Etiology and pathology of pressure sores

Citation for published version (APA):

Document status and date:
Published: 01/01/1996

Document Version:
Publisher’s PDF, also known as Version of Record (includes final page, issue and volume numbers)

Please check the document version of this publication:

• A submitted manuscript is the version of the article upon submission and before peer-review. There can be important differences between the submitted version and the official published version of record. People interested in the research are advised to contact the author for the final version of the publication, or visit the DOI to the publisher’s website.
• The final author version and the galley proof are versions of the publication after peer review.
• The final published version features the final layout of the paper including the volume, issue and page numbers.

Link to publication

General rights
Copyright and moral rights for the publications made accessible in the public portal are retained by the authors and/or other copyright owners and it is a condition of accessing publications that users recognise and abide by the legal requirements associated with these rights.

• Users may download and print one copy of any publication from the public portal for the purpose of private study or research.
• You may not further distribute the material or use it for any profit-making activity or commercial gain
• You may freely distribute the URL identifying the publication in the public portal.

If the publication is distributed under the terms of Article 25fa of the Dutch Copyright Act, indicated by the “Taverne” license above, please follow below link for the End User Agreement:
www.tue.nl/taverne

Take down policy
If you believe that this document breaches copyright please contact us at:
openaccess@tue.nl
providing details and we will investigate your claim.
Etiology and pathology of pressure sores: a literature review

Carlijn V.C. Bouten

WFW report 96.015

Literature review in behalf of the research project

Etiology of pressure sores, conducted by the department of Computational and Experimental Mechanics of the Eindhoven University of Technology, in co-operation with the department of Movement Sciences of the University of Limburg, The Netherlands

January 1996
Contents

1. Introduction 1

2. Skin, subcutis and muscular tissue 4
   2.1 Soft biological tissue 4
   2.2 Skin 6
   2.3 Subcutis 9
   2.4 Muscle 9

3. Etiology of pressure sores 11
   3.1 Pressure 11
   3.2 Shear 13
   3.3 Interstitial changes 14
   3.4 Risk factors 14

4. Pathology of pressure sores 16
   4.1 External loading 16
   4.2 Primary mechanical changes 16
   4.3 Primary physiological changes 18
   4.4 Secondary changes 18

5. Preliminary conclusions 19

6. References

Appendix A Terminology
1. Introduction

Pressure sores - also known as pressure ulcers, decubitus ulcers, or simply decubitus - have defied the best attempts of medical and nursing staff since centuries. They were first described as "gangraena" in bedridden patients by Fabricius Hildanus (1593). In 1777 Wohlleben referred to this pathological phenomenon as "gangraena per decubitum": tissue necrosis by lying down. However, pressure sores must have been known long before, given their description in Egyptian mummies (Thomson-Rowling, 1961). Despite this long 'history', the etiology and pathology of pressure sores remain poorly understood. Pressure sores are now defined as localised areas of tissue degeneration in skin and/or underlying tissue, resulting from a prolonged mechanical load (National Pressure Ulcer Advisory Panel, 1989) but their development may involve many possible contributing factors, like tissue conditions, temperature and humidity, that influence pathological processes.

Etiology

For a long time, pressure sores have been seen as a nursing problem. Therefore, the major part of research in this area has been directed towards prevention by reducing the intensity and duration of the externally applied (i.e. to the skin) mechanical loads - for instance with special mattresses and cushions. Knowledge about the basic mechanisms whereby these loads lead to tissue degeneration, however, is limited.

Since World War II several hypotheses with respect to the etiology of pressure sores have been presented, which can be divided into three main theories. The first and most common theory is that prolonged pressure results in tissue damage due to impaired capillary perfusion, and hence hypoxia, of the skin and underlying tissues (Daniel et al., 1981; Kosiak et al., 1958; Kosiak, 1959 & 1961; Larsen et al., 1979). The second theory states that besides from pressure, pressure sores will result from shear stress. Shear has been described as being "more disastrous than the more vertical pressure" (Reichel, 1958) and can significantly decrease the time needed to develop a pressure ulcer. The mechanisms by which shear causes the rapid development of pressure sores are not fully understood; they have been ascribed to a higher internal (within the tissues) mechanical load than resulting from pressure alone (Dinsdale, 1973), the stretching and angulating of tissue layers, and the grating of superficial tissue layers over the deep fascia (Reuler & Coonery, 1981). The last theory aims at the interstitium between cells and terminal capillaries. It is based on the assumption that an (externally) applied mechanical load will change interstitial pressure, interstitial fluid flow, and concentrations of molecules and ions, thereby impairing the transport of nutrients to the cell as well as the lymphatic drainage of metabolic waste products (Krouskop, 1983; Miller & Seale, 1981; Oomens, 1985; Reddy et al., 1981). These processes result in a disturbance of the metabolic equilibrium within the tissue, eventually leading to tissue necrosis. Researchers adhering the first two theories usually try to describe the relationship between strictly defined external mechanical loads and the onset of tissue damage, whereas researchers adhering the interstitium theory also try to describe the link between the external load and the mechanical conditions and physiological changes within the tissue, which may be relevant for tissue damage. The interstitium theory gets more and more attention (Dodd & Gross, 1991; Vohra & McCollum, 1994), but has not been experimentally demonstrated to be related to the onset of pressure sores.
Pressures sores usually develop in tissue covering bony prominences. Daniel's classic studies in swine showed that initial changes and damage at these sites occur in deep muscle tissue with progression towards the skin (Daniel et al., 1981). Most commonly pressure sores occur on the lower half of the body, particularly over the sacrum (43%), greater trochanter (12%), heel (11%), ischial tuberosities (5%), and lateral malleoli (6%) (Peterson, 1976). These are the bony prominences that support the body during lying, sitting, and standing.

Clinical classification
Several classification schemes have been devised for pressure sores (Guttmann, 1976; Parish et al., 1983; Shea, 1975; Yarkoni et al., 1990). A commonly used classification scheme for clinical use is the one recommended by the American National Pressure Ulcer Advisory Panel (1989), which is given in Table 1. Note that these schemes do not inform about the primary onset and causal factors of changes in deep tissue layers, as they are based on visible superficial alterations when damage has already occurred. Therefore, these schemes cannot be used as guidelines for prevention, but may help in predicting prognoses and to select treatment possibilities.

Table 1. Clinical classification of pressure sores

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage I</td>
<td>Non-blanchable erythema of the intact skin. This is a red or violaceous area that does not blanch when pressed, indicating that blood has escaped from capillaries into the interstitial space.</td>
</tr>
<tr>
<td>Stage II</td>
<td>Partial thickness skin loss. The skin surface is broken resulting in an abrasion or shallow crater.</td>
</tr>
<tr>
<td>Stage III</td>
<td>Full thickness skin loss and extension into subcutaneous fat but not through underlying fascia.</td>
</tr>
<tr>
<td>Stage IV</td>
<td>Extensive destruction involving damage to muscle, bone, or tendon.</td>
</tr>
</tbody>
</table>

Prevalence and costs
Pressure sores are painful, difficult to treat, and can occur in all situations where people are subjected to prolonged mechanical loads: when bedridden or (wheel)chair bound or when wearing a prothesis. Most pressure sores develop early during hospitalization, with 70% of the sores occurring within the first two weeks of hospitalization (Norton et al., 1975). Elderly people are particularly susceptible, with 70% of all pressure sores occurring in patients aged over 70 years (Young & Dobrzanski, 1992). Young patients usually have an underlying neurological disorder, and patients with cerebral palsy, multiple sclerosis, and spinal cord lesions are particularly susceptible: up to 85% of paraplegics develop a pressure sore (Barbenel et al., 1977; Reuler & Coonery, 1981).
Reports of the prevalence of pressure sores vary greatly, depending on the description and classification of pressure sores and the accuracy of registering patients with pressure sores in the community. A survey among persons in acute care hospitals in the United States revealed a prevalence of 9.2% (Meehan, 1990). The prevalence of pressure sores among hospital inpatients in the United Kingdom is about 8% (Dealey, 1991). Haalboom (1990) estimated that in the Netherlands 10% of all patients in general hospitals and 15% of the total population of somatic and psychogeriatric nursing homes are suffering from pressure sores. From an inquiry among general practitioners he estimated the prevalence in the community to be about 0.2% of the mean total of 2000 patients. This implies that the total number of pressure sore patients in the total population of 15 million in the Netherlands is estimated to be 44000.

The financial consequences of pressure sores are considerable. Estimates of average per case in acute care hospitals range widely from $15000 to $25000 in the United States (Sacks, 1989) to about 26000 pounds in the United Kingdom (Hibbs, 1982), mainly caused by prolonged admission. The total costs of caring for pressure sores are estimated to be 150 million pounds per year in the United Kingdom and more than $3 milliard in the United States (Young & Dobrzanski, 1992; White et al., 1989). In the Netherlands the total annual cost is calculated to be between Hfl. 800 million and Hfl. 1.4 milliard (Haalboom, 1990; Molleman, 1995).

Outline
The high prevalence of pressure sores, the consequences for patients and health care, and the costs involved justify massive effort to reduce the problem. Efforts are already being made in clinical practice to prevent and cure pressure sores, but research efforts are limited. From an inventory of current research on pressure sores in the Netherlands in 1989, it can be estimated that the annual research effort represents only about 0.1% of the annual costs of pressure sores (Den Ouden et al., 1989).

This report reviews the relevant literature with respect to the causes, onset, and pathology of pressure sores in order to provide lines of action for a new research project on the etiology of pressure sores. The project starts from the afore-mentioned interstitium theory and concentrates on muscle tissue, which is highly susceptible for pressure sores. Two strategies are used to validate and test the hypothesis. The first strategy focuses on the development of a numerical model of muscle tissue and skin to describe the transition from external mechanical loads involved in pressure sores to relevant mechanical loads within the tissues. Triphasic modelling is used to describe processes within the interstitium of the tissues. The second strategy aims at experimental validation and testing of the numerical model as well as the interstitium theory using an animal model. The structure and mechanical characteristics of muscle and skin are described in Chapter 2, while Chapter 3 gives a synopsis of the current knowledge of the etiology of pressure sores. Chapter 4 deals with the pathology of pressure sores and reviews the cascade of tissue changes and damage involved in pressure sores as described in the literature. Finally, Chapter 5 gives preliminary conclusions and recommendations for the new research project.
2. Skin, subcutis and muscular tissue

As mentioned in the Introduction, pressure sores usually develop in deep tissue layers near bony prominences and then progress towards the more superficial tissues. A full thickness pressure sore (stage IV) affects the tissues of the muscle, the subcutis, and the skin. Each of these soft biological tissues has its own specific structure and accompanying function and mechanical properties. These aspects are reviewed below, preceded by a description of soft biological tissue in general.

2.1 Soft biological tissue

Soft biological tissues mainly consist of cells, extracellular fibres, nerves, bloodvessels and lymphatics, surrounded by an interstitial fluid containing a varying amount of mucopolysaccharide groundsubstance. Traditionally, the fibres have been considered to be of three kinds: collagenous, elastic and reticular, but recent evidence indicates that collagenous and reticular fibres may simply be different morphological expressions of single fibrous protein. Cells can be classified as common to all tissues, like fibroblasts, macrophages, and lymphocytes, or as tissue specific cells, like muscle cells or keratinocytes. The relative abundance of and micro-architectural arrangement of various cells, kinds of fibres, and groundsubstance vary greatly from tissue to tissue and is predetermined by their functional aspects and mechanical requirements. Soft biological tissues are inhomogeneous, non-linear, visco-elastic, and anisotrophic in nature. Their mechanical behaviour primarily depends on the collagen and elastin networks as well as the groundsubstance in the interstitium.

The extracellular components common to soft biological tissue (collagen, elastin, groundsubstance) are described here; structures mainly build from these components are usually referred to as connective tissue. Tissue specific cells are described in the relevant sections below.

Collagen

The basic unit of collagen fibres is the tropocollagen molecule, which is synthesized by the fibroblasts. Tropocollagen consists of three polypeptide chains of about 1000 amino acids. These chains, termed α-units, have a helical configuration. They and are coiled around one another in a right-handed super helix and cross-linked by hydrogen bonds (Stryer, 1981). Examination of the collagen molecule has shown that 12 different types exist, depending on the sequence of amino acids (Nimni, 1988). For the mechanical properties of skin and underlying tissues only type I and III are of importance. The tropocollagen molecules are aligned in a \( \alpha \)-by a quarter of their length - staggered arrangement, which results in a characteristic banding. They are held together by a variety of inter- and intramolecular cross-links to form microfibrils and fibres of different lengths and with diameters of 0.2 - 12 \( \mu \)m (Viidik & Vaust, 1980). Collagen fibres are arranged in a three-dimensional array in the groundsubstance. Upon stretch they become gradually straight, due to the intertwisting of the α-units, until they straighten completely. This process is accompanied by an increasing stiffness. Furthermore, phenomena like creep, relaxation, and hysteresis
can be observed. The stiffness of collagen is impressive: Young’s moduli of about $10^9$ N/m² are reported (Fung, 1993). The ultimate strain, the strain at rupture, is relatively small: about 6-8% (Abrahams, 1967). It is assumed that the breaking of collagen occurs by failure of the intermolecular bonds within the fibre.

**Elastin**

Elastin fibres are composed of a core of elastin which constitutes as much as 90% of the fibre and a non-elastin microfibrilar cortex (Stryer, 1981). Structural units are the tropoelastin molecules built by the fibroblasts. Tropoelastin is based on hydrophobic amino acids that are poorly solved in the interstitial fluid. The tropoelastin molecules are cross-linked by intermolecular bonds to form elastin fibres. Elastin behaves almost linear and may play a role in recovery after tissue deformation. The thin fibres (0.5 -3 µm in diameter) can be almost reversely extended to about twice their length (Gosline, 1976). Usually a Young’s modulus of $5 \times 10^6$ N/m² is used (Daly, 1969). Unlike collagen fibres which are unbranched, elastin fibres form a widely branched network.

**Groundsubstance**

The groundsubstance in the interstitial fluid consists mainly of proteoglycans and glycoproteins (the mucopolysaccharides), which are also made by the fibroblasts. Beside these complex molecules enzymes, metabolites, and small ions are dissolved within the fluid. Proteoglycans are the most important components. They are large molecules consisting of various glycosaminoglycans (GAG) linked to a protein core. An important fraction of the GAG exists of hyaluronic acid, chondroitinsulphate, and keratan sulphate. The GAG have repeating carboxyl and sulphate groups at distances of 6-10 Å (Stryer, 1981). At physiological conditions these groups are ionized within the interstitial fluid. The density of these charges is called fixed charge density. Large amounts of proteoglycans usually aggregate into supra molecular structures by nonconvalent attachment to chains of hyaluronic acid. These proteoglycan aggregates entangle to form three dimensional networks which are stretched in space guided by the fixed charge density of the GAG. Due to the fixed charge density the proteoglycan aggregates are also able to bind water up to a 50 fold their own mass. The water retaining proteoglycan aggregates then behave like a gel which can be regarded as a solid. Collagen fibres are bound to the proteoglycans by electrostatic and covalent bonds. In this way the fibres are positions and stabilized in the groundsubstance. Tissue fluid and mobile ions can flow through this solid collagen-proteoglycan matrix.

The glycoproteins in the groundsubstance have a structure analogous to that of the proteoglycans. They assist in coupling proteoglycan aggregates as well as in the binding of proteoglycans to collagen. Vessels, nerve fibres and lymphatics are anchored in the ground substance, but assumed not to influence the mechanical properties of living tissue.

The groundsubstance probably plays a major role when tissues are deformed by mechanical or chemical loading. An external load is counterbalanced by an exchange of fluid and ions to adjust the internal ionic concentrations and tension in the solid matrix. As a result of fluid and ion content the tissue swells or shrinks depending on the load applied. The mobile ion concentrations inside the interstitial fluid are different from the ion concentrations outside
the interstitium due to the presence of the fixed charge density of the collagen-proteoglycan network. This ionic imbalance gives rise to an additional pressure in the interstitial fluid. The resulting pressure difference is known as the Donnan osmotic pressure (Smidt & Thews, 1983). When the interstitium is in equilibrium with its environment this osmotic pressure is balanced by the tension in the collagen-proteoglycan network.

With respect to pressure sores compressive loading of tissues is of relevance. Under this loading condition fluid is expelled from the tissue. Due to the loss of fluid, the concentration of fixed charges, and hence the osmotic pressure, increase, while the tension in the collagen-proteoglycan network decreases. The fluid flow succeeds till the compressive load is balanced. Removal of the compressive load results in an uptake of fluid by the tissue, resulting in a decrease in osmotic pressure and an increase in tension of the network until the original equilibrium is reached.

**Microcirculation and lymphatics**

Soft biological tissues are vascularized and innervated to a specific degree depending on their function and metabolic rate. The main task of the microcirculation in the tissues is the exchange of nutrients, metabolites, gases and heat between blood and interstitium. The microcirculation is a broadly branched part of the vascular system. Consequently the blood flow and pressure in the vessels is relatively low. Within the terminal capillaries the flow rate is about 1 mm/s. The pressure of blood as it enters the capillaries is about 4 kPa and decreases to about 1.5 kPa at the venous side of the capillaries (Smith & Thews, 1983). Due to this arterial-venous pressure difference and the osmotic pressures in the capillary and interstitium, blood plasma and plasma proteins are filtrated out at the arterial side of the capillary. At the venous side blood plasma is resorbed. The filtration rate, however, is somewhat higher than the resorption rate, resulting in an accumulation of blood plasma in the interstitium. Furthermore, plasma proteins accumulate in the interstitium since they cannot pass back into the capillary at the venous side. The excess of proteins and blood plasma is removed from the tissue by the blind starting lymphatic system, together with particulate and antigenic material. The ionic concentration inside this system is similar to that of the interstitial fluid. A disturbance of the equilibrium of tissue pressures and flows is easily restored by autoregulation of the lymphatic clearance and local blood pressure as well as the afore-mentioned exchange of fluid and ions in the interstitium.

### 2.2 Skin

The skin, or cutis, is the largest organ of the human body. It can be divided into two main layers: the thin cellular epidermis (0.1 - 1.5 mm) and the underlying dermis (1 - 4 mm). The epidermis protects against injury from the environment and acts as a two-way barrier to prevent the inward or outward passage of water and electrolytes. The primary function of the dermis is to provide nourishment and mechanical support to the epidermis. Beside these functions, the skin acts as a receptor for external stimuli, a regulator of body temperature, and as a producer of differentiated cells and vitamins. Typical derivatives of the skin are nails, hairs and sweat glands.
Epidermis

The avascular epidermis is a differentiated, stratified epithelium. The dominant cells are the keratinocytes which originate from continuous cell division in the basal layer of the epidermis and migrate towards the skin surface, forming several skin layers. These are the stratum basale, the stratum spinosum, the stratum granulosum and the stratum corneum. In the palmair and plantair skin there is an additional zone between the stratum granulosum and the stratum corneum: the stratum lucidum. During their progression through the distinct layers the keratinocytes are keratinized. In the upper layer, the stratum corneum, the cells have lost their nuclei and cytoplasmatic organelles and become dehydrated. Other cells in the epidermis are the melanocytes, Langerhans Cells, and Merkel cells.

The structure at the junction between the epidermis and dermis consists of an anatomical functional junction: the dermo-epidermal junction. This loose, undulated layer provides mechanical support for the epidermis and acts as a partial barrier for cells and large molecules.

Dermis

Two layers can be distinguished in the dermis: the papillary layer and the reticular layer. The papillary layer is found adjacent to the dermo-epidermal junction and forms about 10% of the full dermis thickness. It is composed of a loose (type III) collagen network embedded in groundsubstance. Besides fibroblasts, macrophages, mast cells, plasma cells, and leukocytes can be observed, and the papillary layer is therefore important during allergic reactions and inflammation processes. Below the papillary layer, the reticular layer, composed of a dense (type I) collagen network, forms the main body of the dermis. It contains a few cells, which are mainly fibroblasts for the production of collagen and elastin fibres and the groundsubstance.

The fibrous network of the dermis is traversed by numerous bloodvessels, nerves, nerve endings, and lymphatics. Nerve fibres form a two-dimensional network, parallel to the skin surface. Most of the fibres end in the dermis; some penetrate the stratum basale, but do not travel far into the epidermis.

Mechanical properties

It is generally assumed that the mechanical properties of the skin mainly depend on the dermis. It should be realized, however, that with regard to pressure sores certain loading cases may occur when the epidermis is also important. For instance a shear stress acting on the skin a often results in a detachment of the stratum corneum from the other layers (Dinsdale, 1973). Furthermore, the importance of blood vessels and lymphatics with respect to the mechanical behaviour is not completely clear. Many authors neglect their influence (Kenedi et al., 1975), but they may be of relevance to the pressure sore problem due to their role in the water content - and hence the internal pressure - of the skin.

Extensive work has been conducted by many workers in an attempt to describe the mechanical properties of skin under controlled loading conditions. Comparison of the quantitative results from these investigations is hardly possible due to the variety in experimental set-up. Therefore, the description here is restricted to qualitative observations. All experiments on skin confirm that it shows a highly non-linear stress-strain relationship under extension as well as compression.
The initial response of the skin to extension appears to involve a reorientation of collagen fibres towards the load axis, and a decrease in their convolution. Simultaneously the elastin fibres are stretched, probably to maintain the tonus of the skin. At this stage low loads cause a rather large extension of the skin. When the collagen fibres are straightened high loads are needed to elongate the tissue even a little further: the stress-strain relationship gradually changes from that of the elastin to that of the collagen in the skin (Gibson & Kenedi, 1968; Millington et al., 1971). This non-linear behaviour of skin is time dependent: Significant hysteresis loops exists in the stress-strain relationships under constant rate of strain, the stress relaxes under constant strain level, and the skin will creep under constant load. Furthermore, different stress-strain relationships are observed at different strain rates (North, 1978).

The behaviour of skin under compression is controlled by the mechanisms described above for compressive loading of soft biological tissue. An example of this behaviour can be observed in Figure 1, where the compression of skin over the anteromedial surface of the tibia is shown in response to a constant load of 50 kPa, applied for 10 min. The figure shows an immediate elastic response to both application and removal of the load. This is followed by a viscoelastic response to the constant load or a similar recovery over time to the original tissue thickness (Daly, 1982).

![Figure 1](image-url)
2.3 Subcutis

The subcutis, or hypodermis, is a collagenous connective tissue, that connects the dermis to the underlying tissues. Due to its loose structure it allows the movement of the skin over the underlying tissues at most places of the body. The subcutis contains an abundance of bloodvessels, lymphatics, nerves and fat cells (adipocytes). When the fat cells dominate, we speak of subcutaneous fat. Functionally, the fat cells act as fuel and water reservoir, thermal insulation layer, and a buffer to external mechanical forces (mainly compressive forces). The subcutis is attached to a strong connective tissue, the fascia, that surrounds underlying organs or muscles. The thickness of the subcutis is dependent on gender, age, nutritional status, and location of the body.

**Mechanical properties**

Very little is known about the mechanical response of the subcutis to extension and compression. It is difficult to separate the subcutis from the skin and samples of subcutaneous fat deteriorate strongly during in vitro experiments. There is reason to believe that the qualitative mechanical properties are similar to those of the dermis, since the subcutis is a loose continuation of this collagenous tissue. The influence of varying amounts of fat cells on the mechanical behaviour of the subcutis, however, cannot be neglected.

2.4 Muscle

The highly vascularized muscular tissue can be regarded as composed of a contractile part (muscle fibres with actin and myosin) and a part consisting of collagenous connective tissue. A complete description of the organization and properties of the contractile part is beyond the scope of this report. Therefore, only the connective tissue is reviewed here. Collagenous connective tissue in skeletal muscles has at least two functions: 1) to bind muscle fibres together insuring proper alignment and 2) transmission of the force of contraction (Winegrad & Robinson, 1978). The protection of muscle fibres against excessive strain has also been attributed to connective tissue (Morree, 1989). The arrangement of the connective tissue can be divided into three levels of organization: 1) the epimysium, a strong collagenous tissue which surrounds the entire muscle, 2) the perimysium, which consists of collagenous septa that surround bundles or fasciculi of muscle fibres and interconnect to the epimysium, and 3) the endomysium, a network of thin collagen fibres which represents the association of connective tissue with the individual muscle fibres and interconnects to the perimysium. It also connects the capillaries to the muscle fibres. At the ends of the muscle the connective tissue proceeds into the tendons via myotendinous transitions.

**Mechanical properties**

The mechanical properties of muscles largely depend on their contractile status. Little is known about the properties of the resting muscle, more relevant to the pressure sore problem. Passive elongation of isolated muscles in vitro shows stress-strain relationships similar to those presented in Figure 2.
This behaviour is mainly attributed to the connective tissue within the muscles. To date no information about the behaviour of isolated skeletal muscles under compression is available.

Figure 2. Stress-strain relationships of isolated muscles during passive elongation from rest ($L_0$). The curves show the stress-strain relationships for a muscle with a large amount of connective tissue (1) and a small amount of connective tissue. (2) (From: Morree, 1989).
3. Etiology of pressure sores

Since the 1940's many authors have tried to describe the relationship between the application of a certain external mechanical loads and the onset of pressure sores during well controlled animal experiments. The onset of pressure sores was usually defined from tissue necrosis observed during histological examinations. External mechanical loads were described in terms of intensity and duration or as being constant or intermittent. These experiments have led to the common opinion that pressure sores result from tissue necrosis due to impaired capillary perfusion or mechanical damage following prolonged external pressure or shear stress. With the development of new measurement techniques and the new insights in tissue mechanics it became possible to relate external mechanical loads to the internal mechanical and chemical conditions of the tissue. It has been hypothesised that these internal conditions, which do not necessarily result in impaired perfusion, pose an extra threat to the development of pressure sores.

This chapter reviews the different opinions and hypotheses on the etiology of pressure sores, which mainly focus on pressure, shear, and changes within the interstitium of tissue.

3.1 Pressure

As a guide for pressure sore prevention many attempts have been made to determine the minimal degree of pressure which will consistently result in tissue damage (pressure sore threshold). Typically such values derive from animal experiments in which indentors with different geometries are pressed into soft tissue. Groth (1942) was the first who published an extensive study on the relationship between applied pressure and the onset of tissue damage. He intended the gluteus muscle of rabbits with varying intensity over different time periods and reported a risk curve for the onset of muscle damage, defined as degenerative muscle changes observed during histological examination. This curve showed an inverse relationship between the intensity and the duration of indentation, indicating that the greater the intensity of pressure, the less time is needed for muscle damage to occur. The same phenomenon was reported by Husain (1953) and Kosiak (1959, 1961). Husain (1953) noted microscopic changes in the muscles of a rat when pressures of 13 kPa were applied for two hours. While no gross changes were noted 24 hours after pressure was applied, there was macroscopic evidence of cellular infiltration, interstitial capillary hemorrhage, and various stages of cellular degeneration. Pressures of 13 kPa applied for six hours produced similar but more severe changes. Husain also observed that pressure applied over large surfaces is less harmful than locally applied pressure.

Kosiak (1961) applied pressures of 4.5 - 32 kPa to the hamstrings of rats for different lengths of time. He found that muscle tissue of both normal and paraplegic rats is more susceptible to the application of a constant load than to the application of intermittent loads with the same intensity. The degenerative changes he observed were a decrease or loss of cross-striations and myofibrils, hyalinization of fibres, and infiltration by macrophages and neutrophils. Initial changes during constant pressure occurred after 2-3 hours at pressures of 9.3 kPa.
A threshold pressure of 12 kPa during a period of 13 hours was reported by Lindan (1961) who compressed rabbit ears. Nola and Vistnes (1980) applied pressures to rats at locations where skin is directly overlying bone (posterior trochanter) and at places where muscle separates skin and bone (midshaft of the tibia). After application of 13 kPa for six hours a day over a four day period there was a 100% incidence of epidermal breakdown at the posterior trochanter. The same pressure regimen applied to the skin and biceps femoris at the tibia did not result in skin breakdown, but in a mild degree of muscle fibre necrosis and muscle oedema.

From their pressure experiments on pigs Daniel et al. (1981) also found muscle to be more susceptible to the effects of pressure than skin. Muscle damage at the greater trochanter occurred at low pressure with short duration (67 kPa, 4 hours), whereas skin destruction required high pressure with long duration (105 kPa, 8 hours). The higher susceptibility of muscle is attributed to its increased metabolic activity.

The onset of tissue damage due to pressure is generally believed to be the consequence of ischemia and altered tissue metabolism following occlusion or collapse of capillaries. Burton (1951) has suggested that the capillaries are either open or closed, depending on whether the pressure outside the vessel is higher or lower than the pressure inside the vessel (critical closure pressure). Many authors have pointed out that the blood pressure within human capillaries is about 3.5 - 4 kPa and even lower in the venules. However, external pressures well above capillary pressure can be supported by skin and underlying tissues before blood flow is seriously impaired. Hickman et al. (1966) have studied in man the effect of pressure applied to the forearm on blood flow by means of a radiosodium tracer method. At a pressure of about 3.5 kPa the radiosodium clearance rate was still about 89% of normal. A pressure of 6.7 kPa was required to reduce the clearance of sodium by half, and about 10 kPa was required to reduce it to 25%. Daly et al. (1976) measured skin blood flow following compression by isotopic clearance. They showed that flow is reduced by pressures up to 1.3 kPa. Then the flow is constant up to 4 kPa. For higher pressures the flow monotonically decreases to zero as systolic pressure is approached. A striking fact was found by Husain (1953) who noted that localized pressures obliterated more vessels in the skin and subcutaneous tissue than in muscle, while the last was severely damaged and the skin and subcutis were not.

Much of the external pressure applied to tissues is carried by the connective tissue matrix and the cellular structures surrounding the capillaries and larger vessels. Furthermore, when external pressure is applied to the body, an autoregulation process results in a corresponding offsetting rise in local venous and arterial pressure. Landis (1930) has noted that within one minute from the time of application of external pressure (8 kPa) a rise of arteriolar pressure will occur, stabilizing at a value roughly 1.3 kPa higher than the external pressure. The constant blood flow during external pressures from 1.3 - 4 kPa reported by Daly et al. (1976) also points to this autoregulatory mechanism of blood pressure. Similar autoregulation processes have been reported for the lymphatic system (Barbenel, 1991, Miller & Seale, 1981).

In addition to the autoregulation processes a disturbance of the equilibrium of tissue pressure can be restored by an exchange of fluid and ions in the interstitium (See also section 2.1 Microcirculation and lymphatics).
Another way to study the influence of ischemia with respect to pressure sores is the measurement of tissue oxygen tension (pO₂) under increasing pressure. In human skin a pO₂ level of 1.3 kPa is usually associated with ischemia (Bar, 1988). By determining the external pressure at the skin at which pO₂ is 1.3 kPa a pressure threshold can be defined. Seiler and Stähelin (1979) measured skin pO₂ under increasing pressure exerted on skin tissue at bony prominences and muscle-padded areas in humans. They found that at bony prominences the skin pO₂ decreases rapidly under increasing pressure, while at muscle-padded areas the fall in pO₂ is less steep. It should be realized that the application of localized pressure results in an additional shear stress within the tissues due to the large pressure gradients at the boundaries of the indentor. Therefore, the stresses within the tissue are higher than can be expected from the normal pressure alone (Bennett & Lee, 1988). This must be considered when pressure sore thresholds are evaluated.

3.2 Shear

Reichel (1958) was probably the first who pointed out the danger of shear stress. He reported that patients more often developed pressure sores in sacral tissues when the head of the bed was raised. The skin and superficial tissue adhere to the bedclothes and are pulled tightly over the deep fascia, thereby stretching, angulating and traumatizing the blood vessels. The subcutaneous fat lacks tensile strength and is particularly susceptible to damage by shearing stress (Reuler and Coonery, 1981).

Based on theoretical considerations, it can be expected that shear leads to much greater stress within the tissues than normal forces and therefore can add significantly to the effectiveness of externally applied normal forces in occluding blood flow. This has also been observed in model simulations (Subroto, 1991). In an experiment on young healthy volunteers Goossens et al. (1994) showed a significant lower pressure threshold (8.7 kPa) for critical oxygen tension at the sacrum (1.3 kPa) when a shear stress of 3.1 kPa was applied than when no shear was applied (11.6 kPa).

Dinsdale (1974) reported that shear can also significantly reduce the time needed to develop a pressure sore. He analyzed the role of pressure and friction in the production of pressure sores over the posterior superior iliac spine for both normal and paralysed swine. Simultaneously, he studied blood flow cessation by isotope clearance techniques. Normal pressure combined with friction was much more harmful to tissue. However, the rapid onset of pressure sores was not produced by an ischemic mechanism, but merely by the detachment of the stratum corneum from other skin layers (Dinsdale, 1973).

Several phenomena contradict the major role of ischemia due to pressure or shear in the causation of pressure sores. For instance, tissue can remain viable for extended lengths of time with a blocked circulation (i.e. during surgery), while pressure sores develop much faster (Krouskop et al., 1978). Furthermore, higher pressures are required for blood flow cessation in muscle than in skin, whereas at equal pressure muscular tissue is more sensitive to develop pressure sores than skin. These features have motivated investigators to look for other factors than ischemia causing tissue damage.
3.3 Interstitial changes

Under normal physiological conditions soft biological tissues are in equilibrium (homeostasis). In healthy subjects the autoregulatory capacity of the body is able to keep the equilibrium at an acceptable value despite mechanical or chemical loading. However, at some instant the effects of external loading may exceed the autoregulatory capacity and the equilibrium is disturbed. Failure to restore the equilibrium within a short time interval eventually results in damage due to tissue hypoxia and an accumulation of metabolic waste products.

Krouskop et al. (1978) hypothesized that disturbance of the tissue equilibrium is mainly caused by an impaired lymphatic drainage, causing an accumulation of metabolic waste products. Impairment of lymphatic drainage results from mechanical occlusion of lymphatics or hypoxia of lymphatic smooth muscle for periods exhausting their anaerobic capacity. The pressure inside the lymphatics is equal to the interstitial fluid pressure, but transport against pressures as high as 8 kPa is possible (Zweifach, 1973). External pressures sufficient to occlude lymphatic drainage, as measured with radioactive sulphur, are about 10 kPa for skin lymph flow (Miller & Seale, 1981) and 8.0 - 9.3 kPa for subcutaneous tissues (Barbenel, 1991). Reddy (1981) and Oomens (1985) analyzed the effects of external pressure on interstitial fluid flow. They hypothesized that when interstitial fluid is squeezed out of tissue the delicate equilibrium of pressures in blood vessels, interstitium and lymphatics is disturbed. This may lead to serious complications due to a deficit of metabolic supplies and an accumulation of waste products, even when the circulation is not completely blocked. When the circulation is blocked the interstitial fluid flow adds an extra risk factor to tissue necrosis.

A major advantage to consider the interstitium in pressure sore etiology is that relevant changes in internal tissue conditions (fluid and ion flows, stresses, strains) following external loading or tissue relaxation, provide useful information about changes in tissue equilibrium and can be used to indicate the initial risk of damage.

3.4 Risk factors

Previous studies have attempted to set thresholds beyond which pressure sore will develop. However, clinical studies have shown repeatedly that pressures well below thresholds can develop sores. It is also possible that thresholds are surpassed by patients without apparent damage to tissue (Fisher & Patterson, 1983). Thus, it becomes important to consider what other factors contribute to tissue resistance or to susceptibility to the formation of pressure sores. Clinically, risk factors like increased age, impaired sensation, medicine use (particularly hypotensive agents), increased temperature, weight loss, poor nutritional status, and the duration of paralysis have been identified (Leigh & Bennett, 1994). Daniel et al. (1985) showed that pigs with transected spinal cord had a great reduction of soft tissue below the
level of paralysis after 6 weeks. This is significant because the thicker the tissue layer, the more area over which the pressure can spread, thereby reducing the stress on the tissue. The authors also pointed out that paralysis results in other factors which contribute to the development of pressure sores. Among these factors are impaired mobility, loss of sensation, and incontinence, which macerates the skin and facilitates skin breakdown. In a study by Narsete et al., (1983) it was cited that normally innervated skin can withstand ischemia for approximately 3 hours longer than skin of spinal cord injured subjects without showing signs of breakdown leading to necrosis. The elderly may be at particular risk for pressure sore formation for several reasons: Ischemia may be induced more easily in elderly persons than younger persons and they may develop more shear while sitting (Bennett et al., 1981). Ageing skin with its associated physical, structural, physiological and immunological changes, may have a major impact on pressure ulcer development (Yarkoni, 1993). Aged skin has a diminished barrier function, increased susceptibility to shear stress, and a decreased vascularity.

Norton et al. (1975) and Braden & Bergstrom (1989) have developed scales for predicting the risk of pressure sores. These scales quantify a range of risk factors by using ratings whose summative scores are the basis for risk of pressure sores. Predictions are based on mobility, activity, level of consciousness or sensory perception, incontinence, nutrition, pressure and shear. The scales are widely employed in clinical practice as guidelines for risk assessment and the possible prevention of pressure sores.

It will be clear that investigations on the etiology of pressure sores, which focus on a single or a well defined set of risk factors, should control the other predisposing factors.
4. Pathology of pressure sores

The pathogenesis of pressure sores is hazy. Many authors have described their observations following the application of certain controlled external loads. However, as the experiments are performed under strongly varying conditions using different experimental settings, there is no clear view of the changes in time. Moreover, these changes may vary with the external load applied (pressure versus shear) and from subject to subject (animal to animal), depending on predisposing factors such as physical condition or environmental temperature. This chapter tries to describe the cascade of tissue changes that is believed to occur in skin, subcutis and muscle during the development of pressure sores. Damage to other tissues (i.e. bone) and organs as well as tissue repair and the healing of pressure sores is not reported here. The description of the pathogenesis is based on the interstitium theory for pressure sore development and is therefore partly hypothetical in nature. The sequence of tissue changes and damage involved in pressure sores is schematically represented in Figure 3 and described in more detail in the following sections.

Tissue changes have been divided into primary changes, which are either mechanical or physiological in nature, and secondary changes, which may follow primary changes, usually within 24 hours. Secondary changes involve pathological changes and damage, where pathological changes are defined as being reversible (e.g. oedema) and damage as being irreversible (e.g. tissue necrosis). Note that the definition of damage as being irreversible does not imply that damaged tissue cannot be replaced by new tissue.

4.1 External loading

External loading in pressure sores is usually mechanical in nature, although chemical loading may occur for instance during incontinence. Mechanical loading is described in terms of intensity and duration and the type of loading (shear, pressure, intermittent, constant). The time of onset and further development of pressure sores will strongly depend on these characteristics. During compressive loading the geometry of the indenting apparatus may be important with respect to the area of compressed tissue and the resulting stresses and strains within the tissue.

4.2 Primary mechanical changes

Primary mechanical changes involve the pressures, stresses, strains, and fluid and ion flows within the tissue as a consequence of the externally applied mechanical load. Fluid and ion flow will result in altered ion concentrations and concentrations of nutrients dissolved in the interstitial fluid. The primary changes determine the internal load of the tissue, relevant for tissue damage. The degree of primary changes due to external loading is dependent on the type/intensity of loading as well as on the amount of ground substance and fibre content and organization in the interstitial space of the tissue.
Figure 3 Schematic representation of changes and damage involved in pressure sore development

**External mechanical loading**
- pressure gradient (described in terms of intensity and duration)
- shear stress

**Primary changes**

**Mechanical**
- local stresses
- local strains
- fluid and ion flows
- molecule and ion concentrations
- deformation of tissue layers and grating of tissue layers over deep fascia due to shear

**Physiological**
- autoregulation processes (within 1 minute after load application)
- ischemia due to capillary occlusion or collapse and impaired lymphatic clearance
- disturbed metabolic equilibrium due to ischemia and accumulation of waste products (within several minutes after occlusion)
- cell poisoning

**Secondary changes** (usually within 24 hours)
- oedema
- superficial skin damage due to shear
- phagocytosis by neutrophils and macrophages
- leukocyte infiltration in capillaries
- hemorrhage
- changes in interstitial matrix structure
- hyalinization
- loss of cross-striations and myofibrils in muscle
- inflammation
- necrosis
- acute rhabdomyolysis
4.3 Primary physiological changes

As a consequence of an altered internal load several primary physiological changes occur in the tissues. An increased tissue pressure will change blood flow and lymphatic flow. Initially, a rise in tissue pressure causes a corresponding rise in local blood and lymph vessels. Consequently, fluid leaks out from the microcirculation and lymphatic drainage is enhanced. With increasing pressure the blood and lymph vessels will close or even collapse, resulting in tissue ischemia and an accumulation of metabolic waste products within several minutes. Together with the diminished supply of nutrients due to interstitial fluid flow, this may lead to a serious disturbance of the metabolic equilibrium of the tissue. When the metabolic disturbance is maintained the tissue may poison itself. Muscular tissue, due to its high metabolic rate, is particularly susceptible for this poisoning. Values for internal tissue pressure sufficient to occlude blood and lymph flow as well as the time interval for tissue poisoning to occur are not exactly known. However, external loads for occlusion of both blood and lymph vessels are relatively low (8 - 12 kPa, Barbenel, 1991; Goossens, 1994; Miller & Seale, 1981) and the consequences of these loads for muscular tissue may be found within several hours after application (Kosiak, 1961).

Internal shear stresses produced by friction or pressure gradients in the tissue are most harmful for skin. At this site shear stress usually results in stretching and grating of superficial skin layers over deep fascia, leading to mechanic disruption of the skin microvasculature and a detachment of the stratum corneum (Dinsdale, 1974).

4.4 Secondary changes

With maintained load or several hours after prolonged mechanical loading, a range of secondary changes and indicators of damage are found. Oedema is formed rapidly in all tissue layers. Lindan (1961) observed oedema in rabbit ears within 0.5 hours after applying a constant pressure of 13 kPa for three hours, or 5.2 kPa for 13 hours. Eighteen hours later the oedema was further increased. In muscle tissue oedema was already observed after 2 hours of constant external pressure (9.3 kPa) by Kosiak (1961). He noted that oedema enlarges the distance between capillaries and muscle cells, thereby impeding the transport of oxygen and nutrients to the cell.

Besides the formation of oedema, Kosiak (1961) reported a decrease of cross-striation and myofibrils, hyalinization of fibres and infiltration by neutrophils and macrophages in the hamstring muscles of rats 24 hours after load application. Hyalinization is accompanied by damage of the mitochondria, the sacroplasmatic reticulum, and the plasmalemma within the muscle fibres (Vleet & Ferrans, 1991). The presence of neutrophils and macrophages (e.g. monocytes, lymphocytes) points at the defense mechanism of the tissue and indicates the destruction of degenerative and toxic materials. Husain (1953) described cellular degeneration and capillary hemorrhage in rat muscles 24 hours after application of pressure (13 kPa for 2 hours). The release of Fe^{3+} ions during hemorrhage may interfere with the bonds within the collagen-proteoglycan matrix of the tissue interstitium. As a consequence collagen fibres precipitate and the tissue becomes less resistant against mechanical loading (Morree, 1989).
Complication of pressure sore development in muscular tissue may involve myositis (muscle inflammation) and rhabdomyolysis. Inflammation is characterized by an influx of inflammatory cells and serous fluid, vascular congestion, and proliferation of interstitial fibroblasts (Vleet & Ferrans, 1991). Rhabdomyolysis is occasionally seen as a consequence of acute pressure sores (Levine, 1993).

Pathological changes in the subcutis initially concern atrophy and hyalinic changes of subcutaneous fat. At a later stage, released cholesterine and lipids from the necrotic fat tissue cause a reactive inflammation (Vandeberg & Rudolph, 1995).

The skin is mainly susceptible to shear stress, but full-thickness pressure sores caused by compression alone also affect the skin. Dinsdale (1973) described pathological changes in the dermis of swine due to friction. Friction initially removed the stratum corneum. The superficial cells at the epidermis separate from the basal cells because their bridges are brittle. With pressure and friction superficial dermis became hyperaemic, and with increasing pressure there was hemorrhage, and leukocyte infiltration in the capillaries of the dermis. The superficial dermis then became necrotic.

Pathological changes and damage in human skin were studied by Witkowski & Parish (1982). They observed a sequence of capillary and venule dilatation followed by oedema of the papillary dermis and a perivascular infiltrate of lymphocytes. This was followed by platelet aggregates, red blood cell engorgement and perivascular hemorrhage. As the vascular changes occur, the sweat glands and subcutaneous fat show signs of necrosis with eventual epidermal necrosis.

5. Preliminary conclusions

A new research project on the etiology of pressure sores will be based on two strategies. As outlined in the Introduction (Chapter 1) the first strategy aims at the development of a numerical model of the soft tissues involved in pressure sores, whereas the second strategy aims at the development of an experimental animal model. The numerical model of the tissues can be used to predict the primary changes due to externally applied loads and some of the secondary changes, like closure of blood and lymph vessels. (Note that modelling of vessel closure should take into account the initial autoregulatory mechanisms of the tissue at increasing external loads.) The animal model can be used to describe a number of primary changes, secondary changes, and damage due to external loads in experimental settings when adequate measurement techniques are used. The overlap between numerical predictions and experimental measurements, i.e. the predicted and measured primary and secondary changes, should then be used to validate the numerical model. Obviously, experimental determination of primary changes for validation of the numerical model requires in-vivo measurements.

After validation both the numerical and the animal model can be applied to investigate the etiology of pressure sores, which is primarily based on the interstitium theory.
6. References


Fabricius, G. (Hildanus Chirurgicus), De gangraena et sphacelo tractatus methodicus, Leyden, 1593.


Meehan, M., Multi-site pressure ulcer prevalence survey, Decubitus, 3, 14-17, 1990.


Appendix A: Terminology

- **erythema:** Inflammation of the skin.
- **hemorrhage:** Bleeding of arterial, venous, or capillary vessels. The surrounding interstitial spaces are distended by extravasated erythrocytes.
- **hyalinization:** Waxy degeneration.
- **hypoxia:** Decreased oxygen tension.
- **necrosis:** Cell or tissue death.
- **oedema:** Accumulation of body fluid in extra- and/or intracellular spaces.
- **phagocytosis:** Ingestion of large particulate matter by a cell such as the ingestion of a bacterium or particles of degenerating tissue.
- **rhabdomyolysis:** The constellation of physiologic disturbances resulting from skeletal muscle injury with release of muscle cell contents into plasma.