Assessment of the impact of acute burn oedema: validation of outcome measures of temporal recovery in adults

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Abstract

Oedema, or swelling, after burn injury is a natural consequence of the human inflammatory response. Oedema is, therefore, an integral part of wound healing. However, after burn injury the response is exaggerated, causing both local and systemic oedema. Excessive local oedema causes deterioration in the viability of the marginal cells in the zone of trauma, leading to further increases in macroscopic tissue death by 3 days post-injury. Systemic oedema accumulation occurs in non-injured tissues and in the lungs, where excessive oedema may be lethal. The timeframe in which oedema is present in injured tissues also impacts on the healing process. The longer oedema remains in situ, the greater the impedance to enzymatic and chemical healing processes leading to slowing of wound healing. This, in combination with increased tissue loss, compounds to prolong burn healing time. The risk of hypertrophic scarring in the skin post-burn period increases in proportion to the time to wound closure. Burn scar causes functional and movement limitation, challenges psychological well-being and social reintegration or participation and leads to unacceptable aesthetic outcomes in the months to years after the initial burn injury.

The overall aim of the project was to improve the management of acute burn oedema. The initial aim of the project was to review critically the relevant literature. Consequently, the analysis aimed to provide a detailed synthesis of evidence to illustrate the gaps in and knowledge of treatment for acute burn oedema. Finally, the review of literature determined the current understanding of methods to measure of the outcomes post-intervention in the burn patient population. Subsequently, a series of novel studies was designed with two major objectives. To aid the planning of treatments and research, the investigations first examined the contents of acute burn oedema and its temporal change during the acute inflammatory period. The second research objective aimed to establish a set of valid and reliable outcome measurement options both after and during interventions to control post-burn oedema.

The review of literature summarised the factors, which influence the amount of acute burn oedema and demonstrated that techniques of assessment were either invasive, infeasible or lacked clinical utility for consistent use. The key points to note from the synthesis of literature were that the quality of acute burn intervention studies and, or reporting of these studies was poor. The results of a Cochrane Systematic Review collated a number of small, single centre studies, which indicated that local burn wound oedema was reduced by electrical muscle stimulation and the use of

continuous high dose vitamin C during acute burn resuscitation. Further, for the treatment of systemic burn oedema, the results of drug trials were equivocal except for the addition of albumin to the acute fluid resuscitation regime. Single centre studies demonstrated this intervention increases deposition of acute oedema into the lungs and the risk of death.

The review of literature summarised the current body of knowledge related to the temporal changes in acute burn oedema volume and constituents. It is limited in its application for both clinical practice and research design as it is based on animal models of injury and, or expert opinion. Thus, novel scientific studies in the acute burn patient population were designed and completed to examine the microscopic contents of oedema. For other patient populations such as those post-mastectomy and lymphatic clearances, clinicians described the importance of understanding the temporal change of composition of oedema fluid. In particular, oedema composition influences the timing of treatment application and the potential for the tissues to respond after the intervention. While parallels exist between oedema states in different patient groups, there are unanswered questions with respect to the patho-physiology and management of acute oedema, particularly after human burn injury. The scientific studies in this project initially described the daily tissue volume changes and bi-daily laboratory assessments of oedema contents during the first seven days post-burn.

In humans with partial thickness burn injury, the volumetry and wound fluid studies conducted demonstrated four outcomes. Firstly, oedema peaks on day one post-burn for those who do not require formal fluid resuscitation. The studies indicated that the peak was on day two for burns requiring resuscitation. The results contrast animal studies, which suggest that the peak of oedema in the tissues occurs at about day one post-injury. The findings confirmed the marked disparity in post-burn oedema volume responses, and the potential pitfalls of performing oedema specific treatment studies in animal models and, assuming direct relevance to humans. Secondly, the rate of volume change over time tapered to clinically insignificant levels after day four post-burn. Thirdly, the wound fluid studies confirmed that interstitial acute burn oedema was a high protein fluid (i.e. ≥ 10 g/L protein) throughout the acute inflammatory period. Again, wide variation existed with sample concentrations between ~10 and 64 g/L. However, these results were up to a factor of scale greater than previous studies examining human burn fluid collected passively or from blister fluid. Further, apart from the first day post-burn, oedema protein levels remained, on average, above the human interstitium physiological norm of 20.6g/L. The presence of high protein oedema in the

tissues suggests notable challenges with respect to future treatment choices. Lastly, the wound fluid studies indicated that that acute burn oedema was ~98% (by weight) fluid and particles < 100μm in diameter. Conversely, the remainder of the oedema fluid contained large proteins and debris. The implications of the particulate matter results were promising. As the oedema fluid volume post-burn contributes significantly to wound depth conversion, the findings suggested that active removal of greater than 98% of the interstitial fluid barrier was possible through patent lymphatic collectors (and the open wound). Overall, the scientific studies provided new detail as to the parameters of research and clinical treatment design for efficacious management of acute oedema in burn survivors. The results indicated a necessity for urgent intervention to incorporate the active stimulation of the lymphatic system. The findings do not, however, inform the reader of the implications of full thickness burn injury as the study samples by design, lacked patients with significant areas of deep injury.

An extensive series of original studies investigated the application of measurement tools for the post-burn recovery continuum. The outcome tool research presented includes assessment of the clinical utility of individual measures for a) the acute burn environment and b) longitudinal bio-psycho-social assessment of all patients with a burn. The reliability and sensitivity of whole upper limb water displacement volumetry, bioimpedance spectroscopy and upper limb Polhemus FastSCAN 3-D laser scanning were investigated in the acute post-burn period. All of these methods posed significant challenges with respect to clinical and research application for management of swelling with open burn wounds. Of the three methods, water displacement volumetry was the most readily available, relatively sensitive and applicable in the clinical environment. Bioimpedance spectroscopy requires more study to develop its broad applicability in the acute period but its reliability was confirmed for patients with up to 30% body surface area burn. While cost of equipment was a barrier for widespread use of both bioimpedance and Polhemus 3-D scanning, the laser method was further demonstrated to be insensitive and lacked feasibility in the acute burn unit environment.

Thus, with the confirmation of the difficulties in acute environment burn oedema measurement, the long-term bio-psycho-social recovery assessment tools became an important focus with the ongoing studies. Burn patient outcomes were collected for up to two years post-burn, though the availability of data for analyses at the final time point were limited. This longitudinal clinical research confirmed the reliability, sensitivity and, or validity of the QuickDASH, upper and lower limb joint goniometry, hand linear

and scale measures, single leg stance, timed up and go, tandem walk tests and the SF-36 (version 2) acute recall for the burn population. The initial outcome tools chosen were not planned to be an exhaustive list. Rather, the tests were included due to clinical applicability, literature, 'ratio' of administration time to information gained and physiotherapist preference, with particular reference to the WHO International Classification of Function framework. In presenting this novel work, whilst designed to assess burn survivors of all severities, it was appreciated that the Western Australian adult burn population lacked significant numbers of severe burns, except in times of mass casualty disasters, to extensively evaluate the outcome measures of interest. During the candidacy, two major disasters occurred spurring a number of investigations, which have complemented the body of knowledge relating to each of the outcome measures presented in the thesis. Further, it was during these unique mass admission events that the combined performance of a rapidly applied, multi-faceted outcome battery was explored. Therefore, the final paper in the Results chapter presents an example of an outcome battery modelled from the clinical evidence for the measurement of recovery after lower limb burn.

The work to determine the most applicable components, and combination thereof, for a multidimensional longitudinal burn recovery battery is ongoing. However, the findings of this project provide a starting point for assessment of the global burden of burn disease as the population validated outcome measures may be adapted to apply in any burn care environment.

Conclusions

It was determined during this research that human acute oedema peaks between the first to second day dependent on medical interventions. Acute oedema volume tails off markedly after day four post-burn. Acute burn oedema was confirmed to be a high protein oedema but > 98% by weight in fluid and small particles. Therefore, clinicians are challenged to apply treatment methods as soon as possible before day two post-burn in order to reduce the peak of swelling and negate its impact on wound conversion. Treatment during the acute period should include intervention to stimulate absorption via the lymphatic system, at least to the end of day four post-burn.

Burn oedema was difficult to measure in the acute inpatient environment. Water displacement volumetry for the whole upper limb was shown to be sensitive and reliable. Similarly, bioimpedance spectroscopy was shown to be sensitive and reliable but further work is required to determine its validity in the burn population. Polhemus FastSCAN 3-D laser scanning is not feasible for acute oedema measurement at this time.

This project assimilated and validated a number of individual uni-dimensional and complex outcome assessment tools for use up to 2 years post-burn. Adjunctive studies determined the reliability and responsiveness of these measures in the clinical setting. Finally, a lower limb burn outcome battery was devised and its optimal longitudinal use was described.

Statement of Originality

This thesis is presented for the degree of Doctor of Philosophy for the University of Western Australia. This thesis comprises an extensive series of published, submitted or prepared manuscripts with supporting text and supplementary material. Collaborations were established on many of the submissions; however, I maintained significant involvement in all contributions relating to acute burn oedema and the assessment of the immediate and longitudinal consequences of its presence in the tissues.

The studies undertaken were completed between December 2000 and June 2009 in association with the staff of the Medical Physics Department, Royal Perth Hospital (RPH); staff and patients of Burn Unit and Telstra Burn Outcome Centre, RPH and the staff and students of Curtin University of Technology, Perth. Since February 2005, the McComb Foundation of Western Australia has supported my clinical research time.

The research was undertaken with the assistance of my initial supervisors, between 2000 and March 2008, Professor Emeritus Joan Cole and Associate Professor Kathy Briffa in the Curtin University of Technology, School of Physiotherapy in conjunction with Winthrop Professor Fiona Wood, University of Western Australia. Subsequently, the project was finalised continuing with Fiona Wood (School of Surgery) and Professor Kevin Singer and Dr Barby Singer (Centre for Musculoskeletal Studies) at the University of Western Australia.

Mr Rob Day, Department of Medical Physics, RPH assisted with data collection, customisation of software linkage and provision of computer script for data analyses during the Polhemus 3-D laser trials.

Mr Michael Phillips, biostatistician, Western Australian Institute of Medical Research (WAIMR), contributed since June 2007, assisting with data analyses for the bioimpedance and the compilation of outcome batteries examining burn recovery.

Ms Elspeth Mackay, biostatistician, UWA assisted with the data analyses for the negative pressure dressings and volumetry studies.

Mr Alan Morling (RPH) and Dr Mark Fear (UWA) coordinated specific laboratory testing of acute oedema fluid samples.

Senior physiotherapy colleagues, Mr Andy Wu, Mrs Vidya Finlay, Mr Matt McClure and Mr Mark McAloon have assisted with data collection and, or have contributed to the editing of co-authored, submitted manuscripts where noted. Junior rotational physiotherapist colleagues, medical students and physiotherapy students have assisted with data collection when it was appropriate to do so.

I have participated in, or independently performed, all aspects of the research represented in this thesis. This includes the critical review and summation of relevant literature; conceptualisation, coordination and enactment of investigations (unless otherwise stated); completion of appropriate ethics applications, data collection, reduction and analysis; authorship or co-authorship of included manuscripts and subsequent compilation of the thesis. When the published work of others was consulted, this is attributed clearly.

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

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Statement of Candidate and Co-author Contributions

The candidate independently prepared all submitted and draft manuscripts, revisions and responses to reviewers where he was attributed as first author. Where the candidate was last author, he conceptualized the manuscript and, or study and was involved in the preparation and editing of the manuscript, revisions and responses to reviewers. The specific contribution of co-authors on all jointly published work is detailed in Appendix 1. Individual co-author sign-off is recorded where appropriate in the DVD Appendix, Folder A.

Acknowledgements

The research undertaken for this PhD project would not have been possible without the support and practical contributions of many individuals. I would like to acknowledge and thank these people:

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My principal supervisor, Professor Kevin Singer, whose executive and organizational prowess have focused and re-defined the body of work which had meandered over a number of years prior to the commencement at the Centre for Musculoskeletal Studies. His academic and research acumen have been invaluable and I thank him for his learned input during the compilation of this thesis.

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I, not only thank Debbie Somers, McComb Foundation of WA, for her administrative and practical help but also for her support in times of insanity. The McComb Foundation support was 'enacted' by Debbie and without this, the project could not have happened. The opportunity to think and develop novel ideas can only stem from having the time to do just that. In practical terms, funding support was necessary to allow me to step out of my usual role to appreciate the 'bigger picture'. For this, I am eternally grateful to the McComb Foundation and LotteryWest for the infrastructure and monetary support which ensured the completion of this project.

The nursing team have been constant allies throughout the project. Special thanks for their 'hands on' assistance go to Joy Fong, Sharon Rowe, Cathy Tonkin, Wena Willis, Seih-Ling Dickson. I extend my gratitude to the happy band of expert clinicians who make the RPH Burn Unit a merry place despite all odds.

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For the Cochrane Collaboration submissions, I acknowledge the input of the Cochrane Wounds Group members, in particular Sally Bell-Sayer and Ruth Foxlee. Further, I thank my Canadian collaborators including Dr Manuel Gomez and Dr Joel Fish. May that work be only the beginning.

Finally, I acknowledge the input and assistance of my initial supervisors from Curtin University of Technology, including Professor Tony Wright. I would like to thank Professor Emeritus Joan Cole for guiding me through the initial candidacy process and facilitating my research journey with flexibility, practical support and editorial wisdom. I also thank Associate Professor Kathy Briffa for her insight and guidance with respect to methodological design and academic process.

This thesis is dedicated to my family, my gorgeous wife, Suse and my three cheeky monkeys Harry, Tali and Lily who all came along during this candidacy.

Life is short, even in its longest days....
John Mellencamp – *Life, Death Love and Freedom*.

If you want to be a passenger, climb aboard with me, we're leaving now....
Bernard Fanning – *Internationalist*.

Never doubt that a small group of thoughtful, committed citizens can change the world. Indeed, it is the only thing that ever has.
Margaret Mead.

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List of Abbreviations and Terms

ADF	Australian Defence Force
AHMAC	Australian Health Minister's Advisory Council
AHMC	Australian Health Minister's Committee
AHDMPC	Australian Health Disaster Management Policy Committee (now AHPC)
AHPC	Australian Health Protection Committee
ANZBA	Australian and New Zealand Burns Association
BMDS	Burn Minimum Dataset (of the Burn Service of Western Australia)
BSHS	Burn specific health scale
BSWA	Burn Service of Western Australia
CSQU	Clinical Quality and Safety Unit (RPH Ethics sub-committee)
DDB	Deep dermal burn
DoHA	Department of Health and Ageing (Commonwealth)
EMA	Emergency Management Australia
FTB	Full thickness burn
HTS	Hypertrophic (burn) scar
IL	Interleukin (cytokine molecule)
LD50	Lethal dose 50%
LPC	Lipid-protein complex (burn toxin)
MBT	Multidisciplinary Burn Team
MDB	Mid-dermal burn
MDD	Minimum detectable difference
NBPCC	National Burn Planning and Coordination Committee
NHMRC	National Health and Medical Research Council
NMoBC	National Model of Burn Care
RACS	Royal Australian College of Surgeons
ROS	Reactive oxygen species (includes oxygen free radicals)
RPH	Royal Perth Hospital
SDB	Superficial dermal burn
SIRS	Systemic Inflammatory Response Syndrome
TBSA	Total Burn Surface Area (commonly expressed as percentage TBSA)
VSS	Vancouver Scar Scale

Thesis Manuscripts and Publications: Abstracts

A total of 21 co-authored original manuscripts or texts and one *Letter to the Editor* were prepared, submitted or published during the candidacy (Table 1). The candidate's contribution to each paper is outlined in Appendix 1. However, the following abridged list of eight manuscripts demonstrates those papers that contribute directly to the thesis text in the order they appear. The thesis papers are cited with titles, co-authors and abstracts are included. The Cochrane Systematic Review and all other publications cited are presented in full for perusal in DVD Appendix, Folder B.

Chapter 2: Review of Literature

I (A): Local and systemic treatments for acute oedema after burn injury (Protocol). Edgar DW, Fish JS, Gomez Ospina M, Wood FM. *Cochrane Database of Systematic Review*s 2007, Issue 3.

I (B): Local and systemic treatments for acute oedema after burn injury (Review). Edgar DW, Fish JS, Gomez M, Wood FM. Submitted to *Cochrane Wounds Group Editor for final review for publication in Cochrane Database of Systematic Review*s.

Abstract:

Background: Burn injury is one of the most complex and painful traumas. In addition to the local burn response, there is a systemic inflammatory response. The result is both local and generalised oedema. Oedema fluid limits the exchange of vital nutrients in the healing burn. Vulnerable tissues are at risk of compromise if oedema is present. The concept of tissue salvage is centre stage and the effectiveness of treatment is now measured in terms of the quality of survival. Interventions on burn oedema have the potential to influence survival and the scar worn for life. The importance of oedema control in tissue salvage is recognized, however, treatments targeted at oedema control have not been critically reviewed.

Objectives: The objective of this review was to assess the evidence for the effectiveness of local and systemic treatments for oedema management immediately after burn injury.

Search methods: Online searches were conducted as per protocol. Papers were not limited by language or time of report. Hand searches were conducted retrospectively to 1995. Grey literature was searched and attempts were made to contact all authors to clarify study details. Bibliographies were reviewed for all included studies.

Selection criteria: All studies were RCT's involving oedema treatments in patients with acute burn injury. Studies were not limited by severity, burn agent, gender or age.
Data collection and analysis: All published studies were considered to April 2009. Searches accessed online databases, journal and conference abstracts, grey literature and bibliographies of included papers. Two authors independently completed data abstraction and risk of bias assessments. Synthesis of data and subgroup and sensitivity analyses were planned.
Results: A total of 8 single facility studies were included. All except one demonstrated moderate to high risk of bias due to study methods, poor reporting or both. Each study construct and, or sample population and, or outcome measurements were individual. Therefore, study data was unable to be synthesised or sub-analysed. Each review outcome was based on a single facility study.
Authors' conclusions: Management of acute burn resuscitation including colloid significantly increases lung oedema and mortality. Addition of continuous high dose vitamin C in acute burn resuscitation significantly reduces local burn tissue oedema, systemic fluid retention and resuscitation fluid requirements. Local acute hand burn oedema is significantly reduced and, active hand motion significantly increased, with addition of electrical stimulation to usual physiotherapy.
Future research must focus on multi-centre trial groups, validation of oedema and longitudinal outcome measures in the burn population for research to progress in the area of acute burn oedema management.

Chapter 4: Results

II: Whole arm water displacement volumetry is a reliable measurement technique for acute volume change: Caution with clinical use and research design in patient populations. Edgar DW, Briffa NK, Cole J, Wood FM. Submitted to *Lymphology* September 2009.

Abstract:
Introduction: Water displacement volumetry (WDV) is a reliable method for measurement of wrist and hand volume in lymphoedema patients. However, within session WDV reliability for the whole arm lacks comprehensive investigation, particularly in acute oedema populations. This study aimed to confirm the reliability and investigate the impact of time between repeated trials on the sensitivity of WDV as a measure of whole upper limb volume change.

Methods:

Within session, duplicate measures of WDV were recorded in two groups of non-injured volunteers. Each group differed only in the time between repeats. The reliability trials were performed <10 minutes apart (T_{10}) and 20-30 minutes apart (T_{20}).

Results:

Both groups demonstrated excellent correlation between trials (ICC_{T10}=0.999, ICC_{T20}=0.997). Despite this, a systematic bias was demonstrated between the T_{10} group means. The T_{20} group trials did not indicate such error upon statistical testing (p=0.297). The minimum detectable difference for WDV when measuring whole arm upper limb volume change was 46.2 mls (T_{20}).

Conclusion: This study confirms that WDV measures of non-injured upper limbs are reliable and sensitive, if used at least 20 minutes apart. Researchers and clinicians are reminded to consider the performance of WDV when designing investigations in specific patient populations.

III: Measurement of acute edema shifts in human burn survivors – the reliability and sensitivity of bioimpedence spectroscopy as an objective clinical measure.

Edgar DW, Briffa NK, Cole J, Tan M, Khoo B, Goh J, Wood FM. *Journal of Burn Care and Research*. 2009, 30: Accepted to print JBCR-D-08-00314.

Abstract:

Objective**:** Improvements in treatment for acute burn edema have stalled in comparison to other areas of burn care. Designing acute edema treatment studies in humans is hindered by the lack of objective, sensitive methods of measurement in the burn population. Bioimpedence spectroscopy (BIS) is a non-invasive method of measuring fluid volumes in the body. The aim of this study was to examine the reliability and sensitivity of BIS in the measurement of acute edema shifts in burn survivors, including assessment across different wound conditions.

Methods**:** BIS measurements were collected in triplicate from 21 burn patients in total. Phase I (n=13) examined BIS under 3 different dressing conditions. Phase II (n=8) considered only patients with dressings intact. Sensitivity (minimum detectable difference) was examined with total body water (TBW), extra-cellular fluid (ECF) and intra-cellular fluid (ICF) volume measurements.

Results: BIS demonstrated excellent reliability across all dressings conditions, including when open wounds were present (ICC's= 0.975 – 1.00, 95% CI's = 0.938 – 1.00). Clinically useful levels of sensitivity, or minimum detectable difference (MDD),

were calculated. BIS MDD for TBW (open wounds) = 360mls; ECF (open wounds) = <10mls; ECF (new dressings) = 540mls and ICF (open wounds) = 310mls.

Conclusion: BIS analysis is clinically applicable for real time, non-invasive monitoring of whole body fluid shifts in acute burn survivors with ≤30% TBSA.

IV: Volume measurement using the Polhemus FastSCAN 3D laser scanning: A novel application for burns clinical research. Edgar DW, Day R, Briffa NK, Cole J, Wood FM. *Journal of Burn Care and Research*. 2008, 29(6): 994 -1000.

Abstract:

Objective: The *Polhemus* FastSCAN® system offers a non-contact method of quantifying limb edema volume by combining laser scanning with 3D spatial orientation. The aim of this study was to investigate the reliability, validity and clinical utility of this assessment technique in the burn environment.

Method: *Pilot Studies:* Completed in order to develop a standardised scanning procedure. *Inter-tester Reliability:* Two testers each scanned 30 uninjured upper limbs. *Intra-tester Reliability:* One tester conducted repeated scans for burn survivors (n=6). *Validity:* The scan volumes were compared with water displacement measures for all volunteers (n=36).

Results: Inter-tester reliability was moderate for whole arm scans (R=0.59; 95%CI=0.28-0.78) and excellent with hand truncated (R=0.95; 95%CI=0.90-0.98; MDD=242.1cm^3). Intra-tester reliability was inconclusive (R=0.72; 95%CI=-0.07-0.96) but qualitative assessment confirmed poorer quality scans. The FastSCAN system overstated the arm volume by 49.3 cm^3 on average, but 95%LOA when compared to water displacement demonstrated the limitations as a clinical or research tool in the burn environment.

Conclusions: The Polhemus FastSCAN system provides a non-contact method of limb volume measurement. The reliability was good only with the hand removed from calculations. The accuracy of the system compared poorly with water displacement measures in the burn clinical environment. Using the currently available software and method, the change detectable by this technique was too large for monitoring the efficacy of acute burn edema interventions.

V: The QuickDASH is an appropriate tool for measuring quality of recovery after upper limb burn injury. Wu A, Edgar DW, Wood FM. 2007, *Burns*; 33: 843 – 849.

Abstract:

Background**:** Upper limb (UL) burn injuries commonly result in significant dysfunction. The measurement of disability is vital to assess recovery after burn injury. The *Quick*DASH questionnaire was developed to evaluate UL disorders. The aim of this study was to evaluate its validity, repeatability and responsiveness for burn patients.

Methods**:** In 2006, 85 patients with UL burns were recruited at Royal Perth Hospital. Each completed both *Quick*DASH and Burns Specific Health Scale – Brief (BSHS-B) at regular intervals after their burn. Further, 67 patients repeated the questionnaire one day after completing it at discharge.

Results: *Validity:* Criterion validity was demonstrated between *Quick*DASH and BSHS-B through good correlations (r^2 = -0.79 to -0.89). Construct validity was demonstrated using burn severity markers. *Quick*DASH scores significantly differed when grouped according to major burn, full thickness burn, surgery and need for hospital admission. *Repeatability: Quick*DASH showed excellent repeatability (ICC = 0.93). *Responsiveness:* Effect size of *Quick*DASH was demonstrated to be greater than BSHS-B at all measurement points.

Conclusions: This longitudinal study confirms the validity, repeatability and responsiveness of the *Quick*DASH outcome measure in patients with upper limb burn injuries. It supports the use of the *Quick*DASH in this population to help assess change in functional level.

VI: Goniometry and Linear Assessments to Monitor Movement Outcomes: Are They Reliable Tools in Burn Survivors? Edgar DW, Finlay V, Wu A, Wood FM. 2009*, Burns,* 35(1): 58 – 62.

Abstract:

Background: Despite common use and theoretical construct validity, goniometry has not been reported to be reliable for the measurement of burn affected joint range of motion. Similarly, a number of simple objective measures commonly used to document hand mobility have eluded this rigour. This study aimed to examine the within session intra-rater and inter-rater reliability of active joint range of motion measurement in patients with burn injuries.

Methods: *Intra-rater reliability:* One physical therapist (PT) recorded duplicate measurements on each burn affected joint after a 5 minute interval in a subset of

patients (n=21). *Inter-rater reliability*: Four qualified PT's took part in repeated measures testing of 45 patients on the same day.

Results: Intra-rater reliability was excellent with ICC's > .99 (95% CI's =.99 to 1.0). Inter-rater reliability was also excellent with ICC's >.94 (95% CI's = .90 to .99). The minimum detectable change using goniometry at the ankle was ≥ 5° and for all other joints tested was ≥ 9°. For linear hand measures a change of > 1cm and thumb opposition ≥ ½ of one scale point indicated measureable difference.

Conclusion: This study demonstrated excellent intra- and inter-rater reliability and measurement of clinically relevant change for all measurements when applied with a standardised protocol. Therefore, assessing joint ROM with a goniometer or hand movement with linear or scale measurements, can provide accurate, objective measures in the burns population.

VII: A reliable and valid outcome battery for measuring recovery of lower limb function and balance after burn injury. Finlay V, Phillips M, Wood FM, Edgar DW. Accepted to print Burns October 2009 - JBUR-D-08-00172.

Abstract:

Introduction: The measurement of recovery after burns to the lower limbs is hampered by an absence of validated injury specific tools. This research aimed to select and validate a battery of outcome measures of recovery after lower limb burn injury (LLBI).

Method: Reliability study: Reliability of the single leg stance (SLS), the Timed Up and Go (TUG) and the tandem walk (TW) tests were measured using a test-retest trial involving 28 patients with LLBI. Validity study: Clinical data from172 patients with LLBI were used to compare changes in each LL outcome measure with changes in the Burn Specific Health Scale–Brief (BSHS-B).

Results: All tests, except the SLS test with eyes closed, demonstrated excellent inter-rater reliability (ICCs = 0.81 – 0.93). The TUG and the TW-forwards tests were shown to be valid and to provide additional information to the BSHS-B when combined as a battery. The TW-backwards test was redundant while the SLS and ankle DF measures did not correlate highly with the BSHS-B.

Conclusion: This study shows that the TUG test and the TWF are reliable and valid in the burns population and along with the BSHS-B form a useful test battery for measuring recovery from LLBI.

VIII: Demonstration of the validity of the SF-36 for measurement of the temporal recovery of quality of life outcomes in burns survivors. Edgar DW, Dawson A, Hankey G, Phillips M, Wood FM. Revision submitted to *Burns* September 2009 – JBUR-D-09-00342.

Abstract:

Objective: Outcome assessment post-burn is complex. Determination of quality of life is often measured using the Burns Specific Health Scale (BSHS), a validated tool in the burn population. The SF-36 is a generic quality of life questionnaire that is validated for numerous populations, but not in burns. The aim of the study was to examine the validity of SF-36, using the BSHS as a reference.
Methods: 280 burn patients were recruited. Each completed SF-36 and BSHS-B at regular intervals to 2 years post-burn. Regression modelling was used to assess the temporal validity and the relative sensitivity of the measures.
Results: SF-36 domains and BSHS-B demonstrated significant associations at all time points ($r=0.37$-0.76, $p<0.002$). In the months post-burn, SF-36 domains: Role Physical; Bodily Pain; Social Function and Role Emotional out performed BSHS-B total score and domain scores. Greater measurement sensitivity was demonstrated in all SF-36 summary and subscales measures (except General Health) when compared to BSHS-B and sub-domains.
Conclusion: This study demonstrated SF-36 was a valid measure of recovery of quality of life in the burn patient population. The data suggests that SF-36 components were more sensitive to change than the BSHS-B from ~1 month post injury.

Table 1 – Submitted manuscripts and publications cited in the thesis by chapter. Titles in bold indicate where the manuscript contributed text to the thesis.

Chapter	*Title of Paper*	*Publisher*	*Year*
Introduction	Active Burn Rehabilitation Starts at Time of Injury: An Australian Perspective. (Letter to Editor)	JCBR*	*2009*
	Development of a National Burns Network: Providing a coordinated response to a mass casualty within the Australian Health System.	EHTJ#	2008
	Development of a National Model of Care for Burn Patients: Core Business Standards to Support the Activation of AUSBURNPLAN.	WA DoH (Strategy Paper)	2004
	Occupational Therapy and Physiotherapy for the Patient with Burns: Principles and Management Guidelines.	JCBR	2003
	ABC of Burns: Rehabilitation after burn injury.	BMJ£	2004
	ANZBA Burn Survivor Rehabilitation: Principles and Guidelines for the Allied Health Professional.	ANZBA (e-book)	2007
Review of Literature	**Local and systemic treatments for acute oedema after burn injury (Protocol).**	Cochrane DoSRα	2007
	Local and systemic treatments for acute oedema after burn injury (Review). (submitted)	Cochrane DoSR	2009
	Pharmaco-management of inhalation injury for burn survivors.	DDDT€	2008
	Core Outcomes for Adult Burns Survivors: A Clinical Overview.	Burns	2009
Results	**Whole arm water displacement volumetry is a reliable measurement technique for acute volume change: Caution with clinical use and research design in patient populations. (submitted)**	Lymphology	2009
	Measurement of acute edema shifts in human burn survivors – the reliability and sensitivity of bioimpedence spectroscopy as an objective clinical measure.	JCBR	2009
	Volume measurement using the Polhemus FastSCAN 3D laser scanning: A novel application for burns clinical research.	JCBR	2008
	The QuickDASH is an appropriate tool for measuring quality of recovery after upper limb burn injury.	Burns	2007
	Goniometry and Linear Assessments to Monitor Movement Outcomes: Are They Reliable Tools in Burn Survivors?	Burns	2009
	A reliable and valid outcome battery for measuring longitudinal recovery of lower limb function and balance after burn injury.	Burns	2009
	Demonstration of the validity of the SF-36 for measurement of the temporal recovery of quality of life outcomes in burns survivors. (submitted)	Burns	2009

Discussion	Maintaining physical therapy standards in an emergency situation: solutions after the Bali bombing disaster.	Burns	2005
	First Response, Rehabilitation, and Outcomes of Hand and Upper Limb Function: Survivors of the Bali Bombing Disaster. A Case Series Report.	Journal of Hand Therapy	2006
	Upper Limb 3D Motion Analysis- An Advanced Assessment Tool following Burn Injury. (submitted)	JCBR	2009
	Lower limb functional outcome assessment following burn injury: A novel use for 3D laboratory-based movement analysis	Burns	2009
	Assessing the impact of missing data in evaluating the recovery of minor burn patients.	Burns	2009

*JCBR – Journal of Burn Care and Research (or Rehabilitation); #EHTJ – Emerging Health Threats Journal; €DDDT – Drug Design, Development and Therapy; £BMJ – British Medical Journal; αCochrane DoSR – Database of Systematic Reviews

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Chapter One

Introduction

Burn injury is one of the most complex and unique traumas a person may suffer. The effect of the burn toxin was demonstrated on 'all cells of all organs' (2008) confirming it to be a 'maximal trauma, where all systems are affected' (Montgomery 1979). It is no surprise, therefore, that burns lead to significant medical and rehabilitation challenges (Esselman et al. 2006). The response to the local burn wound is compounded, and confounded, by the systemic inflammatory response syndrome (SIRS) and the immune system compromise (Hiebert et al. 1979) that develops after even a moderate size burn (Sherwood and Traber 2002). Acute swelling secondary to burn trauma is integral to the body's inflammatory response (Demling 1982). Swelling, or oedema, is defined as *an abnormal accumulation of liquid in cells, tissues, or cavities of the body (pg 207)* (Demling 2005). The extent of oedema produced immediately after a burn is a marker of the severity of SIRS and the injury itself. However, oedema is causally linked to retarded wound healing (Heughan et al. 1972a; Niinikoski et al. 1972), burn wound extension (Zawacki 1974; Rice 2000; Greenhalgh 2005), excessive scar formation (Cubison et al. 2006) and increased wound infection (Hunt et al. 1975). Despite the obvious detrimental effects of oedema in the tissues, in the timeframes where other areas of burn care have progressed markedly, treatments to control and manage swelling have not advanced in the same degree (Demling 2005). While consensus exists to support the principles of treatment for burn oedema (Richard et al. 2009), the importance of simple actions in the acute phase that could reduce it and therefore, infection, scar and poorer functional outcome are often neglected.

1.1 Burn Care: The Past, Present and Future

Medical care for burn survivors has developed significantly over the last 50 years but most rapidly at times of conflict and war (Burke 2005). Significant advances in the quality of clinical care and burn mortality were seen in and subsequent to, the Second World War (Jackson 1979). In particular, during that period, the value of appropriate first aid was linked to a reduction in burn severity and mortality. However, at that time, burn injuries involving more than one third of the body surface area were fatal, even in young, fit people. It was not until the 1950's and 60's that major advances were made in fluid resuscitation and infection control (topical wound antimicrobial products), resulting in marked reduction in burn mortality for all patients under the age of 55 years (Phillips and Cope 1960). It was around this time that the concept of the burn team was introduced (Colebrook 1950; Warden 2002). The multi-disciplinary burn team approach was reported to enhance patient survival and reduced length of stay (LOS) in hospital (Collings 2004). The unique phenomenon of burn wound 'conversion' was also documented around this time (Jackson 1970; Zawacki 1974). Improvement in skin grafting techniques were also attributed to the further steady reduction in burn mortality during this period (MacMillan 1959; Jackson 1960).

In the 1970's and 80's, advances were made in the treatment of massive burn injuries. The positive effect of early burn excision, combined with techniques to reduce blood loss, improved facilities for patient isolation and cross infection control was demonstrated (Herndon 1985; Munster and Smith-Meek 1994; Muller, Ralston et al. 2002). The 'burn toxin', implicated in the 'whole body' reaction to burn injury, was isolated and typed during this period (Allgower et al. 2008). Related to that work, the 1980's was a period devoted to explaining the immuno-suppression and generalized induced cell death, or apoptosis, the causes of 'late death' after burn injury. Reduction in mortality rates continued with the development of intensive care techniques, the management of inhalation injury and manipulation of the hypermetabolic systemic inflammatory response syndrome (SIRS) (Cox et al. 1991; Herndon and Blakeney 2002; Murakami and Traber 2003). In the last 10 years, the advanced development of intensive care burn units, nutritional management and improved wound dressing technologies has lead to a further marked improvement in burn mortality as measured by the (lethal dose) LD50, or the total burn surface area (TBSA) resulting in 50% chance of survival. In addition, skin replacement techniques such as skin substitutes (Atiyeh 2005; Horch et al. 2005; Wood et al. 2007) and cultured cells (Wood et al.

2006; Atiyeh and Costagliola 2007) have become a mainstay of burn treatment to reduce mortality and more importantly, to improve the post-burn functional outcome.

The present day situation in burn care is a product of the improvement in mortality to the point that, in developed countries with available health care, the chances of surviving a devastatingly large burn injury are high. Further, recent studies in the United States of America, have also demonstrated the value of specialised treatment centres for the burn injured in terms of mortality, LOS and cost to the health system (Palmieri et al. 2008). Despite this, apart from Blades et al's (1982c) ground-breaking work, before the 1990's the literature discussions involving patient quality of life, scar quality, functional outcomes and societal impact of burn injury were conspicuous in their paucity and lack of progress. Subsequently, scar outcomes became a focus during the 1990's (Sullivan et al. 1990). Medical and scientific 'pathology based' approaches have continued in this area with the refinement of skin reconstruction or surgical technologies and advanced wound biotechnology including, for example, the development of artificial dermal constructs and interactive dressings (Thomas et al. 2002). However, until very recently, the drive to apply a bio-psycho-social model and measure improvement in burn outcomes other than by mortality and length of stay has not been evident (Esselman et al. 2006; Richard et al. 2008).

It is clear that every intervention from the point of injury influences the outcome after burn. The future progress in burn care is likely to be incremental in high-risk patients, rather than watershed events through international research as was experienced previously (a possible exception being the development of a viable vaccine for burn toxin and, or hypertrophic scar). Regardless, it is important to look to the future of total burn care and the role of the therapists, as part of the multi-disciplinary burn team. Physiotherapists' skills support the prevention of burn injury and education; reduction of the negative impact of burn injury when it occurs; management of wound healing; improvement of burn survivor functional outcomes; improvement burn survivor re-integration back to society; and temporal measurement of functional and quality of life outcomes after burn injury (Richard et al. 2008; Edgar 2009).

Thus, considering physiotherapy treatments that aim to improve clinical outcomes for burn patients, optimal control and treatment of acute swelling after burn injury directly influences all post-burn aspects. As an adjunct, education of the patient, carers, hospital and pre-hospital staff, and the community where possible, is integral to improving acute burn oedema management. Further, education provides a vehicle for

the communication and translation of clinical research into evidence-based practice. Lastly, to determine efficacy of application of novel treatments and education input, outcomes must be measureable across the continuum of burn recovery.

Physiotherapists, as part of the burn team, must develop their skills at multiple levels, within their individual service environment, to reduce the impact of acute burn oedema on patient quality of life outcomes. The premise of the studies described henceforth, is to provide burn clinicians and researchers with new assessment tools and knowledge for treatment of human oedema in any local burn environment.

1.2 Burn Care Advancement in the Australian and New Zealand Environment

Past development of burn care in Australasia was marked by the translation of milestones of international research into the local context. However, recent developments in the research culture in the region have lead to unique systems, innovations in and barriers to progress in burn care. These warrant describing to place the development of this project in context.

Over the last 10 years, Australian burn care development has been catalysed by disasters. The prominent political profile of the specialty since 2002 accelerated the most recent advances. The first Bali Bombing focussed burn care and disaster preparedness and ensured national attention to the issues. However, well before the Sydney Olympics in 2000, the members of the Australian and New Zealand Burns Association (ANZBA), lead by Professor Fiona Wood, noted the unique challenges faced by burn care professionals in our region (Wood et al. 2008). The need to overcome the mismatch between vast distance medical transportation requirements and scattered population density with access to definitive, specialised health care was evident. Coupled with the fact that 10-15 severe burn patients would stretch and possibly overwhelm the burn centres in any State or Territory, it was clear that a National Burn Disaster Plan was required urgently. In order to optimize preparedness and response, that plan required coordination through a National Model of Burn Care (NMoBC) (Wood et al. 2008). The events in Bali catalysed the development and publication of AUSBURNPLAN (Hovarth 2005) as the blueprint for burn (and trauma) disaster response. Subsequently, the National Burns Standards, Education and Training paper (Robertson et al. 2005) was developed, within the Western Australia Department of Health, in consultation with members of ANZBA and disaster (planning, preparedness and response) groups. This document articulated the requirements, at

that time, for burn care (facilities and teams) in Australia to optimize disaster preparedness, surge response and importantly, the protracted treatment response, should a burn mass casualty disaster occur. Further, the document, while never formally ratified, is the basis of the current Australian NMoBC.

The Australian NMoBC was developed on the basis of evidence based literature and consensus guidelines particularly as high level human burn studies are lacking. However, in contrast to international models of care, the underlying premise of disaster preparedness within the Australian NMoBC remains with a planned infrastructure development to support preventative medicine and a focus on translational research.

An indication of the recent scientific research in line with the NMoBC strategies includes: stem cell regulatory manipulation in burn wound healing (Rea et al. 2009a); topical manipulation of the burn wound environment (Giles et al. 2008; Morellini et al. 2008; Muller et al. 2009); contribution of sex hormones to burn wound healing (McLean et al. 2008); burns first aid efficacy (Rea 2005a; Cuttle et al. 2008a); animal burn models of hypertrophic scarring (Cuttle et al. 2006; Kempf et al. 2009); application of foetal scarless healing (Fraser et al. 2005; Fraser et al. 2009); and the contribution of the (peripheral) neural system to wound healing and long term functional outcomes (Anderson 2007). Examples of clinical practice papers developed in the region included surgical technique (Kimble et al. 2008); dressings studies (Cuttle et al. 2007; Cuttle et al. 2008c); pain management interventions (Miller et al. 2008; Mott et al. 2008) and psychological input and risk management (Martin et al. 2008; Andrews et al. 2009). Further, surgical advances involving cell therapies, were developed in Australia and have recently gathered international momentum. The most developed of these techniques included the use of ‘spray on’ keratinocytes (Horch et al. 2005; Wood et al. 2006; Gravante et al. 2007). To ameliorate the tyranny of distance and lack of health infrastructure in rural Australia, a number of telehealth projects have demonstrated benefit to the model of care (McWilliams et al. 2007; Higgins and Kimble 2008). These strategies are also cost effective. Epidemiological studies are prevalent in the Australian and New Zealand region (Rea 2005b; Choo et al. 2008; Khalessi et al. 2008; van den Boogaard et al. 2008; Burlinson et al. 2009; Jeremijenko et al. 2009). The dissemination of research from our region has contributed to the advancement of burn care around the world (Wolf 2008; 2009). In contrast, burn wound care development has been hindered compared to other parts of the world. For example, the regulatory authority (Therapeutic Goods Administration)

has refused application for the use of cerium preparations which have been demonstrated to be of benefit in reducing acute toxin load from burned tissue (Allgower et al. 2008).

The regional burn care and research environment, with small numbers of professionals bonded and supported by ANZBA, directed this project. While acute oedema management remained a primary focus throughout, related components were incorporated in the thesis due to clinical, political and research development in Australia and New Zealand. The assimilation and presentation of evidence-based guidelines for Allied Health Professionals (AHP) (Simons et al. 2003; Edgar and Brereton 2004) demonstrated the ability of ANZBA therapists to document consensus in burn care practice. These papers lead to the ANZBA AHP Principles and Guidelines (Edgar et al. 2007). The clinical pathways detailed for acute burn oedema management lacked a robust evidence framework. Thus, the laboratory analyses and outcome measurement aspects of the thesis developed aimed at facilitation of clinical intervention and research. Predictably, throughout 9 years of candidacy, the focus of the relevant literature evolved and subsequently, so did the project. Anecdotal reports indicated that burn oedema treatments were simple and effective. For instance, sitting the Bali burn patients upright during air transfer was reported to prevent the need for intubation (Tran et al. 2003; Read and Ashford 2004). In contrast, little high level evidence was available to guide burn oedema management.

The next chapter, aims to articulate the known evidence, and creep of knowledge underpinning the paucity of valid options for assessment and management of acute burn oedema.

1.3 Chapter Summary

This thesis was developed in the context of the Australian burn care environment. Multidisciplinary burn treatment, focussing on functional outcome and a rapidly developing, competitive research community have underpinned the longitudinal progress of the project. The Australian and New Zealand Burn Association was, and remains, the regional professional network which provided the platform for stimulation, interaction, practical discussion and honest dissemination of the available thesis results. That said, acute burn clinicians around the world are aware of the benefits of reducing oedema but the optimal tools for measuring and treating it remain obscure. Thus, the novel research studies described in this doctor of philosophy thesis were designed to assist any and every adult burn patient, supported by any burn clinician, in any burn care environment around the world.

Chapter Two

Review of Literature

This chapter provides an overview of the body of research examining the factors influencing the development of acute burn oedema. Sections 2.1 – 2.3 summarize the review pertaining to these concepts. The following Sections 2.4 and 2.5 describe the current understanding of the impact of acute oedema on the burn wound and functional and scarring outcomes. The final sections provide an abridged summary of the methods available for assessment (Section 2.6) and treatment (Cochrane Review: Section 2.7). The chapter concludes by listing the key issues raised through the Review of Literature.

Introduction

This thesis will focus on the provision of new detailed knowledge and assessment tools to monitor the treatment of acute burn oedema. Acute oedema is defined as the fluid present in the tissues up to, and including, seven days post-burn. While defined as a fluid, oedema in the body is not solely made up of liquid. It contains biological and chemical solutes which impact on its physical properties. Sub-acute and chronic oedema states are defined and reviewed in other contexts within the literature (Casley-Smith and Casley-Smith 1994; Sitzia et al. 1997). The timeframe of onset was variable from greater than 14 days in a trauma context (Griffin et al. 1990) and at least one month post-lymph node surgery (Bates et al. 1992; Stanton et al. 1997a). In contrast after burn injury, chronic oedema has been defined as that which remained after wound closure (Ause-Ellias et al. 1994). The understanding of treatment and measurement of post-intervention outcomes for chronic oedema is more established than for the acute burn situation. Integrated knowledge and recognized treatment regimes are particularly evident in the management of oncology patients (Rockson et al. 1998; Casley-Smith 2000; Liao et al. 2004) and acute and chronic hand disability (Burkhardt and Joachim 1993). However, while appearing applicable for acute swelling, the underlying causes, patient factors and physical environment causing an acute post-burn oedema state are markedly different to a chronic situation. The unique challenges posed immediately after burn injury include the presence of open wounds, medically unstable patients, a potentially compromised immune response with a high risk of repeated wound infection and rapidly changing oedema volume and constituents influenced by medical management. Further, burn damage inherently causes necrosis of lymphatic structures, thus impacting negatively on the primary

oedema fluid and debris transport system. Without an understanding of the impact of these factors any treatment strategies may be ineffective, inefficient and at worst, detrimental. For instance, beneficial treatment for chronic lymphoedema using benzo-pyrone medication was shown to have an adverse effect on acute experimental foot oedema (Casley-Smith 1983a). It was important to indicate that any new intervention, or assessment technique addressed in this thesis, will comply with the *do no harm* medical ethos. Further, evidence for efficacious treatment must be derived from the use of reliable and valid assessments.

Due to the protracted rehabilitation of burn patients, these measurements must aim to quantify a) acute oedema volume change; b) oedema contents; c) functional (and scar) outcomes and d) impact on quality of life, to provide a clinically meaningful analysis. Therefore, this chapter presents an assimilation of the literature beginning with a broad description of skin and burn wound healing and progressing to discuss the factors which impact on acute burn oedema production in humans. The remainder of the chapter will discuss the current evidence for choices of assessment and treatment options specifically for acute burn patients. Excepting where there were specific comparisons and, or contrasts to be highlighted, detailed discussion of sub-acute and chronic oedema states is beyond the scope of this thesis.

2.1 Inflammation: Natural Skin Healing

All healthy tissues regenerate and repair via complex wound healing, or scar, pathways until complete closure, or epithelialisation in the case of skin injury. The skin is a very individual organ in its healing capacity. Factors such as: injury severity; age; race; ethnicity; hormonal changes (eg pregnancy) and past medical history impact on the time to complete skin closure (Hardy 1989; Bombaro et al. 2003; Cubison et al. 2006). The longer a skin wound remains unhealed, or 'open', the greater the risk (and amount) of hypertrophic scar (HTS) formed and, or other complications, such as infection (Deitch et al. 1983). HTS is a common, negative byproduct of moderate to severe burn injury (Schneider et al. 2006). Scarred skin does not return to its usual function or appearance and therefore affects patient outcomes across a multitude of activity and psychological domains (Altier et al. 2002; Blakeney et al. 2008).

The aim, therefore, of health professionals, in co-operation with the patient, is to facilitate the most rapid healing of a wound. The general principles of wound management are as follows: prevent and treat infection (reduce colonization by micro-organisms); cleanse the wound to remove debris and facilitate the body's repair

process; debride the wound to remove necrotic or dead tissue and foreign matter; provide an optimal healing environment by ensuring a degree of moisture at the wound surface; and relieve pain and discomfort (van Rijswijk 1995).

The majority of skin wounds are healed by secondary intention. For instance, ~60% of admitted patients do not require surgery (RPH unpublished data, 2006-7). In contrast, closure by primary intention is achieved through surgical intervention (Muller et al. 2002). The time to complete closure of a burn wound, regardless of the method used, is directly related to the *probability* of HTS formation (Cubison et al. 2006). Thus, surgical techniques, where available, are an important component of the management strategies to facilitate improved scar quality and reduce mortality and morbidity (Engrav et al. 1983; Robson 2002; Ong et al. 2006).

Therefore, after a burn injury functional rehabilitation, including oedema management, must be considered with wound healing activities and surgery. Rehabilitation is integral to ensure that the impact of a wound, and subsequent scar, is minimized in a patient's life and the expected return to usual activity (Serghiou et al. 2002).

2.2 Human Skin Healing After Burns: The Pathway to Oedema

2.2.1 The Complement Cascade

As with other forms of injury, burns trauma evokes an inflammatory reaction (Arturson 2000). Firstly, the traumatised area must achieve haemostasis and containment of the initial injury (Friedl 1989). In response to tissue hypoxia, death and injury, there is an initial release of chemical, humoral and vascular mediators (Demling 1982). These chemical attractants initiate, and perpetuate, a marked response via the 'alternate' pathway of the complement cascade (Drost et al. 1993). There are two major pathways of the complement response. The immunologic pathway, is the specific response to foreign antigens activated by antibody reaction while the alternate pathway is characterised by a non-specific cellular response to damaged tissue and signals of cell death (Gelfand et al. 1983). In these early studies, it was demonstrated that the markers of the immunologic pathway were significantly less activated than the alternative pathway during the acute burn inflammatory response. Subsequent work has challenged these assumptions showing that the 'classic' immune cellular response is immediately engaged and strongly *suppressed* by 'burn toxin' (Allgower et al. 2008). Studies examining the immune response to burn injury have provided unequivocal evidence that, regardless of the pathway, this series of events is the commencement

of wound healing through an inflammatory process which is *unique* to burn injury (Willoughby et al. 1969).

2.2.2 Unique Nature of the Acute Burn Response

The acute injury will evolve after the initial burn injury during the first 5 to 7 days due to a moderated, specific inflammatory response (Hinder and Traber 2002; Kramer et al. 2002; Sherwood et al. 2002). Acute management is important to limit the extension of injury in the days immediately after injury (Zawacki 1974; Zawacki 1974; Boykin, Eriksson et al. 1980). In the first 48 - 72 hours, the *zone of stasis* that surrounds necrotic tissue is potentially salvageable, even though it is within the zone of injury or trauma (Watts 2001) (Fig. 2.1). Conversely, this tissue may die and further 'extend' the burn even after the burning agent has been removed. The concept of wound depth 'conversion', or ongoing worsening, is unique to and well accepted by professionals who manage burn injury (Brown and Muller 2004).

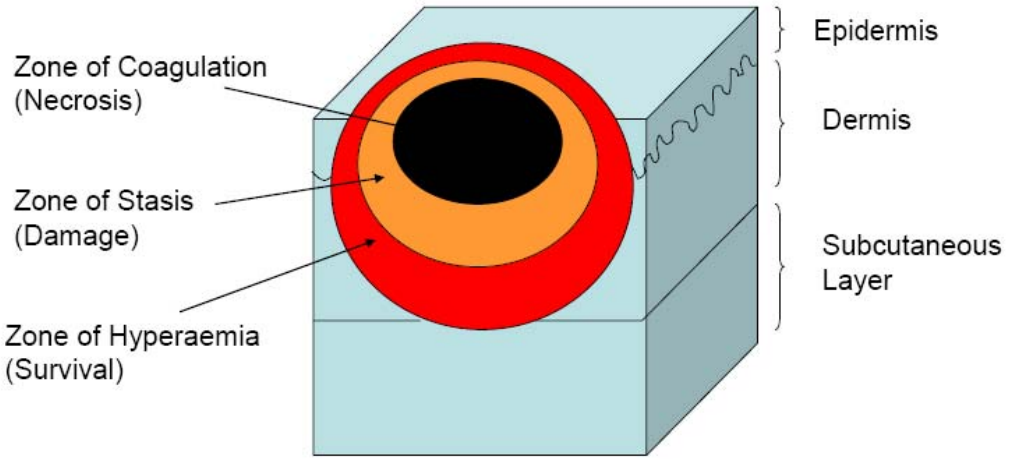


Figure 2.1: Diagramatic representation of the zones of injury within a 3-dimensional wound construct. (Reproduced with permission, F. Wood)

Within 90 minutes in rats, burn injury causes micro-thrombi in blood vessels surrounding the initial wound (Remensnyder 1972). Without treatment, and restoration of blood flow, tissue anoxia and extension of the necrotic area (zone of coagulation) occurs rapidly. These phenomena parallel the clinical situation described in humans (Brown et al. 2004). Further, inflammatory factors, in addition to the inhibition of blood flow, contribute to the conversion process. The complex nature of the interdependence and redundancy of the inflammatory pathways after burn injury means that integration

of scientific evidence with clinical management lacks consensus. An indication of the complexity is evident when examining acute burn oedema production in the tissues. Human and animal studies indicate:

Tissue damage and hypoxia cause activation of the complement system, leading to the degranulation of mast cells and the release of a multitude of vaso-active substances, such as histamine and substance P (Friedl 1989; Detmar et al. 1997);
Histamine upregulates xanthine oxidase, in turn increasing production of reactive oxygen species (ROS) which have broad reaching negative effects when unchecked including the degranuation of mast cells and histamine release, leading to widespread tissue damage and a cycle of vascular hyperpermeability (Till et al. 1989; Santos et al. 2000);
Neuropeptides, such as substance P, are implicated in neurogenic (axon-reflex) vasodilation, mast cell degranulation and also increase vascular permeability via this mechanism (Foreman 1987);
Increased vascular permeability is also perpetuated through the arachidonic acid pathway known to eventuate the release of cytokines (eg IL-2, VEGF, IL-6, IL-1β) and complement components (eg C_{1Inh})(Camp and Greaves 1987; Friedl 1989; RaviKumar 2001); and
The lipid-protein complex (LPC), isolated as 'burn toxin', damages all cell membranes leading to increased cellular permeability, leaking oedema into the extracellular space (Allgower et al. 2008).

Acute burn inflammation is characterised by rapid leaking of fluid and proteins from the blood vessels through the first 24 – 36 hours, producing swelling in the area of burn damage (Jelenko et al. 1973; Cassuto 2005). In addition to the local inflammatory response at the site of injury, there is a confounding systemic inflammatory response syndrome (SIRS) directly related to the severity of injury (Lund et al. 1992; Sherwood et al. 2002). The result is both local and generalised oedema, with authors indicating up to 50% of the volume of swelling after major burn, is associated with non-burn areas (Kramer et al. 2002; Cassuto 2005). Particular to acute burn, is the increase, as noted above, in vascular permeability and leaking of fluid, large proteins and debris in and around the zone of stasis (Arturson 1979; Detmar et al. 1997) (Fig 2.1). To survive a major burn with fluid shifting into the tissues, or extracellular third space, the body requires urgent fluid resuscitation to maintain the circulating blood volume and supply to vital organs (Rice 1991; Lindblom et al. 2000). Resuscitation treatment itself is therefore, a source of fluid which leaks around the burned tissues contributing to the

local and generalised oedema (Rice 1991; Zdolsek et al. 2001). The initial management of a burn injury has a significant influence on burn wound conversion (Warden 2002). The value of appropriate immediate treatment, related to the burn severity, is well documented, as it impacts positively on the final outcome and reduces scar formation (Cox et al. 1991; Murakami 2003). Acute burn treatment increases in complexity with increasing burn size and severity. However, further discussion of the specific multi-disciplinary burn team input is beyond the scope of this thesis. This thesis will focus on the issues of acute oedema in healing tissues which result in long term sequelae after burn injury.

2.3 Factors Contributing to Acute Burn Oedema

The impact of burn severity varies for individuals as pre-morbid condition influences the response to injury and therefore the outcome. Acute oedema formation and resolution are related to burn factors such as depth and area of the burn, presence of inhalation injury, fluid resuscitation parameters, pharmacological interventions, infection and patient inherent factors such as nutrition and co-morbidities (Hunt, M. et al. 1975; Deitch, Wheelaham et al. 1983; Rice 1991; Lund, Onarheim et al. 1992; Sherwood and Traber 2002).

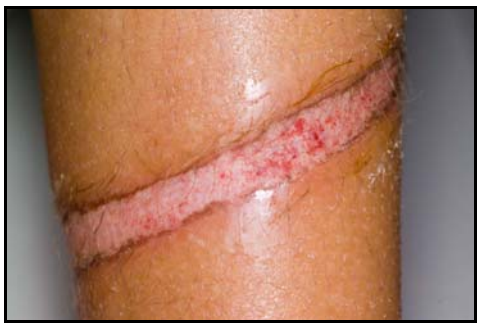
2.3.1 Burn Depth and Agent

Deeper burns result in a greater volume of oedema overall compared to superficial injuries (Papp et al. 2005). However, these authors demonstrated, in a swine model, that mid-dermal burn (MDB) injuries were associated with the greatest volume of oedema in the *skin tissue* compared to superficial and full thickness burn (FTB) injuries. Further, deeper burn injuries are associated with slower resorption of oedema due to the damage to lymphatic vessel occlusion through clotting and damage (Papp et al. 2005).

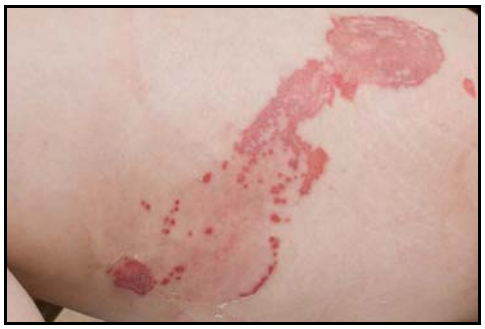
The burn agent may impact on the amount of oedema produced also (Fig 2.2). For instance, a chemical injury, such as that caused by caustic fluids, may cause ongoing post-exposure breakdown of tissue and increasing oedema due to the exothermic lysis of adipose tissue that occurs due to the chemical creation of lipid proteases (Rao and Menezes 2009). Electrical injuries cause extensive tissue damage which is not easily quantifiable during the acute post-burn period (Handschin et al. 2009). The deep tissue damage including muscle necrosis, illicits widespread and vast oedema deposition in the skin and underlying tissues in volumes far greater than the visible skin injury indicates (Ratnayake et al. 1996; DeBono 1999; Masanes et al. 2000).

Regardless of the circumstances of the injury, or cause of subsequent burn conversion, the significance of an increase in wound depth, is that it represents the death of more tissue and increases the risk profile related to burn severity. In the skin, the epidermis was thought not to specifically aid regeneration of tissue defects (Fore-Pfliger 2004). It was postulated that epidermal cell stratification served to indicate complete wound closure as the signal for cessation of wound healing. However, more recent research indicates that, in vitro, that keratinocytes, the germination cells in the epidermis, signal throughout healing via the release of growth factors such as endothelin-1 (Oshita et al. 2006). Further, keratinocytes guide the wound repair through interaction with dermal fibroblast mediated activity, particularly in the immediate post-burn days (Harrison and MacNeil 2008).

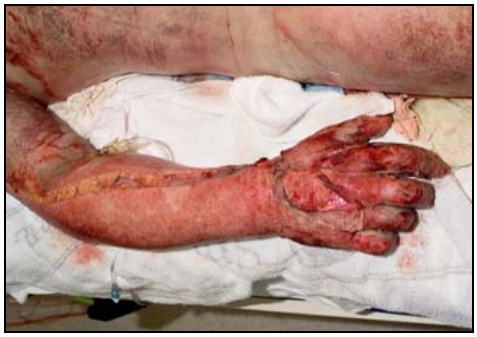
Closure of a wound indicates the physiological end point to the initial wound healing processes of inflammation and proliferation (van Rijswijk 1995). Of primary importance to skin tissue repair and bulk regeneration through secondary intention, is the dermis. It contains integument elements capable of rapid regeneration for a skin defect (Dziewulski 1992). The proliferative phase is an important stage of the wound healing and scarring process (Hardy 1989). The chemical status of the wound bed, or dermis itself also impacts on the speed and quality of healing (Caulfield et al. 2008). However, simple physics obviates that the greater the loss of dermal tissue, the more time required to repair a wound defect, all other factors being equivocal (Dziewulski 1992). While clinicians understand that a burn wound is a mosaic of degrees of tissue damage, it is undisputed that prolonged time to wound closure is a key indicator in the development of HTS after burn injury (Cubison et al. 2006). These authors demonstrated in children with burns, wounds that healed after 10 days had at least 8% chance of HTS. Tay et al (2008) in the subsequent study showed that the results in adults were not as definitive though a similar pattern emerged with higher risk of HTS after 16 days of open wound. The exact reasons why some individuals develop HTS despite healing within two weeks is an ongoing debate (Bombaro et al. 2003). However, as burn care has advanced, the concept of tissue (dermal) salvage, and consequent prevention of burn conversion, has become the key focus in the prevention of HTS formation (Zor et al. 2005; Mahajan et al. 2006).



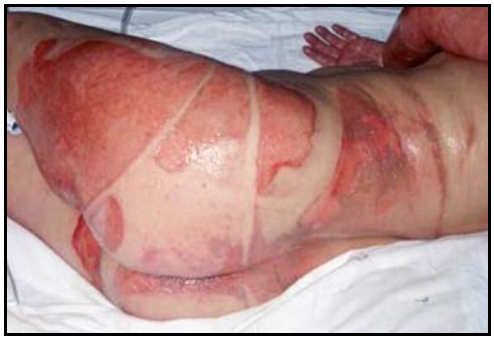
(a) Friction (rope)



(b) Chemical (acid)



(c) Flame (explosion)



(d) Scald (shower)

Figure 2.2: A demonstration of the difference in size and appearance of burns due to differing agent or mechanism.

Burn clinicians appreciate that prompt, optimal intervention for a burn wound relies on accurate assessment of wound depth. The most common technique used in the acute environment is, of course, clinical assessment which usually combines visual inspection with burn wound blanching tests and, or sensory (light touch and sharp – blunt) tests (Devgan et al. 2006). Depending on the agent of injury and location, burn damage may extend deep to fascia and involve nerves, tendons, muscle, bone, viscera and any associated soft tissue. However, Table 2.1 provides a list of clinical (visual) descriptors of burn depth assessment in human skin (Fig 2.3). The current burn depth assessment categories as described in Australia and New Zealand, are as follows:

Epidermal (aka erythema) – injury which involves the epidermis only (Fig 2.3.a);

Superficial dermal (SD) (aka superficial partial thickness) – injury involving the loss of epidermis and damage extending into the papillary dermis (Fig 2.2.b);

Mid-dermal (MD) (aka intermediate partial thickness) - injury extending into the upper and middle reticular dermis (Fig 2.3.c&d);

Deep dermal (DD) (aka deep partial thickness) – injury extends into the deep reticular dermis, including involvement of the reticular plexus (Fig 2.2.e); and

Full thickness (FT) – injury extends through the complete depth of skin layers, and possibly fat, to the level of fascia (Fig 2.3.f).

Table 2.1: Definitions and descriptions of burn depth.

Depth	Colour	Blisters	Capillary Refill	Sensation	Healing
Epidermal	Red	No	Present	Present	Yes
Superficial Dermal	Pale Pink	Small	Present	Painful	Yes
Mid-Dermal	Dark Pink	Present	Sluggish	+/-	Usual
Deep Dermal	Blotchy Red	+/-	Absent	Absent	No
Full Thickness	White	No	Absent	Absent	No

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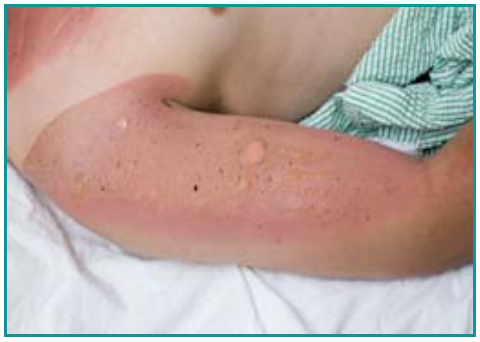
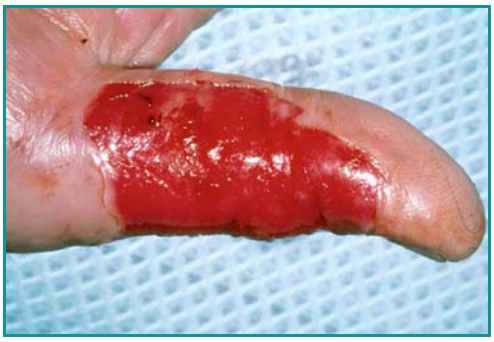
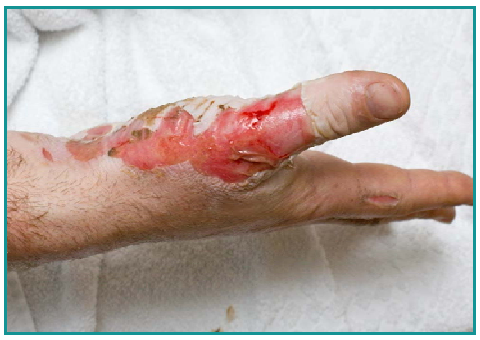
The volume and location, within the tissues, of acute oedema differs with depth of burn. It is generally accepted that superficial and mid-dermal burn injuries cause a greater local response than deep dermal or full thickness injury (Hamar et al. 1979; Kramer et al. 2002; Demling 2005). Burn oedema is present in surrounding dermis and subfascial tissue for all depth burns and also found in the underlying adipose and skeletal muscle tissue after FTB injury (sheep) (Sakurai et al. 2002). This differs from chronic lymphoedema where swelling is demonstrated to reside primarily in the dermis (Idy-Peretti et al. 1998).



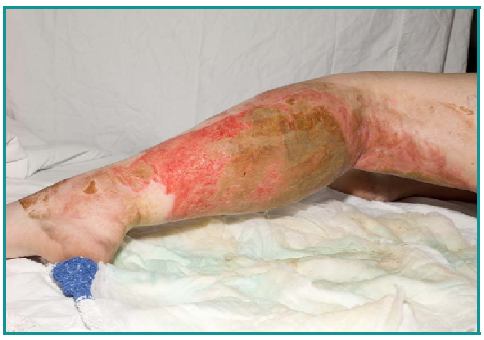
(a) Epidermal (erythema)



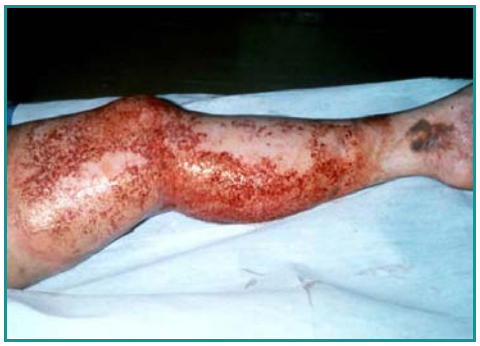
(b) Superficial dermal



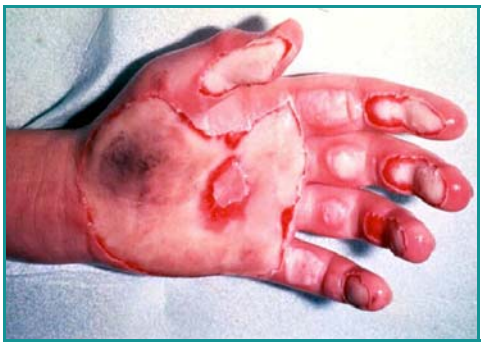
(c) Mid-dermal



(d) Mid-dermal + slough



(e) Deep dermal



(f) Full thickness

Figure 2.3 (a-f): Burn depth as defined by clinicians involves assessment of history, colour, pain and sensation in combination with other objective methods where available. NB All wounds have areas of different depth and (d) indicates the difficulty of assessment when the wound is obscured with slough.

2.3.2 Total Burn Surface Area (TBSA)

The size of burn for an adult, is generally determined by assessing the area of injury with reference to the apportioning of the body surface according to the 'rule of nines' (Fig 3). TBSA directly impacts on oedema production in the lungs and non-burned tissues. A major burn with an area > ~20-25% TBSA invokes hyper-permeability in enough capillary bed vasculature to create central plasma hypo-proteinaemia in the immediate post-burn period. Animal studies have demonstrated a two-fold increase in lymph flow, indicating increased oedema production, which was reversed and normalized when plasma protein levels were restored (Demling et al. 1984). Oedema production (lymph flow) around the burn wound, however, was five to 10-fold baseline levels, indicating a significantly greater volume of fluid in the injured tissues contributes to the multiple processes noted above. Thus, oedema related to TBSA may be ameliorated dependent on fluid resuscitation parameters (Herndon et al. 1987).

TBSA is a marker of the overall burn severity and is a primary variable in the Parkland fluid formula, which is debatably the basis for the most common resuscitation guidelines used by burn clinicians today (Greenhalgh 2008). Baxter and Shire's (1968) formula for early fluid resuscitation for burn shock, revolutionized major burn survival at that time. However, despite fluid resuscitation using the formula, plasma protein levels in sheep, were demonstrated to be sub-physiological, contributing to acute tissue oedema, at least 48 hours after injury (Sakurai et al. 2002). Thus, research continues to determine the optimal post-burn fluid resuscitation parameters. Further, the temporal peak of acute oedema in tissues is influenced by fluid resuscitation parameters and the impact on the patho-physiologogy of burn inflammation. Thus, it is not surprising that there remains a lack of consensus as to the time to the peak of oedema in human tissues, a primary indicator for fluid management in the major burn patient (Alvarado et al. 2009).

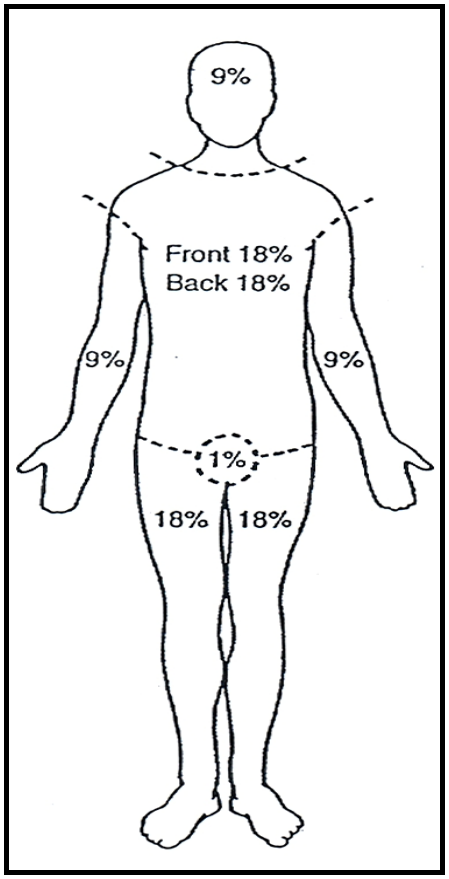


Figure 2.4: 'Rule of nines' schema for estimation of surface area (severity) of adult burn injuries.

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2.3.3 Inhalation Injury

Oedema production due to inhalation injury is primarily related to the effect of smoke within the lungs and thermal injury to the upper airways and naso-pharynx. It is the leading cause of death in burn patients with a mortality rate of up to 42% (Suzuki et al. 2005). Many factors impact on prognosis after inhalation injury in burn patients, with increasing TBSA (concomitant skin injury) and age associated with a greater length of stay and decreased survival rate (Edelman et al. 2006). The pathophysiology of inhalation injury has been described extensively elsewhere (Enkhbaatar and Traber 2004; Cancio et al. 2007). However, in terms of the burn wound, inhalation injury slows healing through associated hypoxaemic episodes, due largely to lung ventilation-perfusion mismatches and poor oxygen transfer to the systemic circulation (Niinikoski et al. 1972; Jeng et al. 2008). This results in reduced oxygen tension in the

tissues for varying lengths of time (Venkatesh et al. 2001). Prolonged reduction in tissue oxygenation results in poorer tensile strength of the healed wound, and as noted earlier, an increased incidence of wound infection (Niinikoski et al. 1971; 1972; Hunt et al. 1975).

Inhalation injury is also associated with a higher rate of pulmonary and systemic infections (Tranbaugh et al. 1983; Herndon et al. 1988). Management of these sequelae remain essentially supportive in nature through optimising ventilation and extra-corporeal electrolyte and pharmaco-management strategies (Murakami, Enkhbaatar et al. 2003; Cancio, Batchinsky et al. 2007; Mlcak, Suman et al. 2007; Bartley, Edgar et al. 2008).

The lungs are particularly susceptible to oedema accumulation due to the acute microvascular changes up to five days post-inhalation (Herndon et al. 1987; Abdi et al. 1991; Soejima et al. 2001). In severe inhalation survivors, bronchoscopy and biopsy confirmed the presence of excessive sputum and bronchial oedema after lung epithelium had healed (Arakawa et al. 2007). Few papers consider, or poorly describe, the physical and systemic impact of lung tissue responses such as airway oedema, alveolar flooding, airway occlusion due to endobronchial debris and reduction in lung compliance due to inactivation of surfactant (Sheridan 2002; Mlcak et al. 2007). These factors exaggerate ventilation-perfusion mismatching and impede oxygen and waste transport as noted in peripheral wound situations.

2.3.4 Acute Medical Management

The evolution of a burn wound is a result of the initial injury and the subsequent therapeutic inputs. The treatment may be self administered, provided by a pre-hospital paramedic, supplied by health care workers at a peripheral hospital or burn centre staff or a combination of any or all of these. Clinicians expect that the first intervention, which is of utmost importance to the prevention of wound conversion, is burn first aid. This is not the case in the majority of burn presentations to RPH as shown by Rea et al (Rea and Wood 2005). Optimal first aid after thermal injury, after adhering to ‘at scene’ trauma principles (ie DR-ABCDE), is 20 minutes cool running water at 15 - 18°C (Bartlett et al. 2008). Chemical injuries may have specific antidotes and further in depth discussion of these is not warranted or beyond the scope of this thesis.

There is debate as to how long after injury first aid remains of benefit to the reduction of burn inflammation. Burn first aid was promoted to be of benefit to 3 hours post-injury

(ANZBA Education Committee Chairman 2008) but this has been challenged by Cuttle et al (2008b) who demonstrated that first aid applied greater than one hour post-injury is of little or no benefit to six week scar outcomes, in a porcine wound healing model. Thus, it seems that reduction of inflammation and prevention of oedema and burn wound conversion will rely on self or paramedic administration of appropriate first aid. Unfortunately, studies indicate that knowledge of correct burn first aid and its administration is less than 50% of those surveyed, even in health care workers (Rea 2005a). The lag time between effective education for first aid and advice regarding positioning during transfer in combination with targeted community prevention programmes suggests that inadequate early burn oedema management will remain a factor for a large proportion of burn survivors.

As discussed above, fluid resuscitation is an important component of acute medical management of burn trauma. Resuscitation is accepted to contribute to the volume of tissue oedema (Ahrns and Harkins 1999; Demling 2005). What remains a contentious issue is the parameters of fluid resuscitation which minimise tissue oedema, overall fluid requirements or both (Zdolsek et al. 2001; Blumetti et al. 2008; Engrav 2008). Important considerations during acute resuscitation include: the protein (colloidal) content and, or tonicity of the fluid; the rate of fluid delivery with respect to time of injury; time of onset of diuretic phase or normalisation of blood vessel permeability and peak of oedema extravasations; and the use of adjuvant pharmacological therapies such as vaso-dilating analgesics or continuous Vitamin C infusion (Jelenko et al. 1978; Tanaka et al. 2000; Greenhalgh 2007; Jeng et al. 2008). Early evidence suggests an overall reduction of oedema was realized through maintaining ‘normal’ acute serum protein levels (Kramer et al. 1982; Settle 1982). This indicates the possible impact of pre-burn nutritional status and provides evidence to support the importance of managing post-burn nutrition. This group also demonstrated that non-burn oedema was limited through the use of non-protein colloids during the immediate post-burn inflammatory period (Demling 1987). Medical and patient factors increase with burn severity. It is understood that early fluid resuscitation which, is essential to maintain vital organ function and circulating volume, will remain an additional contributor to acute burn oedema. Further discussion regarding the use and timing of acute burn nutritional interventions designed specifically for oedema reduction is beyond the scope of the thesis. Further, due to the developing and complex nature of the evidence surrounding this issue, nutrition or more specifically, protein balance manipulation is not appropriate to discuss in greater detail here.

Pain relief is necessary for all burn injuries (Montgomery 2004). As the extent of burn increases, so too does analgesic requirements, in most circumstances (Choiniere 2001). For minor to moderate severity burns, pain relief is an important adjuvant to ensure that active therapy is achievable within the limits of a patient's pain tolerance. After such injuries, inadequate analgesia will hinder movement therapy and muscle pump facilitation of lymphatic drainage, effective and consistent positioning and compression therapy. These form part of the current optimal treatment regime for acute burn oedema. For severe injuries, analgesia and muscle relaxants are necessary to achieve safe mechanical ventilation and, or early surgery such as escharotomy. The delivery of large quantities of narcotic analgesics, however, has been postulated to contribute to vasodilation and the documented over-resuscitation of patients which contributes to prolonged and excessive oedema (Greenhalgh 2007; Engrav 2008).

2.3.5 Infection

Damage to the epidermis has a negative effect on the body's physical barrier to infection. A burn injury and subsequent open wound provide a perfect medium for opportunistic organism colonisation, local wound infection and potentially, life threatening, systemic infection (Sheridan et al. 1994; Zor et al. 2005; Silla et al. 2006). A review of burns healed without surgery indicated that wound colonisation, without clinical signs of infection, was associated with an 88% chance of HTS (Baker et al. 2007).

The presence of microorganisms is a stimulus to the immune system response prolonging the inflammatory, complement and humoral response further. This leads to a further increase in local tissue oedema and circulating inflammatory cells, particularly cytokines (Drost et al. 1993). Acute burn oedema is associated with a reduction in deep dermal blood flow and consequent increased incidence of infection (Papp et al. 2005). Similarly, Niinkoski et al (1972) demonstrated that reducing tissue oxygenation was associated with an increased chance of infection.

Unique to burns is the presence of the LPC 'burn toxin' which evokes an initial rapid anti-antigen response through the T lymphocyte pathway but consequently suppresses proliferation of that system through receptor blocking and apoptosis (Dyess et al. 1991; Allgower et al. 2008). It is likely that this response contributes primarily to the presentation described as SIRS (Lavrentieva et al. 2007). Ultimately, this process leads to the fatigue, and potential failure, of the body's infection defence systems.

Dependent on the size of burn; amount of burn toxin and type of organisms present, repeated infective challenges continue while wounds remain open. Systemic infection leads to altered fluid dynamics throughout the body, extravasation of oedema and contributes to multi-organ failure (Airaghi et al. 2000; Sherwood et al. 2002; Lavrentieva et al. 2007). The presence of inhalation injury leads to an increased incidence of infection in the lungs (pneumonia), wounds and systemic circulation (Hunt et al. 1975; Dehring et al. 1988; Herndon et al. 1988; Cioffi et al. 1991). Lastly, the presence of lymphoedema in the tissues is associated with an increased incidence of cellulitic infection with time (Mondry et al. 2004). It is postulated that the presence of fluid stasis, proteins and debris in the tissues provides an environment for proliferation of organisms, especially in the presence of open wounds (Casley-Smith 2000; Rice 2000). The parallels with the acute burn situation are evident and further indicate the necessity to remove oedema as rapidly as possible.

2.3.6 Patient Inherent Factors

Patient co-morbidities will influence their ability to heal a burn wound. Patients with diseases of circulation such as diabetes or peripheral vascular disease are unable to mount the same level of inflammatory response as seen in those with normal vasculature. Patients with inflammatory conditions such as rheumatoid arthritis demonstrate a more reactive response to burn injury and increased oedema. Further, advancing age increases the likelihood of co-morbidities and changes the inflammatory response or healing process. Thus, there are multitudes of co-morbidities, which may increase or decrease the inflammatory response, alter the healing process or contribute to acute oedema.

Nutrition, in itself, is not a marker of burn severity but an assessment of pre-morbid nutrition (including fluid status) provides an insight into the ability of the patient to respond to the challenges such as wound healing and burn hypermetabolic response, massive fluid flux during resuscitation and infection. During the period of wound healing, and up to 9 months beyond burn for severe injuries, the body is catabolic (Cree et al. 2009). It requires extra-ordinary quantities of macronutrients including protein to rebuild defects, energy (carbohydrates) to sustain the hypermetabolism and micronutrients, or trace elements to promote efficacious healing for example. Further, the importance of meeting the nutritional requirements has been linked to poorer wound healing outcomes (Lobo et al. 1999; Whitney and Heitkemper 1999). Adequate feeding assists the maintenance of gut integrity, which limits gastric organism

translocation, which is implicated as a source of systemic and wound sepsis (Herndon et al. 1989).

In summary, the markers of burn severity, and ongoing inflammation, are indications of the expected extent and duration of acute burn oedema. When considering the influence of oedema on wound healing all of these factors must be accounted for on the background of their interaction with the intrinsic patient factors.

2.4 Negative Impact of Acute Oedema in Healing Tissues

After burn injury, the interstitial and cellular oedema volume is altered by many co-dependent factors. This has negative consequences for wound healing, HTS formation and consequent functional, aesthetic and psychological sequelae individual to each survivor.

2.4.1 Physical Barrier to Healing

Excessive oedema volume within the zone of stasis increases the distance between normal, vascularised tissue and the necrotic zone (Hardy 1989). Diffusion of nutrients and waste products to and from normal blood vessels is physically retarded by this increase in distance. The presence of oedema in the interstitial tissues was shown to inhibit adequate oxygen perfusion and nutrition of an affected area (Remensnyder 1972; Hofman 1998; Papp et al. 2005). For every linear unit of oedema, the rate of oxygen diffusion reduces inversely, proportional to the square of this distance (Gosling 1996). Thus, a relatively small increase in the oedema increases rapidly the time required for nutrients to traverse this barrier. As a result, the potential for increasing the zone of necrosis due to excessive oedema volume is a significant issue in the management of patients with an acute burn injury.

Prevention of further tissue necrosis into the zone of stasis by timely removal of the 'oedema barrier' may have a direct benefit to burn survivors by reduction of wound healing time. In particular, the aim of early wound management is dermal preservation, as stated above.

2.4.2 Oedema Composition

Based on the theories and understanding of human chronic oedema states, acute burn oedema was suggested to have a high protein content which alters during the healing period (Demling 2005). High protein oedema fluid is defined as containing > 1g/dL (1% by volume) protein. One study of subeschar fluid confirmed the high protein

nature of the burn oedema (Crockett 1956). The author collected tissue oedema with pipettes from one burn patient demonstrating it to be a high protein fluid. In contrast, samples of human burn blister fluid indicated a low protein oedema, ranging from 0.029-0.52 g/dL (Heggers et al. 1980). Further, these studies provide single time point sampling and neither define the period of oedema collection adequately. It is unknown if all samples were collected within the acute period. Thus, to date the temporal changes of burn oedema, during the acute period, have not been documented accurately or have been conflicting dependent on the sampling method.

With time, oedema composition changes viscosity to increase the stiffness in the extra-cellular matrix tissues due to deposition of glycosaminoglycans and other organising chemicals (Bates et al. 1993). In rabbits, increased fluid viscosity, related to higher protein content creates 'sludging' in post-capillary vessels reducing oxygen tension and, increasing oedema, in an experimental wound situation (Heughan et al. 1972b). Reduced oxygen tension in actively healing tissues was associated with an increased rate of infection (rabbits) and reduction in tensile strength of subsequent repaired skin (Niinikoski et al. 1972; Hunt et al. 1975). Conversely, application of normobaric oxygen therapy in healthy human subjects, increased the rate of removal, via the lymphatics of proteins introduced into the tissues (Balestra et al. 2004).

At a macroscopic level, the resistance to movement created by hyper-viscous, persistent oedema contributes to the potential loss of a patient's functional ability and joint range of movement. Burn oedema has been shown to reside in muscle tissue, thereby reducing muscle action potentials (Baxter 1974). Thus, oedema compounds the challenge of maintaining muscle mass after a burn. A marked, progressive loss of muscle tissue is likely due to the effects of burn hyper-metabolism (Alloju et al. 2008). The net loss of muscle mass continues for an extended period (six to nine months post severe burn injury) compounded further by prolonged oedema in the tissues (Hart et al. 2000). Thus, the removal of oedema may assist to ameliorate muscle mass loss, though such a contribution would be difficult to quantify.

2.4.3 Prolonged Oedema Presence in Tissues

As the acute phase of inflammation progresses, the volume of oedema in the tissues should subside and allow effective progression to the proliferative phase of wound healing (Rice 2000). If oedema remains in the tissues beyond the acute timeframe, wound closure will be hindered (Hardy 1989). While oedema hinders acute healing, this is compounded by the impact of the impaired local, superficial lymphatic system

function and the presence of high concentrations of protein in the tissue leading to progressive fibro-sclerosis (Clodius et al. 1976; Brautigam et al. 1998). The extremities of lymphatic collector vessels originate in the dermis and then progress to transport fluid and debris centrally (Crockett 1965). Thus, a burn affecting the dermis and, or deeper tissues causes lymphatic vessel damage and impedes the essential transport mechanism. Early animal studies showed initial restoration of disrupted lymphatics by ~ 10 days (Reichart 1926). However, in the presence of extensive tissue damage after burn, it is likely to require longer to restore local lymphatic function (Demling 2005). Notable for burn clinicians, it was shown that the drainage capacity of the subfascial muscle compartment, rather than the epifascial lymphatics, correlated with the degree of chronic oedema after breast cancer treatment (Stanton et al. 2003; Stanton et al. 2009a).

Within weeks of onset, oedema has been associated with deposition of fat in the muscles, deposition of calcium in the tissues and thickening of the perimuscular fascia (Marotel et al. 1998). Histological analysis of lymphatic vessels in the ‘initial stage’ of lymphoedema shows occlusion of the proximal lymphatic trunks with increased deposition of collagen and degradation of smooth muscle (Koshima et al. 1996). Though the authors did not define the timeframe of onset, the condition parallels that of persistent post-burn oedema. Such changes to the lymphatic system cause a reduction in vessel patency and ongoing deposition of distal oedema. Further, prolonged presence of oedema in the tissues was associated with increased dermal angiogenesis (Mellor et al. 2002) but counter intuitively, a reduction in skin blood flow (Stanton et al. 1996). Similarly, post-burn healing and HTS deposition is associated with increased blood vessel growth

It is clear that oedema in the tissues has significant consequences during the acute period. The local responses lead to ongoing of complications related to the tissue fluid constituent composition which changes over time. The presence of tissue oedema impacts all burn injured patients.

2.5 Significance of Rapid Burn Closure: Removal of Oedema

While it was proposed that oedema is necessary to circumscribe and contain an injury field during the initial inflammatory period, manipulation of excessive oedema volume and the time it is present in the zone of injury may prevent tissue necrosis (Hardy 1989). This in turn, reduces wound healing time. As noted earlier, burn wounds, which heal under ~ 14 days post-injury, pose less risk for HTS development. Additionally, for the burn survivor, this means: improved regenerated skin strength; sensory discrimination; secretory function and aesthetic appearance; and reduced: psychological trauma; length of hospital stay and time off work and fewer: anaesthetics; risks of surgery and long term reconstructive surgeries (Ward 1991; Muller et al. 2002; Ong et al. 2006; van Baar et al. 2006; Anderson 2007).

All of these authors indicated improved bio-psycho-social outcomes described in terms of the WHO ICF framework by describing a burn survivor's health and body functions, their participation, activity and social functioning while minimizing the impact of their personal and environmental factors (WHO 2001).

For the community and health system, the significance of reducing wound healing time is: reduced hospital costs; reduction in bed days; theatre costs and skin biotechnology and dressing product usage.

While a number of these outcomes are measureable in terms of overall patient outcomes, the primary challenge remains the ability to determine the degree of causality linked to the presence of acute burn oedema and, or the effect size of interventions designed to positively impact on it. Thus, assessment of outcomes both in the burn unit environment and across burn scar recovery, underpins the capacity of clinicians and researchers to improve patient care in the area of burn oedema management.

2.6 Assessment of Acute Burn Oedema

Within the evolving model for burn survivor rehabilitation, an understanding of effective oedema interventions is gained through appropriate assessment. The unique nature of acute burn injury, and the individuality of the long term responses to it, necessitates that consideration be given to specific post-burn measurement tools or alternatively, the validation and, understanding of sensitivity of outcome assessment tools previously used in the burn population. Further, because of the complexity of acute burn injury, clinical environment and management, a bio-psycho-social battery of appropriate outcome measures is indicated. The battery of tests must be capable of objectively mapping recovery in multiple domains, across the acute and protracted burn scar maturation phase and beyond (particularly in the case of mental health outcomes).

In a recent review paper, a comprehensive, though not exhaustive, list of potential outcome measurement tools for the burn patient population was presented (Falder et al. 2008). The vast majority of the scales and physical assessments discussed in the review had not been tested for reliability or validity in the burn population. Prior to this work, the tests which had been reported to be valid for use in the burn patient population and, have been accepted for widespread use, were the Burn Specific Health Scale (BSHS) and the modified Vancouver Scar Scale (VSS). The BSHS and its revised forms combine patient self rated Likert scales (21 – 80 items) to quantify overall post-burn recovery and 4 to 9 sub-domain scores (Blades et al. 1982c; Blalock et al. 1994; Kildal et al. 2001a; Moi et al. 2003). The modified VSS followed the original tool developed at the Vancouver General Hospital in the late 1980's (Sullivan et al. 1990). It is a subjective (experienced) therapist rating of the patient's scar and, as with the BSHS, describes the quality of the healed burn scar in terms of a total and, or 4 sub-domain scores (colour, redness, pliability and height). The VSS has been demonstrated to have limitations with respect to inter-rater reliability, particularly with inexperienced users (Baryza and Baryza 1995). Further, a recent abstract presented the ambiguity of the VSS scoring schema and cast doubt on the validity of previous scar outcome papers that have used the VSS total score as their primary measure (Simons and Tyack 2009). The BSHS was developed for the burn population specifically and has been demonstrated to suffer significant ceiling effects in longitudinal measurements; particularly in Western burn patient populations (see Results Chapter). However, like the VSS, it remains the most widely used post-burn quality of life (QoL) measure available.

The short comings of these well established scales may be addressed through the use of measures or batteries of measures designed to address the aspects of the ICF framework in totality. For instance, the psychometric properties of the BSHS parallel the Medical Outcomes Study 36-Item Short Form Health Survey (SF36) (Ware et al. 1993). The SF36 QoL measure has been employed in a number of burn population studies without validation (Turner-Bowker et al. 2002; Moi et al. 2006). However, due to its alignment with the domains of the ICF, the SF36 may be an appropriate and generally applicable tool to allow comparison of burn population with others. Secondly, the Patient Objective Scar Assessment Scale (POSAS) developed in the Netherlands, provides additional scar measurement components when compared to the VSS (Draaijers et al. 2004). The scale includes a patient self-rated scar satisfaction component, which broadens its application in line with the principles of the ICF framework. The POSAS was demonstrated to be reliable (Draaijers et al. 2004; van de Kar et al. 2005) but the variable validity of the components against the VSS may indicate the reasons for the relatively limited use in clinical practice and rarity in publications at this time.

Falder et al (Falder et al. 2009) noted a multitude of objective scales developed to address aspects of recovery though the vast majority remain unvalidated for burn patient use. The accuracy of scales and measurements without appropriate validation in the burn population is uncertain because of factors such as component or total subjectivity or development of the measure in patient populations with dissimilar outcome attributes. Further discussion or comparison of these measures with those tested in this project, where appropriate, will be found in the Results Chapter.

Discussion regarding the unlisted measures for scar quality; pain; itch and components of skin function is not warranted in this thesis. A large number of scales are available which focus on the analysis of psychological functioning, social coping and adjustment for the sub-acute to chronic post-burn period. These scales will not be discussed and further they are beyond the expertise of the candidate. Detailed understanding of the psychology of burn recovery within the context of this thesis is not warranted. Readers should refer to the review paper and, or the source articles cited therein. However, it is worthy to note a developing area touched upon by Falder et al's (2009) description of Burn Specific Pain and Anxiety Scale (BSPAS) (Taal and Faber 1997). Fear avoidance of movement is a recognized impediment to post-burn function and re-integration and,

readers might consider exploring this area through use of scales such as the modified Tampa scale of kinesophobia (Vlaeyen et al. 1995; Roelofs et al. 2004).

Finally, outcome measurement after paediatric burn injury is a progressive area and many scales have been developed to measure aspects of a child's recovery and the impact on carers. The focus of this thesis is adult burn injuries and for a detailed examination of paediatric outcome measures available, the reader is directed to literature review in Simons' PhD thesis (Simons 2008). Further discussion regarding the relevance, reliability or validity of the outcome assessments developed specifically for paediatric patients is outside the scope of this thesis.

It is clear that a large number of scales and outcome measurements have been utilized for burn patient outcome research. However, there is a paucity of reliable, validated individual tools, or batteries of assessments, to objectively monitor acute and, or longitudinal burn patient functional outcomes with surety. In terms of understanding the efficacy of an intervention for acute burn oedema, consideration must be given to the development of measures which are both clinically applicable in the acute burn environment and, or those which can sensitively monitor long term recovery and quality of life outcomes in the months to years after burn injury.

2.7 Management of Acute Burn Oedema

The management of acute burn oedema is largely based on empirical or animal model evidence (Demling 2005). There is unresolved debate as to the most appropriate animal model for burn research due to the limitations of approximating human tissue responses, particularly with respect to hypertrophic scarring and inflammatory processes (Sauerstein et al. 2000; Greenhalgh 2005). Examining the virtues of different animal models is beyond the scope of this thesis and henceforth, the research presented will comprise only results gathered from the study of humans.

The current principles for treatment of acute oedema are based on studies in critical care patient, sports or soft tissue trauma and healthy non-injured populations (Richard et al. 2009). The principles include the use of elevation (Boland and Adams 1998), muscle pump or movement (Griffiths and Gallimore 2005) and external compression (Meeusen et al. 1998; Myerson et al. 2000) to remove, or limit, swelling. The inclusion of static splinting is common to position patients to prevent the negative impact of acute oedema but is not uniformly used for reduction of swelling (Richard et al. 2009). In other populations, the components of oedema management are used in conjunction

with ice therapy (MacAuley 2001). However, ice therapy is contraindicated in acute burn wounds because of the likelihood of increased skin tissue necrosis (ANZBA Education Committee Chairman 2008; Cuttle et al. 2008a). Despite this, as noted earlier, evidence indicates the benefit of appropriate cooling, or first aid, in the burn wound. Studies investigating oedema control principles for acute burn patients are absent in the literature. Expert opinion, mathematical models and the theories of liquid physics support the use of elevation, movement and compression (Kramer et al. 2002). Clinicians employ these routinely but in combinations and prescriptions without consensus (Richard et al. 2009). Benefits associated with the use of these methods relates to the optimisation of the lymphatic system action, opposing or reducing tissue fluid accumulation and the physics of removal.

To assess systematically, the body of evidence supporting specific treatments for acute burn oedema a Cochrane Review was performed (Thesis Paper I:a&b). The results of the following review examine local and systemic oedema management interventions for the acute burn population. It further illustrates and discusses the specific limitations to research progress related to measurement of burn oedema change in the acute environment and longitudinal assessment of the impact of acute oedema management on functional and quality of life outcomes.

2.7.1 Excerpt from Paper I: Cochrane Review Study Inclusion Criteria

(Submitted Cochrane Review manuscript is available in full: DVD Appendix, Folder B.)

Types of studies: Randomised controlled trials (RCTs) will be included in the review.

Types of participants: Studies of people of any age and in any care setting with a burn wound of any origin and any depth will be included. Most injuries are traumatic in origin, however, we will include self inflicted burns, or those caused by chemical agents, electrical current and medical treatment e.g. cardioversion or radiation therapy. The presence of inhalation injury as a co-morbidity will not exclude patients.

Studies which include participants with significant soft tissue or bony injury not caused by a burning agent will be excluded.

Types of interventions: Studies will be included if the primary or secondary aim of the intervention is to prevent, or limit, oedema formation, or to manage, or control, it when

it develops. Results presented, and outcome measures used, will clarify if management of oedema is a primary or secondary focus of the study.

Trials will be excluded if the aim is to prevent or manage oedema in non-burned tissues, despite the presence of injury elsewhere in the body. The following list of interventions represents methods used to affect swelling in a clinical setting. Studies will be included if interventions are compared with usual care, placebo /sham interventions, or another intervention.

Local oedema prevention and control techniques:

- First aid after burn: studies of pre-hospital care, cooling the burn, chemical antidotes;
- Mechanical interventions: massage, topical negative pressure dressings, external compression or bandaging, elevation or positioning, movement and exercise, splinting or plastering;
- Surgical interventions: escharotomy, early debridement of eschar, skin reconstruction techniques (autograft, allograft, dermal templates, zenograft); and,
- Electrotherapy: transcutaneous electrical stimulation, ultrasound (US) therapy.

Systemic oedema prevention and control methods:

- Drugs: anti-oxidant therapies e.g. high dose vitamin C, NSAID's, inflammatory mediator blockers, analgesics, steroids; and,
- Medical: fluid resuscitation parameters, resuscitation fluid constitution, renal filtration.

Types of outcome measures:

Primary outcomes:

- Time to complete wound closure or epithelialisation;
- Percentage wound area change between measurement points in the study;
- Incidence of contracture requiring acute or reconstructive surgical correction; and,
- Scar quality assessments such as the Vancouver Scar Scale (Sullivan et al. 1990).

Secondary outcomes:

- Oedema volume change, quantified by any one of the following methods: wound tissue biopsy for comparison of wet to dry weight (Tanaka et al. 2000); volumetry or water volume displaced after immersion of a limb (Megens 2001; Farrell et al. 2003); flexible tape measurement combined with absolute volume change calculations such as circumferential limb girth (RaviKumar 2001; Karges et al. 2003) or hand ‘figure 8’ measures (Dewey et al. 2007); non-invasive scanning methods such as

dual energy X-ray absorptiometry (DEXA), computerised topography (CT), magnetic resonance images (MRI), or bio-impedance analysis (BIA) (Stanton et al. 2000); non-invasive linear measures of oedema thickness such as high frequency US (Li et al. 2006; Caulfield et al. 2008); invasive scanning methods such as injected labelled water scans (Jensen 1993), contrasted CT or MRI; and body weight (Tanaka et al. 2000; Infanger 2004).

- Lung oedema change, quantified by: extra-vascular lung water volume using a dual gas rebreathing methodology (Goodwin et al. 1983).

- Clinical and quality of life measures: length of stay (LOS) - hospital, intensive care unit (ICU); burn wound infection rate (Silla et al. 2006); pain scores / questionnaires; and quality of life measures such as the Burns Specific Health Scale (BSHS) questionnaire (Blades et al. 1982c).

2.7.2 Excerpt from Paper I: Cochrane Review Results

Of the 338 abstracts screened, 311 were ineligible, predominately because the investigations were not RCTs, or were not undertaken in humans. A review of full copies of the remaining 27 papers revealed nine papers, involving a total of 244 (human) participants, that were eligible for inclusion in the review. The nine papers described eight RCTs that investigated an intervention that impacted on acute burn oedema. One of these included studies was represented by two conference abstracts in continuation, published three years apart, one of which was noted in a previous Cochrane Review (Wasiak and Cleland 2007).

Three of the studies were conducted in the last 10 years and the remaining five were undertaken prior to 1984. No two studies reported the same outcome measures and intervention construct for either local or systemic responses to the interventions. People included in the trials varied from healthy volunteers to acute major burn patients, with and without inhalation injury. One study was conducted in a male sample population (Sevitt et al. 1952). Six studies assessed systemic interventions and of those, three compared different fluid resuscitation regimes, while the remainder examined the effects of oral or intravenous drugs. Two studies examined local wound treatments for acute oedema reduction.

Risk of bias in included studies

Overall, due to poor methodological design, lack of reporting, or both, the risk of bias for included studies was moderate to high (Fig. 2.5), with the exception of (Sevitt et al. 1952). Three studies reported adequate randomisation procedures (Sevitt et al. 1952; Levine et al. 1978; Goodwin et al. 1983). (Sevitt et al. 1952) was the only study that also reported adequate allocation concealment and blinding of outcome measurements.

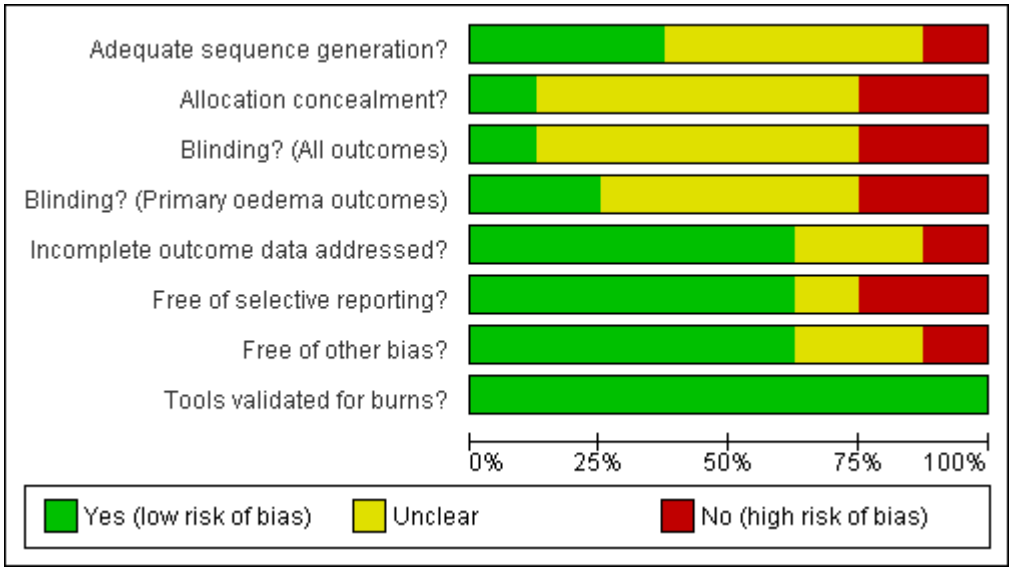


Figure 2.5: Methodological quality graph: judgements about each methodological quality item presented as percentages across all included studies.

Method of randomization: Allocation sequences were generated in a number of ways, but were unreported, or not completed, in the majority of studies (i.e. five out of the eight included studies). Acceptable methods that were reported included the use of a random-number table (Levine et al. 1978; Goodwin et al. 1983), and drawing lots (Sevitt et al. 1952). Sub-optimal use of allocation by month of admission was also reported by one study (Tanaka et al. 2000).

Allocation concealment: Allocation concealment was described in one study only (Sevitt et al. 1952). The risk of introduction of bias to results due to randomisation methods was moderate for all studies except this one.

Blinding: One small study with eight participants reported adequate blinding of subjects and outcome assessors to treatment allocation (medication trial) (Sevitt et al. 1952). Furthermore, according to the abstract, (Molnar et al. 2004a) indicated that burn wound area outcomes were measured by a blinded assessor, but no mention was made of blinding of the hand oedema outcome assessor(s). The methodology of their study prevented blinding to treatment allocation.

In all other studies, blinding of treatment and / or providers, patient and outcome assessors was not reported and, due to trial methodologies in acute burn unit environments, likely to be compromised. This is an area of significant concern overall with respect to possible risk of introduced bias in results. It is appreciated that trial reporting standards may contribute to the lack of reporting rather than poor scientific method.

Incomplete outcome data: All the included studies, apart from Molnar et al (Molnar et al. 2004a), presented information on all patients and loss to follow up, particularly when mortality was the cause. The variability of final grouped outcome statistics in Omar et al (Omar et al. 2004) raised suspicions that patient numbers had reduced, but the results that were presented did not reflect this. Furthermore, one inconclusive study excluded a patient outlier from analyses without adequate justification (Burge and Gilbert 1979). Incomplete data, however, were not an obviously significant source of bias, or overstatement of effect, for any of the results presented in this review.

Selective reporting: Apart from Molnar et al (Molnar et al. 2004a) and (Burge et al. 1979), the included studies presented all the outcome data indicated in the Methods sections of their trial reports. There was no significant evidence of selective reporting in any other study.

Other potential sources of bias: The baseline characteristics of all study comparison groups was equivocal. Four of the eight included studies published negative or equivocal results, indicating that this was not a significant potential source of bias to the findings presented.

Theoretically, the oedema control interventions were appropriate, in that all the methods employed reduce local or systemic oedema in animals, or other patient populations. Local interventions included physical oedema removal by topical negative pressure (TNP) dressings and pulsed electrical stimulation of the upper limb muscle pump. Changing acute burn resuscitation fluid parameters using hyperosmolar solution and/or albumin is the subject of numerous clinical trials to reduce prescription in burns and other patient populations (Alvarado et al. 2009). Vitamin C is an anti-inflammatory and free-radical neutralising agent that was included appropriately as part of an acute burn resuscitation fluid regime (Rabl et al. 1995; Tanaka et al. 1999). Finally, the drug trials used anti-histamine and parenteral steroid, which are both anti-inflammatory agents with the potential to reduce tissue oedema (Friedl 1989; Rantfors and Cassuto 2003).

None of the studies reported intention-to-treat analyses. Omar et al (Omar et al. 2004) presented a non-validated, culturally-specific functional assessment battery which was

poorly defined in the study. Consequently, these data were not included. All the other studies scales possessed construct validity but had not been validated specifically for burn injured patients. This aspect of potential study bias may impact on the findings presented but it is difficult to quantify the degree or direction of such bias.

2.7.3 Excerpt from Paper I: Cochrane Review Conclusions

Implications for practice (Fig. 2.6)

Local wound treatments: Weak evidence from one small study, suggests that topical negative pressure dressings reduce local acute oedema and burn wound area. A small, single centre study provided moderate evidence that high-voltage, pulsed, galvanic electrical stimulation reduces local wound oedema and improves the rate of functional movement return when added to traditional physiotherapy.

Systemic treatments: A well-performed, single centre study demonstrated that administration of albuminated resuscitation fluids significantly increased lung oedema and the rate of mortality after major burn. A small, single centre trial concluded that the use of high dose Vitamin C infused as an additive during acute major burn resuscitation reduced local wound oedema, systemic fluid retention and number of days on mechanical ventilation. Lastly, weak evidence from small and / or underpowered single centre studies suggests that: the use of hypertonic albuminated resuscitation fluid reduces systemic fluid retention; antihistamine administration during acute inflammatory period does not reduce local acute hand burn oedema or improve burn wound epithelialisation rate; and administration of parenteral steroid after acute inhalation injury and major burn provides no benefit to reduce respiratory complications caused by oedema, or to reduce mortality.

local and systemic treatments for oedema management for acute burn injury

Patient or population: patients with acute burn injury
Settings: Burn Centres
Intervention: local and systemic treatments for oedema management

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk Control	Corresponding risk local and systemic treatments for oedema management				
Mortality Follow-up: mean 7 days[1]	120 per 1000[2]	440 per 1000 (139 to 1390)	RR 3.67 (1.16 to 11.58)	50 (1 study[4])	⊖⊖⊖O moderate[3]	
Respiratory Complications pulmonary oedema present on chest xray Follow-up: mean 7 days	40 per 1000	200 per 1000 (25 to 1592)	RR 5 (0.63 to 39.79)	50 (1 study[4])	⊖⊖⊖O moderate[5]	
Wound Healing / Epithelialisation Unavailable Follow-up: mean 4 days	See comment	See comment		58 (1 study[8])	⊖⊖OO low[6,7]	
Oedema Change ml/g. Scale from: 1 to 10. Follow-up: mean 15 days	The mean oedema change in the control groups was 6.1 ml/g	The mean Oedema Change in the intervention groups was 3.5 lower (4.63 to 2.67 lower)		37 (1 study[9])	⊖⊖⊖⊖ high	
Functional Outcome degrees range of motion. Scale from: 0 to 240. Follow-up: mean 15 days	The mean functional outcome in the control groups was 44 degrees range of motion	The mean Functional Outcome in the intervention groups was 23 higher (19.24 to 26.76 higher)		30 (1 study[9])	⊖⊖⊖O moderate[10]	

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio;

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] Study follow-up was 7 days but mortality statistics collated according to patient disposition at discharge from the burn centre.

[2] Mean baseline risk taken from the included study only as this particular study population excluded patients with inhalation injury. All other resuscitation studies in this review include patients with inhalation injury.

[3] Allocation concealment, assessor blinding not reported. Single gender population.

[4] Goodwin et al, 1983. Acute burn resuscitation using colloid regime vs usual care (crystalloid) regime.

[5] Allocation concealment, assessor blinding not reported. Single gender population. Rare event rate. Small effect size, not statistically significant (Z=1.52, p=0.13).

[6] Measured wound area reduction which is not equivalent to wound healing. Wound area may be reduced by contraction alone and not necessarily represent more rapid epithelialisation.

[7] Molnar et al's study is yet to be published though the results have been presented in at least 2 conference abstracts without raw or grouped data. Co-authors are the inventors of the technique and unlikely to present negative results in view of affiliations.

[8] Molnar et al 2007. Negative pressure dressings trial. As yet, unpublished in peer reviewed forum.

[9] Tanaka et al, 2000. High dose vitamin C acute burn resuscitation regime compared to crystalloid resuscitation.

[10] Randomisation method, allocation concealment and assessor blinding not reported.

Figure 2.6: Summary of findings table extracted from Cochrane Review.

Implications for research:

The lack of high quality research in this area, and the variability of existing studies, indicates that future studies should: as a priority, be concerned with recruitment of subject numbers to ensure appropriately-powered studies and, therefore, as with many other burn care areas, studies of acute oedema management should strive for a multi-centre methodology; measure and report consistent outcomes for local acute burn wound oedema intervention effect using wound biopsy (wet to dry weight), where possible, and volumetry (absolute change); validate and determine reliability and

sensitivity of outcome measures that will allow researchers to measure long term functional outcomes and/or acute clinical impact of treatments for acute burn oedema; increase the clinical utility of research findings by including standardised, longitudinal functional measures, with consideration for appropriate study numbers based on outcome tool accuracy; include valid outcome measures for local burn wound healing including (repeated) wound area measurements and/or rate of wound area change; use consistent outcome measures for acute systemic oedema change, such as standardised body weight change in combination with complication event rates or final outcome measures; repeat single centre studies to confirm or deny generalisability of findings and improve the clinical applicability of studies through attention to representative population sampling and recruitment.

2.8 Chapter Summary

It is clear that acute burn injury poses unique and complex challenges to health care providers. It was foreseeable, due to the noxious and lethal nature of burns, that while extensive, the sources of evidence were confirmed to originate primarily from expert opinion, empirical study and work with animal models. Demling's (2005) review eloquently summed up the state of science relating to acute burn oedema pathogenesis and assessment. In clinical practice, first aid measures and appropriate cooling, elevation of injured body part, compression and movement are advocated and regularly used as acute treatment to manage post-burn oedema and, reduce the negative impact of fluid in vulnerable tissues.

Uncertainty remains in specific knowledge of the human acute oedema response due to the lack of high quality human studies. The review of literature highlighted a significant number of quality of life and, or discipline specific outcome measures used in burn care and research. The widespread clinical application of the individual or grouped measures is hindered by a lack of consensus on, or availability of, validated assessment tools that could be used to measure the impact of acute burn oedema. The results of the Cochrane Review concur with these findings and further indicate that the design and completion of clinical research is obstructed by the same shortcomings.

With respect to interventions to manage local and systemic acute burn oedema, the review of literature was unable to identify any human study, which reported definitive outcomes, that was not likely to be biased according to Cochrane Review criteria. There was a complete absence of multicentre trials and a number of the single centre studies were conducted in single gender samples.

These findings indicate reasons for the limited consensus and inconsistent translation of beneficial treatments, identified during the Cochrane Review, into clinical practice. The intervention studies of use include: electrical muscle stimulation; acute resuscitation after major burn using continuous high dose vitamin C and omitting colloid from early resuscitation. These studies should be repeated, with attention to: representative population sampling and recruitment; improved understanding of the temporal pattern of acute burn oedema and utilisation of validated post-burn outcome measures to confirm or deny the generalisability of the single centre trials. The primary aims of this thesis were designed to take steps to address these issues.

Chapter Three

Methods

The overall aim of the thesis is to provide clinicians with specific knowledge to improve the efficacy of acute oedema interventions and, to provide researchers with tools to design and conduct higher quality studies. In order to provide new understanding and address a number of the gaps, the series of studies, described below, was developed. The methodologies of these studies are presented in sections. The aim of each section is to address separately the three primary focus areas of this thesis, namely, scientific knowledge of acute burn oedema, acute oedema assessment and longitudinal outcome measurement. The aims of each section are:

Aim 1: To describe the contents of human acute burn oedema and investigate the change over time;
Aim 2: To examine the reliability and validity of oedema measurement methods in the acute burn environment; and
Aim 3: To examine the reliability and validity of longitudinal outcome measures in the burn population.

3.1 Acute Burn Oedema: Scientific Analysis

To determine the most efficacious temporal application of an intervention, an understanding of the change in volume and acute oedema constituents over time is necessary. Appreciating the interaction of oedema with the local burn wound environment is important also. Further, the ability to optimise lymphatic activity in relation to acute burn oedema is not well understood. Unique to the lymphatic system, is the ability to physically remove large volumes of oedema fluid from tissue and extract extravasated proteins and cellular debris (Casley-Smith 1968; 1993). With the surrounding integument, the lymphatic system also provides an effective immune response to antigens. Increased incidence of wound and systemic infection impact negatively on burn patient mortality and scar morbidity (Demling 2004; Baker et al. 2007).

Acute burn wound healing challenges are unique and differ from other wound states due to the disruption of the lymphatics of the skin itself (Zawacki 1974). Further, it is well documented that oedema states change with time in the tissues (Bates et al. 1993). However, current understanding of the human acute oedema state is based on

studies in chronic oedema patient populations, animal models or single time point sampling in humans (Demling 2005). The interested reader is referred to the key papers by Judith and John Casley-Smith (Casley-Smith 1985; Casley-Smith et al. 1998) and Ethel and Michael Foldi et al (Foldi et al. 2000; Foldi and Foldi 2006). Consequently, a detailed, specific knowledge of acute burn oedema contents and its temporal change is lacking. The following studies describe the methodologies chosen to explore some of the questions regarding acute burn oedema.

3.1.1 Study 1: Negative Pressure Dressing (NPD) Study

This study was designed to collect acute oedema fluid directly from the burn wound, during the first week post-burn. The primary point of difference to previous studies relates to the novel use of repeated, bi-daily sampling across the whole acute burn period.

The data gathered aimed to provide detailed insight into the particulate contents of acute burn oedema and the changes in composition over the first 5 – 7 days post-burn. Finally, the rate of fluid production from the open wound, with a constant negative pressure applied in this way, provided an indication of daily volume of acute burn oedema. Greater efficacy in removal of oedema through informed intervention or research design may lead to faster removal of fluid and aid burn wound healing. Consequently, the following hypotheses were derived:

Study 1 Hypotheses

1. Human acute burn oedema protein content peaks on day 2 post-burn.
2. Human acute burn oedema has a greater protein concentration than chronic oedema.
3. The particle size of solid matter within human acute oedema is not consistent across the first 7 days post-burn.

Study 1 Procedure

To ensure accurate assessment of oedema changes over time, the study involved the collection of sequential wound fluid samples. To reduce the patient burden of invasive procedures, this was achieved by using a vacuum sealed foam dressing that extracted fluid from the wound and underlying tissue due to the negative pressure interface on the open burn (Fig 3.1). NPD therapy has a long history in the wound healing literature indicating healing benefit to open skin areas and difficult wounds (Valenta 1994; Mullner et al. 1997; Blackburn et al. 1998; Morkywas et al. 2006). In contrast, for the treatment of acute burns it is a relatively recent, though well established, procedure

which is gaining stronger evidence based support for its use (Schrank et al. 2004; Schintler et al. 2005; Molnar 2007).

Pilot Trials: To standardise the methodology and demonstrate feasibility in the burn unit environment, NPD oedema sampling was initially completed in chronic and sub-acute burn wound models.

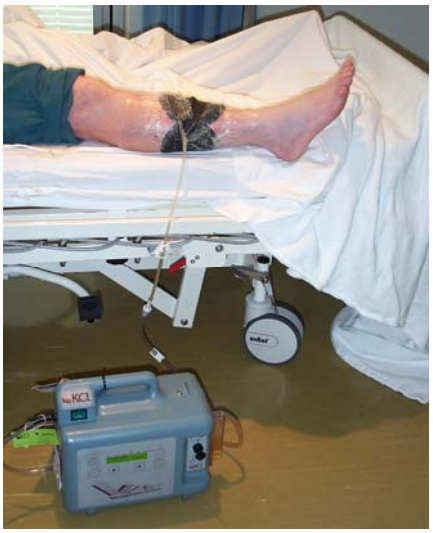


Figure 3.1: Pilot trial sub-acute burn wound with KCl NPD applied.

Acute Oedema Sampling Procedure: Acute burn patients were recruited upon admission to the RPH Burns Unit. A total of 5 patients were planned for recruitment during the candidacy, with a potential of 60 – 70 samples in total (see below). Patients were included if an available NPD site was a partial thickness or mid-dermal burn wound of a TBSA small enough to seal the dressing (~ 1-2% TBSA). Thus, data to analyse the response of full thickness burn was not gathered. Further, the NPD was not an appropriate intervention for superficial injuries. In parallel, a control site with similar burn depth was chosen to compare the benefits to wound healing offered by the NPD system. The wound area chosen could be larger in area than the NPD site (Fig 3.2). This study was adjunctive and further discussion of the methods, outcome measures and results of that aspect of the trial are out of the scope of this thesis.

Patients were excluded if the wound was assessed, by a senior medical clinician, to be full thickness and, or superficial; contained macroscopic debris or otherwise clinically required immediate antimicrobial dressings according to the RPH burn unit wound infection protocol (Silla et al. 2006). Patients were also excluded if >12 hrs transfer time to the burns unit as this was likely to prevent an adequate time to recruit patients and access the Day One fluid sample.

Day One – Seven: Previous studies suggested that burn swelling subsides significantly by the end of the first seven days post-burn (Leape 1971). Oedema fluid was therefore collected from the trial site twice each day to provide on average 12 – 14 samples per patient during the study. One sample was sterile (via an in series, sterile trap) and one was a clean sample (collected from NPD machine receptacle). To provide an adequate volume for all planned laboratory tests, 3 - 5 mls of fluid was required if possible. The trial continued until day seven or for as long as the patient remained comfortable with the treatment intervention.

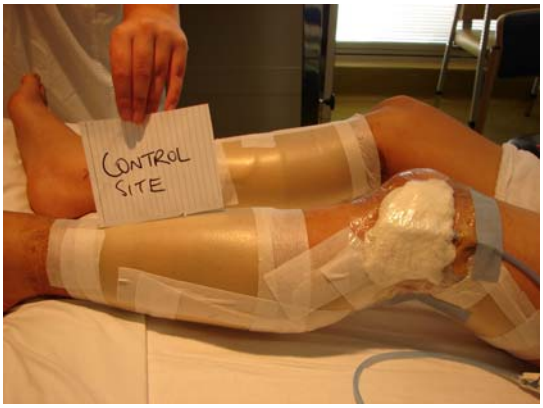


Figure 3.2: Day three post-burn: NPD study site (lateral knee) adjacent to control site (hydrocolloid) dressing.

Equipment: Two types of NPD system were utilised during the course of the study due to changes in supply chain arrangements at the RPH. The NPD equipment used was either the first model of the KCI *Advanced Therapy System* VAC® (KCI Therapies, UK) or the first released model of the Smith and Nephew *Versatile 1*® (Blue Sky Medical, Florida, USA) negative pressure system. Important to this study, both machines provide equivalent pressure application at the wound interface. The pressures were set at 80 or 125 mmHg (continuous) depending on patient comfort and, or manufacturer's protocol. Each therapeutic system differed in their sterile dressing interface. The KCI dressing applied was standard black polyurethane GranuFoam®. Differences in dressing interface have been noted to alter healing (Timmers et al. 2005). However, this potential limitation to the wound healing trial was not considered significant in the collection of fluid and, or assessment of microscopic fluid contents as both dressing interfaces were porous upon visual inspection. Thus, the combined results of both NPD systems are presented.

Oedema Sample Analysis: A number of laboratory studies were used to assess the exudate contents. These studies were conducted by laboratory staff at Royal Perth Hospital or University of Western Australia. Each of the samples was collected, collated, decanted and sent to the laboratory by the candidate. Analyses were conducted and interpreted with direction from senior scientists – Alan Morling (RPH) and Dr Mark Fear (UWA). The components of the analyses included: microscopy; protein level assay; albumin level assay; sample filtration and weighing and finally, Coomassie gel assay.

Standard microscopy views were taken at equivalent magnification to provide a visual analysis of particulate matter in the oedema fluid (Fig. 3.3).

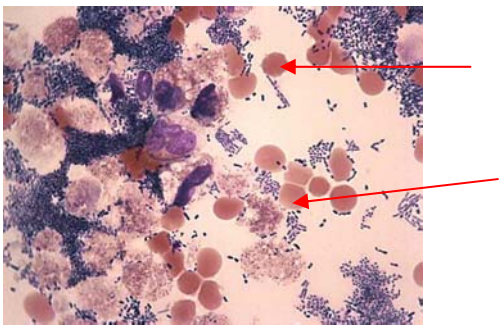


Figure 3.3: A typical standard microscopy image of sub-acute oedema fluid particulate matter, collected during pilot trials. Viable cells are denoted by arrows and dark staining indicates cell debris.

Specific components in the fluid were assessed by laboratory assay. Total protein assay (*TP*, Roche Diagnostics, Indianapolis, USA) was used to quantify the changes in sample protein content over time. Protein concentration is derived from photometric comparison of the post-reaction (with divalent copper ions) shift of colour intensity to baseline (blank reagent). Total albumin assay (*ALB plus*, Roche Diagnostics, Indianapolis, USA) was used to quantify albumin through colourmetric shift using bromcresol green (BCG) as the reagent.

Particle size was determined from samples decanted and frozen at the time of collection. The quantification of the amount and size of particulate matter in the oedema sample was determined by relative sample and supernatant weight after passing the fluid through a 100µm filter. A Coomassie gel assay was conducted to provide a visualization of the relative quantity and molecular weight of proteins, and protein cell debris, in the fluid. The width (and intensity) of the stain band indicates the

relative concentration of the protein within the sample. A set of standardized protein markers were used to estimate the size of migrating protein and, or debris.

Data Analyses: Data were analysed using SPSS v 17 (SPSS Inc, USA). Recognising that the sample numbers were small, distributions were tested for normality using the Shapiro-Wilk test. Where the distribution did not deviate significantly from normal, paired t-tests were used to examine the differences between grouped sample means. If the distribution was not normal, Wilcoxon signed ranks test was used. This form of testing was applied to chemical content of the oedema fluid. Where quantitative analysis was not feasible, qualitative description of oedema fluid contents were presented. Descriptives are presented as mean and standard deviation (SD) as appropriate.

Ethics: The NPD study was approved by the RPH Ethics Committee (EC) (RPH EC# 2002/028) (DVD Appendix, Folder C).

Significance: The hypotheses of the NPD study were devised to specifically inform acute burn oedema intervention studies. The study was designed to examine if the majority of particles and proteins were too large for early translocation based on the anatomy of the lymphatic collector organs. This new knowledge could then be used to adjust a study before applying a fallible methodology to at risk patients. Also, the constant topical negative pressure applied to the wound interface potentially provided information regarding the rate of oedema production or the volume of oedema produced on different days post-burn. Thus, the results of Study 1 aim to provide further evidence to confirm or deny the findings of Study 2 (Section 3.1.2).

3.1.2 Study 2: Tracking temporal volume change of acute burn oedema

The measurement of acute burn oedema volume change is a unique challenge on the background of large fluid shifts immediately after burn injury (Demling 1982). Subsequently, Demling (2005) also noted that oedema volume in the tissues relates to burn depth but other authors noted that absolute oedema volume shifts do not relate consistently to burn severity, TBSA or other covariates, such as age (Lund et al. 1988; Kramer et al. 2002). Further, the peak of oedema volume in humans was reported variably between days 1 to 3 post-burn (Kleinzner et al. 2005; Caulfield et al. 2008). Also, an understanding the magnitude of this acute volume change has not been presented in the literature to date. Changes of 200mls between treatments for a single upper limb were considered a clinically significant difference in patients with chronic

lymphoedema (Box et al. 2002). Specific information regarding the temporal response of human acute burn oedema was required to inform treatment and research programmes.

Study 2 Hypotheses

1. The peak of acute oedema volume occurs by day 2 post-burn injury.
2. Greater than 200 ml daily volume change occurs to day four post-burn in an acutely injured upper limb
3. Volume change reduces to sub-clinical levels from day 4 – 7 post-burn.

Study 2 Procedure

The study involved serial surveillance of patients (random sample of convenience) with acute upper limb burn injury. A total of 20 patients were planned for analysis during the candidacy. Patients were recruited during the studies related to the testing of validity of acute oedema measures (Section 3.2). Repeated measures of UL volume were collected from each patient using water displacement volumetry (WDV) as described in Section 3.1.1.

Data Analysis: Data were analysed and plotted using *R* (v 2.8.1), by E. Mackay. The results of this study will be provided as a qualitative and quantitative description of acute oedema volume change and peak in the upper limb related to patient and burn severity demographics.

Ethics: As interventions to alter acute oedema were not involved in either study, surveillance using water displacement volumetry was approved by RPH EC (RPH EC # 2004/027), as a component of the 3-D laser study (see Section 3.2.5) (Folder C, DVD Appendix).

Significance: The lack of understanding of the acute oedema temporal change and timing to peak volume is a potential factor in the paucity of high quality research in the area. A more indepth knowledge of the acute oedema production process will aid in the efficacious design of intervention studies and to further justify their application in the highly demanding acute burn environment.

3.2 Measures of Acute Burn Oedema

Investigation of the reliability and validity of longitudinal outcome measures is necessary to provide objective assessment of the temporal sequelae of acute oedema and as part of the overall impact of burn injury. The initial challenge was therefore to compile a group of clinically appropriate, sensitive individual measurement tools applicable to all stages of the burn wound healing and the scar maturation process. The next challenge was to explore the development of a battery of tests by examining the relative performance of the individual component measures (Moyé 2003b). By determining the optimal tests to apply at each time point throughout post-burn recovery, patient and therapist burden may be reduced. According to the clinical outcomes in the RPH environment, the majority of patients demonstrated that the scar maturation process had reached a plateau after one year (unpublished data, D. Edgar). Thus, testing and validation of the outcome measures focused on the performance of individual and combined tests on patients up to one year post-burn, unless otherwise stated.

3.2.1 Data Analyses for Outcome Battery Components

To reduce duplication in the description of the ensuing series of studies, the following section describes the data analyses techniques applied for reliability and validity analyses, unless otherwise justified in a specific study. The data analysis software used was SPSS v 16/17 and, or STATA v 9 for the more complex regression analyses (with assistance from M. Phillips).

Reliability and Sensitivity: The components of reliability for the following studies were described in terms of concordance, indicated by intraclass correlation coefficient (ICC acceptable 0.75 - 0.89; excellent ≥ 0.9) (Portney and Watkins 2000); variance, described by 95% confidence interval (95% CI) and presence of systematic bias, or consistent (procedural) error, between trials ($p < 0.05$). Sensitivity of the measure was indicated by the minimum detectable difference (MDD) calculated as follows: $MDD = SEM \times \sqrt{2} \times t_{(df,.05)}$ (Bland and Altman 1990), where SEM = standard error of the mean.

To provide inferential power of 80% ($\alpha=0.05$), Donner and Eliasziw (1987) indicated that 27 individuals is sufficient to test reliability for duplicate and, 12 for triplicate repetitions, of a method. Numbers were adjusted upwards to accommodate possible dropouts with the exception of joint range of motion measures. Due to the number of

measures requiring assessment, the impact on resource (staff) availability and the clinical environment, a minimum of 15 repeated measures for each test were accepted as the primary analyses. Where the reliability was not clearly established according to the criteria listed above using these numbers, the repeated measures trial progressed to 30 repetitions whereupon they were re-analysed (Gebski and Keech 2003). To minimise burn patient inconvenience, reliability (and safety) testing in burns patients ceased at n=10 unless otherwise indicated.

Validity: For any individual measure that was shown to have acceptable reliability the study progressed to include testing of validity. Exception was applied: where an individual outcome measure was deemed to lack a clinically useful degree of sensitivity in the acute burn population. The validity of individual measures were confirmed or denied using: errors-in-variables regression (EVIR); minimum least square (MLE) longitudinal regression modelling or analyses of sub-groups using repeated measures analysis of variance (ANOVA), particularly if data points were limited in number. The EIVR analysis is statistically robust as it considers individual measure, population specific reliability in estimation of concordance across different time points (Dunn 2007). The MLE longitudinal regression is one of the most robust statistical analyses available for clinical data as it is resistant to bias introduced by missing data (Little 1995).

The temporal validity of a combined outcome battery will be examined against clinical outcome and recovery data collected since January 2006 by the candidate in his clinical role with the assistance of other burn team members acknowledged at the start of the thesis. The method of analysis will once again be MLE regression modelling.

3.2.2 Objective Measurements: Acute Post-burn Period

RPH burn patient data indicates that 82% of patients suffer UL burn. Therefore, to provide options for assessment of the majority of patients during the acute phase, outcome measure reliability and validity studies are primarily conducted using UL measurements. As noted earlier, clinically significant differences in UL volume are in the order of 200 mls between daily or weekly measurements (Box et al. 2002). However, a smaller volume change, over a shorter period, must be considered when studying acute burn oedema interventions. To assess the efficacy of an intervention on acute burn oedema, measures must detect smaller changes in volume (~100mls) between repeats half to one hour apart, for instance. This was in order to reduce the impact of confounding large daily fluid shifts during acute burn resuscitation. In

practical terms, the acute burn inflammation also leads to rapid shifts of fluid and the quandary is whether the measurement of translocation of such small changes in oedema, on the background of such large fluid fluxes, is possible using any available method.

3.2.3 Study 3: Reliability of UL Water Displacement Volumetry In Acute Burn Patients

The 'gold standards' for measuring changes in limb volume are WDV and circumferential limb measures (CLM) (Casley-Smith 1994). CLM is more frequently used in the clinical setting due to ease of application (Shanley et al. 2002; Brown 2003). Despite popular use, CLM is demonstrably inferior to WDV for measurement of volume change as it lacks standardization of spacing, procedure and volume calculation formulae used (Latchford and Casley-Smith 1997; Sitzia et al. 1997). Further, in the burn setting, open wounds severely hamper the utility of CLM, rendering it non-feasible for assessment during the candidacy.

This study will firstly examine the reliability of whole arm WDV in healthy subjects to gain greater understanding of the sensitivity, standardization and application of a novel technique in the acute burn environment, with the aim of reducing patient burden. Then, the feasibility and safety of use in the acute burn environment will be tested.

Study 3 Hypotheses

1. WDV is a reliable measure of upper limb volume change.
2. WDV detects < 100mls of volume change between repeated, within-session measurements.

Study 3 Procedure

For each of 30 healthy subjects, whole UL WDV was repeated twice in a session. Subjects were recruited from RPH and Curtin University (WA) students and staff. Each person provided one single limb, randomized by coin toss, as the test limb. The UL was dried by the participant as the water vessel was topped up for reassessment. If reliability was established in healthy subjects, the same procedure would be used to assess reliability and sensitivity for up to 10 patients with burn to the upper limbs (Fig 3.4).

Data analysis: As noted in Section 3.2.1.

Ethics: This study was approved by RPH EC (# 2004/027) as a component part of the 3-D laser study as the trials did not include interventions (DVD Appendix, Folder C).

Significance: Literature presents the reliability and sensitivity of hand and forearm WDV but the use of whole arm WDV was relatively rare (Shanley et al. 2002; Sagen et al. 2005). The novelty of this study was borne of the fact that, as noted in Chapter Two, clinical or research use of whole UL WDV is not reported in burn literature.

Figure 3.4: Burn survivor commencing upper limb WDV measurement. NB Perspex upright in vessel base.

3.2.4 Study 4: Bioimpedance Analysis In Acute Burn Patients

Bioimpedance analysis (BIA) is a technique first used to accurately measure total body water (TBW) in 1969 (Hoffer et al. 1969). It is now commonly used to measure arm lymphedema following breast cancer surgery (Cornish et al. 1998). The technique quantifies body composition by measuring the impedance and phase angle changes in minute alternating, electrical current as it passes, via intact skin, through the body. In

the 1990's the US National Institute of Health defined BIA approaches according to the number of current frequencies applied while taking a measurement. Thus, BIA is described as single frequency (SFBIA); multiple frequency (MFBIA) (2 - 6) or bioimpedence spectroscopy (BIS) (7 or more). The detail of outputs, and amount of raw data, naturally increases with the number of frequencies and reduces the BIA reliance on population specific, derived constants and algorithms. However, it is unknown if the presence of burn wounds and, or dressings affects the reliability of BIA results. Zdolsek et al's (1998) underpowered study indicated the validity of BIA in acute burn patients and provided insight into the interpretation of findings during the inflammatory process. Miller et al's (1999), again underpowered, study indicated the clinical utility of the BIA method in burns. However, the understanding of BIA use in the acute burn phase and determination of the most appropriate BIA frequency cluster option lacked clarification.

A pilot study was completed (n=5) using the *Lymphometer® (Impedimed,* Brisbane*)*, available at RPH early in the candidacy. This machine was empirically reliable and application of the electrodes safe and feasible. However, further investigation confirmed that the single current frequency system lacked the sensitivity to address the research hypotheses. Subsequently, the *SFB7®* (*Impedimed,* Brisbane), a multi-frequency bioimpedance spectroscopy (BIS) machine became available at RPH in 2006. The following studies therefore investigate the use of BIS technique.

Study 4 Hypotheses

1. BIA repeated measurements are reliable in patients with burn wounds.
2. BIA repeated measurements are reliable across intact dressings and open burn wound conditions.
3. BIA is a valid measure of volume change in burn patients.

Study 4 Procedure

Patients were recruited if admitted to the RPH burn unit with an acute burn wound of any size. In this study, recruitment of 13 subjects was planned. Patients were excluded if they had a BMI outside the ranges stated by the SFB7 manufacturer or a burn location which precluded the standard application of the electrodes on intact skin.

BIS Reliability: Triplicate BIA measures were taken with open wounds to test clinical reliability of the BIA for burn patients (Fig 3.5). Secondly, triplicate measures for the intact old dressings (in situ > 8 hours) and new dressings (in situ ≤ 8 hours), were used

to examine the reliability across all wound situations. The patients were all tested in supine with a minimum of five minutes in that position to ensure a steady circulatory state after returning to bed from the shower, for instance.

BIS validity: Burn patient validity was determined through post-hoc analysis of the ability of BIS to determine differences between mean oedema volumes grouped by severity.

Data analysis: As noted in Section 3.2.1.

Ethics: This study was registered as a quality improvement project (CSQU # 080429-1) (DVD Appendix, Folder C).

Significance: For acute burn patients the potential advantage of BIA use was a novel, sensitive, non-invasive measurement of acute oedema fluid shift, taken in real time, whilst lying safely on a bed, wound dressings intact.

Figure 3.5: SFB7 BIA machine applied to a female patient with 6% TBSA burn to her right UL and LL. The electrodes are placed to derive whole body fluid composition.

3.2.5 Study 5: Polhemus 3-D Laser Scanning In Acute Burn Patients

The Polhemus FastSCAN System (PFS) is a 3-D laser light scanning system. The availability and combination of optoelectronic technologies with computer-assisted design (CAD), provides health professionals with a number of alternative methods to measure change in volume. Through the use of light, these techniques are non-contact in nature and as such, may provide novel solutions in the burn unit environment to the issues related to measurement of acute burn oedema (Mayrovitz et al. 2000). One such system, available at the RPH, was the *FastSCAN* Cobra® (Polhemus Inc,

Colchester, Vermont, USA) which uses a hand held laser scanner in combination with tracking software (Harrison et al. 2004). The *FastSCAN,* an extension of the *Fastrak*® technology (Day et al. 2000), was developed in New Zealand (*Applied Research Associates NZ Ltd*) to scan objects and surfaces in a multitude of medical, artistic and military applications (Biryukova et al. 2000; Polhemus 2007). This is the system examined for reliability and validity in the acute post-burn period.

Study 5 Hypotheses

1. The PFS 3-D laser scan measures are a reliable, valid and sensitive measure of upper limb volume in healthy subjects.
2. The PFS 3-D laser scan measures are a reliable, valid and safe measure of upper limb volume in burn injured subjects.

Study 5 Procedure

After providing informed consent, a 'Class A' laser line scanner was swept repeatedly over the subject's UL, chosen by random allocation. The PFS software orientates data from the handpiece camera and position reference transmitter to generate 3D digital surface maps in real time (Fig 3.6). The scanned 'object' data was then cleaned of light artefact. The truncated UL was processed using *Visual Tool Kit* (VTK) software to provide a volume for comparison to UL WDV validation measures.

Reliability: Initial development of this method included formulation of a standardised scanning procedure for the clinical environment, using inanimate objects (with the assistance of Mr Rob Day, Dept of Medical Physics, RPH) (Edgar et al. 2008a). Due to the technical complexity of laser scanning, duplicate trials (n=30) were completed to test reliability and sensitivity in healthy, uninjured individuals first. Subjects were testing in a standardised sitting position (Fig 3.6). The second phase of the reliability studies included testing on acute patients in the RPH burn unit environment (n=10). As the patient required their dressings removed during the procedure, and had maximal analgesia on board, they were tested in supine for safety. The same positioning rig was used in both portions of the reliability trial.

Validity: Due to the novelty of the application and logistics of comparison measures, single session UL WDV measures were planned for all of the healthy and burn injured participants. If reliability and sensitivity results were supportive of further investigation, serial PFS and UL WDV measures were planned to adequately power analyses.

Ethics: This study was approved RPH EC (# 2004/027) (DVD Appendix, Folder C).

Significance: All burns survivors suffer daily pain (Montgomery 2004) and inherently have increased risk of wound infection. The advantage of the PFS in the clinical environment is oedema volume assessment without contact to open burn wounds. Thus, it is painless and does not increase the risk of infection. Further, the low level laser light is not dangerous to the eye and does not require protective equipment.

Figure 3.6: The candidate performing 3D laser scanning of a healthy subject upper limb

3.3 Measures of Longitudinal Functional Recovery

Burn patient clinical data collection commenced at RPH in January 2006. The physiotherapist burn outcome battery (PT-BOB) was developed after a long period of development and burn team input, catalysed by the Bali bombings of 2002 (Edgar et al. 2005; Edgar et al. 2006). The RPH PT-BOB consists of self-rated questionnaires and physical tests of UL and LL joint range of motion (ROM), balance tests, LL coordination, functional ambulation and fitness. A description of all the measures included in the PT-BOB are provided in Table 3.1. However, discussion regarding specific cardiovascular endurance tests was not within the scope of this thesis and were not elaborated upon. Thus, the equivalent reliability and validity studies for the 'ball bounce' and shuttle tests were not within the scope of the following series of studies.

Table 3.1: Components of the PT-BOB including references.

Outcome Measure	Description of Procedure	Reliability and Validity in Burn Population
Disability of Arm, Shoulder & Hand *(Quick*DASH)	11-item, self report tool measuring *UL dysfunction* (Gummesson et al. 2006).	Nil.
Burn Specific Health Scale-Brief (BSHS-B)	40-item, self-report survey indicating *burn affected quality of life* (Kildal et al. 2001a).	Long form (80 item) validated for burn population (Blades et al. 1982a). Shorter versions (40-, 30-, 21-items) validated against earlier versions (Blalock et al. 1994; Kildal et al. 2001a).
SF-36 v.2 (Australia) Acute Recall	36-item, self report tool measuring overall QoL (Ware et al. 1993).	Nil.
Joint ROM: Goniometry – wrist, elbow, shoulder, knee, ankle.	Measurement of active and passive movement of a joint(s) with standardised procedures (Norkin and White 1988).	Nil.
Composite Finger Flexion	Functional combined movement into full finger flexion (composite fist) (Ellis and Bruton 2002).	Nil.
Hand Span	Linear distance between tips of pulp of thumb and little finger.	Nil.
Thumb Opposition	Thumb to finger movement scale (Kapandji 1986).	Nil.
Single Leg Stance (SLS)	Timed test of *static balance* with eyes open and eyes closed to a maximum of 30 seconds. Normal values available from the literature (Bohannon 1984).	Nil.
Timed Up and Go (TUG)Test	Timed test of *functional walking,* incorporating rising from chair, walk 3 metres, turn and return to sit again on the chair (Nair, Dobson et al. 1999).	Nil.
Tandem Walk (TW): Forward (TWF) & Backward (TWB)	Timed walking test of *dynamic balance* and coordination forwards and backwards over 3 metres (Nelson et al. 1994)..	Nil.
Ball Bounce (BB)	A RPH devised test of *UL function and endurance* that measures the number of times a person can bounce a standard 55cm ball against a wall above shoulder height in 2 minutes.	Nil.
Shuttle Run	A sub-maximal, incremental test of *cardiovascular (CV) endurance* (Leger and Lambert 1982; Leger et al. 1988). Normative values available.	Nil.

The confirmation of reliability, sensitivity and validity of the specific measures noted above was a novel concept and necessary for appropriate widespread use in the burn population. Burn patients pose unique challenges for physical measurement. For instance, during the acute and sub-acute periods they have oedema and variable thickness dressings in situ.

3.3.1 Reliability and Validity Trials of Longitudinal Outcome Measure Battery

Studies 6-8 Procedures

Reliability: Test-retest trials of PT-BOB physical tests on acute and sub-acute (healed) burn patients, were conducted in the clinical environment. Repeated measures (duplicate), inter-tester trials were conducted by a group of up to 4 physiotherapists, coordinated by the candidate. Using pre-determined standardised procedures two separate cohorts of patients were recruited for reliability studies of a) QuickDASH; b) goniometry and hand scale and linear measures; and c) balance, coordination and functional ambulation tests. Reliability studies for the SF36 were deemed unethical with 30+ papers clearly demonstrating this fact in general and patient populations (Turner-Bowker et al. 2002).

Validity: Prior to the commencement of data collection, the only reported valid measures in this population were the Burn Specific Health Scale (BSHS)(Blades et al. 1982c) and the Vancouver Scar Scale (VSS)(Sullivan et al. 1990). After trials of the original and shorter versions, the BSHS Brief was chosen for use as it provided the best balance between patient burden of assessment and sub-domain information for clinical responsiveness. The BSHS-B was used as the 'gold standard' reference for validity testing across the recovery timeframe of interest of one year, for the following analyses.

A team of physiotherapists coordinated by the candidate, collected burn patients' clinical outcomes data. Routine data collection occurred upon admission to the burns unit, at discharge, one month, three months, six months, 12 months and 24 months post-burn injury providing opportunity to examine the performance of various measures across the recovery timeframe. The PT-BOB tests analysed were the self-rated, well-being and functional surveys (BSHS-B, QuickDASH, SF-36) combined with the previously mentioned physical assessments (range of motion affected joints, balance (single leg stance), coordination (tandem walk tests) and lower limb functional measures (timed up and go). Clinical data collection commenced in January 2006.

Each test was validated against an appropriate burn population validated measure using EVIR statistical analyses described previously, using the available data. Temporal efficacy, or optimal contribution of each PT-BOB test at each review time point, will be assessed using longitudinal random-effects mixed regression modelling as noted in Section II.

Ethics: These studies were registered as part of the Burn Clinical Outcomes and Research Project (BCORP) (CSQU # 080429-1) (DVD Appendix, Folder C).

Significance: The demonstration of reliability and validity of individual outcome measures chosen has not been completed to date for the adult burn population. During the candidacy, the focus on longitudinal functional outcome measurement has reached a fever pitch in the international burn literature. However, few authors investigate the reliability or validity of their tools and when this is examined it is only in single tool studies. The combination of measures into a multi-faceted battery is a new concept in burn literature and provides a starting point for the development of a single objective benchmark for comparison of burn patients across the world.

3.4 Chapter Summary

The methodologies of the studies presented in this chapter were designed to provide clinicians and researchers with specific knowledge of: a) the temporal change in human acute burn oedema in macroscopic and microscopic terms; and b) a battery of objective tools to measure change or the long-term impact of change (interventions) at any point to one year post-burn. The studies were conducted throughout the course of the candidacy from 2001 to the present. The results of the studies are presented as both raw results and manuscripts in the Results (Chapter Four). The reader is therefore directed to the publications in that chapter for a detailed description of specific study methods and analyses to reduce repetition.

Chapter Four

Results

This chapter presents the results of the thesis investigations in three sections. The first outlines the new knowledge gained from the basic science trials investigating acute oedema for temporal changes during the immediate post-burn period. The second and third sections are presented as submitted or peer reviewed publications. All manuscripts were included with figures and tables unaltered from the original submitted format, in contrast to the thesis style. Acknowledgements, conflict of interest, funding statements and appendices were removed from each paper and placed in Appendix 1. References are listed in the order they appear at the end of the manuscript to reduce the necessity to return to the end of the thesis in order to cross-reference. Table and figure captions remain in situ but have been altered for ease of reference within the thesis. Australian English was interchanged with American English spelling when papers were published in that style. Discussion of the results and the synthesis of the new knowledge follows in Chapter Five except where Discussion was included in published or submitted manuscripts.

4.1 Acute Burn Oedema: Temporal Changes of Contents and Volume in Humans

The Review of Literature in Chapter Two demonstrated the limited knowledge of a number of parameters relating to human acute burn oedema. The studies presented below, performed in small patient samples, give an insight into the temporal change of acute oedema in the tissues after partial thickness burn. Discussion regarding the results presented in this section is presented in Chapter Five.

4.1.1 Oedema Contents

Results

Acute Burn Patients - Study 1

A total of 6 male patients were enrolled during the available study timeframe. The average burn TBSA was 10.8% (SD=2%, range: 8 – 14%). The average age of the group was 31.2 years (SD=12.4yrs, range: 18 – 48yrs). One patient (#4) withdrew from the study on day four as he was not able to tolerate the NPD (on his buttock) any longer. All available patient data were included in the analyses. One subject (#2) received formal fluid resuscitation after confirmation of an inhalation injury and

intubation though he had suffered 14% TBSA in total. The usual practice at RPH is to provide formal fluid resuscitation for injuries ≥15% TBSA in the absence of other injuries.

Temporal Protein Levels

The mean protein and albumin level results from this trial are shown in Table 4.1. The grouped total protein levels are compared over time in Figure 4.1. The sample distributions did not deviate significantly from normal. The differences between mean protein levels by sample were not significant. Trends towards statistical significance were evident. Paired t-tests indicated that mean albumin levels were significantly different between samples from day one and two (p=0.044) and days three and four (p=0.048). Further, the results demonstrated that protein and albumin levels for each sample over time were highly correlated (r=0.91) (Fig. 4.2). Mean protein levels were consistently greater than mean albumin levels ($p=4.7x10^{-9}$) (Table 4.1).

Table 4.1: Mean protein and albumin assay estimations by sample.

Sample # (n)	Mean Protein (SD) (g/L)	Mean Albumin (SD) (g/L)
1 (n=6)	14.83 (4.1)	9.50 (3.1)
2 (n=5)	25.60 (10.8)	**16.20 (7.4)**
3 (n=6)	33.33 (6.0)	**21.00 (3.6)**
4 (n=5)	38.00 (15.3)	20.20 (4.3)
5 (n=5)	30.20 (15.1)	19.83 (12.2)
6 (n=5)	35.20 (13.2)	**20.40 (6.5)**
7 (n=6)	21.33 (9.0)	**11.17 (5.4)**
8 (n=5)	25.60 (11.5)	14.40 (7.4)
9 (n=5)	30.40 (12.8)	17.20 (9.1)
10 (n=5)	30.00 (13.4)	15.40 (6.9)
11 (n=3)	36.67 (7.6)	19.00 (5.0)
12 (n=3)	34.00 (20.7)	18.00 (12.5)

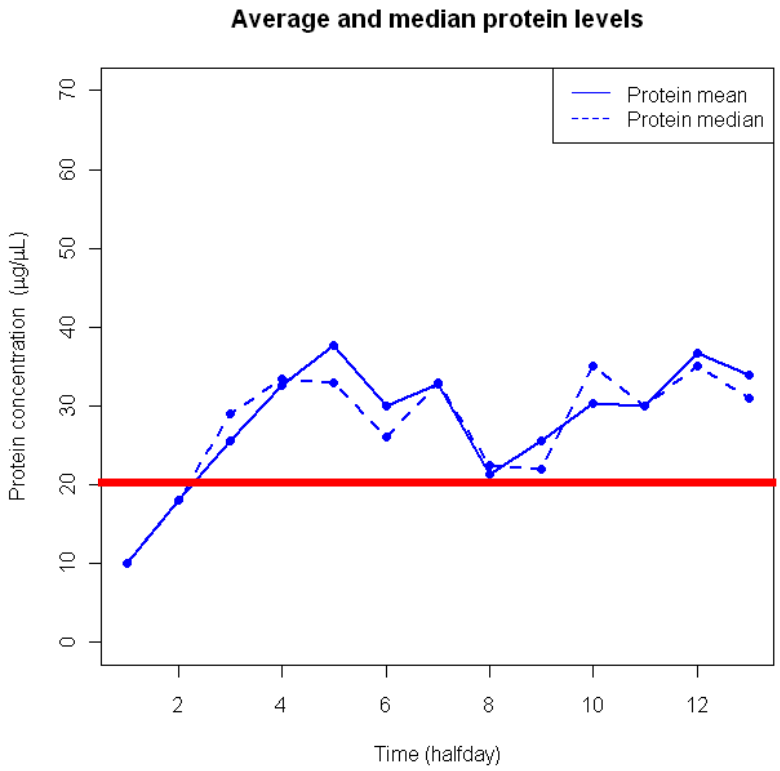


Figure 4.1: A graph of the protein concentrations in acute burn oedema samples demonstrating raised levels above physiological normal interstitial tissue level (red line) after day one post-burn.

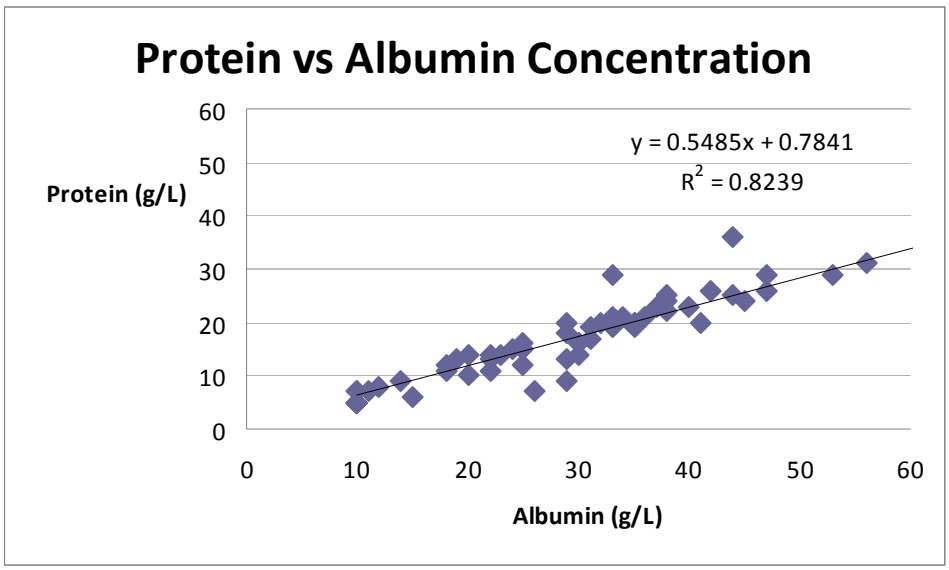
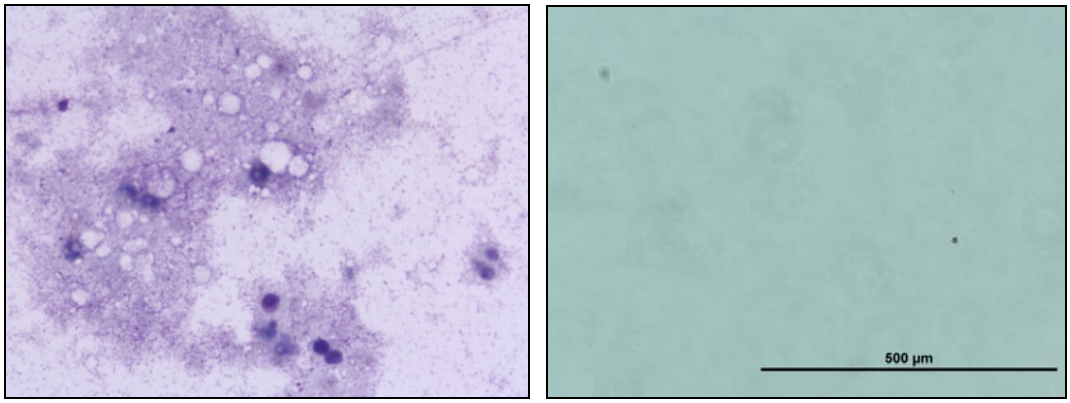


Figure 4.2: A scatter plot of acute burn oedema protein levels plotted against albumin levels.

Particle Size and Composition

Figure 4.3 shows a pair of typical images from the frozen oedema samples, taken through the standard microscope. On average 1.5% by weight (SD=1.8%; range: 0.08 to 8.13%) of the fluid sample was particulate matter as demonstrated by the image taken after the sample was passed through the micro-filter (Fig. 4.3.b).



(a) (b)

Figure 4.3: Acute burn oedema sample before (a) and after filtration through 100µm filter (b).

The Coomassie gel assay indicated that the majority of the protein particles in the samples had a molecular weight between 37 – 75kDa (Fig 4.4). The gel assay further confirmed that the size and relative amounts of protein did not change appreciably across all samples across the first week post-burn.

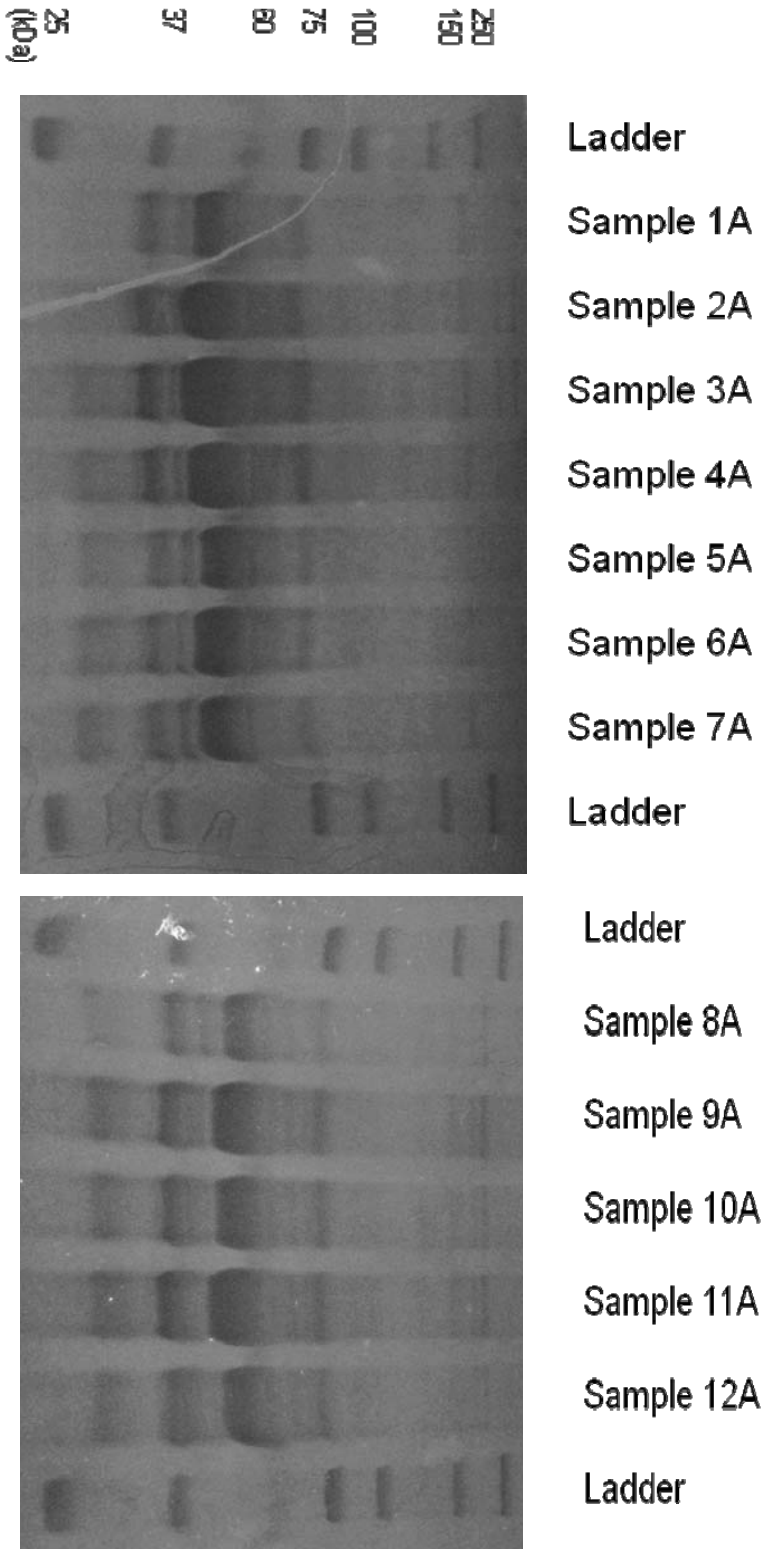


Figure 4.4: Study 1 Coomassie gel assay showing the relative quantity of protein by molecular weight across all samples. The ladder shows known weight markers for comparison.

4.1.2 Oedema Volume

Acute Burn Patients – Study 2

A total of 16 patients were recruited to this portion of the study, eight with bilateral UL burns. The mean TBSA was 18.7% (SD=8.9%; range: 0.5 to 30%) with an average UL TBSA of 2.1% (SD=1.5%; range: 0.5 to 4.5). The average age of the group, including 13 males, was 36.3 years (SD=16.3yrs; range: 15-68). Due to the clinical environment, a total of 17 arms were measured serially within the group, during the first week post-burn (Fig. 4.5). As stated in Chapter Three, data attained from the participants in Study 1, the NPD trial, were included to expand this trial.

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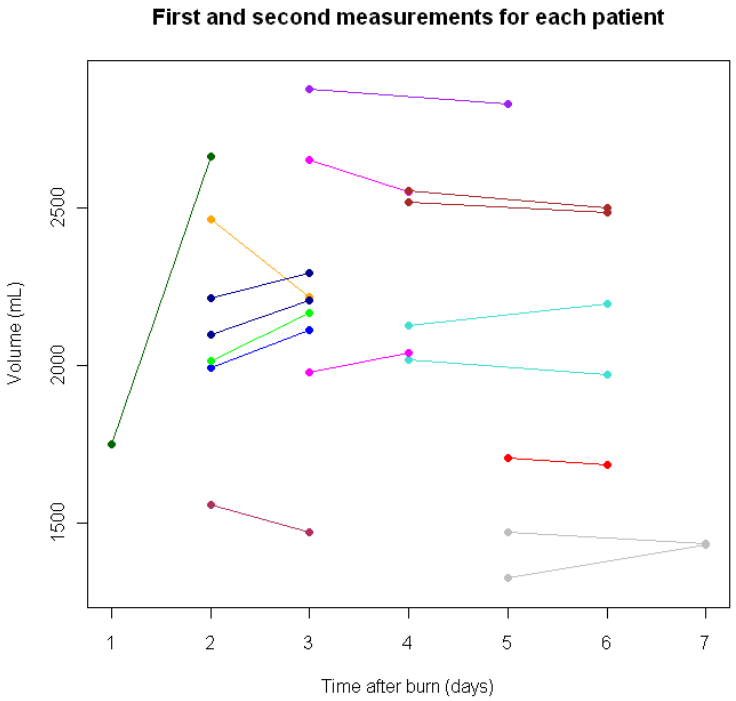
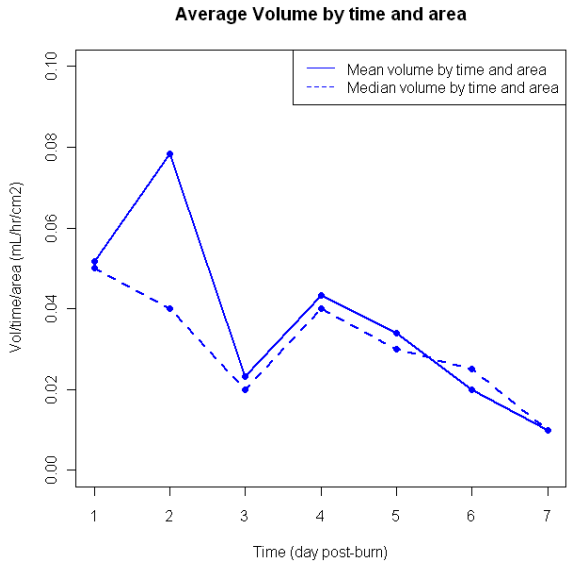


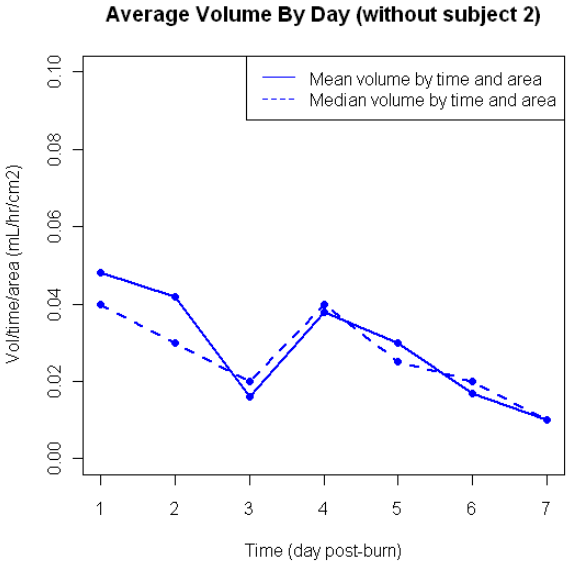
Figure 4.5: Serial UL volumetry measures mapped out by day post-burn. Each colour represents an individual.

Acute Volume Change

With serial water displacement measures, there was marked variability in UL volume and changes between individuals (range: 1.3 – 51.9% of the lowest UL volume measured) (Fig. 4.5). The variability was less pronounced in the NPD study group results though it appeared the change of dressing on day three post-burn affected the results (Fig. 4.6).



(a) n=6 patients



(b) n=5 patients

Figure 4.6: (a) Mean volume change per cm^2 of wound area calculated from the NPD study data. (b) The impact of burn size and resuscitation on oedema volume was demonstrated by the removal of subject #2.

The changes between serial volumetry trials were reduced after day four post-burn (Fig. 4.7). The serial trials from one patient's arm (subject #1) were removed from the absolute volume change analyses as his oedema volume change between day one and two indicated a systemic response (+902 mls or ~51% of limb volume) which was

unchecked as he was medically unwell prior to sustaining his burn injury. He was 66yo with a 24% TBSA burn, including only 0.5% on his tested limb. Further, he was unique within the group as the patient with a serial measurement between days one and two. His data were difficult to compare for these reasons. The adjusted group results indicated that the absolute rate of change of measures after the second post-burn day was less than 250mls (range: 1.3% - 11.1% of lowest UL volume measured) while the average change was ~100 mls (Fig. 4.7). The direction of change was not consistent in this study cohort after the second post-burn day.

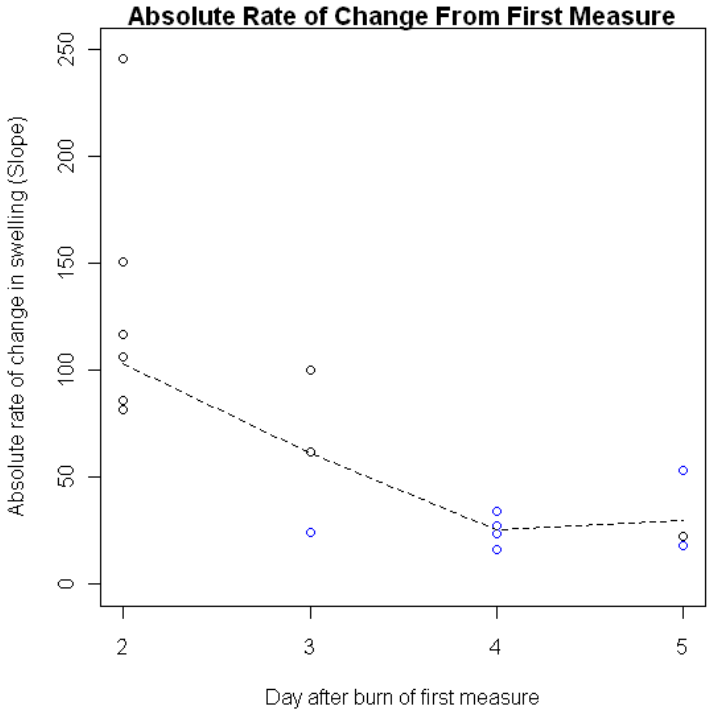


Figure 4.7: The dashed line represents the mean volume change between serial UL measures related to the first day of measurement. Subject #1 omitted from the analysis.

4.2 Measures of Acute Burn Oedema

4.2.1 Paper II: Whole arm water displacement volumetry is a reliable measurement technique for acute volume change: Caution with clinical use and research design in patient populations.

Submitted: Lymphology, September 2009.

Introduction

Edema in the tissues is associated with numerous pathological processes and trauma. Objective measurement of edema volume change in response to an intervention, is an important component of clinical decision making and research. Measurement of acute edema change, such as after burns or trauma, poses greater challenges than encountered during measurement of chronic swelling. Firstly, the physical condition and environment may hinder access to or mobility of the patient and therefore, compromise the technique to the point of being insensitive, or invalid. Secondly, the rapid acute change of underlying patho-physiology and, or body response necessitates certainly more frequent, and potentially 'real time', measurement of volume change in order to achieve accurate assessment. Lastly, the acute condition, or medical management, may confound measurements taken over extended time frames. Examples of potential studies include the assessment of edema interventions during the formal fluid resuscitation period after acute burn injury (Demling 2005) or measuring the effect of using ice after acute sports trauma (MacAuley 2001).

The most objective, and time responsive methods of measuring limb edema, currently available, include magnetic resonance imaging (MRI), computed topography (CT) scans, bioimpedence analysis (Cornish et al. 1998) and ultrasound (2000; Caulfield et al. 2008). Other methods less commonly used include 3-D laser scanning (Johansson and Oberg 1998; Edgar et al. 2008a), infra-red scanning (Stanton et al. 1997b), DXA scanning (Przkora et al. 2008), Xenon scanning (Porter and Swain 1986) and stepped fluid compression apparatus (Stanton et al. 2000).

These techniques all lack validation and, or clinical utility or feasibility for acute edema measurement. The 'gold standards' for measuring limb volume change in a clinical environment are water displacement volumetry (WDV) and circumferential limb measures (CLM) (Casley-Smith 1994; Box et al. 2000). CLM is more frequently used in the clinical setting due to ease of application (Shanley et al. 2002; Brown 2003). For

chronic edema states, literature suggests detection of volume change more than 150 - 200mls (or > 10% arm volume) per week, to be adequate for informed treatment decisions (Box et al. 2002). Both methods have been demonstrated to be sensitive enough to detect changes of such magnitude (Boland and Adams 1996; Karges et al. 2003). However, despite popular use, CLM is demonstrably inferior to WDV for measurement of volume change as it lacks consensus regarding the standardization of spacing, procedure and volume calculation formulae used (Latchford et al. 1997; Sitzia et al. 1997). This fact alone negatively impacts on the clinical utilization and efficacy of the CLM technique. Further, the *estimate* of volume is reliant on arithmetic formulae informed by pressure sensitive and subjective measures. Consequently, there is greater method error, particularly for an inter-rater repeated measures construct (Stanton et al. 1997b). Due to this, CLM is not interchangeable with WDV and lacks the theoretical construct validity to provide meaningful absolute volume change data for comparison between individuals, as might be expected in clinical practice or research (Megens 2001; Karges et al. 2003). All of these facts limit the sensitivity of CLM in the measurement of rapid changes of edema present in acute injury states.

In contrast, WDV has been demonstrated to provide, on the same day, limb intra- and inter-tester volume estimates that are highly correlated (ICC $\geq$ .98) (Farrell et al. 2003; Sagen et al. 2005). However, these particular studies do not completely describe the reliability of whole arm measures. Moreover, the studies do not indicate if the time between repeated trials affects results (Atkinson and Nevill 1998; Dunn and Roberts 1999).

Thus, the aims of this study were to examine the reliability, sensitivity (minimum detectable difference) and interaction of time on whole arm within session, repeated WDV measurements in the non-injured population.

Methods

Subjects

Two groups of non-injured working-aged individuals participated in this study as part of methodology trials for a clinical study approved by Royal Perth Hospital (RPH) Ethics Committee (Ref # EC 2004/027). The participants were employees or students at RPH or Curtin University of Technology, Western Australia. A third, pilot group was tested in the same way during a trial to examine the reliability and validity of 3-D laser scanning in an acutely injured burn patient population (Edgar et al. 2008a). They were included if they had suffered an upper limb burn injury and were admitted to the RPH adult burn

unit. The most relevant time between trials was chosen upon the results from uninjured participant trials.

Procedure

Uninjured Participants: One investigator completed all repeated trials, with the same equipment, at both facilities to minimize error introduced by recruitment of subjects at two facilities. Upon provision of informed consent, the measurement limb was randomized by coin toss for the uninjured groups. The first uninjured subject group (Group T_{10}) repeated the following procedure with 5 – 10 minutes between immersions. The second uninjured group (Group T_{20}) repeated the procedure with 20 – 30 minutes between immersions.

Prior to and between measurements the subjects were free to move between sitting and standing while completing their usual work or study duties. Subjects who wore long sleeves rolled them down between the T_{20} trials to standardize conditions for these individuals. The subjects who completed the shorter repetition trials did not roll down their sleeves between trials. All subjects remained indoors in a temperature-controlled environment which was similar for both sites. Further, they did not engage in strenuous activity between or before measurements.

The subject commenced the measurement, positioned in standing, adjacent to the water displacement vessel which rested on a wheeled trolley (Fig II:1). Long sleeves were rolled up and jewelry removed prior to immersion of the limb in the water. The container provided a standing column of water ~75 cm in height. A vertical piece of Perspex attached to the floor inside the vessel provided a repeatable immersion depth for each individual. The final position of the immersion was standardized by instructing the subject to hold their limb steady at a depth when the web space between ring and middle fingers lightly touched the upper edge of the mount. The subject was instructed to slowly immerse the arm into the water, keeping the wrist neutral and moving elbow into full extension. Each person then held the final position until single drips of water from the overflow spout were more than one second apart by visual inspection. Water expelled from the vessel was captured in a plain plastic bucket and weighed as quickly as possible (to the nearest .01g) using electronic balance scales (Model FP-12K, *Bamrico*, WA). The weight of the dry bucket was subtracted from the combined weight and recorded as the volume of water displaced during the trial before moving onto the second trial. During the time between trials, the subject dried their arm thoroughly and for the T_{20} trial, returned clothing to its original state.

Farrell et al (Farrell et al. 2003) implicated a number of environmental variants as sources of possible systemic error for the WDV technique. These were controlled for in the following ways:

A) *Aeration of the water*: minimised by letting the water stand for at least 10 minutes when first filled. Refilling the vessel after each immersion was completed by slow hand pouring from a jug rather than a hose. Finally, as stated previously, subjects were instructed to immerse their limb very slowly to reduce aeration.

B) *Resolution of the measurement cylinder*: overcome by the use of weighing scales (accuracy to +/-0.1g).

C) *Temperature of the water*: the vessel was filled and used at room temperature. Previous studies indicate that water temperature may contribute to limb volume changes outside the ranges of 20 - 32°C (Boland et al. 1996). Random water temperature assessments ranged from 23.1 – 23.4°C during the study.

D) *Patient posture and forearm position*: controlled by standardized instructions specifically drawing the subjects' attention to the speed of arm movement and position of the elbow, wrist and hand as their limb was moved into the vessel to reduce measurement error. The patient remained standing and did not move their feet during immersion of their arm.

E) *Perspex upright contact pressure:* again addressed by the standardised instructions.

Acute Burn Pilot Group (ABPG): Between November 2004 and April 2005, burn patients were recruited in a random sample of convenience. The upper limb tested was that allocated as the most severely injured according to the largest burn wound area. The patients were tested during their routine dressing change and shower procedures. The testing procedures were the same as that used for uninjured participants except that, as a precaution, patients wounds were covered with a temporary dressing between trials. The dressing consisted of burn gauze soaked with 2% chlorhexidine, held in position by tubular net. The same investigator assessed the ABPG using the T_{20} protocol as detailed above.

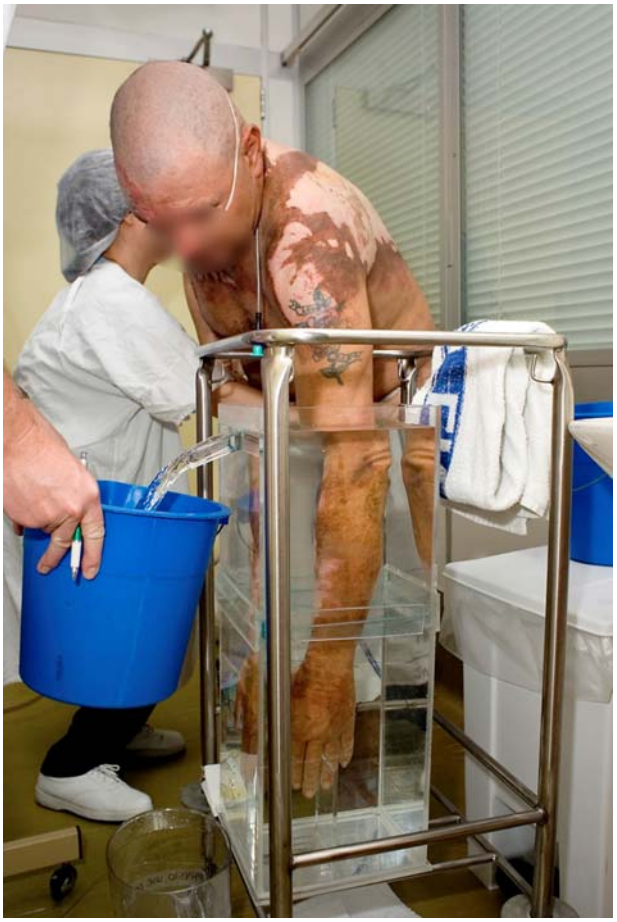


Figure II:1: Major burn survivor demonstrating the use of WDV technique to monitor acute arm swelling in the clinical environment.

Data Analysis

All analyses were executed using SPSS V.17 (SPSS Inc., Chicago, Illinois).
Variables are summarised as mean (X) and standard deviation (SD).

For each uninjured group, 30 subjects were planned for recruitment to appropriately power the analyses of duplicate measures, allowing for possible drop-outs (Donner et al. 1987). The ABPG were those recruited during the allotted research timeframe.

Reliability components were assessed as concordance, described by intraclass correlation coefficients ($ICC_{(2,1)}$); variance, expressed as 95% confidence intervals (95% CI); systematic difference (significant at $p<0.05$) and sensitivity or minimum detectable difference (MDD). The MDD was used for its clinical relevance and defined as the magnitude of real change that is measured with 95% surety using repeated tests such as would be used to assess a treatment intervention, for instance. It is calculated using the standard error of the measures (SEM) where the sample is the

differences between paired trials: MDD = SEM x $\sqrt{2}$ x $t_{(df,.05)}$ (Bland and Altman 1999). The minimum standard for concordance was set at ICC > 0.90 (Fleiss 1986).

Any interaction on the WDV measures by population sampled was examined using a two sample t-test. The group means of between-trial differences were tested in a two-sided, unpaired comparison. Shapiro-Wilk tests confirmed grouped difference data normality and an F-test demonstrated similar variance between the T_{20} and ABPG data (F=0.611; p=0.346).

Finally, to determine if arm sleeve length impacted on the uninjured subject results, a two sample t-test (two-sided, unpaired) examined the T_{20} patients post-hoc. The t-test was appropriate as Shapiro-Wilk tests confirmed the normality of the volume differences between trials and an F-test confirmed that the variance was not significantly different between sleeve length sub-groups (F=0.684; p=0.472). The T_{10} subject and ABPG data were not tested as their upper limb conditions remained the same throughout the study. Post-hoc results are presented as sub-group group means, F statistics and p values.

For ease of description, measurement units were interchanged such that 1 gram of water (gH_20) at room temperature was equivalent to 1 cubic centimetre (cm^3) in water volume (King 1993).

Results

Subjects

Uninjured: The subjects were all of working age ranging from 18-63 years. The T_{10} group (n=30) included 8 females while the T_{20} group (n=30) contained equal numbers of males and females. Seventeen of 30 subjects immersed their right arms in the T_{10} group while the ratio was reversed in the T_{20} group. Both groups had 13 subjects who wore long sleeves on the trial day.

Burn Patients: Seven patients were recruited with a mean age of 35.9 +/- 17 years (range 15 – 66), including two females. The size of burn on the tested limbs ranged from 0.5 to 6 % (X_{UL}=3 +/- 2.1%) of the total body surface area (TBSA) with the right arm being the most injured (tested) in 6 patients.

WDV Reliability

Uninjured: Table II:1 displays the reliability and sensitivity results for each repeated measures trial group. The volume displaced ranged from 1353.7 – 2339.1 gH_20. The analyses indicated that a significant systematic bias was present when the repeated trials occurred <10 minutes apart. The magnitude and direction of this subject-by-method interaction is illustrated by the Bland-Altman plot (Bland and Altman 1995)(Fig. II:2).

Burn Patients: Due to the small numbers, the burn patient reliability analyses were not considered appropriate. However, the MDD was estimated at 96.6mls (X_1=1897.5 +/- 439.4ml; X_2=1881.4 +/- 424.9ml; SEM=28.93mls; t=2.36).

Table II:I: Statistics for repeated WDV measures grouped by time between trials.

Statistic	**Group T_{10}** **<10 min apart** (n=30)	**Group T_{20}** **20 - 30 min apart** (n=30)
X_{Trial1} (SD) (gH_20)	1897.8 (359.9)	1749.6 (279.8)
X_{Trial2} (SD) (gH_20)	1907.0 (360.2)	1754.0 (279.3)
ICC (95% CI)	.999 (.997-.999)	.997 (.993 - .998)
Mean Difference (gH_20)	**9.2 (p= .008)**	4.8 (p=.297)
$MDD_{(29,\ 2.045)}$ (gH_20)	36.3	46.2

Interaction of Population on WDV Measurements

The comparison of uninjured and acute burn sample average arm volumes indicated a significant difference between the groups (t=4.38; mean difference = -16.08gH_20; 95% CI's =0.18-40.76). The burn patients on mean arm volume was less on the second trial in contrast to uninjured subjects where the mean volume increased marginally.

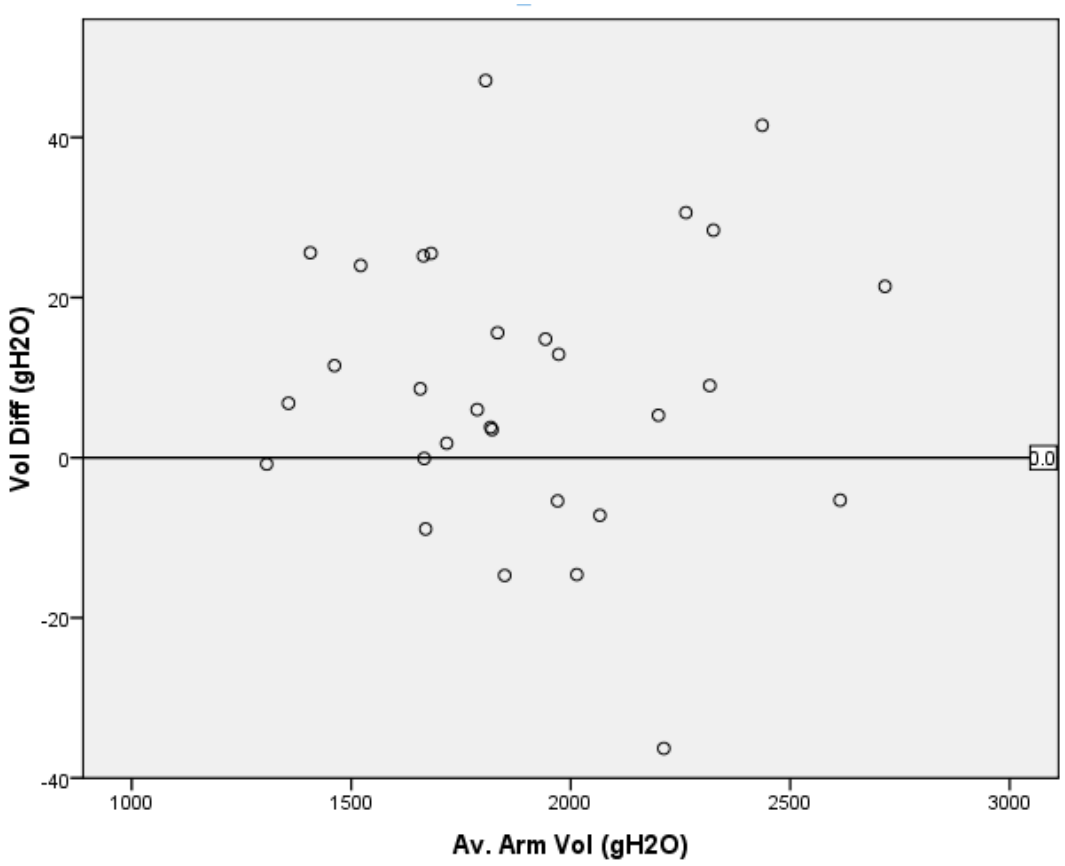


Figure II:2: Scatter plot of T_{10} trial average arm volume against volume difference between trials illustrating the magnitude and consistency of the direction of limb volume interaction with WDV.

Impact of Sleeve Length on WDV Reliability

The post-hoc analyses did not indicate any significant interaction related to the length of sleeves worn tested in uninjured subjects 20-30 minutes apart ($t_{28,2}$=1.52; p=0.14) (Fig II:3).

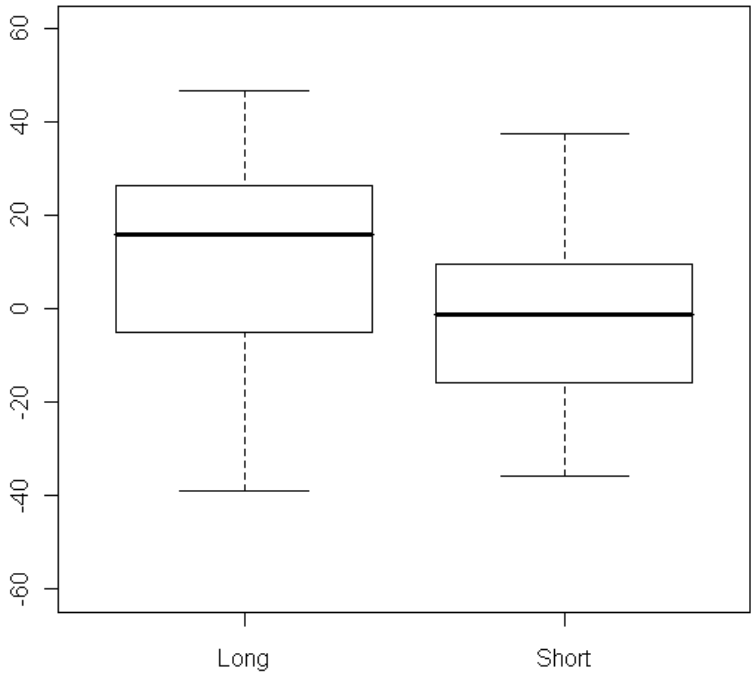


Figure II:3: Boxplot of T20 trial differences by sleeve length confirming that sleeve length did not significantly impact on the results.

Discussion

A primary aim of this study was to confirm the reliability of WDV as a method of whole limb volume measurement. The results demonstrate that the method is a reliable measure of whole upper limb volume, using room temperature fluid, if used greater than 20 minutes apart. Further, the range of ages in sampled subjects indicates applicability of these results broadly across the adult population.

The secondary aim of this study was to examine the sensitivity of the technique for whole arm measurements. The results show that WDV can measure, with 95% surety, changes of < 50 mls of fluid volume in a whole upper limb (Table II:1). This indicates that the technique is a sensitive tool for researchers and clinicians to use in the measurement of change in upper limb volume in response to treatment interventions.

However, the data indicate that the time between repetitions of WDV measures impacts on the results. The unexpected result relates to the significant subject-by-method interaction or, systematic bias, indicated between immersions conducted <10 minutes apart. In 75% of repeated trials, in the absence of pathology, a net increase

was demonstrable in response to the *measurement technique* alone. In this study, the water used for the measurements was at room temperature (~23°C) within a typical clinical, climate-controlled environment. The differential between this and the external body temperature was postulated to have caused a vasodilation (thermoregulatory) response immediately after immersion though it was not possible to investigate the specific cause with the available data. While the results confirm the sensitivity of the WDV measure, in uninjured limbs, a maximal discrepancy between trials of 47mls was measured. This constituted a 2.6% change of the individual's upper limb volume. In the context of clinically significant change, indicated to be ≥150mls, the confounding interaction contributed up to ~30% error. Further, the bias was measured in the direction of a false negative, masking the effect of an intervention. The reader may, however, question the clinical implications of these results based on the mean data presented which are much less compelling. Alternatively, the reader may dismiss the implications by finding it difficult to imagine what type of clinical situation may call for such rapid volumetric assessments. However, were the subject-by-method interaction to compound in acute patients the masking of treatment effect may be significant. For instance, during inflammatory period after acute trauma, the differential between room temperature water and the tissues is often greater. A rapid and more reactive vasodilation response could be expected, compared to that measured in this study and, or it may not settle within 20 minutes depending on any concomitant vascular or autonomic nervous system pathology. The results indicate that researchers and clinicians must carefully consider the construct of their measurement strategies for changes in acute swelling.

To test this further, the small pilot sample of acute burn patients were tested. The preliminary results indicated that WDV measures decreased on average at the second trial and the mean differences between the uninjured and burn group were significantly different. This is an interesting result, suggesting that specific testing of the reliability of WDV for patient populations and measurement conditions was again indicated.

A number of limitations are identifiable in this study. Firstly, differences existed between the groups with respect to the rest time protocol. Due to the logistics of measurement, the T_{20} group returned their long sleeved clothing to its original position if they had them. This may have impacted on the response to immersion. However, the post-hoc analyses did not indicate any significant interaction by the clothing worn by the subjects. When considering the burn patient group, however, the application of

cold, moist dressings may be implicated as the cause of the direction of limb volume change. Further study of this situation is therefore warranted.

Future Studies

Any future intervention studies, in specific patient populations, particularly after acute injury, should validate the use of whole arm WDV as an appropriate measurement tool in the research or clinical environment before commencing. An alternative is to incorporate a reliability trial designed as the assessment strategy for a control group during a randomized trial, for instance. A corollary to this suggestion is that researchers and clinicians may use the WDV technique for acute edema measurement necessitating repeated measures at least 20 minutes apart, if there is no suspicion of abnormal thermoregulatory responses in the patient group.

Conclusion

The results of this study demonstrate that water volume displacement is a sensitive and reliable measure of whole upper limb volume change if used at repeated time intervals >20 minutes apart. Researchers and clinicians who wish to assess the efficacy of (acute) edema interventions must consider the construct of their assessments or studies in light of these findings.

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4.2.2 Paper III: Measurement of acute edema shifts in human burn survivors – the reliability and sensitivity of bioimpedance spectroscopy as an objective clinical measure.

Published: Journal of Burn Care and Research, 2009.

Introduction

Acute burn edema negatively impacts on burn wound healing (Demling 2005). Improvements in treatment for acute burn edema have stalled in comparison to other areas of burn care. A major impediment to clinical research in this area is the lack of a sensitive, objective method of measuring edema in patients with acute burns. Unique assessment challenges encountered in patients with burns include large areas of open wounds, pain and the associated use of behaviour modifying medications, dressings, impaired patient mobility and, when assessing an intervention immediately post-burn, the need to measure small volume shifts on the background of large resuscitative fluid movements.

Currently, the most popular clinical edema measurement for the limbs is volume estimates from circumferential limb measures (CLM) (Shanley et al. 2002). However, inter-rater reliability is poor (Boughey and Rogers 2000). In the acute burn environment, CLM poses increased risk of infection and pain due to the contact of the tape measure with the open wounds. Further, the method was demonstrated to be insensitive to small changes (< 200mls) in limb volume (Box et al. 2000; 2002).

The gold standard for accuracy in limb edema measurement is water displacement volumetry (WDV) (Casley-Smith 1994). However, this method is cumbersome and poses patient and staff safety issues, especially if measuring whole limbs, due to the equipment bulk and weight of water required. Further, volumetry and CLM cannot easily provide volume information about the trunk or head and neck.

In contrast, bioimpedance analysis (BIA) is a technique first used to accurately measure total body water (TBW) in 1969 (Hoffer et al. 1969). It is now commonly used to measure arm lymphedema following breast cancer surgery (Cornish et al. 1998). The technique quantifies body composition by measuring the impedance and phase angle changes in minute alternating, electrical current as it passes, via intact skin, through the body's tissues and fluids. In the 1990's the US National Institute of Health defined BIA approaches according to the number of current frequencies applied while

taking a measurement. Thus, BIA is described as single frequency (SFBIA); multiple frequency (MFBIA) (2 - 6) or bioimpedence spectroscopy (BIS) (7 or more). The detail of outputs, and amount of raw data, naturally increases with the number of frequencies and reduces the BIA reliance on population specific, derived constants and algorithms. For instance, SFBIA lacked precision and overstated whole body fluid changes in organ failure patients, exhibiting a standard error of the mean (SEM) 4 times that of a normal control group (Foley et al. 1999). BIS has been shown to be more sensitive than MFBIA post gastric bypass surgery (Dobratz et al. 2007). Further, BIS was shown to be more sensitive than CLM for chronic edema states (Cornish et al. 1996) and to be an accurate and valid measure of small volumes of swelling flux during short periods of standing (Seo et al. 1995).

BIA reliability has been described in other patient populations (Kushner 1992). The manufacturer notes up to 10% variability in healthy participants, dependent on the type of BIA machine. Where careful attention is given to subject preparation, typical variation for within session measures ranges from 0.3 to 3% for multiple frequency devices (per manufacturer's specifications).

As BIA equipment is portable and measurements are non-invasive, pain free and require no contact with open wounds; it may provide a solution to certain hurdles faced when measuring acute edema after a burn injury. In particular, if reliable across multiple dressing conditions, BIA may offer a non-invasive measurement option with dressings in place. The conceptual merit of BIA after acute burn injury was previously described by Miller et al (1999) and Zdolsek et al (1998). However, these studies lacked power or were not designed specifically to make statistical inferences regarding reliability in the unique burn population. It is not known whether underlying fluid shifts, wound areas and, or dressing conditions confound BIA results.

Thus, the aims of this study were to: a) examine the reliability of BIS volume measurements under different burn dressing conditions, in the clinical environment; b) to quantify the sensitivity or minimum detectable difference (MDD), in BIS measures and c) to determine if TBSA (burn severity) impacted on the reliability of BIS measures.

Methods

Subjects

Patients admitted to the burn unit at Royal Perth Hospital (RPH) were consented into the study in two phases (Phase I: 2006 and Phase II: 2008). Patients were included irrespective of burn size or depth. Participants were excluded if, when assessed with dressings removed, they showed signs of local wound infection (Silla et al. 2006), or the burn area completely precluded standardised application of electrodes; or if their body mass index (BMI) was less than 10 kg / m^2, at first BIS measure. Manufacturer's contraindications also excluded patients with cardiac pacemakers and, or electronic life support devices and pregnant patients. As this was a surveillance trial, all patients signed informed consent documentation and the study was registered with the RPH Clinical Safety and Quality Unit (CSQU # 080429-1), a subgroup of the RPH Ethics Committee, as part of the Burn Clinical Outcomes and Research Project (BCORP).

Equipment

BIS: The *ImpediMed* SFB7 (*ImpediMed*, Brisbane, Queensland, cost ~ $AUD15000) was used to collect tissue composition and fluid variables. The equipment applies 256 discrete current frequencies (4-1000Hz) to interpret each measurement. Output includes direct impedance data in addition to derived values. Important to this study, BIS computes absolute values of whole body extracellular fluid (ECF), intracellular fluid (ICF) and TBW. The algorithms for these values are stable with BMI > 10 kg/m^2 as per the manufacturer. During Phase I, the equipment was on loan from the manufacturer. After a period to assess the product and preliminary data, the Burn Service of Western Australia purchased the SFB7 for use during Phase II.

Data collection

To examine reliability, BIS measurements were collected for each dressing condition in triplicate. A sample size of 13 patients per condition was planned, a priori, to adequately power the analyses (α=0.05, β =0.2) (Donner et al. 1987). Height and weight are required for BIS algorithms. These values were taken prior to application of the BIA electrodes.

BIS Reliability Phase I – all dressing conditions: BIS data were collected, as able, before, during and after a burn dressing change. The 3 dressing conditions were defined as a) old dressing, in situ > 8 hours; b) open wound or dressing removed; or c) new dressing, in situ ≤ 8 hours. Electrodes remained in situ between triplicate measures but were replaced at each new dressing condition as patients showered

while dressings were removed. This emulates clinical use of BIS and further, reduces artificial reduction in error between repetitions and possible over-statement of sensitivity and narrowing of confidence intervals. Patients were positioned supine, with the electrode applied on intact skin, with minimal or no deviation from standard, left limb midline configurations as indicated by the manufacturer (Fig. III:1).

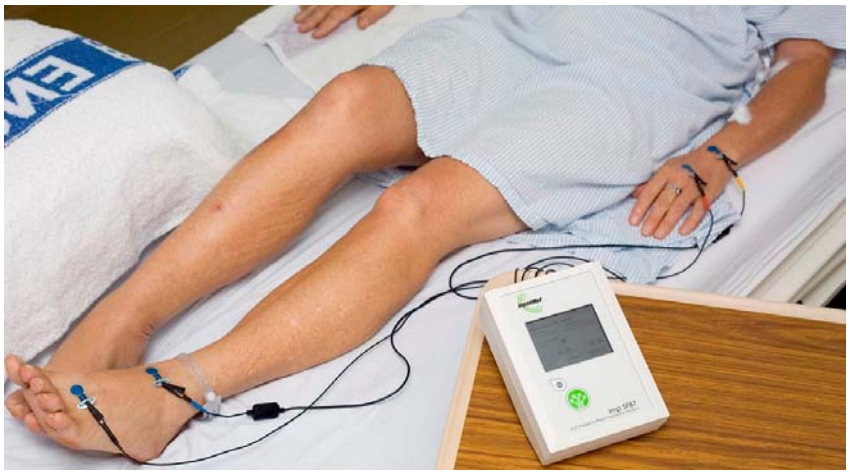

Figure III:1: Typical electrode placement and SFB7 machine in foreground for whole body measurements on a patient with 6% TBSA.

BIS reliability Phase II - old and new dressing conditions only: The coordination of data collection in the acute clinical environment led to missing data for the old and new dressing conditions. Thus, a second group of patients was tested as previously with their dressings in situ. Testing in this phase did not include patients with their dressings removed.

Validity: BIS validity has been demonstrated in a number of patient populations but has not been reported in acute burn patients. A method comparison study to demonstrate the absolute accuracy of BIA against a gold standard, such as WDV, must adhere to statistical protocols (Bland et al. 1995). To adequately power such studies, ~200 paired observations with a constant state between repeated single measures, are necessary (Dunn et al. 1999). Clearly, such analyses are beyond the scope of this study though severity sub-group analyses are designed to investigate the construct validity of the BIA technique (see *Data Analysis*).

Data Analysis

Results were analysed using SPSS (V.16) statistical software. Repeated measures ANOVA (absolute consistency) was performed to examine the components of reliability. A two-way mixed model was chosen as SFB7 results are not generalizable

to other forms of BIA. Reliability is presented as concordance by intraclass correlation coefficient (ICC: acceptable 0.75 - 0.89; excellent ≥ 0.9) (Portney et al. 2000); variance, estimated as 95% confidence interval (95% CI) and, systematic bias between trials (considered significant at $p < 0.05$). Data are reported using mean (X) and standard deviation (SD) with statistical differences from t-test quoted where appropriate.

The sensitivity of BIS was quantified by the MDD as per the formula:

$$MDD = SEM^* \times \sqrt{2} \times t_{(df,.05)}$$

(where *SEM = standard error of the residuals between repeated trials) (Bland and Altman 1996).

The MDD is the magnitude of real (volume) change measureable with 95% sureness. It provides a robust indication of clinical utility of a measure. One set of triplicate measures per individual was included within each sensitivity analysis by dressing condition.

A two-way repeated measures ANOVA was performed to examine the impact of TBSA (severity) on the reliability of BIS measurements and provide preliminary indications of validity of the BIS technique in burn patients. To make meaningful comparisons, the reliability of a minor burn (≤10% TBSA) was compared with a moderate burn (11-30% TBSA) sub-group, rather than an arbitrary halving of the grouped data. If a statistically significant difference existed between the mean fluid volumes of the sub-groups defined by markers of injury severity, this indicated that BIS exhibited construct validity. Where Mauchly's test of sphericity was violated ($p<0.05$), p values are presented following a Greenhouse-Geisser correction.

Results

Demographics

Twenty-one subjects were recruited during both phases of the trial. A total of 22 patients were approached during the two prospective recruitment periods, one patient declined involvement and data from one patient (male, patient 8) had to be excluded. The patient was removed from analyses after it was noted, during data extraction from the SFB7 machine, that it had malfunctioned. The system was subsequently replaced by the manufacturer, before patient #9 was recruited.

The average age of the group (n=21) was 35.86 years (SD = 13.27 yrs, range 16 – 67) including 17 (81%) males. All patients were measured on, or before, 5 days post-burn,

with 67% (n=14) tested on day 1 or 2 post-burn. The mean total burn surface area (TBSA) was 10.45 % (SD = 9.02%, range 1 – 30). Six patients had TBSA ≥15%. The average BMI for the group was 26.47 kg/cm^2 (SD = 4.26, range = 18.18 – 34.09).

Reliability and Sensitivity

Table III:1 presents the analyses of reliability and calculated MDD of BIS measurements for each dressing condition. The final patient numbers for each dressing condition analysis were: old (n=13); open (n=12) and; new (n=14).

Table III:1: Absolute volume results, reliability and sensitivity analyses for all 3 dressing conditions.

Volume Measured	Dressing Condition	Mean (SD) (L)	ICC (95% CI)	F Value (p value)	MDD (L)
TBW	*Old*	46.29 (10.56)	0.993 (0.983-0.998)	1.65 (0.213)	2.61
	Open	46.07 (8.98)	1.00 (1.00-1.00)	0.17 (0.841)	0.36
	New	46.99 (14.89)	0.998 (0.996-0.999)	0.75 (0.482)	1.89
ECF	*Old*	21.99 (6.57)	1.00 (1.00-1.00)	1.21 (0.316)	1.20
	Open	20.39 (4.78)	1.00 (1.00-1.00)	0.86 (0.439)	0.09
	New	20.67 (5.16)	0.999 (0.997-1.00)	0.85 (0.439)	0.54
ICF	*Old*	24.3 (5.89)	0.976 (0.940-0.992)	1.57 (0.228)	2.76
	Open	25.68 (4.58)	1.00 (.999-1.00)	0.11 (0.901)	0.31
	New	26.33 (10.27)	0.994 (0.986-.998)	0.75 (0.482)	2.34

Impact of Severity

The results of repeated measures ANOVA analyses for BIS data are shown in Table 2. The minor and moderate burn sub-group analyses show that reliability of BIS is not affected negatively by TBSA. For all variables, across all conditions, the BIS demonstrated that smaller TBSA burns had lower mean volumes of TBW, ECF and ICF than the larger TBSA subgroup (Table III:2). Statistical significance was reached in 6 of the conditions (Table III:2 in bold). Body weight demographics were not significantly different (p=.646) between groups: $X_{\leq 10}$ = 83.16 +/- SD = 16.28kg, range: 49.5 – 108 kg and for the larger TBSA group: $X_{11\text{-}30}$ = 81.6 +/- SD = 9.88kg, range: 70 – 95.8 kg. Despite reduced higher TBSA sub-group numbers, the estimated power of F tests of mean differences was: TBW = 0.50-0.91, ECF = 0.68 – 0.91 and ICF = 0.28 – 0.83.

Table III:2: Impact of TBSA on reliability and measureable difference using BIS.

Volume Variable	**Dressing Condition (Sub-gp n's: $TBSA_{\leq 10}$ /$TBSA_{11\text{-}30}$)**	**$X_{\leq 10\%}$ (SD) (L)**	**$X_{11\text{-}30\%}$ (SD) (L)**	**Reliability x TBSA Interaction: F value (p*)**	**TBSA Sub-gp Mean Test: F value (p)**
TBW	*Old (n=9/4)*	41.68 (8.80)	56.65 (7.12)	0.37 (0.574*)	**8.04 (0.016)**
	Open (n=8/4)	42.52 (7.81)	53.18 (6.81)	1.53 (0.239)	4.76 (0.054)
	New (n=11/3)	41.48 (7.57)	67.21 (17.92)	0.33 (0.603*)	**12.8 (0.004)**
ECF	*Old (n=9/4)*	19.26 (5.31)	28.13 (5.05)	0.55 (0.585)	**7.08 (0.022)**
	Open (n=8/4)	18.23 (3.43)	24.73 (4.18)	2.17 (0.144)	**7.33 (0.022)**
	New (n=11/3)	18.74 (3.13)	27.74 (5.08)	0.49 (0.504*)	**13.24 (0.003)**
ICF	*Old (n=9/4)*	22.42 (4.99)	28.53 (6.20)	0.35 (0.577*)	3.26 (0.099)
	Open (n=8/4)	24.29 (4.69)	28.46 (2.89)	0.80 (0.461)	2.32 (0.158)
	New (n=11/3)	22.74 (5.32)	39.47 (13.41)	0.20 (0.675*)	**10.21 (0.008)**

*** Indicates corrected p value by the Greenhouse-Geisser method.**

Discussion

In patients with < 30% TBSA, BIS fluid composition analyses using the SFB7, is reliable regardless of dressing conditions. The data demonstrated excellent concordance (ICC's from 0.976-1.00) on a background of acceptable variance (95% CI's from 0.940-1.00) with no indication of significant systematic bias (Table III:1). Further, BIS reliability remains high regardless of burn severity or area (Table III:2). These data suggest that the BIS is a reliable method for assessment of acute edema (fluid) shifts within and between whole body compartments. These results are applicable to acute patients with burns ≤ 30% TBSA.

When examining the sensitivity of the measurements, dressing condition clearly influences the BIS analyses. In the first instance, BIS is most sensitive when the wounds are open or with dressings removed. The MDD result for TBW without dressings confirms that a change of ~360mls, within the burn patient as a whole, would indicate a true volume change. In the context of massive fluid shifts during acute burn resuscitation, for instance, monitoring the whole body fluid flux within 0.5L of fluid is a clinically useful degree of accuracy. Further, the clinical and research advantages of BIS are more evident when examining the change in volume within the fluid compartments. In particular, the MDD for the ECF volume change measureable was more accurate than TBW by 4 times at <10mls. This indicates that BIS is able to track fluid movement into the tissues accurately over time when dressings are removed. This is particularly useful if wishing to study acute edema shifts into the extra-cellular compartment. The ICF sensitivity result for the open wound condition is superior but similar to TBW, with an MDD of ~310mls. As a clinical context example, BIS measurements could be used to monitor over-resuscitation. Real time increases in BIS ECF (vis tissue fluid volume) while BIS ICF (vis central circulation volume) remained stable between two time points, indicates a need to reduce the resuscitation fluid rate. Finally, despite only seconds between trials, the relative insensitivity of ICF compared to ECF results may be explained by the measurement of intra-cellular fluids involving rapidly changing, non-static volumes such as those within the vascular, gastro-intestinal and lymphatic transport systems. This compares favourably with other studies of non-injured participants where the standard error of the estimate for SFB7 BIS was ~ 2L (Moon et al. 2008).

However, a reduction in sensitivity (MDD) of BIS is evident in the presence of dressings (Table III:1). The dressing protocol in the first 2 – 3 days post-burn at the

RPH includes nano-crystalline silver / moist gauze / bandage dressings. After this time, the dressings change to a hydrocolloid in most cases. Both of these dressing systems contain variable levels of moisture, and interact over time, in continuity with the open wound. Despite this, the MDD results for ECF readings remained within clinically useful ranges in the context of whole body fluid shifts. BIS ECF measures taken within 8 hours of dressing application indicated that a flux of ~0.5L within all body tissues is a true change. With dressings that have remained intact for longer than 8 hours, the whole body ECF MDD was 1.2L. These data therefore indicate that monitoring of acute burn fluid shifts is feasible with BIS. Further, practitioners can monitor fluid movement into the extra-cellular tissues in real time. With appropriate corrections, finely titred fluid resuscitation monitoring in an individual with burns, would be possible with dressings in place. Further, the results provide evidence of a clinically significant level of precision or sensitivity to change compared with the clinical measurements in other patient populations. For instance, clinical intervention decisions for patients with post-mastectomy lymphedema are based on the premise that ~200mls of change is significant in a single upper limb (Box et al. 2002).

The limitations of the BIS technique in the acute burn population relate to the appropriate placement of electrodes over intact, non-glaborous skin. The resistance of intact skin is taken into account in the BIS algorithms. A marked alteration of skin resistance will invalidate the volume calculations. Clearly, burn wound distribution affects the utility of the method in this regard, as an open wound reduces skin resistance to current flow.

Future Studies

This study has examined the use of BIS for burns of up to 30% TBSA without significant pre-existing co-morbidities. It is undisputed that the clinical utility of this technique would be enhanced by confirmation of reliability in larger burns and patients with medical conditions which may affect their underlying tissue edema status. However, as burn size increases, the likelihood of wounds distributed over the electrode placement areas also increases, making study in the moderate to severe burn population challenging. This is illustrated by a review of RPH acute burn admission data. It showed that there was <20 patients with injuries ≥ 30% TBSA during the recruitment periods and ~95% of those had multiple limb burns that excluded them from the trial of BIS with the current methodology.

To address the issue of electrode placement, future studies might consider alternative electrode placement such as segmental or injured limb monitoring as well as 'within wound' options. Of course, these studies would necessitate the recalibration of standard BIS algorithms.

Finally, the within-condition results indicate that BIS has construct validity in the burn population. Despite small study numbers, and similar group mean body weight parameters, 6 of 9 BIS analyses by dressing condition, demonstrated a significant difference between the mean volume of minor and moderate burn severity sub-groups (Table III:2). This analysis quantified the degree of sensitivity in the measurement for assessing volume change but has not validated the measurement of absolute volumes between individuals. Adequately powered and designed studies are necessary to examine this aspect of BIS use in burn survivors.

Conclusion

BIS is a reliable, non-invasive technique for analysis of total body fluid compartment volume change in acute burn survivors. The reliability of the technique remained high whether dressings were applied or removed. The application of wound dressings decreased the sensitivity of BIS measurement of fluid volume change. However, the measurable volume difference in the extra-cellular tissue compartment, with dressings intact, remained within a useful range. Thus, BIS analysis is clinically applicable for real time monitoring of whole body fluid shifts in acute burn survivors with ≤30% TBSA.

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4.2.3 Paper IV - Volume measurement using the Polhemus FastSCAN 3D laser scanning: A novel application for burns clinical research.

Published: Journal of Burn Care and Research, 2008.

Introduction

All burns survivors suffer daily pain (2004) and inherently have increased risk of wound infection (Herndon et al. 1989). The impact of minimising acute edema and, therefore decreasing wound conversion, pain and infection immediately after a burn, is a current focus of clinical practice (Demling 2005). Measurements used to assess the benefit of acute edema management techniques must provide accuracy and, outweigh the potential risks of increased pain, infection and other factors that negatively influence scar outcomes. For example, although water displacement volumetric assessment is a valid and reliable method to estimate upper limb volume, (Karges et al. 2003; Meijer et al. 2004) the technique may lead to physical contact of wounds with instruments. Further, in the acute burn unit environment, whole limb water displacement has inherent safety concerns due to the high probability of spillage of fluid onto the floor, patient ambulation in this environment and the weight of water to be transported by the assessor. This increases the aforementioned risks, and reduces its clinical utility.

The availability, and combination, of optoelectronic technologies with computer-assisted design (CAD) provides health professionals with a number of alternative methods to measure change in volume. Through the use of light, these techniques are non-contact in nature and as such, may provide solutions to a number of the issues related to measurement of acute burn edema (Mayrovitz et al. 2000). One such system, is the *FastSCAN* Cobra® (Polhemus Inc, Colchester, Vermont, USA) which uses a hand held laser scanner in combination with tracking software(Harrison et al. 2004). The *FastSCAN,* an extension of the *Fastrak*® technology(Day et al. 2000), was developed in New Zealand (*Applied Research Associates NZ Ltd*) to scan 3D surfaces in a multitude of medical, artistic and military applications (Biryukova et al. 2000; Polhemus 2007). In this system, a 'Class A' laser line scanner is swept repeatedly over the object. The *Polhemus FastSCAN* system (PFS) software orientates data from the handpiece camera and 3D position reference transmitter to generate digital surface maps in real time (Fig IV.1).

Figure IV.1: Demonstrates the use and orientation of *FastSCAN* scanning hand piece, including camera, while subject is positioned for 3D access of upper limb. (The transmitter is mounted beneath the black velvet cover.)

The advantage of this system in the clinical environment is edema volume assessment without contact to open burn wounds. No studies, however, have reported the reliability or validity of the system to measure the volume of the upper limb, a part of the body frequently injured by burns.

The primary aim of this paper was to document the reliability of hand held laser scanning to measure the volume of an uninjured upper limb. Secondly, validation of limb volumes determined using the laser scans will be assessed by comparison against water displacement volumetry. Finally, this study will examine the application of this technique in patients with upper limb burns.

Methods

Participants

Data were collected between January and December 2005 from two groups of volunteers. Each person provided informed consent to undertake the testing protocol approved by the Royal Perth Hospital (RPH) Ethics Committee (Ref # EC 2004/027).

The study protocol was approved for 30 uninjured individuals (Group One) and 10 burn patients with acute upper limb burns (Group Two).

Procedure

Group One – Uninjured Subjects

A single subject arm was randomly assigned, by coin toss, for water displacement volumetric measurement. Previously reported upper limb volumetric displacement methods have been limited to the hand and forearm (King 1993; Boland et al. 1996; Farrell et al. 2003). This study also included the upper arm. At RPH, this study method was shown previously to be reliable on 30 uninjured controls between two repeated trials (ICC = 0.99; 95% CI = 0.93-0.99, p=.297; UL volume range = 1251 – 2197 gH_20).

Prior to removal from the immersion tank, 3 random points were marked, with pen, at the water level to define the proximal arm 'water plane'. The weight of water displaced, quantified to the nearest $0.01gH_2O$, representing the volume of the arm.

After the immersion, each subject removed and dried their arm, before being positioned for the surface scan, which was then conducted according to the standardised procedure (Table IV.1). The time taken between measurements was 5 to 10 minutes.

In random order, by coin toss, each of two examiners performed a single scan of the full upper limb. Each scan included the digitising of the three marked points, denoting the proximal limit of volume calculation, using the stylus point tracking technology of the PFS (Fig. IV.2). The image and scan data were stored to file after each trial.

Table IV.1: Standard protocol developed to reduce variation and unwanted scan artefact when 3D scanning of upper limb.

Source of Possible Variation	Standard Protocol
Light artefact	All overhead lights turned off. Filtered lighting from adjacent room.
Light reflection	Black velvet sheet covering all non-target surfaces within scanning field.
Maintain immobile subject position	Hand supported by Perspex stand, fingers and thumb gently held together.
3D access to subject limb	Finger pads, resting on Perspex stand. Upper limb in abduction (approximately 75° – 90°). Subject sitting.
Unwanted antennae	No metal objects within 2 m of hand piece. Chair and support apparatus should be plastic or wood.
Transmitter position	Mounted on Perspex stand. Outer point of scanned arm within 75cm radius of transmitter(Day et al. 2000).
Tester technique	Sweeping or 'spray painting' motion with hand piece. Monitor progress in surface completion through real time raw surface image on laptop.
PFS software parameter settings	Raw surface calculation: • Sweep smoothing* = 2.5mm • Raw mesh facet resolution§ = 2.0mm Smooth surface generation: • Accuracy# = 0.3mm • Mesh facet resolution = 2.0mm

**Sweep smoothing*: least squares distance vertical adjustment used to combine sweeps up to 2.5mm apart into a single raw surface.

§*Facet resolution*: triangular facet size used to map sweeps to a single surface. Smaller facets retain more of the original scan data.

#*Accuracy*: smooth surface facet mesh is created by combining raw surface facets that were up to 0.3 mm apart.

Group Two - Burn Patients

Single tester, repeated trials of the worst burned arm, by total burn surface area (TBSA), were performed using a slightly modified protocol, altered to improve patient safety, immobility and comfort. Individuals were assessed in supine with the arm abducted over the edge of the bed. The upper limb remained supported with their fingertips resting on the Perspex upright. The tester ensured that the limits of the scanning field were within 75cm of the PFS transmitter. Each participant was assessed with dressings removed and wounds exposed. Testing in burn patients commenced prior to the finalisation of the volume calculation software (see below).

Scanning Protocol

Pilot testing, with inanimate objects and human volunteers, was used to optimize physical factors that affect scan quality, such as ambient light conditions. Also, the process included testing of *Fastrak*® technology previously used to monitor upper limb movement (Biryukova et al. 2000). There was no demonstrable benefit, by the inclusion of a mobile reference transmitter, to the quality of scanned images. As a result, they were excluded from the final protocol due to the potential risks and difficulties associated with affixing them to patients with open wounds. Table IV.1 identifies the protocol established for this study for the PFS capture and processing of upper limb data.

Volume Calculation – Software Interfacing

Arm volume calculation required both the PFS software (steps 1 – 6 below) and custom software written in Python, using the Visualisation Toolkit (VTK). Volume, in cm^3, was calculated from the digitised upper limb object, using the steps below, in the following order:

1. The raw scan was saved as a single surface ensuring automatic deletion of outlying scanned points and, or artefact not in contact with the primary scanned object.
2. Manual removal of non-confluent points created by light artefact and superfluous handpiece sweeps from each raw scan.
3. Scan sweeps were ‘registered’ to create a single scanned surface by least squares distance algorithm.
4. Exportation of a single object to volumetric software occurred after the rendering process created a smooth surface profile (Fig IV.2) (PFS User Manual, pg 33).

5. If the smooth, or 'rendered', shape was obviously non-anatomical, steps 2 – 4 were repeated until no further improvement could be made with the 3D arm construct (Fig IV.2).

6. Rendered file was exported in VTK format, linked to the stylus point data in ASCII (TXT) format.

7. The custom software then fit a bounding plane through the three stylus points (Fig IV.2). The software calculated the volume of the 3D object created, after removing extraneous smooth surface information orientated outside the bounding plane. A check plot of the measured shape was also produced for visual verification.

8. The custom software re-processed the data after introduction of a second plane, 200mm proximal to the tip of the finger, orthogonal to the long axis of the scan. The new 'two plane' volume calculated, reduced the error introduced by distal hand anatomical anomalies (noted in step 5) (Fig IV.2).

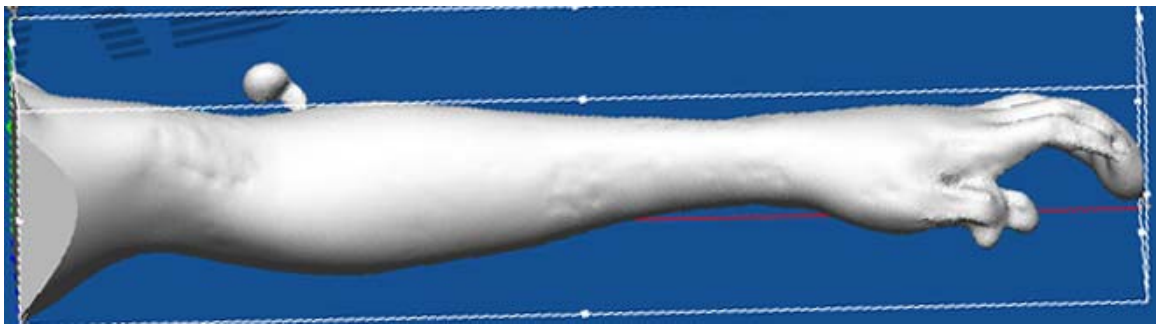

Figure IV.2: Smoothed burn patient scan, demonstrating anatomical anomalies, particularly around the fingers.

Data Analysis

All analyses were formulated using SPSS V.15 (SPSS Inc., Chicago, Illinois).

Variables are summarised as mean (X) and standard deviation (SD).

Reliability was assessed using concordance, calculated as intraclass correlation coefficients ($ICC_{(2,1)}$), variance, expressed as 95% confidence intervals (95% CI), the presence of systematic difference (significant at $p<.05$) and minimum detectable difference (MDD). The MDD, defined as the magnitude of real change measured with 95% surety using repeated tests, was calculated using the standard error of the measure (SEM): $MDD = SEM \times \sqrt{2} \times t_{(df,.05)}$ (Bland et al. 1999). The minimum acceptable standard for concordance was set at $ICC \geq .75$ (Fleiss 1986).

To determine the validity of the 3D scan method, correlation and mean difference are described as for reliability while the magnitude of difference to water displacement was expressed as 95% limits of agreement (95% LOA). The 95%LOA is calculated as X_{diff} $\pm$ 2sd, where X_{diff} = mean difference (volumetry – scan) and sd = standard deviation of the differences between methods (Bland et al. 1990). Burn patient (initial scan) and uninjured subject scan data were pooled to optimise the method comparison (Bland et al. 1999; Bland and Altman 2007). As method comparison statistical analyses suffer with reduced sample size, it is argued that the data should be combined to increase power and provide a more realistic estimate of the true measureable difference and congruency of the scan technique compared to water displacement.

In method comparisons, measurement units were considered interchangeable, with 1 gram of water (gH_20) at room temperature equivalent to 1 cubic centimetre (cm^3) in water volume (King 1993). Random testing confirmed the water temperature to be at 23.1 – 23.4°C.

Results

Participants

As planned, Group A comprised 30 adult uninjured volunteers (19 males and 11 females). Each participated in the reliability trials conducted by two operators and the validity testing on 16 right and 14 left arms (size range: 1307 to 2705 gH_20).

Group B included 6 patients with upper limb burns (5 males:1 female, X_{age} = 33.3 years, range 15 – 66, 5 right:1 left arm, X_{TBSA} = 12.3%; range 0.5 – 24%). Recruitment was abandoned because of the relatively poor quality of all burn patient scans noted as ‘gapping’ between raw scan sweeps, and irregular surface contours on smoothed images (Fig IV.3). In contrast, the same artefact was visualized in only one of 60 uninjured subject scans.

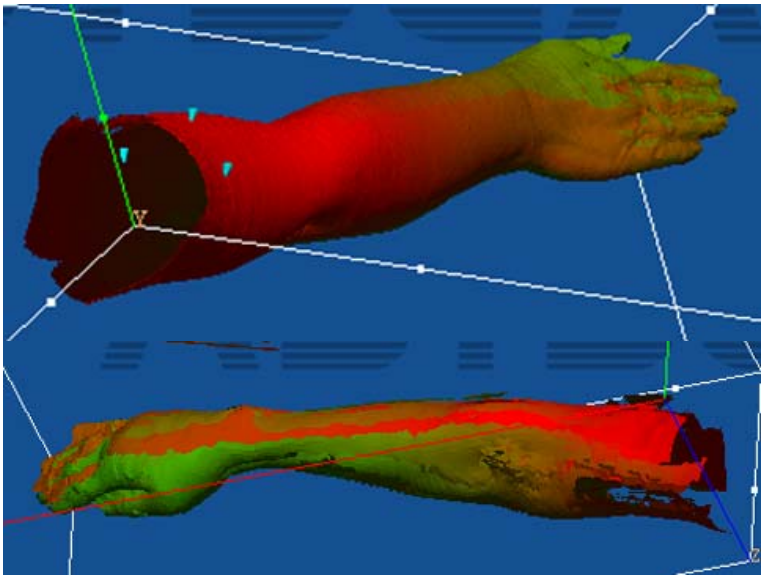

Figure IV.3: Raw scans comparing typical quality of uninjured (top) and burn patient (note 'gapping' between scan sweeps). Digitised stylus points (cones) are also visible on the uninjured arm scan.

Interrater Reliability – Uninjured Subjects

Table IV.2 displays the Group A statistics of scans by both testers. A moderate correlation and systematic difference were shown when the whole arm scans were compared. In contrast, scan group means were not statistically different and in excellent agreement using two plane, or truncated hand, scan data (Table IV.2). Of 60 scans, 10 (12%) were noted to have minor anomalies, 9 of those around the finger tips and one related to sweep 'gapping'.

Table IV.2: Repeated scan data for Group One (n=30) comparing whole arm and two plane (truncated hand) data.

Statistic	Whole Arm Scans	Two Plane Scans
$X_{Rater\ 1}$ (SD) (cm^3)	**1928.1 (367.5)**	1758.1 (383.3)
$X_{Rater\ 2}$ (SD) (cm^3)	**1767.9 (504.6)**	1774.8 (381.9)
Mean Difference (cm^3)	**160.2 (p = .04*)**	16.7 (p = .46)
ICC (95% CI)	**0.59 (0.28 - 0.78)**	0.95 (0.90 - 0.98)
$MDD_{(29,2.05)}$ (cm^3)	824.6	242.1

Intra-rater Reliability – Burn Patients

Analysis of the intra-rater reliability, using repeated two plane scan data, confirmed a poorer, unbiased correlation, inconclusive due to small numbers, variance and MDD values for Group Two (ICC =0.72; 95% CI's = -0.07-0.96; p = .973; MDD $_{(5,2.57)}$ = 748.1cm^3, UL volume range = 1296.2 - 2486.1cm^3).

Validity of Scan Volume Measures

The repeated trial estimations by both methods were highly correlated (ICC=.875, 95% CI= .77 to .96) without systematic bias (p=.111). Table IV.3 presents the grouped data from Rater 1, including the results of combined subject data analysis examining the magnitude of differences between estimations by each method.

Table IV.3: Group data comparing water displacement and 3D scan measures using 95% LOA method (interchangeable volume units: g$H_2$0 or cm^3).

Whole Arm Statistics	Uninjured (n=30)	Burns (n=6)	Combined (n=36)
$X_{volumetry}$ (SD)	**1845.6 (354.9)**	**1813.7 (419.3)**	1840.3 (360.0)
X_{scan} (SD)	**1928.1 (367.5)**	**1749.0 (352.7)**	1889.6 (365.7)
X_{diff} (*sd*)	**-82.5 (148.3)**	**116.7 (250.6)**	-49.3 (181.3)
95% LOA	- 379.1 to 214.1	-384.5 to 617.9	– 411.9 to 313.3

X_{diff} = mean of differences between volumetry measure less 3D scan volume

sd = standard deviation of differences between measurements

Discussion

According to the criteria set, the PFS volume calculations were highly reliable for uninjured subjects with the distal fingers removed from the scans (Table IV.2). This indicates that the technique warranted our investigation with respect to the theoretical construct. However, the clinical utility of 3D scanning is markedly reduced as the hand is an important site to measure when observing and, or treating acute burn edema. The results collected in the burn unit reinforce this, though a number of other factors which impact on the method, must be understood in that environment. For instance, since dressing time coincides with maximal analgesia, the patient's ability to concentrate and hold limbs immobile was reduced compared to uninjured subjects. This was confirmed by 'gapping', or incongruity between successive sweeps, in all burn patient scans, indicating involuntary movements, insensible to the naked eye, during scanning (Fig IV.3). While this problem was foreseen, supine positioning of the

patient in the burn environment obviously could not completely ameliorate this problem. In contrast, movement artefact was only evident in <2% uninjured subject smoothed scans upon visual inspection. Further, in the RPH burn unit, all beds have steel frames and thus, some metal was inevitably located within 2 meters of the proximal scanning field of the arm. However, the visual distortion of scanned objects during pilot trials was insignificant. Further, as noted by Day et al (Day et al. 2000), metal antennae cause minimal distortion when the transmitter is within 80 cm of the scanner as was the case in our study. Finally, the presence of open wounds was examined. Upon review, the quality of the scanned smooth or raw images were not altered by acute burn or the variable relative size of the wound. In the burn patients, close observation of scan sweeps confirmed that increased light artefact was not recorded in the presence of a burn wound. Further, the sweep assessments showed that surface contours remained anatomically correct despite transitioning from burn wound surface (mixed depth injuries) to normal skin.

In addition to issues of the clinical environment, the MDD of the measure is of concern with regard to the clinical utility for objective assessment of acute burn edema change. At best, the inter-rater reliability (truncated hand) data suggests that a change of 242.1cm^3 (~14% of mean arm volume) must occur before the PFS can categorically measure volume change in the arm. As a guide, a measured change < 200mls is considered adequate in chronic upper limb lymphedema studies (Box et al. 2000). Further, the scan MDD compares poorly with that of water displacement which was calculated to be 36.2 gH_20 (~2%) upon assessment using our technique and purpose built apparatus. Thus, with this scan methodology, small changes pre- and post-intervention, for instance, would be difficult to measure in comparison.

A number of studies have examined the reliability and validity of optoelectronic volumetric assessments. Relatively few studies, specifically investigate laser methodology. A recent paper by McKinnon et al (2007) investigated the use of PFS with newly developed volumetric software in the lymphedema population. The study, with similar methodology to that presented here, compared multiple measurements of 10 healthy subject upper limbs with water displacement. The authors concluded that the arm scanning was more reliable than water displacement with an MDD of ~ 27mls. However, this figure is certainly under-stated as the group pooled the same-subject duplicated data for the reliability analyses. Johansson and Oberg (1998), studying the volume of lower limb amputee prostheses using the *CAPOD*® laser system from Sweden, demonstrated a validity error of ~3%. However, their simplified study

compared water displacement volume within human prostheses only, not live subjects. Harrison et al (2004), assessing facial swelling after dental removal with the PFS, reported 0.5 cm^3 (~4%) error in a mannequin with standardized 'swelling' using putty. Repeated facial measurements in healthy subjects demonstrated an MDD of 3.4 cm^3 (group mean not reported).

Several studies examine the use of the *Perometer*® (*Pero-System*, Juzo Inc, Germany). Designed to measure limb volume (excluding feet and hands), the *Perometer*® uses intersecting infra-red beams to measure limb circumference at regular points perpendicular to the limb, informing software which calculates volume using a truncated cone formula(Stanton et al. 1997b). The reliability of the technique was reported as high for upper and lower limb volume calculation though all papers underestimated this error through the statistical assumptions used when pooling data (Stanton et al. 1997b; Mayrovitz et al. 2000; Man et al. 2004). With respect to validity, the authors present that the *Perometer*® overstates the true volume of the limb when compared to water displacement or circumferential tape methods, in the order of 4% error for legs and 7% error for arms. Therefore, the *Perometer*® may provide a reliable measure for volume change but not of absolute volume. These facts, combined with the 'excluded hand' measurement construct, lead our group to disregard this method for measurement in the burns population.

Finally, in the present PFS study, scan data demonstrated that the method systematically overstated the limb volume by ~50 cm^3. However, while the 95% LOA method comparison according to Bland and Altman (Bland et al. 1995; 2007) is statistically robust, as expected, it is sensitive to the variation of differences between measurements. The mean (systematic) difference between trials grouped by method was, at worst, clinically acceptable at 116.7cm^3 (Table IV.3). This compared favourably with the McKinnon et al (2007) study at ~152 cm^3. However, the 95% LOA estimation of true measurable difference is actually 4 times the standard deviation calculated from the grouped residual errors of each pair of trials. Thus, the scan method cannot be interchanged with water displacement volumetry in a clinical or research context because it cannot measure, with surety, a volume change <740 cm^3 according to this statistical methodology. This is well outside a clinically useful range. These facts render the method not useful in our environment in its studied format.

Future Studies

Open wounds did not hinder the capture of scan data and as such, this system theoretically offers a non-contact measurement technique, given further consideration of the procedures. In order to measure volume, a standardized laser scanning data capture protocol was developed. It is clearly not robust enough, to give reliable scans in uninjured subjects (without truncating the fingers) or in the burn clinical environment (Figs IV.2 & 3). Future studies must improve subject immobility, without hindering access during scanning. As the shape of the arm does not impact on the ability of the software to calculate volume, a feasible solution would be to scan the limb resting on a solid transparent surface like glass or Perspex. The PFS software used in this study could not accurately scan through transparent materials. At the time of writing, new software is emerging that has the potential to rectify the issues indicated in this study.

Conclusions

The *Polhemus FastSCAN* system offers a non-contact method of limb volume measurement. The conceptual merit of the system for burns is obvious. However, the reliability was good only with the fingers removed from the calculations. The accuracy and sensitivity of the system compared poorly with water displacement measures. Using the currently available software and standardized method for upper limb measurement, the accuracy of the PFS in the clinical environment was inadequate for monitoring the efficacy of interventions to minimize acute burn edema.

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4.3 Measures of Longitudinal Functional Recovery

4.3.1 Paper V: The QuickDASH is an appropriate tool for measuring the quality of recovery after upper limb burn injury.

Published: Burns, 2007.

Introduction

Upper limb function is vital for performance of activities of daily living and specific professional or sporting activities. At the Royal Perth Hospital (RPH), more than 83% of burn patients have an upper limb injury. When compared to other parts of the body, burns to the face and, or hands causes greater physical, psychological and body image dysfunction as measured by the Burns Specific Health Scale (BSHS) (Blades et al. 1982b).

The Burns Specific Health Scale (BSHS) is a population specific, self-rated questionnaire developed to assess the quality of recovery after a burn injury. It has demonstrated validity and reliability (Blades et al. 1982b). The BSHS was revised to create the BSHS brief version (BSHS-B) to reduce the administration issues and increase user compliance (Appendix 3). Again, it was demonstrated to have validity and reliability in the burns population (Kildal et al. 2001a). However, neither version of the BSHS has a specific domain for upper limb function. Thus, in view of the high proportion of hand and upper limb injuries rehabilitated in the Western Australian (WA) Burns Service a more specific instrument was desired to detect smaller, yet clinically significant, changes in upper extremity recovery after a burn injury. It was proposed that the disability of the arm, shoulder and hand (DASH) questionnaire could constitute such a measure.

The DASH is a patient self-rated questionnaire that is upper extremity specific. It was introduced by the American Academy of Orthopaedic Surgeons, in 2001, to measure disability caused by various upper limb disorders (Beaton et al. 2001). The validity and reliability of the DASH has been demonstrated in the general population but not in burns (Beaton et al. 2001) (Appendix 3). Beaton *et al.* (Beaton et al. 2005) established its validity and reliability while Gummesson *et al. (Gummesson et al. 2006)* have shown that it can be interchanged with DASH without loss of precision. Gummesson *et al.* also demonstrated the ability of the shortened instrument to detect changes in upper limb function, or measurement of response to treatment (Gummesson et al. 2006).

Aims

In patients with upper limb burn injuries, this study aimed to:

- Test the criterion and construct validity of *Quick*DASH;
- Examine the reliability of the QuickDASH; and
- Examine the responsiveness, or sensitivity to measuring change, of the *Quick*DASH.

Methods

Patients: Eligible participants consisted of all patients with upper limb burn injuries who were either admitted to the burn unit or treated as an outpatient in burn clinic at RPH, Perth, WA from 1st January 2006 to 30th September 2006. The exclusion criterion was non-English speaking, as during the study timeframe, only an English version of the *Quick*DASH was available. Informed consent was obtained from all eligible patients to participate in this longitudinal study.

Measures

*The Quick*DASH *questionnaire:* The *Quick*DASH consists of 11 items from the original DASH concerning the patient's health status during the preceding week (Appendix 3). Each item has five response scores and the scores for all items are used to calculate a scale score ranging from 0 (no disability) to 100 (most severe disability).

The Burn Specific Health Scale (BSHS-B): For the purpose of validation, the BSHS-B was administered together with the *Quick*DASH. The BSHS-B is a self-rated questionnaire developed to assess dimensions of health in individuals recovering from burn injury. It covers four main domains that are important in the rehabilitation of a burn injury: Physical, Mental, Social and General and has been demonstrated to have accepted validity and reliability (Kildal et al. 2001a) (Appendix 3).

Procedure

Study participants were asked to complete both questionnaires at the following times: discharge; one month, three months, six months and twelve months post injury date. In addition to this, each patient also completed a *Quick*DASH within 48 hours of admission to the burns unit or on the first day of attending the burns clinic. This is to ascertain each patient's self-rated pre-injury, or baseline, upper limb functional level. As the BSHS-B is injury specific, it is not appropriate to use this measure to gather pre-injury data. Finally, a number of patients were randomly requested to complete the *Quick*DASH in order to examine repeatability.

Validity in Burns Population

In this study, both the criterion and construct validity of the *Quick*DASH are to be assessed.

Criterion validity: The burns validated BSHS-B is used as the criterion measure for the QuickDASH. It must correlate well with the scores of BSHS-B to be a valid measure (Fayers and Machin 2000). Sub-group analysis of *Quick*DASH scores and the physical domain of the BSHS-B will further indicate validity as this domain is concerned with the ability to perform activities of daily living.

Construct validity: Construct validity is demonstrated if statistically significant differences in the *Quick*DASH scores are shown between patients grouped by markers reflecting change in burn severity. The clinical variables chosen to examine construct validity include: total body surface area (TBSA) burned, presence of full thickness burn, necessity for hospital admission and / or surgical intervention.

Repeatability in Burns Population

The repeatability of the *Quick*DASH is assessed by a test-retest procedure (Fayers et al. 2000). Random sample of burn unit inpatients were asked to repeat the *Quick*DASH questionnaire one-day apart at discharge. The *Quick*DASH was also mailed out to random sample of burns clinic outpatients a day after completing the one on discharge.

Responsiveness

Responsiveness, or sensitivity, refers to the ability of the measurement to detect change over time and can be used as a measure of treatment effectiveness (Gummesson et al. 2003). It is part of the validation process. In this study, the difference between discharge and subsequent follow-up scores of the *Quick*DASH are used to establish its ability to detect change over time. Comparison of *Quick*DASH and the BSHS-B is used to determine the effect size and relative sensitivity of each measure.

Statistical Analyses

All statistical analysis was conducted using SPSS (version 14.0, SPSS Inc., Chicago, Illinois).

Variables are summarised with counts, mean (X), standard deviation (SD), range, and percentage wherever appropriate. To test for differences between patient groups the χ^2-test, t-test and Mann-Whitney test were used. A $p < 0.05$ was considered statistically significant.

Criterion validity was assessed using the Spearman's rank correlation to determine the association between the scores of *Quick*DASH and BSHS-B at each assessment date following the onset of burn injuries (Lohr et al. 1996; Fayers et al. 2000). It must be noted that in this study, there is a negative correlation as the two questionnaires have opposite scoring systems. Construct validity was tested by the Mann-Whitney test, as there were several patient groups with small patient numbers (< 25).

Effect size was used to measure the responsiveness of the *Quick*DASH and BSHS-B. It was calculated, as per the formula for Cohen's *d* (Cohen 1988):

$$d_{1mth} = X_{1mth}\text{-}X_{D/C} \text{ / sqrt } [SD^2_{D/C} + SD^2_{1mth} / 2]$$

For this study, a Cohen's *d* greater than 0.5, indicated that the instrument was suitably responsive to change over time (Cohen 1992).

For test-retest repeatability, mean change scores and paired t-test p values were calculated and correlation coefficients were obtained using the Spearman method. Intraclass correlation coefficients (ICCs) were also calculated and a coefficient between 0.90 and 0.95 were considered as a minimum standard for repeatability (Lohr et al. 1996).

Ethics

This study was approved by the RPH Ethics Committee as part of the WA Burns Clinical Outcomes and Research Project (BCORP) and individual informed consent was provided by all subjects to allow data to be used for research purposes.

Results

Sample Description

Eighty-five patients with upper limb burns were serially recruited to the study. Of those, 63 were admitted to the burns unit and 22 attended the burn clinic. The demographic and clinical characteristics of the participants are shown in Table V:1. Burns unit inpatients had significantly larger total body surface area (TBSA) burn and full

thickness burns than burns clinic outpatients. The majority of burns clinic outpatients (90.9%) had burns to their upper limb only.

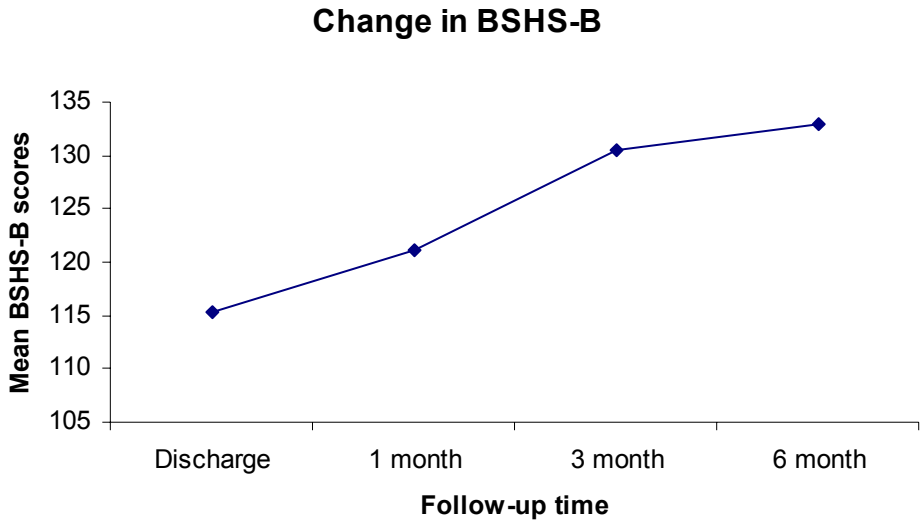
Sixty nine, 56, 51 and 44 patients completed both the *Quick*DASH and BSHS-B at the time of discharge, one month, 3 months, and 6 months follow up respectively. Patient attrition is related to timeframe from injury and 9% were lost to follow up. At each measurement time point, there were no differences between patients who completed the questionnaires and those lost to follow up regarding sex, age, TBSA burn, full thickness burn, length of hospitalisation, and surgical interventions received.

The mean scores of the *Quick*DASH and BSHS-B at each follow-up time are shown in Figure V.1. Mean scores of the *Quick*DASH decreased over the study period, indicating patients' improved upper limb functional level (reduced disability score) over time. The mean admission score for the QuickDASH is included for reference.

Table V.1: Demographics and clinical profiles of the study participants

Clinical Characteristics	Total participants (n = 85)	Burns unit inpatient (n = 63)	Burns clinic outpatient (n = 22)
Injury locations			
UL only*	53 (58.1%)	33 (52.4%)	20 (90.9%)[a]
UL + LL*	32 (41.9%)	30 (47.6%)	2 (9.1%)
Age (years)			
Mean (SD)	38.2 (14.7)	37.4 (15.2)	43.2 (10.9)
(range)	(15-78)	(15-78)	(26-61)
Sex (% Male)	73 (87.8%)	57 (90.5%)	16 (72.7%)
TBSA[α]			
Mean (SD)	8.1 (9.4)	12.2 (13.2)[a]	2.9 (2.0)
(range)	(.5-60)	(1-60)	(0.5-7)
FT [#]			
Mean (SD)	3.0 (8.1)	3.8 (9.0)[a]	0.1 (0.2)
(range)	(0-40)	(0-40)	(0-0.5)
Length of hospitalisation for inpatients (days)			
Mean (SD)	16.8 (18.9)	19 (20.1)	5.3 (4.7)
(range)	(1-100)	(1-100)	(1-12)
OR			
Number of outpatient clinic attendances			
Mean (SD)			
(range)			
Surgery			
Yes	26 (35.1%)	26 (41.3%)[a]	0
No	59 (64.9%)	37 (58.7%)	22 (100%)

* UL = upper limb, LL = lower limb
[α]TBSA = Total body surface area burn (%)
[#] FT = Full thickness burn (%)
[a] Significant at $p = 0.05$ level



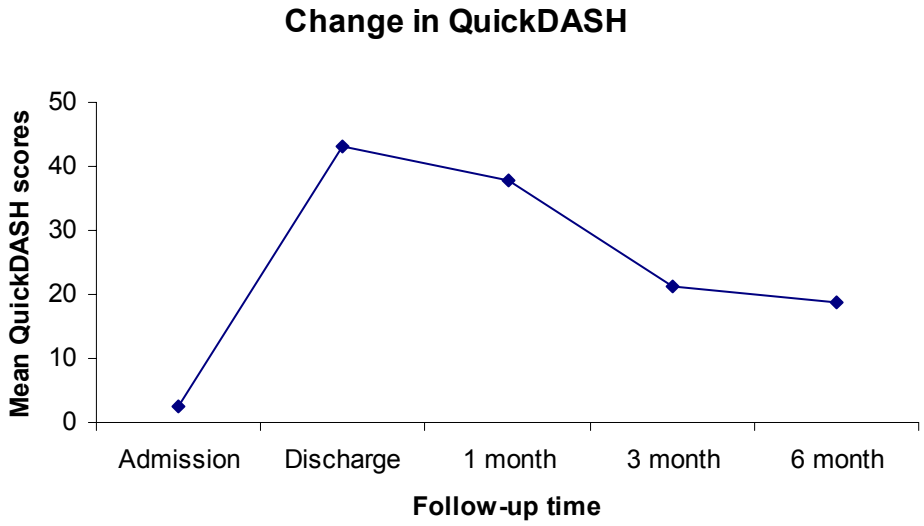


Figure V.1: The mean scores of the *Quick*DASH and BSHS-B at each follow-up timepoint

The mean scores of the BSHS-B over the study period appeared to mirror that of the *Quick*DASH, except that it was a positive trend reflecting the reverse scoring system. The positive slope of the BSHS-B graph demonstrates improved global quality of life over the study period.

Both outcome measures demonstrated more significant change in scores during the period between discharge and 3 month follow-up time. This is consistent with our clinical experiences in which improvement in patients' recovery progress is most significant during this time. However, the slopes between the *Quick*DASH scores were steeper than between the BSHS-B scores. This is possibly due to the *Quick*DASH being more responsive to changes in patients' functional level and was able to identify smaller but still significant changes in patients' upper limb function.

Criterion Validity: Spearman rank correlation of association between the *Quick*DASH and BSHS-B at each follow-up time demonstrated a correlation coefficient ranging between -0.79 to -0.89 (Table V.2). The associations were greater between the *Quick*DASH and the physical domain of the BSHS-B (Spearman correlation coefficients ranging between -0.82 to -0.90).

Table V.2: Criterion validity for *Quick*DASH

***Quick*DASH**		**BSHS-B**	***r*** [a]
Discharge (n = 69)	vs.	Total	-0.80
	vs.	Physical domain	-0.82
1 month (n = 56)	vs.	Total	-0.79
	vs.	Physical domain	-0.82
3 month (n = 51)	vs.	Total	-0.89
	vs.	Physical domain	-0.90
6 month (n = 44)	vs.	Total	-0.81
	vs.	Physical domain	-0.85

r = Spearman rank correlation of association between *Quick*DASH and BSHS-B total scores and the physical domain.

[a] all correlation coefficients significant at p = 0.01 level

Construct Validity: The *Quick*DASH was able to differentiate different groups of patients (Table V.3). Patients with TBSA more than 25%, patients with full thickness injuries, burn unit inpatients and patients who underwent surgical interventions had significantly higher scores (therefore greater disability) than the rest of the patients.

Table V.3: Construct validity for *Quick*DASH – comparison of burn severity measures.

*Quick*DASH Comparison Group	n	*Quick*DASH Mean Score	*p-value* [a]
TBSA (%)			0.018[b]
≤ 25	50	34.65	
> 25	19	48.92	
Full thickness injury			0.004[b]
Yes	30	41.39	
No	39	32.88	
Surgical interventions (inpatients only)			0.012[b]
Yes	24	39.63	
No	45	31.99	
Patient groups			0.003[b]
In-patients	53	42.42	
Out-patients	16	23.55	

[a] Mann-Whitney test

[b] Significant at $p = 0.05$ level

Reliability: Sixty-seven patients (total n = 85, 78.8%) completed the repeatability test for the *Quick*DASH outcome measure. The mean change score was 0.09 % (SD = 4.20) and there was no significant difference in scores between repeated tests (paired t-test, p = 0.78). The Spearman correlation coefficient between test and retest scores was 0.91 and the ICC was 0.93, indicating excellent test-retest repeatability.

Responsiveness: Table V.4 shows the magnitude of change between discharge scores and subsequent follow-up times for both the *Quick*DASH and BSHS-B (total and physical domain scores). The effect size for the *Quick*DASH was shown to be greater than the effect size of the BSHS-B for each measurement interval.

Table V.4: Comparisons of Responsiveness of the *Quick*DASH and BSHS-B at different follow-up time, expressed as effect sizes

*Quick*DASH	Differences Mean (SD)	Effect Size	BSHS-B	Differences Mean (SD)	Effect Size	
					Total	Physical domain
Discharge – 1 month	14	0.591	Discharge – 1 month	10	0.208	0.489
Discharge – 3 month	22	0.781	Discharge – 3 month	16	0.380	0.644
Discharge – 6 month	24	0.818	Discharge – 6 month	20	0.146	0.595

Discussion

This longitudinal study has provided evidence of the validity, test-retest reliability, and level of responsiveness of the *Quick*DASH outcome measure in patients with upper limb burn injuries.

The mean QuickDASH scores showed a trend towards the admission score over time and therefore pre-admission upper limb functional level. This demonstrated the improvement in patient's upper limb outcomes over time and showed that the

admission score should be one of the goals towards which patient rehabilitation is aimed.

Both the criterion and construct validity was assessed in this study. The correlation coefficients between the *Quick*DASH outcome measure and the total score of the BSHS-B at different follow-up times (r = -0.79 to -0.89) indicating a good to excellent criterion validity. The negative correlation reflected the opposite scoring systems in which a higher score on the *Quick*DASH reflected greater disability, while a high score on the BSHS-B reflected greater quality of life. It was also interesting, though expected, to note the higher correlation between the *Quick*DASH and the scores from the physical domain of the BSHS-B – relating to physical functioning (r = -0.82 to -0.90) (Table V.2). These data further confirmed the criterion validity of the *Quick*DASH.

The construct validity of the *Quick*DASH was demonstrated as it was capable of differentiating between groups of patients with differing severity of injury (Fayers et al. 2000). The results showed that the patients with a significant burn (> 25% TBSA), noted full thickness burns, had surgical interventions or who were burn unit inpatients had significantly higher scores (therefore greater disability) than the alternative group.

The *Quick*DASH demonstrated test-retest reliability with an excellent Spearman coefficient (0.91) and the ICC (0.93). This confirms results obtained by other studies in other patient populations (Gummesson et al. 2006).

The *Quick*DASH was shown to be responsive to changes in patients' disability over time. Effect sizes ranged between 0.591 to .818 when comparing the scores between discharge and one, 3 and 6 months after injury (mean difference were 14, 22, 24 respectively). (Cohen 1992). Furthermore, the *Quick*DASH showed greater sensitivity to change than the BSHS-B in patients with upper limb burns. This suggests that it is appropriate to use the *Quick*DASH to monitor patients' functional recovery and it may detect smaller changes in upper extremity recovery, after a burn injury. The effect sizes calculated with the BSHS-B physical domain scores, were more comparable to those of the *Quick*DASH, reflecting the broader range of questions used by the BSHS-B (Table V.4).

Future studies will examine the relationship between the *Quick*DASH and the physical outcomes as routinely measured in the RPH burns population. Further, with the collection of more longitudinal data and greater patient numbers, clinically significant

performance indicators will be developed to allow group comparison and benchmarking with comparable burn services.

Conclusion

Due to advances in burn injury management, the focus of outcome assessment has shifted from mortality to morbidity. Patients' functional recovery and quality of life now constitute an important part of burns care outcome assessment. This study demonstrates that for patients with upper limb burns, the *Quick*DASH questionnaire is a reliable and valid outcome measure. We have demonstrated that it is more sensitive to change than the BSHS-B in patients with upper limb burn injuries. This study has shown that the use of *Quick*DASH questionnaire is an appropriate measure to assess, monitor and guide rehabilitation of upper limb functional recovery after a burn injury.

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4.3.2 Paper VI: Goniometry and linear assessments to monitor movement outcomes: Are they reliable tools in burn survivors?

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Background

In the acute inpatient phase, the inflammatory nature of burn injury results in pain, edema and avoidance behaviour contributing to loss of joint range, muscle imbalances and subsequent dysfunction (Willebrand et al. 2006). With protracted wound healing time, soft tissue contracture and reduced joint movement are more prevalent (Cubison et al. 2006) and expose burn survivors to the risk of long-term functional impairment (Pruitt et al. 2002).

Objective assessment of functional recovery after burn injury is a major focus in the literature (van Baar et al. 2006). Despite this, reliable, validated measures for the burn population are limited primarily to patient self-rated scales (Blades et al. 1982c; Wu et al. 2007b). Physical measurements, such as joint range of motion (ROM), provide information on recovery and maintenance of movement (and muscle strength) across all time points of burn recovery. In clinical practice, visual or 'eyeball' assessments are common, however, objective measurements are more sensitive to small changes that indicate early joint movement loss and accurately monitor, in real time, the efficacy of rehabilitation interventions (Allington et al. 2002).

The use of goniometry to objectively measure joint angle, or ROM, is common in clinical practice. Joint specific reliability of the goniometry technique is established in healthy and other populations (Low 1976; McWhirk and Glanzman 2006) but it has not yet been reported in the burn setting. In burn patients, bulky dressings over wounds may confound measurement in the acute period and over time, the presence of scar tissue challenges therapists due to alteration of surface landmarks conventionally used when assessing joint range of motion.

In the hand, goniometry is also an established method of measuring individual joint movement (Groth et al. 2001). Despite this, there remains a lack of consensus as to the most accurate methods (Kato et al. 2007) and, assessment of multiple joint functional movements such as a) composite finger flexion (CFF), b) hand span (HS) and c) thumb opposition (TO) is time consuming. This study included a number of linear measurement scales in lieu of goniometry for a) finger pulp to distal palmar crease (PDPC)(Ellis et al. 2002); b) little finger to thumb span; and c) Kapandji TO

scale (Kapandji 1986). The measures were included as they are much more efficient (per finger) than goniometry and therefore more clinically applicable for objective measurement of functional hand movements for an individual. Further, linear thumb span measures have been demonstrated to be more reliable than angular thumb abduction measures (Murugkar et al. 2004).

This study aimed to examine the within session intra-rater and inter-rater reliability and responsiveness of joint ROM assessment using goniometry, linear measures of CFF and HS and the TO scale in the patients with burn injuries. A secondary aim was to assess the impact of dressing type on the reliability of repeated measurements.

Method

Subjects: Data were collected during the project period allocated between June and October 2006. The sample of convenience was recruited randomly from both inpatient and outpatient environments. All subjects provided informed consent. The study was approved by the Royal Perth Hospital (RPH) Ethics Committee (Quality Improvement Subgroup) as part of the Burn Clinical Outcomes and Research Project (BCORP) audit.

Procedure: Burn rehabilitation aims to achieve independent functional movement and preservation of muscle strength to overcome the restriction of scar. For this reason, the study assessed active, rather than passive or therapist assisted ROM. The procedure for each measurement was standardised prior to the commencement of the study through demonstration and verbal agreement between the PT's involved. To emulate clinical practice, surface landmarks were not marked up and more than one affected joint was measured on most individuals. The focus of this study was therefore, measurement technique, not the quality of patient movement.

Goniometry Protocols: The equipment used in the study was the Baseline^{TM} 12.5", 360° transparent plastic goniometer marked in 1° increments. The Norkin and White (1988) standardised protocols, with lateral goniometer placement for the shoulder, elbow, wrist, knee and ankle joint measurement were used. The patient moved their burn affected joint to the maximal ROM of available, at which point the fulcrum of the goniometer was placed over the anatomical landmark indicating the axis of the joint. The position of the limb was then supported in situ by the measurer and the arms of the goniometer were aligned with the pre-determined anatomical surface landmarks

specific for each joint movement. The individual's ROM was then read with the goniometer in situ and recorded.

Linear Finger Measures (PDPC & HS): In this study, the distance between the fingernail to pulp junction of the affected finger and the distal palmar crease was measured to represent CFF. If more than one finger was involved then the middle finger measurement was recorded. This measurement was taken using a ruler marked in millimetres.

Hand span was recorded as the distance between tips of little finger and thumb in maximum combined abduction. With the hand placed on a piece of paper resting on a flat surface, the most distal points of the digit pulp were marked. After removing the hand, a standard ruler was used to measure the linear distance between the marked points in millimetres.

Thumb Opposition Scale (TO): The Kapandji opposition scale measured TO such that each movement was scored 0 (no movement) or 1 (lateral aspect of the second phalanx of the index finger) to 10 (ulnar distal palmar crease) depending on the surface landmark touched with the thumb tip (Kapandji 1986).

Reliability: To provide a clinically relevant assessment of reliability, 4 qualified PT's took part in the testing procedures.
Intra-rater: One PT (PT_1) recorded two repeated measurements on each joint for a subset of patients with a 5 minute interval between individuals. Inter-rater: On the same day, one of the remaining PT's (PT_{2-4}) from the testing group, allocated randomly, repeated the measures. All PT_{2-4} data from the second trial were grouped together for comparison to PT_1's first measurement. All PT's were blind to each other's measurements. The time between measurements was not > 60 minutes, with most < 30 minutes, particularly for inpatients, to control for the impact of analgesia on movements. Each patient performed 3 – 5 movements to 'warm up' prior to each measure.

Data Analysis: A repeated measures ANOVA analyses was performed with SPSS statistical software (SPSS version 16.0 for Windows, SPSS Inc). To reduce bias and improve robustness of results, reliability was assessed where the number of assessments was ≥ 15 pairs of repeated trials (with the exception of wrist movements). PT_1's first trial data were analysed against grouped trial (PT_{2-4}) data for inter-rater

assessment. The components of reliability assessed were concordance, indicated by intraclass correlation coefficient (ICC acceptable 0.75 - 0.89; excellent ≥ 0.9) (Portney et al. 2000); variance, described by 95% confidence interval (95% CI) and presence of systematic bias, or consistent (procedural) error, between trials ($p < 0.05$). The responsiveness of the techniques was assessed using the minimum detectable difference (MDD) statistic, defined as the magnitude of real change measureable with 95% surety. To provide a robust indication of sensitivity, the MDD was calculated using the residual standard error of the measure (SEM) extracted such that each patient contributed only once to the calculation, if bilateral limbs were injured: $MDD = SEM \times \sqrt{2} \times t_{(df,.05)}$ (Bland et al. 1990). The use of critical t-values in this way provides a conservative estimate of the sensitivity of the measure. A decrease in subject numbers increases the value of t and the calculation consequently indicates that a larger change is necessary before a technique can detect it with surety.

Where sufficient data permitted sub-grouping of data, repeated measures general linear modelling (SPSS V.16) was used for a post-hoc analysis of the impact of dressings on results. In the study group, outpatient dressings were flexible, low profile and adhesive, if present at all. In contrast, inpatient dressings were all thicker incorporating anti-microbial products, gauze and bandages. For the purpose of the analysis, subjects were dichotomised to inpatient and outpatient sub-groups as a proxy measure for dressing type, and the Greenhouse-Geisser correction was used, due to the unequal variance terms between sub-groups. A $p< 0.05$ indicated the presence of a statistically significant interaction of dressing type (thickness) on repeated measurements (Portney et al. 2000). Post-hoc results are presented as estimated group means, F statistics and p values.

In all other instances, data are reported using mean (X) and standard deviation (SD) where appropriate.

Results

Participants: The total group consisted of 45 patients (38 males and 7 females), with an age range between 17 and 78 years (X = 39.5 years, SD = 14.4). The inpatient group (n=26) demonstrated a mean total burn surface area (TBSA) of 15.6% (SD = 18, range = 0.25 to 60%). Seventeen of the 19 outpatient participants had single limb injuries and the average TBSA was 1% (SD = .6%, range .25 – 5%). Twenty- eight (63.6%) patients had burn injuries to upper limbs (UL) only, 4 (9.1%) to lower limbs

(LL) only and 12 (27.3%) had burns involving upper and lower limbs (UL + LL). All outpatients were recruited and measured at, or before, 1 month post-burn.

The intra-rater subset of 21 patients, 18 males and 3 females, had an age range of 20 and 78 years (mean age = 40.6 years, SD = 18.5). Burn distributions were as follows; 7 patients (33.3%) upper limb only, 3 (14.3%) lower limb only, 10 (47.6%) upper and lower limbs, and 1 (4.8%) trunk and lower limbs.

Intra-rater Reliability: Repeated measurements recorded during the recruitment period for elbow (n=4), wrist (n=6), HS (n=12) and TO (n=12) were too few to statistically analyse as per the criteria noted a priori. However, shoulder flexion (n=31), knee flexion (n=18), ankle DF (n=19) and CFF (n=21) demonstrated the excellent agreement with ICC's ≥ .996 (95% CI's =.990-.999), without systematic bias ($p>0.05$) between grouped, repeated trials.

Inter-rater Reliability: Table VI.1 demonstrates that all ROM measurements were in excellent agreement for all of the joints assessed (ICC's ≥ 0.94) without systematic bias between trials. As only 9 patients with a burn-affected wrists were recruited during the data collection period and, as goniometry measurement technique and landmarks are the same (notwithstanding the direction of movement about neutral), flexion and extension measurements were pooled to provide an inter-rater analysis for the wrist. Of the patients recruited, 5 sustained elbow injury providing 6 burn-affected elbows for the trials. After pooling data as above, only 12 repeated measures were available thus providing a 'preliminary' analysis indicating a MDD of 7.4º.

Table VI.1 - Inter-rater reliability results by joint range of motion measurements (systematic differences were not demonstrable)

Movement Assessed **(# pairs; movement range)**	**PT_1 : X (SD)**	**PT_{GP}: X (SD)**	**ICC (95% CI)**	**MDD**
Shoulder F (n=36; 70 to 183º)	163.9º (20.2)	163.8º (20.5)	.983 (.97-.99) (p=.898)	8.1º
Wrist F & E (n=22; 56 to 105º)	76.8 º (13.7)	77.3 º (11.9)	.960 (.90-.98) (p=.526)	7.7º
Knee F (n=28; 95 to 150º)	126.6 º (16.7)	125.3º (15.9)	.968 (.93-.99) (p=.081)	6.7º
Ankle DF (n=24; -7 to 30º)	8.2º (8.5)	8.3º (9.1)	.982 (.96-.99) (p=.903)	4.1º
CFF (PDPC) (n=50; 0 to 5.2cm)	.32 cm (.88)	.31 cm (.93)	.940 (.90-.97) (p=.893)	.7cm
Hand Span (n=52; 14.3 to 25.3cm)	21.5 cm (2.3)	21.5 cm (2.2)	.975 (.96-.99) (p=.848)	1.0cm
TO (Scale) (n=50; 0 to 10)	9.0 (2.2)	9.1 (2.2)	.996 (.99-.99) (p=.159)	0.3

Inpatients vs Outpatients: Impact of Dressings on Hand Measures

More detailed analysis of elbow ROM data was not possible as indicated above. For the shoulder, wrist, knee and ankle the post-hoc analyses were also not viable as number of outpatient measures available for comparison were too few being 4, 2, 0 and 0 respectively. Post-hoc testing for the hand measures (CFF, HS & TO) is presented in Table VI.2, indicating a lack of significant impact on reliability due to differences in dressing thickness.

Table VI.2 – Post-hoc analyses of hand reliability results.

Hand Movement	$X_{Inpatient}$	$X_{Outpatient}$	**F Value**	**P value**
CFF (PDPC)	0.42cm (n=30)	0.17cm (n=20)	0.51	0.48
HS	21.3cm (n=32)	21.8cm (n=20)	0.90	0.35
TO (Scale)	8.7 (n=30)	9.6 (n=20)	2.93	0.09

Discussion

The primary outcome of this study was demonstration of excellent intra- and inter-rater reliability for goniometry and linear measurements for a number of joints across a wide ROM and cross section of the burn population in a burn center (ICC's ≥ 0.94, without systematic bias). As expected from previous literature, the inter-rater reliability was marginally more variable than the intra-rater reliability in this study (Low 1978; Mayerson and Milano 1984; Gregg et al. 1990; Hogeweg et al. 1994; Rocksen et al. 2003).

Acceptable discrepancy for goniometric measurements is quoted as 5° despite the SD of those inception studies being in the order of 3.5 – 5.7° (Groth et al. 2001; Ellis et al. 2002). In this study, the MDD was used as it was considered a more robust indication of the true measurable difference by a method than SD or SEM (Bland et al. 1999). Goniometry figures demonstrated that real change was indicated by ≥ 9° change between joint angle measurements, excepting the ankle, where a ROM change of ≥5° indicated real change. The linear measurements MDD data showed that a measureable change of > 1cm was a real change for hand span and CFF measures.

Lastly, the MDD derived for the Kapandji TO scale indicated that change of < ½ of one scale point represented true change. Based on this data, therapists can make decisions reliant on clinically relevant increments of change using any of these objective techniques. The result for individual burn survivors is the potential for effective targeted interventions directed by the results of objective measurements.

The demonstrated responsiveness of the measures was attributed to a standardised protocol and provision of training with specific discussion related to technique and identifying surface landmarks. In the burn unit clinical setting, this reduced the potential for variation in measurements due to wound dressings, patient positioning and the impact of patient motivation on the outcome of repeated active movements. Further, the post-hoc analyses confirmed that, as expected, inpatient wound dressings reduced mean hand ROM compared to outpatient dressings (Table VI.2). However, importantly, they do not impact significantly on the reliability of the tests used to measure said movement. Further, these results promote the use of the functional hand battery used in this study in preference to goniometry, which has greater potential for methodological error where finger dressings are present and, is more time consuming. These results confirm, therefore, that the use of standardised goniometric, linear measurements and Kapandji TO scale have the potential to be reliable in the burn population regardless of the presence of open wounds and dressings or early scar development.

Future Studies

An appropriately powered study is required to confirm (or refute) the reliability and MDD of goniometric measurements for elbow ROM. Further, this study did not investigate the measurement of neck, trunk or hip measurements. These areas require careful methodological consideration with respect to choice of segmental and, or global measures to indicate outcome and quality of movement. Finally, further study is required to determine the impact of dressing type on shoulder, elbow, wrist, knee and ankle.

Conclusion

In this study, the data demonstrated excellent intra- and inter-rater reliability for repeated goniometric, linear and scale hand ROM measurements in the burn population using a standardised protocol. Further, the data showed that goniometry measured change of ≥5° in ankle ROM and ≥ 9° in shoulder, elbow, wrist and knee ROM, > 1 cm change in linear hand measures and change of ≥½ of one thumb opposition scale point, indicates real change in active range of motion. Dressing type did not impact on the reliability of the functional hand measures. Therefore, assessing joint position with goniometry and linear and, or scale measurements of the hand can be accurate measures in the burns population and comprise valuable components within a standardised, functional assessment battery.

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4.3.3 Paper VII: A reliable and valid outcome battery for measuring longitudinal recovery of lower limb function and balance after burn injury.

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Background

At the Royal Perth Hospital (RPH), the Burn Service of Western Australia manages up to 600 adult patients per year, with approximately 200 each year admitted to the burn center. Of these, ~40% have burns to their lower limbs and, or trunk. Pain, scar tissue contracture, impaired sensation, muscle weakness and postural imbalance are all potential complications of lower limb burn injury (LLBI) which negatively influence a person's ability to function normally (St-Pierre et al. 1998; Kowalske et al. 2001; Leblebici et al. 2006; van Baar ME et al. 2006). Burn injury affects dermal tissue which contains sensory neurones that contribute to the conscious and automatic feedback systems which in turn, control balance and coordination (Helm et al. 1985; Hermanson et al. 1986; Malenfant et al. 1998; Nedelec et al. 2005). Impediments arising from LLBI are similar to those observed in other populations suffering lower limb disease or pathology and further, these complications cause balance dysfunction (Richardson et al. 1996; Hurvitz et al. 2001; Bear-Lehman et al. 2006; Cimbiz et al. 2006; Gajdosik 2006; Holviala et al. 2006). Balance and mobility are complex bodily functions integral to discharge disposition, social function and quality of life (Duncan et al. 1993; Cho et al. 2004b; Sang-I and Woolacott 2005; Farrell et al. 2006). Therefore, to guide recovery accurately and facilitate rehabilitation after LLBI, multi-factorial assessment is required.

An online search in *Medline*, demonstrates that papers describing recovery from upper limb burn are at least twice as frequent as those regarding LLBI. In patient and non-injured populations, there is an abundance of literature and reference values for tests of function involving the lower limb, including balance and coordination (Berg et al. 1992b; Fox et al. 1996; Rinne et al. 2001) Despite this, a validated, population specific set of tools for measuring recovery of balance and mobility after LLBI are yet to be established.

The RPH team philosophy for recovery after burn injury focuses on the benefits of rehabilitation from the day of injury (Sheridan et al. 1999; Okhovatian and Zoubine 2007). Therapy input is designed to restore an individual's pre-injury status and should

be directed by longitudinal objective outcome measurements. The use of valid assessment tools provides an accurate picture of patient recovery to guide clinical practice while minimising the impact of unnecessary clinical testing on patients and health services.

In examining tests to be used clinically to measure lower limb outcome, common, standardised tests should be considered (Staley et al. 1996). Initially, tests considered for implementation at RPH were examined for clinical utility in the burn environment and for their scientific value against the time taken to perform the test. Pilot trials in small cohorts of burn patients, confirmed that elements of the Berg Balance Scale (Berg et al. 1992b), 10 meter walk (Rossier and Wade 2001), the Functional Independence Measure (FIM) (Keith et al. 1987) and the Queen's College step test (Zaidi et al. 2000), demonstrated ceiling effects and, or lacked sensitivity (Edgar, D. 2004, unpublished data). Functional 'cardio-vascular fitness' tests (Solway et al. 2001) such as the six minute and two minute walk tests were piloted also with similar results. Further research occurred through discussions with experienced physical therapists in the areas of acquired and spontaneous brain injury and gerontology. Finally, the LLBI battery chosen for testing on the basis of their brevity, sensitivity and applicability in the RPH environment was as follows: the Burn Specific Health Scale-Brief (BSHS-B), the single leg stance (SLS) tests, the Timed Up and Go (TUG) test, tandem walk (TW) tests and ankle range of motion (Tinetti 1986; Podsiadlo and Richardson 1991; Shumway-Cook and Woollacott 1995; Kildal et al. 2001b).

To compile a battery of outcome tools for measuring recovery after injury it is also important that each item 'adds value'. To this end certain, statistical criteria must be met. Each variable or tool must be valid and reliable in the relevant population group, and significantly but only moderately correlated with each other (Moyé 2003b). Where two or more tools are highly correlated they are essentially duplicate measurements and only one is necessary in a battery (Moyé 2003b). Further, it is important to ensure that each tool demonstrates adequate sensitivity, over time, within the population of interest (2000).

The BSHS-B and ankle goniometry, were proven to be reliable, valid and sensitive in the burn population (Berg et al. 1992a; Munster et al. 1996; Franchignoni et al. 1998; Bennie et al. 2003; Littleré Moi et al. 2003; Nilsson et al. 2006; Edgar et al. 2008b; Edgar et al. 2009b). The BSHS-B is a validated population specific quality of life measure that, to date, is the only existing measure of overall recovery from burn injury

(Munster et al. 1996; Littleré Moi et al. 2003; Wu et al. 2007b). It is considered a 'gold standard' measure and therefore, was the comparator for validity for the tests of physical function. The TUG, TW and SLS have previously been validated in other injured and non-injured populations but have yet to be tested in burn patients (Podsiadlo et al. 1991; El-Kashlan et al. 1998; Franchignoni et al. 1998; Rinne et al. 2001; Lin et al. 2004; Vereeck et al. 2007).

Thus, the primary aim of this study is to examine the reliability (and responsiveness) of the SLS, TUG and TW in a representative sample of the burn population. Secondly, this paper will use clinical outcome data to examine validity of the individual tests against the BSHS-B. Finally, a standardised battery of lower limb outcome measures for measuring temporal recovery after LLBI will be described.

Patients and Methods

Reliability of LL outcome measures

Patient population: Patients with burns to one or both legs were recruited prospectively for population specific reliability testing. The participants who underwent testing included 28 patients (22 males, av. age = 33.4 yrs +/- 12.2, range: 18 – 66, av. TBSA= 3.8% +/- 4.1%, range: 1-20). Patients were excluded if they had undergone scar revision or release surgery. The group included both inpatients and outpatients with LLBI who were over 18 years of age, could understand the requirements of the tests, could weight bear fully on each LL and perform the test without compromising their safety (as assessed by an experienced physical therapist at the time of testing). All patients provided informed consent and this study was registered with the RPH Clinical Safety and Quality Unit (CSQU # 080429-1), a subgroup of the RPH Ethics Committee, as part of the Burn Clinical Outcomes and Research Project (BCORP).

Development of Procedure: Practice attempts to reduce systematic bias and overstatement of treatment efficacy due to a learning effect in test-retest trials of stability tests are presented frequently in the literature (Birmingham 2000; Nordahl et al. 2000; Rinne et al. 2001; Ageberg et al. 2003). For each of the balance and mobility trials a practice attempt was included. A pilot study confirmed findings of a learning effect for the TUG and TW. A repeated measures ANOVA demonstrated this to be between 5 – 12% for the TUG ($F_{df=1}$= 14.1, p< 0.001) and TW ($F_{df=1}$ = 5.3, *p*= 0.028).

Reliability Testing Procedure: To broaden the clinical applicability and reduce the likelihood of overstatement of concurrence of the tested assessments, the tester group included a mixture of experienced physical therapists and students (for reliability trials only). All staff were trained in the standardised procedures of each test, as documented below, prior to commencement of the reliability trial. In random order, two examiners blinded to each other's activity, performed test-retest reliability trials. All LL tests were performed on a firm surface with the distances clearly marked on the floor. A stopwatch was used to time each test. Each tester repeated the trials within 20 minutes of each other, on the same day.

Lower Limb Test Protocols: The SLS (Tinetti 1986; Bohannon 1995; Jonsson et al. 2004) is a test of static standing balance with eyes open (SLS-eo) and eyes closed (SLS-ec). Each participant was timed as they balanced on a single leg, on a hard surface, with arms crossed across the chest. The timing ceased at 30 seconds or if the patient moved their arms or foot significantly from their starting position. Inability to achieve a 30 second limit had previously demonstrated an increased risk of falling and increasing the length of the test did not increase sensitivity (Komatsu et al. 2006). One-leg standing for 30 seconds is functionally relevant as in tasks such as donning socks and bathing.

The TW tests are timed assessments comprised of forward (TWF) and backward (TWB) components. The participant placed their toes or heel at the starting point, then walked a three meter marked line, placing one foot in front of another, adjoining their feet with each step (Gill-Body et al. 2000; Cho and Scarpace 2004a; Low Choy et al. 2006). Timing ceased when either foot crossed the finish line.

The TUG test recorded the time taken to rise from a chair, walk three meters, turn around and return to sit down, whereupon timing ceased. The legs of the chair were aligned with the starting line. The same chair was used each time. As per the original protocol, the patient was allowed to use a walking aid if required (Podsiadlo et al. 1991)..

Data Analysis: The data was analysed using SPSS (V.15) (SPSS Release 15). To indicate the reliability of repeated measurements, intraclass correlation coefficient (ICC) and 95% confidence intervals (95% CI's) were estimated by repeated measures ANOVA. ICC values were accepted as moderate (<0.75), good (0.75-0.89) or excellent (> 0.9)(Landis and Koch 1977). Only tests that demonstrated reliability of 0.75 or

higher were considered eligible for inclusion into the lower limb test battery. Significance was set at $p<0.05$.

To assess the clinical utility of the tests, minimum detectable difference (MDD) was calculated from the repeated trials by using the standard error of the mean (SEM) as follows: MDD = SEM x $\sqrt{2}$ x $t_{(df,\ 05)}$ (Bland et al. 1999). The MDD indicates the magnitude of real change measureable by a test with 95% surety.

Validity of LL outcome measures and battery

Patient population: A LLBI patient cohort (n= 172) was extracted from data collected from January 2006 to August 2008, to examine the validity and contribution over time of the balance and mobility tests used to assess outcome after LLBI in the RPH burn population. Again, patients who had undergone scar revision or reconstruction surgery were excluded. The mean age and %TBSA for the group was 38.2 +/- 16.3 years and 10.1% +/- 14.1 respectively. 78.5% were male and 56% had surgical intervention to facilitate wound closure.

Data Analysis: The data was analysed using STATA (V. 9.2) statistical package. Limbs were categorised as most and least burned instead of right and left for analysis because some patients had burns to both limbs and others had single limb burns.

The criterion validity of the each of the balance and mobility tests was examined at 1, 3 and 6 months from injury. The association between the physical measures (functional tests and ankle dorsiflexion) and BSHS-B scores was determined using an errors-in-variables (EIV) regression analysis. Variability of each test was incorporated using the ICC's from the reliability analysis (Draper and Smith 1998). So as not to exclude possibly useful components in the LL battery, a p value < 0.10 was used to indicate a significant association with time within the EIVR analysis.

Combinations of the individual tests were analysed to determine their contribution to the measurement of recovery over time and thus construct validity of the test battery. According to Moyé, tests contribute significantly to a battery if this association is between 0.4-0.7 and $p<0.05$. If the correlation is >0.8, then the test is redundant and should be excluded from the battery (Moyé 2003a). The analysis was performed using a random-effects regression model with maximum likelihood estimation for all valid measurements as determined from the EIV regression analysis (Cohen 1977). The random effects regression analysis with maximum likelihood estimation and

bootstrapped standard error provides a robust methodology to prevent overstatement of concordance (Dunn 2007).

Results

Reliability of LL outcome measures (n=28)

Inter-rater *Reliability:* One patient (#13) was excluded from the analyses, as he was deemed unsafe to complete the balance tests after recruitment (SLS and TW). The ICC's for the TUG, TWF and TWB ranged from 0.87 – 0.93 indicating good to excellent inter-rater reliability. Of the SLS tests, the scores for the eyes open test showed greater concurrence than those for the eyes closed test. The ICC's for the SLS-ec reflect a moderate level of reliability (Table VII.1).

Table VII.1: Descriptive statistics and reliability values for balance measures (n = 27)

	Mean (SD) Trial 1 (sec)	Mean (SD) Trial 2 (sec)	ICC (95% CI)	p	MDD (sec)
SLS-eo (most injured)	27.02 (0.42)	26.84 (1.11)	0.81 (0.58 – 0.91)	0.52	12.61
SLS-eo- (least injured)	25.30 (8.59)	25.07 (9.53)	0.93 (0.85 – 0.97)	0.14	9.27
SLS-ec (most injured)	9.00 (7.73)	9.79 (9.33)	0.63 (0.18 - 0.83)	0.36	17.29
SLS-ec (least injured)	12.04 (11.22)	13.15 (10.28)	0.89 (0.75 - 0.95)	0.42	14.31
TUG	5.82 (1.06)	5.95 (1.11)	0.93 (0.85 - 0.97)	0.17	1.13
TWF	8.42 (1.70)	8.16 (2.06)	0.88 (0.74 - 0.95)	0.68	2.54
TWB	10.06 (3.27)	9.45 (2.77)	0.87 (0.71 - 0.94)	0.76	4.24
Ankle DF	8.2 (8.5)	8.3 (9.1)	0.98 (0.96-0.99 0	0.90	4.1

Note: Ankle DF reliability has been estimated in a previous study and those estimates were used in this paper (Edgar et al. 2009a).

The MDDs for each variable are also shown in Table VII.1. For TUG, TWF and TWB the MDDs (1.13, 2.54, 4.24 seconds) indicate that these are clinically sensitive to

changes in patient function. For the SLS tests the high MDD's (between 9.27 and 17.29 seconds) indicate low sensitivity.

Validity of LL outcome measures (n=172)

Validity of individual tests (Table VII.2): The EIV regression analysis indicates the degree of association between each measure and the BSHS-B. TUG was significantly associated with BSHS-B at one and six months (p=0.004 and 0.006) post injury with one second on the test corresponding to a clinically significant change score on the BSHS-B as indicated by the regression coefficient. It is also apparent that the coefficients increase with increasing time post-burn. TWF showed a strong association with the BSHS-B (p= 0.056, 0.065) at the same assessment time points. Although not statistically significant at each time point they contribute to the clinical validity of the battery over the whole time period (see below). Neither SLS tests, nor ankle ROM (dorsiflexion) showed an association with BSHS-B at any of the observation times. As TWF and TWB are highly correlated (r^2= 0.91, p<0.0001) having both tests in the battery is unnecessary.

Table VII.2: EIVR results at discharge and post-injury follow-up to six months

Variable	Time	EIVR coefficient *	95% CI of coeff.		*P*
			LCL	UCL	
SLS-eo leg (ln)	Discharge	0.05	-6.32	6.42	0.988
	One month post-injury	11.8	-4.08	27.66	0.141
	Three months post-injury	-4.63	-16.3	6.99	0.423
	Six months post-injury	-2.32	-36.8	32.1	0.891
SLS-ec leg (ln)	Discharge	-1.11	-10.44	8.22	0.813
	One month post-injury	8.31	-3.09	19.7	0.149
	Three months post-injury	10.0	-3.78	23.8	0.149
	Six months post-injury	-3.67	-17.8	10.5	0.598
Ankle DF injured leg	Discharge	0.04	-0.12	0.20	0.605
	One month post-injury	0.05	-0.11	0.21	0.545
	Three months post-injury	-0.05	-0.29	0.19	0.664
	Six months post-injury	0.22	-1.41	1.84	0.781
TUG (ln)	Discharge	-0.83	-4.43	2.78	0.650
	One month post-injury	-6.30	-10.5	-2.09	0.004
	Three months post-injury	-3.85	-8.55	0.85	0.105
	Six months post-injury	-44.1	-74.6	-13.5	0.006
TWF (ln)	Discharge	-2.14	-4.70	0.43	0.102
	One month post-injury	-3.03	-6.15	0.09	0.056
	Three months post-injury	-2.38	-5.13	0.37	0.088
	Six months post-injury	-36.6	-75.7	2.43	0.065
TWB (ln)	Discharge	-2.25	-4.83	0.14	0.064
	One month post-injury	-2.04	-5.29	1.20	0.210
	Three months post-injury	-1.74	-4.81	1.32	0.255
	Six months post-injury	-3.37	-43.5	36.7	0.864

*The EIVR coefficient indicates the degree of change in the dependent variable (BSHS-B) which is associated with one unit of change in the independent balance variable after allowing for the error in the measurement of that variable. The greater the value of the coefficient the greater the strength of the association.

Validity of test battery: The longitudinal random-effects regression analysis examines the change in the BSHS-B over time (Table VII.3). As expected, the changes in BSHS-

B responses were non-linear, demonstrating a plateau effect from ~one month post injury. Of all the tests TUG and TWF add significantly more information to the BSHS-B over the six month recovery period (p=0.02, 0.042) for the whole patient group. SLS-ec and ankle DF only add significantly for cases that required skin grafting surgery (p= 0.044 and 0.020 respectively).

Table VII.3: Results of longitudinal random-effects regression modelling indicating the value of tests included in the proposed lower limb burn outcome battery.

Variables added to BSHS based model	χ^2_{LR}α	*P*
Time	reference	
Time+Time squared	7.73	**0.005***
Time+Time squared+TUG(ln)	5.44	**0.020***
Time+Time squared+TUG(ln)+TWF(ln)	4.15	**0.042***
Time+Time squared+TUG(ln)+TWF(ln)+SLS-ec(ln)	1.24	0.265
Time+Time squared+TUG(ln)+TWF(ln)+SLS-ec(Y/N)	0.05	0.829
Time+Time squared+TUG(ln)+HTfwd (ln)+SLS-eo(ln)	0.85	0.358
Time+Time squared+TUG(ln)+TWF(ln)+SLS-eo(Y/N)	0.58	0.448
Time+Time squared+TUG(ln)+TWF(ln)+Ankle DF	1.09	0.297

α χ^2_{LR} Likelihood ratio chi squared. Indicates the strength and size of the association with BSHS as each variable is added to the regression model.

***** Indicates the variables that significantly contribute to explain LLBI patient outcome over time (P<0.05).

Discussion

According to the standards set a priori, the SLS-eo, TW and TUG have shown a good to excellent level of reliability. The SLS-ec demonstrates fair reliability, an outcome that can be attributed to a variety of factors, including the possible impact of impaired proprioceptive feedback post-burn. This is not an unexpected finding as a broad variations in results across a number of sample populations have previously been reported (Fox et al. 1996; Birmingham 2000). Blinded testers with varying levels of expertise and familiarity with the tests were employed to increase the clinical utility and relevance of our tests. The high proportion of young males with small TBSA burns in the reliability sample was an accurate reflection of all patients in the RPH burns population. It is important to remind all future users to examine the test-retest

reliability of tests in their own clinical environment in order to understand how they perform with their casemix.

For the TUG and the TWF tests, the MDD indicates that a change of 1.1 seconds and 2.5 seconds respectively, is required to indicate improvement or deterioration (Table VII.1). These values are useful in the clinical environment. In contrast, the amount of change required to show improvement in the standing balance tests is between 30% and 52% suggesting that the tests lack sensitivity.

Establishing the ability of the individual balance and mobility tests to measure recovery from LLBI is more involved. The TUG has the strongest relationship (EIVR coefficient) with the BSHS-B total and therefore is most valid of those tested, particularly at one and six months from injury. The TWF is also significantly associated with the BSHS-B over time. This demonstrates that functional performance mirrors self-rated recovery. Further, up to six months post-burn the TUG and TWF tests add significantly more information to the BSHS-B in the process of assessing recovery from LLBI (Table VII.3).

The results support the construction of a lower limb outcome battery (LL-BOB) consisting of the BSHS-B, TUG and TWF to measure functional recovery from LLBI up to six months from injury. Further, SLS-ec and ankle DF have clinical utility at discharge for patients who have had skin reconstructive surgery.

In summary the LL-BOB described above has the ability to accurately measure and monitor recovery of balance and mobility after burn injury and to assist in the design of individual rehabilitation programs over time.

Future Study

The next phase of the LL-BOB project involves detailed investigation of the predictive value of the battery and evaluation of other, potentially more sensitive tools for measuring recovery from burn injury such as the HiMAT (Williams et al. 2006), the Lower Limb Functional Index (Gabel et al. 2005), 3-dimensional movement analysis (Grisbrook et al. 2009b) and the SF-36 (Cromes et al. 2002a). The role of joint ROM in measuring burn outcome, stratified by severity markers such as skin graft surgery requires examination in greater detail. Data collection is ongoing to allow greater stratification of reference values for assessment of functional recovery after burn

injury. Time to recovery involving the use of reference values is an important area for further exploration and will presented in due course.

Conclusion

This paper presents a battery of valid, reliable, standardised, clinically useful tests comprising the TUG, TWF and the BSHS-B to measure the recovery of lower limb function after burn injury.

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4.3.4 Paper VIII: Demonstration of the validity of the SF-36 for measurement of the temporal recovery of quality of life outcomes in burns survivors.

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1. Introduction

The World Health Organization (WHO) International Classification of Functioning (ICF) provides a framework to measure health status, quality of life (QoL), or well being in terms of impairment, activities, participation and environment (WHO 2001). Burn injury affects the QoL of patients and causes a multi-factorial, long-term, residual burden of disease (van Baar et al. 2006; Falder et al. 2009). To date, the most common tool for quantifying QoL after adult burn injury has been the Burn Specific Health Scale (BSHS). A brief version was developed to reduce patient burden (Kildal et al. 2001a). However, it is debatable whether the BSHS provides a 'gold standard' measure of the recovery of QoL. In that, the limitations of the measure lie in the population specific nature of most of the scale items; the relative lack of sensitivity, particularly in less severe burns; the demonstration of a 'premature' ceiling effect (Cromes et al. 2002b) in temporal studies and the lack of normative data for comparison with other patient or healthy populations (Blades et al. 1982c; Wu et al. 2007b).

It was proposed that other QoL measures could be valuable adjuncts to the BSHS and address these shortcomings. Thus, the Medical Outcomes Study 36-Item Short Form Health Survey (SF-36) was investigated for this study. The original measure was described by Ware (Ware and Davies 1988). In development since the late 1980's, the SF-36 is a generic, psychometrically based, self-rated questionnaire. No less than five versions are available for use though the second (V2) and most recent format is the recommended option (Ware 2000). It maps closely to the ICF domains and has published gender and age stratified norms for grouped, condition specific and individual comparisons. The SF-36 describes outcomes in terms of 8 separate sub-scales (domains) and three summary measures incorporating the domain scores. The survey may be administered in the standard or acute forms requesting responses in terms of recall of activity or feelings in the previous 4 weeks or 1 week, respectively. The SF-36 reliability and validity has been extensively reported in patient and general populations but never reported in the burn injured group (Ware JE 1993 ; McHorney CA 1994).

While useful, previous studies have not demonstrated the validity of application of the SF-36 as a longitudinal measure of the recovery of QoL in the burn population. Appropriate validation of the SF-36 will improve burn care through increased potential

for local and international burn service benchmarking, understanding of burn patient recovery patterns through comparison with norms and facilitate the development of multi-center research.

Thus, the aims of this study were to examine the validity of SF-36 in the longitudinal measurement of post-burn QoL recovery based on correlation with an established burn outcome measurement (BSHS-B). Secondly, the supplementary aim in this study is to describe and illustrate the sensitivity and pattern of change for subscales and summary scores to 2 years post-burn.

2. Materials and Methods

2.1 Subjects

Between August 2006 and March 2009, a random sample of convenience including admitted and ambulatory patients treated by the Royal Perth Hospital (RPH) burn team, were recruited prior to discharge. Participants were included independent of TBSA or agent or mode of burn injury and if they understood written English or, could complete the questionnaires with a hospital interpreter if available, as the resources were available only in English during the recruitment period.

2.2 Measurement Methodology

After recruitment and provision of consent, each patient was asked to complete both the SF-36 and the BSHS-B at 1, 3, 6, 12 and 24 months post-injury. Not all patients were recruited at 1 month post-burn. The planned methodology provided an opportunity to quantify the longitudinal recovery of QoL post-burn. The surveys were both completed on the same day in the burn outpatient clinic and where possible, without staff supervision or assistance. Where the patient was not present for physical review, questionnaires (see 2.2.1-2) were mailed to the patient to be returned by self-addressed envelope. Phone interviews were not conducted with this cohort.

2.3 SF-36

The survey version used during this study was the SF-36 (V.2) Acute Recall (Australian English). The one week recall version was chosen because the standard (4 week recall) version was considered difficult to interpret during the sub-acute burn period and early scar maturation phase, where significant changes occur in QoL, social participation and environment, particularly for more severe burn patients.

Completion of the 36 items yielded an 8-subscale profile of patient functional health and well-being, as well as empirically derived physical and mental health component summary (PCS & MCS) measures. The subscales are scored as percentages and the summary measures are scaled to provide a score out of 50%. The SF-36 domains are well understood and used by clinicians across a broad range of patient populations, age ranges and settings (Quality Metric 2009). The V2 acute recall possessed good to excellent internal consistency across all domains in the US general population (Cronbach's α=0.81-0.95) (Ware et al. 1993).The subscales are as follows:

1. *Physical Functioning (PF)*, measuring how health limits vigorous, moderate and easy activities.
2. *Role Physical (RP)*, measuring how much health interferes with ability to perform daily activities and normal work.
3. *Bodily Pain (BP)*, measuring how much pain interferes with normal work.
4. *General Health (GH)*, measuring perception of health generally.
5. *Vitality (V)*, measuring perceived personal energy level.
6. *Social Functioning (SF)*, measuring how health interferes with social activities.
7. *Role Emotional (RE)*, measuring how much emotional states of mind interfere with ability to perform daily activities and normal work.
8. *Mental Health (MH)*, measuring perceived mental (emotional) status.

As stated previously, shorter versions of this scale exist but the longer version was chosen to improve clarity and detail for validity assessments (Ware et al. 1996; Turner-Bowker et al. 2003). Further, the shorter versions have been demonstrated to be less sensitive than SF-36 for comparison of groups with <200 participants (Riddle et al. 2001). A third summary measure, the Health Utility Index (SF-6D) is available to supplement the PCS and MCS, with the appropriate scoring software (Brazier et al. 1998). As the Index was derived primarily for health economics and treatment efficacy comparisons, it was not included in this study (Brazier et al. 2002).

Lastly, in view of the work reported in ~24 patient populations, from >30 papers, the investigators considered that including test-retest reliability in this study was unethical (Turner-Bowker et al. 2002). The subject burden related to routine clinical outcome assessments during the course of the study was considerable. Up to 17 physical or survey tools were applied at the same time points as utilised during the study. While studies of subgroups indicate slight declines in reliability with increasing respondent disadvantage, reliability coefficients consistently exceeded standards for group level analysis, as planned in this study. Further, it was considered a reasonable assumption

that serial measurements within 1-2 days would be relatively stable for patients from 1-3 months or greater post-burn injury as in the recruited burn subject population.

2.4 BSHS-B

The original BSHS, validated for burn patients, comprised 80 questions (Blades et al. 1982c). A 40-item tool, the BSHS-B (Brief) was then developed and validated, indicating patient outcomes in terms of domains: Heat Sensitivity, Affect, Hand Function, Treatment Regimens, Work, Sexuality, Interpersonal Relationships, Simple Abilities, and Body Image (Willebrand et al. 2002). These authors demonstrated that the internal consistency of the BSHS-B was good to excellent across the sub-domains (Cronbach's α=0.75-0.93). The shorter version was chosen to reduce patient burden in this study and, it was reported to be as sensitive as the longer version. Further, it provides more detail than other modified versions including the BSHS-A (Kildal et al. 2002) and BSHS-R (Blalock et al. 1994). To provide a more meaningful analyses against the SF-36 domains, the BSHS-B was analysed in combined domains defined as: Physical (Hand Function + Simple Abilities); Social and Emotional (Affect + Work + Sexuality + Interpersonal Relationships + Body Image) and Non-physical / Burn Specific (Heat Sensitivity + Treatment Regimens).

2.5 Statistical analyses

Demographics analyses were completed with SPSS v.17 and described using mean and standard deviation (SD) where appropriate. As the outcomes of this study were collected prospectively, the data analyses utilized longitudinal regression (LR) modeling (STATA V.10). Being a clinical study, variation and missing data were assumed. LR modeling combinations were chosen as robust methodologies to accommodate data missingness and to reduce the likelihood of overstatement of concordance (Dunn 2007). All correlations were reported in terms of Pearson's coefficient of correlation (r) with corresponding 95% confidence intervals (95% CI's). P-values were considered significant if < 0.05. The number of patients differed for each comparison due to the recruitment pattern during the study and, or missing responses which excluded individual's subscale or summary measures. Tolerance for missing values for the BSHS-B has not been described in the literature. Therefore, if missing values existed the whole survey was excluded from the particular comparison.

Criterion (Temporal) Validity: The BSHS-B was used as a criterion validity comparison for the SF-36. As both scales attempt to quantify the recovery of QoL, criterion validity

in this study referred to the comparison of concordance of the domains and summary scores of the SF-36 against the BSHS-B over time. To provide meaningful comparisons, the BSHS-B scores were re-scaled as percentages. While it was appreciated that the temporal pattern of recovery is not linear, to simplify results, a random effects model (REM) linear regression was used to compare the degree (slope) and direction of change between assessment time points. A significant correlation of the linear slopes between assessments was considered to demonstrate validity throughout recovery. If the calculated correlation was $r > 0.8$, indicating measurement of equivocal outcome construct(s), the two scales were to be considered interchangeable and conversely, one would be considered redundant (Fayers et al. 2000).

Construct validity: A statistically significant association of the SF-36 temporal change scores with indicators of burn severity by definition indicates the construct validity of the scale. To determine the ability of the SF-36 to measure expected differences in outcome related to burn severity, total burn surface area (TBSA) was chosen as the most illustrative (Willebrand et al. 2001; Kildal et al. 2002). Assuming that all variables affecting outcome are not fixed, a longitudinal *random effects* regression model was used as a robust method to assess the association of SF-36, in comparison with BSHS-B, over time across the broad range of TBSA's in the RPH sample population. The regression coefficient indicated the correlation of the BSHS-B and SF-36 summary measures and sub-scale scores to TBSA. Further, the magnitude of the coefficient provides their relative contribution to, or accuracy in modelling TBSA, as the dependent variable.

Sensitivity: The sensitivity of a measure to detect change indicates the clinical efficacy of the outcome tool (Gummesson et al. 2003). A multi-factorial LR analysis estimated the relative change, or effect size, of survey scores per month, as recovery occurs with time. This method allowed the inclusion of all factors that influence burn QoL outcome, modeled using the study data. The percentage change per month was presented for both scales to illustrate the relative capacities of the SF-36 and BSHS-B to quantify recovery of QoL. A greater regression coefficient indicated the more sensitive measure when comparing between survey summaries and, or subscales.

2.6 Ethics

This study was registered, and approved, as a component of the Burn Clinical Outcomes and Research Project (BCORP), with the Clinical Services and Quality Unit (CSQU # 080429-1). At our facility, all non-interventional trials are required to be registered and assessed by the CSQU, a subsidiary group of the RPH Ethics Committee. All patients provided informed consent prior to inclusion into the study.

3. Results

3.1 Sample description

A total of 280 patients with burns treated in RPH were recruited to the study, providing a total of 413 repeated survey comparisons. Males made up 81% of the group (mean age of 37.4 yrs, SD=15.1, range: 16 - 84 yrs). The study group mean TBSA was 8.9% (SD=11.6, range: 0.25 – 60%). Mean LOS was 11.9 days (included 5 outpatients) (SD=14.0, range: 0-100 days). Of the group, 50% had a full thickness burn and 3% had a burn TBSA >10%. Ten patients (5.6 %) were admitted to the Intensive Care Unit (ICU) with mean LOS of 9.4 days in ICU. Analysis of burn location indicated that 70.6% suffered upper limb burn injuries, 59.8% lower limb burn injuries and 10.7% of the group had trunk injury. Surgery was necessary for 60% of patients. The sample is a representative subset of the RPH Burns Unit population as all demographic and severity descriptors are not significantly different from data available from all inpatient admissions between 2006 and 2008. Individuals SF-36 missing item responses ranged from 2 - 18/413 (0.5-4.4%). The total missing scores for BSHS-B were 6/413 (1.4%). The resultant maximum number of missing data points from any sub-scale comparison was 10/131 (7.6%) and summary scores was 6/97 (6.2%). Finally, 11 comparisons were available at two years' post-burn. Thus, due to the sample size, grouped data at this time point was excluded from all but the descriptive analyses for pattern of recovery.

3.2 Validity

Criterion (temporal) validity

According to linear regression analyses, correlation coefficients ranged from 0.37 - 0.79 for the SF-36 domains and summary scores against the BSHS-B (Table VIII:1). All correlations were significant, and differed at every time point. The range of correlation coefficients demonstrates the subscales and summary scores show moderate to good correlation with the BSHS-B.

Table VIII.1: Strength of correlations between SF-36 domains and summary scores against BSHS-B total between 1 and 12 months post-burn injury (p<0.0001 unless otherwise specified).

	SF36 Subscale Correlation with BSHS-B Total			
	Physical Function		**Vitality**	
Month	**n£**	**r**	**n**	**r**
1	131	**0.557**	125	**0.666**
3	106	**0.456**	102	**0.516**
6	96	**0.572**	90	**0.678**
12	76	**0.596**	77	**0.649**
	Role Physical		**Social Function**	
Month	**n**	**r**	**n**	**r**
1	119	**0.487**	129	**0.580**
3	99	**0.767**	105	**0.745**
6	95	**0.617**	97	**0.688**
12	73	**0.612**	75	**0.793**
	Body Pain		**Role Emotional**	
Month	**n**	**r**	**n**	**r**
1	121	**0.512**	123	**0.536**
3	106	**0.638**	100	**0.759**
6	96	**0.652**	96	**0.726**
12	76	**0.681**	73	**0.610α**
	General Health		**Mental Health**	
Month	**n**	**r**	**n**	**r**
1	131	**0.530**	126	**0.713**
3	106	**0.426**	102	**0.531**
6	97	**0.369***	91	**0.654****
12	77	**0.463**	73	**0.691**
	SF36 PCS		**SF36 MCS**	
Month	n	**r**	n	**r**
1	124	**0.537**	124	**0.655**
3	101	**0.592**	101	**0.639**
6	92	**0.558***	91	**0.728****
12	72	**0.521**	72	**0.704**

α p=0.0001 ***p=0.002** ****p=0.0006**

£ 'n' indicates the number of available data points for each subscale at each time point. The numbers vary as individual's data for all questions of all subscales and summary scores were not complete and thus were omitted.

Construct validity

The random effects longitudinal regression model coefficients of association were calculated using all data available across all time points. Table VIII:2 demonstrates the significant correlation of BSHS-B (total and domains) and similarly SF-36 domains (PF, RP, BP & SF) and physical component summary score with TBSA. The relative size of the coefficient provides a comparison of the relative sensitivity of each of the measures to describe (predict) outcomes in terms of TBSA.

Table VIII.2: The association of each survey and component scores to TBSA.

Outcome variable	Coefficient	95% CI		P>|z|
		LCL	UCL	
BSHS-B	-0.516	-0.636	-0.396	<0.001
Total Score				
Physical	-0.122	-0.151	-0.093	<0.001
Mental Health	-0.187	-0.239	-0.134	<0.001
SF36				
PF	-0.324	-0.506	-0.142	<0.001
RP	-0.591	-0.824	-0.358	<0.001
BP	-0.373	-0.589	-0.157	0.001
GH	-0.093	-0.256	0.070	0.264
VT	-0.104	-0.292	0.084	0.280
SF	-0.412	-0.619	-0.205	<0.001
RE	-0.232	-0.444	-0.020	0.032
MH	-0.152	-0.317	0.012	0.070
PCS	-0.162	-0.238	-0.086	<0.001
MCS	-0.106	-0.203	-0.009	0.033

Sensitivity

Overall, the SF-36 was more sensitive to change, over whole study timeframe, than the BSHS-B. While the SF3-6 summary scores demonstrate similar responsiveness to the BSHS-B total scores, the subscales show greater relative change than the BSHS-B domains (Table VIII.3). The SF-36 role physical and bodily pain (physical) domains are the most responsive of any measure components followed by social function and role emotional (mental health) domains.

Table VIII.3: Demonstration of the relative sensitivity of BSHS-B total and subscales compared to SF-36 domains and summary scores.

	Coefficient*	95% CI		*P*
		LCL	UCL	
BSHS-B Total and Combined Domains				
Total				
Change per month	2.39	2.66	5.00	<0.001
Constant [α]	130.14	127.60	132.68	<0.001
Physical				
Time (months)	1.17	1.53	2.21	<0.001
Constant	28.62	27.96	29.28	<0.001
Social and Emotional				
Change per month	0.23	-0.30	1.04	0.276
Constant	74.39	72.97	75.81	<0.001
BSHS-B Non-Physical				
Change per month	2.34	1.34	3.33	<0.001
Constant	98.30	95.82	100.79	<0.001
SF-36 Domains and Summaries				
Physical Function				
Change per month	4.78	2.97	6.59	<0.001
Constant	73.55	69.56	77.54	<0.001
Role Physical				
Change per month	14.28	11.31	17.25	<0.001
Constant	42.00	36.06	47.94	<0.001
Body Pain				
Change per month	10.89	8.40	13.38	<0.001
Constant	49.84	44.65	55.04	<0.001
General Health				
Change per month	1.90	0.18	3.61	0.030
Constant	71.52	67.81	75.23	<0.001
Vitality				
Change per month	5.04	2.86	7.21	<0.001
Constant	52.62	48.14	57.09	<0.001
Social Function				
Change per month	9.06	6.43	11.70	<0.001
Constant	57.12	51.86	62.39	<0.001
Role Emotional				
Change per month	7.21	4.67	9.75	<0.001
Constant	67.92	62.85	72.99	<0.001

Mental Health				
Change per month	3.66	1.73	5.59	<0.001
Constant	66.75	62.78	70.71	<0.001
Physical Component Summary				
Change per month	3.37	2.51	4.22	<0.001
Constant	42.47	40.70	44.25	<0.001
Mental Component Summary				
Change per month	2.43	1.30	3.55	<0.001
Constant	43.17	40.85	45.48	<0.001

* The regression coefficient indicates the average percentage change of the scale per month.
[α] The constant represents the average value of the each score at one month post-injury.

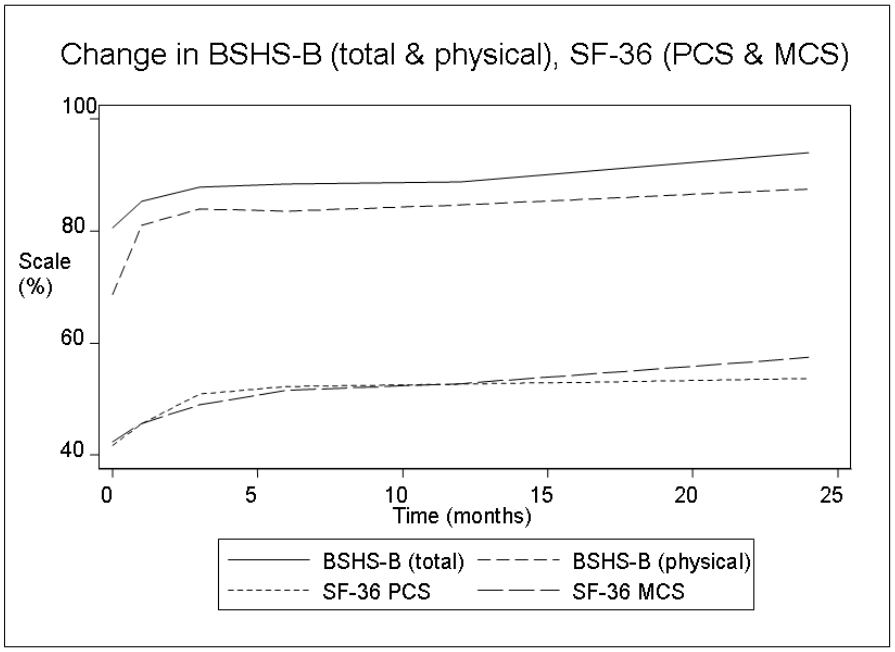

Figure VIII.1: Illustration of the pattern of change to 2 years post-burn comparing re-scaled BSHS-B total and physical domain scores against SF36 summary scores.

Pattern of Recovery

Figures VIII:1 to 4 display the similarity of the SF-36 summary scores and the BSHS-B measurements. Both outcome measures demonstrated their most significant change in scores during the period between 1 and 3 months follow-up. Between discharge and 1 month, the BSHS-B displays statistically significant changes in burn recovery, but ceases to do so beyond 1 month. Both questionnaires demonstrate a ceiling effect, and a reducing ability to measure statistically significant change from ~6 months.

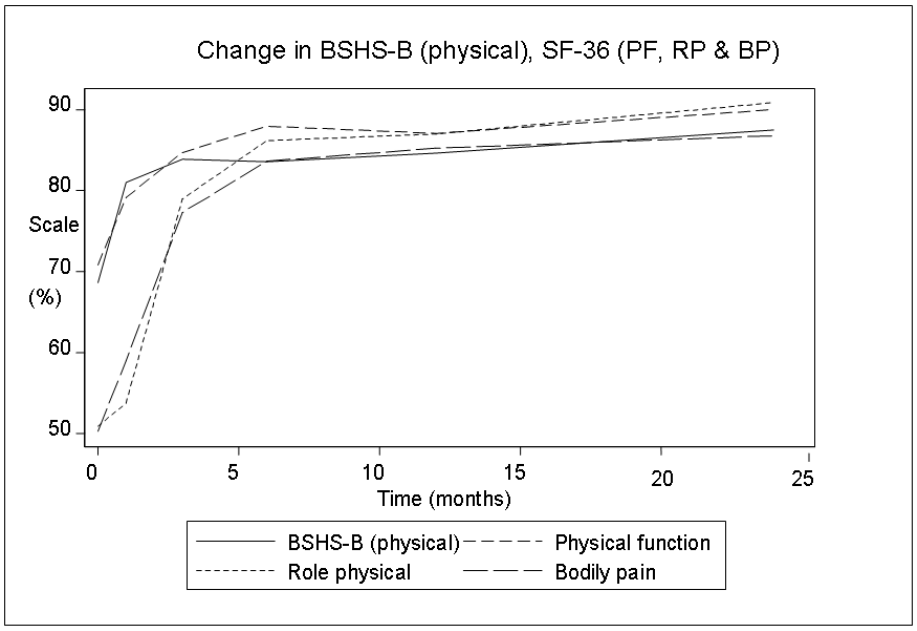

Figure VIII.2: Comparison of the pattern of recovery in the physical domains of each survey tool.

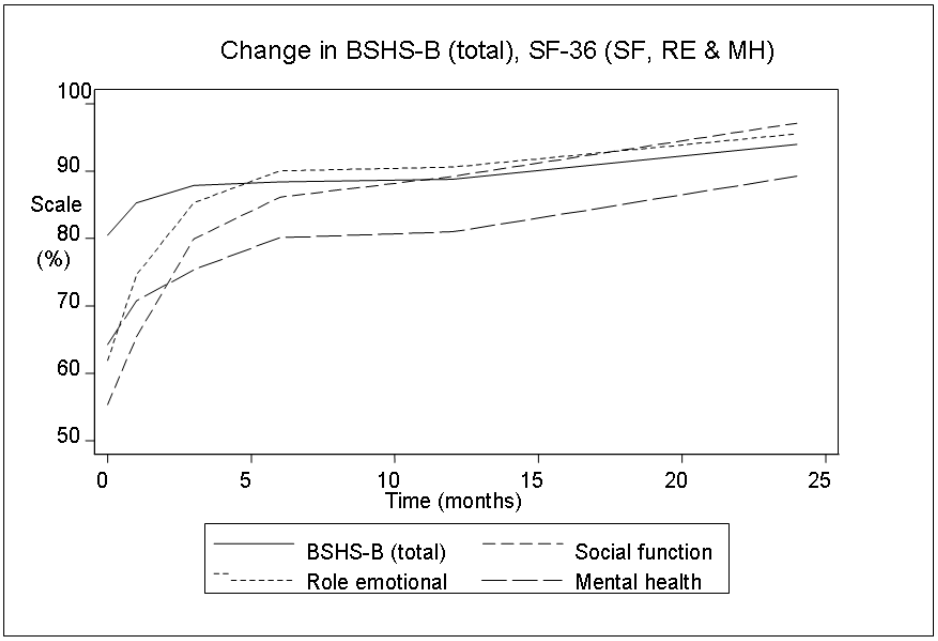

Figure VIII.3: Comparison of mental health subscales against BSHS-B total score.

4. Discussion

These data confirm that the SF-36 is a valid QoL measurement in the burns population tested. Further, this study confirms its temporal measurement efficacy by demonstration of superior subscale sensitivity compared to BSHS-B and its domains across assessment time points. Interestingly, the SF-36 summary scores were not more sensitive than the BSHS-B total or combined domain scores, whereas the subscales compared favorably.

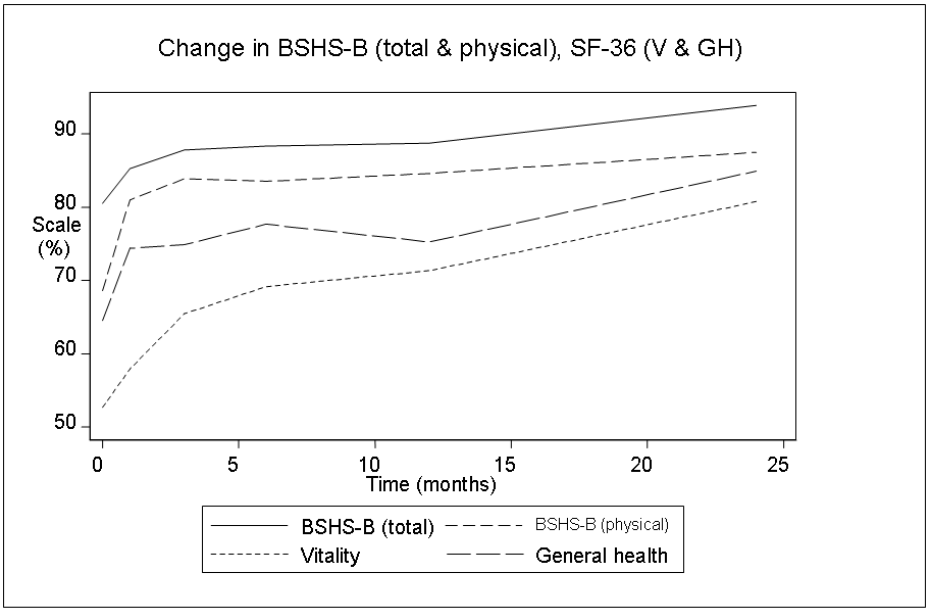

Figure VIII.4: Recovery pattern of the general health and vitality domains of the SF36.

Four subscales of the SF-36 showed the most significant changes over time and may be considered the 'sentinel domains' to monitor post-burn recovery of QoL. These were: role physical; bodily pain; social functioning and role emotional. The SF-36 domains of RP and BP continue to measure significant changes to ~ 6 months post-injury unlike the BSHS-B physical domains (Fig VIII:2). Similarly, the SF and RE SF-36 subscales show greater relative sensitivity to change than the BSHS-B total which is determined largely by the mental health domains (Fig VIII:3). It is postulated, therefore, that these 'sentinel' domains track early burn recovery closely and provide more information than the BSHS-B. In contrast, the remaining SF36 domains do not change as appreciably during the first 6 months post-burn. This phenomenon may be a result of changes in attention and focus for different facets of QoL, during the extended recovery from a burn. This theory was supported in part by the apparent measured change in the grouped general health and vitality domains after 12 months post-injury

particularly (Fig VIII:4). However, it was appreciated that these results may be biased due to reduced sample numbers at the two-year post-injury assessment.

These findings validate the use of SF-36 in earlier studies. Despite the lack of understanding of the performance of the survey in burn survivors, the use of SF-36 in the post-burn research is becoming more frequent. Thombs et al (2006) reported the pre-burn SF-36 PCS to demonstrate physical status association with depression, as per the Becks Depression scale (Bouman and Kok 1987). Interestingly, the SF-36 was collected while the patients were in the burn unit, posing questions as to the validity of responses as this time point falls outside that used in this study. However, the study concluded that inpatient depression levels were predictive of poorer physical status at 2 months post-discharge. Moi et al (2006) concluded that SF-36 possessed a greater relative sensitivity in contrast to the 'generic' Quality of Life Scale (QoLS)(Burckhardt and Anderson 2003). Lower norm stratified SF-36 scores in post-burn patients were evident while the QoLS indicated the cohort scores to be similar to the general population. Higher scores on both tools indicate an improved recovery of QoL. It was also possible that the discrepancy was due to subtle differences between the measurement constructs. Altier et al (2002) used SF-36 MCS to conclude that major burn patients, several years post-injury, have similar mental health outcomes to age, sex and education level matched controls. However, in their sample containing greater mean TBSA burns than in this study, the authors reported that burn patients described poorer scores in the general health domain. Moi et al (2003) conducted research to validate the Norwegian version of the BSHS against the SF-36. They reported correlations between 0.62-0.81 and concluded that the BSHS-Norway was a valid tool for international comparison. The correlations in this study concur with these values (Table 1). However, the authors used the 80-item BSHS and in the study of 95 patients, surveys were completed only at a *single* time point, at any time up to 5 years post burn-injury, according to their stated inclusion criteria. Finally, a recent study by Oster et al (2009) incorporated the domains of the SF-36, amongst a number of assessment tools, as comparators to demonstrate the validity of the EuroQol-5 Domains (EQ-5D), a health related quality of life survey specific to European countries. However, the authors did not validate the use of SF-36 in burn survivors.

Patient attrition in this study was contributed to by non-response to mail out questionnaires, patients not reaching the latter assessment periods before data collection ceased and non-attendance at review, due to the long distance travel required, a particular issue for the Western Australian (WA) population.

The impact of data missingness was minimised by the repeated measures design and choice of statistical analyses. However, when examining the pattern of recovery, this limitation affects the interpretation of long-term grouped results as noted above. In the study, the decline in patient numbers was seen particularly in the minor burn patients. A recent study by our group indicated that those who do not return to follow-up have an equivalent or better result than those who did provide their longitudinal recovery information (Finlay et al. 2009a). Thus, the ceiling effect or lack of appreciable change between measurement time points, indicated recovery on various scales after ~ 6 months post-burn may understate the WA burn population recovery as quantified by SF-36. Conversely, the patient sample lacked those with severe burn injury and it was probable that their outcomes would differ from the cohort presented.

A similar limitation of the sample population was that only 10 patients required ICU admission. This number was too small for a conclusive subgroup analysis. A longer study would yield more severe burn admissions, which would allow investigation of the impact of this factor and severity on recovery outcomes measured by the SF-36.

Future Studies

As noted above, the performance of the SF-36 after severe burn injury and for patients who require extended ICU admissions requires clarification. With acceptance of the SF-36 instrument in other burn centers, future multi-center trials involving larger TBSA cohorts would address this question.

This study lacks the data to explore the relative performance of SF-36 and BSHS-B between discharge and 1 month post-injury. Future studies, comparing these time points, could confirm whether BSHS-B is less sensitive than SF-36, as was indicated from the results of this study. However, questions arise as to the relevance, validity and synchronicity of discharge scores for either measure, rather than an assessment tagged to the universally comparable, post-burn injury date.

Future comparisons of burn population outcomes may include investigations stratified against general population norms for the SF-36 as well as similar trauma populations. Further, with the advent of a universal QoL assessment tool burn data may be reliably transferred and benchmarked between burn services.

In order to decrease assessment time and simplify analyses, other studies have focused on the use of SF-12 or SF-8, the shorter versions of the SF-36 (Ware et al. 1996; Turner-Bowker et al. 2003). Those authors noted a reduction in precision using these instruments. However, with adequate statistical power considerations, patient burden will be reduced by developing future research for multi-site, clinical trials in burn survivors using these instruments. Further investigation is necessary before their use could be justified.

Finally, preliminary analyses, by the RPH Burns Team, has indicated that the data collected at 1 month post-burn provides us with a strong ability to predict the long term outcome of a burn patient (unpublished data, D. Edgar). The predictive model has been developed around the BSHS-B. To ensure that all of the RPH (and international) data remains valuable, and to allow ongoing use of the SF-36 scores, our group plans to investigate a translation of BSHS-B scores to SF-36 scores.

5. Conclusion

The study has demonstrated that the SF-36 is a temporally valid measure of the recovery of QoL for burns patients. The results indicate that four of the SF-36 domains (role physical, bodily pain, social functioning, role emotional) provide more sensitive information than the BSHS-B total score or domains, particularly from ~1 month post-burn.

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4.4 Chapter Summary

This chapter presented the primary results of the candidacy. The clinical and laboratory studies of acute burn oedema were presented with discussion to follow in the next chapter. The subsequent results regarding acute and longitudinal measurement of the impact of acute burn oedema were presented as peer reviewed or submitted manuscripts.

Chapter Five

Discussion

The opening of the chapter briefly revises the history of the project in the context of the burn literature in order to place the findings in perspective. The interpretation and integration of results follows with a focus on the application of findings in clinical practice for any adult burn setting. Research design is discussed where appropriate and the chapter concludes with statements of limitations where these were not previously available in the manuscripts presented in Chapter Four.

5.1 Introduction

In 1997, a core group of ANZBA burn therapists identified the need to develop guidelines for patient treatment based on the multidisciplinary bio-psycho-social management construct. A relative paucity of high level scientific evidence existed and the initial iteration took the form of consensus guidelines (Simons et al. 2003) or descriptive papers for occupational and physiotherapists (Edgar et al. 2004). The subsequent edition of the ANZBA Guidelines was expanded to include multiple allied health disciplines (Edgar et al. 2007). The use by an international burn therapists group at the inaugural Burn Rehabilitation Summit in San Antonio, Texas (May 2008), indicated the value of the document. The publications cited within this thesis forecast a future of verifiable standards specific to allied health professionals in burn centres. These criteria once defined will provide a framework for clinical and research excellence in therapy management across the continuum for post-burn patients.

The identified gaps 'between' the early consensus-based and descriptive publications influenced the direction of the thesis and helped to define the hypotheses tested by the research presented herein. The lack of advanced research to define acute burn clinical care was, and remains, an impediment to progress of burn therapist interventions in general. In particular, significant challenges existed with limited evidence based treatment options available to therapists in the immediate post-burn period for containment and reduction of acute oedema. Thus, this candidacy was embarked upon with a focus to increase and, or confirm efficacious treatment choices for acute burn oedema, an acknowledged and major contributing factor to increasing morbidity, as well as mortality. However, early in the project, the reduced ability to measure the effectiveness of interventions within the burn environment, was noted. Thus, an

important component of the project was developed to address this significant impediment, to evaluate methods to reduce the negative impact of acute burn oedema.

The understanding of the factors worsening the extent and impact of post-burn oedema in the tissues was derived largely from early animal work, observational studies and expert opinion documented between the 1950's and 1970's. The Cochrane Review presented in Chapter Two, revealed gaps in detailed knowledge and poor evidence for the treatment alternatives in the human context. Further, the review confirmed a lack of a systematic approach to the analysis or increase in the number of novel clinical interventions for oedema. A paucity of treatment choices was noted as a primary stressor for patients when surveyed (Barratt et al. 2000). Increasing stress in an acute burn care environment leads to poorer coping and pain tolerance (Choiniere 2001; Montgomery 2004). Treatment plans for acute burn oedema were empirical or extrapolated from findings in other injury populations as stated in Chapter Two. The core principles of intervention include tissue cooling or first aid, elevation, compression and movement, which were not derived through randomised human trials in the acute burn environment. Treatments adjunctive to the core options were supported by single centre randomized trials. However, they are not universal in their clinical application. The obvious lack of consensus between clinicians, or clearly documented protocols, was confirmed not only by analysis of the literature but was noted during observational visits to major burn facilities in Australia, New Zealand, USA, England, France and Nepal.

Translation of research findings from the definitive, small sample, single site studies has not occurred. However, clinicians should consider that the use of pulsed high voltage galvanic muscle stimulation will lessen local hand oedema (Omar et al. 2004) and, acute burn resuscitation fluids fortified with continuous high-dose vitamin C will reduce local wound and systemic oedema (Tanaka et al. 1999). Similarly, the use of colloid in resuscitation fluids was associated with positive wound outcomes, dependent on the timing and dosage parameters, which remain under debate. However, Goodwin et al (1983) clearly demonstrated that resuscitation including colloid, commonly albumin, increases burn patient mortality, fluid deposition into the lungs and respiratory complications. Single facility, small sample studies deny any benefit of the use of anti-histamine on local wound oedema (Burge et al. 1979) and, parenteral steroid (lung oedema post-inhalation injury) (Levine et al. 1978). It is likely that these medication trials were underpowered and were inconclusive for this reason; hence, they may not

provide definitive results. Previous evidence also denies the benefit of steroid use in acute and sub-acute burn patient care and these studies are unlikely to be repeated (Herndon et al. 1988; Cha et al. 2007).

While it is important to note the available evidence indicates there are a number of treatment options to limit acute burn oedema, a combination of factors has impeded translation of research into practice. The Cochrane Review (Chapter Two) highlighted significant limitations to progress through the lack of specific understanding of oedema processes in human beings and, the lack of techniques for, and challenges to, accurate measurement in the unique patient population and, or acute burn environments. The translation of evidence to practice was further confounded by the low relative weighting of data derived from studies in animal models and the debate regarding applications in acute and post-acute burn (scar) research. The series of planned studies and clinical measurements was carried out since December 2000 to address these core issues related to improving the translation of evidence into clinical (and research) practice.

The studies were both enhanced, and hindered, by two significant mass burn casualty incidents during the candidacy. The adjunct publications which arose, document the clinical trials and outcome battery developments during and subsequent to these events (Edgar et al. 2005; Edgar et al. 2006). The cohorts involved with common injury demographics offered unique opportunities to measure objectively, and reflect on, the efficacy of oedema treatments, and to trial individual and grouped outcome measures. Comparison of the incidents highlighted the empirical nature of understanding of post-burn oedema and the positive impact of early interventions on oedema and subsequent outcomes after severe burn injury (Rea et al. 2009b).

5.2 Clinical Treatment and Research Design

The studies investigating acute oedema were designed to describe microscopic and macroscopic change during the first week post-burn. At the RPH, routine oedema therapies were applied during all the studies and the onset and absorption timeframes for oedema were likely to be affected by the treatment input. However, for acute clinicians and researchers the results provide novel information, which provide considerations for the timely introduction of interventions or design of future research studies.

The confirmed presence of high protein oedema and known link to progressive stiffness in the tissues and muscles, suggested that swelling reduction interventions should be prophylactic and urgent. It is unknown if increases in viscosity and tissue turgor occurred during the early post-burn period as these physical properties of the fluid samples were not tested during the project. In previous studies of acute burn wounds, early changes were indicated by the up-regulation of pro-inflammatory cytokine *activin A* within day eight post-injury (McLean et al. 2008). These cytokine cells were linked to the development of increased cellular matrix stiffness and scar deposition beyond day 28 post-burn. Chronic oedema literature suggested that changes occur within weeks if high protein oedema remains static in the tissues (Casley-Smith et al. 1994). While the peak of protein concentration was reached by three days post-burn, the levels remained above the physiological range for at least seven days. It was unknown how long the protein levels remained elevated after the Study 1 endpoint and this has not been documented in the literature. Regardless, studies showed that normalizing tissue protein levels impacted positively on wound healing (Kramer et al. 1982; Demling 1987). Thus, optimizing the timely removal of acute oedema will aid wound healing and reduce tissue stiffness.

In order to examine the protein concentration results of Study 1 further, two distinct comparisons were pertinent. Firstly, high protein oedema fluid is defined as a solution with ≥ 1 g/L of protein. Whereas, when fluid was sampled from within normal tissue, the protein concentration was demonstrated to be 20.6 g/L (Fogh-Andersen et al. 1995). In situations where oedema was present in the tissues, high protein fluids were more resistant to strategies for removal. Further, such disease states including post-surgical lymphoedema, were likely to demonstrate less rapid resolution from the tissues (Bates et al. 1993). For comparison of Study 1 findings to chronic oedema, the

tissue protein levels reported in the literature post-mastectomy and axillary node clearance were used. In that chronic oedema population, the protein concentration was 32.4 - 35.8 g/L (Bates et al. 1993). While Crocket (1956) demonstrated that the underlying disease or cause of oedema impacted on the tissue protein levels, the surgical lymphoedema comparison to Study 1 results was considered reasonable. This was due to the parallels between the damage to the lymphatic system continuity. However, it was appreciated that partial thickness burn affects the superficial lymphatics while excision of lymph vessels and nodes impacts both superficial and deeper tissue structures. The findings of the study confirmed that acute oedema was a high protein fluid throughout the first 7 days post-burn except day one. Samples on the first post-burn day had lower mean protein levels than both normal and chronic tissue protein levels (Section 4.1; Fig. 4.1). Though not proven, the findings were postulated to be due to a greater local flux of fluid, relative to solutes, through the hyper-permeable blood vessels in that timeframe (Szabo et al. 1980). The peak protein level was reached on the third day post-burn, not on day two as hypothesized (Study 1; Hypothesis 1; Section 3.1.1). The mean protein concentrations were in the order of that reported for chronic lymphoedema as stated above, apart from the first day post-burn. While variability existed in the daily mean protein concentrations, the results suggest that acute burn oedema levels are similar to, not greater than, that noted for chronic lymphoedema (Study 1; Hypothesis 2; Section 3.1.1).

The oedema protein concentration after acute burn has been described in animals and humans with conflicting results. In dogs with mid-dermal burn injuries, Arturson (1979) showed that lymph fluid protein concentration was 5 g/L. However, the group sampled the fluid by canulating lymph vessels, not burned tissue. Similarly, in male patients with large TBSA burns requiring fluid resuscitation, a mean wound fluid protein of 6.2 g/L was determined (Lehnhardt et al. 2005). The authors studied the wound fluid collected in the first 48 hours only. Further, the group sampled by passive collection of fluid from the wound surface using silicone bags. The results of Study 1 demonstrated protein levels of ~two to ten times greater than the above studies. Oedema fluid sampling from human blisters post-burn showed that the protein level, reported as 0.029 - 0.052 g/L, was ~ 100 times less than the mean values in this study (Heggers et al. 1980). The range of protein concentrations, varying from 10 - 64g/L in this study, concur with Crockett's (1956) study indicating a markedly high protein content in the tissue fluid. Crockett (1956) quoted the acute tissue oedema within 24 hours post-burn to be 47 g/L using an invasive tissue glass capillary method. Despite being conducted on 115 patients with >400 samples collated into six categories of oedema, only one acute

burn case was reported in that study. The variation in protein concentrations reported in the literature was likely due to the differences between the sampling method and, or the acute burn models used.

The examination of the particulate matter confirmed that despite being a high protein fluid, acute burn oedema was >98% fluid by weight (Section 4.1; Fig. 4.3). The majority of the solute particles were large being > 100μm. The size of particles may influence negatively the ability of the lymphatic system to mobilize such debris. The initial lymphatic pre-collectors were reported to range from 30 - 100 μm in diameter in rabbits (Rutili and Arfors 1977) and ~ 100 μm in humans (Mellor and Mortimer 2006). The lymphatic pre-collectors are larger than the lymphatic capillaries which range from 10 – 70 μm. However, despite the mismatch between particle debris and lymphatic collector 'resting' lumen size, investigators have used the absorption of dyes up to 150kDa to visualize the distal lymphatic system (Fischer et al. 1996; Franzeck et al. 1996). Further, the Coomassie gel results show that the solid matter contained in acute oedema fluid was protein in essence, or of protein origin (Section 4.1; Fig. 4.4). In this study, the protein particles ranged in size from 25 – 250kDa with the predominant bulk of the matter between 37 – 75kDa. The molecular weight of human serum albumin falls in this range at 66-69kDa (Krishnan et al. 2004; Jachimska et al. 2008) and ~two-thirds of the protein concentration in the samples was contributed by albumin, confirming a lack of particulate material other than protein (Section 4.1; Table 4.1 & Fig. 4.2). The Coomassie analyses (Section 4.1; Fig. 4.4) further supported the hypothesis that the size of the protein particles remained consistent across the first week post-burn (Study 1; Hypothesis 3; Section 3.1.1). Interestingly, this may indicate a lack of impact of inflammatory processes such as macrophage breakdown of non-viable tissue, on the size of proteins in the samples as the relative distribution (and intensity of staining) of the particle sizes did not change during the collection period.

The urgency of input to reduce acute burn oedema was reinforced by the studies of the temporal pattern of volume change measured across the inflammatory period. In the oedema fluid collection studies (Section 4.1; Fig. 4.6), the volume was seen to peak in small burns by day one and in larger burns by day two, in contrast to the study hypothesis (Study 2; Hypothesis 1; Section 3.1.2). Acute oedema fluid poses an immediate barrier, which contributes to wound depth conversion if not removed. The findings suggested that active removal of up to 98% of the interstitial fluid obstruction may be facilitated through the lymphatic system (and the open wound). It was noted previously that lymphatic flow was not consistent along the axes of the limbs or

between superficial and deep compartmental systems in chronic lymphoedema situations (Stanton et al. 2009b). With the additional insult of burn injury, multiple modes of input are needed to gain maximal lymphatic activity. Techniques that may therefore be considered include complex physical or 'decongestive' therapy. Treatments planned with an understanding of the diseased or damaged areas of lymphatic system have proven beneficial for oedema volume reduction (Yamamoto and Yamamoto 2007; Kim and Park 2008). The core principles of massage, breathing, exercise, positioning and low-stretch compression have been demonstrated to be effective components for chronic oedema removal (Casley-Smith 1996; Foldi et al. 2000; Cheville et al. 2003). The optimisation of the drainage using massage techniques must take into account the epifascial damage to the superficial lymphatic collectors and the location of the burn. Further and applicable to a burn injury, strong massage is detrimental, particularly in the presence of friable tissue (Eliska and Eliskova 1995; Foldi 1995). Maximal use of breathing techniques will encourage proximal lymphatic return, regardless of the burn location (Negrini et al. 1994; Mason 2001). The presence of swelling in the superficial compartment of the lymphatic system was shown to reduce the rate of lymph flow and ability to drain through the deep or subfascial route (Stanton et al. 2003). Thus, circumventing the burn damaged lymphatics also relies on optimizing large amplitude exercise or muscle activity in the subfascial compartments (Modi et al. 2005). Elevation, with consideration for the unidirectional lymphatic valves should be applied. Effective limb drainage was achieved at an elevation of 30° or greater above supine for at least two hours (Boland et al. 1998). However, important to the acute burn clinician, it was shown that oedema in normal subjects takes less than 10 minutes to traverse from the hand to the axilla indicating the possible benefit of much shorter periods of positioning (Modi et al. 2007). Conversely, relatively short-term poor positioning may cause a pooling effect, particularly of distal oedema. This phenomenon was confirmed by the variability in the direction of fluid flux during Study 2 (Section 4.1; Fig. 4.7), measureable with volumetry despite the small changes, particularly after day three post-burn. Further, the elevated position should be adjusted to accommodate any head up tilt as this negated the limb drainage effect in Boland's (1998) study. Finally, compression is recommended with a distal to proximal gradient to facilitate lymphatic return. The mechanisms of action are related to positioning and both muscle contraction and lymphatic smooth muscle motility (Foldi 1994; Liao et al. 2004). Though difficult to ascertain in practice, tissue pressure should not exceed 24 mmHg in swollen limbs to prevent obstruction to the lymphatic pump (Modi et al. 2007). Clinical and research intervention should therefore

aim to include all methods to optimize oedema removal: massage / effleurage, elevation, compression, muscle contraction and breathing strategies.

The final aspect in describing the temporal patterns of acute burn oedema, involved quantifying volume change. The information from both Studies 1 and 2 were used to provide a picture of the volume flux after partial thickness burn injuries. The peak of oedema according to the serial measures was difficult to determine due to individual and daily variability (Section 4.1; Fig. 4.5). However, the peak of oedema was evident during the NPD trial (Study 1). For a burn injury requiring formal fluid resuscitation, oedema volume peaked on the second day post-burn (Section 4.1; Fig. 4.6a). For burns that do not require resuscitation, the oedema volume peaked by the end of the first day post-burn (Section 4.1; Fig. 4.6b). At the RPH, burns of less than 15% TBSA do not routinely receive intra-venous fluid resuscitation. Further, the methods of volume comparison differed slightly. In the NPD study, the oedema volume was calculated per square centimetre of wound area while UL volumetry measures could not provide such detailed information. The limitations of the whole limb volumetry (Demling 2005), sample collection and the small patient sample were evident from the results of these studies.

The pattern of serial assessments for the UL showed that net volume changes after day one post-burn were less than 200 mls (or 10% UL volume) per day with the exception of one patient (#9). She demonstrated a volume change of 245mls between days two and three post-burn. Similar to patient #1 (excluded from Fig 4.7), this elderly (68yrs) female who suffered a 1.5% TBSA burn, had a previous history of a cerebro-vascular insult and vascular co-morbidities. Patient #1 displayed clinically relevant change or UL volume change greater than 200mls but the result was recorded between the first and second post-burn days. The findings therefore refute the hypothesis that all volume changes up to day four post-burn are measurable as clinically significant in the UL (Study 2; Hypothesis 2; Section 3.1.2). However, the hypothesis held true when diagnosed vascular co-morbidities were present (and if the patient was > 65 years old). However, it was considered reasonable to surmise that advanced age was not the primary factor implicated for either of these two patients.

After the fourth post-burn day, however, less than 50 mls of change occurred per day. This supported the final hypothesis for Study 2 (Hypothesis 3; Section 3.1.2) in that a reduction of oedema volume change occurred from day four to seven post-burn. The change was reduced to a level, which was not clinically significant. The results suggest

that clinically relevant changes between daily UL measurements may be difficult to confirm in similar cohorts, particularly after day one post-burn. Alternatively, the findings suggest that clinically significant change in the acute burn environment may require definition related to the area of burn or initial UL volume. The findings raise the question as to whether UL volumetry, or other acute oedema measures, are sensitive enough to detect the relatively small volume changes, which occurred in the patient cohort in the RPH environment.

Finally, the application of the results presented here were limited to partial thickness burns injuries only. The results do not provide an indication of the volume change after full thickness burn injury which has been shown to have decreased skin oedema and increased adipose and muscle tissue oedema (Sakurai et al. 2002).

5.3 Tailored Post-burn Assessment Options

In order to develop an understanding of how patients live and return to function after burn injury assessment tools, which are applicable for burned individuals in a number of environments, are required. The chosen outcome measures varied in their construct and methods of application for this reason. Preliminary work by the RPH group, using statistical modelling to predict long-term burn recovery from injury demographics and the BSHS response at 1 month post-burn, explained ~75% of the variance in all burn patients' recovery (unpublished data, M. Phillips et al). The relatively poor specificity in predicting outcomes indicated the individuality of response to burn injury, regardless of severity. This work demonstrated the importance of longitudinal measurement of recovery from the immediate post-burn period and through the years beyond. The incidence of long term sequelae is well documented but the time translation to reach an acceptable quality of life is variable for burn injured individuals (Willebrand et al. 2002; Esselman et al. 2006).

5.3.1 Immediate Post-burn Response

For measurement of human acute burn oedema, WDV was demonstrated to be feasible and reliable for widespread research application (Study 3; Hypothesis 1; Section 3.2.3). With a simple, relatively inexpensive, water-tight vessel, whole arm WDV was shown to be sensitive to changes of < 100mls of burn oedema in the upper limb (Study 3; Hypothesis 2; Section 3.2.3). This result was similar to that derived by McKinnon et al (2007) in healthy subjects. Further, the result demonstrated an assessment option sensitive enough to measure less than the volume considered clinically significant in the treatment of the UL lymphoedema population (Box et al. 2000).

As most patients (~80% at RPH) injure their UL (Chapman et al. 2008), the enhanced understanding of arm volumetry for clinical use was an important consideration also. Further, while hand and wrist WDV are common in other clinical populations, the lack of whole arm measurement was considered a major limitation as burns, and consequent local swelling, often involved areas proximal to the wrist. However, the lack of published data other than that taken for distal hand and wrist research, serves to illustrate the challenges in a clinical setting. Whole upper limb WDV is clearly a difficult technique to use for clinical populations and this is particularly true of burn patients. In the burn environment, widespread clinical use of WDV is hampered by the

fact that the patient must have all dressings removed to achieve an accurate measurement. Further, dependent on the apparatus, cleaning procedures and frequency of use, WDV may also pose an increased risk of pain, infection or cross-infection in this particularly susceptible group of patients. For these reasons, it remains difficult to justify WDV use except for formal research during the acute post-burn period.

In contrast, bioimpedance spectroscopy offered a method of non-invasive, immediate assessment of whole body oedema volume change. The clinical and research utility of this technique was demonstrated to be high in specified contexts. The method was applicable and reliable in major burns from 15 – 30 % TBSA who require formal fluid resuscitation (Study 4; Hypotheses 1 & 2; Section 3.2.4). Notwithstanding a demonstration of validity of the measure, the current findings suggest that relative tissue compartment changes, particularly extra cellular fluid, is measurable in many burns with less than 30% TBSA (Study 4; Hypothesis 3; Section 3.2.4). Further, the studies demonstrated that these measures were repeatable with burn dressings in place under appropriate conditions. This was an important and novel finding for burn patients as all other methods of assessment of tissue and total body oedema required invasive monitoring or assessments on equipment housed outside the burn unit environment. However, it is appreciated that the cost of both bioimpedance (and Polhemus 3-D laser) systems is prohibitive for the majority of burn services. Thus, due to the difficulty of use of WDV and the limited scope for use of bioimpedance and laser scanning (Study 5; Hypotheses 1 & 2; Section 3.2.5), the most widespread application of the findings in this project relate to the measurement of long-term bio-psycho-social recovery after burn injury.

5.3.2 Measuring Long-term Recovery

Developed or high income nations continue to reduce the overall burden from burn injury in response to objective outcome measurement and longitudinal data relating to burn recovery. While not quantified in detail in the literature, burn care is recognised as labour intensive and expensive. In developed burn services, post-burn survival, as measured against TBSA, has steadily improved with the advent of new technologies (Pereira et al. 2004). This is not the case for developing countries (Mock et al. 2009). Unchecked translation of modern technologies into these environments, without safety controls or the resources to rehabilitate surviving patients, poses important ethical questions. Clinicians in developed nations debate how much staff and health

resources are necessary or available to achieve a *quality of life which is worth the pain of survival* (Wood 1995; Holmes 2008). In contrast, developing nations have significant barriers in order to demote mortality as the premier outcome measurement tool after burn injury (Park et al. 2009). It was estimated that 90% of burn injury in the world occurs in low income countries and the LD50 in these nations was ~40% TBSA (Potokar et al. 2008). The LD50 in high income countries was noted to be closer to 90% TBSA (Esselman et al. 2006; Herndon 2007). This paradigm can only be addressed through intervention implementation and assessment based on longitudinal data (Peck et al. 2008). In order to assess the global burden of burn disease, beyond mortality, clinicians should start with burn population validated tools that are adaptable to apply in any burn care environment. Thus, the discussion highlights a fundamental question: *What is acceptable post-burn recovery of quality of life?* This project has provided a firm starting point in quantifying the many facets of quality of life. The burn patient assessments options presented may be tailored and adapted for any local burn service and used for clinical audit and, or research. The outcome measurement tools potentially allow comparison across multiple burn service environments and contexts.

While there were a multitude of discipline specific and domain focused objective measures noted in the Review of Literature (Chapter Two), very few, if any, had been validated for use in burn patients. The BSHS was unique in its psychometric construct and application in the burn population. However, it demonstrated a number of limitations. In the RPH cohort it showed a loss of sensitivity due to the condensation of scores at the highest end of the scale, or ceiling effect, particularly after two to three months post-burn (Edgar et al. 2009c). Further, BSHS was demonstrated to be less sensitive than either the QuickDASH or the SF36 over time (Wu et al. 2007a). These results substantiate that the acceptance of an outcome measure without analysis of its performance in specific patient cohorts may pose a risk to patients. In the RPH example, the BSHS potentially overstates the quality of life recovery in less severe burn injury. The risks are amplified if an outcome measure does not quantify an aspect of post-burn recovery as was intended in the original disease or injury population. All the measures chosen in this project were developed in disease or injury populations other than burns. While the necessity for testing the reliability and performance of these measures in the burn population was evident, the measures possessed advantages over a number that were discarded during the candidacy (unpublished data, D. Edgar). The selected outcome tools showed promise in the measurement of comparable outcomes and, or parallels in aspects of the disease morbidity during burn recovery. However, fundamental differences remain between burn trauma and

recovery, and other disease and injury states. For example, orthopaedic traumas, particularly fractures, have a protracted recovery pathway, which has quite a different course compared to burn scar healing. While the QuickDASH was developed to measure disability after UL orthopaedic trauma (Beaton et al. 2005; Gummesson et al. 2006), it could not be assumed initially to provide an accurate or sensitive quantitation of the effect of burn scar in the UL. Thus, validation of QuickDASH against a burn population measure was completed during the project (Wu et al. 2007a).

The outcome measurement tools were examined for their reliability and validity as individual measurement options for burn patients. The publications presented in Chapter Four document a new set of longitudinal outcome measures beyond the BSHS. The outcome measurements incorporated individual tools to examine upper limb and lower limb function and quality of life in order to address the multi-dimensional bio-psycho-social response to burn injury. However, the measures could be grouped together as a single summary, or multiple domain scores, which could be used to describe the overall and, or facets of post-burn quality of life recovery mapped to the ICF. Developing a battery of tests with a planned application timeline may improve longitudinal sensitivity and reduce redundancy and patient burden. The construction of such a battery to measure limb burn recovery was demonstrated by the investigation presented in Chapter Four (Finlay et al. 2009c). This study demonstrated that the timed up and go and tandem walk tests, were adjunctive to the BSHS in describing outcomes after LL burn up to six months post-burn.

The widespread application of the findings of this portion of the research was enhanced by the inclusion of self-rated surveys as core components of a measurement battery. While the QuickDASH provided sensitive assessment of burned upper limbs, the novel validation of the SF36 for burn survivors was a key finding. The SF36 has been translated for use in over 60 countries (Quality Metric 2009). It has undergone rigorous testing and validation for over 20 years and has normative datasets which continue to evolve (Ware et al. 1993). The utility of the SF36 is therefore enhanced by the ability to compare between burn service outcomes in different countries. Thus, the SF36 may provide a key to measuring the global burden of burn injury. Further, its low cost application may enable clinicians to examine in more detail the impact of introduced technologies in all countries but particularly low income nations.

Thus, the results of the thesis have potential application in many adult burn service environments around the world. However, effective use of the oedema contents information and outcome measures is conditional upon the understanding of local service variability, cultural factors and casemix as well as the limitations in the development of the thesis findings.

5.5 Research Limitations

5.5.1 General Limitations

The patient population of the RPH Burn Service was included in all clinical studies. Thus, general application of results must be tempered by several caveats. Firstly, the Australian occupational and general safety legislation and standards provides a high level of protection from thermal injury for citizens. Thus, the RPH population was relatively low in total numbers compared to other services. It took some years to recruit adequate patient numbers for longitudinal analyses. As a corollary, the impact of low numbers was compounded due to relatively fewer major and severe burn injured than may be expected in other burn casemixes or in developing countries. However, all outcome measure studies were designed, and analyses applied, to provide the most robust presentation of the findings. The performance of the assessment tools was presented with open qualification and explanations in order to be applied universally, despite burn size or depth. Secondly, the cohorts did not include paediatric patients though occasionally pubescent teenagers were treated by the RPH burn team. Thus, the results are not necessarily applicable to children.

The low patient numbers impacted on the type of statistical analyses available and the strength of inferences with respect to measure validity. To achieve a gold standard in dual method comparison, studies should aim to collect 200 data points minimum from each measure to adequately power the statistical analyses (Dunn et al. 1999). A study design such as this was not feasible for the acute oedema measures during the study timeframes.

The measurement of patient's muscle strength was not included in this series of outcome measures. A number of reasons contributed to the omission. Firstly, it was considered that pain and fear avoidance of activity in burn patients would impact negatively on the reliability of manual muscle testing, particularly in the acute period. Secondly, without access to relatively bulky and expensive equipment to measure muscle torque objectively, incorporating muscle strength testing was not considered viable during this project. The use of a hand held dynamometer to regulate the application of manual resistance testing was considered. However, at the time of inception of longitudinal outcome studies, standardised protocols or indication of the reliability of the testing technique were not available in the literature. It is important to note that all joint range measures were tested with patients performing active muscle

contractions. Consequently, those measures such as goniometry and hand linear measures indicated end of range isometric muscle activity and through range muscle strength to hold, and achieve, the measurement position. Further, monitoring the quality of active movement patterns is not possible with the outcome measures examined. The use of 3D motion analysis has been explored to address the issue (Palmieri et al. 2003). However, while the concept showed promise, it remains an expensive research tool which was not considered viable in the acute burn environment (Grisbrook et al. 2009a; Stearne et al. 2009).

Though the manuscripts presented in Chapter 4 discuss the limitations of individual studies, the presentation of these discussions was moulded by the individual journal requirements and peer reviewer's comments. There were subsequent issues, not detailed previously which are considered in more detail below. Further, each paper was included to demonstrate the assimilation of knowledge developed throughout the candidacy.

5.5.2 Study 1 NPD Acute Oedema Collection and Storage

There are questions regarding the use of NPD sampling and storage techniques employed in Study 1 and therefore, whether the results represent analysis of acute burn oedema. The choice of method for collection of fluid from burn wounds and, or surrounding tissue was a source of debate for this study. A number of techniques were described in the literature including sampling blister fluid (Heggers et al. 1980; Shaked et al. 2007); 'vinyl wound chambers' (Lehnhardt et al. 2005); needle aspiration (Bates et al. 1993); insertion of micropipettes or glass tubes (Lund et al. 1988; Negrini 1995); intradermal wicks (Lund et al. 1989) and negative pressure dressing application (Collier 2003; Molnar et al. 2004b).

Overall, the choice of the techniques was related to the ethical treatment of acute patients and resource issues. All methods of acute burn oedema collection demonstrated significant limitations and, or ethical issues. Blisters may form for several days after burn injury but timeframes are not consistent. Further, evidence based practice at RPH includes the de-roofing of blisters upon admission or at the first formal dressing change (Caneira et al. 1996; Sargent 2006). Thus, as the study planned to collect fluid for analysis up to 7 days post-burn, the technique was considered not feasible. Similarly, the application and maintenance of wound chambers for such a period was impractical. The invasive techniques including wicks and micro-pipettes posed ethical challenges with respect to study design. The studies

noted above described the use of prolonged insertion of such equipment in animals more than a decade ago. Similarly, the insertion of long term catheters for analysis of lymphatic fluid flow was described by the Galveston group and remains in use to date (Herndon et al. 1984). However, the only reports of invasive tissue fluid collection in human subjects were short term or single episode needle aspiration (Bates et al. 1993; 1994). Thus, it was difficult to justify the infection risk of invasive catheterization for up to one week, or short term needle aspiration, in acute burn patients to the RPH Ethics Committee. These techniques were not considered ethical for this type of study. In contrast, the use of negative pressure dressings (NPD) was approved by the Ethics Committee. The decision to use NPD was supported further by the documented increased use of the technique and an associated improvement in acute burn wound outcomes (Krasner 2002; Kamolz et al. 2004; Molnar 2004). The results of the study suggest that use of the NPD method provides an indication of tissue protein concentration rather than passive collection external to wounded tissue. These findings confirm the value of the NPD method in acute burn oedema research.

However, as noted in Section 3.1.1, questions remained as to the consistency of the samples collected by the technique despite a constant application of the vacuum. Fluid taken at the wound interface has been argued to represent inflammatory tissue fluid due to the presence of high molecular weight proteins, parenteral anti-biotics and cytokine markers, some higher in concentration than serum (Heggers et al. 1980; Robson and Heggers 1981). Thus, it was considered that the use of a negative pressure dressing at the wound interface would provide an accurate representation of acute oedema fluid constituents.

The negative pressure applied to extract fluid was low for patient comfort and wound healing benefits (Molnar 2007). All samples were collected with the NPD system set at 125mmHg constant vacuum. The ability of this level of negative pressure to extract particulate matter and overcome the physical and chemical bonds within the extra-cellular matrix remains unanswered. The level of vacuum used was similar to the greatest interstitial imbibition pressures measured after a 40% TBSA burn injury in rats (Lund et al. 1988). The interstitial tissue pressure reduced with TBSA such that after a 10% burn, the maximum negative tissue pressure measured was 95 mmHg. However, this value was not the net force binding the oedema contents within the interstitium and it is not surprising that the pilot trials demonstrated that the study NPD method extracted both adequate fluid and cellular contents from the sub-acute wounds (Section 3.1.1).

It was therefore considered that with the NPD system in series with the open wound would extract all of the primarily extra-cellular tissue fluid and debris from the small TBSA, partial thickness wounds recruited in the study. It was unknown if the continuous vacuum would alter, over time, the concentration and volume of fluid in the tissue. For example, increased fluid may be removed, thereby reducing artificially the protein concentration in the sample. However, without an invasive tissue comparison, the question remains unanswered. There was indication that a subject by method interaction occurred. The troughs in values coincided with the change of the NPD dressing on day three impacted on both the tissue protein concentration and volumes (Section 4.1.1, Fig. 4.1 and Section 4.1.2, Fig. 4.6).

Due to the difficulty of the clinical environment, the changing rate of oedema production over one week and patient access, sample collection times were not uniform in length. However, the bi-daily samples were timed to be representative of each 12 hour period post-burn, except where the volume of fluid was insufficient to allow analysis, as was generally the case for the final samples (Section 4.1.1, Table 4.1). Finally, the NPD system was shown to cause an increased blood flow in normal skin with NPD pressures applied up to 300mmHg (Timmers et al. 2005). Theoretically, it was likely that the NPD method impacted on the volume of fluid transferred into the tissues to some degree.

Finally, some of the analyses took place on frozen and thawed samples. This potentially affected the ability to discern intact cell matter but it was unlikely to impact on particulate size and concentration inferences. The findings presented in Chapter Four were unlikely to be affected by the storage method due to the techniques of analysis.

5.5.3 Study 2 Tracking Temporal Volume

The study numbers recruited during the trial, between patient variability and low incidence of severe burn injuries in the RPH environment meant that data available was not adequate to subgroup patients by burn severity or burn depth.

5.5.4 Study 3 Volumetry Reliability Trial

In progressing this study, the construct validity of the WDV technique was assumed. However, the research limitations of such assumptions, particularly in burn patients, were noted previously by Demling (2005). The clinical and research applicability of WDV in the burn unit environment was hindered by safety issues for patient (water on floor, small increased risk of infection with open wounds) and staff (ergonomic issues of disposal and water on floor) as well as environmental issues (waste of water). Thus, alternative methods of volume measurement were investigated for use in the acute environment to address a number of the challenges and offer new ergonomic solutions to researchers and clinicians. The presentation of results in a single unit of measure may also be challenged. It was appreciated that weight of tissue and volume of water were not interchangeable. However, the complexity (and expense) of determination of tissue density was considered excessive for the assumed small benefit to the accuracy of results.

5.5.5 Study 4 Bioimpedance Reliability Trial

In discussion with the manufacturers, it was noted that body composition algorithms were based on American population sampling. A second pilot trial using healthy Australian subjects (n=4) indicated that there were significant discrepancies between the SFB7 and DXA scan findings. Thus, a normal Australian population pilot sample (n=20) was collected also during the candidacy to provide baseline reference for future research in this area for Australian burn survivors.

5.5.6 Study 5 Polhemus Reliability and Validity Trial

Both the complexity of wireless data transcription and burn unit environmental factors impacted on the accuracy of the PFS equipment. The standardised protocol for testing aimed to reduce variation but the sensitivity of the reflected light to minute movements was a challenge to effecting precise 3D measurements. Lastly, the PFS was costly (~AUD$30K) and while this hinders clinical applicability, these costs are ‘within reach’ for research applications.

5.5.7 Studies 6-9 Long-term Outcome Measures

Missing data, or patients not returning for review, potentially posed significant issues for longitudinal clinical data integrity and therefore the validity analyses. As stated in Section 2.2.1, MLE longitudinal regression modelling was chosen over other methods to deal with missingness, such as general estimating equations (GEE's), Heckman method or multiple imputations (Little 1995; Sales et al. 2004). The primary reason for the choice was that the planned (validity) analyses did not require the more involved methodologies to predict or statistically correct bias introduced by missingness. Further, to understand the impact and reasons for patient non-attendance, the RPH burn team demonstrated that minor burn patients who do not return to review were satisfied with their treatment and had equivalent outcomes to those who were assessed (Finlay et al. 2009b).

5.6 Chapter Summary

This chapter has reiterated the issues and questions which were addressed by the research project. As per the primary concerns presented in Chapter Two, the key findings from the studies were discussed relating the significance of and possible application of these results by either burn clinicians, researchers or both. Lastly, the limitations of the studies which were not elucidated in manuscripts presented in Chapter Four were discussed. Where applicable, strategies used to minimize the impact of specific and general limitations were included.

Chapter 6

Conclusions

6.1 Conclusions

The novel findings of this thesis relate to the establishment of a) detailed scientific knowledge of acute burn oedema contents and temporal volume change; and b) of measurement tools for monitoring of acute burn oedema management and resultant long-term sequelae. The study series was designed to provide results to inform efficacious clinical treatment as well as planning and execution of formal research projects.

Paper I:
With respect to the treatment of human acute burn oedema (HABO) the literature indicated:

- *For local wound treatments:* Topical negative pressure dressings and high-voltage, pulsed, galvanic electrical stimulation, with traditional physiotherapy, reduce local wound oedema and improve the rate of functional movement return.

- *For systemic treatments:* Albuminated resuscitation fluids increase lung oedema and the rate of mortality after major burn. High dose Vitamin C during acute major burn resuscitation reduced local wound oedema, systemic oedema retention and days of mechanical ventilation. The use of hypertonic albuminated resuscitation fluid reduces systemic oedema retention. The use of antihistamine during acute inflammatory period does not reduce local acute hand burn oedema or improve burn wound epithelialisation rate. The use of parenteral steroid after acute inhalation injury and major burn provides no benefit.

Section 4.1:

The scientific studies HABO fluid provided the following information for developing research or increasing the efficacy of clinical interventions:

- After partial thickness burn injury, HABO peaks on day one post-burn when fluid resuscitation is not instigated;
- When formal fluid resuscitation is required, HABO peaks on day two post-burn;
- Notwithstanding pre-existing vascular co-morbidities, between days two and four post-burn, the daily change in HABO volume in the UL decreases rapidly to levels < 200mls per day, independent of burn size;
- After day four post-burn, the change in HABO volume in the UL is < 50 mls per day;
- HABO is a high protein fluid but is > 98% by weight liquid;
- The solid or particulate matter contained in HABO fluid is relatively large at > 100µm in diameter;
- The size of solid matter contained in HABO remains unchanged in samples throughout the acute post-burn period; and
- Lymphatic system stimulation treatment may be beneficial in oedema management strategies immediately and up to four days post-burn.

The studies of measurements for oedema change in the presence of open wounds, in the burn unit environment, showed:

Paper II:

- Whole UL water displacement volumetry is reliable and sensitive to < 100mls of change between trials;

Paper III:

- Bioimpedance spectroscopy (BIS) is reliable in patients with wounds ≤30% TBSA;
- BIS is reliable and sensitive, in patients with ≤30% TBSA, with open wounds and with wound dressings in situ ≤8 hours;
- BIS demonstrated construct validity in the same patient group; and

Paper IV:

- Polhemus FastSCAN 3-D laser scanning technique was not reliable or valid for clinical application.

Papers I-IV:

- Research projects employing acute oedema volume change measurements should include a reliability trial and calculation of the minimal detectable difference within the specific environment or context.

Examinations of the measurements of longitudinal recovery up to two years after burn injury demonstrated:

Papers V & VIII:

- The QuickDASH and SF-36 V2 acute surveys were valid and more sensitive than the BSHS-B;

Paper VI:

- Joint goniometry, hand scales and linear measures were reliable and minimum detectable difference values were presented;

Paper VII:

- Lower limb measures including single leg stance, Timed Up and Go Test (TUGT) and tandem walk tests (forward and backward) are reliable and valid; and
- Minimum detectable differences and statistical analyses indicated that the TUGT and the tandem walk forward test were adjunctive with BSHS-B in quantifying lower limb recovery.

6.2 Recommendations for Future Research

The group of outcome measures, which provide assessment information across the continuum of recovery post-burn, is a starting point for clinicians and researchers. Future projects therefore must examine the development of outcome measurement systems, which are individualised for burn centres around the world. Such systems should be adjunctive to, and support the development of, local burn assessment batteries, which may use individual components of the tools presented here in combination with appropriate measures for the context and cultures of the patients in question.

The outcome measurements presented extract information on recovery in mental, sensory and pain, respiratory, reproductive and neuro-musculo-skeletal body functions and structures, activities and participation across all ICF domains and environmental factors including support, relationships and attitudes (WHO 2001). As previously alluded to, representation of the global burden of burn injury on society is possible through the use of the outcome measurements in both low and high socioeconomic nations. Epidemiological and outcome research is feasible with the proposed measures due to their simplicity and minimal need for equipment. Further, the application and simplicity of the lower limb battery indicates the need for repetition of the methodology in Paper VII to develop an UL battery.

Following on from concepts touched on in the Discussion (Chapter Five), studies must examine how much staffing, resources and infrastructure are required to achieve a 'good recovery outcome' in the local burn service context. Thus, defining or quantifying adequate recovery and the timeframes of measurement are an important next step in the process. Studies documenting the comparison of individual patients and, or grouped patient scores against normative databases, published or developed through local sampling, are necessary. The battery of assessments across multiple domains, in conjunction with mortality, injury and casemix demographics and staffing and resource parameters, enable accurate benchmarking between burn services. For instance, it is feasible that a developed burn team partnership now includes outcome measurement to determine if new technologies introduced are of tangible benefit to a developing burn service and patients.

While mortality is an important indicator of effective burn treatment, its value as an outcome measure is reducing in developed nations. Thus, meta-analyses and multisite

trials using functional outcome assessment and recovery of quality of life are necessary to examine the questions, which defy consensus, or lack the support of strong evidence related to mortality. A number of research questions surround the use of surgical intervention, for example. Studies should address or determine: (a) 'What day post-burn is the best to provide skin reconstruction (acute grafting) surgery?'; and (b) 'What is the best surgical technique for full thickness burn or dermal injury?'. Similarly, research questions around the parameters of acute burn fluid resuscitation warrant further examination, particularly in the context of oedema control.

The findings in this thesis also warrant development of specific assessment of the impact of acute burn oedema on the lungs, respiration and cardiovascular endurance. Investigation, in the form of reliability and temporal validation studies, is required for the aerobic fitness recovery particularly after inhalation injury and, or major (>25% TBSA) burn injury where the systemic inflammatory syndrome is present. In the clinical environment, tests providing sensitive feedback, especially in young adult patients, would be useful. Mobile respiratory function tests, where apparatus is available, could provide norm-referenced measures of lung capacity, which could be used effectively in the acute environment. As stated above, the use of normative data facilitates broader application of study findings. For the interested reader considering such studies, our group previously demonstrated the ceiling effects of standard respiratory tests such as the six minute walk test (Enright 2003) and two minute walk test (Solway et al. 2001) (D. Edgar et al, unpublished data). Thus, functional options within a burn unit environment, could include incremental endurance tests such step tests (Zwiren et al. 1991) or the various shuttle walk or run tests (Ramsbottom et al. 1988; Revill et al. 1999; Boddington et al. 2001; Boddington et al. 2004; Eaton et al. 2006). These require small testing areas and minimal, inexpensive equipment. Other measures are more difficult to justify or generalise for all burn units due to cost and bulk of equipment. That said where funding and space are available, standardised treadmill (Bruce 1973) and cycle or arm ergometer protocols are appropriate due to their utility in clinical and research settings. As with the outcome measures examined in the thesis, the questions remain as to the validity and timing of such assessments during the acute burn period and beyond.

It is likely that research and clinical utility for the bioimpedance spectroscopy technique and equipment would be markedly enhanced if applicable in large TBSA burns. The primary barrier is the current electrode application and algorithms of analysis, which rely on intact skin placement. There is opportunity for development of electrodes,

which allow accurate and extended application of bioimpedance. Specifically, the electrodes should read in or around open wounds. Analysis algorithms would need to be developed specific to the low impedance electrode readings. Were this hurdle to be overcome, the possible applications of the method expand markedly. For instance, 'wet surface' electrodes could provide accurate assessment of tissue and body compartment oedema volumes for larger TBSA burns and when burns cover electrode sites. However, the options to combine bioimpedance spectroscopy machines with energy delivery systems would be far more enticing. Such combinations could introduce electrical, bio-active and chemical mediators directly into the wound to control the wound surface environment. The status of the wound surface chemistry and enzymes has been shown to impact directly on the quality of scarring (Caulfield et al. 2008). Software developed to use the assessments of tissue composition, temperature and chemical status could provide real-time, local delivery of intervention, minutely titred using bioimpedance and, or in combination with other assessment techniques. For instance, it would be possible to deliver pro-active inflammatory mediators and, or growth factors, from reservoirs impregnated into electrodes. These could be released slowly and directed using electromagnetic charge and, or electrical current. Another iteration of this concept includes the combination of negative pressure dressing foam with BIS (electrode) capability. For instance, through assessment of the wound tissue oedema content (and volume) the delivery system could respond immediately and appropriately with changes in vacuum level (or deform pore size of foam to alter the movement of protein and debris at the wound interface).

Following on from the results of Paper II (Chapter Four), confirmation of criterion validity of bioimpedance spectroscopy in burn injured patients (in the short term), could provide accurate measurement of tissue compartment and importantly, both upper and lower limb oedema volumes. The clinical and research applications of a non-invasive tissue oedema measurement technique abound, enhanced by the ability to measure while dressings are in situ. Research and, or assessment of interventions such as: specific positioning regimes; bandaging techniques; multi-chambered compression devices and oedema and protein reducing medication and, or fluid resuscitation regimes.

With respect to drug trials, there was a surge of studies in the 1990's and earlier this decade which indicated the benefits of non-steroidal anti-inflammatory drugs (NSAID's) for pain and the inhibition of the markers of inflammation (Moiniche et al. 1994; Enkhbaatar et al. 2003; Ambler et al. 2005; Kleinzner et al. 2005). These

studies, while promising, require redesign in order to be repeated to investigate specific benefit for acute burn oedema and, or clinical utility. Redesign is necessary due to the impractical timing for post burn drug administration in earlier studies, rather than the possible benefit of reducing acute burn oedema per se. In parallel, studies of local and infused anaesthetic agents demonstrated variable results for post-burn pain and inflammatory erythema (Jonsson et al. 1998; Mattsson et al. 1999; Mattsson et al. 2000). Again, these studies lack specificity in design, outcome measurements and, or applicability to confirm benefits for acute burn oedema control.

A second group of medications are worthy of mention due to the theoretical potential for application in the management of acute burn oedema. In the early 1980's, the benzopyrone group of drugs were shown to reduce swelling in chronic high protein oedema states (Casley-Smith 1983b; 1985). However, the side effects of liver toxicity lead to the removal of these preparations in Australia earlier this decade. Studies involving acute burn oedema are not available in the literature. However, emergent literature indicates the synthesis of new preparations and novel understanding of the dose dependent nature of the side effect profile warrants further consideration as an application for acute burn patients (Scott et al. 2004; Felter et al. 2006; Amin et al. 2009).

Adjuvant to the tissue fluid protein studies presented in Chapter Four, research should address the understanding of the post-inflammatory and, or sub-acute phase burn oedema. Studies of fluid contents and its properties beyond seven days post-burn are required. Further, physical properties such as the viscosity of fluid remain unquantified throughout the acute inflammatory period. The development of stiffness in the wound and surrounding tissues is related initially to the fluid properties. Exactly when acute burn oedema becomes 'stiff' has not been measured (or defined). Study 1 procedure would be appropriate to repeat with the inclusion of new analyses and an extension of the collection period into the second week post-burn, where wounds remain open. It is unlikely that studies beyond 10 to 14 days post-burn are feasible in modern burn units. Further, with time, the stiffness and limitation to function and movement, increases considerably due to the development of hypertrophic scar. Understanding the impact of the contact time of high protein oedema on scar fibroblast phenotype and wound matrix construction requires investigation. While previous discussion noted the issues with collection of tissue fluid, such studies could be completed in vitro using similar techniques to previous burn fluid studies (Dyess et al. 1991; Caneira et al. 1996). Questions have arisen during the course of the scientific studies related to the impact

of high protein oedema on the spectrum of infection. While it was shown that relative tissue hypoxia increases infection, does high protein oedema lead to an increased rate of infection and, or colonisation post-burn? Lastly, the presence of 'burn toxin' and its negative impact on all tissues of the body were noted (Allgower et al. 2008). It is unclear how much burn toxin deposits in the tissue or tissue fluid and how that changes over time. Similar studies as noted may offer insight into topical treatment options which bind burn toxin to ameliorate its influence on cell death (burn conversion) and immune compromise at the local wound level. Measurement of the impact of such treatments on local acute burn oedema could employ both tissue oedema assessment such as the BIS and local wound contour measurement as provided by techniques such as Polhemus 3-D laser scanning.

Despite the limitations demonstrated by the Polhemus 3-D laser scanning (Paper III, Chapter Four), the technique warrants further investigation due to the potential to provide real-time, painless, non-invasive assessment. As this or similar optoelectronic technology progresses, the barriers to reliable and accurate measurement using such methods will dissolve. For instance, a primary obstacle to overcome is the issue of metal beds in the acute hospital environment. Further, laser scanning is not hindered by the noted limitations (Paper III) in studies involving the lower limb. Scans for the lower limb are simplified due to the locking of the knee in extension and minimal loss of the scanning field when supporting the limb through a heel cup, for instance. The technique also has potential where the UL rests on surfaces of known refractory index or using a suspension method that does not obscure scanning.

Following on, laser technology has been used in treatment for established burn scar (Gaida et al. 2004) and chronic lymphoedema (Stanton et al. 1996; Carati 2003). However, the control of excessive blood vessels in patients with psoriasis indicates a potential use of laser in the acute wound situation (Hern et al. 2005). Studies to develop the appropriate dosage, timing of application and delivery method parameters are warranted. Further, it is unclear as to the exact mechanism of action through laser therapy in the lymphoedema population. This technology therefore may offer a non-harmful option to optimise lymphatic function and improve wound healing in the acute period post-burn.

In optimising the lymphatic system for removal of acute oedema, it is poorly understood as to how the presence of fluid influences the process of removal. For instance, post-mastectomy a significant decrease in lymphatic flow was demonstrated

in swollen limbs compared to normal despite increased lymphatic collector density in the skin (Modi et al. 2007). Further, with respect to use of pressure bandaging therapy after acute burn, the level of compression that will stop or hinder lymphatic flow is unclear, particularly as the limb continues to swell. Studies of specific techniques for oedema management should consider utilising piezoelectric or other 'in situ' pressure monitoring technology to improve understanding of the process of oedema removal.

Finally, a number of questions remain regarding the anatomy of the skin and the role of the lymphatic system in the removal of oedema. For instance, it is unclear if swelling exists or is possible in the epidermis. However, cosmetic skin treatments purport this phenomenon occurs and offers benefit to the texture and pliability of the skin with long-term use. If swelling is possible in the epidermis, do lymphatic collectors exist in this layer of the skin? Can such structures be utilised or optimised in novel ways to facilitate acute swelling removal from the zone of injury.

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Appendix 1: Candidate and Co-author Contributions (& Acknowledgements) by Manuscript

Refer to Table 1 reproduced below:

I: The candidate prepared this peer-reviewed *Letter to the Editor* in response to a paper describing burn rehabilitation in the United States of America.

II: The candidate conceptualized and compiled this manuscript with substantial editorial input from the co-authors. The candidate revised the manuscript with minor corrections after proof setting.

III: The candidate compiled and referenced the document with editorial input from co-authors and colleagues from the Disaster Preparedness Unit, WA Department of Health. The paper defines the guidelines for maintaining burn unit standards and disaster preparedness, including education and training requirements.

IV: The candidate was a core member of the therapist group who conceptualized and documented the consensus based *ANZBA OT and PT Guidelines,* the source paper for this publication. The publication describes the process of development and gaining consensus of therapists in Australia and New Zealand. The candidate co-authored this paper providing input to conceptualization and editing.

V: The candidate conceptualized and compiled this manuscript with editorial input from Mrs Brereton, occupational therapist. The *ABC of Burns* series was edited by Dr Shehan Hettiaratchy (UK).

VI: ANZBA AH Guidelines: The candidate was the Chief Editor and co-ordinated the second edition and upgrade of the *ANZBA Occupational Therapy and Physiotherapy Guidelines for the Treatment of Burn Patients*. The candidate was a co-author from the core therapist group who compiled the first edition of the ANZBA Guidelines.

VII: The candidate devised and refined the review question, composed the protocol drafts, responses to reviewers and final submission copy with editorial input from all co-authors.

VIII: The candidate assisted with online searches, completed all listed hand, bibliographical and grey literature searches except for the American Burn Association abstract searches (F. Wood). The candidate completed the submitted manuscript with editorial input from co-authors and the Wounds Group editors (S. Bell-Sayer et al, UK). Work included the completion of risk of bias assessments and data abstraction (with independent second assessments by M. Gomez, Canada), data synthesis and collation of results. The candidate further completed a submission checklist pilot project, responded to reviewers and finalized the submitted manuscript (with editorial input from co-authors and external Cochrane Collaboration reviewers).

IX: The candidate conceptualized this project, drafted the manuscript with Dr Bartley and Ms Wood and after responding to reviewers, adjusted the manuscript with co-authors input to finalize the paper.

X: The candidate drafted and, or revised a number of functional outcome sections, substantially edited the response to reviewers and assisted with overall editing of this review publication. The paper was conceptualized and primarily prepared by Dr Falder.

XI: The candidate conceptualized the study and drafted the manuscript with feedback from co-authors. The candidate completed all trials, collected all data and completed the data analysis with assistance.

Acknowledgments: The authors would like to thank Professor Kevin Singer and Dr Barbara Singer, Center for Musculoskeletal Studies, University of Western Australia for their assistance with editing during the preparation of this manuscript. Thank you to all subjects for giving up their time to participate in this study. Thank you to Elspeth MacKay for her assistance with the sleeve length and burn patient statistical analyses.

XII: The candidate conceptualized these trials, acquired Clinical Quality and Safety Unit (CSQU) Ethics sub-committee approval, drafted and finalized the published manuscript and prepared all responses to reviewers with feedback from co-authors. The candidate completed all Phase I data collection, co-ordinated the Phase II data collection and completed the data analyses.

Acknowledgements: Thank you to the *ImpediMed* company for providing the SFB7 machine on loan for Phase I of this trial. Also, thanks to Dr Brian Zigelaar (of

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Conflict of Interest: The analysis of these data was not influenced, or presented to the manufacturer prior to Phase II of this study. A conflict of interest is not evident as the equipment cost was fixed and honoured by both parties, regardless of results presented. Clinical trials of the SFB7 are ongoing at the RPH.

XIII: The candidate conceptualized this study, acquired Ethics approval, drafted and finalized the published manuscript and completed all responses to reviewers. Data collection was completed by the candidate and Mr Day. The candidate processed all raw scans (n=72) prior to batch volume computations and assisted with data analyses.

Acknowledgements: The authors would like to thank all the staff and students at RPH and Curtin University of Technology School of Physiotherapy for taking time from busy schedules to be part of this study.

XIV: The candidate conceptualized this study, acquired CSQU approval, edited and finalized the manuscript and prepared all responses to reviewers with feedback from co-authors. Mr Wu compiled the first draft of the paper and coordinated data collection. The candidate assisted with data collection and assisted with initial data analyses and re-analysed additional data for the second draft after requests from peer reviewers.

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XV: The candidate conceptualized this study, acquired CSQU approval, drafted and finalized the published manuscript and prepared all responses to reviewers with feedback from co-authors. Mr Wu coordinated data collection. The candidate assisted with data collection and completed all data analyses.

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Conflicts of Interest: No conflicts of interest identified.

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XVI: The candidate conceptualized this study, directed the drafting and finalizing of the manuscript. Mrs Finlay drafted the manuscript with input from co-authors. The candidate assisted with data collection coordinated primarily by Mrs Finlay. The data analysis was completed by Mr Phillips with direction from the candidate and Mrs Finlay.

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*Conflict of Interest Statement***:** V Finlay – none; D Edgar – none; M Phillips – none; F Wood – none.

XVII: The candidate conceptualized this study, acquired CSQU approval, drafted the manuscript with co-authors and finalized the manuscript. The candidate assisted with clinical data collection and Ms Dawson and Ms Hankey cleaned and finalized the dataset prior to analysis. The data analysis was completed by Mr Phillips with direction from the candidate and assistance from co-authors.

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XVIII: The candidate conceptualised this paper and drafted the manuscript with feedback from co-authors. The candidate finalised the manuscript after adjustment and provision of the response to reviewers.

XIX: The candidate conceptualised this paper, drafted the manuscript with input from co-authors. After which, the candidate completed multiple revisions, responses to reviewers and finalised the paper.

XX: The candidate was involved in the preparation of this manuscript.

XXI: The candidate was involved in patient recruitment and aided the preparation of response to reviewers and the initial and final manuscript.

XXII: The candidate conceptualised this study, aided with the coordination and supervision of data collection, provided feedback on the first draft of the manuscript, responded to reviewers and adjusted the draft to finalise the paper.

Table 1 (adjusted) – Submitted manuscripts and publications cited in the thesis by chapter. Titles in bold indicate where the manuscript contributed text.

Chapter	*Number and Title of Paper*	*Publisher*	*Year*
Introduction	I: Active Burn Rehabilitation Starts at Time of Injury: An Australian Perspective. (Letter to Editor)	JCBR	*2009*
	II: Development of a National Burns Network: Providing a coordinated response to a mass casualty within the Australian Health System.	EHTJ	2008
	III: Development of a National Model of Care for Burn Patients: Core Business Standards to Support the Activation of AUSBURNPLAN.	WA DoH (Strategy Paper)	2004
	IV: Occupational Therapy and Physiotherapy for the Patient with Burns: Principles and Management Guidelines.	JCBR	2003
	V: ABC of Burns: Rehabilitation after burn injury.	BMJ	2004
	VI: ANZBA Burn Survivor Rehabilitation: Principles and Guidelines for the Allied Health Professional.	ANZBA (e-book)	2007
Review of	**VII: Local and systemic treatments for acute oedema after burn injury (Protocol).**	Cochrane DoSR	2007
Literature	**VIII: Local and systemic treatments for acute oedema after burn injury (Review). (submitted)**	Cochrane DoSR	2009
	IX: Pharmaco-management of inhalation injury for burn survivors.	DDDT	2008
	X: Core Outcomes for Adult Burns Survivors: A Clinical Overview.	Burns	2009
Results	**XI: Whole arm water displacement volumetry is a reliable measurement technique for acute volume change: Caution with clinical use and research design in patient populations. (submitted)**	Lymphology	2009
	XII: Measurement of acute edema shifts in human burn survivors – the reliability and sensitivity of bioimpedence spectroscopy as an objective clinical measure.	JCBR	2009
	XIII: Volume measurement using the Polhemus FastSCAN 3D laser scanning: A novel application for burns clinical research.	JCBR	2008
	XIV: The QuickDASH is an appropriate tool for measuring quality of recovery after upper limb burn injury.	Burns	2007
	XV: Goniometry and Linear Assessments to Monitor Movement Outcomes: Are They Reliable Tools in Burn Survivors?	Burns	2009
	XVI: A reliable and valid outcome battery for measuring longitudinal recovery of lower limb function and balance after burn injury.	Burns	2009
	XVII: Demonstration of the validity of the SF-36 for measurement of the temporal recovery of quality of life outcomes in burns survivors. (submitted)	Burns	2009
Discussion	XVIII: Maintaining physical therapy standards in an emergency situation: solutions after the Bali bombing disaster.	Burns	2005
	XIX: First Response, Rehabilitation, and Outcomes of Hand and Upper Limb Function: Survivors of the Bali Bombing Disaster. A Case Series Report.	Journal of Hand Therapy	2006
	XX: Upper Limb 3D Motion Analysis- An Advanced Assessment Tool following Burn Injury. (submitted)	JCBR	2009
	XXI: Lower limb functional outcome assessment following burn injury: A novel use for 3D laboratory-based movement analysis	Burns	2009
	XXII: Assessing the impact of missing data in evaluating the recovery of minor burn patients.	Burns	2009

Appendix 2: Survey Instruments

Appendix 2 (a) – BSHS-B

BURN SPECIFIC HEALTH SCALE (BRIEF VERSION)

Please answer (circle) ALL questions based on your condition in the last 7 days. If you did not do the activity, please estimate your answer. Please return to Burns Unit physio in the enclosed envelope. Thanks

How much difficulty do you have:	Extremely	Quite a bit	Moderate	A Little Bit	None
1. Bathing independently?	0	1	2	3	4
2. Dressing by yourself?	0	1	2	3	4
3. Getting in and out of a chair?	0	1	2	3	4
4. Signing your name?	0	1	2	3	4
5. Eating with utensils?	0	1	2	3	4
6. Tying shoelaces/bows etc?	0	1	2	3	4
7. Picking up coins from a flat surface?	0	1	2	3	4
8. Unlocking a door?	0	1	2	3	4
9. Working in your old job performing your old duties?	0	1	2	3	4

To what extent does each of the following statements describe you?	Extremely	Quite a bit	Moderate	A Little Bit	Not at All
9. I am troubled by feelings of loneliness.	0	1	2	3	4
11. I often feel sad or blue.	0	1	2	3	4
12. At times, I think I have had an emotional problem.	0	1	2	3	4
13. I am not interested in doing things with my friends.	0	1	2	3	4
14. I don't enjoy visiting people.	0	1	2	3	4
15. I have no one to talk to about my problems.	0	1	2	3	4
16. I have feelings of being caught or trapped.	0	1	2	3	4
17. My injury has put me further away from my family.	0	1	2	3	4

18. I would rather be alone than with my family.	0	1	2	3	4
19. I don't like the way my family acts around me.	0	1	2	3	4

To what extent does each of the following statements describe you?	Extremely	Quite a bit	Moderate	A Little Bit	Not at All
20. My family would be better off without me.	0	1	2	3	4
21. I feel frustrated because I cannot be sexually aroused as well as I used to.	0	1	2	3	4
22.I am simply not interested in sex any more.	0	1	2	3	4
23. I no longer hug, hold or kiss.	0	1	2	3	4
24.Sometimes, I would like to forget that my appearance has changed.	0	1	2	3	4
25. I feel that my burn is unattractive to others.	0	1	2	3	4
26. My general appearance really bothers me.	0	1	2	3	4
27. The appearance of my scars bothers me.	0	1	2	3	4
28. Being out in the sun bothers me.	0	1	2	3	4
29. Hot weather bothers me.	0	1	2	3	4
30. I can't get out and do things in hot weather.	0	1	2	3	4

PLEASE TURN PAGE OVER

BURN SPECIFIC HEALTH SCALE (BRIEF VERSION)

To what extent does each of the following statements describe you?	Extremely	Quite a bit	Moderate	A Little Bit	Not at All
31. It bothers me that I can't get out in the sun.	0	1	2	3	4
32. My skin is more sensitive than before.	0	1	2	3	4
33. Taking care of my skin is a bother.	0	1	2	3	4
34. There are things that I've been told to do for my burn that I dislike doing.	0	1	2	3	4
35. I wish that I didn't have to do so many things to take care of my burn.	0	1	2	3	4
36. I have a hard time doing all the things I've been told to take care of my burn.	0	1	2	3	4
37. Taking care of my burn makes it hard to do other things that are important to me.	0	1	2	3	4
38. My burn interferes with my work.	0	1	2	3	4
39. Being burned has affected my ability to work.	0	1	2	3	4
40. My burn has caused problems with my working.	0	1	2	3	4

Appendix 2 (b) – SF36 Australian Acute V2

Your Health and Well-Being

This questionnaire asks for your views about your health. This information will help keep track of how you feel and how well you are able to do your usual activities. ***Thank you for completing this survey!***

For each of the following questions, please mark an ☒ in the one box that best describes your answer.

1. In general, would you say your health is:

Excellent	Very good	Good	Fair	Poor
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

2. <u>Compared to one week ago</u>, how would you rate your health in general <u>now</u>?

Much better now than one week ago	Somewhat better now than one week ago	About the same as one week ago	Somewhat worse now than one week ago	Much worse now than one week ago
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

(IQOLA SF-36v2 Acute, Australia (English))

3. The following questions are about activities you might do during a typical day. Does <u>your health now limit you</u> in these activities? If so, how much?

	Yes, limited a lot	Yes, limited a little	No, not limited at all
a Vigorous activities, such as running, lifting heavy objects, participating in strenuous sports	☐ 1	☐ 2	☐ 3
b Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	☐ 1	☐ 2	☐ 3
c Lifting or carrying groceries	☐ 1	☐ 2	☐ 3
d Climbing several flights of stairs	☐ 1	☐ 2	☐ 3
e Climbing one flight of stairs	☐ 1	☐ 2	☐ 3
f Bending, kneeling, or stooping	☐ 1	☐ 2	☐ 3
g Walking more than a kilometre	☐ 1	☐ 2	☐ 3
h Walking several hundred metres	☐ 1	☐ 2	☐ 3
i Walking one hundred metres	☐ 1	☐ 2	☐ 3
j Bathing or dressing yourself	☐ 1	☐ 2	☐ 3

4. During the past week, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of your physical health?

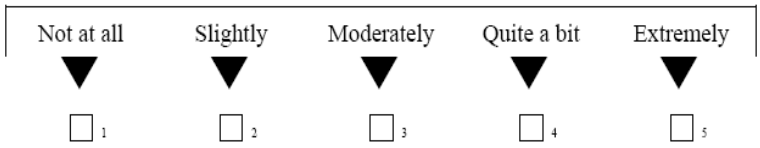
	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a Cut down on the amount of time you spent on work or other activities	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b Accomplished less than you would like	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c Were limited in the kind of work or other activities	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
d Had difficulty performing the work or other activities (for example, it took extra effort)	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

5. During the past week, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?

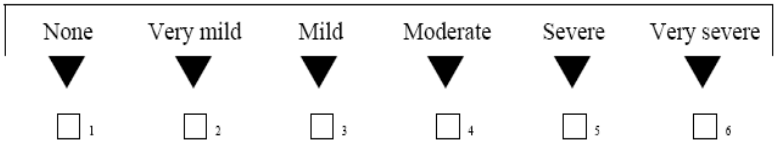
	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a Cut down on the amount of time you spent on work or other activities	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b Accomplished less than you would like	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c Did work or other activities less carefully than usual	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

(IQOLA SF-36v2 Acute, Australia (English))

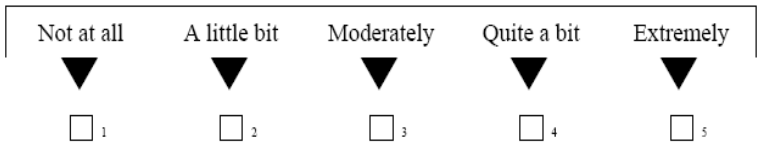
6. **During the <u>past week</u>, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbours, or groups?**



7. **How much <u>bodily</u> pain have you had during the <u>past week</u>?**



8. **During the <u>past week</u>, how much did <u>pain</u> interfere with your normal work (including both work outside the home and housework)?**



(IQOLA SF-36v2 Acute, Australia (English))

9. **These questions are about how you feel and how things have been with you <u>during the past week</u>. For each question, please give the one answer that comes closest to the way you have been feeling. How much of the time during the <u>past week</u>…**

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a Did you feel full of life?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b Have you been very nervous?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c Have you felt so down in the dumps that nothing could cheer you up?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
d Have you felt calm and peaceful?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
e Did you have a lot of energy?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
f Have you felt downhearted and depressed?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
g Did you feel worn out?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
h Have you been happy?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
i Did you feel tired?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

10. **During the <u>past week</u>, how much of the time has your <u>physical health or emotional problems</u> interfered with your social activities (like visiting with friends, relatives, etc.)?**

All of the time	Most of the time	Some of the time	A little of the time	None of the time
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

(IQOLA SF-36v2 Acute, Australia (English))

11. How TRUE or FALSE is <u>each</u> of the following statements for you?

	Definitely true	Mostly true	Don't know	Mostly false	Definitely false
a I seem to get sick a little easier than other people	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b I am as healthy as anybody I know	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c I expect my health to get worse	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
d My health is excellent	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

Thank you for completing these questions!

Appendix 2 (c) – QuickDASH

THE QuickDASH OUTCOME MEASURE

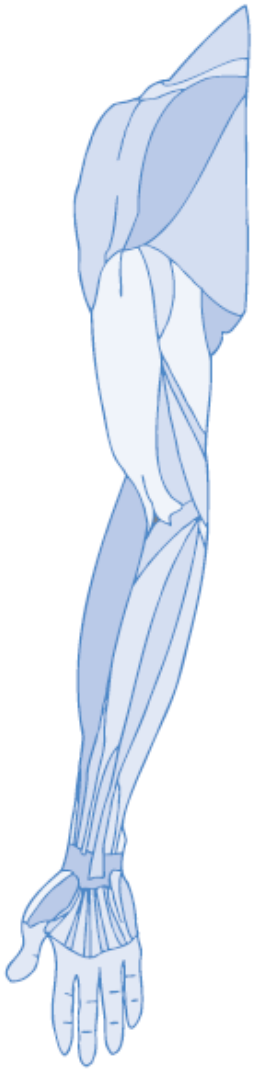
INSTRUCTIONS

This questionnaire asks about your symptoms as well as your ability to perform certain activities.

Please answer *every question*, based on your condition in the last week, by circling the appropriate number.

If you did not have the opportunity to perform an activity in the past week, please make your *best estimate* of which response would be the most accurate.

It doesn't matter which hand or arm you use to perform the activity; please answer based on your ability regardless of how you perform the task.



*Quick*DASH

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

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

A *Quick*DASH score may <u>not</u> be calculated if there is greater than 1 missing item.

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 not be calculated if there are any missing items.