The role of pressure in pressure ulcer aetiology: a review of the literature

Tweed C

Abstract

Pressure ulcers are localised areas of tissue breakdown affecting the skin and/or underlying tissues including subcutaneous fat and muscle. Applied pressure is a major factor in the aetiological process of pressure ulceration, although it is acknowledged that the exact mechanisms are complex and poorly understood. It is not known how external loads affect the tissues and how this eventually leads to tissue damage.

This paper reviews the key scientific literature with specific respect to how pressure affects different functional units of the tissues, namely though occlusion of blood vessels, impaired transport of nutrients through the interstitium and deformation of the cells.

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Introduction

Pressure ulcers represent localised tissue death [1] and present clinically from reactive hyperaemia to blistered, broken or necrotic skin [2]. They vary in size, severity and the underlying structures involved [3] and, despite many studies both in animals and humans, there continues to be a lack of knowledge concerning their exact aetiology. This is particularly so with respect to how external mechanical loads on the skin lead to breakdown within the tissues [3, 4].

Many factors contribute to the development of pressure ulcers and these have been presented as conceptual schemes by several authors [5, 6]. The primary cause, however, is localised interface loading to an area of skin, usually a bony prominence, not adapted to take such mechanical force [3, 7]. The nature of the external load on the skin largely determines the location and primary site of pressure ulcer development. Deep pressure ulcers are caused by prolonged unrelieved compression and develop near to bony prominences, and although it is acknowledged that the forces of shear and friction may be contributing factors in the development of pressure ulcers, they will not be considered in any detail in this paper.

Carol Tweed
BSc (Hons), RGN
Clinical Specialist
Huntleigh Healthcare
Wellington, New Zealand
E-mail: caroltweed@hotmail.com

Masters Candidate
Wound Healing Research Unit
University of Wales College of Medicine
Cardiff, UK

Aetiology of pressure ulcers

Bosboom [4] has discussed three main hypotheses on the aetiology of pressure ulcers. Each of these hypotheses focus on how pressure affects a different functional unit of tissue, namely formation of pressure ulcers by local ischaemia following occlusion of capillaries, impaired transport of nutrients through the interstitium (interstitial change), and cellular deformation. This paper will review how pressure affects each of these factors by reviewing key scientific literature.

Local ischaemia following occlusion of capillaries

Occlusion or partial occlusion of the vasculature may result if the skin is subjected to localised pressure, although the degree to which this occurs is dependent upon the magnitude of the pressure applied [8]. Many studies have been performed using animal models which have attempted to determine the threshold values for external loads [9-18].

Although different methodologies and animal models existed for these studies, most followed a regimen where skin and

muscle tissue were compressed between an indentor and bone with either the magnitude and/or duration of the compressive load being varied. Pressure ulcers were defined from a combination of gross and histological examination of the tissues.

The results of these studies have concluded that there is an inverse relationship between the magnitude and duration of the load in that both high pressure for short periods and low pressure for long periods both cause ulceration. Details concerning the methodology, results and limitations of these studies are described in Table 1.

Criticisms of these studies can be made on several fronts due to poor explanations of the methodology used, the lack of statistical analysis and oversights in the interpretation of results [19]; further limitations related to the use of animal models are discussed later in this paper. The literature demonstrates, however, that both time and pressure magnitude are important factors and once thresholds for each are exceeded, tissue damage will result.

Reswick & Rogers [20] developed a protocol including an 'allowable pressure versus time' curve for use in spinally injured patients suggesting 'safe' maximum periods of time and units of pressure that could be applied over bony prominences. The evidence used to produce this curve was based on studies performed by Kosiak [11] and also on what is described as 'actual patient experience'. This included subjective comments by staff, interface pressure measurements on patients with impending tissue damage and controlled tests on volunteers where tissue breakdown was induced by pressure.

Several criticisms can be made of this research: Firstly an assumption is made that 30-35mmHg is the threshold above which tissue ischaemia occurs – cited as the 'ischaemic pressure' and the source of this figure is not referenced. However, pressure is not the only force affecting tissues in human subjects. Shear and tissue distortion may also affect the vasculature sufficiently to cause ischaemia, thus there should not be reliance upon use of interface pressures as measures of effectiveness.

In addition to the reasons above, interface pressure recordings taken in both patients and volunteers must be interpreted with great caution since they are difficult to measure and subject to error [21, 22].

Finally, it is important to realise that body shapes and tissue characteristics of vulnerable patients may vary widely from healthy persons and results from each set cannot be correlated [23].

Reswick & Rogers [20] do acknowledge that their pressure/time curve should only serve as a guideline as it was developed from "much experience" and "relatively few controlled measurements".

With respect to the study by Kosiak [11] on which the Reswick & Rogers [20] study was based, the limited data shown demonstrated that intense pressures for short periods were just as injurious as low pressures for long periods. Thus the claim that there was an inverse relationship between pressure and time is not strictly justified.

If ischaemia is the only factor involved in pressure ulcer aetiology, all pressure intensities in excess of capillary closing pressure should produce ulceration in the same duration of time [19, 24, 25, 26]. This is clearly not the case and highlights the complex aetiological processes involved. Although it is clear that soft tissue is susceptible to mechanical loading, the variability of individual medical and physical conditions make it impossible to stipulate one universal safe interface pressure threshold [27].

An additional factor involved in pressure ulcer aetiology that has been demonstrated to be of some significance in animal models in the effects of ischaemia is that of reperfusion injury [8, 17, 18]. Despite some biochemical similarities to events which occur following major organ surgery, the evidence remains controversial with respect to pressure ulcers [3] and is outside the scope of this paper.

Interstitial change

The theory behind how interstitial change occurs is based upon the assumption that mechanical loading causes a disruption to the lymph circulation and interstitial transport processes [25, 26, 28-31].

Reddy [29] used a mathematical model to examine the relationship between the interstitial fluids and external pressure investigating rheological relationships. Rheology is defined as the science of the deformation and flow of matter [32]. The results indicated that there is a slow movement of interstitial fluids and ground substances from under the area of pressure application and there was an inverse relationship with respect to the pressure intensity and load duration.

Table 1. Table of pressure/time studies in animals.

Brooks and Duncan (1940) [9]

Animal model – Rat tails

Methods
- 150 rats. Pressure of 20-1419 mmHg applied to tails between 3-48 hours. Histological sections taken to observe change.

Outcome
- Pathological change due to obstruction of circulation – muscular damage noted.
- First set experiments attempted to determine min time and pressure to produce massive necrosis.
- Duration of 17-18 hours defined as critical period with magnitude of 120-130 mmHg.
- Duration of pressure more important than magnitude.
- Venous obstruction has a role in aetiology.

Limitations
- Only healthy animals used – these are not representative of patients. After 17 hours even healthy animals will be affected by stress, lack of water etc – cannot rule out other variables. Only single animals used to determine some results. No statistical testing and no repeating of tests.

Husain (1953) [10] (4 discrete studies)

Animal model 1 – Rat tails

Methods
- 93 rat tails. Pressures of 100-800 mmHg applied for 1-10 hours.

Outcome
- No changes except 800mmHg for 6 hours.

Limitations
- Very poorly described results.

Animal model 2 – Rat legs

Methods
- 60 rat legs.
- 25 legs – Streptococcus haemolyticus injected to observe bacterial permeability.
- 10 legs – observed for capillary permeability.
- 81 rats with compromised blood flow, nervous supply and spinal injuries.

Outcome
- States that time is more important than pressure intensity.
- High pressure and long time duration both cause damage.
- Blood vessel damage appears to occur after release of pressure.
- Capillary permeability is increased after pressure release and bacteria become localised at site of pressure application.
- Threshold pressures decrease after following damage to spinal cord, blood supply or poor nutrition.

Limitations
- Qualitative results – no quantification. No raw data available.
- States that time is more important than pressure intensity but low pressures for short periods also cause marked degeneration. This not discussed.

Animal model 3 – Guinea pig legs

Methods
- 45 legs.
- Some animals scorboritic, some controls.

Outcome
- The scorboritic guinea pig is more sensitive to pressure injury than the control 'normal' animal.

Limitations
- No description of numbers involved.
- No definition of scorboritic.

Experimental model

Methods
- Model of pressure damage. Use of 2 unequal surfaces with sponge rubber between.

Outcome
- Deformation is unequal with higher deformation nearer the smaller surface. Area of compression increases with distance from surface.

Limitations
- Poor description of methodology.

Kosiak (1959) [11]

Animal model – Dogs

Methods
- 16 dogs subjected to pressures of 100-550mmHg for periods of 1-12 hours on bony prominences of hind limbs. Majority followed for 14 days following pressure assault.
- Measured direct interface pressure and transmitted pressures in soft tissues.

Outcome
- Claims that there was a inverse relationship between pressure and time. Limited results demonstrated that intense pressures for short periods are just as injurious as low pressures for long periods.
- Tissue pressure measurements indicated that all tissue types were affected by pressure not muscle first as stated by other researchers.
- Claim that skin exerts a sling like effect resulting in only a fraction of pressure transmitted to deeper structures.

Limitations
- No statistical tests – only qualitative data.
- No randomisation of dogs whose weight ranged significantly from 35-70 pounds. No standardisation of dog type – all were mongrels. Dog skin not representative of human tissues.

Kosiak (1961) [12]

Animal model – Rats: hamstring muscle

Methods
- Total of 40 rats.
- 20 normal healthy, 20 paraplegic.
- Within each group constant (n=12) or alternating pressures (n=8) applied.

Outcome
- Once > 1 hour and > 35 mmHg, extent of tissue damage is same regardless of pressure applied. This is not discussed.

- Ulceration not noted before 3 days.
- Muscle highly susceptible to damage.
- Normal and denervated muscle responded to pressure in similar ways.
- Increase in capillary permeability resulting in interstitial changes.
- Tissues have greater resistance to alternating pressures.

Limitations
- No description of quantification of tissue damage.
- Micro-pipettes used which were likely to provoke damage in themselves and this may explain why lower threshold values were found compared to other investigators.
- Poor methodology description.

Dinsdale (1973) [13]

Animal model – 30 normal pigs, 27 paraplegic pigs

Methods
- Pressures from 45-1500 mmHg applied for 3 hrs. In half of studies, friction also applied every 15 mins.

Outcome
- Pressures < 150mmHg revealed no changes.
- At equivalent pressures, similar pathologies noted in both paraplegic and normal pigs.
- Tissue found to remain ischaemic even after blood flow restoration.
- Pressure + friction resulted in change.

Limitations
- No explanation how friction applied.
- No statistics.
- Poor randomisation methods.
- Different protocol and animals for light and electron microscopy.
- Friction is increased with increasing skin wetness – this was not standardised in this study.

Dinsdale (1974) [14] (4 discrete studies)

Animal model 1 – 10 paraplegic pigs

Methods
- Pressures of 160- 1100 mmHg applied for 3 hours to both iliac spines. In addition friction applied on one side only.
- 7 day observation period.

Outcome
- 480mmHg pressure required to cause ulceration.
- Friction increases susceptibility to skin ulceration if pressures under 500mmHg. Once >500mmHg – no difference.

Limitations Gross classification only by 2 investigators.

Animal model 2 – 8 normal pigs

Methods
- Repeated pressures with and without friction.
- 7 day observation period

Outcome
- Ulceration occurred within 18 hours.
- Pressure only required 290mmHg.
- Pressure + friction required only 45mmHg.

Limitations
- Repeated pressure +/- friction could only take place on one side of pig at time and not simultaneously – possibility of inconsistency and bias.
- No evidence that application was randomised to prevent this effect.

Animal model 3 – 14 normal pigs

Methods
- Friction with repeated pressure of 159mmHg.
- 'Randomised' iliac spines received either pressure alone or pressure + friction.
- Blinded evaluations.

Outcome
- Friction is a statistically significant (P=0.021) factor in development of pressure ulcers.

Limitations
- Gross classification only by 1 investigator although this was blinded.

Animal model 4 – 5 normal pigs

Methods
- Blood flow in skin and sub cutaneous tissues with application of external pressure and/ or friction.
- Randomised design.
- Isotope clearance technique to determine perfusion.

Outcome
- No significant (P< 0.05) difference in perfusion between pressure alone or pressure + friction.
- Friction did not increase production of ulcers by an ischaemic mechanism.

Limitations
- Not real time monitoring of perfusion. Animal required to be sacrificed 30 seconds after isotope infusion. Amount of isotope then measured in tissue.

Nola and Vistnes (1980) [15] (2 discrete studies)

Animal model 1 – 15 rats

Methods
- Split into 2 groups. Pressures of 100mmHg for 6 hours every day for 4 consecutive days. Group 1 had trochanteric pressure applied to skin only.
- Group 2 to skin and muscle over tibia.

Outcome
- In skin only,100% incidence of PU noted.
- In skin + muscle no open PU noted but damage to muscle seen.

Limitations
- Animals only followed up for 3-4 days only. May take 7 days for lesions to exhibit at skin surface.
- No rationale given as to why pressure application of 100mmHg used and why 6 hours for 4 consecutive days.

Animal model 2 – 16 rats

Methods
- Surgery undertaken 3 weeks before pressure application. Muscle flap transposed to cover trochanter on one side (blood and nerve supply maintained). Other side acted as control.

Outcome
- 100% incidence in skin only but 69% incidence in muscle +skin group.
- Although no skin damage, severe muscle damage occurred. Muscle is unsuitable coverage for pressure bearing area.

Limitations
- Only 3 weeks allowed between surgery and pressure application. Likely that wound not fully healed and still inflammatory/ maturational changes occurring.

Daniel *et al* (1981) [16]

Animal model – 30 normal pigs

Methods
- Pressures of 30-1000mmHg applied to greater trochanter of pigs for 2-18 hours in series of 30 experiments.
- Areas of applied pressure observed for 7 days before pig killed. Area visually and microscopically examined.

Outcome
- Muscle necrosis always noticed before skin damage. Lesions classified into 3 groups:
  1. Muscle damage only (caused first next to bone) produced by high pressure and short duration and also low pressure and long duration.
  2. Muscle and deep dermis damage from any pressure over long duration.
  3. Full thickness from any pressure over long duration. Skin lesion presented 1 week following pressure application.
- Skin damage due to secondary ischaemia but muscle damage due to primary ischaemia.

Limitations
- Inadequate description of methodology how 30 experiments were performed.
- Not evident how many pressure injuries made to each animal.

Salcido *et al* (1994) [17] (3 discrete studies)

Animal model 1 – Rats

Methods
- Pressure of 145 mmHg applied to trochanter for 6 hours for 5 daily consecutive sessions.
- Time course studies to describe histology of an evolving PU (5 rats).

Outcome
- Histology of evolving ulcer noted.
- Severity directly related to number of pressure sessions. Application of 5 sessions produced lesions of stages 1 or 2 for 90% of times.
- Muscle and skin damage noted.

Limitations
- 6 hour duration and 145mmHg derived from literature review but no mention of which study/ ies.
- No mention of how sample size calculated.

Animal model 2 – Rats

Methods
- 18 rats – 1 site on each hip to investigate lesion frequency.

Outcome
- Visible dermal ulceration rare even after 5 sessions.
- Severe deep muscle damage noted.

Animal model 3 – Rats

Methods
- Histology quantification.

Outcome
- Pathological conditions graded according to severity to produce a 'standard'.

Limitations
- No mention of how weighting of subjective observations was made.
- No testing of this model undertaken and yet stated that this would be used in future studies.

Peirce *et al* (2000) [18] 3 discrete studies

Animal model 1 – Unanaesthetised rats

Methods
- 16 rats divided into 4 each group receiving different number of ischaemic/ reperfusion (IR) events (caused by surgically inserted magnet) for 1, 2 or 3 days.

Outcome
- Skin blood flow, photographic analysis, $TcPO_2$, and histology noted in all 4 studies.
- Extent of total tissue damage was proportional to IR cycle frequency for all 3 studies.

Limitations
- IR cycle applied only to skin. No muscle or bone involvement – ? applicable to humans.

Animal model 2 – Unanaesthetised rats

Methods
- 32 rats divided into 4 groups. IR events applied to 3 groups for 5 days. 1 control group.

Outcome
- Tissue damage significantly increased when frequency of IR cycles was increased.

Limitations
- Longest study lasted only 5 days. No long term effects noted.

Animal model 3 – Unanaesthetised rats

Methods
- Ischaemia alone compared to IR induced injury.

Outcome
- IR more damaging than prolonged ischaemia alone. Reperfusion suggested as mechanism for tissue injury.

Limitations
- No biochemical analyses to determine if free radicals were evident.

Reddy [29] hypothesised that as the interstitial fluid is squeezed out, direct contact between fibroblasts occurs interrupting collagen synthesis. In addition, it was suggested that as interstitial pressure decreases capillary bursting, oedema and lymphatic damage occur. It must be remembered, however, that this is simply a mathematical model and Reddy [29] highlights that the simple linear model used does not allow for accurate prediction and highlights the requirement for detailed analysis of flow dynamics. However, at the time of publication, it was stated that there was no supporting literature on these parameters. This is also emphasised by Ferguson-Pell [33] in a review of this article who commented how the interpretation of the physiological significance has to be treated with great caution.

Based upon a review of the literature and anecdotal evidence in the laboratory, Krouskop [25] hypothesised that lack of collagen in the skin and supporting structures is a key factor in pressure ulcer aetiology. The role of collagen in the extracellular matrix of healthy skin and as part of normal wound healing is of pivotal importance both in terms of structure and function [34, 35]. With respect to pressure application *in vivo*, it is collagen that is thought to provide a buffer protecting the interstitial fluids and cells of the dermis [25].

Studies by Reddy et al (1975) cited in Krouskop [25] and *in vivo* studies in spinal injured patients (Claus-Walker 1973) cited in Krouskop [25] support the theory that as collagen levels reduce, a larger fraction of the external load is transmitted to the interstitial fluids and cells, resulting in a number of tissue damage mechanisms. A number of intrinsic factors related to pressure ulcer risk such as age, steroid administration and nutritional status also affect synthesis of collagen, demonstrating again the complex aetiological relationships involved.

Le *et al.* [30] used silicon sensors placed under and near to the greater trochanters to measure pressure distribution inside tissues. A pilot study was performed initially *in vitro* using steak followed by two *in vivo* studies using pig models. In these studies, needles were inserted at varying angles into the area of tissue to be studied, which then transmitted recordings back to the sensor for a pressure recording. The results demonstrated that although the surface pressure may stay below capillary pressure, the internal pressure at the bone interface can be three to five times higher, illustrating that the use of interface pressures to monitor patients at risk of pressure ulceration is inappropriate. The researchers hypothesised that a future study may enable a relationship to be predicted between surface and internal pressures, although to date no such evidence exists [36].

The results of this work also provide physiological evidence supporting the use of preventative equipment which relieves rather than reduces pressure due to the pressure gradients around bony prominences [30].

Despite this study providing what was at the time new techniques both *in vitro* and *in vivo*, criticisms can be made on the following points. No mention in the introductory literature review is made of the previous work by Reddy *et al.* [29], cited in Ferguson Pell [33] where a similar technique was used. In the discussion, the authors comment how other local vector forces affect the tissues *in vivo*, a variable that was not able to be measured. No mention is made either of the fact that other mechanical forces such as shear and friction had been demonstrated to be important factors in pressure ulcer aetiology [13, 14, 37].

Finally, despite great care to avoid previous criticisms of use of the 'needle' methodology as described in a previous study by Daniel *et al.* [16], difficulties still existed with this technique as a fluid pocket developed above the needle insertion point affecting measurement. A subsequent study by Bosboom *et al.* [36] has also discussed how use of a needle provokes an inflammatory response and makes the muscle more vulnerable to loading.

Most recently, Bosboom *et al.* [36] used a rat model to relate controlled external loading to local muscle damage using a reproducible method. Using 11 animals, external pressure loads of 10, 70 and 250kPa were applied; these figures were based upon the magnitudes used by Kosiak [12], Daniel *et al.* [16], and Goldstein and Sanders, cited in Bosboom *et al.* [36].

In six of the rats, interstitial fluid pressure was measured invasively using a micro-pipette; in the remaining rats this variable was not measured and acted as the control group. The application of 10kPa or 70kPa only damaged muscle tissue when loading was combined with interstitial fluid measurements. At a load of 250kPa, more damage resulted if the load was combined with the measurement. These results highlight the necessity of using numerical modelling methodology rather than or in addition to actual physiological study for some aetiological experiments.

Cellular deformation

This third hypothesis proposes that prolonged cell deformation triggers tissue damage due to changes in the mechanochemical environment of the cell which in turn enhances tissue degeneration [4].

Ryan [31] hypothesised that mechanical forces alter the balance of biochemical signals, affecting the anatomical configuration of skeletal protein and increasing susceptibility to pressure ulceration. In a controlled *in vitro* study using cultured muscle cells, Bouten *et al.* [38] demonstrated that even if an oxygen and nutrient supply was maintained, prolonged compressive loading led to a significant increase in cell damage compared to the controls.

In a study using five anaesthetised rats, Bosboom *et al.* [4] applied an interface pressure of 250kPa for 2 hours to the anterior tibialis muscle and overlying skin. The rats were allowed to recover from the anaesthetic and mobilise freely for 24 hours, following which they were anaesthetised again, and *in vivo* magnetic resonance imaging (MRI) was performed on both the loaded and control hind limbs. Finally the rats were sacrificed and histological examination of the tissues performed.

Although all rats exhibited muscle damage, the results from both MRI and histology demonstrated that despite strictly controlled loading techniques, there were large variations in the amounts of damage between rats. Within a human population, susceptibility to most pressure ulcers is generally explained by differences in underlying pathology or the variety of risk factors affecting the patient. However, the authors postulate that there is perhaps another reason why this is so and highlight the need for more research since in this study all the rats were healthy, of the same weight, age and sex and tested under virtually identical conditions. The authors suggest that the development of damage to the muscle over time *in vivo* should be performed using MRI.

In addition to the animal studies based upon MRIs, a software package was used to develop a three dimensional finite element model which simulated the shear strain distributions in the muscle as a result of mechanical loading. The benefit of using such a model is that differences in material properties and geometry are accounted for, allowing accurate determination of local forces within the muscle during loading [4]. The results demonstrated that although the shear strain distributions showed some overlap with the area of muscle damage, the results were not convincing enough to conclude that cell deformation is a trigger for muscle damage and further research including validation of this model is required.

Discussion

Limitations of studies in animal models

Much of the work on pressure ulcer aetiology has been undertaken using animal models as they provide a simple and inexpensive way of testing hypotheses without the ethical issues encountered in clinical practice. However, there are many drawbacks and criticisms of using animal models which are discussed below.

There is difficulty in translating research findings on healthy animals into the clinical setting where patients with multiple pathologies are generally exposed to repetitive pressure assaults complicated by friction and shear [39, 40]. The soft tissue layers of animals, particularly the skin, differ to those of human soft tissue [4, 16].

Many of the studies attempted to correlate multiple variables of time and pressure in an attempt to determine a threshold at which pressure injury occurred. Altman [41] describes how frequent misuse of correlation occurs where large numbers of variables have been used which appears to be the case with many of the early animal studies.

Virtually all the early animal studies [9-15, 17] state their results in a qualitative manner and do not list any quantitative results; additionally no statistical analyses have been undertaken. Thus it is with great scepticism that any relationships can be proven.

Applied external loads have not been found to be related to the local loads within the tissues [4, 30] whereas it is the local loads which determine the tissue state and the occurrence of local tissue damage.

Histological examination of tissue demands destruction of part of the tissue and, as a result, it is impossible to measure tissue damage over time. Studies by Bosboom *et al.* [4] have demonstrated that when histology is correlated with MRI, there is 90% agreement, with the added benefit that pressure damage can be followed over time *in vivo*.

In many studies, animals were anaesthetised, enabling accurate pressure applications and a reduction in physiological stress

to the animal. However, physiological consequences of anaesthetic agents may compromise the true effects of pressure on the tissue of unanaesthetised animals [18].

Pressure ulcers normally develop from unrelieved pressure exerted by the patient's own weight over a bony prominence [30]. Thus it could be argued that the animal experiments where pressure was artificially applied are not representative of normal aetiological events.

Persson [42], in a recent debate concerning usefulness of animal models, stated that:

> *No model can be properly validated unless we have a sufficient undisputable knowledge about the human disease itself... perhaps this cannot be accomplished unless the balance is shifted significantly toward patient-orientated research, where* in vivo *paradigms are allowed.*

Persson [42] also suggested that:

> *... progress in medicine has been slowed down by the false inference that a furry, four legged hypothesis generator provides a good model of human disease.*

Although the above statements were made with respect to research into airways disease, perhaps the same can be said of research into pressure ulcer aetiology.

Despite the many criticisms, animal models have and will continue to play a prominent and important role in the evolution of our thinking [43]. In further support of animal models, Bosboom [4] suggests that future animal studies should take place in animals where certain mechanisms involved in the pathways of tissue breakdown have been selectively down regulated – so called 'knock-out' animals. This may enable more insight in to the pathophysiological mechanisms involved in pressure ulcer aetiology.

Conclusion

To date, the relative contribution of each of the three mechanisms as proposed by Bosboom [4], namely the blood vessels, the interstitium and the cells, are unknown. Although the role of each remains to be elucidated, it is highly likely that all are due to local tissue deformation.

Most studies regarding aetiological processes have concentrated solely on one or two variables, with other contributing factors very poorly controlled even though they have been identified by other investigators as significant [25]. It can therefore be concluded that many of the questions concerning aetiology of pressure ulcers remain unanswered or uncertain and demand further investigation [6].

Bosboom [4] discusses how a clear understanding of the pathways leading to tissue breakdown is required and suggests a hierarchical approach to future research involving both *in vitro* and *in vivo* studies. *In vitro* studies of the effect of pressure on single cells as well as cells within an extra cellular matrix would identify the protective role of the interstitium [4]. Bosboom [4] also discusses how the use of animal models is required to study the role of blood perfusion in pressure ulcer aetiology by use of laser Doppler and/or MRI techniques.

A better understanding of aetiological factors involved would facilitate the development of valid pressure ulcer risk indicators which to date have only been based upon very limited research findings and anecdotal practice [44]. Once an understanding of the pathways involved in pressure ulcer aetiology is achieved, it may be possible to improve the load bearing capacity of the tissues, signalling the possibility of significantly reducing or even eliminating pressure ulcer incidence [4].

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