Current multi-disciplinary research in wound care

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Plan of Presentation

- Established facts – conventional wisdom associated with pressure-induced ischaemia
- New investigations of alternative mechanisms of pressure-induced damage
- Emerging technologies leading to focus on soft tissue composite
Prevalence figures for Pressure Ulcers remain high

- Why?
- There are still surprisingly little consensus about the pathophysiological response to mechanical loading that triggers soft tissue breakdown
National Drivers

- In 1997, an audit in the Netherlands indicated that Pressure Ulcers are the Fourth Largest Financial Burden on their Health service
- 10%-20% prevalence in hospitals in the Netherlands
- Value has not changed much in last 10 years
- Estimated cost in the Netherlands 700million Euros per annum
- Are the cost implications similar in all countries?
- The name has changed from bed sores to pressure sores to pressure ulcers (Decubitus)
International Drivers

• Ever ageing population
• EPUAP
• NUPAP
  – February 2005 addressed critical issue of Deep Tissue Injury and possible reclassification of stages of ulcers
• Japanese Pressure Ulcer Society
  – 3500 delegates in 2003, driven by Government and Medical Insurance Companies
• You the audience
Challenge of the 20th Century - increased lifespan

Rapid increase in life expectancy

Challenge of the 21st Century - increased healthspan

Disability increases with age

Medical Engineering Industry to match the unmet medical needs

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Conventional Wisdom

External or Interface Pressures and Shear Forces

Skin

Fat

Muscle

Internal Stresses and Strains

Bony Prominence

Mechanical Properties of Soft Tissues

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Intrinsic Factors
Abnormal Response to Prolonged Loading

- Subjects have limited mobility
  - chair bound, sedated, anaesthetised

- Subjects have impaired sensitivity
  - paralysis, neuropathy

- Soft tissues are more vulnerable to pressure-induced damage than normal
  - atrophy, lack of muscle tone, dehydration

An inevitable consequence of prolonged surgery?
Extrinsic Factors

• Pressure
  – localised pressure
  – pressure gradient
• Shear
  - Semi-reclined in bed
• Temperature
  – a 1% increase in temperature increases metabolic demands by 13%
• Humidity
  – sweating
  – incontinence
• Time

Reswick and Rogers 1975
Research Objectives (circa -1985)

• The development of measurement systems to monitor the interface conditions

• The provision and assessment of novel materials and advanced seating systems

• The prediction of those interface conditions which may lead to tissue breakdown

• The identification of those subjects particularly at risk

• Establishment of objective screening technique
Early Pressure Measurement Systems
Comparison of support surfaces
Interface Pressures

Value of measurement
- Comparison of support surfaces for individuals
- Feedback to individuals/carers to indicate support postures

Safe levels - the myth of 32 mmHg, a value often quoted
- Average pressure in nail-fold capillary (Landis 1932)
- Relevance to interface pressures?
- Relevance to sites of tissue breakdown?
Mapping of interface conditions of a patient with a history of recurrent tissue breakdown at the left ischium
Conventional Wisdom

Pressure measurements alone are not sufficient to alert the clinician to potential areas of tissue breakdown.

The effects of pressure and time on tissue viability or status.
Non-Invasive Techniques for assessing Tissue Viability/Status

- Laser Doppler fluxmetry
  - Schubert and Fagrell 1991 and many other groups
- Reflective Spectrophotometry
  - Hagisawa, Ferguson-Pell et al. 1994
- Transcutaneous gas monitoring ($T_cPO_2$ and $T_cPCO_2$)
  - Bader and co-workers 1985 - 1999
- Sweat Biochemistry
  - Ferguson-Pell 1988; Bader, Knight et al. 1997-2006
Experimental Arrangement

Electrode incorporated into flat indenter

Indenter loading through sacrum
There is no single threshold pressure which will ensure the viability of tissues in all individuals.

- The effect of repeated loading on tissue viability
- Simulate pressure relief
- Wheelchair lift-off
A schematic of two distinct responses with respect to the viability of soft tissues subjected to repeated loading.
Assessing tissue viability in the spinal cord injured
UK National Spinal Injury Centre, Stoke Mandeville

42 SCI subjects
23 lesions above T6
19 lesions below T6
Assessments (2 - 6 within 1 year of injury)
performed on prescribed support cushions
Early progressive changes in tissue viability during sitting

Bogie, Nuseibeh and Bader

*Paraplegia* (1995), 33, 1441-47

- Paraplegics (low level lesions) with flaccid paralysis are at higher risk of tissue breakdown than tetraplegics
- Requirements
  - effective support cushions and
  - adherence to pressure relief regimens
- Since 1995, routine use of selected bioengineering techniques to monitor all SCI patients during sitting
- From research to routine clinical practice
A specialised seating assessment clinic: changing pressure relief practice
Coggrave and Rose
*Spinal Cord* (2003), 41, 692-95

- Retrospective review of 46 newly injured and chronic SCI individuals, median age 41 years
- Interface pressure and measurements useful as a feedback to carer/patient
- Mean duration of pressure relief of 1 min 51 s (42-210 s) required to restore $T_c \text{PO}_2$ levels
- Brief pressure lifts of 15-30 seconds are ineffective.
- Other strategies, such as forward leaning and tilt back, are more effective
Anatomy of skin and subcutaneous tissues

Can we measure tissue metabolites by sweat collected at the skin surface?

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Materials and Methods

- Tests conducted in a controlled room at 35°C
- 31 independent subjects - 19 subjects, mean age 27 (19-41)
- Subjects lay prone on a standard hospital mattress
- Assembly mounted over subject to provide loading at the sacrum for periods up to 60 min.
- Unloaded control site
- Continuous gas monitoring
- Annular sweat pads analysed
- Lactate and urea concentrations
- $T_cPO_2$ and $T_cPCO_2$ monitored

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Pressures 40-120 mmHg
Time 30-60 min

Lactate concentration / mmol/L

Median value of TcPO2 / mmHg

- Loaded sacrum
- Unloaded sacrum

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The relationship between % age reduction in median $T_c$PO$_2$ with (a) lactate ratio (b) $T_c$PCO$_2$ parameter
Summary

- Two techniques proved complementary in assessing tissue status

- Concentration of sweat metabolites elevated as a result of pressure-induced ischaemia

- Threshold Value - 60% reduction from unloaded $T_c$PO$_2$ value. Above this threshold relationship with sweat metabolite ratios

- Potential for screening method for subjects at risk of developing pressure ulcers

Sweat Lactate versus Inverse of Sweat Rate
Loading/Unloading Phases

- Similar test protocols for sweat collection
- Loading periods 0-30, 30-60 minutes
- Unloading periods 60-90, 90-120 minutes
- Analysis of sweat purines using HPLC system
- Peaks identified
  - Uric acid, xanthine, hypoxanthine and inosine
- Compared to lactate profiles
Sweat Purine Profiles during Ischaemia and Reperfusion

Bader et al. 2005 Pressure Ulcer Research
Potential as a Screening Tool

- Variation in number of sweat glands with body site
- Some subject groups subjects exhibit abnormal sudomotor function e.g Spinal Cord Injured (SCI) subjects


Peripheral sweat induced at 2 sites by pilocarpine iontophoresis

- Sweat production was increased with training
- Sweat rate is generally normal above the level of the lesion
- Sweat glands were less sensitive regardless of central or exogenous stimulation
Biochemical Measurements in Wound Fluid

- Can markers be identified which indicate sate of healing
- Criteria
- Simple collection technique
- Reasonable stability of marker in wound fluid
- Large scale studies for validation
- Application in community

*Recent finding by James and colleagues*
Pathophysiology of Pressure Ulcers - Response to mechanical loading

- Localised ischaemia
  - blood vessels in tissues

- Impaired fluid flow and lymphatic drainage
  - interstitial space

- Ischaemic/Reperfusion injuries
  - role of oxygen free radicals

- Sustained deformation of cell

Carlijn Bouten, Cees Oomens, Frank Baaijens and Dan Bader
Archives of Physical Medicine and Rehabilitation, 84, 616-619, 2003
LYMPHATIC HYPOTHESIS *Krouskop et al., 1981*

**TISSUE PRESSURE**

- Occlusion of Blood Flow
  - Hormones Released
    - Lymphatic Smooth Muscle Dysfunction
    - Inhibition of lymph flow
      - Accumulation of metabolic waste products, proteins and enzymes

**TISSUE DAMAGE**
Lymphatic clearance during compressive loading

*Miller and Seale (1981) Lymphology 14, 161-66*

**Methods**

- Animal model - hind limb
- Static applied load
- Injected radioisotope tracer to measure lymph flow
- Standard clearance curves

**Critical closing pressure of lymph vessels**
Pathophysiology of Pressure Ulcers - Response to mechanical loading

- Localised ischaemia
  - blood vessels in tissues

- Impaired fluid flow and lymphatic drainage
  - Accumulation of metabolic waste products, proteins and enzymes interstitial space (Krouskop et al., 1981)

- Ischaemic/Reperfusion injuries
  - Research focused on myocardial tissues
  - Toxic levels of oxygen free radicals and cascade of cellular events (McCord New Eng. J. Med, 1985)

- Sustained deformation of cell
Ischaemia-reperfusion injury – Evidence related to Pressure Ulcers

Ischaemia-reperfusion injury in chronic pressure ulcer formation: a skin model in the rat

Pierce SM et al. (2000) Wound Repair and Regeneration 8: 68-76

The effect of gradually increased blood flow in ischaemia-reperfusion injury


• Implications in pressure relief strategies
• Rate of pressure relief is important
Alternating Pressure Airwave Cushion/Mattress

What are the optimum characteristics of the pressure on/off cycle of such support systems?
Hypothesis

Muscles are more susceptible to mechanical loading than skin. Deep lesions first develop in the muscle tissue.

Nola and Vistnes (1980)
Plastic Reconstructive Surgery 6, 728 - 735

and

Salcido et al. (1999)
Advances in Wound Care 7, 23-40
Deep Tissue Injury (DTI)

A DTI may be misdiagnosed as a mild grade 1-2 pressure ulcer, since the extent of tissue damage is not visible until the gross breakdown of the skin surface.

Consensus Meeting NPUAP, March 2005
Technology Drivers

• Past observations have been limited to the depths of the skin layer
  – blood flow measurements
  – transcutaneous gas measurements

• And to time consuming histology of tissue biopsies

• New techniques are able to examine non-invasively the integrity of cells and deeper tissues using
  – Biosensors
  – Computational modelling
  – Live cell imaging
  – Ultrasound, Terahertz technology
  – Magnetic Resonance imaging
Supported Buttock Contact - FEA Model

Global external loads applied to skin → Local mechanical conditions inside tissue → Tissue damage

Theoretical model of a buttock on a cushion

Bone
Muscle
Fat
Skin
Cushion

Point load = 200N

Earlier Model Studies
Chow and Odell, 1978; Todd and Thacker, 1994

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Results: Reference model

Deformed Mesh

Von Mises Stress

0.00
0.04
0.08
0.12
0.16
0.2 MPa
Cushion more compliant than reference model

Deformed Mesh

Von Mises Stress

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Conclusions

- Mechanical point loading results in two areas with maximum shear strain: one in fat and one in muscle adjacent to bony prominence.

- Parameter variations lead to large changes in mechanical state of fat, but small changes in muscle near to bone.

- Interface normal stress alone has very limited value for evaluation of support surfaces.

Development of pressure ulcers

Current mechanisms:

1. ischaemia = no blood flow (hypoxia)
2. blocking of lymphatic drainage/interstitial transport
3. reperfusion injury
4. mechanical deformation
Test Hypothesis
Prolonged compression induces cell damage in an *in vitro* muscle cell seeded agarose model

Materials and Methods
C2C12 mouse skeletal myoblasts cells seeded in 3% agarose constructs

Characterised system in which cells adopt an elliptical form in compressed constructs

Subjecting constructs to static uniaxial compression of 10% or 20% strain (equivalent to 18 mmHg and 32 mmHg, respectively) up to 12 hours

Evaluating cell damage
Histology, fluorescent probes, apoptosis
Compressive Strain Rig

Culture medium

Cell-agarose cores

Lee and Bader (1997) J Orthop Res. 15:181-188
Histological Features of Viable and Damaged Cells

- Viable myoblasts
- Viable elongated myotubes
- Spherical myotubes with distorted nuclei
- Nuclear fragmentation
- Elongated myotubes with distorted/shrunken nuclei and disrupted membrane
- Vacuoles within the cytoplasm and clustered chromatin

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20% Strain - Histological Assessment

% Cells Damaged/Dead vs Culture Period /hours

- Unstrained
- Strained
Effects of Pressure and Time

Human Data

Cell Data

Reswick and Rogers 1976

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Discussion

• A modest pressure of 32 mmHg (4.3 kPa) cause significant cell deformation and resulting damage in the *in vitro* model

• Significant cell damage occurs within 1 hour of compression

• Sustained deformation of the cells inside the tissue is an important component of cell damage regardless of the level of nutrient and oxygen supply

• Defining thresholds for cell damage may be appropriate if extrapolated to the clinical setting

*Bouten, Knight, Lee and Bader (2001) J.Biomech. Eng 29, 153-163*

Hierarchical Approach

Cell | Tissue | Animal | Human
--- | --- | --- | ---

![Cell Image](image1)

![Tissue Image](image2)

![Animal Image](image3)

![Human Image](image4)
Hypotheses

- Localized ischemia (no perfusion)
- Reperfusion injury
- Impaired interstitial fluid flow and lymphatic drainage
- Sustained deformation of cells
Aim of the study:

Study the effect of ischemia and deformation on the development of muscle tissue damage after compressive loading

Animal model – MR-compatible loading device
Animal model

MRI 6.3 T scanner

Stekelenburg et al. 2006 a and b

- Brown Norway rat
- Apply indenter to tibialis anterior
- 4 months
- 180-210 grams
- Anaesthesia: isoflurane
<table>
<thead>
<tr>
<th>MRI-techniques</th>
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<tbody>
<tr>
<td>T2-weighted MRI</td>
<td>Damage</td>
<td>~e^{-t/T2}</td>
</tr>
<tr>
<td>Contrast-enhanced MRI</td>
<td>Perfusion</td>
<td></td>
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<tr>
<td>Tagging MRI</td>
<td>Deformation</td>
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Measurement protocol

- Damage (T2) and perfusion (PI):
  1. Compressive loading, indenter
  2. Ischemic loading, inflatable tourniquet above the knee
Results - Ischaemic loading

T2w

pre | during | 40 min after | 115 min after

PI

pre | during | 5 min after | 90 min after

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Results - Compressive loading

T2w

pre  during  40 min after

PI

40%  0

pre  during  5 min after

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Results – T2

[tibia image with labeled regions]

- Indenter-experiment:
  - ROI 1
  - ROI 2
  - ROI 3
- Tourniquet-experiment:
  - ROI 1

Normalized T2 vs. Time [min]

[Graph showing data points and error bars for different ROI regions with time on the x-axis and normalized T2 on the y-axis]
Results – Histology

Control

Ischemia

Compression
Discussion

- MR-compatible loading device
- 2D / 3D information on damage/perfusion/deformation
- Importance of deformation

- Clinical practice: standard for manual pressure relief: 2 hours
- SCI: increased susceptibility: larger deformations
- T2 useful for early detection deep tissue injury, however a prescreening method is needed (damage markers in blood)
Pressure Ulcer Research should incorporate an approach involving studies on Patients to Cells

Soft tissue composite over bony prominences

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