systemic oedema following burn injury results in generalised swelling, with an increase in extracellular fluid noted in unburned tissues (Demling, 2005). Systemic oedema is compounded after major burn injury by the requirement of fluid resuscitation, to reduce the risk of hypovolaemic shock due to the generalised vascular leak associated with burn injury, by restoring intravascular volume in order to preserve vital organ and tissue perfusion (Wurzer, Culnan, Cancio, & Kramer, 2018).

Burn injury wounds are characterised into three zones to the injury – the central zone of coagulation, which is the area of tissue damaged by contact with the burn agent; the peripheral zone of hyperaemia, which is the outermost area characterised by the body's natural response to injury – increased blood flow and erythema; and the zone of stasis surrounding the central zone (Jackson, 1953). The zone of stasis is the area that may be preserved and salvaged through optimal management, but is vulnerable to ongoing tissue loss and extending the size of the central zone of coagulation due to host factors and suboptimal management, including but not limited to poor oedema control, infection, use of inotropes, sub-optimal resuscitation or poor first aid (Edgar, Fish, Gomez, & Wood, 2011; Kao & Garner, 2000; Singh, Devgan, Bhat, & Milner, 2007; Zawacki, 1974). There is a lack of high-level evidence supporting the negative

effect of oedema on post-burn healing, however there is a significant body of evidence and theory that has resulted in the belief that poor management of acute oedema following burn injury leads to conversion or deepening of the burn injury, which is associated with prolonged time to burn healing and poorer outcomes (Edgar, Fear, & Wood, 2016).

Investigations in experimental burn wounds have confirmed the time sensitive, negative effects of oedema. Tissue oxygenation was shown to be reduced in the oedematous zone surrounding the zone of necrosis for 20-30 minutes post injury, and permeates across the burn wound-oedema interface (Remensnyder, 1972). Experimental oedema through the injection of dextran and normal saline in rabbits showed decreased wound tissue oxygenation, with elevated CO_2 and pH levels compared to control wounds (Heughan, Zederfeldt, Grislis, & Hunt, 1971). This reflects the impact of wound oedema, in which modelling suggests that if oedema remains unchecked and results in a doubling of the oxygen diffusion distance, oxygen flow to the wound is decreased such that increasing the capillary blood flow twentyfold is insufficient to restore nutrient flow to the wound (Knisely, Reneau, & Bruley, 1969). Reduced oxygenation in wound injury results in a deterioration in wound metabolism, which greatly affects wound healing (Niinikoski, Heughan, & Hunt, 1972), and increases susceptibility to infection (Hunt, Linsey, Grislis, Sonne, & Jawetz, 1975).

In addition to the medical management of systemic fluid losses, the timely proactive management of local wound oedema in acute burn injury is the responsibility of the multi-disciplinary team, to minimise the risk of wound conversion through these mechanisms, and to optimise the outcome for the patient. There is a paucity of high-quality studies investigating peripheral oedema management techniques in acute burn injury (Edgar et al., 2011). Management techniques for oedema in a number of injury populations confirm the use of elevation (Boland & Adams, 1998), the application of compression (Lowell et al., 2003), and active movement and activation of venous and lymphatic pumps (Collings, 1999; Lane, Worsley, & McKenzie, 2005), although none of these are studies in terms of control groups. The only controlled trial in a burn injury population which investigated the use of electrical stimulation in conservatively managed hand burns, demonstrated that stimulation in addition to standard physiotherapy improved hand volume measures and hand range of motion

when compared to standard physiotherapy alone (Omar, El-Badawy, Borhan, & Nossier, 2004).

The challenge of assessing oedema volume or change following burn injury is complicated by pain, impaired movement, open wounds that present a vector to infection, and the use of medications that may alter behaviour. The reference, or gold standard for the clinical measurement of limb volumes is water displacement volumetry, which has been demonstrated to be reliable and valid in burn injured patients (Dewey, Hedman, Chapman, Wolf, & Holcomb, 2007; Edgar, Briffa, Cole, & Wood, 2014). Repeated measures of volumetry provide clinicians with quantitative measures of the effectiveness of oedema management intervention, however it poses potential staff and patient safety issues due to equipment bulk, requires consistent positioning of the hand and a stable surface, and is time consuming to set up, which limits its practicality in the clinical setting (Dewey et al., 2007; Edgar et al., 2009).

The use of a tape measure to obtain circumferential limb or figure of eight measures are popular due to the low cost of the equipment, is a quick measure to perform, and has been shown to be valid in a hand burn population (Dewey et al., 2007). Contact of the tape measure with burn wounds have the potential to increase pain, pose an increased risk of infection, and these measures only provide *estimates* of volume, due to a reliance on subjective pressure imparted during the measurement technique and formulae to calculate the volumes (Edgar et al., 2014). Due to these issues, clinical observation of oedema in the burned hand is often limited to palpation and noting areas of obvious swelling, including the loss of joint creases, and reduced range of movement due to tension in the dorsal compartment of the hand caused by collection of fluid (Collings, 1999; Stanton, Badger, & Sitzia, 2000).

Bioimpedance spectroscopy (BIS) is a measure of body composition, which is performed by measuring the impedance (or resistance) to a low amplitude (alternating) current flow at frequencies varying from 4-1000kHz through the body (Cornish, 2006). At very low frequencies, the current follows the extracellular space, and provides a measure of the impedance of the extracellular water, which is primarily the space where oedema forms (Buendia et al., 2015; Cornish, 2006). As the frequency of the current increases, the current overcomes the natural impedance (or capacitance) of the cell wall, to provide measures of both

intracellular and extracellular water, and therefore total body water (Figure 3) (Earthman, Traughber, Dobratz, & Howell, 2007). Impedance at zero frequency (R_0), and at very high frequencies (R_∞), are predicted by Cole-Cole modelling, due to the impracticalities of passing direct current or alternating current at extremes of (waveform) frequency through the human body (Kyle et al., 2004a). These properties enable BIS to be sufficiently sensitive to measure alterations in impedance associated with increased fluid in pre-clinical lymphoedema following surgery for breast cancer (Ward, Czerniec, & Kilbreath, 2009), and therefore applicable to the measurement of local wound oedema (Ward, Sharpe, Edgar, Finlay, & Wood, 2013). Impedance measures are considered an index of the volume of body fluids, as impedance is inversely proportional to the volume of fluid the current passes through (Ward, 2006).

BIS has been shown to be sensitive for measuring fluid shifts associated with fluid resuscitation in burns of up to 30% total body surface area (TBSA) (Edgar et al., 2009). However, the clinical guidelines for the use of BIS recommend that the skin is intact at the site of the electrodes, and where wounds exist at these locations, alternate electrode positions are recommended (Kyle et al., 2004b). This poses an issue in the use of BIS in the presence of larger burn injury. A proof-of-concept study for the measurement of localised oedema using an array of electrodes around an experimental wound demonstrated that the voltage sense electrodes positioned around a wound in all positions, except perpendicular to the direction of current flow, allowed the accurate measurement of impedance across the wound (Ward et al., 2013). This has been shown to be valid in measuring burn wound oedema (Kenworthy, Grisbrook, Phillips, Gittings, et al., 2017). The use of alternate electrode positions on the palm of the hand and volar wrist has been shown to result in equivalent measures of whole body and upper limb segmental impedance measures for extracellular water in both a non-injured population and a burn injured population (Grisbrook et al., 2015; Kenworthy, Grisbrook, Phillips, Gibson, et al., 2017). The series of studies conducted in this research program applies the findings of these works to investigate, firstly, the applicability of BIS for measuring hand volumes using alternate electrode arrays, and then validate these alternate arrays for measuring hand oedema in burn injury.

The measurement of oedema in the hand is complicated by its complex geometric shape. A novel application of BIS for measuring hand volumes was demonstrated to be highly correlated with perometry (Dylke et al., 2014; Ward, Dylke, & Kilbreath, 2012). This measure using BIS was demonstrated to be sensitive to the venous volume change in the hand elicited by elevating the hand above shoulder level for three minutes (Dylke et al., 2014). This technique offers clinicians a technique that is rapid to perform, sensitive to changes in oedema, and requires minimal input from the patient. Additionally, it has been demonstrated to measure oedema when dressings remain insitu, which is a significant limitation of other methods of measuring limb volumes, and therefore oedema when wounds are present (Kenworthy, Grisbrook, Phillips, Gibson, et al., 2017).

In the presence of an alternating current, the cell membrane behaves like a capacitor. This cell membrane capacitance results in a delay in the flow of current across the cell with respect to the flow of the voltage (Lukaski & Singer, 2011). This lag in current flow across the cell membrane is known as the phase angle, and is calculated as the arc tangent of the reactance (mass and function of the cell membrane) and impedance (resistance to current flow) (Lukaski & Singer, 2011; Mulasi, Kuchnia, Cole, & Earthman, 2015; Norman, Stobäus, Pirlich, & Bosy-Westphal, 2012). The magnitude of this delay in current flow is dependent on the mass of the cell and the integrity and volume of the cell wall, and it is these properties that propose the use of phase angle as a measure of cell health (Moore, Dobson, Castelllino, & Kapp, 2011). Decreased reactance is an indicator of cell breakdown or death, which allows the current to more easily traverse the cell due to decreased cell wall integrity and cell volume. This results in a decrease in measured phase angle. Conversely higher phase angles are associated with increased cell health (Moore et al., 2011). Phase angle has been shown to be decrease in the presence of infection and inflammation, volume overload in cardiac failure and end stage renal disease, in patients with HIV, and is considered prognostic in a number of cancers and in geriatric settings (Lukaski & Singer, 2011; Norman et al., 2012; Urvashi, Adam, Abigail, & Carrie, 2015). The use of phase angle as an index of cell health has also been demonstrated in the healing of chronic wounds (Lukaski & Moore, 2012; Moore et al., 2011). Phase angle has yet to be determined as a measurement of wound or patient status in acute burn injury.

1.2 Statement of the Problem

The aim of prompt, proactive control of localised oedema is to optimise the wound healing environment and to prevent burn conversion, or tissue death. The options available to the members of the burns multi-disciplinary team for the management of localised wound oedema are well described in the literature, however there is only one controlled trial investigating the effect of any of these interventions. As a result, due to the lack of evidence in the literature, therapists likely continue with methods they are familiar or most comfortable with, as no evidence exists supporting the use of one method over another for managing acute oedema through well-designed controlled trials (Edgar et al., 2011; Glassey & Phillips, 2011). One factor contributing to the lack of evidence supporting definitive oedema management interventions in this population is that there remains a lack of sensitive measures of oedema that are easy to implement, rapid, safe, and minimise wound contact and therefore the risk of infection in a patient group that experience increased pain, impaired movement and potentially difficulty cooperating with assessment (Edgar, Day, Briffa, Cole, & Wood, 2008). As a result, interventions are often applied with little objective understanding of the optimal parameters of application or efficacy (Glassey & Phillips, 2011; Mosti, 2012).

1.2.1 Objectives of the Study Program

- To establish the validity of novel electrode positions to measure hand volumes using BIS
- To determine whether BIS provides a reliable and valid measure of oedema volume change in hand burn injury
- To demonstrate the utility of BIS as the primary outcome in assessing the effectiveness of common methods of compression for managing oedema following hand burn injury
- To utilise BIS as an outcome to measure wound oedema in response to an electrical stimulation intervention
- To determine whether BIS raw variables are valid indices of wound healing in acute burn injury

1.2.2   Significance of the Study Series

The series of studies in this research program are designed to build on the previous knowledge and application of BIS in acute burn injury in a novel technique to measure oedema change and test in use with new interventions in the complex structure of the hand, to provide clinicians real-time feedback on the effectiveness of oedema management interventions.

The first aim of this research is to demonstrate the reliability and validity of BIS for measuring oedema change in the hand, especially when complicated by the location of burn wounds, which provides challenges regarding the positioning of electrodes for measuring bioimpedance. The significance of this research will provide burns therapists with an objective and easy to use measure of oedema in the hand, which is involved in more than 50% of burns that present to the State Adult Burns Unit at Fiona Stanley Hospital, and will guide interventions to appropriately manage hand burn oedema. The use of BIS guides the second part of this research program, to measure oedema with a greater sensitivity than current reference standards.

The second part of this research is a series of studies investigating interventions to provide additional evidence to support the tools and techniques available to measure and treat burn wound oedema. This results in a variety of interventions that are used, often with clinicians' preference as the only rationale and anecdotal change as the only outcome measure.

The findings of this research will aim to drive practice behaviour change by enabling therapists to routinely record oedema as an objective outcome measure using BIS, providing real-time feedback on oedema in and health status of the burn wound. This research also provides all multidisciplinary clinicians involved in burn care evidence demonstrating best practise in managing oedema following acute burn injury using BIS in clinical practice. The combination of sensitive real time measures and best practise interventions researched in this program for the assessment and management of oedema will optimise outcomes for burn injured patient.

1.3 Thesis Outline

The rationale for undertaking this study, including the research problem and its significance, are presented in the introduction and the review of the literature. The chapters following the literature review summarise the studies undertaken as part of this research series. The research program presented in this thesis comprises three studies presented in the four published papers, Chapters Three – Six. This study series was undertaken to identify optimal parameters for the assessment and management of oedema following acute burn injury.

In order to adequately measure the change in oedema in the hand, a technique was required to measure often subtle change in oedema, which guided the development of this series of studies. The first study, presented in Chapter Three, investigates the use of alternate electrode positions that would allow the use of BIS to accurately measure hand volumes in a healthy, uninjured population. Each alternate position is compared to a previously described electrode array on the dorsum of the hand and arm for measuring hand volumes (Ward et al., 2012). The results of Study One provide an understanding of the use of BIS for measuring hand oedema, which guides its use in Study Two.

The second study of this research program is presented as two papers (Chapter Four and Chapter Five). Chapter Four applies the findings of Study One to investigate the use of BIS for measuring hand oedema in a hand burn injured population. The second paper from Study Two – presented in Chapter Five – demonstrates the use and sensitivity of BIS for measuring oedema (change) in a randomised controlled trial investigating different methods of applying compression for managing hand burn oedema.

The third study in this research series is presented in Chapter Six. The impact of electrical stimulation as an intervention for improving healing in acute burn wound injury was investigated in this study. During interim data analysis it was shown to positively influence oedema. This study was therefore included in this research series for its oedema management intervention and the application of BIS in measuring different aspects of acute burn injury.

The studies in this research program were conducted at Fiona Stanley Hospital in Western Australia, within the State Adult Burns Unit. Wound management within the State Adult Burns Service is undertaken using a multidisciplinary approach. Oedema management is recognised as a fundamental part of wound management due to its deleterious effect on the zone of stasis, and is performed using a number of modalities, including elevation of the affected limb using bed mechanics, elevating pillows or foam blocks and prototype axilla boards for inpatient admissions, and elevation is educated through the use of pillows and active positioning for patients managed in ambulatory clinic.

The studies in this research program will encourage and guide clinicians involved in burn injury management with interventions for managing acute burn wound oedema, which is often applied according to therapists' preference. This research provides reliable and valid measures for measuring fluid change in complex structures such as the hand and provides a novel method of measuring wound healing in a population where wound healing is influenced by the quality of proactive oedema management.

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CHAPTER 2   **REVIEW OF THE LITERATURE**

2.2 Introduction

This review of the literature provides an overview of the mechanisms of oedema formation following burn injury and its impacts on the outcome for the burn patient. A burn wound is a very susceptible to its initial management, and the role of oedema and its management on burn wounds is discussed in this review. Sensitive and reliable measures of oedema provide clinicians with feedback on patient's response to management interventions. The pathophysiology of a burn injury and oedema is discussed, and its deleterious effects on the burn wound when uncontrolled. The effects of uncontrolled oedema on the hand are then reviewed. Oedema management techniques that are available to the clinician are discussed, and then a review of different measurement tools is provided, with an overview of bioimpedance spectroscopy and how it may be implemented in a burn injury population.

2.3 Burn injury

Burn injury is complex, with an evolving clinical manifestation, due to the mechanism of the injury, the size of the injury, and the time to receive appropriate first aid (Kao & Garner, 2000; Wood et al., 2016). The aetiology of the injury is a predictor of the severity of the injury, due to heat transfer from a thermal source, the type of chemical involved, or the depth of penetration due to exposure to electrical current (Lund et al., 1992; Wolf et al., 2018). The depth and area of a burn injury are important factors relating to the severity of the injury, which results in increased volume of tissue loss, and therefore impacting recovery time and the choice of interventions. Traditional thinking was that there is a systemic physiological involvement with major burn injury greater than 20% total body surface area (TBSA) (Demling, 2005; Kao & Garner, 2000), however recent animal studies demonstrate an increased immune response with minor burn injury, which leads to sustained systemic changes (Stevenson et al., 2017; Valvis et al., 2015). The initial insult to the tissue results in a burn wound that is described in three zones – the central zone of necrosis or coagulation, which is dictated by the mechanism of injury (Figure 1) (Jackson, 1953). The zone of hyperaemia is reflective of the body's natural response to injury. The zone of stasis is that area that is may be salvaged through the proactive management of oedema, but is vulnerable to poor management, which will lead to burn wound conversion, or a worsening of the central zone of necrosis (Figure 2) (Shupp et al., 2010).

Figure 1: Jackson's zones of burn injury (Hettiaratchy & Dziewulski, 2004)
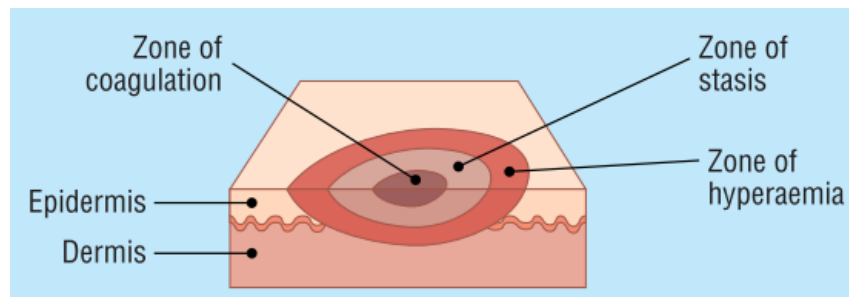
Figure 2: Burn wound conversion (Hettiaratchy & Dziewulski, 2004)
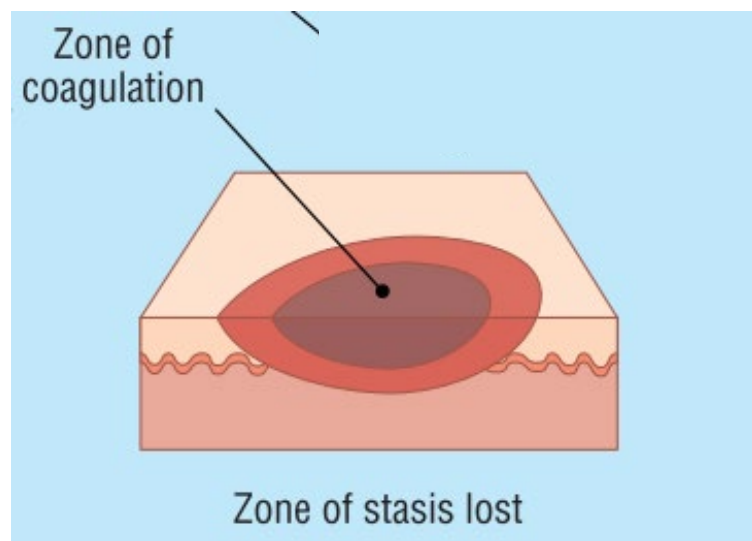
2.4 Burn wound oedema

Oedema is the accumulation of excess fluid, primarily in the extra-cellular compartment, and forms due to an imbalance in the rate of oedema production and its return to the systemic circulation via the lymphatic or venous circulation, due to an imbalance in the effective capillary pressure, an obstruction to the flow of oedema, or by weakness or paralysis in the musculature of the extremity (Palmada et al., 1999; Villeco, 2012). Oedema following burn injury is dependent on the mechanism of the burn injury, the size of the burn injury and the depth of the wound (Demling, 2005; Lund et al., 1992). Burn wound oedema is localised in the wound and surrounding the burned tissues in minor injury (Kao & Garner, 2000).

With increased size of injury, there is an increase in vascular permeability in the immediate post-burn period (Edgar et al., 2011), as a result of the release of cytokines and other inflammatory mediators in major burn injury (Kao & Garner, 2000) caused by the activation of toxic mediators (Allgöwer et al., 2008; Singh et al., 2007). Oedema as a result of burn injury is unique – increase vascular permeability due to burn injury Burn injury affects all of the Starling equation variables that influence transvascular fluid filtration change significantly in the direction required to increase the rate of vascular permeability (Wurzer et al., 2018). Resultant burn wound oedema is rapid in its onset – tissue fluid content doubles within the first hour of injury, however peak oedema volume occurs 12-24 hours post injury (Demling, 2005; Wurzer et al., 2018).

The post burn inflammatory response is mediated by the release of inflammatory cytokines following burn injury. These cytokines are proteins with autocrine and endocrine functions, including the mediation of immune functions, angiogenesis and cell proliferation, and levels of these cytokines remain significantly elevated in the week post injury (Gauglitz et al., 2008). The release of other inflammatory mediators lead to ischaemia, and therefore tissue loss, within the zone of stasis due to thrombosis in microvasculature and the release of proteins increasing capillary leak and subsequent oedema (Demling & LaLonde, 1990; Robson et al., 1979). Elevated cytokine synthesis, while precipitating oedema, also results in hypermetabolism and catabolism, which are associated with major burn injury, and these combined lead to an increased risk of organ dysfunction and failure (Gosling et al., 1996; Wolf et al., 2014).

2.4.1   Burn wound conversion

The zone of stasis is that area surrounding the central zone of necrosis (or coagulation), and is vulnerable to impaired perfusion, which may lead to the zone of necrosis extending in what is known as burn wound conversion (Jackson, 1953). Burn conversion increases the area and depth of the wound, resulting in an increased volume of tissue injury, and increasing the likelihood of scarring, and the need for acute surgical reconstruction of the skin (Singh et al., 2007). Stasis is rapid in onset and associated with oedema accumulation, and is shown to reverse as capillary circulation returns, which aids in the mobilisation of stagnant intravascular material

away from the injury site, and a restoration of vascularisation and circulation to the skin (Zawacki, 1974a). Conversion of the zone of stasis is multifactorial: local wound factors include persistent oedema, infection, circumferential eschar and wound dehydration; while systemic factors relate to impaired wound perfusion, metabolic derangement and the patient's past medical history (Singh et al., 2007; Zawacki, 1974b).

Wound oedema within the extra-cellular space limits the flux of toxic metabolites, and also limits the exchange of vital nutrients such as oxygen, between the circulation and damaged tissues by increasing the perfusion distance between the capillary bed and the skin (Edgar et al., 2011; Gosling et al., 1996; Knisely et al., 1969). Reductions in tissue oxygenation have been demonstrated within the oedematous zone compared to those in normal tissue in the early stages of burn oedema development (Remensnyder, 1972). This is further complicated by an increase in the oxygen consumption of the wounds immediately post injury (Niinikoski et al., 1972). Wound respiration slows in hypoxic environments, resulting in reduced collagen synthesis and therefore impaired wound healing (Heughan et al., 1971). The reduced oxygen environment in the zone of stasis also increases the risk of infection if not corrected (Hunt et al., 1975).

2.5 Hand burn injury

Greater than 55% of all burn injury presenting to the State Adult Burns Unit at Fiona Stanley Hospital involves a portion of the hand, and the hand is involved in more than 80% of severely burned patients (Kamolz et al., 2009; Kreymerman et al., 2011; Pan et al., 2015). This may be attributed to the fact that the hands are generally uncovered during activities of daily living, and in the event of industrial and similar accidents, the hands are often exposed to trauma in a reflexive defensive posture to protect the face and body (Kamolz et al., 2009; Newmeyer & Kilgore, 1977; Pan et al., 2015). The architecture and biomechanics of the hand allows the performance of "tremendous agility and dexterity" in the performance of activities of daily living (Collings, 1999). The complexity of the biomechanics and movements of the hand, coupled with the hands' susceptibility to burn injury and positioning relative to the burn agent during the performance of functional daily activity, necessitates optimal management to avoid severe long term negative sequelae (Abu Sittah et al., 2011; Cartotto, 2005; Collings, 1999).

2.5.1 Oedema following hand burn injury

The skin on the volar surface of the hand is thick, specialised and well protected, and tightly adhered to the palmar aponeurosis (Cartotto, 2005; Kamolz et al., 2009; Newmeyer & Kilgore, 1977). The glabrous skin covering the palm of the hand and digits is characterised by the density of cutaneous innervation and high sensitivity mechanoreceptive units required for the daily performance of complex combinations of motor and sensory tasks (Johansson & Vallbo, 1979; Kamolz et al., 2009). Conversely, the skin on the dorsum of the hand and digits is loose and mobile, and allows a large amount of movement both proximally to distally, and also axially across the breadth of the hand (Collings, 1999). This skin laxity and mobility results in oedema formation in the hand developing preferentially into the tissues of the dorsum of the hand and fingers (Cartotto, 2005). Oedema formation increases tension in the digital extensor system resulting in the characteristic intrinsic minus position - hyperextension of the metacarpal-phalangeal joints, flexion of the finger inter-phalangeal joints and the thumb contracted into adduction (Figure 3) (Moore et al., 2009; Palmada et al., 1999; Sorenson, 1989). This is the characteristic post-burn position of comfort, including forearm pronation and wrist flexion, due to decreased pain, which becomes the position of contracture if oedema is poorly managed and allowed to organise (Boswick, 1974; Moore et al., 2009). The oedema forces the metacarpals into flexion at the carpo-metacarpal joints, and hyperextends the metacarpal-phalangeal joints (MCPJ), effectively re-orienting the insertion of the interossei muscles dorsally, thereby placing the intrinsic muscles of the hand at a biomechanical disadvantage and resulting in MCPJ flexion weakness (Collings, 1999; Lowell et al., 2003; Schreuders et al., 2007). Furthermore, pro-inflammatory states are also associated with increased nociception, with increased volume of oedema correlated with immediate spontaneous nociceptive response (Chesler et al., 2005). Fortunately this does not result in long-lasting hypersensitivity (Chesler et al., 2005).

Figure 3: Intrinsic minus position (claw hand deformity) characterised by MCPJ extension and PIPJ flexion (image reproduced with permission from Winthrop Professor Fiona Wood).

2.6   Anatomy of oedema management

The management of oedema following burn injury is widely described in the literature, however there is a paucity of controlled studies investigating the outcome of oedema management strategies in this population (Edgar et al., 2011; Lowell et al., 2003). Persistent oedema beyond the first 48 to 72 hours post injury potentially results in its organisation - the protein rich fluid leads to thickening of the tissues and excess collagen deposition, which may lead to increased scar formation, and joint contractures (Puddicombe & Nardone, 1990; Sorenson, 1989). Proactive management of oedema reduces the barrier to and restores the exchange of nutrients within the zone of stasis, which reduces tissue hypoxia and therefore wound ischaemia, and minimises wound conversion (Remensnyder, 1972). The capillary network is responsible for the transportation of oxygen and nutrients, and carbon dioxide and waste product exchange throughout the body, as the capillaries are the only permeable component of the vascular system, a role which is essential for body tissue survival (Palmada et al., 1999). The lymphatic system assists in maintaining correct interstitial fluid levels through the process of transudation, enabling the return of excess fluid, proteins and non-soluble fats to the blood, as they are too large to resorbed by the venule portion of the capillaries (Härén & Wiberg, 2006). It is estimated that 90% of the fluid that is filtered out at the arterial end of the capillary is reabsorbed at the venous end, with the remaining fluid removed via the lymph vessels (Guyton & Hall, 1997; Hall, 2016). Approximately 2-3 litres of fluid is returned to the blood per day (Hall, 2016; Lane, Worsley, & McKenzie, 2005). Under normal

conditions, the transport capacity of the lymphatic system is 10 times greater than the physiological lymphatic load (Hettrick, 2003). The superficial lymphatic plexus is positioned within the dermal-epidermal junction, increasing its susceptibility to damage, especially following burn injury (Hettrick, 2003). The lymphatic capillaries, which are part of the superficial lymphatic plexus, connect to lymphatic pre-collectors in the deeper layer of the dermis, which then converge and exit through a larger superficial collecting vessel within the subcutaneous fat (Suami & Scaglioni, 2018).

Deep partial thickness and full thickness burn injury therefore increases the risk of damage to these structures, resulting in further impairment in oedema resorption and transport, and prolonging the oedematous response observed in deeper injuries (Demling, 2005; Hettrick, 2003). Further complications arise when considering the anatomy of the hand, where tendons, joints and blood vessels are positioned very close to the skin surface, when compared to other parts of the body, which makes these structures additionally vulnerable to damage from burn injury (Kamolz et al., 2009). Additionally, the effect of reconstructive surgery to remove and repair burned tissue creates another inflammatory response, which may further stress oedema transport, and should be taken into account when treating the post-operative wound (Szpaderska & DiPietro, 2005).

2.7   Oedema management principles

Techniques utilised in the clinical setting to manage peripheral oedema include a combination of elevation and positioning, compression, and active range of movement exercise (Didem et al., 2005; Park et al., 2016; Salisbury et al., 1973). Other interventions reported to improve oedema following hand burn injury include the use of electrical stimulation as an adjunct therapy, and the use of splints to optimise hand position and minimise oedema formation (Dewey et al., 2011; Omar et al., 2004).

2.7.1   Compression

External compression for oedema management in acute burn injury is frequently applied by burns therapists, although it is an intervention which is applied with little objective understanding of the optimal parameters of application or efficacy (Glassey & Phillips, 2011; Lowell et al., 2003). The use of external compression reinforces

tissue hydrostatic pressure by providing a counter-pressure to working muscles, thereby compensating for the elastic insufficiency of oedematous tissue (Palmada et al., 1999; Villeco, 2012). This improves the efficiency of circulation by promoting venous and lymphatic flow by establishing a pressure gradient from distal to proximal, as tissue fluids flow is dependent on hydrostatic pressure, pressure and resistance differences due to vessel calibre and constriction, blood viscosity and plasma composition, and cell malleability (Brennan & Miller, 1998; Miller et al., 2017; Palmada et al., 1999). Compression is also thought to limit the available potential space in which oedema can accumulate, by increasing the Starling equation variable interstitial fluid pressure (Villeco, 2012).

Compression in burn injury has been investigated for the management of hypertrophic scarring and in chronic oedema, however there are no trials investigating its use in the management of acute oedema. Coban is a semi-adherent cohesive bandaging system that can be used to create a compressive force for oedema control, which is secure, non-adherent to underlying tissues, protective, adaptable to any hand size and shape, permits normal mobility and activity, and can be wrapped directly over dressings (Glassey & Phillips, 2011; Ward et al., 1994). A case-control study investigating the use of Coban to manage post-operative hand burn oedema demonstrated improved reduction in oedema, increased total active range of motion, grip strength and hand function when compared to the (non-dominant) control hand (Lowell et al., 2003).

Lymphatic clearance has been shown to increase with the application of external pressure, with a nonlinear and rapid rise in lymph flow per unit tissue volume as applied external pressure increased, with external pressures of 30 mmHg and 45 mmHg increasing lymph clearance compared to uncompressed tissues (Miller & Seale, 1981). At externally applied pressures of 60 mmHg, the subcutaneous extracellular matrix is excessively deformed, resulting in the collapse of some terminal lymphatic vessels and associated with decreased lymph clearance. External pressures of 75 mmHg caused complete lymph vessel collapse in all animals (Miller & Seale, 1985). Garment pressures of between 30 mmHg to 60 mmHg are prescribed for the management of lymphedema (Brennan & Miller, 1998). External pressures of less than 30 mmHg on the forearms are recommended as optimal for the control of

chronic lymphoedema, to counteract hydrostatic intravenous and intravenular pressures (Partsch et al., 2011).

The majority of studies investigating the use of compression fail to objectively measure the pressure provided by the intervention, which is unique in medical literature as no pressure dosage is prescribed by these studies (Mosti, 2012; Partsch et al., 2011). In lower limb bandaging, a spiral application of Coban, with 50% overlap, was shown in an experimental model to exert a mean pressure of 23.8 mmHg (range 9-40 mmHg) (Ruckley et al., 2002). In a healthy volunteer, pressures exerted by different methods of compression bandaging over the lower limb, showed that simple spiral application of Coban exerted an average pressure of 28.5 mmHg, while a figure-of-eight application of Coban exerted an average pressure of 20.7 mmHg (Lee et al., 2006). Coban also demonstrated reduced pressure compared to other cohesive bandages investigated, and less variation in pressure between leg elevation and when measured in standing (Lee et al., 2006).

2.7.1.1 Compression and hand oedema

Unchecked oedema in the hand results in an increase in the effort required to achieve digit flexion, and the application of external compression in this situation further increases the force required to achieve finger flexion (Buonocore et al., 2012). This has consequences for therapists managing the hand following microsurgical tendon repair. In the management of oedema following burn injury, externally applied compression needs to be effective in oedema control, but should also be applied in such a way to ensure the least amount of movement restriction and function. Glassey and Phillips (2011) compared the application techniques using Coban in a cylindrical and spiral wrap to the thumb, index and middle fingers in 25 non-injured individuals. While both methods resulted in a statistically significant reductions in the flexion of the involved joints in healthy individuals (3.4˚ to 5.0˚, p=0.003 to 0.033), it was thought that the functional effect of the reduction was likely not of clinical importance (Glassey & Phillips, 2011). While these reductions may affect hand function with the compression in situ, the transient nature of oedema post burn injury minimises the duration of inconvenience or discomfort for the patient.

Chapter Five explores the gaps identified in the literature above, and in particular, the effectiveness of different methods of compression application for managing acute hand burn oedema.

2.7.2   Active range of movement

In addition to compression, early range of movement through the prescription of a well-defined exercise program assists in maintaining the normal muscle-pump mechanism for returning venous blood and lymphatic fluid to the heart (Abu Sittah et al., 2011).

Lymphatic fluid will not flow in a resting limb (Sorenson, 1989). The lymphatic capillaries (initial lymphatics) fill only when there are perturbations in the tissue pressures, such as due to forces including muscle contraction compressing tissues against the skin, or externally applied compression (Casley-Smith & Casley-Smith, 1992). The flow of lymphatic fluid is independent of the resting volume of the lymphatic capillary vessels (Schmid-Schonbein, 1990). Similar to the venous system, lymphatic fluid flow from the initial lymphatics to the contractile lymph vessels is dependent on skeletal muscle contraction, external compression and pressure changes due to respiration and arterial contraction and limb elevation (Härén & Wiberg, 2006; Lane et al., 2005; Schmid-Schonbein, 1990; Sorenson, 1989). Gentle skin massage, also known as effleurage, and passive limb movement have also been demonstrated to increase the flow of lymph fluid (Schmid-Schonbein, 1990).

Cardiovascular exercise stimulates the lymphatic system, through increased respiration rates and therefore diaphragmatic activity, which evokes pressure changes and fluid shifts within the thoracic duct due to its anatomical course through the diaphragm (Brennan & Miller, 1998). An immediate five-fold increase in lymph flow is demonstrated with the commencement of cardiovascular exercise for the first 10-15 minutes of steady-state exercise, which then gradually decreases to approximately 130% above baseline for the remainder of the exercise period (Coates et al., 1993; Lane et al., 2005). Normal physiological responses to exercise, including increased cardiac output, sympathetic nervous system activity, skeletal muscle contractions, and respiration, are the same mechanisms that assist with lymph formation and propulsion, where increased capillary filtration and interstitial fluid pressure occurs during exercise, due to increased blood flow and capillary surface area (Lane et al., 2007; Mohsenin & Gonzalez, 1984).

2.7.2.1   Active movement in the hand

In the dependent upper limb at rest, the post-capillary blood pressure facilitating venous return is less than 15 mmHg, whereas the hydrostatic pressure opposing venous return is approximately 35 mmHg (Simons et al., 1996). Active movement is therefore required to augment venous return (Jasiński et al., 2005). The venous systems of the hand are the superficial palmar, deep palmar, and the dorsal veins, which act independently, and are facilitated by palm compression, isometric intrinsic muscle contraction, and dorsal compression respectively (Simons et al., 1996). Increased venous blood flow velocity was shown to occur during activation of each venous system of the hand independently, via ultrasound of the cephalic and ulnar collateral veins. Concurrent activation of all three venous pumps during fist clenching resulted in the greatest mean increase in blood flow velocity, while digit abduction prior to fist clenching resulted in significantly increased mean blood volume flow compared to fist-clenching alone (Simons et al., 1996).

2.7.3   Elevation

Recommendations for the management of oedema of the upper limb include elevation as one part of a combination of therapies (Miller et al., 2017). Postural changes have been demonstrated to affect segmental blood volumes. When the body changes position from supine to standing, hydrostatic pressure and the effects of gravity decrease thoracic blood volume, while increasing lower limb volumes (Smith et al., 1987). Capillary pressures in the fingers remain almost constant with elevation of the hand, however, there is an increase in capillary pressure with positioning of the hand below the level of the suprasternal notch, which is incremental with increased hydrostatic pressure (Landis, 1930), which indicates that increased volumes in the upper limb will occur without elevated positioning. There is no effect on upper limb volume with repositioning via head up elevation from supine to an angle of 14˚ (Boland & Adams, 2000). Elevation of the upper limb to 30˚ whilst lying supine, however, for a period of 2 hours was shown to result in a reduction in hand and forearm volume of 51ml (±27ml) compared to a control group, which remained resting supine with the arms resting by the side (Boland & Adams, 1998). In a burn patient population, there is no evidence that elevation of the arm during the first 48 hours post injury has an effect on hand and wrist circumference (Salisbury et al., 1973). Significant reductions in hand and wrist circumference were achieved with

elevation of the affected limb overnight between days three to seven post injury, although this is consistent with the natural course of burn wound oedema resorption (Demling, 2005; Salisbury et al., 1973).

2.7.4   Electrical stimulation

The use of electrical stimulation in wound populations has demonstrated improvements in the rate of healing in chronic wounds (Gardner et al., 1999), and was investigated in acute burn wounds in animal models in the late 1970s (Dueland et al., 1978). The mechanisms by which electrical stimulation affects wound healing include improved angiogenesis and nutrient flow to the wounds (Kawasaki et al., 2014; Polak et al., 2014; Ud-Din et al., 2015), and improved DNA synthesis within the wound (Bourguignon & Bourguignon, 1987). In burn wounds, electrical stimulation has been shown to increase the rate of healing, with decreased bacterial colonisation compared to control wounds (Ibrahim et al., 2019). There is a natural potential voltage difference between two points on human skin, known as a 'skin battery', and between the stratum corneum and the dermis of -23mV in healthy volunteers (Foulds & Barker, 1983). This skin battery is produced by electrical activity in exocrine sweat glands (Wilcott, 1966). Wounds in the skin short circuit the skin battery, and result in an ionic *current of injury*, which increases the migration of neutrophils and macrophages (Orida & Feldman, 1982), while also stimulating fibroblasts (Bourguignon & Bourguignon, 1987; Cruz et al., 1989). Different modes of electrical stimulation have been demonstrated to improve chronic wound healing – a meta-analysis of stimulation in chronic wounds showed transcutaneous electrical nerve stimulation (TENS) improved healing by 10.87% per week over the control wounds, continuous direct current 12.59% per week and pulsed current 15.5% per week (Gardner et al., 1999).

Electrical stimulation has also demonstrated potential to decrease oedema following trauma. By eliciting involuntary muscle contractions and thereby intermittent venous and lymphatic compression, electrical stimulation is proposed to assist venous and lymphatic flow, which may reduce oedema (Burgess et al., 2019). Reductions in oedema have been demonstrated with electrical stimulation in patients following ankle sprain (Man et al., 2007); complex regional pain syndrome of the upper limb (Devrimsel et al., 2015); and in the upper limb following cerebro-vascular accident (Faghri, 1997). In a burn wound population, electrical stimulation was investigated in additional to traditional physiotherapy intervention in a group of conservatively managed hand burn injuries. Compared to the control group that received only physiotherapy and standard dressings, the addition of electrical stimulation decreased hand volumes at days seven and 15, while improving total active movement of the hand at the same timepoints (Omar et al., 2004).

Adverse effects of electrical stimulation have been reported in the literature, where full thickness burns were inflicted in 1) a patient post knee arthroplasty following the use of interferential current therapy (Ford et al., 2005); 2) in two spinal cord patients receiving functional electrical stimulation (Balmaseda et al., 1987); and 3) in a patient receiving TENS and interferential current therapy over a lower leg injury requiring initially external fixation, followed by definitive internal fixation and a medial gastrocnemius flap (Satter, 2008). The common finding reported across all of these case studies was that the electrical stimulation modalities were applied to tissues with decreased sensation in all patients.

2.8 Oedema measurement techniques

The assessment of swelling following burn injury is complicated by the presence of wounds and dressings, in a patient cohort who experience significant pain, impaired movement, and may require analgesia and other medications that result in modified behaviour. Traditional measures of volume, such as water displacement volumetry or circumferential limb measures are challenging in the presence of open wounds with respect to infection control practices and pain due to wound contact (Pellecchia, 2003), and circumferential measures lack reliability and sensitivity to measure fluid changes in a burn wound population (Edgar, Briffa, et al., 2009; Edgar et al., 2014). As a result, oedema is most often assessed clinically by noting loss of skin creases, areas of visible swelling with palpation, and loss of function (Stanton et al., 2000).

Measurements of limb volume are considered indirect measures of oedema, however, as the extracellular space, which is primarily where oedema collects, accounts for approximately 25% of the total normal limb volume (Cornish, 2006; Czerniec et al., 2011).

2.8.1 Water Displacement Volumetry

Water displacement volumetry, also called the volumeter method, is based on Archimedes principle of water displacement, in which displaced water is measured to determine oedema volume, following immersion of the patient's hand into a water vessel (Palmada et al., 1998), and is recognised as the 'gold standard' (Dewey et al., 2007; Taylor et al., 2006) or 'reference standard' (Hidding et al., 2016) for measuring hand and limb volumes. Its accuracy is within 1% (approximately $\pm$ 5 ml) for measuring hand size (Post et al., 2003; Waylett-Rendall & Seibly, 1991). Variations due to slight changes in water temperature and within-day intra-individual volumes are within the same limit (Grisbrook et al., 2015; Post et al., 2003), although in a burns population there was a 2.6% variation in upper limb volumes (Edgar et al., 2014). In burns populations, hand volumetry testing had an intratester SEM of 7.70mL (Dewey et al., 2007), while in whole arm volumetry the minimum detectable difference of 96.6mL and the SEM was 28.9mL (Edgar et al., 2014). These SEM for water displacement testing in burns patients are comparable to other populations (Farrell et al., 2003).

Although water displacement volumetry has been shown to be both reliable and valid, it has several drawbacks and potential sources of error when considering its clinical efficacy. It is a time-consuming process that requires correct apparatus set-up (Maihafer et al., 2003), and requires a compliant and cooperative patient (Gjorup et al., 2010). The water temperature should remain consistent during the measurement and subsequent re-evaluations (Maihafer et al., 2003), with temperatures ranging from 20-32°C not affecting test-retest volumes (Boland & Adams, 1996).

2.8.2 Circumferential and figure-of-eight measures

Circumferential measurement of the hand and wrist using a tape measure is another method available for the clinical evaluation of oedema, being easy to perform and time efficient, and provide the advantage of determining the distribution of the oedema, which guides treatment technique and efficacy (Boiselle Howard &

Krishnagiri, 2001; Stanton et al., 2000). Circumferential measures are an indirect measure of limb volume, but are strongly correlated with water displacement, are better tolerated by patients and there is a reduced measurement error where patients find it difficult to maintain their arms in position to adequately measure water volumes (Ridner et al., 2007; Stanton et al., 2000). Circumferential measures of the hand record proximal phalanx of each digit, the hand at the level of the digit of the metacarpal heads, and the wrist at the volar wrist crease has been demonstrated to measure the effect of oedema treatments in the upper limb (Boiselle Howard & Krishnagiri, 2001), and is modelled on circumferential measures for the arm that are well described in lymphoedema populations (Karges et al., 2003; Megens et al., 2001). The variations in hand circumference measured by a single tester ranged from 1.6 to 4.5cm (Llanos et al., 2021). Arm circumferential measurements are used to calculate volumes using different geometric volume formulae, such as those for cylinders or a frustrum (truncated cone), with these calculations based on anatomical landmarks being reliable and valid compared to volumetry measures (Taylor et al., 2006). The smallest detectable change for arm circumferential measures was 3.7-7.1mm, the variability range was 13-37mm (Hidding et al., 2016).

The figure-of-eight measure is an adaptation of circumferential measures of the hand, with the tape measure crossing diagonally over the dorsal aspect of the hand, where oedema preferentially forms (Maihafer et al., 2003). Figure-of-eight measurement is reliable and valid compared to water displacement for measuring hand size in uninjured populations (Maihafer et al., 2003) with high intratester (Pellecchia, 2003) and intertester (Llanos et al., 2021) reliability. It has also been demonstrated to be reliable and valid in orthopaedic patients (Leard et al., 2004) and in a hand burn population (Dewey et al., 2007). A limitation of the figure-of-eight measure is that reference landmarks may potentially be unidentifiable in oedematous hands and wrists (Maihafer et al., 2003), and that it lacks standardisation of volume calculation formulae used, and therefore only provides an estimate of the volume of the hand and is not interchangeable with volumetric measures, which limits its ability to compare changes in volume between patients in clinical practice or for research purposes (Edgar et al., 2014). The standard error of measurement for figure-of-eight measures of the hand for a single rater ranged from 2.6 to 7.1mm, while across multiple testers the variability was 2.8 to 6.0mm (Llanos et al., 2021).

2.8.3 Bioimpedance spectroscopy

Bioelectrical impedance analysis (BIA) encompasses a number of techniques that are available to measure body composition, due to the inverse relationship between body water content and impedance (or resistance to current flow) (Kyle et al., 2004a). Single-frequency BIA measures impedance at 50kHz to measure a combination of intra-cellular (ICW) and extra-cellular water (ICW) through the use of mixture theories and empirical equations, while multi-frequency BIA utilises similar equations but measures at multiple frequencies to predict fat free mass, total body water, ICW and ECW (Kyle et al., 2004a). Bioimpedance spectroscopy (BIS) measures body composition through recording 256 discrete impedance measurements over a frequency range from 4-1000kHz and fitting the measured data to mathematical models and mixture equations, known as Cole-Cole modelling, that demonstrates a relationship between the impedance and body fluid compartments (Cole & Cole, 1941; Cornish et al., 1996; Kyle et al., 2004a). Current flow through the cells in the body is frequency dependent (Figure 4) (Buendia et al., 2015; Matthie, 2008). A frequency of 50kHz is recognised as the point where the current passes through both the intra- and extra-cellular water (Ward et al., 1992). With decreasing frequencies close to zero Hz (a direct current), the current passes exclusively through the extracellular space, as the cell membrane acts as an insulator (Ward et al., 1992). This allows the calculation of the volume of the fluid in the extracellular space, which is primarily where oedema forms (Cornish, 2006). The impedance value of the extracellular fluid, known as R_0, and the impedance of the total body water, known as $R\infty$, are extrapolated values determined using Cole-Cole modelling, due to the practical limitations of using direct current and very high frequency alternating current in the human body (Cole & Cole, 1941). The measured impedance of the intracellular fluid is known as R_i.

Figure 4: Current flow through the tissues at differing frequencies (Matthie, 2008)
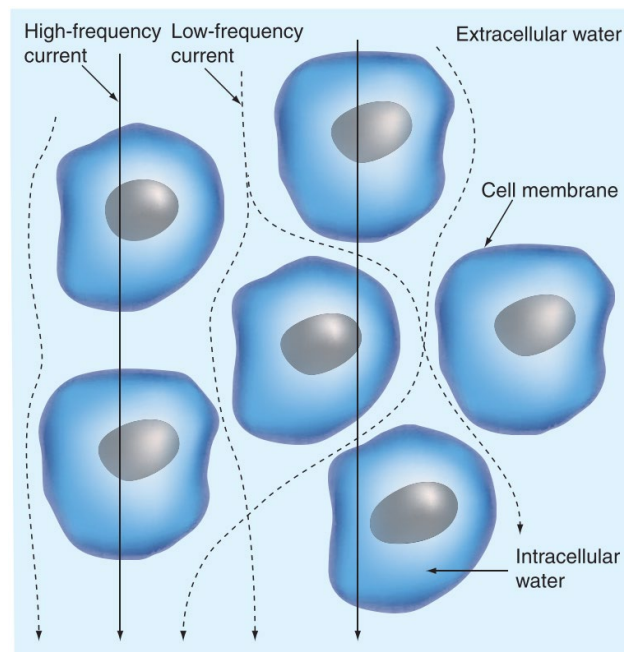
The measured impedance to the flow of the current is inversely proportional to the volume of the fluid content, with higher volumes giving lower impedance values (Svensson et al., 2014). The extracellular water is primarily related to fluid volume status, while the intracellular fluid provides information about the body cell mass (Matthie, 2008). BIS was shown to be sensitive and reliable for measuring whole body fluid shifts in acute burn injury (Edgar, Briffa, et al., 2009). BIS is sufficiently sensitive to detect latent or pre-clinical volumes of lymphoedema, where there are no visible changes to the upper limb but the patient may report differences in sensation, due to its ability to selectively measure extracellular fluid, rather than overall volume of the affected limb (Ward, 2006; Ward et al., 2009b).

The measurement of limb volumes of extracellular water using BIS has been demonstrated with high reliability, sensitivity and specificity in lymphoedema patients, with protocols established to measure the impedance from the wrist to shoulder (Czerniec et al., 2011; Svensson et al., 2014; Ward et al., 2009b). In the same study, Czerniec et al. (2011) demonstrated that BIS is able to measure localised lymphoedema in patients with clinically diagnosed lymphoedema, but whose whole-arm ratio was below the diagnostic threshold, with a higher degree of sensitivity than limb volume measures (seven patients out of seven diagnosed by BIS with at least

one 10cm segment ratio above the diagnostic threshold, compared to two patients out of seven with only one 10cm segment above the threshold as measured by perometry.

The ability of BIS to measure localised extracellular impedance within well-defined body segments minimises the interference of effectors including hydration and body fat percentage (Kyle et al., 2004a). Ward et al. (2012) utilised this ability to develop a technique to measure the localised volume in the dorsum of the hand. This study investigated bioimpedance using sense electrodes placed at the third metacarpal-phalangeal joint and the wrist in line with the ulnar styloid. Using the technique, Dylke et al. (2014) found that BIS was sensitive to small changes in hand volume introduced by a postural change. The hand was initially measured in a horizontal position with the arm extended and the shoulder flexed to 90°. The postural change was achieved by elevating the hand above the head with the shoulder abducted to 90° and the elbow flexed to 90°. The repeat measure of BIS was taken in this position after three minutes, and detected impedance changes in the dorsum of the hand that were not detected using opto-electrical perometry scanning (Dylke et al., 2014).

BIS has also been shown to be sensitive to changes in oedema within wounds. In a proof-of-concept study, bioimpedance measures were obtained prior to and following injections of normal saline in the forearm of healthy individuals, with sense electrodes located at 45° vectors around the measurement area. Bioimpedance was sensitive to detecting a change of 5Ω per millilitre of injected saline, which indicates that bioimpedance devices with a sensitivity of measurement of 0.1Ω would be able to detect changes in wound oedema of as little as 20µL (Ward et al., 2013). These findings were reproduced in burn patients, with BIS proving to be a reliable and valid measure of oedema change in wounds measured at two timepoints, and compared to circumferential limb measures (Kenworthy, Grisbrook, Phillips, Gittings, et al., 2017)

The guidelines for the application of BIS state that there should be no wounds or lesions at the site of the electrodes, and where wounds preclude the positioning of electrodes, the site of the electrodes should be changed (Kyle et al., 2004b). The use of alternate electrode positions has been investigated for the measurement of whole body and segmental upper and lower limb BIS in non-injured (Grisbrook et al., 2015) and burn-injured populations (Kenworthy, Grisbrook, Phillips, Gibson, et al., 2017). These studies demonstrated that alternate electrode positions on the palmar surface of

the hand, and volar wrist, provided comparable measures of whole body and upper limb segmental BIS to standard tetra-polar electrode positioning on the dorsum of the hand and wrist.

Chapter Three investigates the reproducibility of measured values when alternate electrode positions are used for measuring hand volumes in a non-injured population

Chapter Four utilises these alternate electrode positions and investigates their applicability and accuracy in a burn-injured population

2.8.3.1 Phase angle

When measuring body composition using bioimpedance, the capacitance of the cell related to cell membrane structure and function causes the flow of the electrical energy through the cell to lag behind the voltage, which results in a phase shift in the current waveform (Lukaski & Singer, 2011). This delay is known as the Phase Angle, and is calculated as the arc tangent of reactance (Xc) / resistance (R), and is measured in degrees (Lukaski & Singer, 2011). It is the characteristic of current lagging behind the voltage as it passes through the cell membrane which provides the hypothesis that Phase Angle is an indicator of cell health. Reactance is an indicator of cell volume and membrane mass and function: the healthier and thicker the cell membrane, the greater impedance to current flow, which leads to a larger phase angle (Lukaski & Moore, 2012). Decreased phase angle has been associated with poor prognosis in a number of cancer populations, as well as HIV/AIDS, liver cirrhosis, dialysis, pulmonary impairments and sepsis (Moore et al., 2011; Mulasi et al., 2015; Norman et al., 2012; Urvashi et al., 2015). Significantly lower nutritional and functional status, decreased quality of life, and increased mortality were associated with phase angles less than the fifth reference percentile in tumour and leukaemia patients, and phase angle was stronger predictor of survival at six months than malnutrition and impaired functional status (Norman et al., 2010), indicating potential for diagnosis in chronic disease states. Improved phase angle has been shown to occur with healing of chronic wounds (Lukaski & Moore, 2012). Phase angle has been investigated as a measure of wound healing in acute burn injury, however it was not shown to be associated with wound healing markers, due to a small sample size in the wound

healing categories, and a lack of sensitivity of the markers of wound healing used in the study (Kenworthy, Phillips, et al., 2017).

Chapter Six investigates the effects of Electrical Stimulation as an intervention to improve wound healing in acute burn injury, using Bioimpedance spectroscopy, and specifically Phase Angle, as a primary outcome measure.

2.8.4 Other measures

There are a number of other methods that may be used to measure oedema, however these lack feasibility in the acute burn setting due to the time required to perform the testing, a lack of accessibility to the equipment, and expense (Edgar et al., 2014). Optoelectronic limb volumetry, performed using a Perometer, is a 3-dimensional laser scanning system used for the measurement of limb circumference and volumes, and is comparable to circumferential limb measures for the measurement of limb volumes (Stanton et al., 1997). The Perometer requires that the patient hold their arm still in an abducted position, which may be painful for patients with burn injury, potentially leading to measurement error due to movement. Perometry has been used as a reference in many studies of BIS in lymphoedema populations (Czerniec et al., 2011; Dylke et al., 2014; Ward et al., 2009a). Computed Tomography (CT) has been used to assess arm and leg swelling, and additionally allows the cross-sectional area of a limb to be determined, including the subcutaneous and muscle compartments, but exposes the patient to radiation, as does dual energy X-ray absorptiometry (DEXA), which allows the study of soft tissue composition and bone mineral density (Stanton et al., 2000). Magnetic Resonance Imaging (MRI) has been compared to CT for the assessment of lymphoedema symptoms, however is expensive and suffers from a lack of accessibility (Stanton et al., 2000).

2.9 Summary

Minor burn injuries are common and result in the formation of oedema localised to the wound, which if poorly managed, may lead to a worsening of the burn wound that may result in a need for surgery, delayed healing, and an increased risk of scarring. Additionally, unchecked oedema in complex structures such as the hand may lead to poor functional outcomes. The proactive management of oedema following burn injury is important to maximise outcomes for patients and something that should be

performed as part of routine burn care, however there is a paucity of research investigating techniques that optimise oedema management in acute injury. Part of the issue with researching oedema management is the lack of sensitive techniques that are valid for measuring oedema change in this population. The series of studies in this research attempts to identify methods to accurately measure oedema in acute burn injury, and guide clinicians working with burn injured patients by exploring different techniques to optimise the management of acute burn wound oedema.

2.10   Aims of this thesis

The overall aim of this thesis is to understand the effectiveness of interventions for managing acute burn oedema by applying sensitive measures of body composition to the unique characteristics of the burn injured population.

Specific aims are to:

- Explore the use of alternate electrode positions to measure hand volumes using BIS in a non-injured human sample (Chapter 3)

- Evaluate the use of these alternate electrode positions for measuring hand oedema in a burn injured cohort (Chapter 4)

- Evaluate the effectiveness of different methods of compression for managing hand oedema in acute hand burn injury (Chapter 5)

- Investigate the use of electrical stimulation as an adjunct to standard burn wound care improves healing and oedema (Chapter 6)

2.11   References

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CHAPTER 3   **ALTERNATE ELECTRODE POSITIONS FOR THE MEASUREMENT OF HAND VOLUMES USING BIOIMPEDANCE SPECTROSCOPY**

3.1 Abstract

Background: Bioimpedance Spectroscopy (BIS) is a tool that can be used to measure body composition in a variety of populations. Previous studies have investigated novel applications to utilise BIS to measure localised body composition, including in the hand. According to BIS guidelines, there should be no skin wounds at the site of electrodes, and that electrode positions may be modified in specific circumstances, as our group has validated previously in burn wound populations.

Methods and Results: To determine in non-injured participants, whether BIS measurements recorded using alternate electrode positions on the palm of the hand and forearm, or a combination of electrodes on the dorsum and volar surface of the hand and forearm were comparable to electrode positions on the dorsum of the hand and forearm. The study demonstrated that drive and sense electrodes on the palm of the hand and volar forearm, and a combination of electrodes on the palm of the hand and dorsum of the forearm, resulted in comparable measures of impedance of extracellular water (difference from reference position: 1.26-4.75%, p=0.411-0.558) and total water (difference from reference: 2.15-2.40%, p=0.258-0.781). Electrodes on the dorsum of the hand and volar forearm resulted in significantly different measures for the same BIS variables (percentage difference range 4.66-6.15%, p<0.001-0.003).

Conclusion: Electrode positions on the palm of the hand and volar forearm, or on the palm of the hand and dorsum of the forearm are interchangeable as clinical measures of hand lymphoedema and total water impedance.

Keywords: bioelectrical impedance analysis, electrode sites, body composition, body fluid distribution, wounds, hand volume

3.2   Introduction

Oedema is the accumulation of excess fluid, predominantly in the extracellular space, due to an imbalance in the rate of extravasation and subsequent return to the systemic circulation (Palmada et al., 1998). This is caused by an imbalance of effective capillary pressure, an obstruction to the venous or lymphatic flow by trauma or surgery, or by muscle weakness or paralysis in an extremity placed in a dependent position (Post et al., 2003; Witte et al., 1971). Lymphoedema is an increase in protein concentration in addition to an increase in extra-cellular fluid, which results in tissue composition in the skin and subcutaneous tissues (Casley-Smith, 1995), resulting from dysfunction of the lymphatic system, either from congenital abnormality or secondary to treatments, such as those associated with cancer (Hidding et al., 2016). Excessive protein rich fluid in the hand will disperse between structures including joints capsules, tendons and tendon sheaths, and fascial layers (Villeco, 2012) resulting in rapid organisation of proteinaceous fluid, which may result in loss of hand function and deformity through tissue fibrosis causing structural thickening, adherence, and loss of elasticity (Abu Sittah et al., 2011; Ause-Ellias et al., 1994; Villeco, 2012).

The clinical measurement of hand volumes has historically been performed using circumferential or figure of eight measures using a tape measure, or the use of water displacement (Palmada et al., 1998). Figure of eight measures have been shown to be reliable and valid in both non-injured and hand burn injury populations (Dewey et al., 2007; Maihafer et al., 2003). However, this technique only provides a linear representation of the limb volume rather than a physiological measure. In that, volume measures are estimated based on calculations, and the measures, although highly associated, are not interchangeable or interpretable with physical or physiological volume measurements, nor can the measure be extrapolated between subjects (Karges et al., 2003).

Water displacement volumetry, which utilises Archimedes' principle of water displacement, is recognised as the "gold standard" for measuring hand volumes in clinical populations (Boland & Adams, 1996). However, volumetry may be challenging in hands with open wounds with respect to infection control practices,

and dressings may confound accurate volume measures (Pellecchia, 2003). Repeat measures of hands in the clinical setting provides a quantification of a change in lymphoedema, and the effect of interventions for its management (Mayrovitz et al., 2006; Sorenson, 1989). However, water displacement has several drawbacks when considering its clinical application and feasibility, as it is a time-consuming process that requires correct apparatus set-up (Maihafer et al., 2003), and requires patient cooperation and compliance.

While these measures of hand volume are reliable and valid in a variety of non-injured and patient populations, they are reflective of overall volumes, and may not be sensitive enough to detect lymphoedema, or changes in lymphoedema volumes, in the clinical setting (Cornish et al., 2002; Edgar, Briffa, et al., 2009). Responding to and changing lymphoedema volumes is a vital role of clinicians. Similarly, responding to acute episodes of oedema, such as in patients post burn injury or following other trauma, has an impact on the patient's outcome. Clinical assessment of a swollen hand involves observing the hand for loss of skin creases at the joints, and accumulation of fluid beneath the dorsal skin (Stanton et al., 2000). However accurate measures of hand volumes for research are often difficult to obtain (Edgar, Briffa, et al., 2009).

Bioimpedance spectroscopy (BIS) is a non-invasive physiological measure of body composition and has the potential to measure body composition in the clinical setting (Earthman et al., 2007). The impedance to the flow of a small alternating current through the tissues is measured to provide immediate assessment of fluid volumes in the body. The use of BIS which employs multiple frequencies of current to enable the extrapolation of frequencies at zero hertz (R_0), which is representative of the impedance specific to the volume of extracellular water (ECW) in the tissues, and infinite frequency (R_∞) that is associated with total body water (TBW). The BIS algorithms estimate volumes of total and compartmental fluid, using Cole-Cole modelling (Cole & Cole, 1941; Cornish et al., 1999). The measured impedance of the intracellular component of the tissues is R_i.

The use of BIS to measure hand volumes has been investigated in both normal and lymphedema populations. BIS was shown to be more sensitive than 3-dimensional

scanning (Perometry) to changes in hand volume elicited by a postural change for a period of 3 minutes in a healthy population (Dylke et al., 2014; Ward et al., 2012), and is more sensitive in discriminating women with lymphedema than scanning method volume measures (Dylke et al., 2014). Fluid volumes in the body are based on the formula of an equivalent cylinder, and includes coefficients for the length of the body segment and the resistivity of the body fluid (Kyle et al., 2004a).

The guidelines for the measurement of BIS state that there should be no lesions at the site of the electrodes, and should wounds be present then the site of the electrodes should be changed (Kyle et al., 2004b). Broader application of the BIS technique in clinical practice is afforded by the research to date which addresses this issue and confirms novel electrode configurations that provide interpretable BIS measures (Grisbrook et al., 2015; Kenworthy, Grisbrook, Phillips, Gibson, et al., 2017). The use of alternate electrode positions for the measurement of limb segment and whole-body BIS has been examined in non-injured and burn wound populations (Grisbrook et al., 2015; Kenworthy, Grisbrook, Phillips, Gibson, et al., 2017). These studies confirmed that whole body and upper limb segmental BIS measures are equivalent to standard electrode positions in both populations with alternate hand electrode positions and standard foot positions. Localised BIS measures have been shown to be reliable and more sensitive than traditional circumferential measures in detecting volume change in a number of studies (Cornish et al., 2001; Kenworthy, Grisbrook, Phillips, Gittings, et al., 2017), and that alternate electrode positions can be used to assess localised impedance of tissues in a variety of clinically applicable configurations (Ward et al., 2013).

The location of wounds on the dorsum of the hand commonly preclude the use of standard electrode configurations for measuring hand BIS. The aim of this study was therefore to determine whether BIS measurements recorded using alternate electrode positions on the palm of the hand and forearm, or a combination of electrodes on the dorsum and volar surface of the hand and forearm were interchangeable with electrode positions on the dorsum of the hand and forearm.

3.3   Materials and Methods

3.3.1   Subjects

A sample of convenience was recruited from staff and students at Fiona Stanley Hospital. Participants were between the ages of 18 and 65 years, with a body mass index (BMI) within 15-40 kg.m^{-2}. Subjects were excluded from participating based on contraindications according to the manufacturer's specifications, including pregnant or breast-feeding participants, subjects with implantable surgical devices including cardiac pacemakers and/or electronic life support devices. Human Research and Ethics Committee approval from The University of Notre Dame Australia (015158F) was received for the project, and the project was registered with the South Metropolitan Health Service Governance, Evidence, Knowledge and Outcomes System (GEKO) as a Quality Improvement project (10830) as required when health staff are approached for recruitment.

3.3.2   Instrumentation

Bioimpedance measures were recorded using the ImpediMed SFB7 (ImpediMed Ltd, Brisbane, Queensland, Australia) multi-frequency bioelectrical impedance analyser. The SFB7 uses a single channel tetra-polar configuration, and BIS measures are performed at 256 discrete frequencies from 4-1000kHz. The SFB7 records impedance measures in triplicate, with each measure one second apart. The electrodes used were Ag/AgCl Eurotrode PFR2034 disposable resting ECG tab electrodes (reference code 12774, Pirrone srl, Milan, Italy).

3.3.3   Procedures

Prior to the assessment of BIS, participant height, weight and age were recorded, as the software for the SFB7 device requires this information to calculate body composition. Measurement of hand volumes using BIS was previously described with four electrode positions on the dorsum of the hand and forearm (Position 1 – Figure 1) (Ward et al., 2012). The current injection (or drive) electrode is positioned on the dorsum of the distal phalanx of the middle finger, below the level of the nail bed. The distal current sense electrode is at the level of the third metacarpal-phalangeal joint, and the proximal current sense electrode is on the wrist at the level of the ulnar

styloid. The proximal current drive electrode is positioned at mid forearm level, measured as the distance between the olecranon and the ulnar styloid. The distance between the sense electrodes was measured using a non-stretch tape measure.

Figure 1: Electrode Position 1 (reference position)
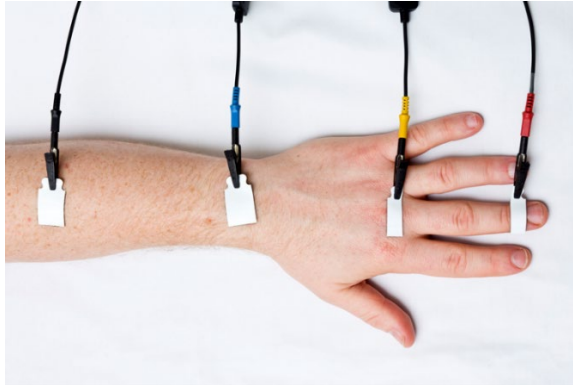
Three alternate electrode positions were investigated, to determine whether these alternate positions resulted in BIS measures equivalent to Position 1. Position 2 (Figure 2) placed the distal current drive and sense electrodes on the dorsum of the hand, and the proximal current sense and drive electrode on the volar surface of the wrist and forearm. Electrode Position 3 (Figure 3) was the reverse of this, with the distal current drive and sense electrodes placed on the volar surface of the middle finger and hand, and the proximal current sense and drive electrodes placed on the dorsum of the wrist and forearm.

Figure 2: Electrode Position 2
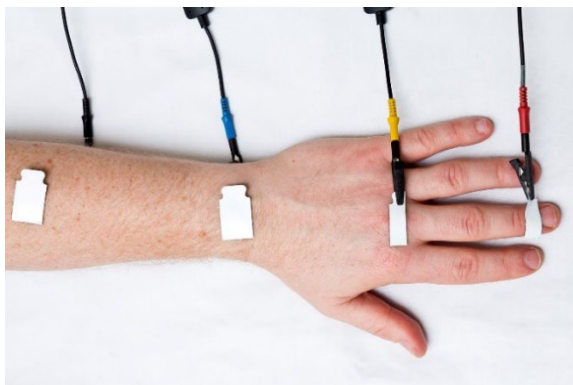
Figure 3: Electrode Position 3
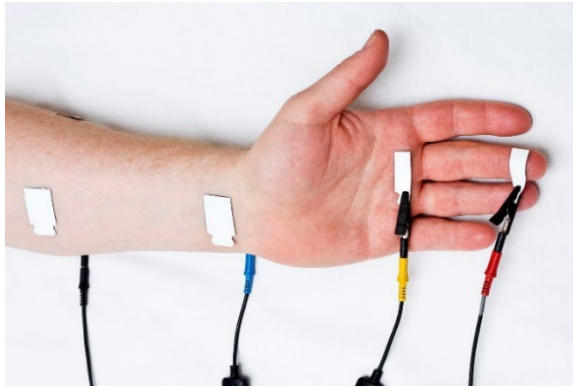
Position 4 (Figure 4) placed the electrodes on the volar surface of the hand and forearm. Distal current drive electrode was on the volar surface of the middle finger distal phalanx. The distal current sense electrode was the palmar surface of the hand in line with the third metacarpal phalangeal joint. The proximal current sense electrode was placed on the volar surface of the wrist in line with the ulnar styloid, and the proximal current drive electrode was placed on the volar mid-forearm.

Figure 4: Electrode Position 4
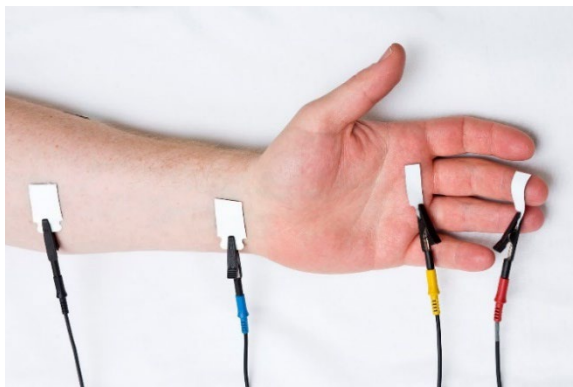
BIS measures were recorded with the participants lying supine, with their hands resting by their sides, arms abducted so that their hands were away from the body, and their legs separated. Prior to application of the electrodes, the skin surfaces were cleaned using alcohol swabs. Where the sense electrodes were on the same side of the hand and wrist, the distance between the closest edges of the sense electrodes was measured using a tape measure, ie between the proximal edge of the distal sense electrode and the distal edge of the proximal sense electrode.

Two different methods were used to assess the distance between the electrodes where the sense electrodes were on opposite sides of the hand (in Positions 2 and 3). The first method recorded a diagonal linear measure of the distance between the electrodes was assessed using a spring caliper. The diagonal distance was measured between the proximal edge of the distal sense electrode and the distal edge of the proximal sense electrode.

The second method used the linear axial measure recorded between the sense electrodes on the same side of the hand and wrist, as the proximal wrist electrode was placed in line with the ulnar styloid at the wrist crease, it was assumed that the theory of equipotential points, where points perpendicular to the longitudinal current flow in narrow sections of the body are equipotential in axial positions, measurement electrode positions on anterior, lateral and posterior surfaces should result in the same measured reading (Cornish et al., 1999). The measure for Position 1 (dorsum of hand and wrist) was used in the analysis for Position 2, while the measure for Position 4 (palmar surface of hand and wrist) was interpreted for Position 3.

Measurements of the volume of the hand using BIS were calculated using the formula described in the literature for the calculation of tissue volumes (Cornish et al., 1999; Kyle et al., 2004a; Ward et al., 2012):

$$V = \rho \frac{L^2}{R}$$

where V is the volume of the hand, R represents R_i or R_0, L is the inter-electrode distance, and ρ is the resistivity coefficient of the fluid, as defined by the SFB7: 235.5 (ECW) and 894.2 (ICW) for females, 273.9 (ECW) and 937.2 (ICW) for males in non-injured, healthy populations (Moon et al., 2009). The volumes were calculated for each electrode configuration, using R_0 to calculate the volumes of ECW and R_i for the calculation of ICW.

An additional parameter that is recorded by the SFB7 is cell membrane capacitance, which is reflective of cell volume and cell membrane thickness and porosity (Matthie, 2008). Cell membranes interact with applied electrical currents, which provides an indicator of tissue composition (Dean et al., 2008). Reduced membrane capacitance is linked to deterioration of muscle cell membranes in neuromuscular disease (Rutkove

et al., 2002), is a prognostic indicator of survival in head and neck cancer (Małecka-Massalska et al., 2016), and is reduced in children with active nephrotic syndrome (Brantlov et al., 2019). Increased membrane capacitance has been noted in disease states resulting in hypertrophy of the cells, such as dilated cardiomyopathy or proliferative vitreoretinopathy (Bringmann et al., 2000; Cerbai et al., 2001).

The electrodes were applied to each point on both hands prior to BIS recordings so that the measurements could be completed in quick succession. The order of the recordings was randomised. Participants were required to abstain from eating, drinking or toileting between measures. Measurements were completed in less than 10 minutes for each participant.

3.3.4   Data analyses

The data was downloaded from the SFB7 using supplied software (Bioimp version 5.4.0.3, ImpediMed Ltd, 2012) and processed for analysis according to the Cole model to determine the resistance at zero frequency (R_0) – impedance of the extracellular water; resistance at infinite frequency (R_∞) – impedance of the total body water; and the resistance of the intracellular compartment (R_i). All analyses were performed using Stata Statistical Software, release 14 (StataCorp LP, 2015, College Station, TX). Descriptive analyses were completed and presented using means and standard deviations (SD). Percentage difference values were also calculated, whereby each BIS variable from the alternate electrode positions were expressed as a percentage change of the value obtained from the standard site (Position 1). All further statistical analyses were performed using the raw BIS (not percentage difference) variables.

All three repeated, within session measurements were recorded and included in the analysis, multilevel mixed-effects linear regression analyses were therefore used to assess associations with differences in BIS variables between the different electrode positions. All models were adjusted for the inter-electrode distance. As BMI, gender, age and hand dominance are known to influence upper limb BIS measures, these factors were also included in the models to assess any interactions. A step-wise, backward elimination of variables was performed to produce the final model, and

only statistically significant interactions were included in the final model. The inter-electrode distance between the sense electrodes was also assessed for interactions with each electrode position. The results of the regression analyses were reported as regression coefficients, with 95% confidence intervals. A *p*-value of less than 0.05 was considered statistically significant.

Bland and Altman (1986; 1999) described statistical measures of agreement between different methods of clinical assessment and is applicable to assessing a new clinical measure against a gold-standard reference. The bias and limits of agreement were calculated for each alternate electrode position against the reference of Position 1.

3.4 Results

3.4.1 Participants

Thirty (30) participants (15 female) were included in the study, with measures performed on 60 hands. Mean age of the participants was 33.9±9.87 years; mean BMI was 25.3±3.89kg/m^2. Summary statistics by gender are shown in Table 1. Two participants (one female, one male) reported being left-handed. The size of the participants' hands and shown in Table 2. There were significant differences between genders for height, weight, and in the measured interelectrode distances for each position (*p*<0.001).

Table 1: Participant summary statistics

	Female Mean (SD)	Range	Male Mean (SD)	Range	*p*-value
Age	34.7 (10.1)	21-55	33.1 (9.93)	19-52	0.6649
Height (cm)	165.9 (5.49)	155-176	180.3 (7.49)	168-197	<0.001
Weight (kg)	65.2 (8.17)	50-79	87.2 (13.6)	54-104	<0.001
BMI	23.7 (2.93)	18.4-29.4	26.8 (4.20)	17.8-35.0	0.0261
Electrode Distance (cm)	7.79 (0.54)	7-8.8	9.08 (0.87)	7.5-10.6	<0.001

Table 2: Inter-electrode distance for each electrode configuration

Electrode Position	Female Mean (SD)	Median (IQR)	Male Mean (SD)	Median (IQR)	*p*-value
1	7.65 (0.57)	7.6 (0.6)	8.67 (0.99)	8.6 (1.4)	<0.001
2	8.65 (0.42)	8.6 (0.5)	9.84 (0.73)	9.85 (1.1)	<0.001
3	8.54 (0.51)	8.45 (0.7)	9.50 (0.95)	9.4 (1.1)	<0.001
4	8.49 (0.49)	8.5 (0.7)	9.45 (0.79)	9.4 (1.2)	<0.001

* measures in cm

3.4.2 Hand BIS variables

Means and standard deviations for hand BIS raw impedance variables for each electrode position are shown in Table 3. Each raw BIS variable has also been adjusted using the distance between the sense electrodes (Ω/cm).

Table 3: Hand BIS impedance variables obtained from the standard position and alternate positions

Data presented at means (SD) and difference (%) of the value obtained from standard Position 1.

BIS variable	Position 1 (Ref)	Position 2 Axial	Diagonal	Position 3 Axial	Diagonal	Position 4
R_0 (Ω)	117.7 (20.9)	124.8 (21.7)		128.6 (24.1)		135.9 (25.0)
R_0 (%*)	-	6.05		9.29		15.5
R_0 /dist (Ω/cm)	14.6 (3.35)	15.6 (3.65)	13.7 (3.12)	14.5 (3.28)	14.4 (3.28)	15.3 (3.36)
R_0/dist (%*)	-	6.17	-6.37	-1.26	-1.29	4.75
R_i (Ω)	533.6 (181.7)	523.4 (181.8)		548.3 (207.3)		533.8 (153.1)
R_i (%*)	-	-1.90		2.76		0.05
R_i /dist (Ω/cm)	66.1 (23.9)	65.1 (24.1)	57.3 (21.3)	61.8 (23.9)	61.6 (24.2)	60.1 (18.3)
R_i /dist (%*)	-	-1.57	-13.29	-6.58	-6.89	-9.12
$R\infty$ (Ω)	95.7 (18.7)	99.9 (18.7)		103.2 (21.3)		107.8 (21.3)
$R\infty$ (%*)	-	4.51		7.88		12.6
$R\infty$/dist (Ω/cm)	11.9 (2.86)	12.5 (3.00)	11.0 (2.59)	11.6 (2.81)	11.6 (2.83)	12.1 (2.79)
$R\infty$ /dist (%*)	-	4.66	-7.71	-2.40	-2.48	2.15

* percentage (%) of Position 1 reference value

Examination of the regression coefficients demonstrated that gender, age and the dominant hand were significantly associated with the raw BIS measures recorded in this study (Table 4). BMI did not significantly influence the BIS measures. Increasing age, being of male gender and the dominant hand significantly decreased R_0, R_i and R_∞ using both inter-electrode measures. There were no interaction effects between the electrode position and the inter-electrode distance for the diagonal inter-electrode distances. The interaction effect between electrode position and the axial inter-electrode distance significantly influenced R_0 and R_∞.

Table 4: Changes in hand impedance variables when alternate electrode positions are compared to the standard electrode position

BIS variable	Covariate	Coefficient	p-value	95% confidence intervals Lower	95% confidence intervals Upper
R_0 (Ω) Diagonal measure	Position2	-0.88	0.304	-2.57	0.80
	Position3	4.55	<0.001*	3.03	6.08
	Position4	12.2	<0.001*	10.8	13.7
	Distance	7.14	<0.001*	6.05	8.23
	Age	-0.74	0.001*	-1.17	-0.32
	Male Gender (ref: Female)	-43.0	<0.001*	-51.4	-34.6
R_0 (Ω) Axial measure	Position2	5.69	<0.001*	4.33	7.04
	Position3	6.25	<0.001*	4.69	7.82
	Position4	13.5	<0.001*	11.9	15.1
	Distance	5.25	<0.001*	4.01	6.49
	Age	-0.70	0.002*	-1.14	-0.27
	Male Gender (ref: Female)	-40.3	<0.001*	-48.8	-31.7
	Position2#distance	-2.96	<0.001*	-4.27	-1.64
	Position3#distance	0.49	0.520	-0.99	1.97
	Position4#distance	0.65	0.411	-0.86	2.10
R_i (Ω) Diagonal measure	Position2	-70.8	<0.001*	-105.2	-36.3
	Position3	-33.1	0.038*	-64.4	-1.80
	Position4	-44.9	0.004*	-75.6	-14.2
	Distance	55.9	<0.001*	34.4	77.4
	Age	-5.12	0.003*	-8.47	-1.79
	Male Gender (ref: Female)	-236.5	<0.001*	-304.8	-168.1
R_i (Ω) Axial measure	Position2	-9.87	0.443	-35.1	15.3
	Position3	-28.6	0.059	-58.3	1.08
	Position4	-43.1	0.004*	-72.8	-13.4
	Distance	53.8	<0.001*	34.3	73.2
	Age	-5.07	0.003*	-8.39	-1.75
	Male Gender (ref: Female)	-232.0	<0.001*	-299.2	-164.9
R_∞ (Ω) Diagonal measure	Position2	-3.09	0.001*	-4.86	-1.31
	Position3	1.66	0.042*	0.06	3.26
	Position4	6.52	<0.001*	4.95	8.09
	Distance	6.66	<0.001*	5.52	7.80
	Age	-0.66	<0.001*	-1.03	-0.28
	Male Gender (ref: Female)	-36.8	<0.001*	-44.1	-29.4
R_∞ (Ω) Axial measure	Position2	3.33	<0.001*	1.93	4.74
	Position3	2.94	<0.001*	1.32	4.56
	Position4	7.21	<0.001*	5.59	8.83
	Distance	5.39	<0.001*	4.11	6.67
	Age	-0.63	0.001*	-1.01	-0.25
	Male Gender (ref: Female)	-34.9	<0.001*	-42.3	-27.6
	Position2#distance	-2.04	0.003*	-3.40	-0.68
	Position3#distance	-0.22	0.781	-1.32	1.75
	Position4#distance	-0.89	0.258	-0.65	2.42

* *p-value<0.05*

Measures of membrane capacitance were compared for each electrode position to assess for differences between electrode positions (Table 5).

Table 5: Changes in membrane capacitance when alternate electrode positions are compared to the standard electrode position

				95% confidence intervals	
BIS variable	Covariate	Coefficient	p-value	Lower	Upper
Membrane	Position2	0.67	<0.001*	0.46	0.87
Capacitance	Position3	-0.77	<0.001*	-0.95	-0.58
(nF)	Position4	-0.42	<0.001*	-0.61	-0.24
	Distance	-0.44	<0.001*	-0.57	-0.31
Diagonal	Dominant hand	0.45	<0.001*	0.34	0.56
measure	Age	0.03	0.008*	0.01	0.05
	Weight	0.03	0.006*	0.01	0.05
	Male Gender (ref: Female)	1.19	<0.001*	0.63	1.75
Membrane	Position2	-1.27	0.056	-2.57	0.03
Capacitance	Position3	-0.34	0.674	-1.90	1.23
(nF)	Position4	-1.09	0.170	-2.66	0.47
	Distance	-0.45	<0.001*	-0.60	-0.31
Axial measure	Dominant hand	0.42	<0.001*	0.31	0.53
	Age	0.03	0.009*	0.01	0.05
	Weight	0.03	0.010*	0.01	0.04
	Male Gender (ref: Female)	1.18	<0.001*	0.61	1.74
	Position2#distance	0.18	0.027*	0.02	0.34
	Position3#distance	-0.49	0.592	-0.23	0.13
	Position4#distance	0.08	0.403	-0.10	0.26

* *p-value<0.05*

The analysis demonstrated that there was a significant difference in membrane capacitance between all positions when using the diagonal measures for the inter-electrode distance. Using the linear axial measure, there was a significant distance x position interaction for membrane capacitance – X^2 (3, N=704) = 7.74, p=0.05. The dominant hand, age, weight and male gender all influenced the measured membrane capacitance.

Hand volumes were calculated using the BIS variables and the interelectrode distances using each configuration, and compared to the volumes calculated for the Position 1 reference (Table 6).

Table 6: Calculated hand volumes using BIS variables.

Calculated Volume	Position 1 (Ref)	Position 2	Position 3	Position 4
Diagonal measure				
R_0 – ECF (mL)	156.0 (60.0)	187.4 (68.2)	172.5 (61.3)	161.0 (55.1)
ECF (%*)	-	20.1	10.6	3.17
R_i – ICF (mL)	130.8 (56.1)	167.9 (64.1)	156.6 (66.8)	153.2 (58.0)
ICF (%*)	-	28.4	19.7	17.1
Axial measure				
R_0 – ECF (mL)	156.0 (60.0)	146.5 (58.2)	170.4 (58.3)	161.0 (55.1)
ECF (%*)	-	-6.10	9.24	3.17
R_i – ICF (mL)	130.8 (56.1)	130.7 (52.8)	154.7 (64.7)	153.2 (58.0)
ICF (%*)	-	-0.10	18.2	17.1

* percentage (%) of Position 1 reference value

Bland-Altman analysis for agreement between Position 1 and each alternate electrode position, using both measures for inter-electrode distance, were calculated for the BIS variables R_0, R_i and R_∞ (Table 7).

Table 7: Bland-Altman limits of agreement with Position 1 for each alternate electrode position

Bias (LoA)	Position 2	Position 3	Position 4
Diagonal measure			
R_0 (Ω/cm)	0.99 (-0.91 to 2.89)	0.25 (-1.78 to 2.27)	-0.63 (-2.72 to 1.44)
R_i (Ω/cm)	8.81 (-27.9 to 45.6)	4.57 (-36.3 to 45.4)	6.05 (-29.6 to 41.7)
$R\infty$ (Ω/cm)	0.96 (-1.02 to 2.93)	0.33 (-1.65 to 2.31)	-0.22 (-2.25 to 1.81)
Axial measure			
R_0 (Ω/cm)	-0.91 (-3.44 to 1.63)	0.18 (-2.31 to 2.67)	-0.63 (-2.72 to 1.44)
R_i (Ω/cm)	1.04 (-37.7 to 39.7)	4.35 (-36.4 to 45.1)	6.05 (-29.6 to 41.7)
$R\infty$ (Ω/cm)	-0.56 (-2.36 to 1.25)	0.28 (-1.94 to 2.51)	-0.22 (-2.25 to 1.81)

3.5 Discussion

The use of BIS in the clinical setting provides a number of variables that enables the clinician to measure lymphoedema. Raw impedance variables provide an index of volume, while measuring inter-electrode distances allows the clinician to gain an understanding of the volume of lymphoedema within the measured segment. This study showed that when measuring the lymphoedema parameters of the hand, compared to the reference electrode array (Position 1), adjusting for axial distance between the electrodes, the alternate positions resulted in variation in R_0 and R_∞ of

less than 5% for Position 3 (-2.48 to -1.26%) and Position 4 (2.15 to 4.75%) (Table 3). This is due to impedance varying with body composition and cross-sectional area (Matthie, 2008).

The regression analysis when using the axial measures showed that there was a significant difference for each alternate position for R_0 and R_∞ (p<0.001). The position x distance interaction, however, showed Position 3 and Position 4 were interchangeable with Position 1 for R_0: X^2 (3, N=7230 = 23.51, p<0.001) and R_∞: X^2 (3, N= 723) = 10.16, p=0.0172, indicating that Position 3 and Position 4 are interchangeable with Position 1 for measuring R_0 and R_∞ (Table 4). This is also reflected in the measurements for membrane capacitance between positions (Table 5).

Hand dominance is known to result in larger hand volumes, requiring the use of ratios to compare dominant and non-dominant hands to inform the measurement of lymphoedema (Dylke et al., 2014; Gaw et al., 2011). The dominant hand in this study resulted in decreased impedance (Table 4) and increased capacitance (Table 5), indicating increased size compared to the non-dominant hand. For the measurement of hand volumes to detect lymphoedema, using these alternate electrode positions, it is recommended that Electrode Positions 1, 3 or 4 may be used to assess the hand volume, however the same electrode configuration should be used on the affected limb and the contralateral limb in order to assess the inter-hand ratio.

Acceptable variations using BIS have previously been investigated. Within day total body resistance varied between 0.3-1.9% in a study by Kushner and Schoeller (1986). Variations of less than 5.6% have been shown to be attributed to measurement error using BIS in performing individual measurements (Pichonnaz et al., 2015). We would consider the acceptable cut off for comparability (interchangeability) to be 5%, as values larger than this were determined to be clinically significant variability for measures of total body fluid (Earthman et al., 2007).

The alternate Positions 2 and 3 placed the sense electrodes on opposite sides of the hand. The inter-electrode distance between the sense electrodes was measured using a diagonal (through the hand) measure, and a linear axial measure along the dorsum or volar surface of the hand to the proximal wrist at the level of the ulnar styloid. Limits

of agreement with Position 1 were calculated for each alternate position, using both inter-electrode measures (Table 7). The results indicate improved agreement with Position 1 for alternate Positions 2 and 3 when using the axial measurements over the diagonal measures.

The improved agreement using the linear axial measures was also reflected in the regression analyses for impedance and membrane capacitance. There was a significant difference between each alternate position and Position 1 using the diagonal measures for each BIS variable (p<0.001-0.042), except for R_0 measured in Position 2 (p=0.304). There was no interaction between electrode position and the inter-electrode distance when using the diagonal measure for each BIS variable (Table 4 and 5), indicating that the alternate electrode positions using diagonal measures are not interchangeable with Position 1 for using BIS to measure hand lymphoedema volumes.

Measures for the impedance of the intracellular component (R_i) compared to Position 1 were significantly different for each alternate position except Position 2 using an axial measure (p=0.443), which was 1.57% less than Position 1. The other alternate positions were also clinically different from Position 1, with greater than 5% variation using both inter-electrode measures. As there was no interaction between electrode position and distance for R_i, the alternate electrode positions investigated in this study are not interchangeable with Position 1 for measuring R_i.

Male gender significantly decreased all BIS impedance variables and increased membrane capacitance using both inter-electrode measures, which has been shown previously (Grisbrook et al., 2015). These results are reflective of the larger hands and increased intrinsic hand muscle bulk in males, and the decreased R_i corresponds with increased muscle mass (Gittings, et al, unpublished data).

The hand volumes were calculated using the formula described by Ward et al. (2012) (Table 6). The formula is validated for calculating the volume of limbs using BIS and is based on the geometric conical shapes of the limbs (Ward et al., 2009b). The measure for ECW using Position 4 and ICW using Position 2 were the only calculated volumes within 5% of the calculated measures for Position 1. The complex

irregular shape of the hand may require the calculation of a formula specific for hand volume calculation to allow use of BIS for volume calculations, which is reflected in the clinically significant differences (>5% difference) calculated for each electrode configuration.

The impedance of the skin is influenced by the thickness of the stratum corneum, and by the hydration status of the skin (Birgersson et al., 2010; Björklund et al., 2013). The standard electrode array places the electrodes over the dorsum of the hand and forearm, and the unique anatomy and function of the hand dictates highly mobile skin, which is thinner than other areas of the body. Several researchers have investigated the electrical impedance of skin at different sites of the body, with increased electrical impedance of the volar forearm skin compared to the skin on the dorsum of the hand (Nicander et al., 1997; Nicander & Ollmar, 2000), indicating that this skin is thicker than that on the dorsum of the hand. Membrane resistance of the stratum corneum decreases with improved hydration, while the effective capacitance increases under the same conditions (Björklund et al., 2013). While the skin was prepared in the same method for each electrode configuration in this study, and the within subject measures were completed within 2 minutes per hand, the use of moisturisers by the participants was not noted.

Mathematical modelling of skin has variously assumed stratum corneum thicknesses of between 10-40µm at the forearm (Martinsen et al., 1999; Yamamoto & Yamamoto, 1976). The thickness of the stratum corneum of the volar forearm was calculated, based on a number of cohort studies of females, to be 14±3µm (Birgersson et al., 2010). In comparison, the thickness of the stratum corneum at the palmar fingertip of the middle finger was measured using optical coherence tomography to be 98±12µm in females and 111±14µm in males (Fruhstorfer et al., 2000). The impedance of the stratum corneum of the palm of the hand is therefore greater than non-glabrous skin. Martinsen et al. (1999) found that the stratum corneum mainly contributes to the measured impedance at frequencies less than 1 kHz, where higher frequency measurements were representative of the deeper viable layers of the skin. The SFB7 measures from 4kHz to 1000kHz, which overcomes the stratum corneum influence, and the tetrapolar arrangement of electrodes minimises the skin-electrode contact impedance so that the measured impedance relates to the underlying body tissues only (Cornish et al., 1999) , however, small area segmental and localised BIS result in

lower tissue impedances when compared to whole-body BIS measures, which the SFB7 is designed to measure (Bogonez et al., 2014).

While the tetra-polar arrangement minimises skin-electrode contact impedance to measure BIS, it is dependent on similar contact impedance at each electrode position. The skin-electrode contact impedance varies according to body site measured, and is relatively large, which can distort the measured tissue impedance (Bogonez et al., 2014). This may lead to high frequency artefact when measuring BIS due to the capacitive effect of the cells, leading to errors in the derived Cole parameters at these increased frequencies (Montalibet & McAdams, 2018). The electrode impedance mismatch does not appear to affect the measures of R_0, which is the BIS measure representative of ECW and therefore lymphoedema, as the artefact occurs at higher frequencies (Montalibet & McAdams, 2018).

The electrode impedance mismatch also allows for spot measurement of lymphoedema. Impedance transverse to the longitudinal direction of current flow, or spot measurement, is calculated using vector algebra from a combination of bipolar and tetrapolar BIS measures. Bipolar measurement techniques measures impedance in the tissues parallel and transverse to the current flow, while tetrapolar BIS measures tissue impedance parallel to the direction of the current flow (Czerniec et al., 2015; Dylke et al., 2013). This technique therefore isolates the impedance of the skin from the underlying soft tissues, which can determine the composition of these tissue changes with the progression of lymphoedema (Czerniec et al., 2015).

3.6   Conclusion

The results in this study indicate that electrodes may be placed on the volar surface of the hand and forearm, or a combination of electrodes on the palm of the hand and the dorsum of the forearm, to measure R_0 and R_∞. This provides a technique to measure hand lymphoedema where wounds otherwise preclude the use of electrodes on the dorsum of the hand and forearm. The raw BIS variables should be interpreted for changes in tissue volumes in a clinical setting, as calculated volumes may result in clinically significant variation.

3.7 Future Studies

Future investigations are required to determine if reverse electrode positions counter the electrode-skin contact mismatch, and if spot measurement of lymphoedema is a valid technique in the hand. The use of hand BIS and these alternate electrode positions needs to be validated in wound populations. Improved formulae for calculating hand volumes using BIS to account for the complex geometrical shape of the hand also need to be determined.

3.8 Conflict of interest statement

There are no conflicts of interest to be reported

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To Whom It May Concern

The PhD candidate, Dale Owen Edwick, contributed 85% to the intellectual property associated with the paper/publication entitled *Alternate electrode positions for the measurement of hand volumes using bioimpedance spectroscopy.* The final 15% is contributed by the co-authors of the paper.

I, as a Co-Author, endorse that this level of contribution by the candidate indicated above is accurate.

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CHAPTER 4   **BIOIMPEDANCE SPECTROSCOPY IS A VALID AND RELIABLE MEASURE OF EDEMA FOLLOWING HAND BURN INJURY (PART 1 – METHOD VALIDATION)**

4.1   Abstract

Introduction: The assessment of swelling following burn injury is complicated by the presence of wounds and dressings, and due to patients experiencing significant pain and impaired movement. There remains a lack of sensitive objective measures for edema in patients presenting with hand burn injury. Bioimpedance spectroscopy (BIS) is a measure of body composition that has been demonstrated by our group to be reliable for measuring whole body and limb edema during resuscitation, and to be sensitive to edema changes within healing wounds. The aim of this study was to determine the reliability and validity of BIS as a measure of edema following hand burn injury specifically.

Methods: One hundred patients presenting with burn injury including a portion of a hand were recruited to this trial. Repeated measures of the hand were recorded using a novel application of BIS, and in parallel with water displacement volumetry (WDV). The results were analyzed using mixed effects regressions.

Results: Paired repeated measures were obtained for 195 hands, using four electrode configurations. BIS demonstrated high reliability in measuring hand BIS – Intra-Class Coefficient 0.995-0.999 (95% CI 0.992-1.000) and sensitivity – Minimum Detectable Difference 0.74-3.86 Ω (0.09-0.48 Ω/cm). Strong correlation was shown with WDV, Pearson's r = -0.831 to -0.798 (p<0.001).

Conclusion: BIS is a sensitive and reliable measure of edema following acute hand burn injury.

4.2   Introduction

In minor burn injury, edema remains localized to the site of the injury, as distinct from systemic inflammation associated with major burn injury (Edgar et al., 2011; Fodor et al., 2006; Kao & Garner, 2000). The accumulation of edema fluid, which occurs primarily in the extra-cellular space, increases the perfusion distance between the skin and the capillary bed, resulting in a decreased exchange of nutrients, which can result in burn wound conversion and delayed healing (Jackson, 1953; Knisely et al., 1969; Remensnyder, 1972). Delayed healing is associated with an increased risk of scarring (Finlay et al., 2017; Ismail Aly et al., 2018), which affects the quality of survival (Wood, 1995).

There is a lack of sensitive, reliable and valid non-invasive measurement techniques to quantify edema following burn injury (Cross et al., 2009; Edgar, Briffa, et al., 2009). Edema measurement techniques that are sensitive, portable and safe provide researchers and clinicians responsive and objective measures to guide the management of edema in patients following burn injury (Palmada et al., 1998; Thomas et al., 1992).

Measurement of edema in the hand is complicated by the complex geometric shape of the hand (Ward et al., 2012). Burn wound edema in the hand invades the normally lax skin on the dorsum of the hand, which is essential for normal function. This, combined with the effects of pain, results in reduced hand mobility and altered skeletal muscle contractions, resulting in a diminished muscle pump that can make it difficult to resolve the edema (Lane et al., 2007; Luce, 2000), as the lymphatic system is reliant on both intrinsic and extrinsic forces to promote edema transport (Lane et al., 2005; Oliveira et al., 2018). Quantifying edema following hand burn injury in the clinical setting is complicated by the presence of wounds and dressings, in a patient cohort who experience significant pain, impaired movement, and may require medications that result in modified behavior. As a result, edema is most often assessed clinically by noting loss of skin creases, areas of visible swelling with palpation, and loss of function (Stanton et al., 2000).

Water displacement volumetry (WDV) is recognized as a reference standard for measuring upper extremity volumes in research (Hidding et al., 2016). The use of

whole arm water displacement demonstrated a MDD of 96.6mL in patients with acute burn wounds (Edgar et al., 2014). Volumetry was used as a comparator for figure-of-eight measures in sub-acute burn injury, and demonstrated an ICC of 0.99, with an SEM of 7.70mL (Dewey et al., 2007).

In the same study, Dewey et al. (2007) assessed the reliability and concurrent validity of circumferential figure-of-eight measurement of hands in a subacute burn patient population. Figure-of-eight measures were highly correlated with water displacement (Pearson's r 0.83-0.90). This compared to a similar study in healthy individuals, where the correlation between the two measures was 0.94-0.95 (Maihafer et al., 2003). Despite being highly associated with volume measures, linear measures such as figure-of-eight measure provide only an estimate of the volume, and therefore suffer from the limitation of lacking construct validity to provide volume comparison between subjects, and therefore should not be interchanged within or between patients (Edgar et al., 2014; Karges et al., 2003; Megens et al., 2001).

The use of Bioimpedance Spectroscopy (BIS) in burn injury populations has been investigated by our group. The use of BIS for assessing fluid composition was shown to be reliable in burns patients with <30% TBSA injury (ICC 0.976-1.00), and reliable for measuring acute edema shifts within and between whole body compartments, which is important in assessing fluid resuscitation in major burn injury (Edgar, Briffa, et al., 2009). The use of alternate electrode positions to account for wounds covering the standard tetra-polar electrode sites was assessed in burn injuries of >12% TBSA. Alternate electrode positions on the palm of the hand and sole of the foot generated measures equivalent to standard tetra-polar electrodes for all resistance measures and volumes of ECF and TBW. Alternate electrode placement on the palm of the hand with standard electrodes on the dorsum of the foot were also equivalent for upper limb segmental BIS (Kenworthy, Grisbrook, Phillips, Gibson, et al., 2017).

The aim of this study was to investigate the use of BIS for measuring hand volumes in acute burn injury, using the technique described by Ward et al. (2012). The guidelines for the use of BIS indicate that the skin at the site of the electrodes should be intact and free from wounds, and that alternate electrode positions should be considered (Kyle et al., 2004b). Alternate electrode positions for using BIS to

measure hand volumes was previously validated in a non-injured population by our group (Edwick et al., 2020a).

4.3 Methods

4.3.1 Participants

Participants in this study were recruited from patients presenting to the State Adult Burns Unit at Fiona Stanley Hospital. Patients were approached to participate in this study if they presented with burn injury including a portion of a hand. Exclusion criteria for this study included BIS manufacturer contraindications of pregnancy or breast-feeding individuals, surgical implants and stimulators, including cardiac pacemakers. Injuries due to exposure to electrical current were also excluded. Participants with peripheral neuropathies and other conditions affecting sensation were also considered contraindications for participation in this study. Burn injury wounds affecting electrode placements for measurement by BIS were also excluded.

4.3.2 Ethics

Ethics approval was granted South Metropolitan Health Service Human Research Ethics Committee (HREC) (reference 16-143) and by The University of Notre Dame Australia HREC (reference 016128F). Recruitment commenced in November 2016, and was completed in August 2019.

4.3.3 Outcome measures

The study is a method comparison study, comparing the measurement of hand volumes using BIS to WDV as a reference comparator (Hidding et al., 2016). Sample size estimation for this study was one hundred (100) patients, as part of a randomized control trial investigating the use of compression for managing acute hand burn edema (reported in Part 2 of this study series). Method comparison studies investigating the precision of a measurement compared to a reference should have a minimum sample size of ~200 paired measurements (Dunn & Roberts, 1999). The design of this study involved initial and follow-up measures for the patients.

Bioimpedance utilizes the electrical properties of tissues and the relationship between electrical impedance and water content within body structures to provide measures of

body composition (Kyle et al., 2004a). There are two characteristic resistances to electrical current in the tissues of the body – resistance, and capacitance (reactance). At a low frequency approximating zero Hz, the current does not penetrate the cell membrane and the current passes through the extracellular space, providing measures for the resistance of the extracellular fluid, known as R_0. As the frequency of the current increases towards infinite frequency, the cell behaves as a near perfect capacitor, which provides a resistance of the total body water, known as R_∞ (Kyle et al., 2004a). Practical limitations of using direct current and very high frequency alternating current in the human body prevent direct measurement at these ideal frequencies, R_0 and R_∞ are predicted using Cole-Cole plots (Cole & Cole, 1941).

Measurements of BIS were recorded for the affected hand using electrode positions enabling electrode placement on intact skin. The bioimpedance device used to obtain the measures was the Impedimed SFB7 (Impedimed Pty Ltd, Brisbane, Queensland, Australia), which is a multi-frequency bioimpedance analyzer, measuring at 256 discrete frequencies between 4-1000 kHz. The measurement of BIS over multiple frequencies increases the accuracy of the Cole-Cole predictions for R_0 and R_∞ (Cornish et al., 1993). The magnitude of the resistance to current flow is inversely proportional to the volume of fluid in the tissues, allowing BIS to quantify body compartment fluid composition (Ward et al., 2009b).

The electrodes used for measuring BIS were Ag/AgCl Eurotrode PFR2034 disposable resting ECG tab electrodes (reference code 12774, Pirrone srl, Milan, Italy). The tetra-polar electrode configuration for the measurement of BIS in the hand placed the drive electrodes at the level of the third distal phalanx, below the nailbed, and at the mid dorsal forearm level, with the sense electrodes at the level of the third metacarpo-phalangeal joint on the dorsum of the hand, and level with the ulnar styloid on the dorsum of the wrist, as described by Ward et al. (2012) (Position 1 – Figure 1). This electrode configuration has been shown to be strongly correlated with perometry, r=-0.794, for measuring hand volumes, and was sensitive to a decrease in hand volume with the left hand elevated above head height, with the arm elevated to shoulder height and the elbow flexed to 90˚ (Dylke et al., 2014).

Figure 1: Electrode Position 1
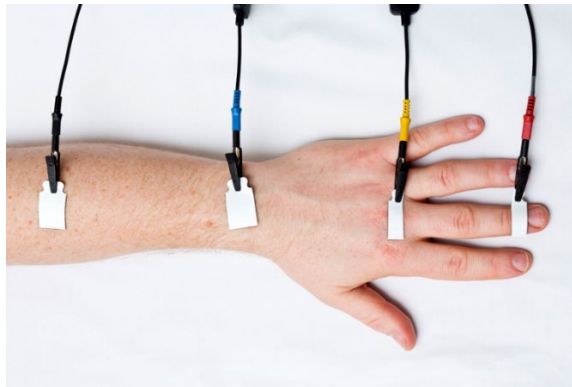
The use of alternate tetra-polar electrode positions was previously investigated by the authors in a non-injured population, comparing the configuration Position 1 to three alternate positions: Position 2 - electrodes placed on the dorsum of the hand and volar surface of the forearm (Figure 2); Position 3 - electrodes placed on the palm of the hand and the dorsal surface of the wrist and forearm (Figure 3); and Position 4 - electrode positions on the palm of the hand and volar forearm mirroring the electrodes in Position 1 (Figure 4). Electrode positions 3 and 4 were equivalent to the Position 1 for measuring ECF in non-injured hands (Edwick et al., 2020a).

Following removal of the dressings and washing of the burn wounds using Chlorhexidine Pre-Op wash, the patient rested in supine with the hand resting by their side, abducted ~30° from the side of their body. After the hand was dried, intact skin at the location of the electrodes was cleaned with an alcohol swab and allowed to dry. Up to four of the electrode positions were investigated, dependent on burn wound locations. The distance between the electrode positions was measured using a non-stretch measuring tape. The landmarks used to quantify the inter-electrode distance were the distal edge of the electrode placed at the wrist, and the proximal edge of the electrode sited level with the third MCPJ. Where the sense electrodes were located on the opposite side of the hand, a linear axial measure was obtained from the proximal edge of the distal sense electrode to the wrist crease in line with the ulnar styloid, at the position of the distal edge of the proximal sense electrode. BIS measures were completed within 10 minutes of removal of the dressings.

Figure 2: Electrode Position 2
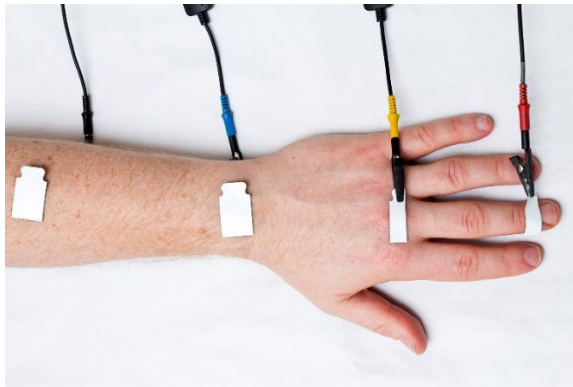
Figure 3: Electrode Position 3
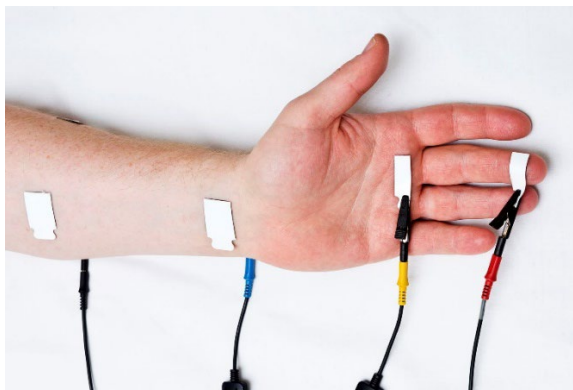
Figure 4: Electrode Position 4
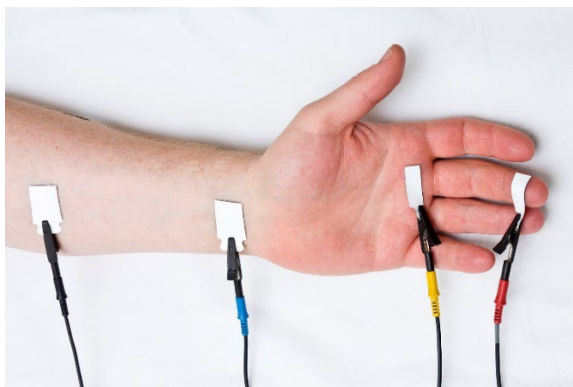
After BIS measures were obtained, the electrodes were removed, and the patient was allowed to stand up and was instructed to keep the hand at heart level. The hand volume was then obtained using a commercially available water displacement volumeter (OPC Health, Port Melbourne, Victoria, Australia), using the technique described by Farrell et al. (2003) (Figure 5). All patients were measured in standing. The water temperature was recorded prior to measuring the hand volume. Overflow

water was collected in a plastic container and weighed immediately using digital scales (Model CBK4, Adam Equipment, Bibra Lake, Western Australia), to the nearest 0.1g, allowing for 1 gram in weight being assumed as equivalent to 1 milliliter of water (Figure 5).

Figure 5: Water displacement volumetry

4.3.4 Statistical analysis

The SFB7 data was downloaded and processed for analysis using the supplied software (Bioimp version 5.4.0.3, Impedimed Ltd, 2012, Brisbane, Queensland, Australia) according to the Cole model to determine BIS variables. All analyses were performed using Stata Statistical Software, release 15 (StataCorp LP, 2017, College Station, TX, USA). Descriptive analyses were completed and presented using means and standard deviations (SD).

The SFB7 was configured to record BIS measures in triplicate. All three repeated, within session measurements were recorded and included in the analysis, using mixed-effects regression analyses to assess associations with the BIS variables and healing of the wounds. Contrasts were used to determine main effects and interactions. The results are reported as regression coefficients, with 95% confidence intervals. A p-value of less than 0.05 was considered statistically significant.

BIS variables recorded have previously been shown to be influenced by height, weight, body mass index (BMI), gender and age. Therefore, a step-wise, backward

elimination of variables was completed using a series of mixed effects regression analyses to assess the effect each of these variables on the BIS measures. Each of the raw resistance values measured by the SFB7 were assessed in each electrode configuration for validity compared to the tetra-polar electrode configuration on the dorsum of the hand and forearm, as described by Ward et al. (2012).

Reliability of the within session triplicate BIS hand measures of resistance was determined by intra-class correlation coefficients (ICC). The ICCs were obtained using a three-level mixed effects model with absolute agreement definition, and reported as coefficients with 95% confidence intervals.

The sensitivity of the BIS measures was determined by calculating the Minimum Detectable Difference (MDD), as per the formula:

$$MDD = SEM \; x \; \sqrt{2} \; x \; t(df, 0.05) \tag{1}$$

where SEM = standard error of the measurement:

$$SEM = SD \; x \; \sqrt{1 - ICC} \tag{2}$$

Bland-Altman analysis (Bland & Altman, 1999, 2007) was performed to assess agreement between the hand volumes measured using BIS with the WDV measures. The limits of agreement are calculated by calculating the differences between the measures obtained using each method, and calculating the mean and standard deviation of each method. The results are described as the bias between the measures, with limits of agreement being 1.96 standard deviations above and below the mean (Bland & Altman, 2007).

4.4   Results

4.4.1   Demographics

Patient recruitment commenced in November 2016 and was completed in August 2019. One hundred (100) patients (68 male) were recruited. Mean age of these patients was 40.1 ± 13.8 years, mean BMI was 28.4 ± 5.8 kg.m^{-2}. Mean total body surface area (TBSA) injured was 0.51 ± 0.96% (Table 1). Mean TBSA injured per hand was 0.35 ± 0.23%. Patients were recruited 2.81±1.69 days post injury (range 0-8

days, median 2 days). Time between measures was 2.11 ± 0.40 days (range 1-3 days). Repeat measures were obtained 4.96±1.80 days post injury (range 2-11, median 4 days). Repeated measures were obtained for 195 hands. 4 patients did not attend their follow-up appointments, and a malfunction of the SFB7 resulted in null data for the follow up measure of one patient.

Table 1: Participant summary statistics

	Female		Male		Total	
	Mean (SD)	Med (IQR)	Mean (SD)	Med (IQR)	Mean (SD)	p-value
N	32		68		100	
Age	42.0 (16.1)	41 (26.5)	39.8 (13.1)	39 (21.5)	40.1 (13.8)	NS
BMI (kg/m^2)	27.8 (6.66)	25.9 (11.3)	28.2 (5.23)	27.8 (4.69)	28.4 (5.84)	NS
Weight (kg)	74.8 (19.3)	73.6 (28.4)	90.5 (21.9)	86.4 (13.2)	86.9 (24.2)	<0.001
Height (cm)	164.0 (8.97)	164.5 (10)	178.7 (8.06)	179.0 (12.0)	174.1 (10.8)	<0.001
TBSA (%)	0.42 (0.54)	0.25 (0.19)	0.83 (1.61)	0.50 (0.59)	0.51 (0.96)	NS
TBSA/hand	0.33 (0.24)	0.25 (0.20)	0.37 (0.23)	0.38 (0.39)	0.35 (0.23)	NS
Depth (SPT / Mixed PT/DPT)	27 / 4 / 1		42 / 19 / 7			<0.001

BMI = Body Mass Index; TBSA = Total Body Surface Area; SPT = Superficial Partial Thickness; PT = Partial Thickness; DPT = Deep Partial Thickness

There were no differences between gender in this study when assessed using a two-sample t-test, except for height: t-test (98) =-8.22 ($p<0.001$); and weight: t-test (98) =-3.46 ($p<0.001$). There was also a significant difference between gender for depth of burn: t-test (98) =-3.68 (p<0.001).

4.4.2   Validity

The raw impedance variables assessed in the regression model were R_0 (impedance of the extracellular compartment), R_i (impedance of the intracellular component), and R_∞ (impedance of the total fluid content. The regression model assessed each of the alternate electrode configurations compared to the dorsal hand / dorsal forearm (Figure 1). The inter-electrode distance, the patient's age and weight, and being male gender were significant covariates in the model (Table 2).

Table 2: Validation of alternate electrode positions for measuring hand BIS impedance

BIS variable	Covariate	Coefficient	p-value	95% confidence intervals	
				Lower	Upper
R_0 (Ω)	Position2	20.4	<0.001*	9.85	30.9
	Position3	9.72	0.144	-3.31	22.7
	Position4	18.3	0.005*	5.44	31.2
	Distance	6.72	<0.001*	5.27	8.17
	Age	-0.40	<0.001*	-0.61	-0.19
	Male Gender (ref: Female)	-22.3	<0.001*	-29.0	-15.6
	Weight	-0.31	<0.001*	-0.45	-0.19
	TBSA/hand	-20.3	0.003*	-33.5	-7.10
	Position2#distance	-2.00	0.005*	-3.41	-0.60
	Position3#distance	-0.79	0.318	-2.34	0.76
	Position4#distance	-1.10	0.160	-2.64	0.43
R_i (Ω)	Position2	-36.7	0.112	-82.0	8.62
	Position3	6.25	0.842	-55.1	67.6
	Position4	-53.5	0.082	-113.7	6.75
	Distance	62.1	<0.001*	35.1	89.1
	Male Gender (ref: Female)	-211.4	<0.001*	-294.3	-128.6
	BMI	-8.11	0.014*	-14.6	-1.65
R_∞ (Ω)	Position2	3.48	<0.001*	2.07	4.89
	Position3	1.82	0.095	-0.32	3.96
	Position4	5.43	<0.001*	3.29	7.56
	Distance	5.60	<0.001*	4.66	6.64
	Age	-0.30	<0.001*	-0.47	-0.14
	Male Gender (ref: Female)	-19.7	<0.001*	-24.9	-14.5
	Weight	-0.26	<0.001*	-0.37	-0.15
	TBSA/hand	-15.1	0.004*	-25.3	-4.93

* $p<0.05$; BMI = Body Mass Index

The validation study shows that there was no position x inter-electrode distance interaction for R_i (X^2 (3, N=1371) = 2.33, p=0.508) or R_∞ (X^2 (3, N=1375) = 6.82, p=0.078), indicating that the alternate electrode configurations assessed were not interchangeable with the electrode array on the dorsum of the hand and forearm for these raw variables. The position x distance interaction for R_0 was significant, X^2 (3, N=1375) = 8.13 (p=0.0435). Position 2 was significantly different to Position 1 (p=0.005), however, Position 3 and Position 4 were equivalent to Position 1 for measuring the impedance of the extracellular compartment of the hand in a hand burn population (Table 2). This reflects the findings in our study of non-injured hands (Edwick et al., 2020a).

The measured water temperature mean was 26.1°±1.45, range 23.6-31.4°. The temperature was within the recommended range for measuring hand volumes (Boland & Adams, 1996).

The raw impedance variables were converted to volume measures using the equation:

$$V = \rho \frac{L^2}{R} \tag{3}$$

where V is the volume of the hand, ρ is the resistivity of the fluid (273.9 for males, 235.5 for females for extra-cellular fluid), R represents the raw BIS impedance value (R_0 or R_i), and L is the measured inter-electrode distance (Cornish, 2006; Kyle et al., 2004a; Ward et al., 2012).

The correlation between the BIS impedance values for R_0, when corrected for the inter-electrode distance (R_0 / distance) and water volume in this study was calculated, Pearson's r = -0.831 to -0.798 (p<0.001). The correlation between the ECF volume (calculated using Equation 1) and the water displacement was calculated, Pearson's r = 0.793 (p<0.001).

Figure 6: Bland-Altman limits of agreement for hand volume measured by BIS and water displacement
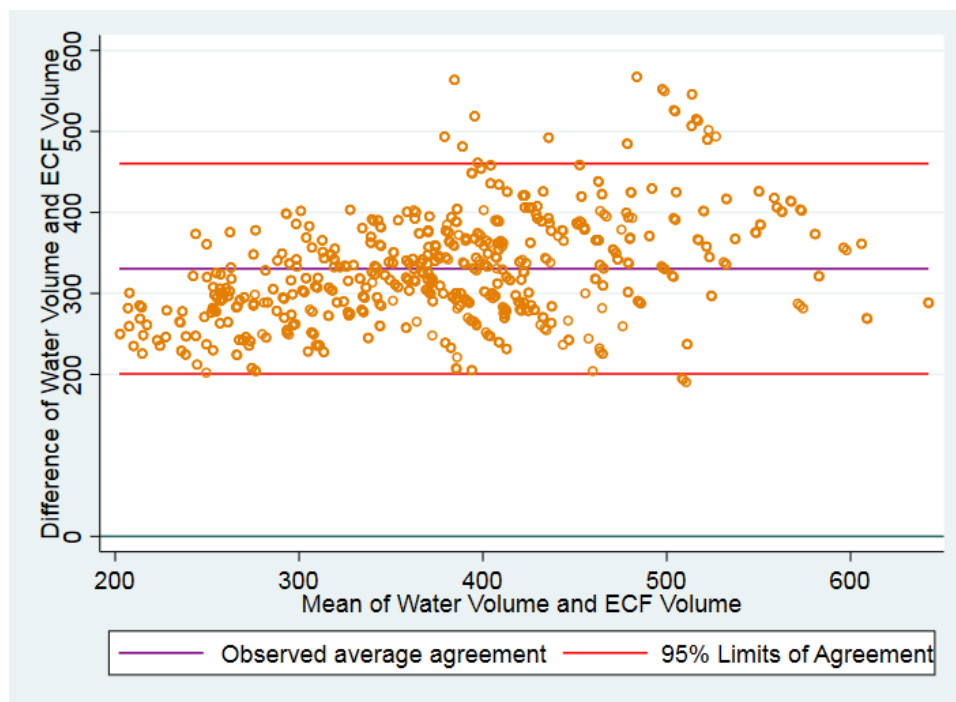
4.4.3 Reliability

As demonstrated in our group's previous studies, there was a high correlation of BIS triplicate measures within the same session and the same electrode position, as determined by the ICCs. The ICCs for R_0 were 0.9947-0.9999 (CI 0.9920-0.9999).

4.4.4 Sensitivity

The MDD is the sensitivity of a measure, and is the magnitude of a change that a measurement tool can detect with 95% sureness. It is an indication of the clinical utility of a measure (Edgar, Briffa, et al., 2009). The hand BIS measures are shown in Table 3.

Table 3: Hand BIS measurements, reliability and sensitivity analyses

Hand BIS	Session	Mean (SD) (Ω)	$MDD_{(99,\ 1.984)}$ (Ω)	Mean (SD) (Ω/cm)	$MDD_{(99,\ 1.984)}$ (Ω/cm)	Within-session ICC (95% CI)
Position 1	1	86.8 (19.0)	3.86 (4.45%)	11.9 (3.15)	0.48 (4.04%)	0.995 (0.992-0.997)
	2	95.5 (20.2)	0.97 (1.01%)	12.9 (3.39)	0.12 (0.96%)	0.999 (0.999-1.000)
*Position 2	1	93.6 (21.5)	1.73 (1.84%)	13.0 (3.70)	0.23 (1.74%)	0.999 (0.999-1.000)
	2	101.4 (23.2)	0.74 (0.73%)	13.9 (3.83)	0.09 (0.66%)	0.999 (0.999-1.000)
Position 3	1	96.8 (20.5)	2.89 (2.99%)	10.9 (2.53)	0.34 (3.10%)	0.998 (0.996-0.999)
	2	105.0 (22.0)	2.09 (2.00%)	11.8 (2.86)	0.19 (1.60%)	0.999 (0.998-1.000)
Position 4	1	100.0 (21.4)	1.66 (1.66%)	11.2 (2.71)	0.17 (1.54%)	0.999 (0.999-1.000)
	2	110.7 (24.9)	0.88 (0.80%)	12.4 (3.14)	0.10 (0.80%)	0.999 (0.999-1.000)

* not valid compared to Position 1; MDD = Minimum Detectable Difference

4.5 Discussion

The findings of this study demonstrate that the use of BIS to measure the impedance of the ECF, and therefore edema, following hand burn injury is sensitive and reliable, and correlates strongly with the reference standard of WDV. Post burn edema formation is rapid, with up to 90% of edema formed within four hours following partial thickness burn injury and maximum edema present between 12-18 hours post injury (Demling, 2005). Resorption of this post burn edema is complete within four days in partial thickness injury, however this is slowed in full thickness injury, due to damage to dermal lymphatics (Pitt et al., 1987). The use of BIS within these timeframes associated with post-burn edema formation and resolution would be reflective of acute burn edema (change). Edema that is poorly managed in the inflammatory period may begin to organize and become more viscous, which results

in organization or fibrosis (Villeco, 2012). Techniques have been described using BIS to measure tissue changes in long standing lymphedema, which may be an applicable technique for measuring chronic burn wound edema (Czerniec et al., 2015; Dylke et al., 2013).

The BIS device used in this study, the Impedimed SFB7, utilizes a tetra-polar electrode array, requiring the placement of two current drive electrodes, and the two current sense electrodes are placed within the drive electrodes to detect the impedance to the current flow within the tissues. It has been reported that decreasing the distance between the drive and sense electrodes results in increased impedance and reactance (Shiffman, 2013). Improved accuracy of BIS for measuring body composition were demonstrated using fixed-distance electrodes, which maintain a standard 5cm distance between the sense and drive electrodes (Moon et al., 2010).

This requirement therefore limits the use of BIS for measuring hand volumes to the "palmar volume" of the hand, being the volume between the sense electrodes (from the base of the carpus, in line with the ulnar styloid, to the third metacarpo-phalangeal joint, or measurement excluding fingers). Additionally, in the initial measures of hand volume using BIS, Ward et al. (2012) investigated the bioimpedance of a hand phantom, and then replicated this in vivo. The authors showed that impedance along the length of the thumb, from the first webspace to the tip, remained constant, indicating that the volume of this part of the thumb is not included in BIS of the hand. As a result, comparisons of BIS measures to WDV results in the introduction of a systematic bias inflating water displacement volumes, compared to BIS, which measures: 1) only the "palmar volume" of the hand; and 2) measures only the extra-cellular component of this part of the hand.

The sensitivity of BIS in measuring only the ECF makes it ideal for measuring edema following hand burn injury. The accepted reference standard of WDV may lack the sensitivity to detect changes in edema, as the extra-cellular fluid, including lymphatic fluid, is approximately 25% of the total volume of the limb. As water displacement measures total volume of the hand, it therefore decreases the sensitivity by four times in comparison to any technique that measures extracellular volumes directly (Cornish et al., 2001; Czerniec et al., 2011). This is reflected in the lack of agreement between water displacement and the calculated ECF volume (Figure 6). Also contributing to

the lack of agreement is the lack of an algorithm to calculate the volume of ECF in the hand using BIS, due to the complex shape of the hand (Ward et al., 1992).

The agreement between BIS and the reference standard of water displacement, and therefore the validity of BIS in measuring hand volume, is affected by the lack of sensitivity of water displacement at measuring changes in the extra-cellular volumes (Ward et al., 1992) (Figure 6). However, the correlation (Pearson's r) between the BIS impedance values in this study and water volume was -0.831 to -0.798 (p<0.001), which compares favorably with the correlation between impedance and perometry of -0.794, as reported by Dylke et al. (2014). Water displacement was found to be poorly correlated with single frequency bioimpedance of the lower leg in a group of patients with vascular ulcers (Barnes et al., 1992).

The measures of WDV in this study were obtained with the patients standing. Effect of posture on performance of volumetry, demonstrated high reliability for test-retest correlations with testing performed in sitting and standing (Stern, 1991). Mean seated posture was 5.3mL less than standing, however this is within the ±10mL test-retest reliability when the correct technique is used, and also less than the 5% margin of error attributed to daily fluctuations and measurement error (Bear-Lehman & Abreu, 1989; Palmada et al., 1998; Stern, 1991).

The sensitivity of the BIS for measuring change in ECF impedance was demonstrated to be <3.9Ω, or <0.5Ω/cm, which equated to <4% of the total measured ECF impedance. This compares to the reported sensitivity for whole arm water displacement volumetry of 47ml (2.6%) in healthy volunteers and 96.6ml in burn patients (Edgar et al., 2014), and the weighted mean smallest detectable change for water displacement in a lymphedema population was reported as 3.6% (Hidding et al., 2016).

Within session reliability of BIS in this study, measured using ICC, was very high, for both R_0 and for R_0/distance 0.995-0.999 (95% CI 0.992-1.00). Similarly high reliability for BIS has been reported previously in studies of burn patients for measuring whole body, segmental limb, and localized wound BIS (Edgar, Briffa, et al., 2009; Kenworthy, Grisbrook, Phillips, Gittings, et al., 2017). The test-retest

reliability for BIS in measuring hand impedance has been shown to be 0.942 (95% CI 0.900-0.967) in healthy volunteers (Dylke et al., 2014).

A limitation of this study is that the patients presented with minor hand burn injury (hand TBSA injury was $0.35 \pm 0.23\%$). The use of BIS to measure edema requires electrodes to be placed on intact skin, which restricts the application of BIS to smaller hand injury where skin is preserved at electrode sites. However, BIS has been demonstrated to be valid in burns <30% TBSA for measuring whole body fluid shifts; and is valid using alternate electrode positions for whole body and upper limb measures in burns >12% TBSA (Edgar, Briffa, et al., 2009; Kenworthy, Grisbrook, Phillips, Gibson, et al., 2017). These studies indicate that BIS should remain valid when measuring hand volumes in larger TBSA, although this is an opportunity for future research.

4.6   Conclusion

This study has demonstrated the use of BIS as a valid, reliable and sensitive in measuring fluid volumes in the extra-cellular space, and therefore edema, following acute hand burn injury. This provides clinicians a real-time indication of (change of) edema to guide the effective of treatment and management techniques.

4.7   Acknowledgements

4.8   References

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To Whom It May Concern

The PhD candidate, Dale Owen Edwick, contributed 85% to the intellectual property associated with the paper/publication entitled *Bioimpedance spectroscopy is a valid and reliable measure of edema following hand burn injury (Part 1 – Method validation)*. The final 15% is contributed by the co-authors of the paper.

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CHAPTER 5   **RANDOMISED CONTROL TRIAL OF COMPRESSION INTERVENTIONS FOR MANAGING HAND BURN EDEMA, AS MEASURED BY BIOIMPEDANCE SPECTROSCOPY.**

5.1   Abstract

Introduction: Compression, a common treatment of choice for the management of edema, is one intervention which is applied with little objective understanding of the optimal parameters of application or efficacy in acute burn wounds.

Aim: The aim of this study was to determine the effectiveness of different methods of compression for the management of hand edema following burn injury. The primary hypothesis tested was: in acute hand burn injury, application of cohesive bandage will reduce edema faster than a generic compression glove.

Methods: A randomized control study of 100 patients presenting with hand burn injury. Compression was randomized to one of three methods of application - 1) spiral application of Coban to fingers, figure of eight to hand and wrist; 2) pinch application of Coban to fingers, spiral application to hand and wrist; or 3) a generic compression glove (control condition). Bioimpedance spectroscopy (BIS) was used to measure hand volumes. Hand and wrist range of movement, pain scores and QuickDASH were recorded.

Results: One hundred patients (68 males) demonstrated significant reductions in hand volumes, using all compression methods. Both methods of applying Coban resulted in significantly greater reductions in edema compared to the generic compression glove. Notwithstanding compression method, all ROM measures improved, with significant improvement in thumb opposition (p=0.046), hand span (p=0.020) and wrist flexion (p=0.020). QuickDASH decreased between sessions (p<0.001).

Conclusion: Different methods of applying Coban are superior to generic compression gloves for managing acute hand burn edema.

Keywords

Hand burn injury; hand volume; edema; compression; bioimpedance spectroscopy

5.2   Introduction

The management of edema following burn injury is integral to the reduction of pain, optimizing function, and minimizing the depth of the burn wound. The three zones of a burn injury are described as the zone of coagulation, the principally damaged tissue due to contact with the burn agent; the surrounding zone of stasis, which may be salvaged but is susceptible to edema; and the outermost zone of hyperemia, which results from an increased perfusion to the injury (Hettiaratchy & Dziewulski, 2004; Jackson, 1953; Wurzer et al., 2018). Edema is part of the body's natural response to injury, and is especially prevalent following burn injury due to vascular permeability changes, resulting in an expansion of fluid, primarily in the extracellular space (Demling, 2005; Lund et al., 1992; Remensnyder, 1972; Wurzer et al., 2018). This increase in fluid forms a barrier between the burned tissue and the vascular bed, increasing the oxygen diffusion distance and resulting in a reduction of nutrient flow (Lund et al., 1992; Sevitt, 1958). Edema management in burns is therefore recognized for its potential to negatively influence the zone of stasis, and therefore potentially prevent burn wound conversion (Lund et al., 1992; Singh et al., 2007; Zawacki, 1974a). In addition, the decreased oxygen perfusion to the wound associated with edema may result in an increased risk of infection, due to tissue hypoperfusion and poorer oxygenation (Heughan et al., 1971; Hunt et al., 2000; Hunt et al., 1975; Lund et al., 1992; Whitney, 1990).

In addition to managing edema for prevention of burn wound conversion, poorly managed edema in hand injuries results in poor functional outcomes. Increased volumes of intra-articular fluid within the metacarpal-phalangeal joint (MCPJ) causes joint extension, which results in flexion of the proximal inter-phalangeal (PIP) and distal inter-phalangeal (DIP) joints (Kamolz et al., 2009). This is exacerbated by the patient naturally adopting this position of comfort (Abu Sittah et al., 2011; Dewey et al., 2011; Smith et al., 1998), which, if allowed to persist and contracture occurs, is known as the claw hand deformity (Fufa et al., 2014; Pan et al., 2015).

Compression is a commonly used therapy for more proactive management of edema following burn injury, however therapists often apply compression with little rationale for their choice of compression or detailed understanding of the method of application (Glassey & Phillips, 2011). The use of compression for managing edema

is proposed to restrict the available space for edema to accumulate, and to provide a counter-pressure to the muscle pump, which improves circulation efficiency by overcoming the elastic insufficiency of edematous skin and tissues (Villeco, 2012). External compression facilitates the flow of edema into the venous and lymphatic systems by the application of a pressure gradient (Brennan & Miller, 1998; Glassey & Phillips, 2011; Puddicombe & Nardone, 1990; Villeco, 2012). External compression has also been shown to increase the efficiency of lymphatic clearance (Miller & Seale, 1981).

The use of Coban compressive bandage has previously been investigated in a case study of a patient following skin grafting to the dorsum of bilateral hands, which demonstrated reduced volumes with the use of compression (Lowell et al., 2003). In another case report, Coban was shown to reduce observable edema when applied in the post-operative period, six (6) days after skin grafting (Ward et al., 1994). However, there is a paucity of controlled studies for managing local edema following burn injury (Edgar et al., 2011).

This study was designed as a randomized control trial investigating the use of different methods of compression to manage acute wound edema following burn injury to the hand. The aim of this study was to investigate commonly applied methods of compression for managing acute hand burn edema to determine whether one method was superior to the others.

5.3 Methods

5.3.1 Participants

Participants in this study were recruited from patients presenting to the State Adult Burns Unit at Fiona Stanley Hospital. Patients were approached to participate in this study if they presented with burn injury including a portion of a hand, without restriction to TBSA injured, however burn injury affecting electrode placements for measurement by BIS were excluded. The cohort studied presented with minor burn injury, with only five of the patients requiring surgery. Other exclusion criteria for this study related to bioimpedance spectroscopy (BIS) manufacturer contraindications and included: women reporting suspected or confirmed pregnancy or breast-feeding individuals, surgical implants and stimulators, including cardiac pacemakers. Injuries

due to exposure to electrical current were also excluded, due to possible altered tissue current transmission when using BIS. Participants with peripheral vasculopathies and neuropathies and other conditions affecting sensation were also considered contraindications for participation in this study.

5.3.2   Intervention

The study was conducted as a randomized control trial. One hundred (100) patients were recruited to the trial. In order to detect a difference of medium effect size (Cohen's d = 0.5) with a paired t-test, assuming an alpha of 0.05, 30 patients per group were needed with 10% redundancy incorporated for drop outs. Patients were allocated to groups using a random number generator within Microsoft Excel 2010 to receive one of three methods of applying compression for managing edema.

The intervention methods investigated were a control application of a generic compression glove (Norco, North Coast Medical Inc, California, USA) (Figure 1), and two methods of applying a customized elasticized cohesive bandage (Coban) formed into a compressive 'glove' to the hand (3M Australia, North Ryde, NSW, Australia). A cylindrical application (Figure 2) of Coban used 10cm Coban applied as a cylinder and pinched along the dorsum of the fingers to achieve a pressure gradient from distal to proximal, and then 10cm Coban was applied in a spiral application with 50% overlap from the hand to the mid-forearm. The spiral application (Figure 3) used 2.5cm Coban applied to the fingers with 50% overlap, and a figure-of-eight application using 5cm Coban to the hand and 7.5cm Coban from the wrist to the forearm. Each application of Coban was applied at an estimated 50% of full stretch (Lee et al., 2006). Latex free Coban was used in those patients who reported a known sensitivity to latex.

The generic compression gloves were sized according to the manufacturer's instructions. The width of the patient's hand was measured from the radial border of the second MCPJ to the ulnar border of the fifth MCPJ, along the distal palmar crease, and the corresponding sized glove was fitted following the completion of dressings. Patients were re-measured for compression gloves at subsequent reviews when ongoing edema management was indicated.

Figure 1: Generic compression glove

Figure 2: Cylindrical / pinch application of Coban

Figure 1: Generic compression glove

Figure 3: Spiral application of Coban

All patients received a standardized home exercise program of active tendon glide exercises, and sustained finger abduction followed by composite finger flexion into a complete fist, which has been demonstrated as resulting in an increased venous outflow compared to fist-clenching alone (Simons et al., 1996). The home exercise program was modified to include additional exercises based on the location of the burn wounds to facilitate active stretch, including first webspace stretching, and active and passive wrist flexion/extension and thumb opposition where appropriate. Patients were encouraged to perform ten repetitions of range of movement exercises hourly when awake, including the use of passive over-pressure.

Patient education was also standardized to encourage normal use of the affected hand during the performance of activities of daily living. At rest, the patient was encouraged to elevate the affected hand above the level of the heart, including elevating the hand on two pillows when asleep in bed, which was encouraged in this patient cohort based on the decreased hand volumes demonstrated with hand elevation of 30°, while the patient rested supine (Boland & Adams, 1998).

Patients were educated and made aware of the requirement to report potential alterations to neuro-vascular symptoms in the fingers and hands (tingling, pins and needles, numbness, and coldness) with the application of compression. The patients were informed to elevate the hand and maintain ROM if these symptoms occurred, and to remove the compression if the symptoms did not resolve or worsened.

5.3.3 Ethics

Ethics approval was granted South Metropolitan Health Service Human Research Ethics Committee (HREC) (reference 16-143) and by The University of Notre Dame Australia HREC (reference 016128F). Recruitment commenced in November 2016. The trial was registered with the Australian and New Zealand Clinical Trials Registry, registration number ACTRN12616000810415.

5.3.4 Equipment

Measurements of BIS were recorded for the affected hand using electrode positions enabling electrode placement on intact skin. The bioimpedance device used to obtain the measures was the Impedimed SFB7 (Impedimed Pty Ltd, Brisbane, Queensland, Australia), which is a multi-frequency bioimpedance analyzer, measuring at 256 discrete frequencies between 4-1000 kHz.

Bioimpedance spectroscopy is a measure of body composition, which utilizes the relationship between electrical impedance and water content in the body to provide measures of body composition (Kyle et al., 2004a). At a frequency approximating 0 kHz, the current does not penetrate the cell membrane and the current follows the fluid in the extracellular space, providing measures for the resistance of the extracellular fluid, known as R_0. The magnitude of R_0 is inversely proportional to the volume of the fluid in the extra-cellular compartment, and therefore tissue edema (Ward et al., 2009b). At very high frequencies, the current overcomes the reactance, or capacitance, of the cells, which provides a measure of the impedance of the total body fluid, known as R_∞. Direct currents result in significant electrode-skin impedances, and there are practical limitations of using very high frequency alternating current in the human body (Kyle et al., 2004a). As a result, R_0 and R_∞ are predicted using Cole-Cole plots (Cole & Cole, 1941). Following removal of the dressings and washing of the burn wounds using Chlorhexidine Pre-Op wash, the patient rested in supine with the hand resting by their side, abducted ~30° from the side of their body. After the hand was dried, intact skin at the location of the electrodes was cleaned with an alcohol swab and allowed to dry. The electrodes used for measuring BIS were Ag/AgCl Eurotrode PFR2034 disposable resting ECG tab electrodes (reference code 12774, Pirrone srl, Milan, Italy). Electrodes placed on the distal phalanx of the middle finger and at the level of the third metacarpo-phalangeal

joint were cut in half lengthways, described by Ward et al. (2012), and using the alternate electrode positions previously investigated by the authors (Edwick et al., 2020a). The distance between the electrode positions was measured using a standard measuring tape. Where the sense electrodes were located on the opposite side of the hand, a linear axial measure was obtained from the proximal edge of the distal sense electrode to the wrist crease in line with the ulnar styloid, at the position of the distal edge of the proximal sense electrode. The use of BIS for measuring hand edema using R_0 has been shown to be sensitive, reliable and valid in patients with hand burn injury (Edwick et al., 2020b). BIS measures were completed within 10 minutes of removal of the dressings.

Active range of movement (ROM) measures for the hand and wrist were obtained with no compression applied, and also with compression in situ at each session. Hand ROM is reduced following burn injury in association with the effects of edema, which alters the biomechanics by stretching the elastic skin on the dorsum of the hand and thereby restricting its normal amplitude of movement (Collings, 1999). Between session measures of ROM without compression will provide an indication of the association of edema on hand ROM. Measures with compression in situ will determine how restrictive each method is to movement.

Wrist flexion and extension were measured using a Baseline^{TM} 8 inch, 360° transparent plastic goniometer; linear measures for hand composite finger flexion - recording the distance from the little finger pulp to the distal palmar crease; and hand span - measuring the distance between the thumb pulp and little finger pulp were obtained using a non-stretch measuring tape (Edgar, Finlay, et al., 2009). Thumb opposition used the Kapandji scale, and measured the location touched by the thumb pulp, with 0 indicating no movement, 1 measured to the proximal interphalangeal joint of the index finger, to 10 (ulnar distal palmar crease) (Kapandji, 1986).

The shortened version of the Disability of Arm, Shoulder and Hand (QuickDASH) was completed after each session to assess changes in the patient's self-reported hand function with changes in edema. The Quick DASH has previously been shown to be reliable and valid in patients following upper limb burn injury (Wu et al., 2007).

5.3.5 Statistical analysis

The SFB7 data were downloaded and processed for analysis using the proprietary software (Bioimp version 5.4.0.3, Impedimed Ltd, 2012, Brisbane, Queensland, Australia), thus applying the Cole model to determine BIS variables. All analyses were performed using Stata Statistical Software, release 15 (StataCorp LP, 2017, College Station, TX, USA). Descriptive analyses were completed and presented using means and standard deviations (SD).

The SFB7 was configured to record BIS measures in triplicate. All three repeated, within session measurements were recorded and included in the analysis, using mixed-effects linear regression analyses to assess associations with the BIS variables and compression methods. A series of mixed effects regression analyses were also performed to determine whether there was a difference in measured ROM outcomes between each session, and between each method of compression applied. Hand composite finger flexion is a linear measure with an optimal outcome of zero (0 cm), so this was analyzed using a mixed-effects negative binomial regression. Thumb opposition was analyzed using a mixed effects tobit regression (censored regression model), to account for the Kapandji measure being bounded at zero and 10.

The results are reported as regression coefficients, with 95% confidence intervals. Contrasts were used to determine main effects and interactions. A *p*-value of less than 0.05 was considered statistically significant.

BIS variables recorded have previously been shown to be influenced by body mass index (BMI), gender and age. The size and depth of a burn injury are also known to affect edema. Therefore, a step-wise, backward elimination of non-significant covariates was completed using a series of mixed effects regression analyses to assess the effect each of these variables on the BIS measures.

5.4 Results

5.4.1 Demographics

Patient recruitment commenced in November 2016 and was completed in August 2019. One hundred (100) patients (68 male) were recruited. Mean age of these patients was 40.1 ± 13.8 years, mean BMI was 28.4 ± 5.8 kg.m^{-2}. Mean total body

surface area (TBSA) injured was $0.51 \pm 0.96\%$. Table 1 displays these variables for each compression group. Patients were recruited 2.81 ± 1.69 days post injury (range 0-8 days, median 2 days). Compression was applied for 2.11 ± 0.40 days (range 1-3 days). Three patients had compression applied for one day, and 13 patients remained in compression for three days.

Four patients did not attend follow-up review - one patient was lost to follow-up, another patient continued treatment at a rural facility, and two others declined additional measurements for the study. In addition, a malfunction anomaly of the BIS device was noted during data download for one additional patient, and this BIS data was unusable, but follow-up ROM measures were included in the analysis for this patient. The data for these five patients were excluded from the analysis.

Additionally, four patients removed the compression from fingers due to complaints of numbness, tightness or restricted movement (three patients from the spiral application group, one patient from the cylindrical / pinch application group). An additional patient (from the cylindrical application group) removed all of the compression, reporting that the dressings were malodorous, which was suspected to be a result of when the dressings and Coban became wet while the patient was cleaning the previous day. There was no clinical sign of infection in this patient. No other complaints or difficulties wearing each method of compression were reported. The data from these patients who broke protocol by removing compression were included in the analysis

.

Table 1: Participant summary statistics

	Glove Mean (SD)	Med (IQR)	Cylinder Mean (SD)	Med (IQR)	Spiral Mean (SD)	Med (IQR)	p-value
N	34		33		33		
Gender	Female = 8	Male = 26	Female = 14	Male = 19	Female = 10	Male = 23	NS
Age	43.2 (14.2)	41 (23)	37.9 (14.5)	34 (21)	40.3 (13.6)	37 (25)	NS
BMI (kg.m^{-2})	26.9 (4.84)	27.0 (4.67)	27.7 (5.71)	27.3 (6.52)	29.5 (6.32)	27.9 (5.84)	NS
Weight (kg)	82.4 (19.5)	83.6 (15.3)	83.4 (19.5)	83.5 (28.2)	90.7 (26.8)	85.7 (18.2)	NS
Height (cm)	174.5 (10.6)	175 (10)	174.3 (12.0)	175 (15.5)	173.5 (9.69)	172 (12)	NS
Hand TBSA (%)	0.36 (0.23)	0.3 (0.39)	0.33 (0.25)	0.25 (0.39)	0.37 (0.22)	0.40 (0.30)	NS
Depth	SPT = 25 Mixed = 8 DPT = 1		SPT = 21 Mixed = 8 DPT = 4		SPT = 23 Mixed = 7 DPT = 3		NS

BMI = Body Mass Index; SPT = Superficial Partial Thickness; DPT = Deep Partial Thickness

There was a significant difference in the efficiency of edema reduction, as measured by BIS, in favor of both methods of applying Coban compared to the generic compression glove (compression x days post injury interaction) – Spiral application X^2 (1, N=720) = 7.31, p=0.007; Cylinder application X^2 (1, N=685) = 6.26, p=0.01. There was no evidence of difference between the efficiency of edema reduction between the two methods of Coban application (compression x days post injury interaction) X^2 (1, N=733) = 0.00, p=0.948. The edema change for each method of compression is displayed in the predicted margins in Figure 4, which accounts for the influence of each significant covariate on the BIS measure R_0.

Figure 4: Predicted margins for the change in edema, measured using BIS (R_0), for each compression method
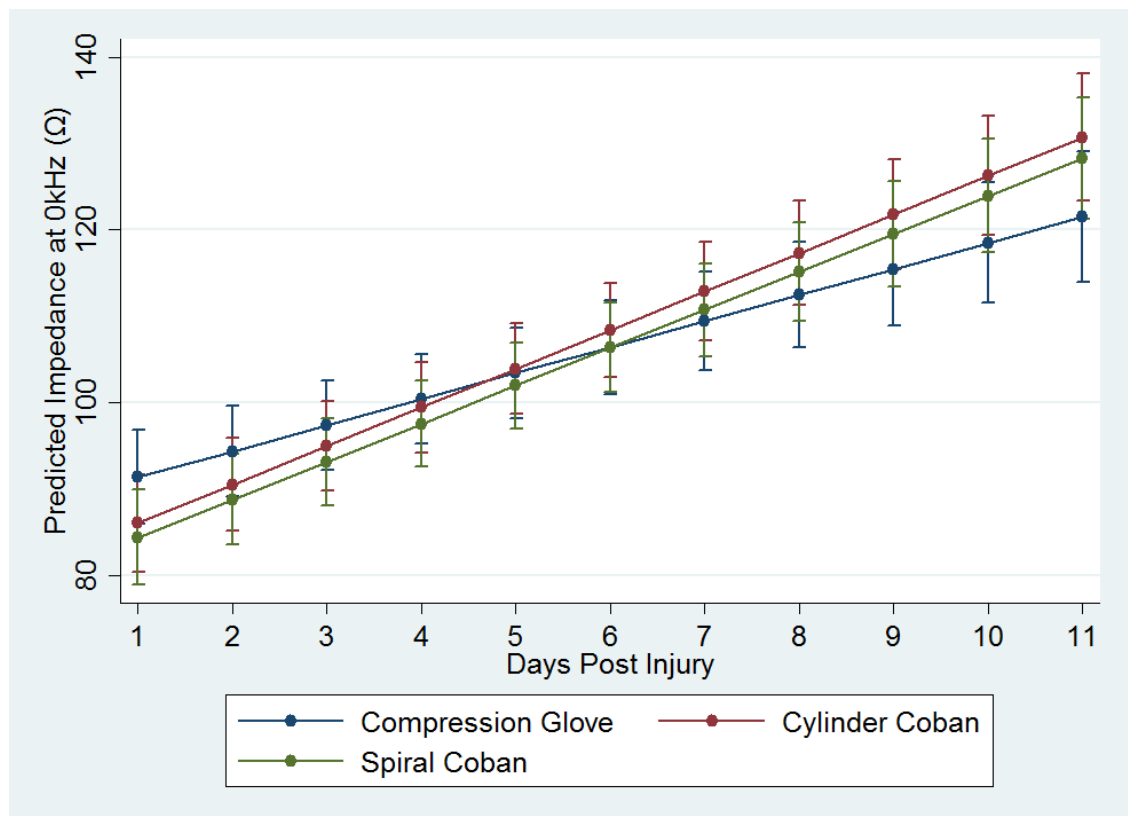
The measures for active ROM were assessed at each session to determine if there were changes as edema changed. ROM was assessed both with no dressings and with compression in situ over the wound dressings. Table 2 presents the ROM measures assessed at the follow-up session for patients following the removal of the dressings, to assess the effect of applied compression, change in edema and function achieved with education and implementation of a home exercise program. There was a non-

significant improvement in hand composite flexion (p=0.467) and wrist extension between sessions (p=0.310). These results are representative of a ceiling effect for these ROM measures, as the measures for hand composite flexion and wrist extension were maximized at both timepoints. All other ROM measures improved significantly. There was a non-significant reduction in pain (p=0.153), while the QuickDASH improved significantly between sessions (p<0.001, CI -15.2 to -8.52).

Table 2: Change in outcome measures between sessions for all compression methods (with dressings removed

ROM measure	Δ Baseline	p-value	95% Confidence Interval	
			Lower	Upper
Hand CFF (cm)	IRR 0.64	0.442	0.21	1.99
Thumb Opp (Kap)	0.36	0.046*	0.01	0.72
Hand Span (cm)	0.29	0.020*	0.05	0.55
Wrist Flex (°)	3.49	0.020*	0.56	6.42
Wrist Ext (°)	1.98	0.247	-1.37	5.32
Pain (VAS)	-0.64	0.086	-1.37	0.09
Quick DASH	-11.9	<0.001*	-16.5	-7.24

*p<0.05. Δ – Difference from baseline measures. IRR – Incidence rate ratio

The outcome measures recorded for each compression method, with the compression removed, are shown in Table 3. These results are compared to the baseline ROM recorded in session one prior to the application of dressings, and demonstrate changes due to changes in edema. Hand span, wrist flexion and Quick DASH improved for all compression methods. Additionally, there was significant improvement in hand composite flexion and wrist extension for the spiral application of Coban, while thumb opposition improved for the compression glove group. There were non-significant decreases in pain scores for each compression method.

Table 3: Change in outcomes between sessions (with dressings removed)

ROM Measure	Compression Glove Δ Baseline	95% CI	Cylinder Coban Δ Baseline	95% CI	Spiral Coban Δ Baseline	95% CI
Hand CFF (cm)	IRR 0.64	0.18, 2.23	IRR 0.61	0.21, 1.79	IRR 0.23 *	0.06, 0.85
Thumb Opp (Kap)	0.359 *	0.02, 0.69	-0.037	-0.33, 0.26	0.291	-0.09, 0.67
Hand Span (cm)	0.293 *	0.07, 0.52	0.386 *	0.10, 0.68	0.403 *	0.15, 0.66
Wrist Flex (°)	3.552 *	1.43, 5.67	3.017 *	0.59, 5.44	4.571 *	1.27, 7.87
Wrist Ext (°)	1.865	-0.75, 4.48	-0.408	-4.00, 3.19	4.143 *	0.51, 7.78
Pain (VAS)	-0.610	-1.41, 0.19	-0.200	-1.14, 0.74	-0.439	-1.20, 0.32
QuickDASH	-11.87 *	-15.1, -8.62	-13.03 *	-16.4, -9.68	-10.44 *	-14.8, -6.12

*$p < 0.05$. Δ – Difference from baseline measures. IRR – Incidence rate ratio

Compression potentially restricts ROM, so to determine if there was a difference between compression methods, active ROM measures were completed with compression in situ. The differences in active ROM between each method of applying Coban, to the control application of a compression glove are shown in Table 4. Both application methods of Coban resulted in a significant reduction in thumb opposition ($p < 0.001$) compared to the compression glove. Non-significant decreased ROM was noted for all other measures for both methods of applying Coban. There was a non-significant increase in hand span with spiral Coban when compared to the compression glove. The reductions in ROM between Coban application methods (when compared to the glove) are not likely to be clinically meaningful due to the short duration that the compression is required to be worn for.

Table 4: Outcomes with application of Coban compared to the control generic compression glove (compression in situ)

ROM Measure	Compression Glove Δ no comp	95% CI	Cylinder Coban Δ no comp	95% CI	Spiral Coban Δ no comp	95% CI
Hand CFF (cm)	IRR 1.00	0.31, 3.25	IRR 0.94	0.33, 2.72	IRR 0.88	0.29, 2.63
Thumb Opp (Kap)	-0.162	-0.41, 0.09	-0.860 *	-1.14, -0.58	-1.354 *	-1.80, -0.91
Hand Span (cm)	-0.341 *	-0.57, -0.11	-0.233	-0.51, 0.04	-0.515 *	-0.74, -0.29
Wrist Flex (°)	-1.252	-4.32, -1.81	-3.484 *	-6.06, -0.91	-2.928 *	-5.57, -0.29
Wrist Ext (°)	-3.534 *	-6.25, -0.82	-4.950 *	-8.19, -1.71	-4.536 *	-7.88, -1.19
Pain (VAS)	-0.121	-0.85, 0.61	-0.504	-1.30, 0.29	-0.380	-1.04, 0.28

*$p < 0.05$. Δ – Difference compared to measures without compression. IRR – Incidence rate ratio

To demonstrate how restrictive to movement each compression method is, the hand and wrist range of movement measures with and without compression in situ were compared, at both sessions. Spiral application of Coban was more restrictive for hand ROM, with all measures except hand composite finger flexion significantly reduced, while the compression glove was least restrictive (Table 5).

Table 5: Reduction in ROM measures with compression in situ, compared to no compression

ROM Measure	Compression Glove Δ no comp	95% CI	Cylinder Coban Δ no comp	95% CI	Spiral Coban Δ no comp	95% CI
Hand CFF (cm)	IRR 1.00	0.31, 3.25	IRR 0.94	0.33, 2.72	IRR 0.88	0.29, 2.63
Thumb Opp (Kap)	-0.162	-0.41, 0.09	-0.860 *	-1.14, -0.58	-1.354 *	-1.80, -0.91
Hand Span (cm)	-0.341 *	-0.57, -0.11	-0.233	-0.51, 0.04	-0.515 *	-0.74, -0.29
Wrist Flex (°)	-1.252	-4.32, -1.81	-3.484 *	-6.06, -0.91	-2.928 *	-5.57, -0.29
Wrist Ext (°)	-3.534 *	-6.25, -0.82	-4.950 *	-8.19, -1.71	-4.536 *	-7.88, -1.19
Pain (VAS)	-0.121	-0.85, 0.61	-0.504	-1.30, 0.29	-0.380	-1.04, 0.28

*$p<0.05$. Δ – Difference compared to measures without compression. IRR – Incidence rate ratio

5.5 Discussion

This study is the first randomized controlled trial investigating the most commonly used methods of applying compression for managing acute hand burn edema. The results of this study demonstrate that in minor burn patients, a spiral application of Coban to the fingers and figure-of-eight application to the hand and forearm (Figure 1) and a cylinder application of Coban to the fingers and spiral application to the hand (Figure 2) result in superior edema reduction compared to a generic compression glove.

A retrospective cohort study of 42 patients with hand burn injury was performed by Park et al. (2016). Of the cohort, 22 patients received a modified hand compression bandaging in addition to standard care and conventional physical therapy, and were compared to 20 patients receiving standard care and physical therapy only for a four-week period post burn. The modified hand compression was applied six (6) days per week during the four-week period, and was applied using one-inch bandage gauze, wrapped from the wrist to all five fingers, which was then bandaged over using short stretch bandage. There was significant reduction in hand circumference, skin thickness measured using ultrasonography, and pain at 4 weeks with the use of the modified compression bandaging (Ause-Ellias et al., 1994; Meyer-Marcotty et al., 2011; Miller et al., 2017; Roper et al., 1999).

In a study investigating edema in acute burn injury, intermittent compression was compared to one cohort treated with immobilization in soft compression and elevation; and to standard dressing with active exercise and elevation in patients presenting within 24 hours of upper extremity burn injury (Salisbury et al., 1973).

Immobilization and soft compression significantly reduced wrist circumference only. Elevation and active exercise had no effect on hand circumferences. Intermittent compression resulted in significantly reduced hand, wrist and finger circumferences, and was significantly better than the elevation and active exercise that patients with bilateral injury received on the contralateral limb. Intermittent compression, however, prevents the patient using the hand normally or performing active range of movement, which has been shown to facilitate edema resorption (Simons et al., 1996).

The number of days post injury in this study was a significant covariate in the analysis, and the compression x days post injury interaction was significant. This is consistent with the pathophysiology of an acute burn injury, where previous research has demonstrated that edema begins to resolve at 24 hours, with complete resolution within six (6) days (Demling et al., 1978). Of the 100 patients recruited to this study, only five (5) required surgery for their injuries. Partial thickness burn injury has been shown to result in greater increases in edema when compared to deep-partial and full-thickness injuries, due to a combination of greater vascular perfusion in partial thickness injury, and greater compromise of vascular and lymphatic structures with increased severity of injury reducing edema resorption in deeper injury (Carvajal et al., 1979; Demling, 2005).

Range of movement (ROM) measures were shown to improve between sessions, and reflects improvements associated with reduction in edema, decreased pain, and as a result of education to continue with active ROM and provision and practice of a home exercise program. Statistically significant improvements in hand composite finger flexion, hand span and wrist flexion were demonstrated with all compression methods. A minimum detectable difference (MDD) of >1cm for linear measures of hand composite flexion and hand span was shown to be a real change in these measures (Edgar, Finlay, et al., 2009), which indicates that edema did not affect these hand ROM outcomes in a clinically meaningful way. Similarly, the changes in wrist ROM measures between sessions in this study were less than the MDD of $\geq 9°$ as reported by Edgar, Finlay, et al. (2009). The improvements in ROM may also be associated with patient confidence and knowledge of importance of maintaining movement, which was part of the education provided to the patients in the initial treatment session. This supports the practice in the author's burn unit of combining

compression and active movement for the proactive management of edema (Puddicombe & Nardone, 1990; Villeco, 2012).

Hand and wrist ROM measures were assessed with compression in situ, and repeated when the compression was removed. Significant reductions in ROM for all measures, except hand CFF, were recorded for the spiral application of Coban with compression in situ (Table 5). Differences in finger ROM have been demonstrated using spiral and cylindrical applications of Coban in healthy populations (Glassey & Phillips, 2011). The cylindrical application of Coban was similarly restrictive, except that hand span was not significantly reduced. Hand span and wrist extension were reduced with the glove in situ. These findings are postulated to reflect the impact of the resistance to active movement due to different levels of compression imparted by these methods of compression, with higher levels of compression hypothesized to be more restrictive to movement. This increased compression associated with spiral application of Coban potentially requires that the patient activate the muscles more strongly against the compression to achieve active ROM. As a result there is potential secondary benefit, with improved ROM for the spiral Coban group once the dressings are removed (Table 3).

Similar reductions in ROM with both cylindrical and spiral applications, when compared to baseline measures for finger and thumb joint measures, were reported in a study in healthy individuals, where spiral Coban applied to the fingers was more restrictive than cylindrical Coban (Glassey & Phillips, 2011). Functional movement and full active ROM was encouraged while wearing the compression to facilitate edema reduction, so while the reduction in ROM is statistically significant, it is not likely to be clinically important given that this compression is temporary during the acute burn period, to facilitate acute edema reduction.

Interface pressure measurement between the skin and compression is measured using either pneumatic pressure transducers, or resistive piezoelectric sensors (Partsch et al., 2006; Partsch & Mosti, 2010). A limitation of this study is that the level of compression provided by each method investigated was not able to be measured, and represents future studies in compression for the management of acute burn edema. Lymphatic clearance has been shown to rapidly increase with an external applied pressure of 30mmHg to 45mmHg compared to uncompressed tissues in animal

models (Miller & Seale, 1981). Application of Coban to the lower leg resulted in mean pressures of 22.8mmHg in a resting elevated position, which was comparable to other cohesive bandages, as well as non-cohesive non-stretch bandages (Lee et al., 2006).

5.6   Conclusion

This study found that there was no evidence of a clinically meaningful advantage between spiral or cylindrical application of a Coban glove to manage acute edema following hand burn injury. In contrast, both methods of applying Coban were superior to a generic compression glove for decreasing hand burn edema. Hand ROM improved between sessions, associated with reduced edema, education, and a home exercise program provided to encourage functional use of the hand.

5.7   Acknowledgements

5.8   References

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To Whom It May Concern

The PhD candidate, Dale Owen Edwick, contributed 85% to the intellectual property associated with the paper/publication entitled *Randomised control trial of compression interventions for managing hand burn edema, as measured by bioimpedance spectroscopy.* The final 15% is contributed by the co-authors of the paper.

I, as a Co-Author, endorse that this level of contribution by the candidate indicated above is accurate.

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CHAPTER 6 **DOES ELECTRICAL STIMULATION IMPROVE WOUND HEALING IN ACUTE MINOR BURN INJURY, AS MEASURED BY BIOIMPEDANCE SPECTROSCOPY? A SINGLE CENTER, RANDOMIZED, CONTROLLED TRIAL**

6.1   Abstract

Background: Electrical stimulation (ES) has been shown to improve wound healing in chronic wounds. Recent studies in burn injured populations have demonstrated that ES improved edema and healing using short duration stimulation. This study utilized a low energy long duration ES using a portable device. The aim was to determine how this mode of stimulation influences the acute burn wound, as measured using bioimpedance spectroscopy (BIS). Our group has previously validated the use of BIS for measuring edema changes with wound healing in burn injured patients.

Methods: This study is a within patient control, randomized study of 30 patients (24 male) presenting with burns to multiple limbs. One affected limb was randomized to receive ES and routine dressings. The other wound received routine care only. Minor burn wounds were stimulated for 10-14 days for more than 20 hours/day. Serial localized BIS resistance and phase angle raw data measures were used to monitor edema and wound responses with treatment.

Results: Multi-level mixed effects regression analyses demonstrated phase angle at 50kHz increased at a faster rate in the stimulated wound. Stimulated wounds exhibited an increased rate of edema reduction as measured by extracellular tissue impedance.

Conclusion: ES was confirmed to be an easily applied adjunct therapy to improve the rate of edema reduction in acute minor burn injury, and positively influences phase angle measures in the acute burn wound.

6.2   Introduction

Electrical stimulation (ES) is an intervention that has been utilized in chronic wound populations, to improve the rate of healing in difficult to heal wounds (Gardner et al., 1999). The tissue level healing outcomes associated with the application of ES is well understood from animal models (Kawasaki et al., 2014). Research confirms improved angiogenesis and nutrient flow to wounds (Kloth, 2005; Polak et al., 2014; Ud-Din et al., 2015), decreased wound edema (Omar et al., 2004), mimicking of the electrical current generated by the 'skin battery' (Foulds & Barker, 1983) which occurs in skin wounds (Kloth, 2005; Weiss et al., 1990), and improved DNA synthesis within the wound (Bourguignon & Bourguignon, 1987).

The use of ES in acute wounds was investigated in a group of 40 healthy volunteers, where an acute cutaneous wound was produced by performing full thickness skin biopsies to bilateral inner upper arms (Ud-Din et al., 2015). The wounds receiving ES showed significant reductions in wound surface area, diameter, volume and depth at time points up to 90 days post intervention. Stimulated wounds also demonstrated significantly increased blood flow and angiogenesis markers across the first 14 days (Ud-Din et al., 2015).

The use of ES has been investigated previously in acute burns populations in two human studies. Microcurrent ES was compared to a negative pressure wound therapy (NPWT) and a control of standard dressings for effect on length of stay, wound colonization and wound surface area by Ibrahim et al. (2019). Compared to the control group, both ES and NPWT showed statistically significant wound area reductions, length of stay and bacterial count. The application of ES was investigated in a group of patients following conservatively managed superficial partial thickness hand burn injury (Omar et al., 2004). There was a statistically significant improvement in hand edema at day 7 and at day 15, with statistically significant improvement in total active movement of the hand at the same time points.

Edema management is critical in acute burn wound healing, as edema forms a barrier increasing the oxygen diffusion distance between the burned skin and the capillary bed leading to skin tissue hypoxia (Demling, 2005; Gosling et al., 1996; Remensnyder, 1972). Mathematical modelling demonstrated that a doubling of the

oxygen diffusion distance due to edema decreases the flow of nutrients to the tissue such that a twentyfold increase in capillary flow rate is insufficient to restore the nutrient flow (Knisely et al., 1969). The zone of stasis is associated with edema formation, and has been demonstrated to be salvageable as accumulated intravascular material is removed with a reduction of edema and a restoration of circulation to the injured skin (Jackson, 1953; Singh et al., 2007; Zawacki, 1974b). Reducing edema in the acute burn wound is therefore one critical method to reducing the risk of wound conversion and improving the outcome for the patient.

Bioimpedance spectroscopy (BIS) is a portable, non-invasive measure of body composition, which has been demonstrated to provide body composition measures in the clinical setting (Earthman et al., 2007). BIS has been used in applications to measure wound healing in burn wound populations (Kenworthy, Phillips, et al., 2017), acute wound pathologies (Kekonen et al., 2017) and in chronic wounds (Lukaski & Moore, 2012), and is shown to be sensitive to reduction in wound edema associated with healing.

The impedance at zero frequency (R_0), which is reflective of the extracellular fluid, and at infinite frequency (R_∞), which is an indirect measure of total body fluid, are extrapolated using Cole-Cole modelling (Cole & Cole, 1941; Cornish et al., 1999). The resistance of the intracellular component of the tissue is R_i. At R_0, the current flow is isolated to the extracellular space, which is a measure indicative of edema (Pichonnaz et al., 2013). Resistance, or impedance, is inversely related to the amount of fluid, so impedance measures should increase with a decrease in edema, due to a decrease in the amount of conductive fluid (Gaw et al., 2011).

Phase Angle (PhA) is a measure obtained using BIS, and is the arctangent of the recorded measures of reactance and resistance, which is expressed in degrees. As the frequency of BIS increases, the current flow overcomes the natural capacitive impedance (reactance) of the cell wall, allowing the current to pass through the cells. The magnitude of the delay to flow of the current through the cell is the PhA, and is believed to be a measure of the health of the cell, as cells with increased integrity have thicker walls and are heavier (i.e. healthier), resulting in an increased delay to the current traversing the cell, resulting in an increased PhA (Moore et al., 2011; Mulasi et al., 2015). Decreased PhA measures are also associated with cell loss,

decreased body cell mass, and deteriorating cell integrity, as well as morbidity in a number of populations, including HIV, renal disease requiring dialysis, liver disease and elderly patients (Jha et al., 2006; Kyle et al., 2004b; Urvashi et al., 2015).

Variations in PhA were demonstrated with chronic wound healing, infection and subsequent breakdown by Lukaski and Moore (2012). Debridement of a chronic wound and application of a skin graft resulted in decreased magnitudes of R_0, PhA and reactance, due to "disruption in cell architecture"; these values increased with wound healing, due to decreases in extra-cellular fluid (edema) and "substantially increased number of cells and wound repair" (Lukaski & Moore, 2012). These findings suggest that BIS can be interpreted as a direct physiological measure of cellular architecture and function (tissue and cellular health) (Foster & Lukaski, 1996; Kumar et al., 2012).

The aim of this study in acute minor burn patients was to determine if local, long duration electrical stimulation improved wound healing compared to control wounds. The secondary aim was to examine if BIS raw variables are a valid measure of acute burn wound healing. It is hypothesized that BIS measures of PhA and impedance will increase with wound healing, and that ES will improve the rate of healing as assessed by these measures when compared to routine care alone.

6.3 Materials and methods

6.3.1 Participants

Participants were recruited from the State Adult Burns Unit at Fiona Stanley Hospital (FSH) from October 2015 to April 2019. Using an internal patient, randomized control design, the sample size of 30 patients was estimated a priori to detect a difference in raw BIS variables of medium effect size (Cohen's d = 0.5) with a paired t-test, assuming an alpha of 0.05. Patients were eligible to participate in this study if they were over 18 years of age, had minor burn wounds of similar size and depth (less than five percent TBSA per limb) to multiple limbs. The design of this study investigated burns of different depths across the participants, however the interventional stimulation wounds and comparator control wounds within the same patient were similar (Figures 1-3).

Figure 1: Control (L) and stimulated mixed partial thickness contact burns.

Figure 2: Stimulated (L) and control deep partial thickness flame burns

Figure 3: Stimulated (L) and control full thickness chemical burns
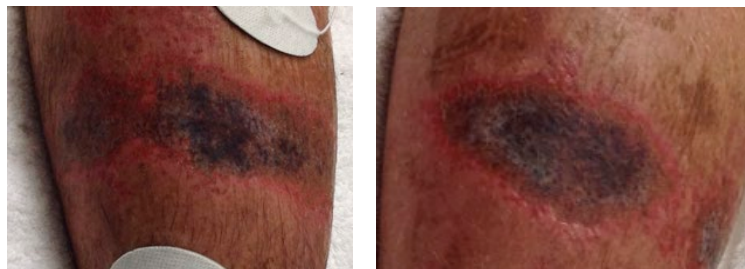
Exclusion criteria included the BIS manufacturer's contraindications of pregnancy and breast feeding individuals, surgical implants and cardiac pacemakers. Peripheral neuropathies or conditions affecting the sensation of the burned limb were also considered contraindications for the ES intervention. Electrical injuries were also excluded.

6.3.2   Intervention

The study was designed as an internal patient, randomized control trial. The intervention wound was randomized by coin toss to received ES in addition to routine dressings, while the control wound received routine dressings only.

The ES intervention duration was for 10-14 days, at >20 hours per day (Figure 4). The intensity of the stimulation was self-selected by the patient, at a comfortable intensity below the level of muscle fiber recruitment (12-30 volts). Frequency of stimulation was 6-12 Hz, and pulse duration was 200 µs, as defined by the ActivMed stimulation device (ActivLife Technologies Pty Ltd, Woodend, Victoria, Australia). ES was delivered using Bio-Flex stimulation electrodes (product code BF-4, Lead-Lok Inc, Sandpoint, ID, USA). One electrode was placed on intact skin at 30mm proximal to the wound, and a second electrode 30mm distal to the wound. This electrode configuration facilitated a current flow across the wound bed with an aim to stimulate the damaged tissues.

Figure 4: Application of Electrical stimulation to burn wound

Patients remained within protocol if stimulation was performed for more than 20 hours per day, and stimulation was not stopped for more than 2 days, except where stimulation was paused during the post-operative period. Patients were excluded where the post-operative pause in stimulation was ≥5 days, and there was only one BIS measure performed prior to surgery. ES was recommenced at the first change of

dressings post-operatively. Patients also received proactive edema treatments from therapists including exercise and compression therapies, and education and facilitation of positioning for elevation of affected limbs, as routine in addition to dressings.

6.3.3 Ethics

Ethics approval was granted by South Metropolitan Health Service Human Research and Ethics Committee (HREC) (EC00265) at Royal Perth Hospital (2014-106), and then FSH when the State Adult Burns Unit transferred to the new hospital in 2015 (ethics approval 14-101). Cross-institutional ethics approval was granted by The University of Notre Dame Australia HREC (EC00418) (reference 019048F). Informed consent was obtained from the patients participating in this study.

6.3.4 Outcome Measures

Serial BIS measurements for impedance (R_0, R_i and R_∞) and PhA were recorded for both wounds at each dressing change, either as an inpatient, or when the patient returned to ambulatory clinics. BIS measures were obtained for bilateral affected limb segments and bilateral wound measures. The bioimpedance device used to obtain the measures was the Impedimed SFB7 (Impedimed Pty Ltd, Brisbane, Queensland, Australia).

The SFB7 is a multi-frequency bioimpedance analyzer, and provides measures of impedance at 256 discrete frequencies from 4-1000kHz, enabling an interpretation of the fluid content of different structures within the tissue. Segmental limb and localized wound measures were obtained using BIS at each change of dressings, and were performed using Ag/AgCl Eurotrode PFR2034 disposable resting ECG tab electrodes (reference code 12774, Pirrone srl, Milan, Italy).

Figure 5: Electrode configuration for localized wound BIS measures
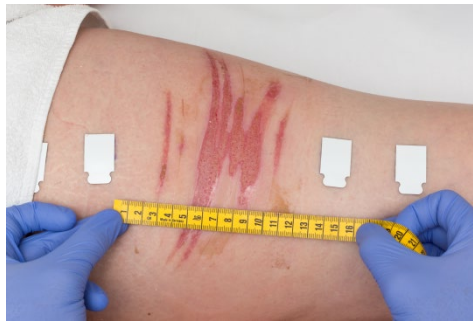
The sites of the electrodes were marked on the intact skin using a surgical marker pen to accurately replicate the positioning of the electrodes over time despite replacement of wound dressings. The electrodes were placed 3cm superior and inferior to the wounds to apply ES, as well as to complete BIS measures. The distance between the electrodes was recorded using a standard, non-stretch tape measure at each session prior to obtaining BIS measures (Figure 5).

Serial wound photographs were performed by the FSH medical illustrations staff using a standardized technique at each dressing change with operator blind to the study methods (Figure 6). These photographs were assessed by an independent, blinded attending burn surgeon to determine percentage re-epithelialization at each repeat measure. This technique has previously been demonstrated to be a valid objective analysis of wound healing as the primary endpoint, with increased reliability noted with experienced observers (Bloemen et al., 2012; Bloemen et al., 2011; Rennekampff et al., 2015).

Figure 6: Image as assessed by consultant burns surgeon for healing
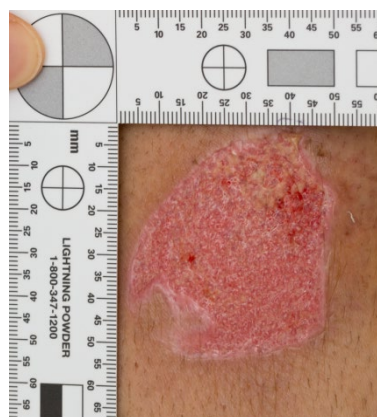
6.3.5   Statistical analysis

The SFB7 data was downloaded and processed for analysis using the supplied software (Bioimp version 5.4.0.3, Impedimed Ltd, 2012, Brisbane, Queensland, Australia) according to the Cole model to determine BIS variables. All analyses were performed using Stata Statistical Software, release 14 (StataCorp LP, 2015, College Station, TX, USA). Descriptive analyses were completed and presented using means and standard deviations (SD).

The SFB7 recorded BIS measures in triplicate. All data from three repeated, within session measurements were recorded and included in the analysis, using multilevel mixed-effects linear regression analyses to assess associations with the BIS variables and healing of the wounds. The analyses were reported as regression coefficients, with 95% confidence intervals. A *p*-value of less than 0.05 was considered statistically significant.

BIS variables recorded have previously been shown to be influenced by body mass index (BMI), gender and age. The size and depth of a burn injury are also known to affect the time to heal, as does the need for surgery. These patient demographics and wound descriptors were assessed for systematic differences, using a paired t-test. A step-wise, backward elimination of these variables was then completed using a series of multi-level mixed effects regression analyses to assess the effect each of these variables on the wound BIS measures.

A series of multi-level mixed effects regression analyses were performed to assess the relationship between wound healing, and the wound BIS variables R_0, R_i, R_∞ and PhA. Similarly, a step-wise, backward elimination of the patient demographic and wound descriptor variables was completed to produce the final model.

Only one patient deviated from the stated protocol, after being discharged following surgery and returning to the ambulatory clinic for first dressings change five (5) days later not having continued the ES intervention. As a result the patient's outcomes were withdrawn from the study. The baseline data for this patient was included in the descriptive data summaries only.

6.4 Results

6.4.1 Demographics

Patient recruitment commenced in October 2015 and was completed May 2019. Thirty (30) patients (24 male, 6 female) were recruited over this period (Table 1). Of the 30 patients in this study, 27 of the patients had burn injury to their legs.

Table 1: Patient summary statistics

	Median	IQR	Range
Age	32.5	27	18-73
BMI	28.1	7.19	17.3-50.5
TBSA Total	4.5	4.1	0.3-15.3

* IQR = Interquartile range; BMI = body mass index

Mean TBSA per wound was $1.61 \pm 1.29\%$, range 0.1-5.5%. There was no evidence of difference between control or ES wounds for TBSA or depth (Table 2). Surgical intervention was required in 20 of the patients, including dermabrasion and ReCell (n=11), and a combination of split-thickness skin graft $\pm$ ReCell (n=9). All wounds were debrided and equivalent surgery technique was applied to each wound of the paired study wounds.

Table 2: Wound summary statistics

	Control Median (IQR)	Stimulation Median (IQR)	p-value
TBSA / wound (%)	1.4 (1.3)	1.33 (1.3)	0.86
Time to heal (days)	19 (10)	19 (12)	0.371
Depth (SPT / DPT / FT)	10 / 14 / 5	11 / 13 / 5	0.91
Surgery type (Conservative / Recell only / SSG)	9 / 11 / 9	9 / 11 / 9	1.00

* SPT = superficial partial thickness; DPT = deep partial thickness; FT = full thickness; IQR = Interquartile range; SSG = split-thickness skin graft

Table 3: Associations of stimulation intervention on localized wound impedance

BIS variable	Covariate	Coefficient	p-value	95% confidence intervals	
				Lower	Upper
R_0 (Ω)	Stimulation ǂ	-4.49	**0.015***	-8.09	-0.88
	Days post stimulation	1.37	**<0.001***	0.99	1.74
	Stimulation x days post stimulation ǂ	0.60	**0.024***	0.08	1.12
	Electrode distance	1.30	**<0.001***	0.93	1.65
	BMI	-2.67	**0.001***	-4.26	-1.08
	Male Gender	-35.4	**0.049***	-70.6	-0.18
R_i (Ω)	Stimulation ǂ	-5.24	0.305	-12.8	4.02
	Days post stimulation	3.26	**<0.001***	1.51	3.36
	Electrode distance	3.93	**<0.001***	2.09	4.82
	Wound TBSA	30.5	**<0.001***	20.1	43.3
	BMI	-5.96	**0.037***	-11.6	-0.37
	Age	3.76	**0.011***	0.88	6.65
	Male Gender	-203.1	**<0.001***	-325.7	-80.5
R_∞ (Ω)	Stimulation ǂ	-3.52	**0.005***	-5.97	-1.07
	Days post stimulation	0.76	**<0.001***	0.52	0.99
	Stimulation x days post stimulation ǂ	0.34	**0.045***	0.01	0.67
	Electrode distance	0.82	**<0.001***	0.57	1.07
	Wound TBSA	4.20	**<0.001***	2.03	6.36
	BMI	-1.45	**0.012***	-2.57	-0.32
	Age	0.70	**0.035***	0.05	1.34
	Male Gender	-45.3	**0.001***	-72.8	-17.8

* $p<0.05$; ǂ Reference values: Stimulation – control wound

Localized wound edema impedance (R_0) in the stimulated wound increased at a faster rate than the control wound (stimulation x days post stimulation interaction, X^2 (1, $N=907$) = 5.06, p=0.024), indicating a faster reduction in ion rich edema in the wound receiving intervention (Table 3, Figure 7). Patient age, depth of wound, the dominant limb, surgery, the mechanism of burn injury and the time post injury were not associated with the measures of R_0.

Figure 7: Mean daily localized wound impedance measures (R_0) for each wound
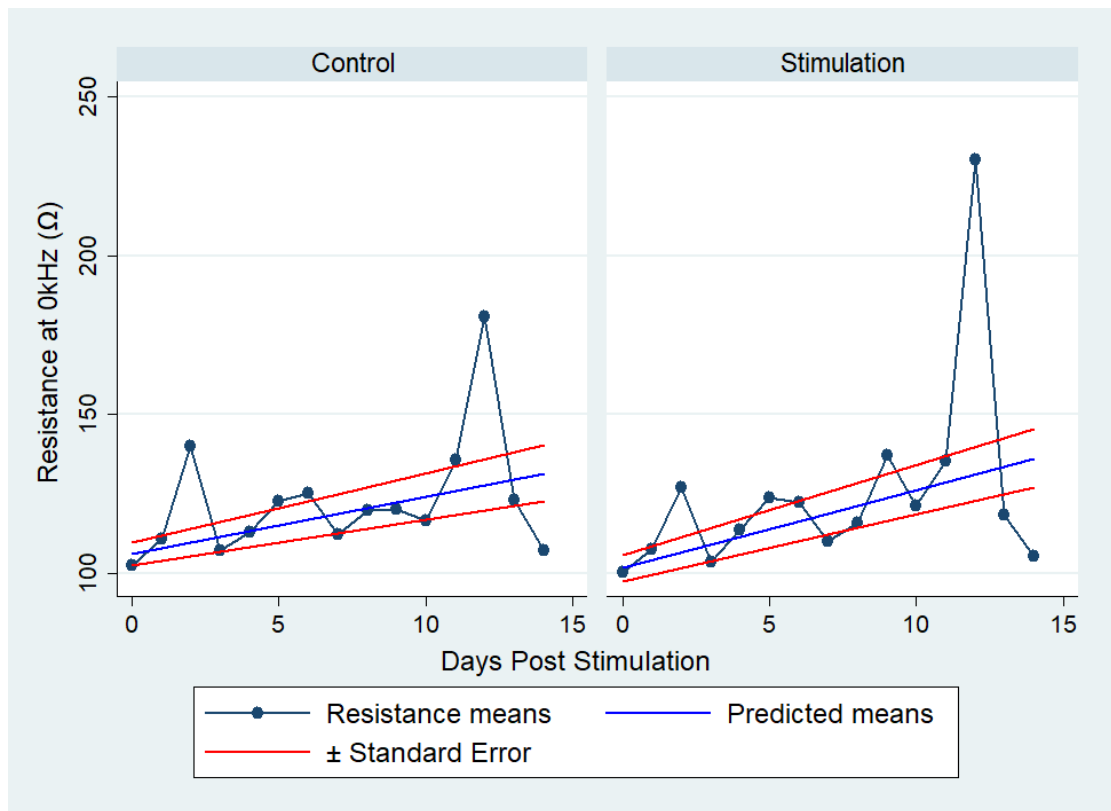
Localized wound intracellular fluid impedance (R_i) increased significantly in both wounds (p<0.001), however there was no difference in the change in R_i between wounds (stimulation x days post stimulation interaction, p=0.135). The mechanism and depth of the injury, surgery, the dominant limb, and the time post injury did not show any evidence of association with change in R_i.

The impedance of the total fluid within the wound (R_∞) increased significantly in both wounds (p<0.001). There was an increase in the rate of change in R_∞ with stimulation compared to the control wound (stimulation x days post stimulation interaction, X^2 (1, N=952) = 4.00, p=0.045). The measures of R_∞ did not show any evidence of association with surgery, the depth of wound, the dominant limb, mechanism of burn injury and the time post injury.

Segmental limb measures (BIS measures of the entire affected limb) failed to demonstrate that ES any evidence of a significant effect on R_0, R_i and R_∞ (p=0.50-0.77). However, impedance measures for R_0, R_i and R_∞ increased significantly in both stimulated and control limbs.

6.4.2   Validity

The BIS measures were pooled for all of the assessed wounds and were analyzed using multi-level mixed effects regression analyses to assess their relationship with wound re-epithelialization (healing). BMI, male gender and wound size were associated with healing. When these were adjusted for, R_0, R_i and R_∞ were significantly associated with wound healing. PhA was significantly related to wound re-epithelialization when fitted into the model independently of the other BIS impedance variables (due to collinearity). As it is a product of impedance and reactance and therefore uses more data to infer a better description of the cell health, PhA may be emerging to be a superior measure of wound healing than impedance alone (Table 4).

Table 4: Relationship of wound healing to localized BIS variables

Wound	Covariate	Coefficient	p-value	95% confidence interval	
				Lower	Upper
Healing	R_0 (Ω)	1.59	<0.001*	1.10	2.08
	R_i (Ω)	0.19	<0.001*	0.09	0.28
	R_∞ (Ω)	-2.14	<0.001*	-3.16	-1.13
	PhA 50kHz (°)	2.25	0.001*	0.87	6.63

* p<0.05

The effect of ES on PhA measures were then assessed. PhA increased significantly in both wounds (p<0.001), however, PhA within the wound increased at a faster rate with stimulation (stimulation x days post stimulation interaction, X^2 (1, N=907) = 9.49, p=0.002) (Table 5, Figure 8). The effects of surgery, the dominant limb, type of injury and the number of days post injury demonstrated no association with PhA changes with ES.

Table 5: Associations of stimulation condition on localized wound phase angle measures

BIS variable	Covariate	Coefficient	p-value	95% confidence intervals	
				Lower	Upper
Phase Angle at 50 kHz (°)	Stimulation ‡	-0.17	0.153	-0.41	0.06
	Days post stimulation	0.03	**0.013***	0.01	0.06
	Stimulation x days post stimulation ‡	0.05	**0.002***	0.02	0.09
	BMI	-0.16	**0.007***	-0.26	-0.04
	Wound TBSA	-0.51	**<0.001***	-0.71	-0.31
	Age	-0.09	**0.004***	-0.15	-0.03
	Male Gender	4.76	**<0.001***	2.14	7.38

* p<0.05; ‡ Reference values: Stimulation – control wound

Figure 8: Mean daily localized wound Phase Angle measures for each wound
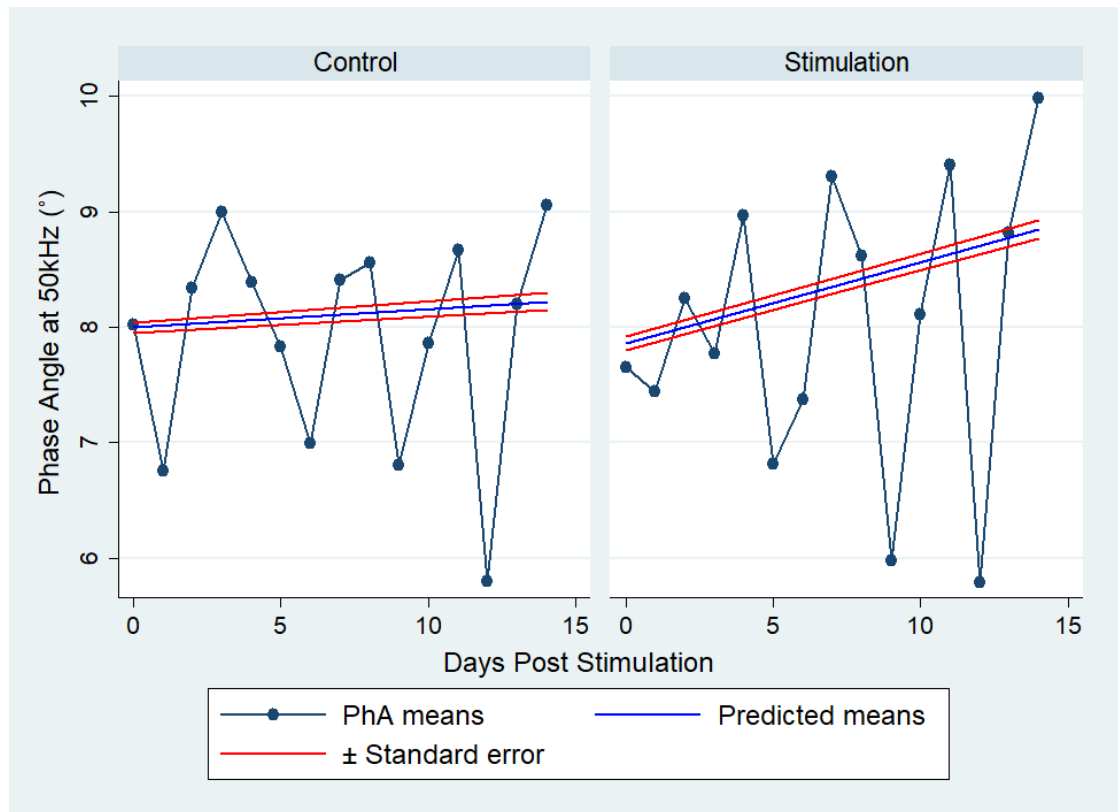
6.5   Discussion

This study is the first randomized trial to investigate a patient applied, long duration, low energy ES intervention in acute burn injury. In comparing burn wounds of similar size and depth within the same patient, our results demonstrate that the use of ES in an acute minor burn wound reduced wound edema at a faster rate (according to the BIS measure of R_0), compared to the control wound. The BIS measure of PhA, also increased in the stimulated wound at a faster rate than the control wound.

The use of BIS to monitor the physiological cellular processes of wound healing, using the PhA measures of cell health, and wound edema impedance measures R_0 and R_∞, may provide a more sensitive measure of burn tissue health at any point in time and be more sensitive than days to to re-epithelialization. Furthermore, wound re-epithelialization can only be measured at dressing changes (and therefore, the outcome is in days), while BIS measures can be applied in real-time and use repeated measures to track tissue health, without the need to remove wound dressings to complete the assessment. The increases in wound impedance measures with increased PhA, R_0 and R_∞, concur with the findings reported by Kenworthy, Phillips, et al. (2017). The measure for R_0, which is indicative of extra-cellular fluid (or edema), and R_∞ (impedance of total body fluid), increased at a faster rate in the stimulated wound, indicating a faster rate of conductive ion rich fluid reduction compared to the control wound. Edema volume reduction in the tissues preserves and salvages the zone of stasis in acute burn injury (Edgar et al., 2011), and ES in this study was associated with an improved rate of edema reduction compared to the control wound. Measures of impedance within the wound for R_i (intra-cellular impedance) increased at significant rates within both the stimulated wound and the control wound. However, there was no evidence that these rates were different between the control and ES treated wounds.

In contrast to the study by Kenworthy, Phillips, et al. (2017), PhA was also demonstrated to be associated with wound healing. The larger dataset, with internal patient control reducing host confounders in this study, in combination with repeated serial BIS measurements up to 14 days, provided adequate statistical power to support a definitive analysis and addressed the sample size limitations in the earlier study.

The lack of a difference in time to re-epithelialize between the control and intervention wounds in this study are due to a) the relatively small size of the wounds (≤5.5% TBSA), and b) in 20 of the patients in this study, the same surgical technique applied to the entire wound surface was consistently performed to achieve rapid closure *in both wounds* (per study patient) involving acute reconstruction (including autologous spray on cell technologies). Due to the study design, it is not surprising therefore, that visual assessment times to re-epithelialization were observed to be similar or equivalent.

This study supports the previous evidence for benefits of ES in acute burn injury (Ibrahim et al., 2019; Omar et al., 2004). While these earlier studies demonstrated positive findings, each imposed significant and unsustainable inconvenience on minor burn patient cohorts to attend hospital to receive ES interventions to achieve the healing outcomes. The ES device used in this study is a small, battery powered device which was easily carried by the patient beneath the dressing bandaging or elasticated tubular retention dressing. The low cost of the device (AUD $235) provides ease of access in the clinical environment. This allowed the participants in this study to continue performing activities of daily living at home while receiving ES.

It has been shown that a 'skin battery' occurs in the presence of wounds to the skin, due to a potential difference between the epidermis and the dermis (Foulds & Barker, 1983). The potential is theorized as a negative gradient between the stratum corneum and the dermis, and the current begins to flow when wounds occur, as the ionic wound fluids short circuit between the layers of the skin causing electricity flow (Gentzkow & Miller, 1991). ES is believed to mimic this battery, and potentially accelerates the wound healing process (Foulds & Barker, 1983; Gentzkow & Miller, 1991).

There are a number of systematic reviews investigating the use of ES in various wound populations (Ashrafi et al., 2017; Gardner et al., 1999; Kawasaki et al., 2014; Lala et al., 2015). Different modalities of stimulation, with variation in duration of treatment were all demonstrated to improve wound healing in chronic wounds when compared to routine care or control wounds. The optimal parameters of ES in chronic wounds are unclear. One hour of stimulation was reported as optimal to observe benefit in healing parameters, with little additional benefit from longer periods of

stimulation in one review (Kawasaki et al., 2014). However, a study of ES in pressure ulcers in patients with spinal cord injury recommended the ES continue for eight (8) hours per day (Houghton et al., 2010). The duration of 20 hours utilized in this study was recommended by the supplier of the ES device. This may help guide future studies investigating ES in burn injury.

The time to heal for burn wound injury is related to the depth and size of the wound, with superficial partial thickness injury usually resulting in unobtrusive, non-hypertrophic scarring (Finnerty et al., 2016). Deep partial thickness and full thickness injuries take longer to heal, which is associated with increased hypertrophic scarring in an animal model (Chan et al., 2012), in experimental human studies (Dunkin et al., 2007) and has been reflected in other retrospective reviews (Cubison et al., 2006; Finlay et al., 2017). Therefore, interventions to increase the rate of healing in burn wound injury may impact positively the scar outcome for the patient. Burn scarring impacts sensation in the skin, thermoregulation and sweating, pruritis, joint mobility and potentially ongoing pain. The application of a wearable ES device in this study improved the rate of wound healing in acute burn injury. A limitation of this study is that long term follow-up was not conducted to determine whether the use of ES had an impact on scarring in this cohort of patients.

Another limitation is that the ES in this study was only applied for up to 14 days, and was not continued until the point of complete re-epithelialization in a small number of study patients, which represents an opportunity for future studies. The authors also reflect that rate of, or percentage area of wound re-epithelialization may not be a good primary outcome in research contexts such as this where surgery is a primary intervention. The authors would therefore advocate that wound healing as measured by re-epithelialization is used only as a secondary or safety (do no harm) outcome.

Future multi-site studies are warranted with an increased sample size and serial measurement of BIS to the point of re-epithelialization, to better identify interpretable differences between wound condition. Additionally, to investigate if there is an impact of an increased rate of healing in acute burn injury using ES on long term scarring, scar outcomes should be investigated in future studies to further support the use of ES in acute wound care. Also, given that proprioception has been shown to be affected by burn injury, and is complicated by scar and tissue contracture, impaired

sensation, muscle weakness and postural imbalance (Finlay et al., 2010), and ES has been demonstrated to improve secondary somatosensory activation in stroke patients (Christensen & Grey, 2013), while knee joint proprioception has improved with ES in a healthy population (Collins et al., 2009), future research into the use of ES in acute burn injury should also investigate the effects of stimulation on neurological recovery.

6.6   Conclusion

The preliminary findings of this single-site study demonstrated a potential benefit for the use of ES an adjunct to standard care for acute burn injury that aids in reducing wound edema, when compared to routine care alone. The use of ES also increased the BIS measure of PhA, at an increased rate compared to routine care. The use of BIS provides a non-invasive physiological measure of cell architecture and function, and should be incorporated into routine research and clinical assessment as an index of wound change in addition to standard methods.

6.7   Declarations

6.7.1   Competing interests

The authors declare that they have no competing interests.

6.7.2   Funding

6.7.3   Authors' contributions

DOE recruited all patients and completed data collection, data analysis and had primary responsibility for preparing the final manuscript. DWE and FW conceived the study; DWE completed all ethics applications and was a major contributor to the editing of the manuscript. DH assisted with the analysis and interpretation of the data. JR contributed to manuscript preparation. All authors read and approved the final manuscript.

6.7.4   Availability of data and materials

6.8   Acknowledgements

6.9   References

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To Whom It May Concern

The PhD candidate, Dale Owen Edwick, contributed 85% to the intellectual property associated with the paper/publication entitled *Does electrical stimulation improve wound healing in acute minor burn injury, as measured by bioimpedance spectroscopy? A single center, randomized, controlled trial.* The co-authors contributed the final 15% to the paper.

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CHAPTER 7   **CONCLUSIONS AND**
                      RECOMMENDATIONS

7.1 Introduction

Physiotherapy in the State Adult Burns Unit at Fiona Stanley Hospital is considered an integral part of the wound management process and outcomes. Physiotherapists encourage and educate patients regarding the importance of regaining and maintaining movement following burn injury, including providing exercises specific to the injury to optimise the patient outcome. After the acute burn injury, physiotherapy interventions are designed to reduce oedema, with education regarding normal use of the hand and exercises to optimise venous and lymphatic return, and the application of compression over dressings to improve oedema reduction. The proactive management of oedema in acute burn injury includes key interventions explored in this research series at this stage of a burn injury that aim to prevent burn wound conversion, optimise healing and therefore reduce the risk of scarring, assist to reduce pain and to prevent loss of function associated with oedema formation.

The aim of this study series was to understand the effectiveness of interventions for managing acute burn oedema by applying sensitive measures of body composition to the unique characteristics of the burn injured population. Bioimpedance spectroscopy (BIS) is a technique that is gaining traction for measuring fluid shifts and oedema in the burn injured population, and has been utilised for measuring hand volumes in a lymphoedema population. The aim of Study One was to validate alternate electrode positions for measuring hand volumes; Study Two investigated the use of these positions in a burn injured population; Study Three used this method to measure the outcome of an intervention trial determining the effectiveness of different methods of compression for managing hand burn oedema; and Study Four was a second intervention trial investigating the use of electrical stimulation as an adjunct to standard burn care for improving oedema and healing rates, measured using BIS.

7.1.1   Study One: Alternate electrode positions for measuring hand volumes, using bioimpedance spectroscopy

A previous investigation of BIS for measuring hand volumes was shown to be sensitive to changes in volume elicited with elevating the hand for a period of three minutes (Ward et al., 2012), however, burn wound injury to the hand complicates the placement of electrodes. The guidelines for the use of BIS state, and clinical experience confirms, that electrodes must be placed on intact skin. Study One

investigated novel configurations of electrodes for measuring volumes in the hand, to enable BIS to be applicable to a range of injuries where wounds are present on the hand. This study compared an electrode array on the dorsum of the hand and forearm previously described in the literature (Figure 1) to electrodes positioned on the volar surface of the finger/hand and wrist/forearm (Figure 2), and a combination of electrodes on the palm of the finger and the hand, and on the dorsum of the wrist and forearm (Figure 3). The findings demonstrated that these alternate electrode positions were equivalent for measuring impedance of the extracellular water (R_0), the impedance of total water (R_∞) and membrane capacitance, where the inter-electrode distance between the sense electrodes was measured axially from the proximal edge of the sense electrode to the ulnar styloid at the level of the distal edge of the proximal sense electrode. Diagonal measures between sense electrodes, where the electrodes were on opposite sides of the hand, were not valid compared to the previously described electrode array on the dorsum of the hand and forearm for measuring bioimpedance of the hand, nor were they clinically acceptable with greater than 5% difference in impedance measures. The alternate electrode positions were also not equivalent for measuring cellular impedance (R_i).

Figure 1: Electrode position 1

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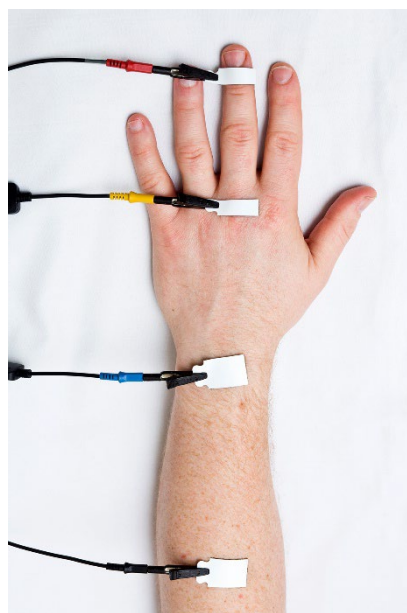
Figure 2: Alternate electrode positions on volar surface of hand and forearm
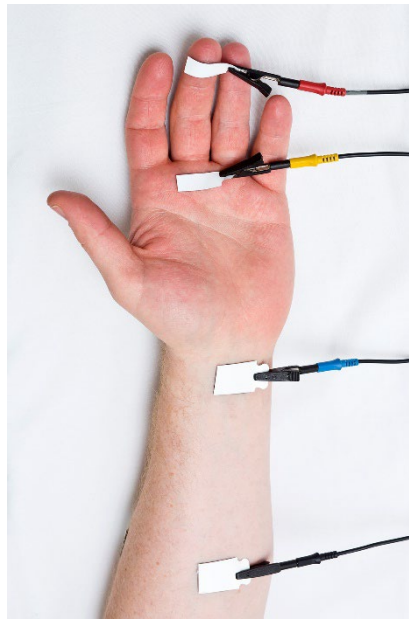
Figure 3: Alternate electrode positions on the volar hand and dorsum of forearm
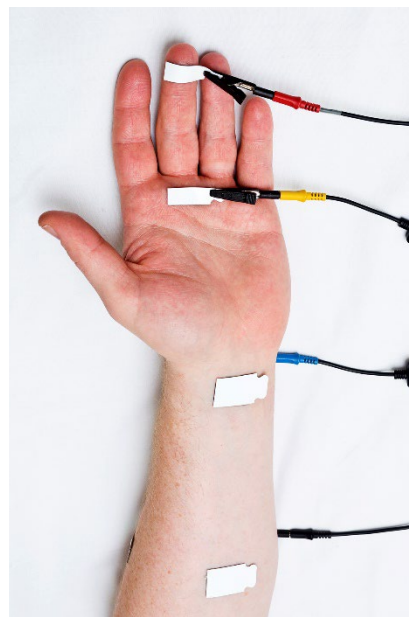
The results of the study indicated, therefore, that the electrode positions on the palm of the hand and volar wrist/forearm, and a combination on the palm of hand and finger and the dorsum of the wrist and forearm, are equivalent to the positions on the dorsum of the hand and forearm for measuring R_0, R_∞ and membrane capacitance, enabling these to be measured where wounds exclude the standard electrode array described by Ward et al. (2012). This provides the ability to measure the impedance of fluid in the extracellular space, as well as the impedance of the total fluid within

the hand. Membrane capacitance is reflective of cell volume and cell wall integrity and thickness. Decreased membrane capacitance is associated with poor outcomes in several disease states. Therefore cell health may be interpreted using BIS, in addition to the measurement of oedema and other tissue fluid volumes. This study provides clinicians and researchers with a novel and extended set of electrode positions which increase the utility of the BIS method for measuring the change in fluid dynamics and tissue characteristics in the hand and upper limb.

7.1.2   Study Two: Bioimpedance Spectroscopy Is a Valid and Reliable Measure of Edema Following Hand Burn Injury (Part 1—Method Validation)

Study Two investigated the applicability of the alternate electrode positions from Study One in a hand burn injured population. Previous studies have investigated the use of alternate electrode positions for measuring bioimpedance in burn injured populations (Kenworthy et al., 2017), with electrodes placed on the palm of the hand and wrist providing equivalent measures for whole body and upper limb segmental bioimpedance. The aims of this study were to contribute to the understanding of a) the validity of bioimpedance for measuring hand volumes in a burn injured population, including the use of alternate electrode positions, and b) establishing the reliability and sensitivity of BIS as a measure of oedema following acute hand burn injury.

The electrode positions on the dorsum of the hand and forearm (Figure 1, above), and the alternate positions that were validated in Study One - the palmar surface of the hand and volar forearm (Figure 2, above), and a combination of palmar hand and finger placement and dorsal wrist and forearm electrodes (Figure 3, above) – were shown to be equivalent for measuring the impedance of the extracellular fluid in burn injured hands.

The results demonstrated that BIS was sensitive, reliable and valid for measuring the volume of oedema, using R_0, in the hand following burn injury, and that alternative electrode positions may be used interchangeably with standard methods, where burn wounds preclude the use of electrodes on the dorsum of the hand and forearm. This study enables clinicians and researchers to further increase the utility of BIS in the burn injured hand and upper limb to measure fluid volume and tissue composition

with novel electrode configurations to permit electrode positioning where wounds preclude the use of the standard electrode array.

7.1.3   Study Three: Randomised control trial of compression interventions for managing hand burn edema, as measured by bioimpedance spectroscopy

To our knowledge, Study Three is the first controlled trial investigating methods of compression for managing oedema after acute hand burn injury. Study Three is informed by the findings from from Study One and Two to implement a clinical application of BIS to measure the (change in) oedema as the primary outcome.

Coban is an elasticised, self-adhesive cohesive bandage that is commonly applied for managing oedema in a variety of pathologies (Lee et al., 2006; Miller et al., 2017; Munk et al., 2013). Coban has been described in the literature for managing sub-acute and chronic burn oedema, although one study is a within-patient case study, while the other lacks a control cohort (Lowell et al., 2003; Ward et al., 1994). Two methods of applying a customised, Coban bandage formed into a compressive glove are described in the literature, however there is little agreement or understanding on the optimal application for managing oedema (Glassey & Phillips, 2011; Villeco, 2012). The application techniques investigated in this study were: 1) a spiral application to the fingers with a figure-of-eight application to the hand and forearm (Figure 4), and 2) cylindrical or pinch application to the fingers with a spiral application to the hand and forearm (Figure 5). These methods were compared to an off the shelf compression glove as the control (Figure 6).

Figure 4: Spiral application of Coban to fingers, figure-of-eight to hand and arm

Figure 5: Pinch application of Coban to fingers, spiral to hand and arm

Figure 6: Off-the-shelf compression glove (Control condition)

Compression has been demonstrated to affect range of movement, with significant reductions in finger joint flexion noted in with the application of Coban in healthy individuals (Glassey & Phillips, 2011). With compression in situ, thumb opposition was demonstrated to significantly decrease (p<0.001) with both methods of Coban, though other hand range of movement measures were not significantly decreased compared to the compression glove The reduced range of movement with Coban in situ is not clinically meaningful, as the magnitude of the loss of ROM was relatively small, and the duration of the restriction with the compression in situ was short.

This study confirmed that in acute hand burn injury, oedema management was superior with the application of a customised, Coban elasticised bandage glove when compared to an off the shelf compression glove. The choice of the most common methods of glove application techniques for fabricating the customised Coban glove did not affect the rate of oedema reduction. This study provides clinicians with high quality Level 2 evidence to guide best practice for management of oedema in acute hand burn injury.   Secondly, the findings remind clinicians that treatment of the hand burn injury should routinely include advice regarding elevation of the affected limb while at rest, and a suitable exercise program should be provided to maintain function and assist with oedema management through venous and lymphatic return (Simons et al., 1996).

7.1.4   Study Four: Does electrical stimulation improve healing in acute minor burn injury, as measured by bioimpedance spectroscopy? A single centre, randomised, controlled trial.

Study Four was the second intervention trial in this research programme. The use of electrical stimulation in acute burn injury was investigated in the study, which was designed as a within-patient control, randomised trial. Thirty (30) patients with burns of similar area and depth to multiple limbs were recruited to this study, with one wound acting as the control for the stimulated contralateral wound. The outcomes of this study were: 1) local wound oedema reduced at a faster rate with the use of electrical stimulation; 2) local wound BIS phase angle measures increased at a faster rate with electrical stimulation; and 3) BIS phase angle is significantly associated with wound re-epithelialisation in acute burn injury. Bioimpedance measures of wound oedema have been described in the Studies Two and Three. In addition, BIS monitoring using phase angle was assessed in Study Four. Phase Angle has been described as a measure of cell health and demonstrated to increase in re-epithelialisation of chronic wounds but has not been validated for application in acute wound monitoring (Lukaski & Moore, 2012).

A long duration (20 hours per day) low intensity electrical stimulation was applied to one wound for a period of up to 14 days in addition to standard dressings, while the contralateral wound acted as the control and received standard dressings only. Wound healing was assessed using standardised photography by an experienced consultant burns surgeon (Bloemen et al., 2012). Serial measures of BIS were recorded for each wound at each dressings change. The electrical stimulation device was small (no larger than the size of a match-box) and able to be easily carried either in a pocket, or beneath the elasticised tubular stocking applied to retain the dressings on the affected limb.

This study showed that electrical stimulation is an inexpensive, easily applied adjunct to standard minor burn wound care that has the capability to improve the rate of wound oedema reduction. The BIS measure of phase angle was associated with the re-epithelialisation, and therefore demonstrated potential to measure acute burn wound healing. This high quality Level 2 evidence provides has demonstrated that a novel intervention of electrical stimulation reduces wound oedema and improves the rate of phase angle increase in the acute minor burn. The definitive results

demonstrated with this technique should change clinical practice to incorporate a small electrical stimulation device as part of standard wound care to improve oedema reduction. These results also confirm this novel research design methodology that should be considered in future studies of minor burn wounds.

7.2   Conclusions

The series of studies in this thesis provide high quality Level 2 evidence for techniques to reduce acute burn wound oedema, through the use of compression bandaging for managing hand burn oedema, and using electrical stimulation for other burn wounds. BIS has been demonstrated in this study series to be a valid, reliable and sensitive measure of oedema in the hand following burn injury, and phase angle was demonstrated to be associated with acute burn wound re-epithelialisation.

Study One provides clinicians with a technique to quickly measure hand oedema volume, with a minimal imposition on the patient, in patient populations that were previously excluded from intervention trials, and where objective measures of oedema were considered contraindicated due to the presence of wounds. This expands the scope of BIS use in the clinical setting, allowing clinicians to incorporate oedema measurement as a day-to-day measure, without the impracticalities of other methods, to provide guidance on the implementation of oedema management strategies in patients with hand wounds.

The second study provides clinicians with a rapid assessment of oedema in the burn-injured hand, as suffered by >55% of patients in WA. The technique is applied with minimal imposition on the patient, enables clinicians to determine the volume change of oedema in the hand objectively using the BIS raw impedance variable R_0. This evidence supports clinicians to actively measure oedema as part of the daily assessment and treatment of the burn injured patient.

Study Three provides Level 2 evidence to encourage clinicians to use the technique for fabricating their glove of choice as routine. For clinicians who have little or no experience managing hand burn oedema, the use of the pinch method for applying Coban, or similar cohesive bandage, minimises the risk of a tourniquet effect if applied with too much tension, but is equally effective at reducing oedema in the hand.

Study Four provides Level 2 evidence demonstrating that electrical stimulation reduces wound oedema at a faster rate than standard care alone. This study also established that the BIS variable Phase Angle provides an index of wound re-epithelialisation in acute burn injury, and that using this measure, electrical stimulation improves the rate of increase in phase angle in acute burn injury when compared to standard wound care alone. This Level 2 evidence supports the use of a small, extremely low risk and low cost, self-applied and patient managed electrical stimulation device to all burn wounds. Larger sample sizes may demonstrate decreased length of stay and a reduction in the requirement for patients to attend ambulatory care clinics for management of the healing wound with improved healing rates.

This study series has contributed to the body of knowledge and progressed the options available and capacity to monitor changes in acute oedema and wound healing in real time. This study series has provided a number of solutions to identified challenges in acute burn patient monitoring and management, to proactively manage acute burn oedema in order to preserve the zone of stasis therefore prevent burn wound conversion.

7.3   Directions for future research

During the undertaking of this research series, further research opportunities were identified, and have been touched on in the published studies. These will be expanded further in this section. As Studies One and Two focussed on the use of BIS and its use in hand volume measurement, the first of the future recommendations will expand on BIS implementation. Study Three, as an intervention study, identified opportunities for future research through what was originally planned for the study, but was unable to be facilitated due to a lack of resources. The use of electrical stimulation in Study Four, and the mechanisms by which electrical stimulation influences recovery in other pathologies, additionally identifies further recommendations.

The formula calculation of hand volumes derived from BIS measures is based on the geometrical conical shape used for calculating limb volumes (Ward et al., 2009). The complex geometric shape of the hand does not lend itself to volume calculations without increased measurements, which may be time consuming and potentially introduces error (Dylke et al., 2014). By comparing raw impedance measures against

measured volumetry of the hand, it may be possible to generate volume formulae based on changes in impedance and the size of the hand, which is measured by recording the distance between the voltage sense electrodes. This would allow clinicians to obtain the recorded impedance value, and together with the inter-electrode distance, quickly produce a volume of oedema within the hand. Study Two generated volume measures in addition to impedance measures, and this may provide the required information to be able to generate such formulae. Impedance measures are dependent on volume of fluids in the body, as well as the resistivity of the fluids, which varies between genders (Cornish, 2006). It is an opportunity for further research that would make BIS measures relevant for clinicians not familiar with its use and implementation.

Another opportunity for future research, including in burn injury featuring chronic oedema, is the measurement of reverse electrode positions to counter electrode-skin mismatch. Electrode impedance mismatch can occur at high frequencies, and results in a "hook" appearance to the normally semi-circular arc of the impedance trace, generated by the application of the Cole model (Montalibet & McAdams, 2018). It often occurs when BIS devices designed for whole body assessments are used in segmental or localised measurements. Montalibet and McAdams (2018) explored a method using the standard and also reverse electrode positions, and generating a mean impedance measure to overcome this hook artefact. The application of the reverse electrode positions to the hand may make this technique suitable for measuring intracellular water and total body water, which was not valid in Study One and Study Two. Additionally, a combination of bipolar and tetrapolar electrode positions may be used to perform a "spot measurement" of lymphoedema, where long standing tissue changes may not be detectable using standard BIS measurement (Dylke et al., 2013), which may be applicable to long standing / chronic oedema following burn injury. This technique may also be applied as an objective measure of scar assessment. Scar tissue has been shown to have higher capacitance and lower resistance than normal skin, and the impedance of the scar changes depending on the depth and density of the scar (Zhao et al., 1998). The variable electrical characteristics of scar tissue offer a potential quantitative measure of scarring.

The proactive management of oedema in Study Three investigated short-term effects of compression on hand oedema and function. One of the principles of proactively

managing oedema is to preserve the zone of stasis, in order to prevent a worsening of the area and depth of the burn injury. Longer term follow-up of patients to assess the impact of different methods of compression on (time to) healing and therefore scarring, function and range of movement represents another future research opportunity. Future studies should also investigate the use of BIS for measuring oedema and the effects of compression following surgical interventions to investigate the same outcomes in a more severe injury cohort. These future investigations should consider biopsies of the healing burn wound to assess the effect of oedema on epithelial migration.

The investigation of compression in the management of acute burn oedema in Study Three highlighted that the resources were not available to provide measures of the interface pressures imparted by the compression. The majority of studies investigating compression methods fail to provide measures of the pressure imparted by the compression in the study, and this was a shortcoming of Study Three (Mosti, 2012; Partsch et al., 2011). Pressures are recommended for garments in managing hypertrophic scarring, lymphoedema, and for the management of venous congestion (Macintyre & Baird, 2006; Ruckley et al., 2002), however there are no guidelines for the management of acute oedema. Different methods of applying Coban to the lower leg resulted in mean pressures of 20.7-37.8mmHg, depending on technique, with spiral application imparting a mean compression of 28.5mmHg, and a figure of eight application 20.7mmHg, which may provide an estimate of the pressures in Study Three (Lee et al., 2006). Additionally, while there is evidence for pressures for managing the above pathologies in lower limbs, there is minimal advice for compression of the upper limb. Determining the optimal compression for the management of acute oedema is also complicated by the presence of wounds. These represent further opportunities for future research. The maintenance of pressure from first application until the point where dressings are changed, noting fluctuations in pressure with active (range of) movement would also better guide clinicians in their choice of compression method.

Future research opportunities also lie in advances with textiles, wearable technologies, and the progression of communication technologies. Remote monitoring of wounds and oedema using BIS embedded in dressings or cohesive bandaging would enable the patient to download information from their wound via Bluetooth and transmit the data to clinicians, providing real-time objective measures, without needing the patient to attend the ambulatory clinic. In addition, BIS electrodes embedded in dressings may overcome the requirement of intact skin for the placement of electrodes, which is another future direction that should be investigated – this would allow the BIS measurement of burn injury of larger TBSA, where there are less options for the placement of electrodes. Textiles such as pressure garments embedded with BIS electrodes or pressure sensors would similarly enable remote monitoring of healing, oedema, and maintenance of pressure for both the management of acute oedema, and the subacute and long-term management of scarring, and identify when compression has decreased to sub-therapeutic levels and require replacement.

A natural extension to oedema management of acute burn injury in the hand is to investigate techniques to manage lower limb burn oedema. As in the upper limb, there is no research into optimal management techniques for the control of oedema following burn injury in the leg. As patients move from supine to standing, the effect of gravity and the arterial circulation contribute to the movement of blood from a central position in the thorax to the lower limbs (Smith et al., 1987). This results in the phenomenon of dependency pain, something that all burn therapists are familiar with, where a patient is overcome with 'blood rush' in their legs and immediately returns to the supine position to elevate their lower limbs in an attempt to reduce the sensitivity in their leg burns. In a clinical environment, the application of compression provides support to the burned lower leg, which anecdotally assists in managing the dependency pain when used in conjunction with activation of the lower limb muscle pump, however this has not been demonstrated in the literature, and represents a future study. The use of electrical stimulation in Study Four demonstrated amelioration in healing and oedema management, but transcutaneous electrical nerve stimulation (TENS) additionally offers analgesic properties, which offers another opportunity for future research.

Future studies building on the findings of Study Four should examine electrical stimulation in a randomised controlled trial, by applying electrical stimulation to a wound in one patient group, and applying sham stimulation to a control group of patients. As this is an easy to apply and use, minimally invasive and low risk intervention, assessing the use of electrical stimulation in a multi-centre trial would generate larger sample sizes. Applying electrical stimulation until complete re-epithelialisation, with controlled photography to assess wound healing in addition to serial BIS measures as outcome measures should be performed as part of future research. While scar outcome is associated with depth and size of the burn injury, it is also associated with time to heal (Finlay et al., 2017). Future studies investigating electrical stimulation should include long-term scar assessments to determine whether accelerated healing due to electrical stimulation has beneficial effects on long term scarring. This will also affect psychological outcomes, and should be investigated. The application of electrical stimulation, as performed in Study Four also offers itself to surgical wounds and chronic wounds, and represent another opportunity for further research.

Other modalities of electrical stimulation are used in a wide range of clinical applications. Nerve fibre recruitment is 100 to 1000 times smaller than the action potential of muscle fibres (Sheffler & Chae, 2007). Electrical stimulation in the hemiparetic upper limb has demonstrated potential for improving proprioception, sensation, and motor performance (Bustamante et al., 2016; Peurala et al., 2002). Cutaneous sensation thresholds for two-point discrimination, pressure, temperature and pain have been demonstrated to be significantly higher in healed burned skin than in healthy controls (Malenfant et al., 1998). Nerve density is not affected in burn scarring, although an increase in Calcitonin Gene Related Peptide (CGRP) fibres has been measured in patients with chronic pain – both in burn scar and in uninjured control sites (Hamed et al., 2011). CGRP fibres are associated with nociception, neuroinflammation, wound repair and related sensory symptoms (Hamed et al., 2011). Furthermore, a study in rats demonstrated that transcutaneous electrical nerve stimulation was shown to decrease pro-inflammatory cytokines (Gürgen et al., 2014). These studies suggest that electrical stimulation may influence neural recovery in addition to wound healing following cutaneous injury. Future investigation into the use of electrical stimulation should include cutaneous and peripheral nerve testing to assess whether stimulation has an impact on improving joint proprioception, skin sensation, and lower limb balance, which have been demonstrated to be affected following burn injury (Finlay et al., 2010).

Advances in textiles and wearable technologies also provide exciting future directions for electrical stimulation. Electrodes embedded in dressings and garments, while offering the opportunity to measure wound healing and oedema using BIS as mentioned previously, provide stimulation through the same electrodes. Devices that measure wound status through BIS and then apply stimulation influenced by these real-time objective measures are an opportunity that would build on the ground-breaking research in this study series. Such a device would also enable the clinician to monitor wound healing using remote technologies and communicate with the patient regarding appropriate progressions as required.

7.4   Significance of this Research

In their 2011 systematic review of local and systemic oedema management techniques, Edgar et al. (2011) found only one controlled trial investigating an intervention for managing local oedema following burn injury. A systematic search of

the literature conducted as part of this research program showed no additional trials in the intervening period. The only controlled trial was an electrical stimulation study in acute, conservatively managed hand burn injury (Omar et al., 2004). The significance of this research program is the contribution of an additional two Level 2 evidence studies to the literature, both investigating techniques to optimise the management of acute burn oedema, and provide clinicians with high quality evidence for the best practise interventions to aid the control of oedema in the burn injured patient. Poorly managed oedema in acute burn injury may result in burn wound conversion, as the oedema increases the oxygen diffusion distance by forming a barrier between the burned tissue and the capillary bed (Heughan et al., 1972).

This research has also significantly demonstrated that BIS measures of the hand may be performed with the use of electrode positions that may be moved to avoid wounds and other lesions in the skin. This research has also presented BIS as a valid, reliable and sensitive measure of oedema in the hand burn injured population to provide researchers and clinicians rapid, non-invasive measures of oedema in the hand, with minimal imposition on the patient. This enables clinicians to respond to worsening oedema with interventions to proactively manage the oedema and optimise the patient's outcome. This research also confirmed BIS as a tool for monitoring wound healing in acute burn injury, which has the potential to guide decision making in difficult to heal wounds by providing a rapid assessment of the status of the wound when measured serially through the patient journey.

As Winthrop Professor Fiona Wood says: "Every intervention, from the time of the burn injury, has an impact on the scar worn for life" (Wood, 2013). Proactively understanding and managing oedema in the acute burn has an impact on the zone of stasis, with the aim of preventing burn wound conversion, and maximising the functional, aesthetic and psychological outcome for the burn injured patient.

7.5   References

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APPENDICES

APPENDIX A DECLARATION AND STATEMENT OF CONTRIBUTION OF OTHERS

This thesis contains published work and/or work prepared for publication, which has been co-authored. The bibliographical details of the work are presented for each study. The work involved in designing the studies described in this thesis was performed primarily by the candidate, Dale Edwick. The thesis outline and experimental design was planned and developed by the candidate, in consultation and with assistance from Mr Jeremy Rawlins, Winthrop Professor Fiona Wood and Associate Professor Dale Edgar, the candidate's supervisors.

All participant recruitment and management was performed or facilitated by the candidate between October 2015 and August 2019. This was completed in association with the staff and patients of the State Adult Burns Unit and the Medical Illustrations Department at Fiona Stanley Hospital.

The Fiona Wood Foundation (Chevron Fellowship) has supported my clinical research time for the duration of the study.

In addition, the candidate was responsible for the data analysis with assistance from Dr Dana Hince, biostatistician, Institute for Health Research at The University of Notre Dame Australia.

The candidate drafted the original thesis, with Associate Professor Dale Edgar and Winthrop Professor Fiona Wood providing feedback on drafts until the examinable version was finalised.

I declare that all of the material presented in this thesis is original.

Dale Edwick
Senior Physiotherapist
State Adult Burns Unit
Fiona Stanley Hospital

Associate Professor Dale Edgar
Principal Supervisor
November 2021

Mr Jeremy Rawlins
Co-supervisor
November 2021

Winthrop Professor Fiona Wood
Co-supervisor
November 2021

Dr Dana Hince
Biostatistician
November 2021

APPENDIX B   LETTERS OF APPROVAL FROM PUBLISHERS

Ballen, Karen <KBallen@liebertpub.com>
Wed 1/7/2020 06:46
To: Edwick, Dale

RE: Copyright permission request for lrb.2019.0078

Dear Dale:

You may include the article in your thesis, but if you wish to deposit it into a publicly accessed repository, there is a one year embargo period, from the date of publication, before you can do that if Open Access wasn't ordered.

Kind regards,

Karen.

Dear Dale O Edwick,

Thank you for selecting your licence to publish. You can find a copy of your licence attached to this email. You can also view your licences online here.

What happens next?

1. If you have selected an Open Access licence, pay any applicable charges in the next two working days if applicable.

2. Your article will be published online once you have checked and approved your proof. If applicable we will send you an email about paying for any colour figure or page charges.

The information below will assist you with any deposit requirements you may have (e.g. the HEFCE REF requirement).

Journal: Journal of Burn Care & Research

DOI: 10.1093/jbcr/iraa104

Article: Randomised control trial of compression interventions for managing hand burn edema, as measured by bioimpedance spectroscopy

Acceptance date: 2020-06-22

Self-archiving information: The embargo period for self-archiving the Accepted Manuscript is 12 months from first online publication. Please refer to the journal's self-archiving policy or your licence agreement for terms and conditions.

Best wishes,

Customer Services

Oxford University Press

DATA COLLECTION SHEET UNDA EC 015158F (FSH Quality Activity 10830)

Validating the use of alternate electrodes positions for bioimpedance measurement of hand volume in a non-injured population.

SUBJECT: ~~MH~~ CS(18)   GENDER: M   DATE: 19/7/16

HEIGHT: 170.5.   WEIGHT: 67.6   AGE: 24

HAND DOMINANT: RIGHT

3RD METACARPAL LENGTH: R) _____   L) _____

FOREARM LENGTH (Olecranon to Dorsum of Wrist): R) 27.5.   L) 27

Bioimpedance Spectroscopy:

Whole Body: [609][610][611]

Right Hand – Dorsal Sense Electrode Distance [6.0]
Dorsum hand – Dorsum forearm: [612][613][614]
Dorsum hand – Volar forearm: [615][616][617]

Right Hand – Volar Sense Electrode Distance [6.2]
Volar hand – Dorsum forearm: [621][622][623.]
Volar hand – Volar forearm: [618][619][620]

Left Hand – Dorsal Sense Electrode Distance [5.9]
Dorsum hand – Dorsum forearm: [624][625][626]
Dorsum hand – Volar forearm: [627][628][629]

Left Hand – Volar Sense Electrode Distance [6.8]
Volar hand – Dorsum forearm: [633][634][635]
Volar hand – Volar forearm: [630][631][632]

APPENDIX D SAMPLE DATA COLLECTION SHEET FOR STUDIES TWO AND THREE

Patient ID: 54 Date of Injury: 21/9/16 TBSA: [ ] Height: 187 Age: 55

Compression Group: Sleeve
Session One: Date: 23/9/16 Weight: 100

BIS Electrodes:
[Dorsum Hand_Dorsum Forearm] Inter-electrode distance: 9.0 BIS: 861 | 862 | 863
[Dorsum Hand_Volar Forearm] 1.2 864 | 865 | 866
[Volar Hand_Dorsum Forearm] 9.0 870 | 871 | 872
[Volar Hand_Volar Forearm] 11.0 867 | 868 | 869

Water displacement volume: 7435 Water Temp: 9 21.7/27.3

Hand ROM without compression: Thumb Opp CFF: 2.7 Hand Span: 26.7 Wrist F/E: 71/70 Pain: 3

Time to apply Compression: 11:55.60

Hand ROM with compression: Thumb Opp 6. CFF: 1.0 Hand Span: 26.3 Wrist F/E: 60/64 Pain: 3

Quick-DASH: [ ]

Session Two: Date: 25/9/16 Weight: 97.7
Exudate: Nil Separation: <2.3456 or MF 4 Photos: 1 CFF: 0.5 Hand Span: 26.6 Wrist F/E: 71/79 Pain: 3

Hand ROM without compression: Thumb Opp 9.5

Time to apply Compression: 9:25.44

BIS Electrodes:
[Dorsum Hand_Dorsum Forearm] Inter-electrode distance: 10.0 BIS: 906 | 907 | 908
[Dorsum Hand_Volar Forearm] 11.2 915 | 916 | 917
[Volar Hand_Dorsum Forearm] 11.2 909 | 910 | 911
[Volar Hand_Volar Forearm] 11.5 912 | 913 | 914

Water displacement volume: 7003 Water Temp: 9 26/26.2

Hand ROM without compression: Thumb Opp CFF: 0.5 Hand Span: 26.4 Wrist F/E: 75/81 Pain: 6

Hand ROM with compression: Thumb Opp 6. CFF: 2.0 Hand Span: 27.2 Wrist F/E: 82/76 Pain: 7

Quick-DASH: [ ]

APPENDIX E **SAMPLE DATA COLLECTION SHEET FOR STUDY FOUR**

DATA COLLECTION SHEET RPH EC 2014/006 (FSH 2014-101)

Does electrical stimulation (ES) therapy improve healing in small area acute burns, as measured by a prototype localised bioimpedance device?

HEIGHT: 174   HAND DOMINANCE: RIGHT.

Session 6:

DATE: 29/10/19   WEIGHT: 72.5.

PAIN – RIGHT: 5.   PAIN – LEFT: 5

Bioimpedance Spectroscopy:

Whole Body: [819][820][821]

Segmental – Right: [822][823][824]

Localised – Right (ECG): STD [834][835][836] REV [837][838][839]

Inter-electrode distance: (ECG) [44.9]   (Bioflex) [44.8.]

Segmental – Left: [825][826][827]

Localised – Left (ECG): STD [828][829][830] REV [831][832][833]

Inter-electrode distance: (ECG) [43.7]   (Bioflex) [44.0]

Localised – Right (Bioflex): STD [840][841][842] REV [843][844][845]

Localised – Left (Bioflex): STD [846][847][848] REV [849][850][851]

BIA: ☑   PHOTOS: ☑

APPENDIX F   CONSENT FORM FOR STUDY ONE

THE UNIVERSITY OF
NOTRE DAME
A U S T R A L I A

CONSENT FORM

I,..(block letters) agree to take part in the research study:

Validating the use of alternate electrodes positions for bioimpedance measurement of hand volume in a non-injured population.

- I have read the Information Sheet provided and been given a full explanation of the purpose of this study, the procedures involved and of what is expected of me.

- I understand that I will be asked to:

    - Allow researchers to measure my weight, height and arm length.

    - Allow researchers to apply gel electrodes to my hand and forearm in order to use the BIS machine.

    - Allow researchers to measure the volume of my hand using BIS using different electrode positions.

    - Rest comfortably while the measures are recorded by the researchers.

- The researcher has answered all my questions and has explained possible problems that may arise as a result of my participation in this study.

- I understand that I may withdraw from participating in the project at any time without prejudice.

- I understand that all information provided by me is treated as confidential and will not be released by the researcher to a third party unless required to do so by law.

- I agree that any research data gathered for the study may be published provided my name or other identifying information is not disclosed.

- I understand that research data gathered may be used for future research but my name and other identifying information will be removed.

Name of participant			
Signature of participant		Date	

- I confirm that I have provided the Information Sheet concerning this research project to the above participant, explained what participating involves and have answered all questions asked of me.

Signature of Researcher		Date	

Consent Form template June 2015

APPENDIX G   **CONSENT FORM FOR STUDIES TWO AND THREE**

Fiona Stanley Hospital

CONSENT FORM

Measurement and management of swelling after hand burn

Chief Investigator: Dale Edwick

- I agree to take part in this research project.

- I have read the Information Sheet provided and been given a full explanation of the purpose of this study, the procedures involved and of what is expected of me.

- I understand that I will be asked to:

    - Allow researchers to measure my weight, height and arm length.

    - Allow researchers to apply gel electrodes to my hand, forearm and feet in order to use the BIS machine.

    - Allow researchers to measure the volume of my hand using BIS

    - Allow researchers to measure the volume of my hand by placing it in a vessel filled with water, and allowing them to collect the run off

    - Rest comfortably while the measures are recorded by the researchers.

    - Allow researchers to apply compression to my hand to manage the swelling

    - Allow researchers to measure the range of movement in my hand

- The researcher has answered all my questions and has explained possible problems that may arise as a result of my participation in this study.

- I understand that I may withdraw from participating in the project at any time without prejudice.

- I understand that all information provided by me is treated as confidential and will not be released by the researcher to a third party unless required to do so by law.

- I agree that any research data gathered for the study may be published provided my name or other identifying information is not disclosed.

- I understand that research data gathered may be used for future research but my name and other identifying information will be removed.

Name of participant			
Signature of participant		Date	

- I confirm that I have provided the Information Sheet concerning this research project to the above participant explained what participating involves and have answered all questions asked of me.

Signature of Researcher		Date	

APPENDIX H   CONSENT FORM FOR STUDY FOUR

CONSENT FORM

Does electrical stimulation improve healing in acute burns as measured by bioimpedance?

Chief Investigator: Dr Dale W. Edgar
Senior Physiotherapist, Burn Service, Fiona Stanley Hospital

Co-investigators:
W.Prof Fiona Wood – Director, Burn Service of WA
Dale Edwick – Research Fellow, Fiona Wood Foundation
Dr Tiffany Grisbrook – Research Fellow, Fiona Wood Foundation

I,....................................... *(block letters)* agree to take part in this research study:

Please mark each box that applies:

☐ I have read the Participant Information Sheet and understand the aims and methods of the study and any risks involved.

☐ I allow the investigator to mark my skin with surgical pen to note electrode positions.

☐ I understand that the *BIRD* device is being trialled during this study and does not have formal TGA approval as yet.

☐ All my questions have been answered to my satisfaction.

☐ I acknowledge that my involvement in the study may not be of benefit to me.

☐ I understand that taking part in the study is voluntary and I am free to withdraw at any time.

☐ I understand that all information gained in the study will be treated confidentially.

☐ I understand that the results from this study may be published in reports or research papers but that my identity will not be disclosed.

☐ I agree that the investigators may supply the results from the bioimpedance analysis of my wounds to Ti_2 Pty Ltd on the strict understanding that my identity will not be disclosed, or decipherable, in any way.

Participant:.. **Date:**...............................
(Signature)

I have explained the aims and methods of the study to the above participant and have answered all their questions.

Signature   ....   **Date**   ....
of person obtaining consent

Name   ....
of person obtaining consent

FSH Site PCF V 1.2 Date 19/5/2015 based on RPH Master PCF V1 dated 11/8/2014

THE UNIVERSITY OF
NOTRE DAME
A U S T R A L I A

PARTICIPANT INFORMATION SHEET

Validating the use of alternate electrodes positions for bioimpedance measurement of hand volume in a non-injured population.

Chief Investigator: Dale Edwick

PhD Candidate, School of Physiotherapy, The University of Notre Dame Australia

Co-investigators:

Assoc.Prof Dale Edgar – Senior Physiotherapist, Burn Service of WA, FSH

Mr Jeremy Rawlins – Consultant Burns Surgeon, Burn Service of WA

W.Prof Fiona Wood – Director, Burn Service of WA

Do you have a pacemaker?	Yes [ ]	No [ ]
Are you pregnant?	Yes [ ]	No [ ]
Have you been diagnosed with renal disease?	Yes [ ]	No [ ]
Do you use diuretic medication?	Yes [ ]	No [ ]

If "Yes" to either of the above: You will be unable to participate in this study. Thank you for your time and interest.

Dear Participant,

You are invited to take part in this research study. This information sheet explains what will be involved should you choose to participate. Please read it carefully and a researcher will be available to answer any questions before you decide to take part.

Who is undertaking the project?

This project is being conducted by Mr Dale Edwick and will form the basis for the degree of Doctor of Philosophy at the School of Physiotherapy, the University of Notre Dame Australia, under the supervision of Associate Professor Dale Edgar. Mr Jeremy Rawlins and Winthrop Professor Fiona Wood are co-supervisors of this research.

What is the project about?

If you consent to take part in this research study, it is important that you understand the purpose of the study and the procedures you will be asked to undergo. Please make sure that you ask any questions you may have, and that all your questions have been answered to your satisfaction before you agree to participate.

Hand Swelling Measurement Procedure:

On the day that you attend, you will have your height and weight measured and the length of your hands and arms will be recorded. Then, baseline measurements of your whole body and hands will be taken using the BIS machine (SFB7). Each set of measures takes less than one minute, is painless and only requires that you do not move for the second or two of each measure. These measures will be undertaken at Fiona Stanley Hospital. Therefore, it is expected that your time commitment would be 10 minutes for these measurements, plus any travel time to and from the hospital.

BIS is a technique often used by dieticians to estimate fat and lean tissue in the body. It is based on the principle that impedance to the flow of electric current is related to the water and tissue composition in the body. In our study, we are interested in the parameters to monitor swelling (water).

The impedance instruments used meet all relevant safety standards. The SFB7 is in wide use throughout Australia. A small electric current is applied to your body via electrodes and the impedance is measured. The battery driven current is so small you will not feel it and it will be of no danger to you. Self-adhesive gel electrodes will be placed on your hands, wrists, forearms, and right ankle and toes, to allow two measures to be taken – one whole body and one for your hand. Both of your hands will be assessed in this study. You will be asked to lie on your back on a bed during these measures.

What are the benefits of the research project?

There will be no immediate benefits to you by participating in this research project. However, the data collected from your participation in this study will enable the researchers to further understand the use of BIS for measuring swelling in hand burn injury. It is hoped that with the findings of this study, we will be able to investigate the use of BIS to measure hand swelling in patients with hand burn injury, using the electrode placements investigated in this study to avoid burn wounds.

What if I change my mind?

Participation in this study is completely voluntary. Even if you agree to participate, you can withdraw from the study at any time without discrimination or prejudice. If you withdraw, all information you have provided will be erased and destroyed.

Will anyone else know the results of the project?

The information gathered about you during the study will be held by the investigator in strict confidence. The study will not keep any data after the research has been completed. All data will be stored securely in the School of Physiotherapy at The University of Notre Dame Australia. All data collection sheets will be stored in a locked filing cabinet for a period of seven years, as required by law. All people who handle your information will adhere to traditional standards of confidentiality and will comply with all relevant privacy legislation. In Australia, this is in the Privacy Act 1988. If the results of the study are published in a journal, as is intended, no reader will be able to identify individual patients.

The results of the study may be published as a journal article and may be included as part of a thesis.

Will I be able to find out the results of the project?

Once we have analysed the information from this study we will mail you a summary of our findings. You can expect to receive this feedback in 12 months' time.

Who do I contact if I have questions about the project?

If you have any questions about this project please feel free to contact me on ▉▉▉▉▉▉▉▉ or Dale.Edwick1@my.nd.edu.au . You can also contact my supervisor, Associate Professor Dale Edgar ▉▉▉▉▉▉▉▉ or Dale.Edgar@health.wa.gov.au. My supervisor and I are happy to discuss with you any concerns you may have about this study.

What if I have a concern or complaint?

The study has been approved by the Human Research Ethics Committee at The University of Notre Dame Australia (approval number 015158F). If you have a concern or complaint regarding the ethical conduct of this research project and would like to speak to an independent person, please contact Notre Dame's Ethics Officer at (+61 8) 9433 0943 or research@nd.edu.au. Any complaint or concern will be treated in confidence and fully investigated. You will be informed of the outcome.

How do I sign up to participate?

If you are happy to participate, please sign both copies of the consent form, keep one for yourself and give the other to me in the envelope provided.

Thank you for your time. This sheet is for you to keep.

Government of **Western Australia**
Department of **Health**

FIONA STANLEY hospital

PARTICIPANT INFORMATION SHEET

Measurement and management of swelling after hand burn

Chief Investigator: Dale Edwick
Senior Physiotherapist, Burn Service of WA, Fiona Stanley Hospital
PhD Candidate, School of Physiotherapy, The University of Notre Dame Australia

Co-investigators:

Assoc. Prof Dale Edgar – Senior Physiotherapist, Burn Service of WA, FSH
Mr Jeremy Rawlins – Consultant Burns Surgeon, Burn Service of WA
W.Prof Fiona Wood – Director, Burn Service of WA

Do you have a pacemaker or implanted stimulator?	Yes [ ]	No [ ]
Are you pregnant?	Yes [ ]	No [ ]
Have you been diagnosed with kidney disease?	Yes [ ]	No [ ]
Do you use diuretic medication?	Yes [ ]	No [ ]

If "Yes" to any of the above: You will be unable to participate in this study. Thank you for your time and interest.

Dear participant,

You are invited to participate in the research project described below.

What is the project about?

This research project is testing a new method to measure swelling after hand burn using electrical impulses known as Bioimpedance Spectroscopy (BIS). BIS measures, made with a SFB7 machine will be compared to water displacement. Swelling after burns of the hand can result in stiffness and deformity and may contribute to increased depth of the burn. This study will test the measurement methods with application of different methods of compression for the treatment of swelling after burn injury.

Who is undertaking the project?

This project is being conducted by Mr Dale Edwick and will form the basis for the degree of Doctor of Philosophy at The University of Notre Dame Australia, under the supervision of Associate Professor Dale Edgar. Mr Jeremy Rawlins and Winthrop Professor Fiona Wood are co-supervisors of this research.

What will I be asked to do?

On the first day, you will have your height and weight measured and the length of your hands and arms will be recorded. Then, baseline measurements of your whole body and hands will be taken using the BIS machine (SFB7). Each set of measures takes less than one minute, is painless and only requires that you do not move for the second or two of each measure.

BIS is a technique often used by dieticians to estimate fat and lean tissue in the body. It is based on the principle that impedance to the flow of electric current is related to the water and tissue composition in the body. In our study, we are interested in the parameters to monitor swelling (water).

The BIS machine used meet all relevant safety standards. The SFB7 is in wide use throughout Australia. A small battery driven current is applied to your body via electrodes and the impedance is measured. The battery driven current is so small you will not feel it and it will be of no danger to you. Self-adhesive gel electrodes will be placed on your hands, wrists, forearms, and right ankle and toes, to allow two measures to be taken – one whole body and one for your hand. Both of your hands will be assessed in this study. You will be asked to lie on your back on a bed during these measures.

After these measures are taken, the volume of your hand will be assessed using water displacement volumetry. You will be required to sit up and allow the researchers to slowly immerse your burned hand into the vessel containing water, and remain still until the water stops flowing from the vessel. You will then be allowed to remove your hand, and Burns Unit nursing staff will then attend to your dressings.

You will then be treated for swelling in your hands, using a method of compression, which will be applied to your hand(s) to manage the swelling associated with burn injury. Pressure monitors may be positioned beneath the compression, to allow measurements of the compression provided by the method of compression applied over your burns dressings.

These measures will be undertaken at Fiona Stanley Hospital as part of your routine appointment. The researchers will work in with your nurse to minimise the disruption to your dressing. It is expected that your time commitment would be approximately 60 minutes in addition to your dressings, plus any travel time to and from the hospital.

Are there any risks associated with participating in this project?

Infection: All equipment will be cleaned according to standard hospital procedures adhered to by the Fiona Stanley Hospital (FSH) Burns Unit. All gel adhesive electrodes are single-use and will be placed on intact skin. There is a negligible risk of infection.

Injury: The BIS device is battery operated. The electrical current from which the measurements are taken is tiny and you will not feel any pain or discomfort while the machine is in operation. The machine has been tested previously on patients and staff in the FSH Burn Unit without injury or ill effect.

Skin Irritation: A minute possibility exists that some participants may experience skin irritation from the electrodes or gel adhesive. If such an event occurs, you will be assessed by FSH Burns Unit

medical staff (W. Prof Fiona Wood or her agent) and treatment will be immediately commenced. You may need to be withdrawn from the study.

What are the benefits of the research project?

There will be no immediate benefits to you by participating in this research project. However, the data collected from your participation in this study will enable the researchers to further understand the use of BIS for measuring swelling in hand burn injury. This will provide clinicians with evidence for and recommendations to guide treatment choices for the management of swelling.

What if I change my mind?

Participation in this study is completely voluntary. Your treatment by the Physiotherapy team within the Burns Unit will not be affected by participating, or choosing not to participate in the study. Even if you agree to participate, you can withdraw from the study at any time without discrimination or prejudice. If you withdraw, all information you have provided will be erased and destroyed.

Will anyone else know the results of the project?

Information gathered about you will be held in strict confidence. This confidence will only be broken if required by law.

Once the study is completed, the data collected from you will be stored in password protected, centrally backed up digital storage within the Fiona Stanley Hospital. Patient privacy and confidentiality will be fully protected in both digital and hard copy formats. Raw data sheets will be stored in locked filing cabinets behind hospital swipe card access doors. While scientific publication of results is planned, identifiable data will not be published in any medium. Only the senior investigators (Dr Dale Edgar and Dale Edwick) and data extractors will have access to identifiable information.

A copy of the de-identified data will also be stored securely in the School of Physiotherapy at The University of Notre Dame Australia, as per the requirements of the University. All people who handle your information will adhere to traditional standards of confidentiality and will comply with all relevant privacy legislation. In Australia, this is in the Privacy Act 1988. If the results of the study are published in a journal, as is intended, no reader will be able to identify individual patients.

The data may be used in future research but you will not be able to be identified. The results of the study may be published as a journal article and may be included as part of a thesis.

Will I be able to find out the results of the project?

Once we have analysed the information from this study we will email you a summary of our findings, if you would like to find out the results of the project. You can expect to receive this feedback in approximately 18-24 months.

Who do I contact if I have questions about the project?

If you have any questions about this project please feel free to contact either myself Dale.Edwick1@my.nd.edu.au or my primary academic supervisor, Associate Professor Dale Edgar █████████ My supervisor and I are happy to discuss with you any concerns you may have about this study.

What if I have a concern or complaint?

The study has been approved by the Human Research Ethics Committee at The University of Notre Dame Australia (approval number 016128F), and the South Metropolitan Health Service (SMHS) Human Research and Ethics Committees at Fiona Stanley Hospital (approval number 16-143). If you have a concern or complaint regarding the ethical conduct of this research project and would like to speak to an independent person, please contact the South Metropolitan Health Service (SMHS) Human Research and Ethics Committee on 6151 1180 or email SMHS.REG@health.wa.gov.au, and also The University of Notre Dame Australia Ethics Officer on (+61 8) 9433 0943 or research@nd.edu.au. Any complaint or concern will be treated in confidence and fully investigated. You will be informed of the outcome.

How do I sign up to participate?

If you are happy to participate, please sign both copies of the consent form, keep one for yourself and give the other to the researchers in the envelope provided.

Thank you for your time. This sheet is for you to keep.

Yours sincerely,

Dale Edwick Phone: ▮▮▮▮▮▮▮▮▮ Email: Dale.Edwick1@my.nd.edu.au Signed:	Mr Jeremy Rawlins Phone: 08 6152 2222 Email: Jeremy.Rawlins@health.wa.gov.au Signed:
Assoc Prof Dale Edgar Phone: ▮▮▮▮▮▮▮▮▮ Email: Dale.Edgar@health.wa.gov.au Signed:	W. Prof Fiona Wood Phone: 08 6152 2222 Email: Fiona.Wood@health.wa.gov.au Signed:

Fiona Stanley Hospital

PARTICIPANT INFORMATION SHEET

Does electrical stimulation improve healing in acute burns as measured by bioimpedance?

Chief Investigator: Dr Dale W. Edgar, Senior Physiotherapist, Burn Service, Fiona Stanley Hospital

Co-investigators:
W.Prof Fiona Wood – Director, Burn Service of WA
Dr Tiffany Grisbrook – Research Fellow, Fiona Wood Foundation
Dale Edwick – Research Fellow, Fiona Wood Foundation

Do you have a pacemaker?	Yes [ ]	No [ ]
Are you pregnant?	Yes [ ]	No [ ]

If "Yes" to either of the above: You will be unable to participate in this study. Thank you for your time and interest.

You are invited to take part in this research study because you have burn injuries on two separate limbs. This information sheet explains what will be involved should you choose to participate. Please read it carefully and a researcher will be available to answer any questions before you decide to take part.

AIMS AND SIGNIFICANCE OF THE STUDY
Across Australia and New Zealand about 1% of people suffer a burn each year. The skin damage, or wound, while present causes pain and inconvenience. Any therapy that decreases the healing time of burns is likely to benefit patients and the health system alike.

Electrical Stimulation (ES) has been used safely and with proven wound healing benefits for the past 40 years. Thousands of people, *mostly with chronic ulcers*, have participated in clinical trials throughout the UK, Europe and the USA. To date research has not been completed in Australia. This new study aims to examine if ES will improve healing if used immediately after a burn.

To measure if your burn is healing faster, another electrical device will be used when you come into the clinic. **Bioimpedance analysis (BIA)** is a quick, safe and non-invasive way to monitor burn wound healing and swelling. BIA uses tiny electrical currents to measure body composition and fluid changes. The current cannot be felt and the method can be carried out without taking off dressings.

Electrical stimulation treatment and BIA monitoring can be used with the same arrangement of electrodes positioned beside the burn wound (Fig.1). For bioimpedance measurements, additional electrodes will be applied temporarily to the hands and feet (non-burned areas).
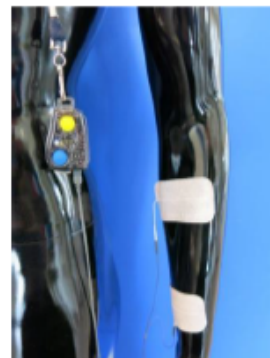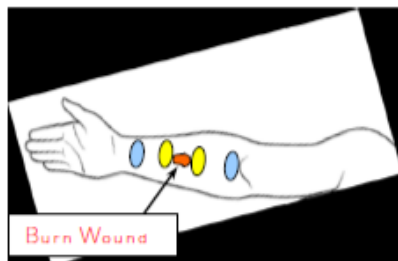
FSH Site PIS V 1.2 Date 19/05/2015 based on RPH Master PIS V1 dated 11/8/2014

Figure 1 - Example electrode placement around a burn wound. Yellow 'electrodes' have dual use (BIA and ES). Blue electrodes will be used for BIA only.

Figure 2 – Size of low frequency TENS device indicated as worn next to an arm with electrical stimulation electrodes in place.

WHAT PARTICIPATION WILL INVOLVE

If you agree to participate, the following will be done:

One of your wounds will be randomly chosen to have electrical stimulation with usual dressings and the other will have usual dressings only.

Electrical Stimulation (ES)

You will be asked to wear a stimulation device with electrodes placed either side of the dressed wound as per Figure 1 (yellow). You should wear the ES device (Fig. 2) during the whole trial (14 days maximum) or until your burn has healed (if earlier). You can do this at home (or in the burn unit). **To ensure the electrode positions are the same, we ask that we may mark your skin using a surgical pen (the dots will fade completely in ~6 weeks).** All that is required is that you leave the (yellow) electrodes in place with the ES attached and carry the small control device at all times, even while sleeping. **The only exception is that the device must not get wet.** An investigator will show you how to operate the device and will give you a fact sheet with operating and adjustment instructions. All you should feel with the stimulus is comfortable tingling. Lastly, we will ask you to estimate how many hours you were able to keep the ES running between dressing changes.

Quickstart instructions:

1. To turn the unit OFF – hold down the yellow MINUS button for 5 seconds
2. To turn the unit ON again – press down on the blue PLUS button
3. To achieve the same level of sensation as when you left the clinic, press the blue PLUS button _____ times (your co-ordinator will confirm at the first visit)
4. **You must disconnect and remove the device prior to bathing or showering.** To do this you will turn the unit OFF and disconnect the leads from the electrodes. The nurse will show you how. Once you have finished bathing, re-connect the leads, turn the unit back ON and re-set as explained in point 3 above.

Wound Healing Measurement Procedure

Two types of bioimpedance measures will be carried out in the clinic each visit to the clinic or at each dressing change if you are in the hospital. On the first day you will have your height and weight measured and your limb length recorded. Then, baseline measurements of your whole body, whole limbs and wound area will be taken using two BIA devices – the clinic machine (SFB7) and the portable device being trialled (BIRD). Each set of measures takes less than one minute, is painless and only requires that you do not move for the second or two of each measure. In addition, digital photographs of your wounds will be taken. The area of your wounds will be traced using a sterile method (Visitrak™). We will also record your pain score, prior to dressings, rated out of 10.

BIA is a technique often used by dieticians to estimate fat and lean tissue in the body. It is based on the principle that impedance to the flow of electric current is related to the water and tissue composition in the body. In our study, we are interested in the parameters to monitor swelling (water) and the wound cell status (healing).

The impedance instruments used meet all relevant safety standards. The SFB7 is in wide use throughout Australia. The BIRD being more portable is a prototype being trialled for the first time in this study. It is supplied by the manufacturer (Ti$_2$ Pty Ltd) free of charge for our use. We want to determine its accuracy and feasibility as a patient centred device. A small electric current is applied to your body via electrodes and the impedance is measured. The

FSH Site PIS V 1.2 Date 19/05/2015 based on RPH Master PIS V1 dated 11/8/2014

battery driven current is so small you will not feel it and it will be of no danger to you. Extra self-adhesive gel electrodes placed on the hand, wrist, ankle and toes to allow two measures to be taken – one whole body and one local to your burn. You will be asked to lie on your back on a bed during these measures.

For your information, the BIRD is a prototype BIA device being trialled in this study. It meets Australian and internationally recognized electrical safety standards defined under International Electrotechnical Commission (60601 requirements). However, it does not have final Therapeutic Goods Administration approval at this time. This study forms part of the process to gain approval. The power supply to the device is from the internal batteries of the laptop or medical cart to which the device is connected.

POSSIBLE RISKS AND BENEFITS OF THE STUDY

Infection: All equipment will be cleaned according to standard hospital procedures adhered to by the Fiona Stanley Hospital (FSH) Burns Unit. Tracing your wound is conducted regularly in normal practice, using sterile dressings. All gel adhesive electrodes are single-use and will be placed on intact skin and will not come into contact with your open wound. Thus there is very minimal risk of infection.

Injury: The BIS and ES devices are battery operated. The current from which the measurements are taken is tiny. The machine has been tested previously on patients and staff in the FSH Burn Unit without injury or ill effect.

Skin Irritation: A small possibility exists that some participants may experience skin irritation from the electrodes or gel adhesive. If such an event occurs, you will be assessed by your doctor and treatment will be immediately commenced. You may need to be withdrawn from the study.

There may be no direct benefit for you from participation in the study if the electrostimulation has little or no influence on the rate of recovery of your wound. However, your participation may benefit burns patients in future.

COST OF PARTICIPATION
There is no cost to you associated with participating.

ACTION IF ADVERSE EVENT OCCURS DURING STUDY
In the event that you suffer an adverse event or a medical accident during this study that arises from the participation in the study, you will be offered all full and necessary treatment by FSH. The Royal Perth Hospital Ethics Committee has approved this study on the basis (amongst others) that the reported risk of such an event is either small or acceptable in terms of the risk you face as a result of your current illness or the benefit that is possible with the new treatment being tested. No provisions have been made in this trial to offer trial subjects who suffer adverse reaction monetary compensation, but the absence of such a provision does not remove your right to seek compensation under common law.

PRIVACY AND CONFIDENTIALITY
The information gathered about you during the study will be held by the investigator in strict confidence. The study will not keep any data after the research has been completed. All data will be stored in a computer in the FSH with access via a password known only to investigators. All data collection sheets will be stored in a locked filing cabinet for a period of seven years, as required by law. All people who handle your information will adhere to traditional standards of confidentiality and will comply with all relevant privacy legislation. In Australia, this is in the Privacy Act 1988. If the results of the trial are published in a medical journal, as is intended, no reader will be able to identify individual patients.

FSH Site PIS V 1.2 Date 19/05/2015 based on RPH Master PIS V1 dated 11/8/2014

One exception is requested. With your permission, the manufacturer of the BIRD wishes to use your bioimpedance data (only) for use in calculating the equations to make the BIRD more user-friendly. Absolutely no identifying information will be shared other than the raw bioimpedance data, with your permission.

VOLUNTARY PARTICIPATION AND WITHDRAWAL

Participation in this study is entirely voluntary. You do not have to participate if you do not want to and your decision to participate or not will in no way affect your current or future care at RPH. You are also free to withdraw from the study at any time without reason or justification.

REQUESTS FOR MORE INFORMATION

The investigators encourage you to discuss any questions or concerns regarding the study with them at any time throughout the study. The chief investigator for this study if Dr Dale Edgar, who can be contacted on ▮▮▮▮▮▮ or email dale.edgar@health.wa.gov.au.

This study has been approved by the Royal Perth Hospital Ethics Committee. If you have any concerns about the conduct of the study or your rights as a research participant, please contact Prof Frank van Bockxmeer, Chairman of the RPH Ethics Committee, via (08) 9224 2292 or rph.hrec@health.wa.gov.au and quote the ethics approval number (REG 14-006).

FSH Site PIS V 1.2 Date 19/05/2015 based on RPH Master PIS V1 dated 11/8/2014

APPENDIX L   THE UNIVERSITY OF NOTRE DAME HREC APPROVAL FOR STUDY ONE

THE UNIVERSITY OF
NOTRE DAME
AUSTRALIA

19 Mouat Street (PO Box 1225) Fremantle WA 6959
+61 8 9433 0555 | enquiries@nd.edu.au

8 December 2015

Associate Professor Dale Edgar & Mr Dale Edwick
School of Physiotherapy
The University of Notre Dame Australia
Fremantle Campus

Dear Dale and Dale,

Reference Number: 015158F

Project Title: "Validating the use of alternate electrodes positions for bioimpedance measurement of hand volume in a non-injured population."

Your response to the conditions imposed by a sub-committee of the university's Human Research Ethics Committee, has been reviewed and assessed as meeting all the requirements as outlined in the *National Statement on Ethical Conduct in Human Research* (2014). I am pleased to advise that ethical clearance has been granted for this proposed study.

All research projects are approved subject to standard conditions of approval. Please read the attached document for details of these conditions.

On behalf of the Human Research Ethics Committee, I wish you well with your study.

Yours sincerely,

Dr Natalie Giles
Research Ethics Officer
Research Office

cc: Prof Peter Hamer, Dean, School of Physiotherapy;
         A/Prof Shane Patman, SRC Chair, School of Physiotherapy.

Broome Campus 88 Guy Street (PO Box 2287) Broome WA 6725
Sydney Campus 140 Broadway (PO Box 944) NSW 2007

| Fremantle | Broome | Sydney |

ABN 69 330 643 210 | CRICOS Provider Code: 01032F   nd.edu.au

Government of **Western Australia**
South Metropolitan Health Service

FIONA STANLEY hospital

Mr Dale Edwick
Physiotherapy
Fiona Stanley Hospital
11 Robin Warren Drive
MURDOCH WA 6150

Dear Mr Edwick

Project Title: Measurement and management of oedema after hand burn injury
Ref Number: 2016-143

On behalf of Fiona Stanley Hospital, I give authorisation for your research project to be conducted at Fiona Stanley Hospital.

The documents approved for use at site are those approved by the HREC in the letter dated 14 October 2016:

Approved document(s)
• Protocol Version 1 dated 27 June 2016
• Participant Information and Consent Form Version 2 dated 14 October 2016

This authorisation is based on the approval from the South Metropolitan Health Service Human Research Ethics Committee and the review from the Research Governance Office. This authorisation is valid subject to the ongoing approval from the HREC, and on the basis of compliance with the 'Conditions of Site Authorisation to Conduct a Research Project' (attached) and any additional reporting required by the Research Governance office and approving HREC.

Non-compliance with these conditions could result in the authorisation being withdrawn.

The responsibility for the conduct of this project remains with you as the Principal Investigator at the site.

Yours sincerely

Taylor Carter
A/EXECUTIVE DIRECTOR
19 October 2016

Fiona Stanley Hospital
11 Robin Warren Drive, Murdoch WA 6150
www.fsh.health.wa.gov.au
www.southmetropolitan.health.wa.gov.au

Government of **Western Australia**
South Metropolitan Health Service

South Metropolitan Health Service
Human Research Ethics Committee (EC00265)

29 August 2016

Mr Dale Edwick
State Adult Burns Unit
Fiona Stanley Hospital
11 Robin Warren Drive
MURDOCH WA 6150

Dear Mr Edwick

Project Title: *Measurement and management of oedema after hand burn injury*
Protocol:
REG Number: **2016-143**
HREC Meeting: **9 August 2016**

The ethics application for the project referenced above has been reviewed by the South Metropolitan Health Service (SMHS) Human Research Ethics Committee (HREC). In reviewing this project, the Committee has considered whether the protocol meets the requirements of the NHMRC's National Statement on Ethical Conduct in Human Research (National Statement).

The SMHS HREC considers that the research meets the requirements of the National Statement and resolved at the meeting to approve the project

This approval is valid to **29 August 2019** and on the basis of compliance with the 'Conditions of HREC Approval for a Research Project' (attached).

The nominated participating site(s) in this project is/are:
- **Fiona Stanley Hospital**

Documents
Protocol version 1, 27 June 2016
FSH PICF version 1 dated 21 June 2016

If additional sites are recruited prior to the commencement of, or during the research project, the Coordinating Principal Investigator is required to notify the HREC. Notification of withdrawn sites should also be provided to the HREC in a timely fashion.

<u>This letter constitutes ethical approval only</u>. This project cannot proceed at any site until separate site authorisation has been obtained from the Chief Executive, or delegate, of the site following Site Specific Assessment by a Research Governance Officer. For further information about obtaining site authorisation, refer to the WA Health Research Governance Framework available at http://ww2.health.wa.gov.au/Health-for/Researchers-and-educators/Research-governance

APPENDIX O   **THE UNIVERSITY OF NOTRE DAME AUSTRALIA HREC APPROVAL FOR STUDIES TWO AND THREE**

22 August 2016

A/Prof Dale Edgar & Mr Dale Edwick
School of Physiotherapy
The University of Notre Dame, Australia
Fremantle Campus

Dear Dale and Dale,

Reference Number: 016128F

Project title: "Measurement and management of oedema after hand burn injury."

Your response to the conditions imposed by the university's Human Research Ethics Committee, has been reviewed and assessed as meeting all the requirements as outlined in the *National Statement on Ethical Conduct in Human Research* (2014). I am pleased to advise that ethical clearance has been granted for this proposed study.

All research projects are approved subject to standard conditions of approval. Please read the attached document for details of these conditions.

On behalf of the Human Research Ethics Committee, I wish you well with your study.
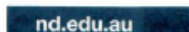
Yours sincerely,

Dr Natalie Giles
Research Ethics Officer
Research Office

cc: Prof Ben Wand, SRC Chair, School of Physiotherapy

Government of **Western Australia**
South Metropolitan Health Service

FIONA STANLEY hospital

Dr Dale Edgar
Burns Unit
Fiona Stanley Hospital
11 Robin Warren Drive
MURDOCH   WA   6150

Dear Dr Edgar

Project Title:	**Does electrical stimulation therapy improve healing in small area acute burns, as measured by localised bioimpedance?**
Ref Number:	**2014-006**
Lead HREC:	**Royal Perth Hospital**

On behalf of Fiona Stanley Hospital (FSH), I give authorisation for the amendment to the above project to be implemented at Fiona Stanley Hospital.

The following documents as approved by the HREC have been approved for use at site:

- Protocol for Electrical Stimulation Project, 9 August 2016

I have been designated the authority to approve amendments by the Executive Director of FSH. This authorisation is valid subject to the ongoing approval from the HREC, and on the basis of compliance with the 'Conditions of Site Authorisation to Conduct a Research Project' and any additional reporting requirements of the Research Governance office or approving HREC.

The responsibility for the conduct of this project remains with you as the Principal Investigator at the site.

If you have any queries, please contact the Research Governance Officers on (08) 6151 1180 or SMHS.REG@health.wa.gov.au.

Yours sincerely

Dr John Anderson
A/DIRECTOR CLINICAL SERVICES

11 November 2016

Cc: Dale Edwick

Fiona Stanley Hospital
11 Robin Warren Drive, Murdoch WA 6150
www.fsh.health.wa.gov.au
www.southmetropolitan.health.wa.gov.au

Government of Western Australia
East Metropolitan Health Service

Royal Perth Hospital
Human Research Ethics Committee (EC00270)

25 August 2016

Dr Dale Edgar
State Adult Burns Unit
Fiona Stanley Hospital

Dear Dr Edgar

Project Title: *Does electrical stimulation therapy improve healing in small area acute burns, as measured by localised bioimpedance?*

REG Number: 2014-006

The following **amendment/s (and associated documents)** were **approved** by the Royal Perth Hospital Human Research Ethics Committee at its **24 August 2016** meeting:

Documents
Protocol for Electrical Stimulation Project, 9 August 2016
WA Health Ethics Application - Elect Stim in Acute Burn Wounds, 8 August 2016

Governance approval for East Metropolitan Health Service (EMHS) sites will be forthcoming.

Please submit a copy of this approval letter to the Research Governance Office at each non-EMHS site.

Yours sincerely

DR RAMIN GHARBI
Chairman | Royal Perth Hospital Human Research Ethics Committee

Research Ethics & Governance
Level 3 Colonial House, Royal Perth Hospital, GPO Box X2213 Perth WA 6847
Telephone: (08) 9224 2260 / (08) 9224 2292
Email: EMHS.REG@health.wa.gov.au

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APPENDIX R   **THE UNIVERSITY OF NOTRE DAME AUSTRALIA HREC APPROVAL FOR STUDY FOUR**

THE UNIVERSITY OF
NOTRE DAME
AUSTRALIA

19 Mouat St (PO Box 1225) Fremantle WA 6959
+61 8 **9433 0555** | enquiries@nd.edu.au

1 April 2019

A/Prof Dale Edgar & Dale Edwick
School of Physiotherapy
The University of Notre Dame Australia
Fremantle Campus

Dear Monica,

Reference Number: 019048F

Project title: "Does electrical stimulation therapy improve healing in small area acute burns, as measured by localised bioimpedance?"
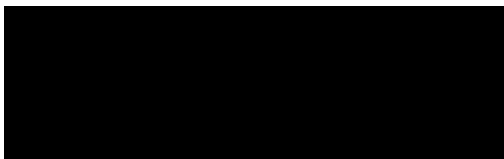
Thank you for submitting the above project for review. It is noted that you have ethics approval for this project from Royal Perth Hospital HREC, reference number REG14-006. Your application has been assessed as qualifying for a Cross-Institutional approval and is therefore exempt from HREC review. I am pleased to advise that ethical clearance has been granted for this proposed study.

Other researchers identified as working on this project are:

Name	School	Role
Prof Fiona Wood	Fiona Wood Foundation	Co-Supervisor
Dr Tiffany Grisbrook	Fiona Wood Foundation	Co-Investigator
Ms Tess Jackson	Fiona Wood Foundation	Co-Investigator

All research projects are approved subject to standard conditions of approval.
Please read the attached document for details of these conditions.

Should you have any queries about this project, please contact me at #2964 or Natalie.Giles@nd.edu.au.

Yours sincerely,
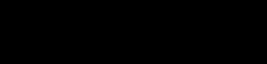
Dr Natalie Giles
Research Ethics Officer
Research Office

Cc: Prof Ben Wand, SRC Chair, School of Physiotherapy

APPENDIX S   QUICKDASH QUESTIONNAIRE WITH GCSQ

QuickDASH

Please rate your ability to do the following activities in the last week by circling the number below the appropriate response.

	NO DIFFICULTY	MILD DIFFICULTY	MODERATE DIFFICULTY	SEVERE DIFFICULTY	UNABLE
1. Open a tight or new jar.	1	2	3	4	5
2. Do heavy household chores (e.g., wash walls, floors).	1	2	3	4	5
3. Carry a shopping bag or briefcase.	1	2	3	4	5
4. Wash your back.	1	2	3	4	5
5. Use a knife to cut food.	1	2	3	4	5
6. Recreational activities in which you take some force or impact through your arm, shoulder or hand (e.g., golf, hammering, tennis, etc.).	1	2	3	4	5

	NOT AT ALL	SLIGHTLY	MODERATELY	QUITE A BIT	EXTREMELY
7. During the past week, *to what extent* has your arm, shoulder or hand problem interfered with your normal social activities with family, friends, neighbours or groups?	1	2	3	4	5

	NOT LIMITED AT ALL	SLIGHTLY LIMITED	MODERATELY LIMITED	VERY LIMITED	UNABLE
8. During the past week, were you limited in your work or other regular daily activities as a result of your arm, shoulder or hand problem?	1	2	3	4	5

Please rate the severity of the following symptoms in the last week. *(circle number)*

	NONE	MILD	MODERATE	SEVERE	EXTREME
9. Arm, shoulder or hand pain.	1	2	3	4	5
10. Tingling (pins and needles) in your arm, shoulder or hand.	1	2	3	4	5

	NO DIFFICULTY	MILD DIFFICULTY	MODERATE DIFFICULTY	SEVERE DIFFICULTY	SO MUCH DIFFICULTY THAT I CAN'T SLEEP
11. During the past week, how much difficulty have you had sleeping because of the pain in your arm, shoulder or hand? *(circle number)*	1	2	3	4	5

QuickDASH DISABILITY/SYMPTOM SCORE = $\left(\left[\dfrac{(\text{sum of } n \text{ responses})}{n}\right] - 1\right) \times 25$, where n is equal to the number of completed responses.

A QuickDASH score may **not** be calculated if there is greater than 1 missing item.

12. With respect to your hand burn injury, how would you describe your hand function now compared to immediately after your burn?

Very Much Worse	Much Worse	Minimally Worse	No Change	Minimally Improved	Much Improved	Very Much Improved
1	2	3	4	5	6	7

*Quick*DASH

WORK MODULE (OPTIONAL)

The following questions ask about the impact of your arm, shoulder or hand problem on your ability to work (including homemaking if that is your main work role).

Please indicate what your job/work is:_____

❑ I do not work. (You may skip this section.)

Please circle the number that best describes your physical ability in the past week.

Did you have any difficulty:	NO DIFFICULTY	MILD DIFFICULTY	MODERATE DIFFICULTY	SEVERE DIFFICULTY	UNABLE
1. using your usual technique for your work?	1	2	3	4	5
2. doing your usual work because of arm, shoulder or hand pain?	1	2	3	4	5
3. doing your work as well as you would like?	1	2	3	4	5
4. spending your usual amount of time doing your work?	1	2	3	4	5

SPORTS/PERFORMING ARTS MODULE (OPTIONAL)

The following questions relate to the impact of your arm, shoulder or hand problem on playing *your musical instrument* or *sport* or *both*. If you play more than one sport or instrument (or play both), please answer with respect to that activity which is most important to you.

Please indicate the sport or instrument which is most important to you:_____

❑ I do not play a sport or an instrument. (You may skip this section.)

Please circle the number that best describes your physical ability in the past week.

Did you have any difficulty:	NO DIFFICULTY	MILD DIFFICULTY	MODERATE DIFFICULTY	SEVERE DIFFICULTY	UNABLE
1. using your usual technique for playing your instrument or sport?	1	2	3	4	5
2. playing your musical instrument or sport because of arm, shoulder or hand pain?	1	2	3	4	5
3. playing your musical instrument or sport as well as you would like?	1	2	3	4	5
4. spending your usual amount of time practising or playing your instrument or sport?	1	2	3	4	5

SCORING THE OPTIONAL MODULES: Add up assigned values for each response; divide by 4 (number of items); subtract 1; multiply by 25.
An optional module score may <u>not</u> be calculated if there are any missing items.