Chapter 10
Microcirculation in Wound Healing

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Abstract The microcirculation has a substantial role in wound healing, as it provides oxygen and proliferative/immunological mediators necessary to the healing process. In this chapter, we discuss the concept of the wound as a temporary added "organ" due to its increased metabolic needs and how the microcirculation functions as a reserve to support healing. We provide a brief overview of the normal healing process, including the factors driving angiogenesis, and address the differences in the microarchitecture of the skin's circulation. While microcirculation is a highly plastic system, we consider aspects that may contribute to dysfunctional perfusion to the skin, such as aging and other pathologies, and their consequences in delayed healing and the development of ulcers. This chapter will provide an in-depth explanation of the structure and physiology of microcirculation in the paradigm of the healing process and address the role of microcirculation in some of the most common chronic and often difficult to heal wounds including venous, arterial, neuropathic, diabetic, and pressure ulcers.

Keywords Venous ulcers · Arterial ulcers · Neuropathic ulcers · Diabetic ulcers · Pressure ulcers · Skin aging · Wound healing and blood flow · Microvasculature and wounds · Leg ulcers · Venous insufficiency

10.1 Introduction

To heal a skin wound or ulcer initially to a certain extent requires adequate blood flow to meet the increased demands of the metabolizing wound tissue. In this sense, as and if the wound goes on to heal, it may be compared to a temporarily added

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"organ." However, if healing is significantly delayed or prevented, a more-or-less permanently added "organ" taxes the localized microcirculatory system with the continued added demand for blood flow. Most of the information that we have regarding the relationship between wounds, their healing and blood flow is derived from measurements and outcomes of wounds that are present on the skin, and of those, most are wounds on the skin of the lower extremities. Blood flow and the microcirculation, in one form or another, play a role in wounds of all etiologies that include arterial ulcers, venous ulcers, and neuropathic ulcers with the latter most notably, but not exclusively, observed in persons with diabetes mellitus (DM).

For arterial ulcers, the causative factor in the development of the ulcer and its difficulty of healing is usually, if not always, inadequate nutritional skin microcirculation, resulting in tissue ischemia as causation and inadequate microvascular reserve to support the healing of chronic ischemic ulcers. The deficit in microvascular reserve may be attributable to structural or functional issues such as may be present in some patients with DM, but in general the main factor is an overall deficient blood flow associated with the presence of peripheral arterial disease (PAD). The situation is quite different in the case of venous ulcers in which skin ulceration is generally secondary to chronic venous insufficiency (CVI) that causes pressure induced injury in superficial lower extremity veins followed by skin breakdown and the occurrence of the venous ulcer. Although full details on the microcirculatory involvement are still not completely clarified, plugging of capillaries via activated leukocytes is at least thought to be involved causing diminished skin nutritional microcirculation. An important nonleg-related ulcer is the so-called decubitus or pressure ulcer. Its linkage to blood flow and more directly to deficits in skin and subcutaneous microcirculation is attributable to nonrelieved skin tissue pressure and shear forces that cause microvascular perfusion deficits sufficient to cause skin break down and ulcer development.

In this chapter, these wounds and others are considered in detail especially with respect to linkages and roles of blood flow and the microcirculation in either or both wound development and healing. Prior to that, a review of the normal wound healing process is described, and the angiogenesis process is presented to provide context. Factors considered in the angiogenesis process are the roles of growth factors, tissue oxygen levels, and the extravascular matrix involvement. Thereafter, further details related to the skin microcirculation are presented followed by microcirculatory aspects of wound healing in specific conditions including aging and ulcers classified as venous, arterial, diabetic and pressure ulcers.

10.2 Normal Wound Healing Process: Overview of Phases

Following injury, most skin lesions heal rapidly, an ability that is vital to human survival and maintaining the protective barrier that lines the body's surfaces and cavities (Hay et al. 2014). Wound healing is an intricate progression of reactions and interactions between cells and mediators, affected by many intrinsic and extrinsic

factors (Broughton 2nd et al. 2006). The wound healing process is divided into four overlapping stages, and an interruption during any of the stages can lead to a spectrum of pathologies: From prolonged inflammation and an inability to re-epithelialize the wound causing chronic ulcers; an overgrowth of granulation tissue leading to pyogenic granulomas; to an excessive fibrotic response generating hypertrophic scars and keloids (Sun et al. 2014). These four stages—hemostasis, inflammation, proliferation, and remodeling—are each characterized by distinct molecular, cellular, and physiological events described in brief below: (Sun et al. 2014; Gurtner et al. 2008).

Hemostasis begins after injury to stop blood loss. Local mediators trigger vasoconstriction in vascular smooth muscle cells to reduce blood flow. Platelets and the coagulation cascade form a fibrin clot, which acts as a reservoir for cytokines and growth factors and, in later stages, a fibronectin-rich scaffold for a provisional extracellular matrix (ECM) (Martin 1997; Li et al. 2007). These platelet-derived mediators and bacterial byproducts act as chemotactic cues to recruit immune cells, initiating inflammation hours after injury (Ross and Odland 1968).

During the inflammatory stage, local vasodilation allows plasma-like fluid to leak into the tissue space. The influx of this fluid transports nutrients, antibodies, and substances such as histamine, serotonin, proteolytic enzymes, kinins, prostaglandins, and cells into the wound bed (Phillips 2000). The wound is infiltrated by immune cells: First by neutrophils, which kill bacteria and degrade the damaged matrix; then monocytes within 24 h. These monocytes then become macrophages which phagocytose microbes and remove debris. Macrophages release growth factors and chemokines, such as platelet-derived growth factor (PDGF), fibroblast growth factor (FGF), vascular endothelial growth factor (VEGF), and Transforming Growth factor-a and -b (TGF-a and TGF-b), which assists in the transition to the proliferation stage (Koh and Dipietro 2011; Werner and Grose 2003).

In this stage, released chemotactic agents induce cells' to mobilize, proliferate, and differentiate (Phillips 2000). Stem cells migrate into the wound bed from the basal layer, as well as a significant contribution from remnants of dermal appendages—such as the residual stumps of hair follicles (Martin 1997). These stem cells and keratinocytes proliferate and migrate to achieve re-epithelialization and coverage of the wound (Phillips 2000; Li et al. 2007). Fibroplasia is the accumulation and proliferation of fibroblasts and their production of collagen and ground matrix proteins forming the granulation tissue. This early ECM includes collagens, proteoglycans, and elastin and fills the wound space acting as scaffolding and contact guidance for migrating cells and supporting angiogenesis (Woodley 1985).

Toward the end of the proliferative stage, the fibroblasts differentiate into actin-rich, contractile myofibroblasts, which pull together the wound edges (Tomasek et al. 2002). The final remodeling stage involves the conversion of the dermis from type III to type I collagen and removing cells from earlier stages. This tightly controlled synthesis of new collagen and lysis of old collagen is mainly achieved through the actions of matrix metalloproteinases (MMPs) (Visse and Nagase 2003). Even during normal physiological wound healing, the end-product is neither

aesthetically nor functionally perfect. The connective tissue scar that reconstitutes the wound consists of poorly reorganized collagen in dense parallel bundles compared to the basketweave configuration of unwounded tissue. Additionally, hair bulbs or sweat glands do not regenerate if the injury is too deep into the dermis, and there are no remnants of these epidermal appendages (Martin 1997).

10.3 Angiogenesis and Microcirculation in Wound Healing

Angiogenesis occurs throughout all four overlapping stages of wound healing and is initiated immediately after tissue injury. New capillaries sprout from pre-existing vessels and penetrate the wound bed forming a microvasculature network and are visible in the wound bed 3–5 days after injury (Tonnesen et al. 2000). The granulation tissue that forms during the proliferative phase acts as a matrix for proliferating blood vessels, migrating fibroblasts, and new collagen (Folkman 1995; Rees et al. 1999). These new proliferating capillaries are vital to tissue regeneration by bringing in oxygen and micronutrients and removing catabolic waste products (O'connor et al. 2000; Tonnesen et al. 2000). Angiogenesis is regulated by complex growth factor–receptor, cell–cell, and cell–matrix reactions in an orderly cascade of molecular and cellular events (Honnegowda et al. 2015).

10.3.1 Growth Factors in Angiogenesis

Regulation of vascular growth is a balance between proangiogenic and antiangiogenic factors present throughout the body. When these angiogenic stimulators and inhibitors are at a physiological balance, vascular growth is suppressed (Hanahan and Weinberg 2011). Antiangiogenic factors include angiostatin, tissue inhibitors of matrix metalloproteinase-2 (TIMP-2), thrombospondin-1 (TSP-1), endostatin, platelet factor-4 (PF-4), and interferon α/β/γ. These inhibitory factors circulate in the bloodstream at low physiological levels and are stored in the ECM surrounding the blood vessels (Honnegowda et al. 2015).

Immediately following injury, proangiogenic stimuli are released into the wound bed, including thrombin, fibrinogen fragments, thymosin-β_4, and growth factors. This initiates angiogenesis and shifts the balance toward vascular growth (Majima et al. 2000; Pugh and Ratcliffe 2003; Semenza 2002). Tissue damage releases basic fibroblast growth factor (FGF-2) from previously intact cells (Matsuoka et al. 2006). FGF-2 and acidic fibroblast growth factor (FGF-1) are synthesized by inflammatory cells and dermal fibroblasts involved in wound healing. FGF-1 and -2 are released from the ECM and bind to the high-affinity protein family of transmembrane tyrosine kinases FGF receptor-1 (FGFR-1), expressed on endothelial cells of different origins, and FGFR-2, expressed under some circumstances (Presta et al. 2005).

Whereas FGF-1 and -2 that are released from endothelial cells act in an autocrine manner, both mechanisms modulate cell proliferation, migration, protease production, receptor expression, and gap–junction communication (Presta et al. 2005; Barrientos et al. 2008). The highly expressed αvβ3 integrin on endothelial cells during angiogenesis and its interaction with FGF-2 augments the cell's mitogenic activity and cell adhesion to ECM, thereby allowing sustenance for neovascularization (Rusnati et al. 1997).

Platelets and inflammatory cells in the bloodstream also store growth factors. During bleeding and hemostasis, thrombin in the wound upregulates vascular endothelial growth factor (VEGF) (Tsopanoglou and Maragoudakis 1999). Platelets release platelet-derived growth factor (PDGF), transforming growth factor (TGF-α and TGF-β), VEGF, FGF-2, platelet-derived endothelial growth factor, and angiopoietin-1 (Ang-1), which then stimulates endothelial proliferation and migration (Hellberg et al. 2010; Li et al. 2001; Pintucci et al. 2002). Also, macrophages provide a source of cytokines to amplify the angiogenesis cascade and stimulate fibroplasia and neovascularization (Tonnesen et al. 2000). Macrophages and monocytes release PDGF, VEGF, Ang-1, TGF-α, FGF-2, IL-8, and TNF-α during the inflammatory phase. PDFG, VEGF, and FGF-2 act with a synergistic ability to vascularize tissues (Grimm et al. 2009).

10.3.2 Role of Hypoxia

Hypoxia is the driving force for vascular proliferation. The hypoxic gradient between injured and healthy tissue promotes the gene expression of HIF-1α and triggers VEGF production (Grimm et al. 2009; Acker and Plate 2003). Expression of COX-2 during the inflammatory stage also leads to the production of VEGF and other promoters of angiogenesis. VEGF that is present in wound tissue and exudate, increases vascular permeability and transwall hydraulic conductivity (Acker and Plate 2003; Howdieshell et al. 2003). The leakage of fibrinogen and fibronectin through these fenestrations is essential to constructing the provisional ECM (Leonardi et al. 2003). Hypoxia also triggers endothelial cell production of nitric oxide (NO), promoting vasodilation and improving local blood flow (Smith Jr. et al. 2009).

10.3.3 Extracellular Matrix Degradation and Vascular Stabilization

When angiogenic growth factors bind to cell surface receptors of pre-existing venules (parent vessels), this growth factor receptor binding activates signaling pathways within these endothelial cells. Activated endothelial cells release

proteolytic enzymes, such as thrombin-exposed endothelial cells releasing release gelatinase A (MMP-2), which dissolves the basement membrane of the parent vessels (Nguyen et al. 2001). Endothelial cells sprout outward through the basement membrane and migrate into the wound bed facilitated by the actions of integrins (αvβ3, αvβ5, and αvβ1). The tissue matrix is dissolved ahead of the sprouting vessel by the MMPs (Honnegowda et al. 2015).

While these proteases break down damaged tissue matrix, proangiogenic stimulators are released, such as fragment E, yielded from fibrin's cleavage, which stimulates angiogenesis directly and enhances VEGF and FGF-2 (Bootle-Wilbraham et al. 2001). As capillary sprouts develop, they digest endothelial cells and infiltrate the ECM after penetrating the vascular basement membrane and continue to branch and form networks (Morgan et al. 2007). These vascular sprouts form tubular channels that connect to vascular loops, which then differentiate into afferent (arterial) and efferent (venous) limbs (Honnegowda et al. 2015).

Vascular stability is controlled by Ang-1 and tyrosine kinase with immunoglobulin-like and EGF-like domains 2 (Tie-2) in the wound bed. Ang-1 binding to its receptor, Tie-2, on activated endothelial cells produces PDGF and recruits mural cells, smooth muscle cells and pericytes (Inoki et al. 2002; Ma et al. 2007; Korff et al. 2001). Stabilizing the vascular architecture allows for blood flow to begin in the mature vessel (Honnegowda et al. 2015). At the terminal stages of healing, growth factor levels decline in the wound, and angiogenesis is suppressed (Kumar et al. 2009). Pericytes secrete an inhibitory form of activated TGF-β that impedes vascular proliferation (Korff et al. 2001; Darland and D'amore 2001). Endostatin, a cleavage product of collagen XVIII, is present surrounding the vascular basement membrane and inhibits wound vascularity (Lange-Asschenfeldt et al. 2001).

10.4 Microcirculatory Aspects of Wound Healing in Skin

Skin circulation has two primary functions: Regulating body temperature and delivering nutrients and oxygen for the skin cell metabolism (Awan et al. 2011). The microvasculature architecture is not homogeneous, as differences depend on anatomical and topographic characteristics specific to the skin area (Braverman 1983). These microcirculatory areas have been classified according to four features: (1) presence/absence of arteriovenous anastomoses (AVAs); (2) structure and location of end arteriole blocking devices; (3) structure of valve-containing venules; and (4) microvessel tissue relationships (Curri 1990). Most skin has nutritive perfusion provided through capillaries. However, specific sites also have arterioles and venules that directly communicate with each other. These AVA provide low resistance pathways from arteriole to vein through which blood flow is modulated to meet thermal demands (Zweifach 1987; Hales et al. 1985). Some anatomical regions, such as the sole and dorsum of the foot, fingertips, and nail folds do not contain these AVAs (Rendell et al. 1993).

The anatomical arrangement of the cutaneous microcirculation is organized in two horizontal plexuses: A deep (lower) plexus containing arterioles and venules starting at the dermal–subcutaneous junction, and a superficial (upper) plexus within the papillary dermis located 1–1.5 mm below the skin surface. These two plexuses are structurally different and connected through paired ascending arterioles and descending venules (Braverman 2000). Autonomic nerves regulate perfusion in the deep plexus, primarily allowing AVA to serve a thermoregulatory function. AVAs act as regulatory capillary flow devices, have a much greater vasodilatory response to heat, and are also affected by emotions (Braverman et al. 1992; Braverman 2000; Charkoudian 2003; Mork et al. 2002). At the dermal–subcutaneous junction, collecting veins, the presence of bi-cusped valves prevent retrograde blood flow (Braverman 2000). The superficial plexus is predominantly composed of smaller diameter (10–20 μm) postcapillary venules that contribute to the capillary loops of the dermal papillae. Arterial capillaries rise to form the dermal papillary loops representing the nutritive component of the skin microcirculation. These capillaries are sites of inflammatory cell emigration, histamine-induced vascular permeability, and deposition of immune complexes in vasculitis (Braverman 2000).

A primary function of skin papillary capillaries is to deliver O_2 and nutrients to maintain and promote epithelial cell proliferation (Sundheim et al. 2017). Pericytes are effector cells involved in regulating some nutritive capillary blood flow via activation of their contractile proteins (actin and myosin) (Attwell et al. 2016; Birbrair et al. 2015). Perfusion in papillary capillaries is regulated locally based on metabolic needs (Mork et al. 2002). Pericytes constrict or dilate in response to PCO_2, pH, and local humoral factors (endothelin and NO) (Chen and Anderson 1997). The O_2 delivery capacity depends on the product of microvascular blood flow and oxygen extraction. Papillary oxygen extraction is high compared to other tissues, limiting the need for a high blood flow (Awan et al. 2011).

Following skin injury or wounding, the skin healing process is associated with an increase in the local metabolic rate that facilitates cellular proliferation and production of the extra cellular matrix. During the repair process, a critical function of this regulatory system is to maintain O_2 delivery for the expansion of stem cells at the epidermal basement membrane. The O_2 is delivered via noninnervated nutritive papillary skin capillaries from the superficial plexus (Braverman 1997). Increased blood perfusion in the deep thermoregulatory plexus occurs between 30 and 60 min after trauma, but papillary capillary nutritive perfusion does not appear to change (Wikslund et al. 2021). As long as the O_2 supply is sufficient, pericytes regulating papillary nutritive perfusion remain contracted, narrowing the diameter of nutritive capillaries. However, beyond about an hour, pericytes experience signals of increased metabolic need, and in response to the acidic extracellular pH and elevated PCO_2, will relax, thereby promoting increased capillary network blood perfusion (Attwell et al. 2016; Birbrair et al. 2015; Chen and Anderson 1997). Blood flow is thus increased in the superficial plexus via ascending arterioles from the deep plexus facilitating increased nutritive perfusion.

Angiogenesis is triggered by multiple cellular signals that occur early in the wound healing process and continues throughout. The plasticity of the

microcirculatory system permits a quick remodeling process that can occur in hours to a few days (Ricard and Simons 2015; Wikslund et al. 2022). After about 24 h, papillary nutritive capillaries are observed to be elongated and dilated, and the superficial vascular plexuses are more visible (Wikslund et al. 2022). As a consequence, the increase in capillary surface area allows for a commensurate increase in diffusion capacity that aids the repair process and corresponds to the rise in the tissue's metabolic rate for stem cell production of new epidermal cells (Wikslund et al. 2022).

During this process, the density of papillary capillaries and erythrocyte velocities in capillaries near the injury site (2 mm distant) are increased (Wikslund et al. 2021). The repair zone, based on the Krogh model and the maximal O_2 diffusion distance, extends up to 1 mm from the injury site (Forster et al. 2017). This zone with increased metabolic and O_2 needs is met by an increased number of O_2-carrying erythrocytes passing through the area and reduced diffusion distances. Beyond 2 mm from the injury site, oxygen may be supplied by erythrocytes in a mechanism analogous to upstream flow-mediated dilation that increases microcirculation to and within the sites with increased needs (Markos et al. 2013).

10.5 Microcirculatory Aspects of Wound Healing in Specific Conditions

10.5.1 Aging and Associated Skin Changes

The aging of the skin is influenced by intrinsic factors related to simple chronological aging effects that are independent of environmental insults and also by extrinsic factors that are related to the cumulative insults of environmental exposure, such as UV radiation (Fisher et al. 1997). The net effect of the these combined aging processes is a diminished ability to maintain homeostasis leading to a progressive loss of function of the skin barrier and increased vulnerability to environmental insults (Gilchrest et al. 1994). At the dermal–epidermal junction, the rete ridges are flattened with senescence. Thus, in this skin area, where the papillary dermis maintains contact with the epidermis, flattening the dermal–epidermal junction results in decreased surface contact between these two layers and gives the appearance of atrophy (Kurban and Bhawan 1990; Montagna and Carlisle 1990). In addition to the decline in epidermal and dermal thickness and composition, most resident cells are reduced in number and there is an associated diminished skin microcirculation (Bentov and Reed 2014; Montagna and Carlisle 1990). The skin microcirculation shows impaired regulation, aspects of inflammatory response changes, decreased numbers of progenitor cells, and declines in circulatory mediators (Bentov and Reed 2014). These age-associated changes impede the microvasculature's ability to thermoregulate and respond to injury, thereby increasing the

chance of tissue hypoperfusion that negatively impacts wounds from reaching the angiogenic stage of repair (Bentov and Reed 2014; Gould et al. 2015).

The literature presents conflicting data, with most showing an age-related decrease in angiogenesis (Holm-Pedersen and Viidik 1972; Swift et al. 1999) and a few showing an increase (Passaniti et al. 1992). Possible mechanisms of impaired angiogenesis are attributed to impaired endothelial cell function and reduced VEGF expression (Rivard et al. 1999). In animal models, delayed wound capillary ingrowth has been partially attributed to reduced angiogenic factors FGF, VEGF, and TGF-β (Rivard et al. 1999; Swift et al. 1999). Additionally, aged endothelial cells secrete less nitric oxide, likely decreasing vasodilation potential (Rivard et al. 1999) and diminishing microvascular reserve.

During wound healing, the ECM of older adults demonstrates prolonged inflammation, increased MMP and elastase expression, reduced TGF-β, and a weakened cellular response (Gurtner et al. 2008). The atrophic skin of the older adult cannot adapt quickly to the mechanical demands of an injury causing the healing response to be prolonged and blunted with amplified inflammation and differences in signal transduction resulting in inferior ECM production (Edwards et al. 2013; Gould et al. 2015). Accordingly, re-epithelialization, collagen synthesis, and angiogenesis exhibit an age-related delay (Swift et al. 1999). Dermal lymphatic drainage has been shown to be decreased in aging skin causing wounds to be less able to clear pathogens and have diminished wound contraction potential (Gosain and Dipietro 2004).

During the proliferative phase of wound healing, older individuals exhibit a 50% increase in time for keratinocytes to migrate from the basal layer to the surface compared to younger individuals (Gilchrest et al. 1982). The number and size of dermal fibroblasts decrease in advanced age (Plisko and Gilchrest 1983), and these fibroblasts exhibit a diminished response to growth factors and capacity to replicate (Plisko and Gilchrest 1983; West 1994). To assemble a new collagen framework, the ECM must first be degraded by MMP during remodeling. Angiogenesis also requires MMP activity to allow for the invasion of endothelial cells (Reed et al. 2000). Older adults have been shown to have higher expression of proteases and higher activity levels, and these proteases, particularly MMP2, are elevated in older postmenopausal women. Thus, estrogen replacement therapy can stimulate the migration and proliferation of keratinocytes and the elaboration of the matrix (Ashcroft et al. 2002). Lastly, in photoaged skin, the MMPs activated by UV radiation produce disorganized collagen fibrils, causing an accumulation of abnormal elastin-containing materials (Fisher et al. 1997). Due to comorbidities associated with older individuals, including vascular disease, venous insufficiency, unrelieved pressure, or DM, this population is more susceptible to chronic wounds. The sequelae of these conditions whether venous leg ulcers, diabetic foot ulcers, arterial ulcers, or pressure ulcers, disproportionately afflict older adults (Gould et al. 2015).

Since blood flow adequacy is an important determinant of wound healing efficiency, it is useful to further consider the potential impacts of age-related changes in skin blood flow. Early work using the hairless mouse skin model demonstrated age-related changes based on laser Doppler perfusion measurements (Mayrovitz

1992). In humans, early measurements of skin blood flow in deltoid skin using ^{133}Xenon washout methods in 65 men aged 20–70 pointed to a 40% skin blood flow reduction over this age range potentially impacting the skin's ability to adapt to stressors (Tsuchida 1993). Laser Doppler methods have also been used to demonstrate reduced microvascular vasodilatory reserve in older vs. younger persons. For example, using direct skin heating as a stimulus, increases in forearm skin blood perfusion were less in men aged 60–79 years than in men between the ages of 20 and 39 years (Richardson 1989). A similar reduction in heat-induced hyperemia was observed in the foot dorsum of elder men vs. younger men that was attributed to a reduction in vascularity of the capillary network (Weiss et al. 1992). A similar conclusion was reported based on laser Doppler measurements of heat-induced hyperemia in a small group of young and older men (Tolino and Wilkin 1988). Further work by Inoue and coworkers compared responses of passive heating of young (20–25 years) vs. older (64–76 years) men and showed a reduced heat-induced skin perfusion increase in skin of the back, chest, forearm and thigh subsequent to passive heating (Inoue et al. 1998). Further evidence for an age-related reduction in the maximum achievable skin blood flow was provided by a sustained one-hour heating protocol that used venous occlusion plethysmography (Rooke et al. 1994).

Given the importance of adequate blood flow increases during the wound healing process, it is likely that the age-related decline in vasodilatory reserve is relevant to slowed or blunted wound healing in some patients. Contrastingly, in at least one study, the postischemic forearm skin hyperemic response was not found to be different based on a three-minute occlusion-release protocol in a small group of 10 young and 10 older subjects (Kelly et al. 1995). More recently, an age-related differential response in finger pad blood perfusion of the third finger was observed during simulated Braille reading with the index finger (Murata et al. 2021). During this procedure, finger pad perfusion decreased in both young (20–24 years) and older (64–70 years) subjects, but a significantly greater reduction was observed in the younger persons. Since it had been established that the finger blood perfusion is subject to neurovascular control (Mayrovitz and Groseclose 2002a, b, 2005; Mayrovitz et al. 2005), it is likely that the age-related features are at least in part attributable to such neurovascular differences. An example of the neurovascular assessment using the response to a deep and rapid inspiratory gasp is illustrated in Fig. 10.1. However, the decreased skin blood perfusion and decreased pulse pressure that accompanies the inspiratory gasp reflex as shown in Fig. 10.1 have not as yet been evaluated with respect to possible age-related differences.

However, the potential role of age-related changes in neurovascular functioning as a contributor to delayed or absent healing has been suggested with possible linkages to sensory nerve function (Ardron et al. 1991). These workers demonstrated a reduced axon reflex vasodilation to be present in 15 elderly patients who were afflicted with chronic venous ulcers, thereby potentially implicating age-related changes in skin C-fiber function impacting skin blood perfusion. Although a major function of these skin sensory nerves is pain signal transmission, they also release

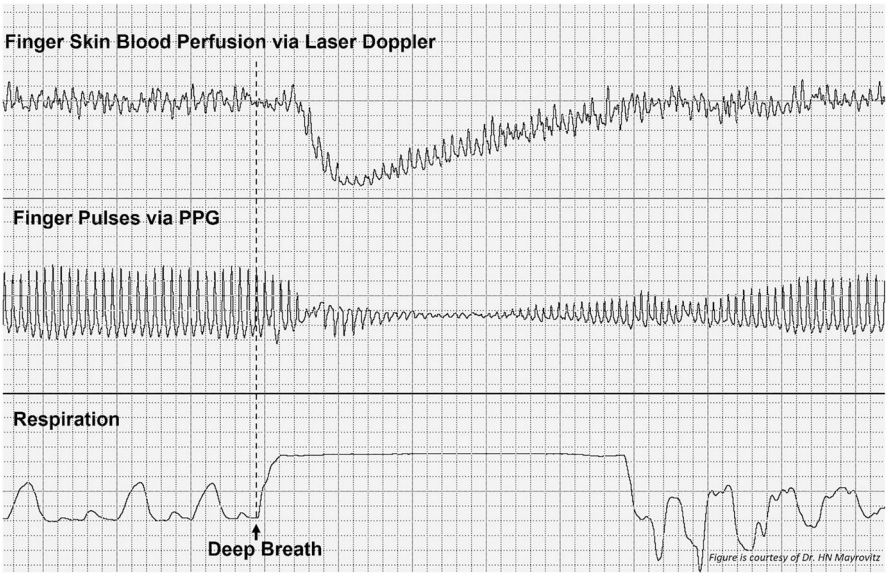

Fig. 10.1 Illustrating the response to an inspiratory gasp held for 25 s
The finger pad skin blood perfusion (upper panel) falls dramatically during a rapid inspiratory gasp, but during the breath holding, it is observed to recover. A similar change is noted in the pulse plethysmographs recording (middle panel) of the index finger pressure pulses of the same hand but with a longer time to recover. Upward movement on the respiration tracing indicates inspiration. Horizontal scale is 1 sec/div. (Figure is provided as a courtesy of Dr. HN Mayrovitz)

substances that impact microvessel vasodilatory states thereby affecting blood flow and, in that way, may impact wound healing.

A potential role of sensory afferent fiber function deficit with increasing age is consistent with the age-related trend in their laser Doppler perfusion response to capsaicin challenge (Munce and Kenney 2003). In this study of a group of eight men between the ages of 65 and 80, the vasodilatory response of forearm skin blood perfusion to capsaicin was significantly less than observed in men either 40–55 years or 18–30 years. When sensory nerve-related vasodilation was blocked using a local anesthetic, the age-related difference in heat-induced vasodilation between young vs. older men was reported to be lost (Tew et al. 2011). This further supports a role for an age-related sensory nerve changes that may impact wound healing via limitations on maximal vasodilation. However, direct linkages have yet to be confirmed experimentally. The use of such localized heating in combination with assessments of skin blood perfusion responses is useful to evaluate microvascular blood flow reserve and its potential limitations. Figure 10.2 illustrates a typical response to local skin heating as influenced by the presence of significant peripheral arterial disease in only the left leg of a patient. The much-reduced microvascular reserve would have a negative impact on wound healing.

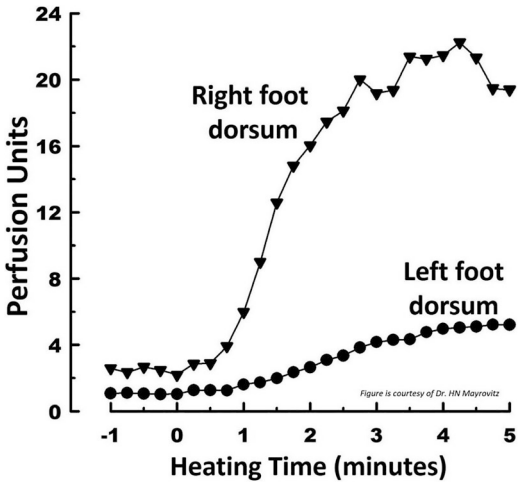

Fig. 10.2 Illustrating the normal and reduced microvascular perfusion response to local heating Skin blood perfusion measured via laser Doppler on foot dorsum of a patient with hemodynamically significant peripheral arterial disease in the left leg only. Heating was local to a skin temperature of 42 °C and maintained. The significantly reduced microvascular perfusion reserve is evident by the differences between the right and left dorsum responses. This would have a negative impact on the healing of a metabolically active wound if present. (Figure is provided as a courtesy of Dr. HN Mayrovitz)

10.5.2 Pressure Ulcers

10.5.2.1 Major Features and Blood Flow Involvement

The Centers for Medicare and Medicaid Services (CMS) has referred to pressure ulcers as describing a chronic skin lesion mainly caused by excess pressure over bony prominences that occlude blood flow (Horn et al. 2015). Although such ulcers tend to develop in elderly and also in persons with spinal cord injury (Harrow and Mayrovitz 2014), they can occur in anyone subject to sufficiently large and unrelieved pressure. Interfaces between the body surface at points of contact at bony prominences such as the trochanter, heel, malleolus, and sacral region are particularly vulnerable to the development of pressure ulcers. Use of thermal scanning of the sacral region to predict sacral ulcer development in hospital admitted patients failed to be sufficient selective (Mayrovitz et al. 2018).

However, measurements of sacral skin blood perfusion via laser Doppler imaging reveal a high level of normal skin blood perfusion in resting healthy persons compared to other nearby and distant skin sites (Mayrovitz et al. 2002). Deprivation of this blood flow during sustained supine lying is likely one factor in pressure ulcer development. Indeed, laser Doppler imaging of acquired sacral ulcers demonstrates increased blood perfusion at the center of the ulcer (Huiming et al. 2021). Measurements of skin blood perfusion and its response to local heating in periulcer regions have demonstrated elevated preheat values and augmented hyperemia in comparison

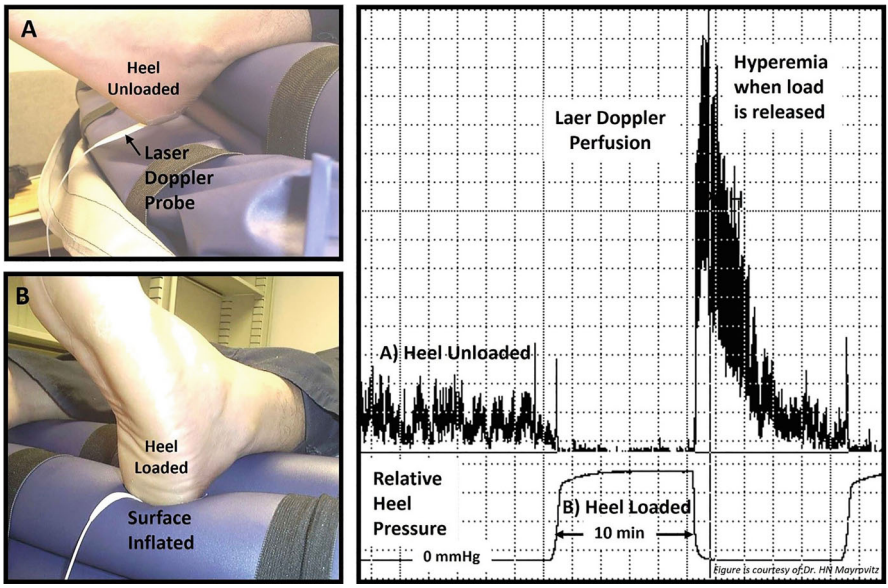

Fig. 10.3 Normal hyperemic response to heel loading and off-loading
A flat laser Doppler probe is placed on the heel in (**a**) with the heel unloaded since the support surface cell deflated. In (**b**), the surface is inflated to load the heel and the blood perfusion is seen to drop to unmeasurable levels as shown in the right panel. Upon deflation, after a loading time of just 10 min, a large hyperemic response is noted that is normal. In persons with compromised vascular and microvascular status, the hyperemic response is much diminished or absent. (Figure is provided as a courtesy of Dr. HN Mayrovitz)

to normal skin but these skin regions have a significantly reduced oxygen as determined by transcutaneous oxygen measurements (Schubert 2000). The important potential role of altered microvascular perfusion as a main source of the genesis of pressure ulcers has been studied by determining the blood flow deficits during tissue loading and subsequent unloading on the foot heel, a common site for pressure ulcer development (Mayrovitz et al. 1997; Mayrovitz and Smith 1998, 2002; Mayrovitz et al. 1999, 2003a, b, 2004). A normal hyperemic response to heel loading on a support surface and its release is shown in Fig. 10.3 demonstrating that even rather short durations of compression-related ischemia are followed by significant hyperemia in normal tissue.

10.5.2.2 Tissue Injury and Risk Factors

Studies of the details of pressure ulcers demonstrate injuries to skin and underlying tissue due to sustained external pressure and shear forces thought to be attributable to internal tissue deformation (Gebhardt 2002; Bouten et al. 2003). This distortion or deformation is caused by compression and/or shear between the skeleton and

support surface (e.g., bed or chair) that leads to localized acute damage associated with the tissue ischemia, and potentially subsequent tissue necrosis (Gebhardt 2002; Gefen 2009a, b). Therefore, this type of injury is commonly found in immobile patients on the skin and soft tissue that as was previously noted occurs most frequently at bony areas of the body, such as the occiput, trochanters, sacrum, malleoli, and heel (Gebhardt 2002). Other common locations include ischial, patella, and pretibial ulcers (Vasconez et al. 1977; Cannon and Cannon 2004).

10.5.2.3 Generalized Risk Factors

It has been reported that pressure ulcers are a significant disease burden worldwide and the highest disability index compared to other dermatological conditions (Hay et al. 2014). As already noted, predisposing factors include loss of movement, loss of sensation, and failure of reactive hyperemia (Bhattacharya and Mishra 2015). The development of pressure ulcers depends on an individual's health status and tissue tolerance. Age, comorbidities (such as Type 2 DM), and nutritional status are significant contributing factors (Coleman et al. 2014) with two-thirds of pressure ulcers occurring in those aged 60–80 years (Leblebici et al. 2007).

Normally as tissue distortion occurs and causes ischemia, CNS signals of discomfort and pain stimulate protective movements to relieve the pressure. However, immobility or a loss of sensation may prevent signals from being communicated to restore circulation to the area, resulting in the development of a pressure ulcer (Bliss 1998). Even in healthy patients, ischemic responses occur with positions such as supine, lateral lying, and high sitting, corresponding to pressures between skin and support surface from 30 to 90 mm Hg (Bader and Worsley 2018). Thus, underlying factors in individual anatomy (tissue structure and geometry) and physiology (microcirculation and nutrition factors) are generalized factors involved (Coleman et al. 2014).

10.5.2.4 Tissue Damage Causation

Prolonged external pressure of sufficient magnitude on skin occludes capillary perfusion resulting in ischemic soft tissue injury, skin breakdown, ulcer development and possible necrosis depending on the amount of pressure and its duration of action. Clinical experience in nursing home facilities and in hospital settings shows that despite proper positional changing, pressure ulcers still occur (Tsuji et al. 2005). Two different damage mechanisms, both of which depend on tissue ischemia, have been put forward to account for the pathogenesis of pressure ulcers. The first is ischemic damage due to interruption of perfusion to tissue that causes direct cell damage (Bouten et al. 2003). The other is ischemic damage caused by decreased nutrients and oxygen and increased toxic metabolites in the tissue. It has been reported that this latter process occurs at relatively low internal tissue strains and can take several hours to develop (Soetens et al. 2019b). Contrastingly, direct cell

damage would be caused by higher pressures and greater internal strains and can happen within tens of minutes. The concept is that the development of a pressure ulcer can be associated with both the magnitude and duration of tissue deformation—high deformation for short durations and low deformation for long periods (Bouten et al. 2003) with the type of injury dependent on the characteristic of the tissue loading pattern (Oomens et al. 2015). Continuous interface pressure monitoring of patients with spinal cord injuries are consistent with this concept (Fryer et al. 2022).

10.5.2.5 Tissue Pressure and Distortion as a Cause of Ischemia

It has been reported that tissues can sustain pressure of around 30–32 mm Hg for a short duration, but pressures exceeding this will cause occlusion of the microcirculation (Gefen 2009a, b). However, these values are in part based on what was assumed to be an average arterial-end capillary intravascular pressure, and thus, larger values would cause sufficient compression to cause capillary occlusion. However, this concept does not take into account the tissue structure and its properties that lay between the pressurized skin surface and the underlying vessels to be compressed. Further, such values do not intrinsically include the fact that skin surface shear and underlying tissue strain may be equally or more important in affecting the underlying tissue and vessels therein (Oomens et al. 2010).

The manner in which surface forces are transmitted to and through underlying tissue to impact the microcirculation is complex and in very much need of new research efforts. The impact of support surface dynamic pressure patterns on underlying microcirculatory parameters are also of interest (Chai et al. 2017). There is also the possibility that the focus on "compressing" capillaries has hidden the potential involvement of the lymphatic vessels that have a much lower internal pressure. It would appear that sustained occlusion of the underlying lymphatic vessels should be considered as a potential contributor to some forms of pressure ulcer development. Some data supports this concept (Gray et al. 2016) and points to the variability of thresholds among patients (Worsley et al. 2020). Despite the caveats of this paragraph, much work in related areas has been done and concepts put forward that help clarify the factors involved as they relate to the involvement of microvascular perfusion.

For example, the potential involvement of venous vessels, that have a low intravascular pressure, and possible effects on the subpapillary thermoregulatory A/V shunts has been described (Ambrozy et al. 2013). Additionally, the concept and potential role of tissue creep that allows soft tissues to accommodate an external load thereby reducing the surface external stress but in so doing, increasing internal tissue strain (Dodd and Gross 1991). Such strain and associated tissue distortion, if large enough, decreases blood flow via a variety of possible mechanisms (Callam et al. 1985). Distortion-related vascular kinking can compromise tissue blood perfusion causing ischemia and possibly necrosis within hours (Bhattacharya and Mishra 2015). Further, such internal shearing forces tend to distort and occlude blood

flow more easily due to bending or kinking vessels rather than direct compression (Goossens et al. 1997).

10.5.2.6 Other Issues and Considerations

Differences in local tissue structure and microvasculature lead to differential abilities to withstand distortion forces and hence different involvements of the localized microcirculation. For example, foot soles have a thin, soft tissue covering blood vessels that are adapted for weight bearing and foot soles rarely develop pressure ulcers. The sacrum and ischial tuberosities do not have such well-adapted blood vessels. Even though these regions have a thicker layer of soft tissue, they can develop pressure ischemia even under light compression.

Depending on the pressure application duration, its relief is normally associated with a reactive hyperemia allowing rapid restoration of O_2 and waste product removal in previously ischemic tissue. A failure of the reactive hyperemic cycle or a major deficit in it, will prevent the tissues from recovering from the pressure-induced ischemia and, eventual permanent damage. In addition, following periods of ischemia, cellular injury resulting from reperfusion may occur when blood flow is restored. Nutrient and oxygen-deprived tissue may reduce metabolism to preserve function. When perfusion is restored, high levels of cytotoxic reactive oxygen species may be produced that exceed the capacity of the free radical scavenging mechanism (Tsuji et al. 2005). It is likely that ischemia-reperfusion injury, in addition to ischemic necrosis, contributes to the formation of some pressure ulcers (Salcido et al. 1994; Tsuji et al. 2005).

In addition to hyperemic responses to prior ischemia, some blood vessels exhibit pressure-induced-vasodilation (PIV) in which a pressure applied to skin causes cutaneous microvessels to vasodilate thereby potentially mitigating ischemic effects (Fromy et al. 2000). However, once a threshold level is exceeded, the PIV response doesn't compensate for compression pressures that would normally be experienced. At these higher pressures (as low as 60 mmHg), complete microvascular occlusion has been observed (Worsley et al. 2020). Similar pressures were shown to cause local ischemia and inflammation and accumulation of metabolites due to anaerobic metabolism (Allman 1997; Soetens et al. 2019a; Knight et al. 2001). Additionally, persons with an already compromised microcirculation are at greater risk of a pressure ulcer and once it occurs may require a longer recovery period (Bogie et al. 1995).

10.5.3 Venous Ulcers

10.5.3.1 Incidence, Location, and Factors

About 80% of lower extremity wounds are venous ulcers with nearly 95% of them located in the gaiter area, somewhere between ankle and knee, but often closer to the malleolus than knee. An example of a venous ulcer located in the gaiter area is shown in Fig. 10.4**.** This figure demonstrates some of its common features such as being a shallow ulcer with irregular margins often with surrounding hyperpigmentation. The predilection for the gaiter area may be related to reported differences in the veno-arterial vasoconstrictor response evaluated by assessing the skin perfusion reduction from supine to standing (Bull et al. 1995).

Factors involved in venous ulcer development include venous reflux and venous hypertension due to incompetence of deep and communicating vein valves and thrombosis of deep vein segments (Gschwandtner and Ehringer 2001). Also, CVI is often present and associated with venous drainage obstruction and increased venous pressure and reflux due to arteriovenous fistulas. Previous leg injuries, deep vein thrombosis, phlebitis, and older age are among the risk factors for the development of venous leg ulcers (Nelson et al. 2000; Collins and Seraj 2010). Approximately 1.5% of Americans have venous ulcers with a female to male ratio of near 1.6 to 1. About 20% of those developing venous ulcers do so prior to age 40 and about 40% of patients that develop venous ulcers have a history of deep vein thrombosis and have a diagnosis of CVI. Although the evolution of skin ulcers

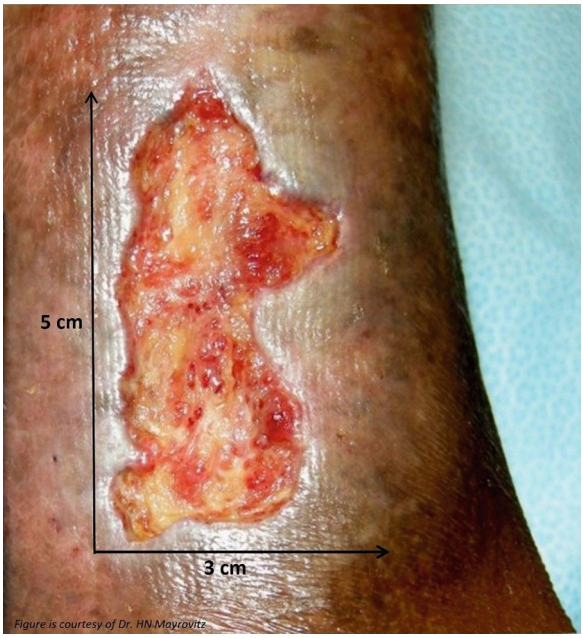

Fig. 10.4 Venous ulcer located on the lateral gaiter area
These ulcers typically have an irregular shape and characteristic wound bed granulation tissue and surrounding tissue hyperpigmentation. (Figure is provided as a courtesy of Dr. HN Mayrovitz)

from venous hypertension is not fully understood; contributory factors include inflammatory processes, intercellular and vascular adhesion molecule upregulation, protein rich edema, leukocyte trapping, oxygen deprivation, and microcirculatory deficits (Robles-Tenorio et al. 2022).

10.5.3.2 Microvascular Involvement

Although the precise pathophysiology of venous ulcer development is unclear, various theories have been described (Vasudevan 2014), and early reviews have considered multiple factors as contributory (Shami et al. 1992). For example, the "white cell trapping" theory describes a release of free radicals that result in tissue death as a consequence of venous hypertension (Brem et al. 2004). And as noted, microcirculatory deficits due to increased activation of platelets, monocytes and neutrophils leading to microvascular aggregation and microvascular entrapment of neutrophils has been reported (Robles-Tenorio et al. 2022).

10.5.3.3 Microvascular Linkages to CVI

It has been proposed that the link to CVI may be that the microvasculature can no longer fully regulate cutaneous blood flow in skin areas severely affected by the CVI (Junger et al. 1996b). Accordingly, the venous congestion leads to capillary and postcapillary hypertension during ambulation that is manifest in the skin as edema, hyperpigmentation, induration, white atrophy, and skin ulcers (Junger et al. 2000). Earlier work by this group described a lack of cutaneous microvascular reserve that prevents blood flow from matching sudden changes in tissue demand due to orthostasis (Junger et al. 1996a). Since cutaneous microangiopathy appears to precede the development of trophic skin alteration in the presence of chronic venous congestion, and there appears to be a close correlation between the extent of the clinical manifestation and severity of microangiopathy (Junger et al. 1996a, b), it is likely that cutaneous microcirculation forms the link between venous hemodynamics and congestive dermatoses.

In mild CVI, morphological changes in the capillaries, such as moderate dilatations and increased tortuosity, can be seen via capillary microscopy. The higher the ambulatory venous hypertension, the more enlarged and tortuous the capillaries (Fagrell 1995). The increased diameters of pericapillary spaces create a halo effect, that indicates increased transcapillary filtration, that varies in size along the outer border of the dermal papillae, thereby creating a cobblestone appearance (Speiser and Bollinger 1991; Junger et al. 2000). In severe CVI, many or most capillaries are occluded by white blood cells and hemorrhagic disturbances, leading to decreased capillary density (Coleridge Smith et al. 1988). In areas of white atrophy, there is an avascular field in which few or no capillaries are found (Franzeck et al. 1984).

Compression therapy is the mainstay of treatment for CVI, which has been shown to improve most subjective symptoms in patients. Clinically effective compression

therapy reverses the pathogenic processes of CVI on the microcirculation and interstitial architecture by improving nutritive blood flow in congested areas (Abu-Own et al. 1994; Christopoulos et al. 1991; Leu et al. 1993). One mechanism by which compression therapy improves the situation is by recruiting previously under perfused capillaries thereby increasing capillary density and nutritive blood flow and by promoting angiogenesis. An improvement in nutritive perfusion generally accompanies improved healing of venous ulcers. In the first 2 weeks, changes in the capillary density can be seen to have prognostic significance. Increased capillary density suggests accelerated healing within approximately 6 weeks of therapy, while a lack of angiogenesis is related to delayed healing (Junger et al. 2000).

10.5.3.4 Normal and Abnormal Calf Pump Function

Normally the venous calf muscle pump helps propel blood in leg veins against gravity toward the heart (Gschwandtner and Ehringer 2001), with each calf muscle contraction compressing the deep veins forcing blood forward with function venous valves preventing backflow into superficial veins. The pressure gradient in the deep veins and the presence of functional valves in the communicating veins, allows blood from superficial veins to flow normally (Back et al. 1995). However, with dysfunction or failure of the valves each contraction of the leg muscles propagates an associated pressure peak into the superficial venous system. The ambulatory venous hypertension is propagated into the nutritive capillaries, and these high-pressure peaks eventually deteriorate the microcirculation of the skin—initially through capillary dilatation, followed by gradual rarefaction (Junger et al. 2000).

These events and the blood flow dynamics that occur are schematically illustrated in Fig. 10.5 in which the normally low-pressure superficial veins become exposed to the high pressures induced by the reverse flow pathways associated with incompetent valves. Concomitant with the tissue injury are inflammatory processes, increased vascular permeability and edema and or lymphedema. In Fig. 10.6, two examples of venous ulcers are shown in which skin blood perfusion assessed via laser Doppler methods is being measured in the periulcer region of two patients. The initial blood perfusion measurement is made at a skin temperature of 35 °C and then locally heated to 44 °C with responses as shown in Fig. 10.7**.** The responses shown in Fig. 10.7 demonstrate a common finding for ulcers of venous origin; an elevated periulcer basal resting flow with little if any microvascular reserve when stimulated with heat as shown in part B, but with normal responses in healthy control skin as shown in part A. It has been reported that in patients in which the microvascular reserve is relatively maintained healing of venous ulcers is expedited (Mlacak et al. 2005).

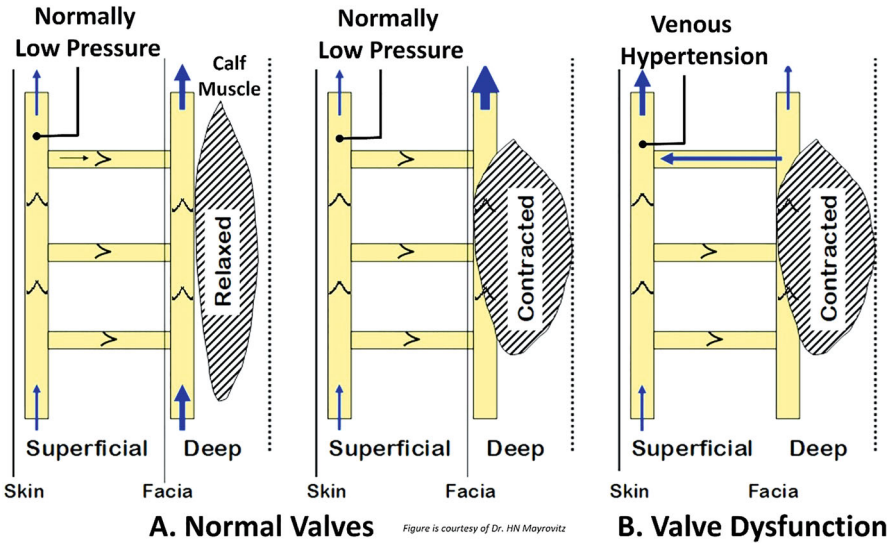

Fig. 10.5 Schematic of the impact and hemodynamics of incompetent venous valves
The normally low pressure experienced by the superficial veins is subject to high pressures in the presence of the valve incompetency as shown in part B. This elevated pressure is not well tolerated and causes venous injury that triggers a sequence of events that may lead to the development of a venous ulcer. (Figure is provided as a courtesy of Dr. HN Mayrovitz)

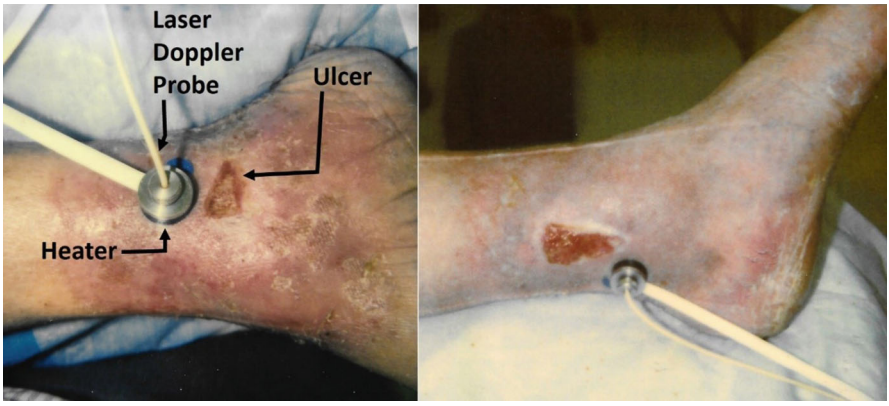

Fig. 10.6 Illustrating periwound skin blood perfusion measurement in venous ulcers
A laser Doppler probe is fitted through a concentric hole in the heater that is in contact with skin. Localized heating produces an increase in microvascular perfusion in healthy skin but with a differ pattern in periwound skin as shown in Fig. 10.7. (Figure is provided as a courtesy of Dr. HN Mayrovitz)

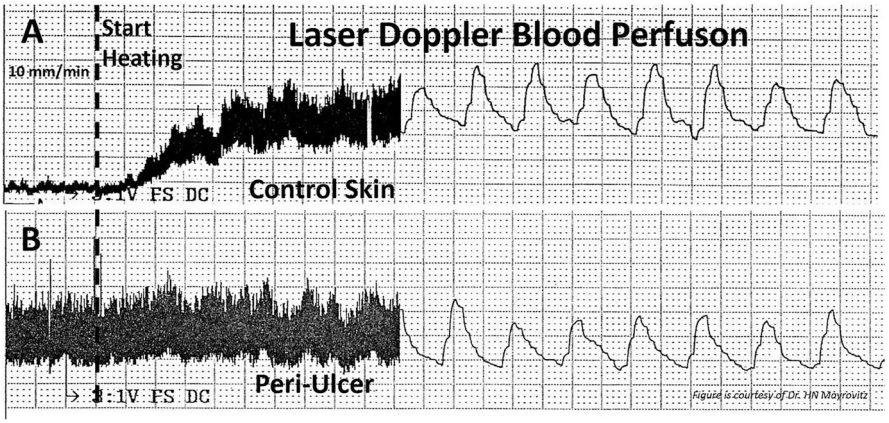

Fig. 10.7 Skin blood perfusion responses to heating in healthy vs. periulcer skin
The responses show a normal response to localized heating (**a**) and a common finding associated with venous ulcers (**b**). In B, an elevated periulcer basal resting perfusion is noted with little if any microvascular reserve when stimulated with heat. Contrastingly, in control skin as shown in part (**a**) a normal active hyperemia is noted in response to the heating. (Figure is provided as a courtesy of Dr. HN Mayrovitz)

10.5.3.5 The Wound and the Periwound Skin

Within the wound bed of venous ulcers, the capillary density is reported to be heterogeneous (Burnand et al. 1981; Leu 1991). Almost no capillaries are seen in areas without granulation tissue. These areas have poor nutritive microcirculation contributing to the formation of venous ulcers but moderate subpapillary blood flow. This moderate subpapillary perfusion may likely facilitate future wound healing and the construction of granulation tissue (Gschwandtner and Ehringer 2001).

As venous ulcers heal, they form granulation tissue seen grossly as erythematous areas within the ulcers (Ambrozy et al. 2013), as may be visualized in Fig. 10.4. In these areas, a few capillary sprouts are found embedded in small edematous pockets (Leu 1991; Burnand et al. 1981; Gschwandtner et al. 1999). This stage of healing is characterized by a distinct increase in subpapillary perfusion and increased appearance of visible capillaries. Nutritive perfusion in or adjacent to venous ulcers is lower than in normal skin areas although is reported to be higher than in ulcer areas without granulation tissue (Gschwandtner and Ehringer 2001). Thus, subpapillary perfusion appears to be crucial not only for thermoregulation but also for wound healing at this stage (Ambrozy et al. 2013). Capillary density is significantly improved but still low compared to noncompromised tissue. Additionally, these capillaries appear long and dilated, unlike the typical glomerular-like morphology in patients with chronic hypertension (Ambrozy et al. 2013; Gschwandtner et al. 1999, 2001).

At the scarring stage, the microvascular pattern of the skin differs from that observed in previously intact periulcer skin (Gschwandtner et al. 1999, 2001) and has glomerular-shaped capillaries characteristic of what is seen in CVI (Ambrozy

et al. 2013). The nutritive capillary density was found to be relatively high and similar to that seen in the early stages of venous ulcers prior to the ulcer developing granulation tissue (Ambrozy et al. 2013, Gschwandtner et al. 1999, 2001). The capillary density was considered to be moderate (20–30 capillaries/mm^2) in comparison to healthy skin (Lamah et al. 1996), although it is unclear if this capillary density is due to neoangiogenesis or contraction of the tissues. In healed periulcer skin, there is high nutritive and moderate subpapillary blood perfusion that appears close in value to normal skin (Konecny et al. 1987).

10.5.4 Arterial Ulcers

Arterial ulcers represent about 5% of all leg ulcers and are commonly located on the leg or foot and represent about 10–20% of all nonhealing lower extremity ulcers (Mekkes et al. 2003). The most prevalent predisposing condition for the development of an arterial ulcer is advanced peripheral arterial disease (PAD) present within arteries that supply the lower leg and foot (Spentzouris and Labropoulos 2009). Skin breakdown and ulceration is thus attributable to inadequate microvascular perfusion causing ischemic and hypoxic effects on skin and subcutaneous tissue (Grey et al. 2006). These ulcers will often occur in areas subject to pressure or trauma such as at the malleolus or posterior heel or the toes leading to necrosis and the need for amputation as illustrated in Fig. 10.8. Arterial ulcers are difficult to heal in the absence of an adequate restoration of blood flow, which itself may be more difficult to accomplish due to the presence of comorbid conditions (Greer et al. 2012). In

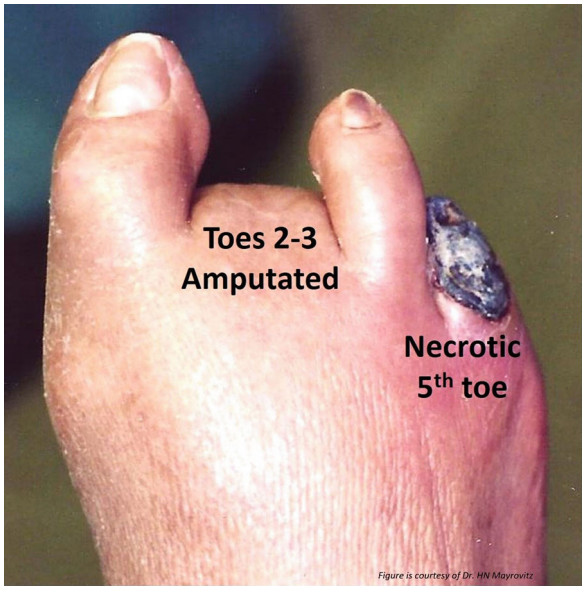

Fig. 10.8 Illustrating aspects of an arterial ulcer A patient with critical ischemia due to significant PAD in whom toes 2–3 were previously amputated and toe 5 is necrotic. (Figure is provided as a courtesy of Dr. HN Mayrovitz)

patients such as illustrated in Fig. 10.8, assessments of the response to local periulcer heating that is used to measure microvascular perfusion reserve are similar to that illustrated for the left foot dorsum in Fig. 10.2 or in more extreme cases, with even less or an absent perfusion increase. The presence of this microcirculatory deficit is accompanied by abnormally low levels of tissue oxygen levels as assessed by transcutaneous oxygen tension measurements (Ueno et al. 2010; Cina et al. 1984; Mayrovitz and Larsen 1994). Patients with PAD who also have DM and a foot ulcer are at greater risk of amputation (Azhar et al. 2021). However, that risk depends on the revascularization approach used (Butt et al. 2019) and on the extent of the PAD (Apelqvist et al. 2011). An epidemiological study reported that about 0.5% of the Korean population had both PAD and a diabetic foot ulcer (Chun et al. 2019).

10.5.5 Wounds in the Diabetic Patient

Persons with DM are generally at increased risk of developing skin ulcerations in part related to the presence of neuropathy, ischemia, and poor glycemic control (Clayton Jr. and Elasy 2009), although the development of DM foot ulcers has been reported to be less with improved glucose control that also improves microcirculation (Rathsman et al. 2014). The higher likelihood of PAD and the presence of microvascular deficits in DM (Thiruvoipati et al. 2015) increase the chances of ischemia, tissue to breakdown, and ulcer formation. In diabetic patients with PAD, the nature and distribution of leg arterial stenoses causing the ischemia is varied (Graziani et al. 2007) but even without the presence of significant PAD, foot ulcers in diabetic patients are often more difficult to heal for reasons that include reduced blood flow (Dinh et al. 2011; Catrina and Zheng 2016), wound oxygen deficits (Okonkwo and Dipietro 2017), and infection. Although wound healing in patients with DM tends to be inferior in the presence of reduced microcirculation (Lowry et al. 2017), the relationship between microvascular assessments and wound healing is not always easy to predict (Mennes et al. 2021).

In some patients with DM, it takes less local pressure to reduce skin blood flow in regions of bony prominence thereby laying the groundwork for ulcerations at these sites. When sensory neuropathy is present, normal pressure/pain signals are diminished or absent, thereby removing warning of developing tissue injury. Most of these types of ulcers develop on the foot, with plantar ulcers often associated with neuropathy. An example of such an ulcer is shown in Fig. 10.9. In these cases, elimination of elevated foot pressures combined with standard wound care are indicated. Statistics suggest that about 15–25% of persons with DM will get a foot ulcer (Yazdanpanah et al. 2018) with an annual incidence rate of 2–4% (Crawford et al. 2011). Diabetic-related nonhealing ulcers account for 140,000 extremity amputations per year in the USA (Mizelle Jr. 2021) and an annual amputation incidence rate between 0.5% and 0.8% (number of amputations per patient-year).

In terms of mechanisms and processes, DM causes structural and functional metabolic alterations to the arteriolar and microcirculatory systems, especially in

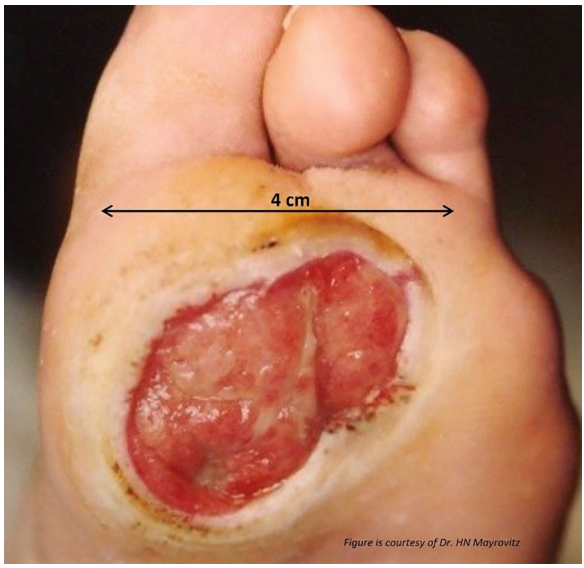

Fig. 10.9 An example of a plantar diabetic neuropathic ulcer. (Figure is provided as a courtesy of Dr. HN Mayrovitz)

the lower extremities of poorly controlled blood sugar patients (Cohen 1993; Nathan 1993; Raskin et al. 1983). In the capillary circulation, lumen size is reduced, and the vessels have increased stiffness (Jaap et al. 1996; Rayman et al. 1995). The increased stiffness is due to a thickened basement membrane and arteriolar hyalinosis, as well as glycosylation and formation of nonenzymatic advanced glycosylation end products (AGEs) (Hile and Veves 2003), thus limiting the vessel's ability to vasodilate and eventually autoregulate (Tooke 1995). Simultaneous measurements of transcutaneous oxygen, laser Doppler perfusion, cardiac output, and leg blood flow in 60 patients with and 60 patients without DM led to the conclusion that there was a direct linkage between a diabetic-related deficit in tissue oxygen and a submaximal microvascular vasodilatory reserve with little dependence on other circulatory factors(Mayrovitz and Larsen 1996). Other work indicated elevated levels of skin tissue water although apparently not significantly related to HbA1c values in patients with DM (Mayrovitz et al. 2013, 2016). Such alterations are likely to impact wounds when present in persons with DM.

Indeed, diabetic complications have been associated with impaired vasodilatory capacity. Nitric oxide (NO)-dependent smooth muscle vasodilation has been shown to be abnormal in patients with diabetic foot ulcers, and endothelium-dependent and -independent vasodilation is abnormal in diabetic neuropathy (Korzon-Burakowska and Edmonds 2006). However, in early work, it has been reported that within the arteriolar circulation, blood flow may be normal or even increased (Parving et al. 1983). It was posited that these characteristic changes are caused by endothelial injury attributable to increased microvascular pressure and shear force in leg microcirculation and leads to an injury response and proliferation of extravascular matrix proteins (Ajjam et al. 1985; Tilton et al. 1985). The thickened membranes impair

leukocyte transwall emigration, thereby increasing the susceptibility of the diabetic foot to infection, and additionally reduce the needed hyperemic response to injury (Flynn and Tooke 1992; Rayman et al. 1986). As nutritive perfusion of the skin plays a role in ulcer development and wound healing, these changes are a major concern in diabetic patients who have microvascular deficits (Korzon-Burakowska and Edmonds 2006).

As discussed, PAD and peripheral neuropathy are both major causes of a patient developing a diabetic ulcer and contribute to poor healing outcomes (Hinchliffe et al. 2016; Prompers et al. 2008). However, in many patients with microvascular deficits, there is no corresponding clinical evidence of lower extremity macrovascular disease. However, dysfunctional vessels of the microvasculature and impairment of the nerve-axon reflex may be concomitant abnormalities contributing to the neuroischemic diabetic limb—leading to ulceration and impaired wound healing (Hile and Veves 2003; Quigley et al. 1991). It has been shown that revascularization significantly improves, but does not completely resolve, these impairments (Arora et al. 2002). However, microangiopathy as a direct cause of ulcer development has not been fully confirmed, and in fact, one study did not find a relationship between microvascular abnormalities and wound healing (Korzon-Burakowska and Edmonds 2006).

10.6 Conclusion

Proper wound healing is inseparable from a functional microcirculation, as adequate localized blood flow and metabolic waste removal are necessary to meet the increased demands of healing tissue. Normal wound healing consists of four overlapping phases: Hemostasis, inflammation, proliferation, and remodeling, and microcirculation participation is to varying degrees present at each phase. Throughout these phases, angiogenesis occurs to supply nutrients and O_2 to wounded tissues, with the microcirculation delivering growth factors and other needed substrates. Skin has nutritive blood perfusion (via the superficial plexus) regulated by metabolic needs with some areas supplied by arteriovenous anastomoses (the deep plexus) largely under autonomic control. Following wounding, the latter vasodilate to provide increased microvascular blood flow to support the wound healing process including increased nutritive perfusion to support stem cell expansion and production of new epidermal cells. Angiogenesis occurs rapidly, thereby increasing microcirculatory potential to meet the needs of healing wound.

Aging affects skin's composition and its microcirculation. Age-associated changes include decreased blood flow, impaired ability to adapt to stressors (including thermoregulation and vasodilatory reserve), prolonged inflammation, decreased progenitor cells and mediators, increased migration time for keratinocytes, and increased matrix metalloproteinase activity. All these factors can contribute to delayed and dysfunctional wound healing. Derangements of the microcirculation can also contribute to the development of wounds, including arterial, venous,

pressure, and diabetic (neuropathic) ulcers. In these pathologies, microvascular perfusion is impeded in some way: Peripheral artery disease causes occlusion and ischemia in arterial ulcers; venous congestion, which may contribute to ischemic and inflammatory conditions in venous ulcers; external pressure causes direct damage and ischemia in pressure ulcers; metabolic and structural alterations impair vasodilatory capacity and contributing to possible infectious processes in diabetic ulcers. In summary, wounds can be viewed as an added "organ" that taxes the microcirculatory system with continued demand for blood flow. These wounds exemplify the effects of dysfunctional microcirculation when the increased needs cannot be met, not only impeding healing but taxing the system to such a degree that the skin structure cannot be maintained.

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