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CME ARTICLE

Microcirculation disorders of the skin

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Summary

Changes in the microcirculation of the skin are a frequently observed accompanying phenomenon of many diseases, far beyond the spectrum of dermatological diseases. Not all of these changes are pathological, many are transient and have no serious consequences. This is true for many inflammatory diseases such as psoriasis vulgaris or atopic eczema.

However, there are also diseases in which functionally and morphologically recognizable microangiopathies lead to severe disease consequences. One of the most important diseases in this context is systemic sclerosis, an autoimmune systemic disease with multiple organ manifestations. Investigations of the cutaneous microcirculation are of great importance for the initial diagnosis as well as for prognosis and assessment of disease progression.

In peripheral hemodynamic disorders such as peripheral arterial disease (PAD) and chronic venous insufficiency (CVI), understanding microcirculatory disturbances also plays an important role in therapy and in monitoring the success of therapeutic interventions.

INTRODUCTION

Vascularization of the skin occurs essentially in two vascular compartments located in different layers of the skin. The deep vascular plexus is located in the subcutis with transition into the reticular dermis. From the deep arteriolar vascular plexus, arterioles emerge perpendicular to the skin surface and enter the second compartment, the subpapillary vascular plexus, through the stratum reticulare of the dermis. This is where the capillaries of the epidermal papillae originate. This subepidermal plexus is the actual correlate of the nutritive microcirculation, it represents the supply network of the epidermis (nutritive capillary network). Numerous invaginations in the epidermis create a large contact and exchange area.

The skin's constant need to adapt to external and internal influences, such as thermoregulation in response to external temperature, requires complex regulatory mechanisms within the skin's vascular system. Just as complex as the functionality of the system are the malfunctions that can occur.

Pathological changes in the microcirculation can be divided into four major subcategories: Changes in blood rheology, changes in vessel wall permeability, changes in intravascular and interstitial pressures, and changes in the regulation of vascular tone.[1]

Microcirculation disorders occur in the context of many diseases, especially in vascular diseases, but also in metabolic diseases such as diabetes mellitus, arterial hypertension, and many autoimmune diseases, with

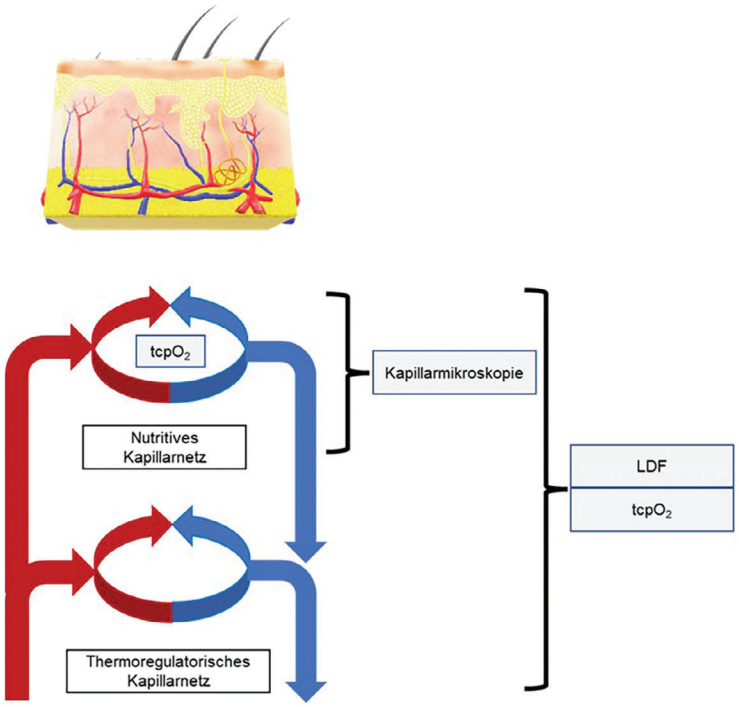

FIGURE 1 Schematic illustration of skin microcirculation. In addition, the examination techniques are shown with the corresponding target structures.

systemic sclerosis being particularly noteworthy in this category.

PHYSIOLOGY, PATHOPHYSIOLOGY, AND PATHOGENESIS OF MICROCIRCULATORY DISORDERS

Blood rich in nutrients and oxygen enters the capillary network of papillae in the stratum papillare of the dermis through the arterioles, which originate from the arteries of the subcutis. From the arterioles, the blood passes through the main channels to the precapillary sphincters. The capillaries themselves lack a vasomotor system and instead rely on pressure from precapillary vessels (arterioles, sphincters), postcapillary venules, and arteriovenous anastomoses.[2] Blood flow in the capillary bed is influenced by the secretory highly active endothelium and the extracellular matrix (Figure 1).[1]

In the area of the capillary walls, fluid exchange, including nutrients and metabolic products, takes place by filtration, adsorption, and diffusion. According to the Frank-Starling equation, maintaining nutritive metabolism and physiological fluid content in the tissues requires a filtration pressure in the arterial system that corresponds to the resorption pressure in the venous vascular limb. Diffusion processes along the basement membrane zones transpire through a combination of active mechanisms, which involve the endothelial cells of blood vessels, and passive processes driven by concentration gradients as described by Fick's principle. For the reabsorption of fluid from tissue, the lymphatic capillaries, not the venous capillaries, are responsible. In addition to parameters that depend on vessel walls and pressure ratios, the actual rheological properties of the blood are critical to skin microcirculation. The viscosity of blood depends on the properties of the blood and the vessel walls: In addition to the size and deformability of the erythrocytes (internal viscosity), the geometry and adhesive properties of the vessel wall play a role. It is also influenced by the aggregation of erythrocytes, viscosity of plasma, and the "tank treading motion" of red blood cells. Tank treading motion describes the interaction of deformable particles in viscous fluids, in particular the motion of erythrocytes in shear flows. The flow of blood, a complex fluid with nearly 50% of its volume occupied by erythrocytes, is strongly dependent on the different morphologies of these erythrocytes in the surrounding plasma. Erythrocytes have traditionally been considered as viscoelastic capsules composed of a lipid membrane containing an incompressible Newtonian fluid. At equilibrium, erythrocytes have a biconcave shape, resulting in a surface area that is 40% larger than necessary for their volume. This distinctive morphology allows them to bend and fold while maintaining a constant surface area.

In non-equilibrium situations, such as those that occur under shear flow conditions, erythrocytes can tumble, roll, and take on different shapes, such as expanding into an ellipsoid. Under such conditions, the cell membrane can perform a relative movement around the static cytoplasm, similar to a tank chain running around a wheel. This is why this phenomenon is also called *tank tread-like motion*.[3,4]

A low viscosity plasma layer flows directly along the endothelium, keeping corpuscular components away from the vessel walls and positioning them in the center of the flow path, which results in a low frictional resistance.[2] Viscosity physiologically decreases with decreasing ves-

sel diameter and is lowest in the microvascular pathways because the capillary hematocrit is significantly lower than the large vessel hematocrit.[5,6]

Skin blood flow ranges from 1 to 150 ml/100 ml tissue/min.[2] An important function is thermoregulation, and about 15% of blood flow is required for tissue nutrition. From a functional perspective, vasoconstriction and vasodilation are the primary mechanisms that enable adaptation.

Skin blood flow is highly variable and plays an important role in thermoregulation and tissue nutrition. Vasoconstriction and vasodilation are the main adaptive mechanisms.

Neurological functions, controlled by oxygen and carbon dioxide saturation, cardiovascular receptors and the autonomic nervous system intervene in this interplay via alpha and beta receptors in the vessel walls, with the adrenergic system classically responsible for vasoconstriction and the cholinergic system for vasodilation. Skin vessels have predominantly alpha receptors.[1,2] The musculature of the precapillary and sphincter vessels is independent of the autonomic nervous system; here, central blood pressure and metabolic products control the contractile elements. The musculature of the precapillary and sphincter vessels operates independently of the autonomic nervous system. In these vessels, the contractile elements are controlled by central blood pressure and metabolic products.[2] Various mediators such as catecholamines, histamine and the angiotensin-bradykinin system act on the vascular wall. Vascular tone is also regulated in the venous system by alpha and beta receptors. Unlike arterial vessels, venous vessels react to even small differences in pressure with a change in volume. The endothelium responds to metabolites, hormones, and physical stimuli by releasing locally active mediators. Thus, an increase in blood flow velocity with an increase in shear forces leads to the release of endothelium-derived relaxing factor (EDRF), leading to vasodilation.[1,2]

The heterogeneity of morphological (diameter, vessel length) and rheological-functional parameters (flow velocity, intravascular pressure) in the terminal vascular bed of the different extremities is important for the observation of pathophysiological conditions.[1] In the acral skin, vasodilation primarily results from a decrease in sympathetic-adrenergic vascular wall tone, with additional active vasodilation occurring via the cholinergic system in more proximal areas.[2]

The viscosity of the blood is largely determined by the hematocrit; the corpuscular components increase quantitatively in myeloproliferative diseases (polycythemia vera), among others. In certain hematologic diseases, such as multiple myeloma, circulating paraproteins can result in an increase in plasma viscosity. An increase in blood viscosity alters the blood flow properties, and there is a slowing of blood flow in the terminal vascular bed. Especially in vessels with physiologically low flow velocities, reversible erythrocyte aggregation and stasis occur.[1,6] Inflammatory processes also lead to an increase in viscosity mediated by proteins (fibrinogen, immunoglobulins). Changes in vascular wall permeability are typically of an inflammatory origin. This can manifest in inflammatory skin diseases such as cutaneous vasculitides. Secondary effects of previous thermal, mechanical, or other physical and chemical stimuli to the tissue can also lead to inflammation. These stimuli cause the release of vasoactive mediators such as histamine, prostaglandins, and cyclins, leading to vasodilation and increased permeability. In this process, fluid and plasma proteins leak into the tissue. Classic disease entities include systemic sclerosis and the vasculopathies associated with diabetes mellitus. Diabetes mellitus also leads to an increase in intravascular pressure within the capillary network, and this change can lead to leakage of blood components into the interstitium due to increased permeability of the vessel walls. Another typical disease of this group is chronic venous insufficiency, in which the capillary pressure is increased due to a flow disorder in the venous vascular limb. Another typical condition within this group is chronic venous insufficiency, which is characterized by increased capillary pressure due to venous outflow obstruction.[1]

Disorders of vascular muscle tone may have multifactorial causes, including nervous, humoral, local metabolic, myogenic, and endothelial factors. The secretory function of the endothelium seems to play a central role. For example, in patients with diabetes mellitus, the production of prostaglandin E2 and EDRF is reduced, which is associated with a pathological increase in vascular tone.[1]

DIAGNOSTIC METHODS FOR THE ASSESSMENT OF CUTANEOUS MICROCIRCULATION

In diagnosing microcirculatory disorders, a clear distinction must be made between invasive and noninvasive techniques. The assessment of skin blood flow is easily accessible through noninvasive optical methods. The conjunctival and nailfold capillaries are particularly valuable for evaluating the capillary layer because these vessels run parallel to the skin's surface, as opposed to the vertical orientation found in the rest of the integument.

The assessment of skin perfusion using non-invasive optical methods is especially effective with the capillaries of the conjunctiva and the nailfold because the vessels run parallel to the surface.

All of the listed techniques can be applied to other areas of the skin.

Noninvasive Diagnostics

Capillary microscopy is the standard for noninvasive routine diagnostics, while dermatoscopy has gained significance in recent years,particularly in the initial and follow-up diagnostics of patients with systemic sclerosis. In both

TABLE 1 Relevant parameters/patterns of capillary microscopy findings: normal findings, non-specific abnormal findings, and abnormal findings associated with systemic sclerosis (scleroderma pattern; EULAR Study Group: Microcirculation in Rheumatological Diseases, standardized capillary microscopy reporting).[38] It is important to note that in the "non-specific abnormal findings" category, abnormal parameters should not occur simultaneously or serially.

Relevant parameters capillary microscopy	Normal findings	Unspecific abnormal finding (each parameter separately, no combination concurrently and serially)	Specific abnormal finding systemic sclerosis: findings combined concurrently or serially = early, active, and late pattern.
Density (capillary number/mm)	≥ 7/mm	< 7/mm	Early: ≥ 7/mm Active: 3–6/mm Late: < 3/mm
Diameter of the capillary loop in the tip in μm	20–50 μm	20–50 μm	Early: > 50 μm, giant capillaries Active: > 50 μm, giant capillaries Late: none
Capillary morphology	Hairpin pattern Crossed capillary loops Torqued capillary loops Each with convex tip	All other formations Non-convex tip	Early: normal formations Active: abnormal formations + Late: abnormal formations ++
Hemorrhages	–	+	Early: +/– Active: +/– Late: –

techniques, capillaries are functionally magnified, typically by a factor of 200 in capillary microscopy and by a factor of 10 to 15 in dermatoscopy. Dermatoscopy allows the secure recording of still images, while with a capillary microscope, dynamic video recording is also possible. Dermatoscopy is highly suitable for routine diagnostic screening; USB capillary microscopes offer similar applications. Nailfold capillary microscopy is currently one of the most standardized methods for the diagnosis of collagenoses. Established scoring systems not only assist in the diagnosis of these conditions, but also help to determine the severity of the disease.

Capillary microscopy, especially of the nailfold

Capillary microscopy enables morphologic evaluation of the subpapillary capillary plexus, which plays a critical role in nutrient supply. In addition, capillary video microscopy can be used for functional evaluation of capillaries. To evaluate the microcirculation, it is common to correlate these findings with laser Doppler flowmetry.

On both hands, fingers 2 to 5 are examined, with nailfold density decreasing from the second to the fifth finger, making fingers 4 and 5 the best for evaluation. Four 1 mm thick sections should be evaluated on each of the four fingers. A room temperature of 20–23 °C and a well acclimatized patient are important. For the actual examination, an immersion oil is needed to overcome the space between the objective lens and the skin and make the capillaries visible.[8,9]

The following factors are included in the actual findings: capillary density (number of capillaries), capillary morphology (structure of the capillary loop, assessment of the inflowing and outflowing limbs), capillary diameter (measured at the apex), and extracapillary changes (hemorrhages, edema, pigmentation) (Table 1).[8–10]

A physiologically configured capillary has a hairpin shape and is convex at the tip; tortuous and crossed variants are possible and represent normal shapes (Figure 2a, b). All other formations and figures are considered abnormal, but not necessarily clinically relevant (Figure 3a). Only in combination with other pathological parameters, such as an increase in capillary diameter > 50 μm and/or a decrease in capillary number, can an abnormal capillary formation become a structure that can be classified as pathological (Table 1, Figure 2a, b).[8–10]

There are 1–3 capillary loops per dermal papilla.[1] A capillary density of > 7/mm in the nailfold area of the fingers is considered physiologic.[11] A capillary diameter of > 50 μm is considered pathological, and such vessels are referred to as megacapillaries (Figure 3c).[8]

1–3 capillary loops per dermal papilla can be detected by capillary microscopy. The density of capillaries in the nailfold area of the fingers should be > 7/mm, and their regular diameter should be < 50 μm.

Extracapillary changes should only be evaluated in conjunction with the other parameters mentioned. For example, hemorrhages alone have limited clinical significance, but when observed together with megacapillaries, they have a high early diagnostic value for systemic sclerosis. The hemorrhage itself is an expression of increased vascular permeability or endothelial damage. Initially, a diffuse, cloud-like hemorrhage appears within the precapillary edema; later, dome-shaped, consolidated hemorrhages appear over the capillaries (Figure 3b, d).

Several scores have been established for diagnostic purposes. The *Microangiopathy Evolution Score* for systemic sclerosis, defined by the *European League Against Rheumatism* (EULAR) and the *American College of Rheumatology*

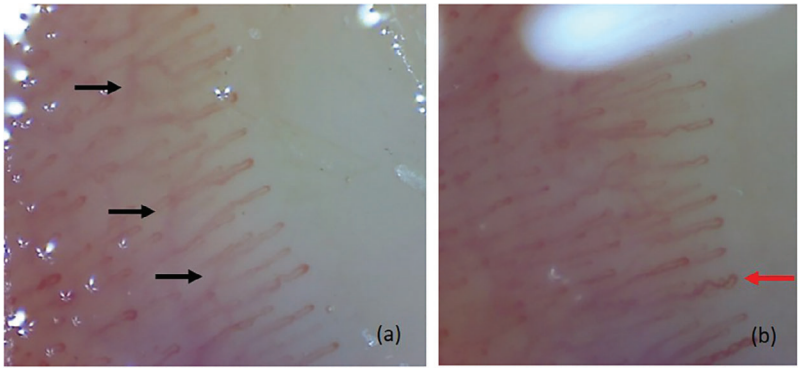

FIGURE 2 (a) In the capillary microscope image of a physiologically structured nailfold capillary system, the capillaries of the nutritive vascular plexus become visible and the capillaries of the deeper thermoregulatory plexus (black arrow) shine through. (b) The capillary loops are recognizable, with a diameter of between 20–50 μm at the apex. The capillary loops show predominantly hairpin formations, occasional torqued (red arrow) and crossing courses. The apex of the capillary loops has an inconspicuous convex configuration. The capillary density is > 7/mm, the capillaries are symmetrically distributed.

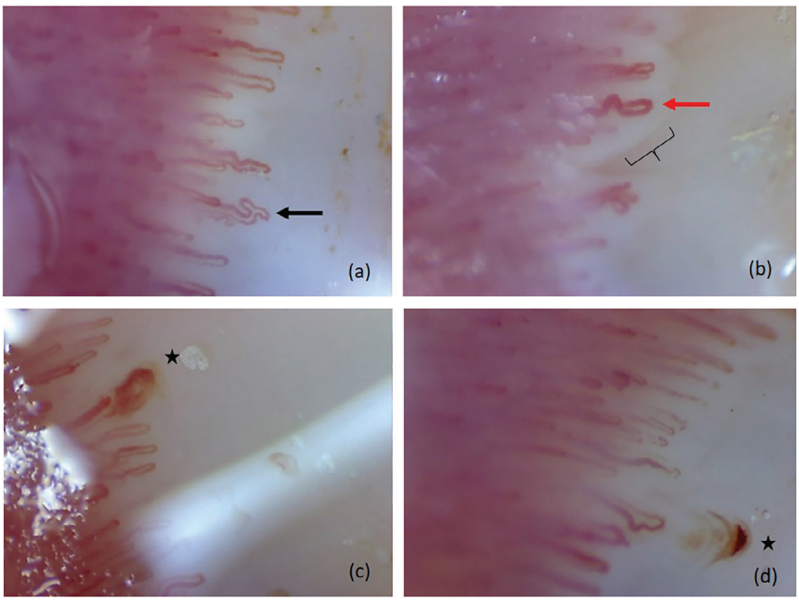

FIGURE 3 (a) Capillary microscope image of an abnormally constructed capillary with a non-convex tip (black arrow). (b) Ectatic capillary (red arrow) (a giant capillary is present if the diameter of the tip or limb is > 50 μm) with visible pericapillary oedema (bracket). (c) Fresh pericapillary hemorrhage, cloudy leakage into the interstitium (asterisk). (d) Visible dome-shaped older hemorrhages (asterisk) above a pathological capillary loop as indirect evidence of an increase in permeability of the vessel with exudate leakage into pericapillary tissue (as a result of an intracapillary pressure increase or in the course of inflammatory changes, for example) and final destruction of the papillary tip (rejection). All four images together form the so-called "scleroderma pattern", the typical capillary microscopy image for systemic sclerosis.

(ACR), grades changes in capillary morphology and density as 0 (no change), 1 (< 33%), 2 (33%–66%), and 3 (> 66%). Each finger is scored individually, and an overall score is calculated.[9–13] In systemic sclerosis, the classification into "early", "active", and "late" in terms of visible changes is widely used (Table 1).[13,14] In some diseases, some of the above parameters are used for prognostic assessment, e.g., capillary density in systemic sclerosis.[10–16]

Capillary videomicroscopy can be used to assess additional dynamic parameters such as blood flow and velocity. Blood flow can be assessed from 100x magnification provides insights into functionality. Parenterally applied dyes, such as sodium fluorescein (NaF), provide information about capillary inflow and blood distribution (microvascular flow distribution). Inhomogeneous distribution patterns may indicate rheologic dysfunction and vasospasm. The absence of dye perfusion is indicative of microthrombosis.[1,17] While NaF diffuses rapidly into the interstitial space, allowing conclusions about the interstitium around capillaries and fluid flow, the dye indocyanine green remains strictly intravascular due to its 95% binding to plasma proteins. This provides valuable information about the capillary diameter and the plasma space between the erythrocyte column and the capillary wall. Bollinger et al. demonstrated approximately twice as many microaneurysms at or near the tip of capillary loops in patients with systemic sclerosis using indocyanine green videomicroscopy compared to conventional capillary microscopy.[18]

Capillary microscopy is possible on the entire integument and shows different changes and patterns that vary depending on the disease's underlying pathogenesis.

Vascular dermatoscopy

Nailfold capillary microscopy is currently the gold standard in the morphologic diagnosis of microcirculatory disorders. Alternatively, the examination can be performed with a dermatoscope, which is widely accessible, inexpensive, and easy to learn.

Nailfold capillary microscopy is the gold standard in the morphological diagnosis of microcirculatory disorders. Alternatively, an initial assessment can be conducted using a dermatoscope.

FIGURE 4 Dermatoscope with digital recording option via mobile phone.

FIGURE 5 USB capillary microscope.

This type of examination can be performed at the patient's bedside, irrespective of the location, can be repeated as needed, and provides at least an orienting overview. Dermatoscopes offer magnification of up to 20x and are often equipped with a dual light system with six polarized and six white LEDs. Before nailfold dermatoscopy, the patient should rest for 15 minutes at room temperature. In contact dermatoscopy, the dermatoscope with polarized light is placed on the skin without pressure after applying a gel, immersion oil or disinfectant fluid. In several studies, the results of the examination of eight fingers were compared with the results of capillary microscopy.[19,20] Cell phones can be used for photo documentation with the help of adapters (Figure 4). The widely available USB capillary microscopes are similarly convenient (Figure 5). However, magnification and image quality are limited.

Transcutaneous oxygen partial pressure measurement (tcpO2)

This examination technique also represents a functional measurement. It allows statements to be made about nutritive microcirculation performance.

During the actual measurement, the core of an electrode placed on the skin is heated to 43 °C, which causes dilation of the capillaries in that area of the skin, resulting in local hyperemia. The tcpO2 measurement obtained via the probe indicates the amount of oxygen supplied to the tissue, which depends on local diffusion processes, oxygen consumption, cardiopulmonary state, and microcirculation.[20,21]

Laser Doppler fluxmetry (LDF)

This method represents another noninvasive examination of the skin microcirculation, mainly showing the blood flow of the thermoregulatory subpapillary vascular plexus. The principle is based on the Doppler shift of laser light from a helium-neon laser as it moves through tissue and reflects off moving objects such as circulating red blood cells. The actual LDF signal is a stochastic representation of the number of erythrocytes in the tissue section under study multiplied by their velocity, the flux. Red blood cell flow correlates linearly with blood flow through the skin and can therefore be used to estimate blood flow.

The laser Doppler flux signal (LDF) provides information about the number of erythrocytes in the examined tissue section and their velocity. This correlates with the blood flow in the skin.

Of importance is that the laser light penetrates to a skin depth of 1–6 mm, allowing it to capture not only the blood flow of the upper nutritive capillary plexus (approximately 15%) but also, more significantly, that of the thermoregulatory plexus (85%). This enables the assessment of blood flow at this level. The derived signal contains information about capillaries, arteriovenous anastomoses, arterioles, and venules. With this diagnostic method, flow can be visualized both at rest and during various provocative maneuvers such as venous and arterial occlusion. This allows for insights into the venoarteriolar reflex during stress and cutaneous vascular reserve under arterial inflow obstruction.[20–23]

In the visual representation, a curve for the skin under examination, typically pathologically altered skin (ulcer edge), is compared with a curve from a healthy skin area. This allows for a comparison between diseased and healthy skin, providing insights into the perfusion of the skin in the affected area.

Invasive Diagnosis of Microcirculation

In invasive microcirculation diagnostics, intracapillary pressure measurements are performed. Under the video capillary microscope, the nailfold capillaries are cannulated with glass capillaries in the apex area guided by a micromanipulator.[16] Capillary pressure can be measured at rest and during various maneuvers to provide information on capillary pressure and flow disorders in the nutritive microcirculation of the skin in different diseases.[16]

FUNCTIONAL CIRCULATORY DISORDER

Raynaud's phenomenon (RP) is an episodic vasospasm typically characterized by digital vasospasm occurring after exposure to cold and/or emotional stressors. The prevalence of Raynaud's syndrome in the general population is estimated to be about 5%, and it is higher in colder climates, and more common in women (Garner et al., 2015). The majority of patients (80%–90%) suffer from primary (idiopathic) Raynaud's phenomenon. An underlying pathology cannot be identified. Secondary Raynaud's phenomenon, called Raynaud's syndrome, occurs in a variety of diseases (rheumatologic, hematologic, endocrinologic and vascular pathologies, trauma) and may also be triggered by drugs. Symptoms of Raynaud's phenomenon typically manifest in the first half of life. If the symptoms occur later in life, it is more likely to be secondary Raynaud's syndrome.

Primary RP likely involves several different entities, including a functional vasospastic disorder, a physiologically inadequate thermoregulatory response, subclinical atherosclerosis, and a "cold intolerance".[24–26]

Raynaud's phenomenon is caused by deregulated stenosis of the precapillary arterioles, resulting in skin discoloration, swelling, and paresthesias. Fingers and toes are most commonly affected, but the nose, ears, and mammillae may also be affected.

Raynaud's phenomenon is caused by dysregulation of the precapillary arterioles. There is skin discoloration, swelling, and paresthesias, especially in the fingers and toes.

Clinically, there is a serial sequence of a triad, beginning with pallor of the skin due to vasospasm associated with decreased motility and sensitivity, followed by cyanosis due to tissue hypoxia and subsequent redness in the setting of reactive hyperemia. Symmetric involvement is typical but not obligatory. The thumbs are typically not involved, nor are the dorsum and palms (Figures 6a, b, 7).

The clinical presentation can be highly variable, ranging from benign vasospasm to progressive obliterative microangiopathy of systemic sclerosis with severe digital ischemia, digital necrosis, and ulceration.[26]

The appearance of pathologic patterns on capillary microscopy of the nailfold is critical in distinguishing primary from secondary Raynaud's phenomenon.

An unremarkable capillary morphology with regular capillary density supports the diagnosis of primary Raynaud's phenomenon. In contrast, an abnormal morphological pattern is pathognomonic for secondary Raynaud's phenomenon associated with systemic sclerosis or mixed collagenosis. The scleroderma pattern on capillary microscopy is the most sensitive marker for the presence or development of systemic sclerosis.[15,16,27]

Increased vascular tone, including episodic vasospasm, in digital arteries is crucial in Raynaud's phenomenon. In systemic sclerosis, endothelial dysfunction is associated with overproduction of vasoconstrictors (e.g., endothelin-1 and angiotensin II) and impaired vasodilation with decreased production or efficacy of vasodilators (e.g., nitric oxide and prostacyclin).[17] In primary Raynaud's phenomenon, a vascular dysfunction related to thermoregulation is assumed. Cold stimuli cause a translocation of alpha-2c-adrenergic receptors from the Golgi apparatus to the cell surface through activation of Rho kinase, increasing the sensitivity of contractile proteins and subsequent vasoconstriction. In Raynaud's phenomenon, increased expression of alpha-2c adrenoceptors in vascular smooth muscle cells has been demonstrated.[24–26] Vasoconstriction affects arteriovenous anastomoses and blood flow within the vessels themselves, which is exacerbated in patients with systemic sclerosis due to preexisting vascular damage and occlusion.[24–26] Intravascular factors, such as increased viscosity in hemodynamic disorders, also play a role in the pathogenesis of Raynaud's phenomenon. Platelet and leukocyte activation, structural deformation of erythrocytes, and impaired fibrinolysis are also among the driving mechanisms.

Unlike other regional circuits, which are supplied by both vasoconstrictor and vasodilator sympathetic fibers, the cutaneous vessels of the hands and feet are innervated exclusively by vasoconstrictor sympathetic fibers. Vasodilation is achieved by reducing the trigger for vasoconstriction. The balance between arterial wall tension (which favors closure of the vessel) and intravascular distending pressure (which favors opening of the vessel) is important in maintaining the patency of a blood vessel. Individuals with Raynaud's syndrome have lower brachial and digital artery pressures compared to control subjects.[24–26]

The diagnosis of Raynaud's syndrome is primarily based on a thorough history and physical examination. The classic Allen and Brown criteria for the diagnosis of primary Raynaud's phenomenon include: *(1)* episodes triggered by cold or other provoking factors (e.g., emotions), *(2)* bilateral involvement of the extremities, *(3)* absence of necrosis or limitation to the skin of the fingertips, *(4)* no evidence of underlying comorbidities, and *(5)* presence of symptoms for at least two years. The diagnosis of primary Raynaud's syndrome is supported by the patient's age at first manifestation (usually before the fourth decade of life), unremarkable capillary microscopic findings, and the absence of evidence of secondary causes, and *vice versa*. Additionally, assessing digital pressure values, pulse vol-

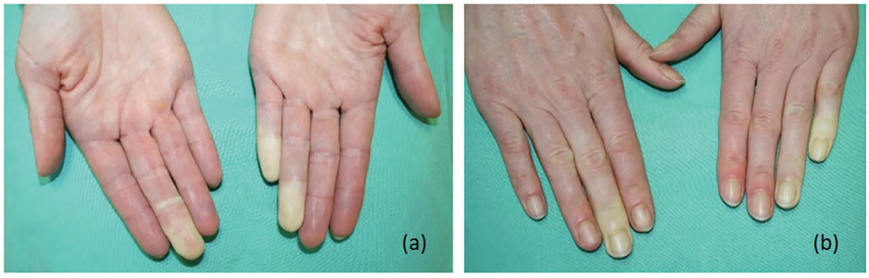

FIGURE 6 (a, b) The typical clinical finding of Raynaud's phenomenon is visible pallor of individual finger segments. The thumbs, palms, and backs of the hands are usually unaffected.

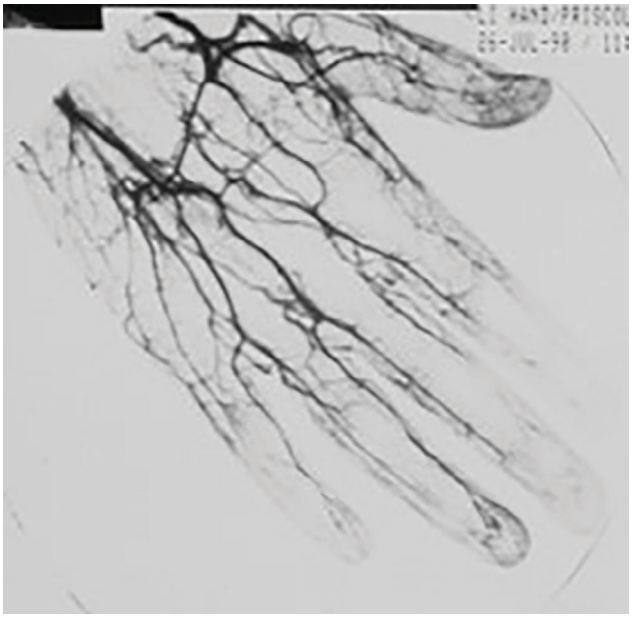

FIGURE 7 In the arteriography of the right hand shown, there is a cessation of contrast inflow in the digitus manus I and II with an existing vasospasm in the context of a Raynaud's phenomenon (Figure taken from a presentation by Jünger et al. 1995).

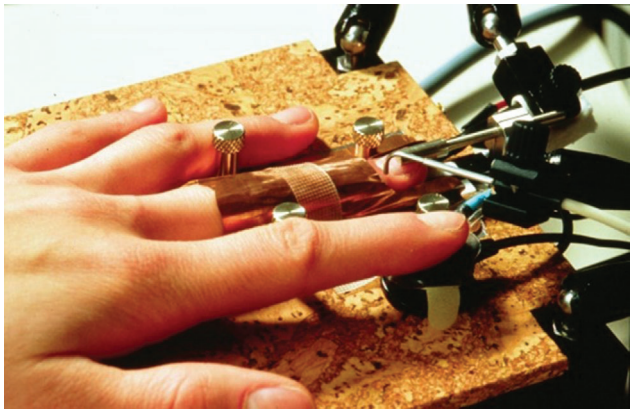

FIGURE 8 Cold provocation test in patients with Raynaud's phenomenon. The finger to be examined is fixed in a finger holding device under the microscope while the nailfold is selectively cooled with a thermoelectric Peltier element.

ume curves, or laser Doppler flow studies with exposure to cold and/or rewarming can be helpful (Figure 8). In primary Raynaud phenomenon, digital pressures and laser Doppler flow decrease with cold exposure and normalize with warming. In secondary Raynaud's syndrome, the flow rate is already reduced at rest at room temperature; after exposure to cold, the baseline value is not reached or is reached with delay.[28]

Laser Doppler flowmetry is a valuable noninvasive method for evaluating early skin venoarteriolar dysfunction, focal autonomic dysregulation, and skin vasomotor abnormalities in patients with Raynaud's phenomenon. Several studies have demonstrated that initial mean skin temperatures and blood flow rates are significantly lower in the Raynaud's groups compared to healthy controls. The venoarteriolar indices differ between the groups with secondary Raynaud's phenomenon and the healthy control subjects, as well as between the groups with secondary and primary Raynaud's phenomenon. The venoarteriolar indices differ between the secondary Raynaud's phenomenon groups and the healthy controls, as well as between the secondary and primary Raynaud's phenomenon groups. The higher prevalence of impaired venoarteriolar reflex in patients with secondary Raynaud's phenomenon demonstrated in the studies is evidence of local vasomotor dysfunction and reflects either postganglionic sympathetic insufficiency with loss of vascular tone or altered smooth muscle cell response.[24–26]

DISEASES WITH MICROCIRCULATION DISORDERS OF THE SKIN

Microcirculatory disorders in connective tissue diseases

Vascular alterations characterized by functional and structural microcirculatory abnormalities play an important role in the pathogenesis of connective tissue diseases. Morphological and functional analyses of the microcirculation are objective criteria used for diagnosing and classifying connective tissue diseases when clinical signs of microcirculatory disorders, such as Raynaud's phenomenon, are present. Microangiopathies are present in 82% of systemic

sclerosis patients, 54% of mixed connective tissue disease patients, and only 2% of lupus erythematosus patients.

Microangiopathies are most common in systemic sclerosis, frequent in mixed connective tissue disease, and rare in lupus erythematosus.

Nailfold capillary microscopy is used for early diagnosis, but also for monitoring disease progression, for example in patients with dermatomyositis.

Systemic Sclerosis

Systemic sclerosis (SSc) is probably the disease most commonly associated with skin microcirculatory dysfunction. It is a systemic autoimmune disease characterized by a triad of vasculopathy, autoimmunity, and progressive fibrosis. The vascular involvement includes macrovascular and microvascular disease. Macrovascular disease is a relatively rare manifestation of SSc. In contrast, microvascular disease is responsible for the initial clinical manifestations of SSc (e.g., Raynaud's phenomenon and nailfold capillary changes) and plays a crucial role in the development of disseminated telangiectasias, digital ulcers, pulmonary arterial hypertension (PAH), renal involvement, gastrointestinal complications, and even coronary microvascular changes.[29,30]

The microvascular component is characterized by vasculopathy with vasospasm, thrombophilia with thromboembolic events and fibrin deposition, as well as impaired angiogenesis.

In systemic sclerosis, vasculopathy is manifested by vasospasm, thrombophilia, fibrin deposition, and impaired angiogenesis.

At the onset of the disease, endothelial cell damage is observed that can be attributed to factors such as autoantibodies, infections (e.g., cytomegalovirus [CMV]), cytotoxic T cells, and the presence of reactive oxygen species. Autoantibodies associated with these injuries include anti-endothelial cell antibodies (AECA), anti-angiotensin II receptor antibodies (ATRA), and anti-endothelin type A receptor antibodies (ETRA). Anti-endothelial cell antibodies are detectable in 28%–85% of patients with SSc and, after binding, lead to apoptosis of endothelial cells and subsequent secretion of chemotactic mediators. Clinically, AECA are associated with nailfold capillary abnormalities, digital infarcts, and PAH.[29,30] ATRA and ETRA cause vasoconstriction via corresponding receptors on endothelial cells and induce obliterative vasculopathy.[29,30]

Endothelial cells maintain the physiological vascular tone by reciprocally releasing nitric oxide (NO) and endothelin-1 (ET-1). Nitric oxide is a potent vasodilator that inhibits platelet aggregation, smooth muscle cell proliferation, and cytokine-induced endothelial activation. Endothelin-1 is a vasoconstrictor that induces smooth muscle cell proliferation, fibrosis, and inflammation. In systemic sclerosis, microvascular endothelial cells exhibit decreased expression of endothelial NO synthase, resulting in decreased production of nitric oxide and increased production of ET-1, leading to a vasoconstrictive state.[29,30]

The presence of an additional procoagulant state contributes to the vascular abnormalities observed in SSc. This condition results from an imbalance between coagulation and fibrinolysis, increased platelet activation, and pro-atherogenic oxidized low-density lipoprotein (LDL) levels. Patients with systemic sclerosis have elevated levels of von Willebrand factor (vWF), fibrinogen, tissue plasminogen activator (tPA), and/or tPA inhibitor, resulting in microvascular thrombosis and fibrin deposition.[29,30]

Chronic tissue hypoxia resulting from microvascular disorder, vasoconstriction, and microthrombosis triggers dysregulated neoangiogenesis. This abnormal vascularization results from dysregulated expression of proangiogenic factors, such as vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF), and fibroblast growth factor-2 (FGF-2), as well as angiostatic factors like endostatin, soluble endoglin, and CXC chemokine ligand (CXCL). Vascular endothelial growth factor is associated with reduced nailfold capillary density and pulmonary hypertension, while endoglin is associated with telangiectasia and digital ulceration.[29,30]

The capillary microscopic pattern of SSc was first described by Maricq et al. in 1980.[15] The morphological vascular changes associated with SSc mainly affect the smaller vessels such as arterioles and capillaries. The clinically visible disseminated telangiectasias on the fingers, toes, face, lips, and oral mucosa are an expression of the existing microangiopathy (Figure 9a–c).

Maricq et al. were the first to introduce a classification system for capillary changes in SSc. Nailfold capillary enlargement and reduction in capillary density are particularly important for diagnosis and assessment of disease progression (Table 1).

Enlarged nailfold capillaries and loss of capillary density play an important role in the diagnosis and assessment of the progression of systemic sclerosis.

Atrophy-blanche foci also occur in the skin (Figure 9d). These are surrounded by branching capillaries and small comma and punctate vessels.

With sodium fluorescein, the changes become even more evident. The typical pericapillary halos manifest as a sign of increased permeability due to endothelial damage, with the halo at the capillary tip being especially prominent, creating the image of a "dwarf hat" (Figure 10a–c).

Histological examination shows intimal hyperplasia of the arterioles and endothelial damage. The basal lamina is thickened and divided into separate layers. There are also thrombosed vessels.[29–31]

The morphological changes of the capillaries in the nail fold are prognostically relevant. They are indirect markers of visceral involvement in the disease. Alternation between complete absence of capillaries and rapid

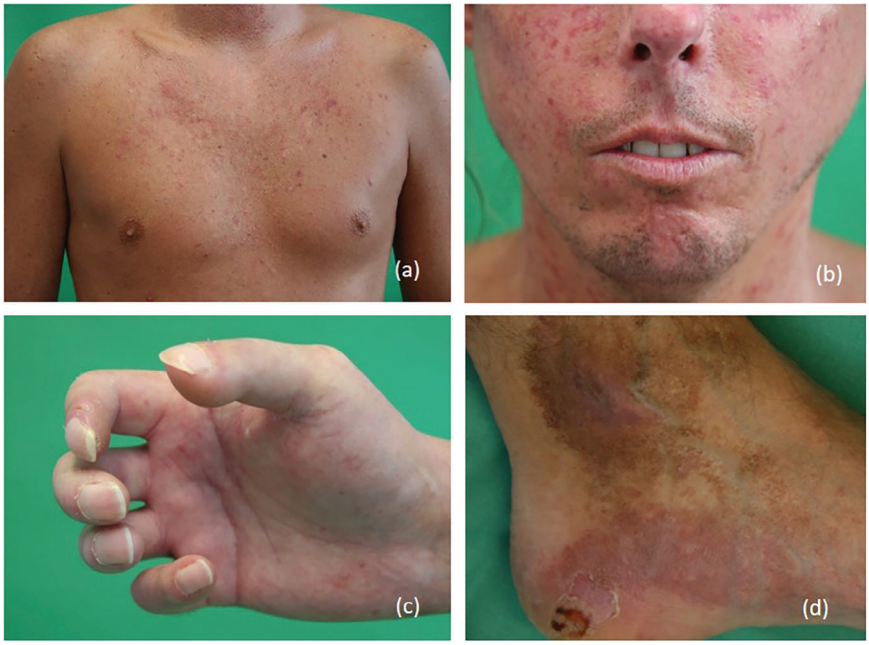

FIGURE 9 (a–c) Several clinical presentations of a patient with systemic sclerosis are shown. There are disseminated telangiectasias all over the skin, including the palms and the face. (d) Foci of atrophy blanche may also appear on the skin.

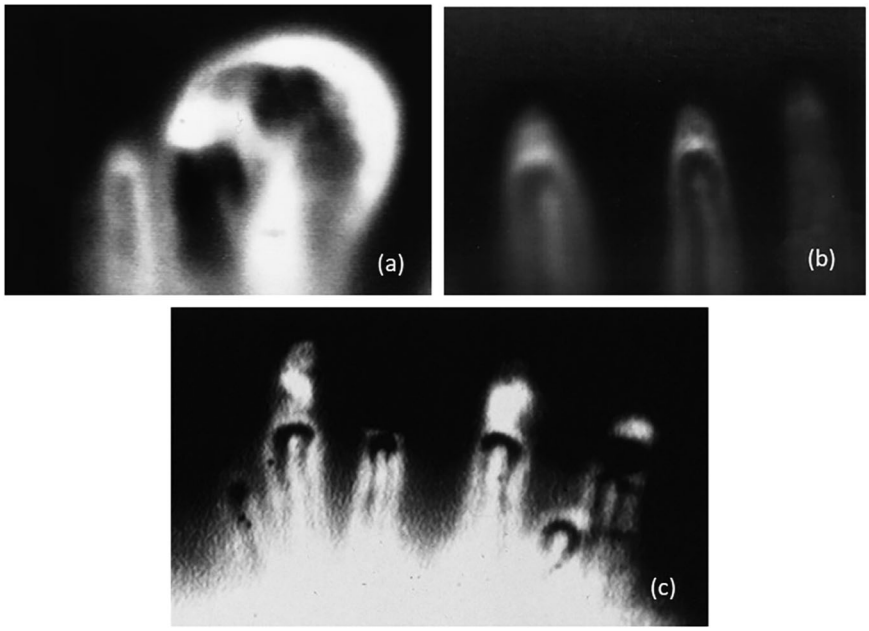

FIGURE 10 Nailfold capillaries: after application of sodium fluorescein, the changes associated with systemic sclerosis are even more evident. (a–c) As a sign of endothelial damage with increased permeability, the dye penetrates into the pericapillary tissue, forming halos, the halo around the capillary tip being particularly pronounced, creating the image of a "dwarf hat".

neovascularisation is associated with a poor prognosis. Capillary telangiectasia and/or giant capillaries and no or little capillary loss are associated with a good prognosis.[29–32,36–38]

The morphological changes of the capillaries in the nail fold are prognostically relevant.

Different patterns are distinguished: The early pattern is characterized by the appearance of a few dilated and/or megacapillaries and a few hemorrhages. The distribution is relatively well preserved with no loss of capillaries. The active pattern shows a large number of megacapillaries and hemorrhages and is accompanied by moderate capillary loss and diffuse pericapillary edema (Figures 3a–d, 11a–f). The late pattern shows severe capillary loss with extensive avascular areas (Figure 12a–f). Bushy and branched capillaries or multiple capillary loops in a dermal papilla are striking morphologic correlates of impaired neoangiogenesis. Clinically, digital necrosis and ulceration, so-called rat-bite necrosis (digital pulp necrosis), now appear as an expression of critical nutritive ischemia (Figure 12a, b). Blood flow in the capillaries is markedly reduced and decreases further with exposure to cold. In some cases, there is a complete cessation of erythrocyte movement.[33–36] This cessation also lasts longer in patients with SSc than in healthy subjects.

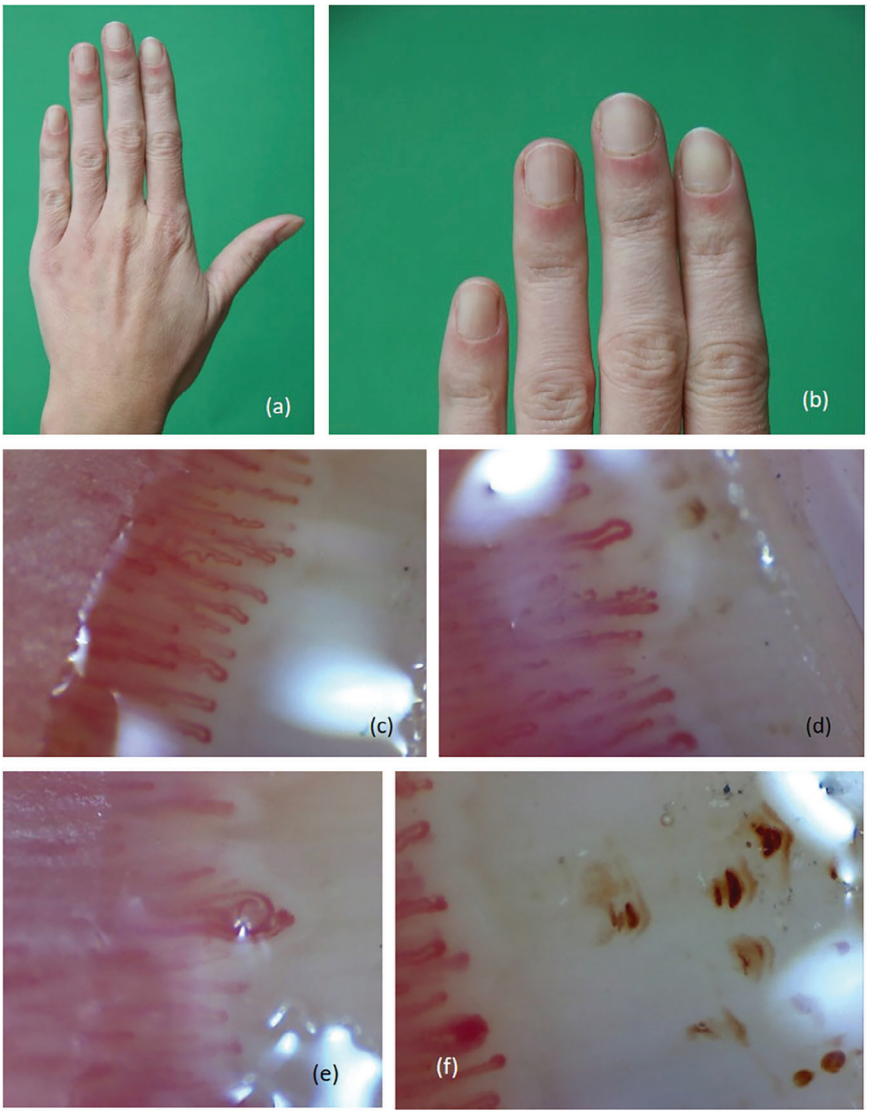

FIGURE 11 Patient with secondary Raynaud's syndrome associated with systemic sclerosis. (a, b) Even without magnification techniques, the nailfold is markedly erythematous, and splinter hemorrhages are visible. (c-f) Capillary microscopy: typical scleroderma pattern, active form. (c) Physiological capillary density with abnormally constructed capillaries with non-convex tips (d, e) and visible ectasia (c, d) and older dome-shaped hemorrhages (f) are visible above the pathological capillary loops as indirect evidence of destruction of the papillary tip (rejection).

This difference in findings is not reflected in LDF measurements because subpapillary perfusion is not initially impaired.[34]

Dermatomyositis

Dermatomyositis is an autoimmune disease of the connective tissue that presents with varied clinical symptoms. Inflammatory changes in both the skin and muscles contribute to the clinical presentation.

Dermatomyositis is an inflammatory condition that affects the skin and muscles and is associated with a variety of corresponding symptoms.

Dermatomyositis has two distinct age-related peaks in its incidence: the juvenile form, which often responds to immunosuppressive therapy, and the adult form, which typically presents around the age of 50. The adult form is often associated with tumor disease and may present as a facultative paraneoplastic syndrome. Females are significantly more affected than males. Classically, lilac erythemas appear on the skin. If they occur periorbitally, they are often accompanied by swelling, resulting in the characteristic depressive facial expression seen in Figure 13a and b. On the body, disseminated and polymorphic efflorescences appear, with lesions prone to ulceration and healing as atrophic scars. In addition, hypo- and hyperpigmentation occur, especially in UV-exposed skin, resulting in a poikilodermic skin pattern (Figure 13c–e). Further diagnostically relevant skin changes are found on the dorsum of the hands and fingers. Initially, lichenoid erythematous papules appear, which later develop into whitish atrophic patches known as Gottron-Heuck patches (Figure 13f–i). Painful erythema, swelling, and telangiectasia (Keining's sign) of the nailfold of the fingers may also be observed (Figure 14a). Dermatomyositis shows a marked disruption of microcirculation with a decreased number and irregular pattern of capillaries, many of which are tortuous, dilated, and branched (Figure 14c–e). Capillaries often show

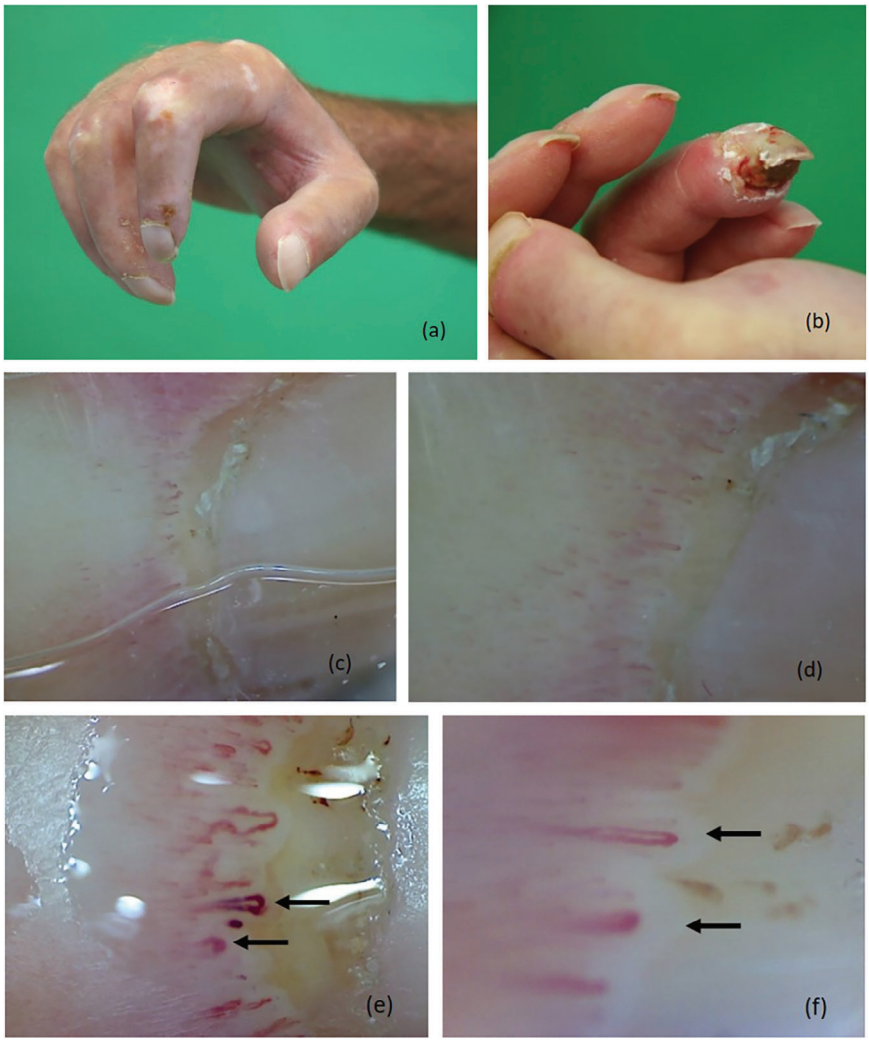

FIGURE 12 (a, b) Clinical picture of a patient with advanced systemic sclerosis with digital necrosis and ulceration. (c, d) Capillary microscopy shows the late pattern with markedly reduced capillary density, (e) single dilated capillaries, (f) single giant capillaries with surrounding marked edema, (e) single thrombosed vessels, and (f) hemorrhages.

decreased blood flow and increased vascular permeability. Capillary loops may be lost. With sodium fluorescein, increased diffusion into the pericapillary tissue is seen as a sign of increased permeability (Figure 15a, b).[39,40] Rheological examinations revealed increased blood viscosity. Elevated fibrinogen levels were measured, which were associated with increased aggregation of erythrocytes and platelets.

Capillary microscopy can be used to monitor the progression of the disease in terms of activity, which is particularly important in the juvenile form.[29]

Lupus erythematodes

Systemic lupus erythematosus (SLE) is another complex, multiorgan autoimmune disease characterized by autoantibody formation, immune complex circulation, and activation of the complement system. Vascular manifestation is considered the most common fatal complication in SLE patients and manifests as vasculopathic and/or vasculitic symptoms.

Vascular manifestations in the form of vasculopathic and/or vasculitic symptoms are the most common fatal complication in SLE patients.

Vascular involvement in SLE can be generalized, affecting all types of blood vessels in the body. Conditions of the medium and large vessels include accelerated atherosclerosis, frequent thromboembolic events often associated with antiphospholipid syndrome, and vasculitides of the visceral, coronary, and cerebral vessels. Clinical manifestations of microvascular involvement may include livedo reticularis, cutaneous vasculitis (Figure 16a–e), lupus nephritis, pulmonary vasculitis, pulmonary arterial hypertension (PAH), and intestinal vasculitis.[38,41]

SLE is characterized by polyclonal activation of B cells and the formation of autoreactive memory B cells that secrete a variety of autoantibodies. These autoantibodies form immune complexes that tend to be deposited in vascular branches and small vessels, leading to vasculitic and non-inflammatory vasculopathic changes and thrombotic microangiopathy.[42,43]

Anti-endothelial cell antibodies are detectable in more than 80% of SLE patients and play an important role

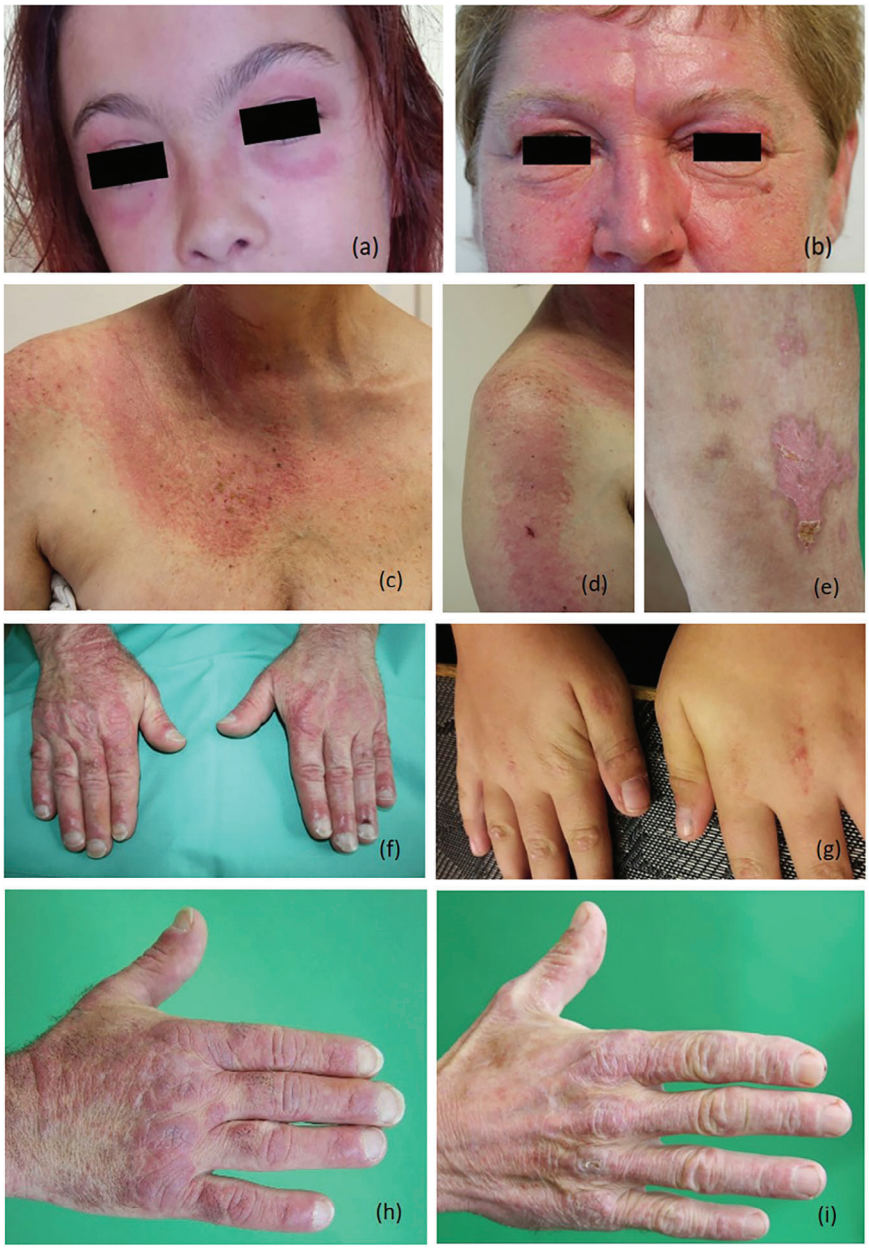

FIGURE 13 Clinical aspects of dermatomyositis. Lilac periorbital erythema (a) in the juvenile form and (b) in a 56-year-old woman. (c–e) Poikilodermic skin with exanthematous findings in addition to erosions and ulcerations that heal with scarring and atrophy. (f, h) On the dorsum of the hands and fingers there are lichenoid papules, which in the adult form are extensive and (g) in the juvenile form are more sporadic and finely erythematous. (i) Over time, the efflorescences heal with atrophic scarring.

in microvascular dysfunction. Anti-endothelial cell antibodies activate endothelial cells with upregulation of leukocyte adhesion molecules (E-selectin [*syn.:* endothelial leukocyte adhesion molecule-1], intercellular adhesion molecule-1 [ICAM-1], vascular cell adhesion molecule-1 [VCAM-1]), secretion of chemokines, and increased recruitment of leukocytes into the vessel wall. Anti-endothelial cell antibodies additionally cause endothelial cell injury through complement- and antibody-mediated cellular cytotoxicity.

However, diagnostic markers of microangiopathy play a minor role in SLE compared to systemic sclerosis. The observed alterations are mainly giant capillaries and rarefaction of vessels in the nailfold (Figure 17a–d).[41] Here, vasculitis is the primary pathomechanism (Figure 18a, b).

However, diagnostic markers of microangiopathy play a minor role in SLE compared to systemic sclerosis.

Antiphospholipid Syndrome

Antiphospholipid syndrome may be primary idiopathic or secondary to lupus erythematosus and pathophysiologically represents a vasculopathy. Besides the macroangiopathy, there is often a microangiopathy affecting the papillary supplying plexus. Similar to systemic sclerosis, disseminated telangiectasias may occur as an expression of this microangiopathy (Figure 19a–c). In addition, acute, clinically highly inflammatory, painful ulcerations frequently appear and heal as porcelain-colored, bizarrely formed

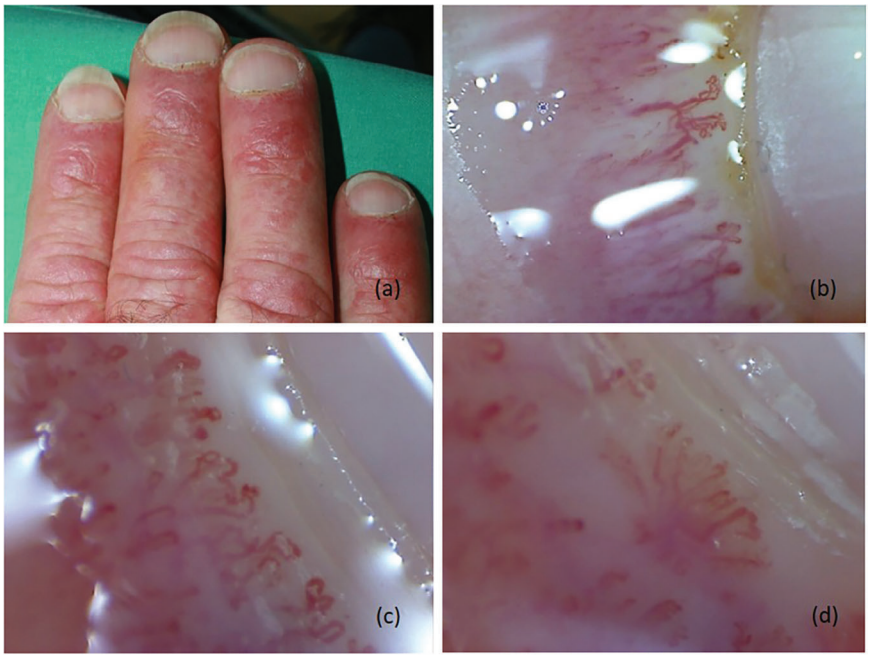

FIGURE 14 (a) Typical clinical aspects of dermatomyositis are inflammatory changes on the dorsum of the fingers with lichenoid papules and a reddened nailfold with visible capillaries. (c) There is a decrease in the number of capillaries and irregular patterns of capillaries form, (b) many are highly tortuous, dilated and branched, (d) show bushy formations.

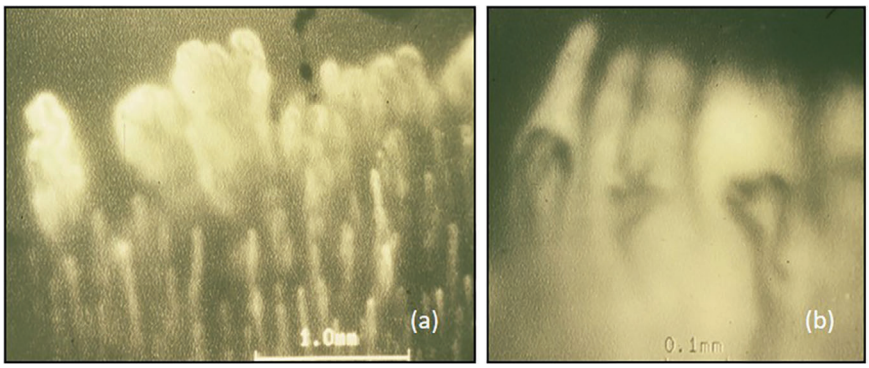

FIGURE 15 (a, b) Dyed with sodium fluorescein, increased diffusion into the pericapillary tissue is also seen in dermatomyositis as a sign of increased permeability (Figures from Patheiger et al. 1988).

atrophy-blanche foci (Figure 19d–g). They are an expression of critical ischemia caused by vascular occlusion in the papillary vascular plexus. The ulcers are surrounded by linear, usually corkscrew-shaped capillaries, a sign of vasculopathy (Figure 20a–d).[44] Antiphospholipid syndrome is associated with thromboembolic events and, in women, with pregnancy complications.

Antiphospholipid syndrome may be primary idiopathic or secondary to lupus erythematosus and pathophysiologically represents a vasculopathy.

Diseases arising from hemodynamic microcirculatory dysfunctions

Understanding the pathomechanism of microcirculatory dysfunction may provide therapeutic targets in various vascular diseases with arterial and/or venous components.[45]

Microcirculatory disorders in chronic venous insufficiency (CVI)

In chronic venous insufficiency, in addition to macroangiopathy, which often manifests clinically as truncal and lateral branch varicosis, the increased pressure within the venous system leads to microangiopathy at the capillary level as the disease progresses. Chronic venous insufficiency is caused by varicosis (primary or secondary) of the epifascial veins and/or insufficiency of the main venous system, e.g. as a result of thrombosis. Impaired valve function and reduced flow resistance lead to chronic venous congestion. Peaks in venous pressure are transmitted directly to the capillary level via the muscle pump. This pressure increase, if sustained, leads to the destruction of the skin's capillary network (Figure 21).[46–49] In addition, microthrombi occur at the capillary level, further exacerbating the microcirculatory disorder.[46] In the end, it must be noted that microcirculation disorders in the context of chronic venous insufficiency (CVI) are multifactorial.

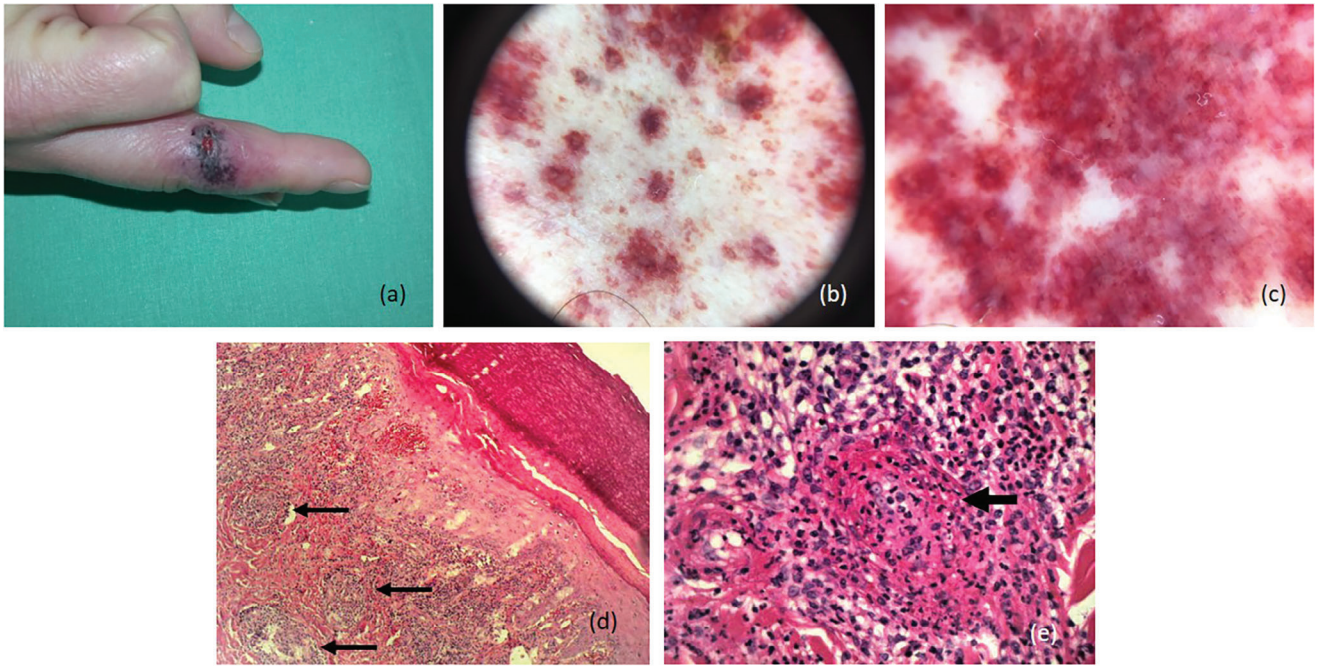

FIGURE 16 (a) Clinically, a patient with systemic lupus erythematosus shows a bullous necrotic vasculitis with central ulceration. (b) Dermatoscopy: Full picture of the cutaneous immune complex vasculitis: Along with the progression of the inflammatory process, the perivascular infiltrate and oedema and the erythrocyte extravasation increase; this corresponds to the clinically existing palpable purpura. (c) Full-blown cutaneous immune complex vasculitis: in the efflorescences, centrally located prominent vessels become visible as dots and globules with a surrounding hemorrhagic-purpuric blurred background (= typical of a vasculitic event). The background correlates clinically with the livid-erythematous undertone and corresponds histologically to the erythrocyte extravasations. (d) Histological complete picture of a cutaneous leukocytoclastic vasculitis with ectasized wall-thickened vessels (black arrow) in the papillary plexus with surrounding granulocytic-lymphocytic infiltrates (hematoxylin-eosin stain [HE]) (e) Histological full thickness cutaneous leukocytoclastic vasculitis with wall thickened thrombosed vessel (black arrow) in papillary plexus with surrounding granulocytic lymphocytic infiltrates (HE).

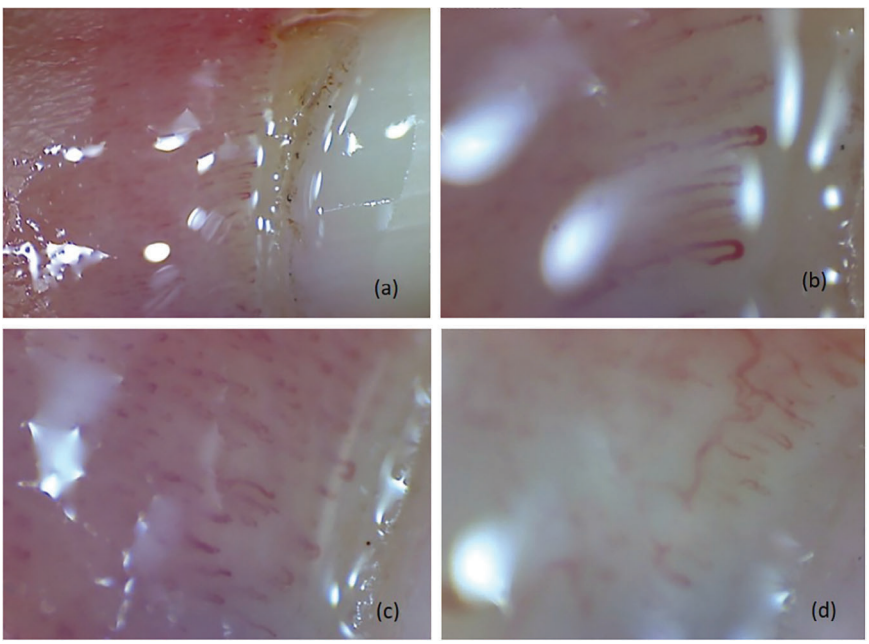

FIGURE 17 (a, c, d) Systemic lupus erythematosus shows rather unspecific changes in the area of the nailfold. There is a rarefaction of the capillary density and (b) giant capillaries sometimes occur.

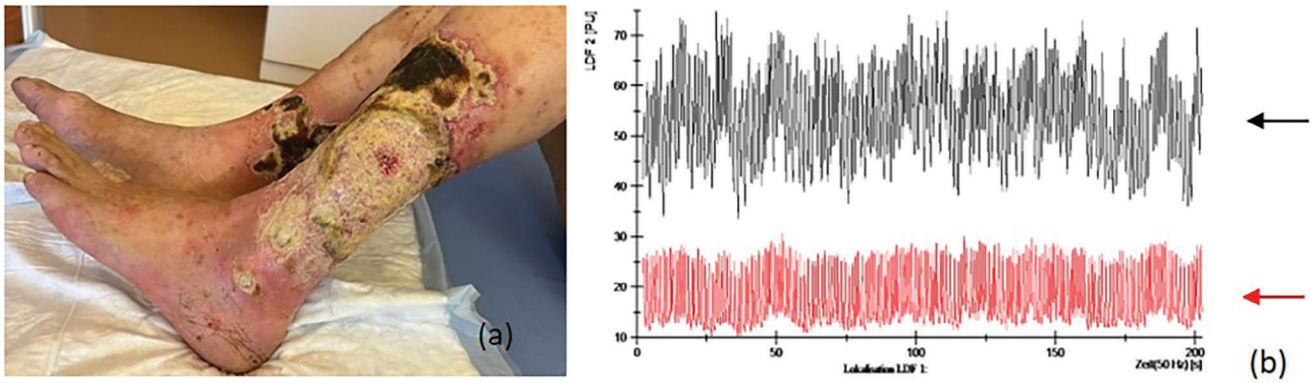

FIGURE 18 (a) There are acute ulcerations on both legs, very painful, PAD has been excluded. Serology showed vasculitis in the context of systemic lupus erythematosus (high ANA titer with positive ENA screen for dsDNA antibodies). (b) LDF shows significantly increased flow (black arrow) in the marginal area of the ulceration in the context of inflammatory multiple perfusion compared to the unaffected thigh (red arrow).

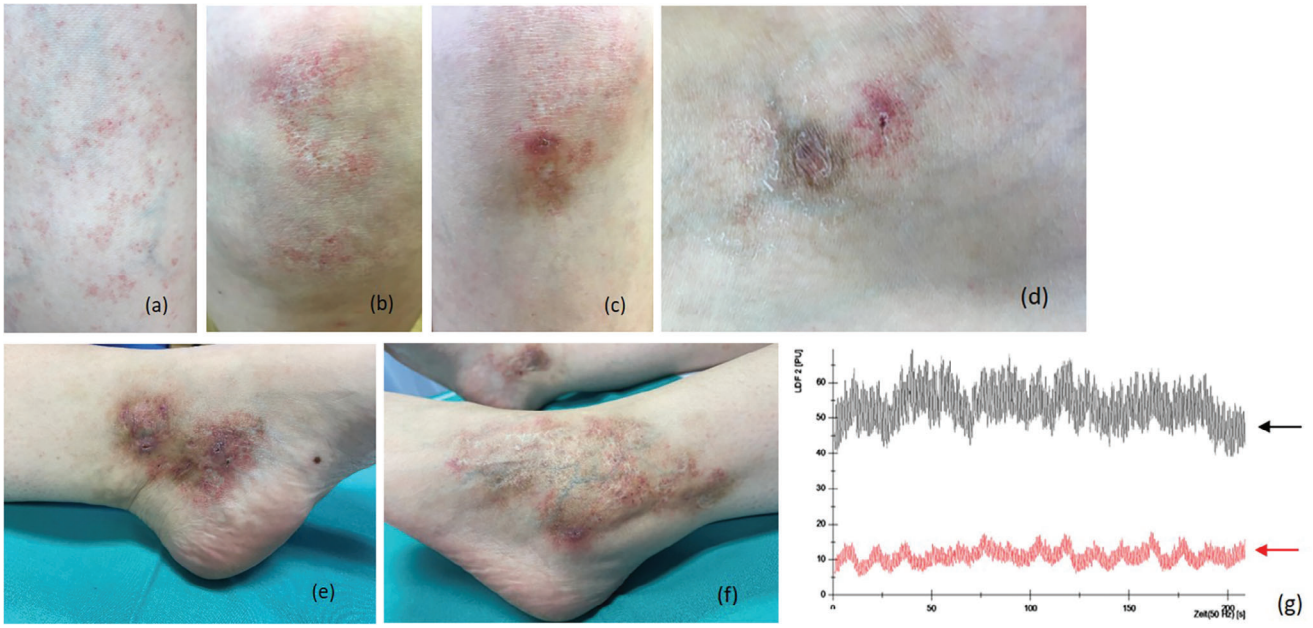

FIGURE 19 Clinical picture of primary antiphospholipid syndrome. (a, b, c) There are disseminated telangiectasias, especially in the lower extremities, some of which surround an ulcer, indicating the presence of vasculopathy (c, d). Multiple small inflammatory ulcerations are often seen next to hyperpigmented, bordered atrophie blanche foci (d, e, f). (g) LDF shows hyperperfusion (black arrow) in the area of active-florid lesions in the ankle regions compared to the thigh, which is free of lesions (red arrow).

Cuff-like fibrin deposits in the capillaries are also part of the pathomechanism, hindering the diffusion of oxygen into the tissue. Inflammatory infiltrates, composed primarily of leukocytes, are another contributing factor. These infiltrates release inflammatory cytokines and chemokines that increase capillary permeability to fluids and blood components.[46]

Clinically, visible cyanosis is followed by edema, hyperpigmentation, induration, and trophic skin changes (atrophie blanche), which may progress to ulceration (Figures 22a–d, 23a–e).

Bellinger et al. were the first to systematically investigate these pathomechanisms. In areas of skin with atrophie blanche, they found a markedly reduced capillary density to complete absence of capillaries, associated with an extremely low tcpO2 (Figure 23d, f).[16,46]

Atrophy-blanche areas in venous ulcers show severely reduced capillary density to complete absence of capillaries, associated with impaired transcutaneous partial pressure of oxygen.

The situation is similar in florid ulcers associated with chronic venous insufficiency. Capillary microscopy reveals a progressive reduction in capillary density that corresponds with the worsening of clinical symptoms. Juenger et al.

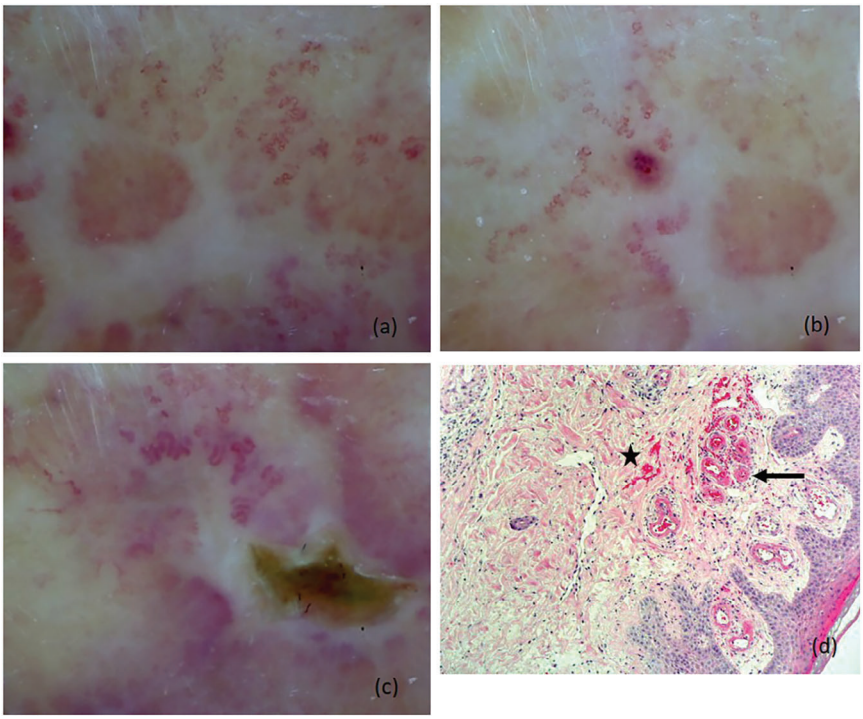

FIGURE 20 Capillary microscopy and histology of IgA antiphospholipid syndrome. (a) A vessel-free atrophy blanche is shown surrounded by linear corkscrew-like vessels as an indication of the underlying vasculopathy. (b) A freshly thrombosed vessel is shown within atrophy blanche with surrounding corkscrew-like vessels. (c) A serum crust-covered ulcer is shown in healing as atrophy blanche, the wall thickened, partially thrombosed capillaries are shown at the edge. (d) Histological picture of a vasculopathy: Subepidermally there is an increased number of small vessels arranged in groups (black arrow) (corresponds to the clinical correlate of the corkscrew-like pattern) with hyaline thickened walls without perivascular infiltrate, in addition there are erythrocyte extravasations (asterisk) (hematoxylin-eosin stain).

showed that in stage I (edema) 26 capillaries/mm^2 were still detectable, whereas in the presence of induration this number decreased to 14 capillaries/mm^2. In stage III, as defined by Widmer (characterized by atrophie blanche and ulcus cruris), only an average of 5 capillaries/mm^2 were detectable due to venous stasis.[46] In addition to the quantitative decrease, typical morphologic changes of the capillaries occur, ranging from dilation, corkscrew-like twisting, branching and ramification to glomerulus-like formations of the capillary loops, which are an expression of the increased capillary pressure (Figure 23a–c). Histologically, congested capillaries are seen in the dermis with surrounding fibrosis of the stroma (Figure 24).

Transcutaneous oxygen partial pressure correlates closely with the clinical severity of chronic venous insufficiency. As clinical symptoms worsen, the tcpO2 continuously decreases. LDF measurements in florid ulcers show complete depletion of vascular reserve. There is no reactive hyperemia due to back pressure in the arterial capillaries. Mean flux is significantly increased in patients with CVI, and the level correlates with the clinical severity of the disease. Subcutaneous flux is increased due to decreased tcpO2. (Figure 25a–c).[46,50]

Microcirculatory disorders in peripheral arterial disease (PAD)

Ulcers associated with arterial occlusive disease are an expression of impaired perfusion of both the macrocirculation and the nutritive microcirculation, resulting in tissue hypoxia. There is a direct correlation between the risk to the skin and the severity of ischemic microangiopathy. For example, areas of skin in which no blood-filled capillaries are visible by light microscopy have a necrosis risk greater than 90% (Figure 26c,d).[51]

In the advanced stages of peripheral arterial disease (PAD), dilated capillaries in the nutritive layer become visible. In addition, aneurysms may be seen. As the disease progresses, the capillaries become less distinct due to increasing papillary edema. Capillary hemorrhages due to extravasation of erythrocytes become visible (Figure 26a, b). They are an indicator of impaired vessel wall integrity. Optically visible capillary density continues to decrease until no capillaries can be detected in the final stage of the disease. Capillary perfusion is no longer detectable. Skin necrosis occurs (Figure 26c, d).[16,51–53]

There is a discrepancy between the total microcirculation and the purely nutritive microcirculation due to a maldistribution of blood flow between nutritive and non-nutritive vessels in ischemic skin. While nutritive blood flow in PAD patients has been comparable to that of healthy subjects for some time, total blood flow, as measured at the capillary level by LDF, is increased in PAD patients compared to healthy subjects. The maldistribution of blood flow is induced by mediators released during ischemia. These mediators cause dilation of the arterioles and opening of the AV anastomoses in the subpapillary region. This, in turn, leads to an increase in pressure in the post-capillary venous area, causing the blood flow in the nutritive capillary network to initially appear unchanged compared to healthy subjects. However, the effective blood flow within the nutritive capillaries decreases even as overall skin blood flow increases (Figure 27).[54]

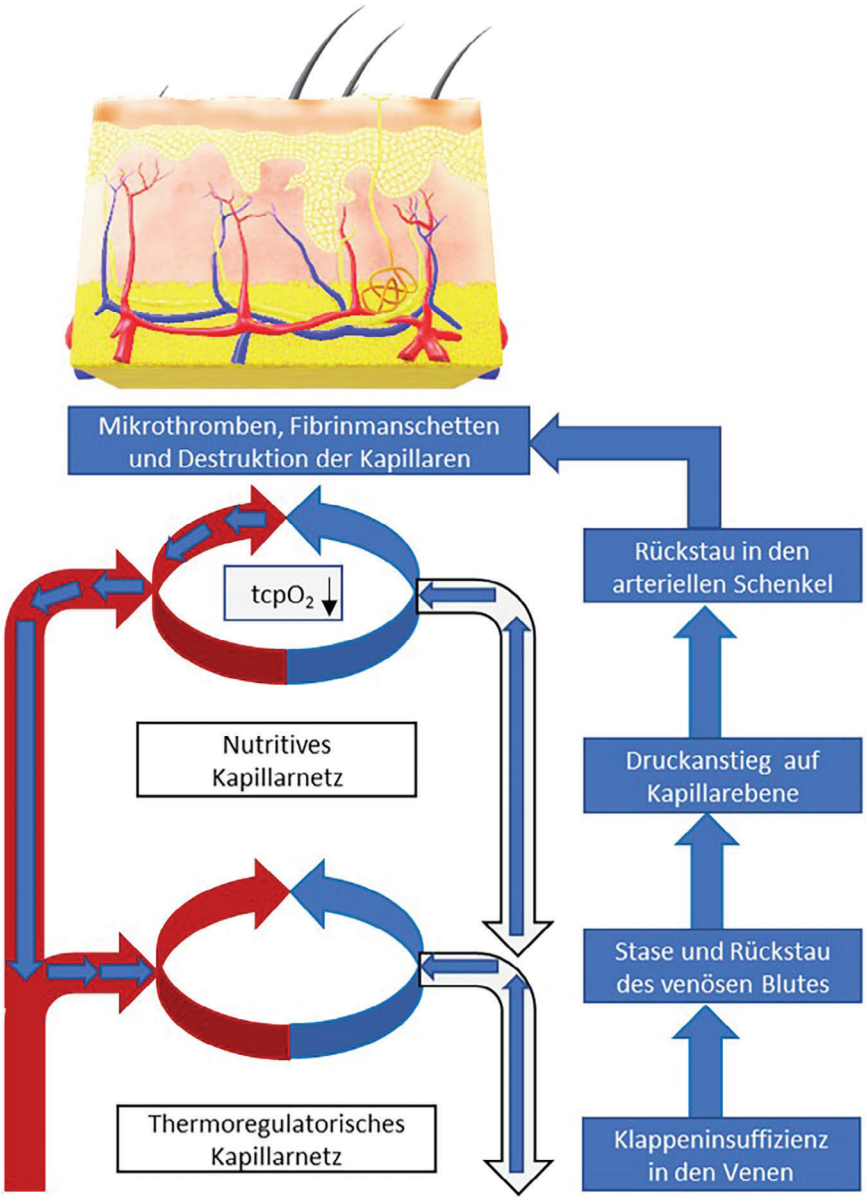

FIGURE 21 Schematic illustration of the characteristics of microcirculatory dysfunction in chronic venous insufficiency.

There is a discrepancy between the total microcirculation and the purely nutritive microcirculation due to a maldistribution of blood flow between nutritive and non-nutritive vessels in ischemic skin.

The increase in steady-state vasodilation, limitation of relative vasodilatory responses and maintenance of cutaneous microcirculatory blood flow and venous filling pressure suggest a compensatory mechanism in which vasodilation is increased distal to an occlusion to reduce resistance. Even at rest, patients with critical limb ischemia exhibit maximal arteriolar dilation. This sustained vasodilatation results in increased tissue edema, which leads to decreased nutrient delivery to the tissue. Clinically, this manifests as progressive edema in the affected lower limb.

Within the arterial system, there are regulatory differences between skin areas with hair follicles and those that are hairless. Skin with hair follicles has vegetative innervation mechanisms that control vasoconstriction and vasodilation of blood vessels.[52] In addition, the skin has another regulatory function, the venoarteriolar reflex (VAR). The venoarteriolar reflex (VAR) plays a physiological role in counteracting blood pressure fluctuations. When orthostatic pressure changes occur due to positional shifts and cutaneous venous pressure increases, the VAR, which is a local sympathetic reflex, is activated, resulting in vasoconstriction of the arterioles, which protects the capillary level from changes in blood flow and pressure.[52]

In hairless skin, especially on the soles, the VAR is absent, but in the area of microcirculation there is a kind of autoregulation. A functional feature of these zones are the arteriovenous anastomoses (AVAs). Arteriovenous anastomoses are direct connections between dermal arterioles and venules, but are not involved in nutrient circulation. The endothelium of AVAs consists of thick concentric layers of

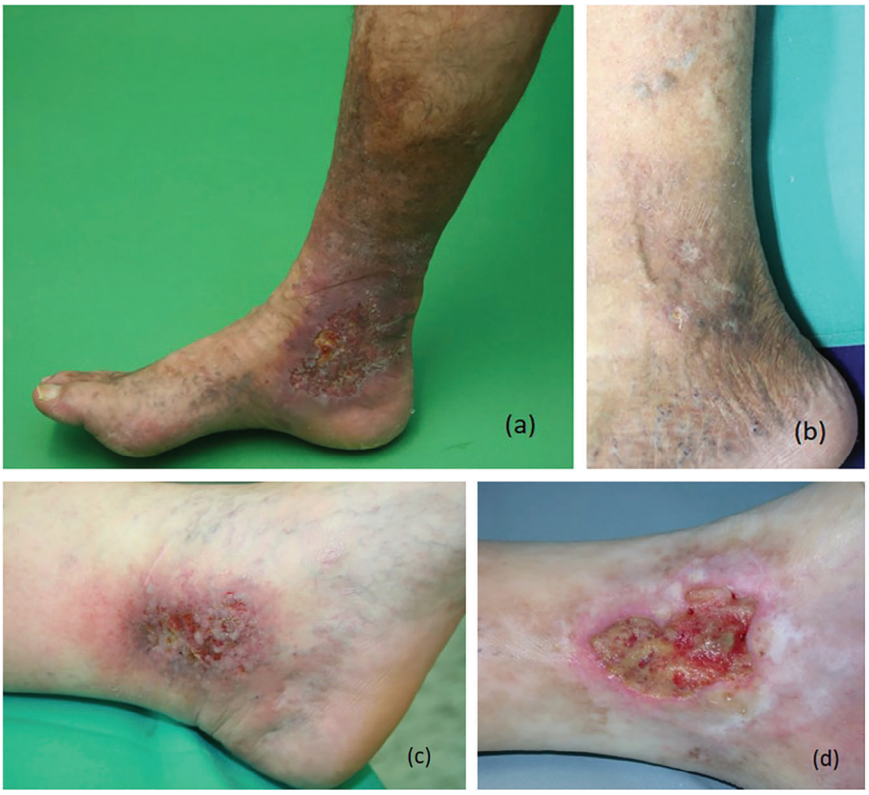

FIGURE 22 (a) Clinical changes in Widmer stage III chronic venous insufficiency with hyperpigmentation, induration, and ulceration. (b) Areas of atrophy blanche associated with Widmer stage II chronic venous insufficiency. (c) Ulcerated areas of atrophy blanche in indurated skin. (d) Venous leg ulcer with surrounding avascular atrophy blanche.

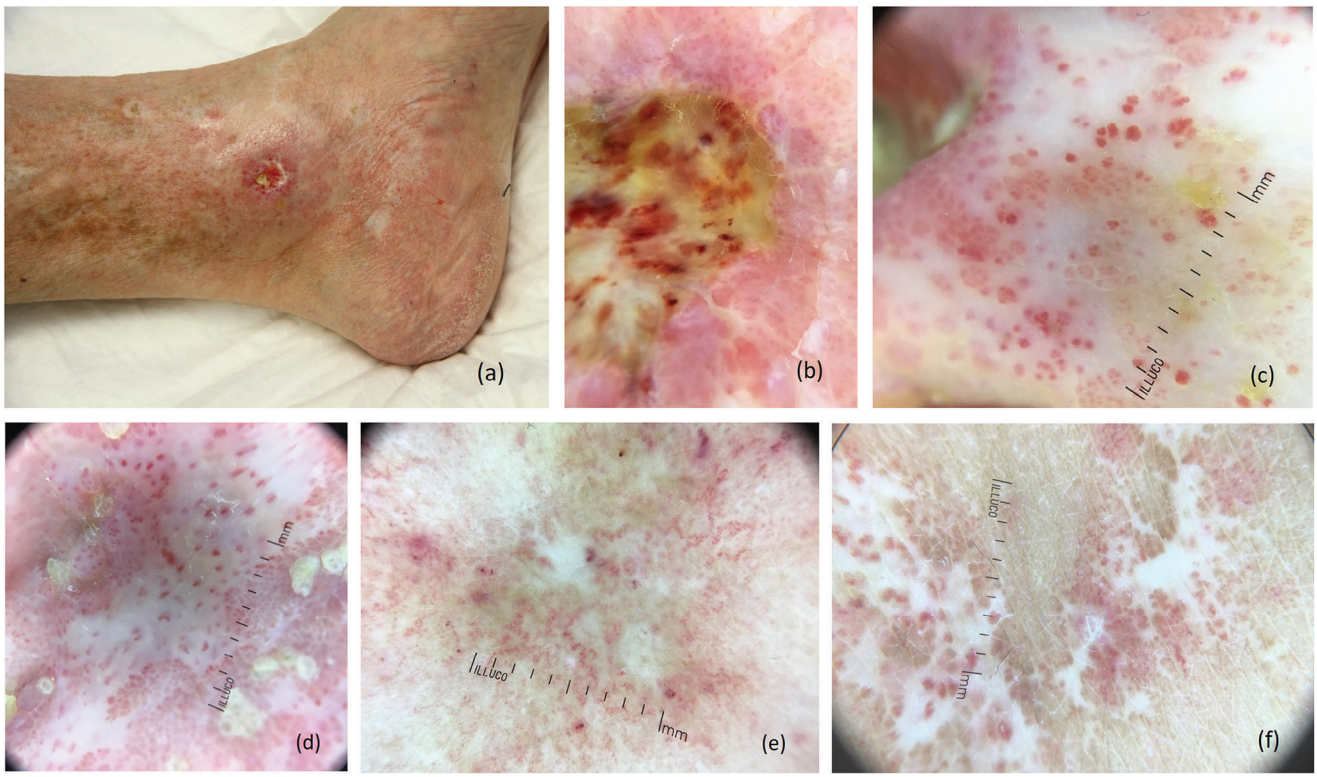

FIGURE 23 (a) Ulcerated atrophy blanche of the medial ankle with surrounding areas of atrophy blanche and visible capillaritis alba. (b) Ulcer margin with visible capillary congestion. (c, d) Glomerular capillary formations at the margin of a venous leg ulcer as an expression of the increased capillary pressure associated with venous stasis in chronic venous insufficiency. Dermatoscopy image, polarized light. (e) Atrophy blanche foci with corkscrew-shaped capillaries and capillary-less white skin areas. (f) Atrophy blanche foci without capillaries.

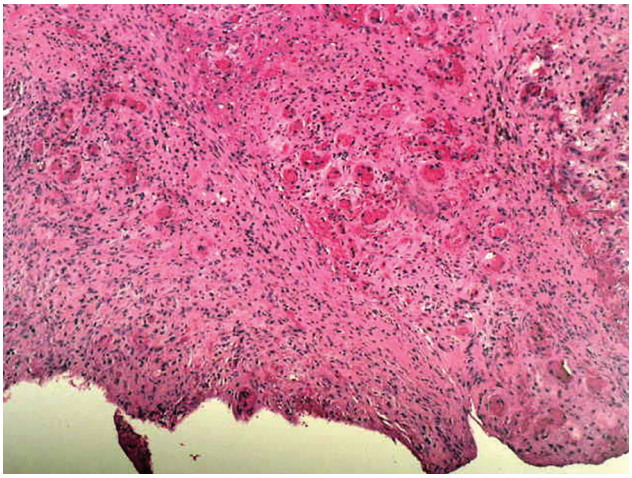

FIGURE 24 Histology from a venous leg ulcer, showing congested vessels in the papillary and reticular dermis, fibrosis of the dermis (hematoxylin-eosin stain).

smooth muscle and is innervated by sympathetic adrenergic nerves.[52] Arteriovenous anastomoses do not respond to metabolites with vasodilatory activity. They are centrally controlled and play a critical role in the regulation of core body temperature.

When the microcirculatory network shows dysfunction in the setting of chronic ischemia in PAD, the autoregulatory potential, as well as the functions of VAR and AVA, are also compromised.

In clinically symptomatic patients with PAD (Fontaine stage II–III), Midttun et al. demonstrated that orthostatic changes of the leg (elevation above heart level) alone lead to changes in the nutritive microcirculation. As long as the leg is at heart level, perfusion in PAD patients is comparable to that of healthy subjects. Patients with PAD show a 1.6-fold increase in blood flow when the leg is lowered.[55] This lack of perfusion control (increase in blood flow with increase in orthostatic pressure) in patients with PAD reflects a weakened autoregulatory potential.[21] Such provocative tests of the vasculature (LDF measurement under different positioning maneuvers) allow reliable causal classification of clinical disease patterns (Figure 28a–d).

The increased hydrostatic pressure in the lower extremity with the concomitant loss of autoregulation leads to an increase in pressure in the capillary plane, particularly in the plantar region. This increased pressure causes the vessels to become permeable, leading to tissue edema, which in turn promotes ulceration. Chronically elevated hydrostatic pressure in the capillaries leads to thickening of the capillary basement membrane, thereby increasing the diffusion distance for oxygen. This effect increases ischemia and contributes to the progression of tissue damage.[52]

Ischemically damaged capillaries show leakage (candlelight phenomenon), increased transcapillary and interstitial permeability (detectable with sodium fluorescein). With good skin transparency, capillary blood flow velocity can be detected and measured by the plasma gaps in the elongated nailfold capillaries that move with the blood flow.[26] Similarly, microbleeds occur as an indication of impaired capillary wall function. Nutritive capillaries that are no longer perfused are not visible by capillary microscopy (Figures 26c, d, 28b).

As PAD progresses, the vasomotion assessed through laser Doppler flowmetry typically undergoes changes, transitioning to a pattern characterized by high frequency and low amplitude. In extreme cases, no vasomotion is detectable, and the prevalence of low-frequency vasomotion decreases.[56,57]

Under physiological conditions, adult tcpO2 in the lower extremity is 5% to 20% lower than the systemic partial pressure of oxygen. The tcpO2 is also strongly dependent on local and regional skin perfusion. A value of 40 mmHg is considered a clear tcpO2 threshold (healthy vs. PAD) with high specificity.[51]

The determination of tcpO2 is particularly useful for monitoring the success of interventions.

Microcirculatory disorders in mixed ulcers

Mixed ulcers pose a significant therapeutic challenge. The different networks of the skin microcirculation are functionally affected, both the deep thermoregulatory network and the superficial nutritive capillary network. Ambrozy et al. demonstrated differences in microcirculation between well-granulated and non-granulated areas of these ulcers. In areas where granulation is entirely absent, capillaries are also almost completely absent (resulting in a loss of the supplying capillary network).

In addition, subpapillary perfusion is significantly reduced in these areas.[58] The microcirculation is consistent with advanced CVI or PAD. Furthermore, regions with good granulation and visible capillaries are frequently encountered in mixed ulcers, signifying partially preserved or regenerating nutritional supply to the skin.

In mixed ulcers, areas of good granulation and visible capillaries may be present as a sign of partially preserved or regenerated nutritional supply to the skin.

The capillaries are morphologically conspicuous; they are notably elongated and dilated, displaying classic morphological changes associated with CVI, particularly glomerular vascular patterns.[16,58] In LDF measurements, these sections exhibit significantly higher subpapillary perfusion compared to the non-granulating areas of the ulcer. Corresponding LDF measurements often emphasize the arterial microcirculatory disorders, which become evident through positioning maneuvers (Figure 29a–c).

Both the nutritive and subpapillary capillary networks are essential for the healing of mixed ulcers. Subpapillary perfusion compensates for the high blood demand during the healing process. Healed lesions show not only moderate

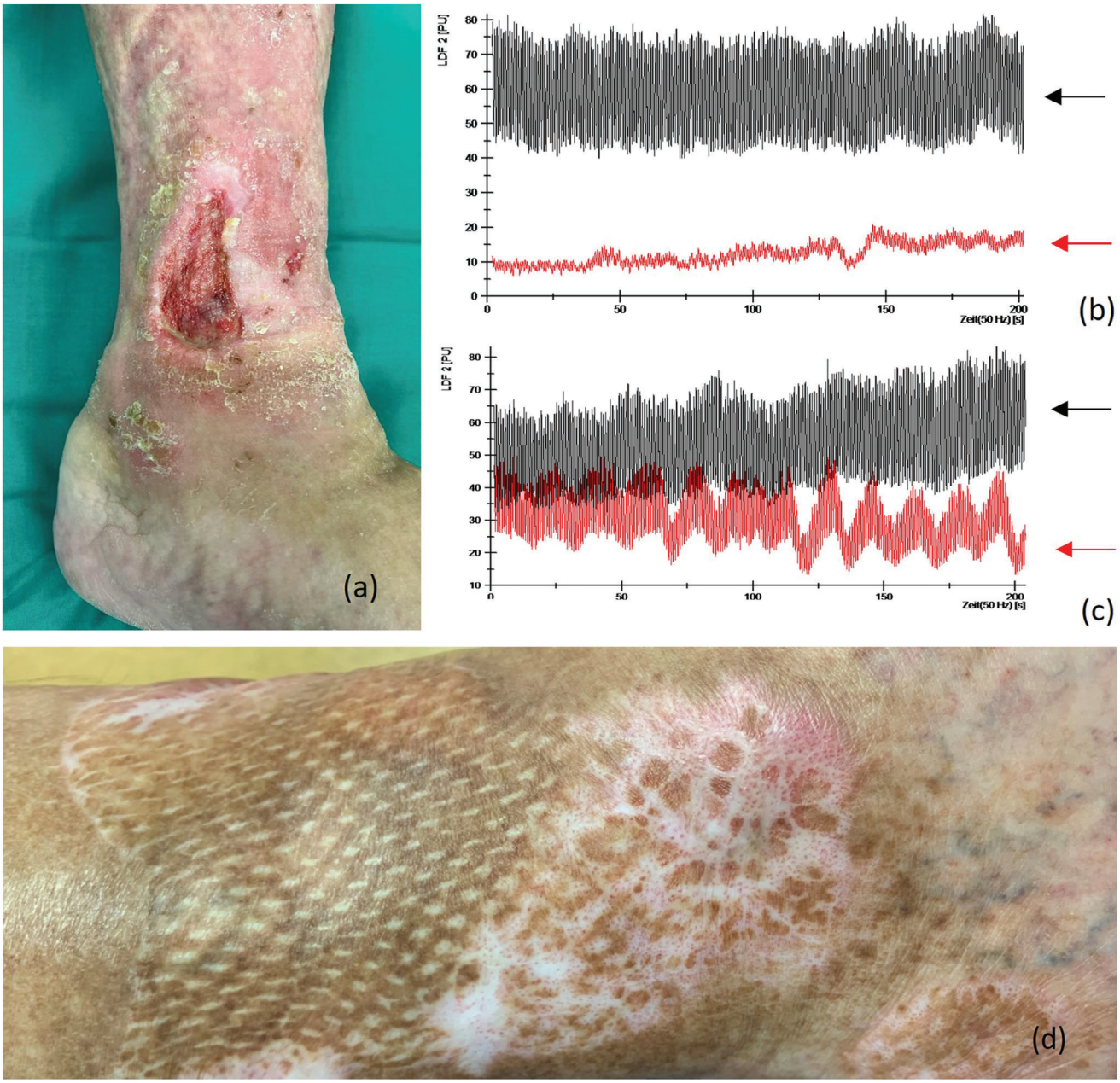

FIGURE 25 (a) Newly developed venous leg ulcer within a split-thickness skin graft for chronic venous insufficiency in postthrombotic syndrome. The underlying cause of the CVI is not curatively treatable at this time. (b) LDF measurement in the supine position with the leg in the horizontal position, probe 1 at the ulcer edge (black arrow), probe 2 at the ipsilateral thigh (red arrow). There is a high flow at the ulcer margin compared to the healthy skin area of the thigh, which is related to inflammatory hyperperfusion and corresponding luxury perfusion at the ulcer margin. (c) LDF measurement in the supine position with the leg in horizontal position, probe 1 at the ulcer margin (black arrow), probe 2 at the margin of the previous split skin graft (red arrow). Increased flow is also seen in the area of the vital healed graft, indicating ongoing venous microcirculatory dysfunction. (d) Macroscopically visible venous microcirculatory disturbance in the context of CVI in postthrombotic syndrome and after split-skin grafting with newly formed atrophy blanche foci within the grafted skin as an expression of the continuing microcirculatory disturbance. It is interesting to note that not all areas of split skin are affected with the same intensity. The atrophy blanche foci are most pronounced in the area of the medial malleolus, a typical primary site of leg ulcer in truncal varicosis of the great saphenous vein.

capillary density but also increased flow, indicating sustained nutritive perfusion provided by the subpapillary plexus.

Of particular importance for the healing of ulcers of any origin is the surrounding skin. In these areas, the primary microcirculation defect becomes visible, characterized by a high nutritive and reduced subpapillary perfusion. This factor is important for wound healing. In legs that have not been therapeutically compensated, there is a reduced nutritive perfusion compared to compensated legs, indicating

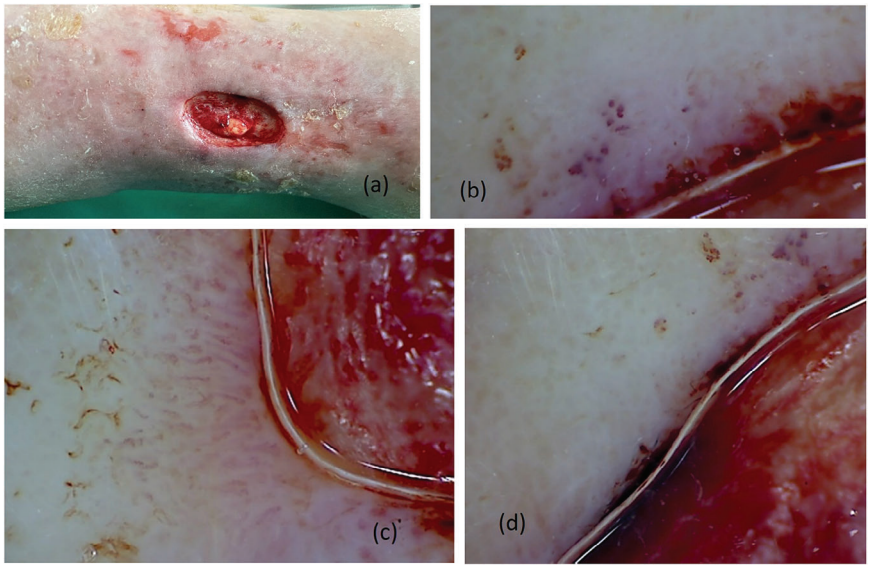

FIGURE 26 (a, b) Clinical aspect of an arterial leg ulcer after surgical debridement of the necrosis demarking a tendon at the base of the wound and predominantly avital appearing surrounding skin and (c) capillary microscopy of the skin in the vicinity of the ulcer: dilated capillaries with wall irregularities, abrupted vessels and isolated aneurysms are seen. (d) As the disease progresses, the capillaries are no longer clearly delineated due to increasing papilledema, they perish, and in the case of critical ischemia, often no capillaries at all can be delineated at the wound margin.

that the nutritive perfusion of peri-ulcer skin is significantly influenced by arterial compensation. Arterial intervention (recanalization of occluded or narrowed vessels) prevents ulcer enlargement.

Arterial intervention (recanalization of occluded or narrowed vessels) prevents ulcer enlargement.

Microcirculatory disturbance in diabetic ulcers

Among other factors, an ankle-brachial index (ABI) < 0.5 has been defined as an indicator for vascular intervention. However, it has been shown that the ABI does not accurately reflect the prevalence of PAD in diabetic patients because circumferential arterial calcification is associated with reduced vessel wall compressibility (medial sclerosis). One of the most serious complications of diabetes is diabetic foot syndrome, a combination of macroangiopathy, polyneuropathy and infection. It is associated with high morbidity, reduced quality of life, increased mortality, and significant costs. Peripheral polyneuropathy (PNP) and PAD are the two main factors in the development of foot ulcers, with PAD in particular impeding healing.[59] All the microcirculatory disorders described for PAD are also found in diabetic microcirculatory disorders but are additionally triggered by dysfunction resulting from polyneuropathy.

The presence of hyperglycemia leads to changes in the endothelial cells, basement membranes, and vascular smooths muscle cells. Proteins become non-enzymatically glycosylated. These glycosylated proteins accumulate in the vessel wall, where specific macrophage receptors bind to them in an attempt to degrade them. The resulting inflammatory cascade releases interleukin (IL)-1 and tumor necrosis factor (TNF)-α.

Protein-macrophage interactions at the vessel wall lead to an inflammatory cascade with release of IL-1 and TNF-α in diabetic ulcers.

Tumor necrosis factor-α causes endothelial and extracellular matrix dysfunction, resulting in increased permeability. This process also leads to changes in the contractile properties of the vessel walls, and consequently to changes in hemodynamics. These initially reversible changes eventually lead to a loss of elasticity in small blood vessels, causing stiffening and thickening of the vessel walls. Aneurysms and occlusions may occur. Vascular regulatory mechanisms have no effect on these vessels, and no vascular adaptation is seen in relevant positional tests.[59,60]

A second pathological biochemical mechanism, known as the polyol-inositol pathway, causes damage to both nerve fibers and the walls of small blood vessels. Hyperglycemia stimulates this pathway, leading to impairment of the sodium-potassium ATPase involved in a plasma membrane transport pathway, which further reduces small vessel contractility.

A second pathological biochemical mechanism, known as the polyol-inositol pathway, causes damage to both nerve fibers and the walls of small blood vessels. Hyperglycemia stimulates this pathway, resulting in impairment of the sodium-potassium ATPase, which is involved in a plasma-membrane transport pathway, further reducing small vessel contractility. A thickening of the basement membrane in the capillaries is one of the most important changes in diabetic microangiopathy.[59,60]

Simple nailfold capillaroscopy without fluorescent dyes reveals minimal morphologic changes. However, hemodynamics are impaired in almost all organs. The severity depends on the current metabolic situation and treatment. The stiffened vessel walls exhibit a delayed response to both vasodilator and vasoconstrictor stimuli.[59,60]

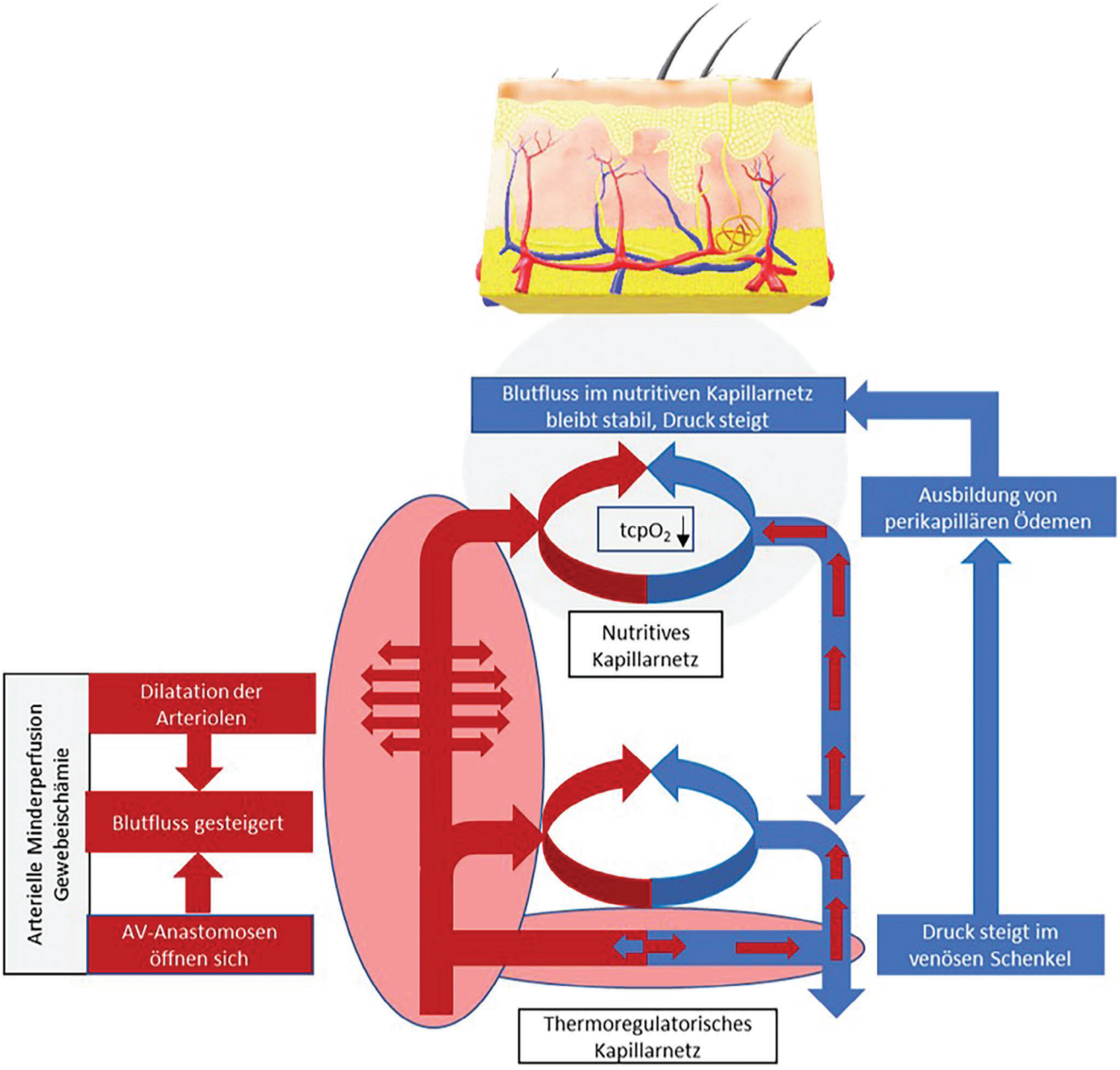

FIGURE 27 Schematic illustration of the characteristics of microcirculatory dysfunction in peripheral arterial occlusive disease (PAD).

Na-fluorescein can be used to visualize pathologically increased capillary permeability in capillary microscopy. These changes are also seen in the perilesional skin of plantar ulcers. The resulting edema of the skin in the context of increased vascular permeability with increased hydrostatic pressure in the capillary beds contributes significantly to ulcer development.[52,59,60] Neuropathy, which often coexists, also affects vasomotor function.

Microcirculation can be assessed by measuring transcutaneous partial pressure of oxygen (tcpO2), with a value above 25 mmHg shown to be associated with a higher chance of healing. However, tissue edema interferes with the measurement, and the measurement is also restricted to the dorsal side of the foot; measurements on plantar ulcers are not possible.

New optical imaging techniques such as laser speckle contrast imaging (LSCI) provide a noninvasive method for imaging skin blood flow in patients with diabetic foot disease. Laser Speckle Contrast Imaging can provide real-time visualization of blood flow changes and map the microcirculation in the skin, both within and around the ulcer.

In addition to these classic hemodynamic vascular conditions, microcirculatory disorders can also occur in certain systemic diseases, particularly in arterial hypertension and eclampsia.

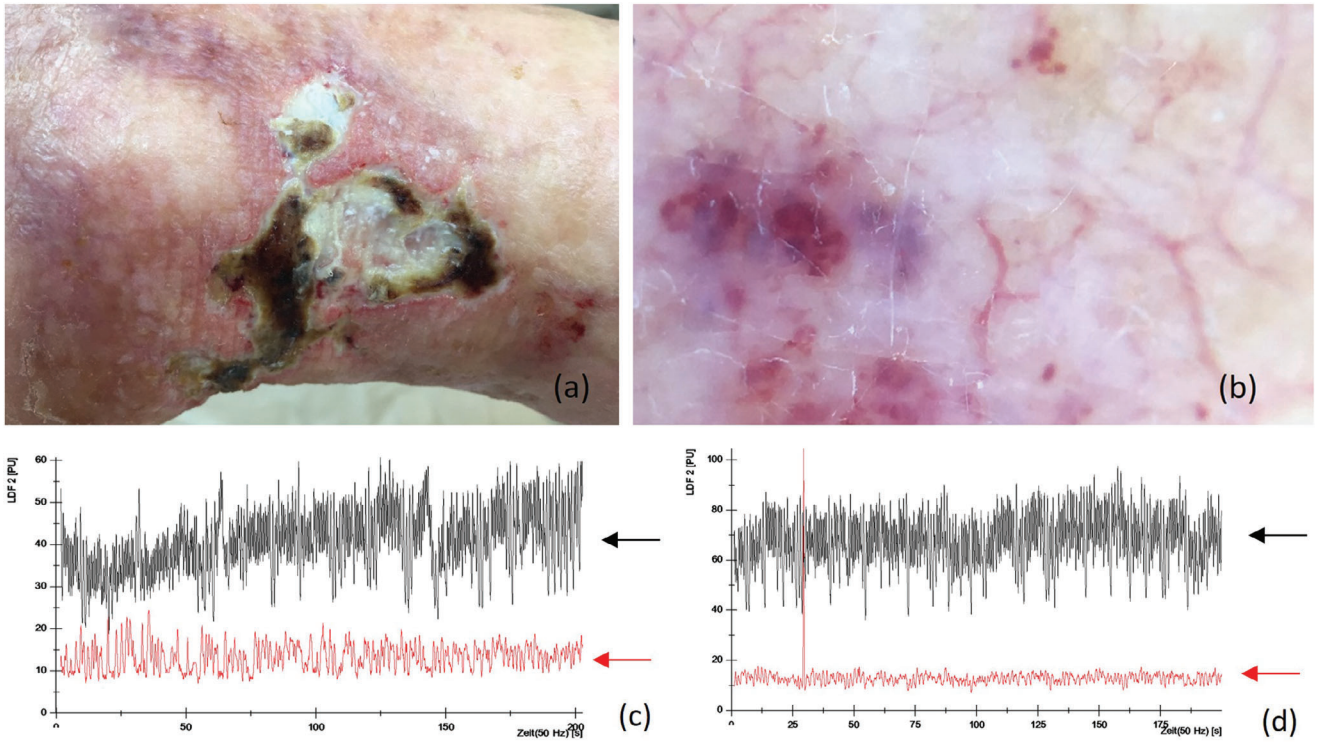

FIGURE 28 (a) Ulcus cruris above the right lateral malleolus, present for 3 months. Clinically there is necrosis and severe pain. ABI and Doppler sonography were performed on suspicion of PAD. Monophasic flow signals were detected over the popliteal, anterior tibial and dorsalis pedis arteries, and the ABI was 0.84. For further clarification, optical pulsoscillography was performed and showed good perfusion in all toes. (b) Capillary microscopy revealed capillaries with wall irregularities, vascular abruptions, and an overall rarefied vascular density in addition to hemorrhages. LDF measurement then showed an increase in flow (black arrow) when the leg was elevated (d) compared to the horizontal leg (c), suggesting preserved regulation of vasomotion and arguing against critical ischemia as the cause of the ulcer. In addition, polyneuropathy and Parkinson's disease are known comorbidities, suggesting a mixed genesis of the ulcer without arterial perfusion playing a dominant role.

Microcirculatory disorders in arterial hypertension

Numerous studies have demonstrated microcirculatory changes in arterial hypertension. The focus is on a reduced number of capillaries and arterioles, a condition called "microvascular rarefaction", which can be seen in many tissues. There is an increase in vascular resistance, accompanied by an uneven distribution of blood flow, which often precedes a persistent increase in blood pressure.

The focus is on a reduced number of capillaries and arterioles, a condition called "microvascular rarefaction", which can be seen in many tissues.

Changes in pressure and flow can lead to impairments in muscle perfusion and metabolism. Serne et al. demonstrated that the recruitment of initially non-perfused capillaries after post-occlusive reactive hyperemia is reduced in hypertensive subjects compared to normotensive subjects (with an inverse association with blood pressure), despite otherwise minimal differences in the resting state in this study.[61]

Debbai et al. showed that systolic blood pressure was inversely correlated with basal and post-occlusive capillary density in normotensive subjects. This correlation disappeared in hypertensive subjects. Capillary density was demonstrated to be significantly influenced by two independent variables, firstly, antihypertensive drug therapy and secondly, existing obesity.[62,63]

Antonios et al. have shown that capillary rarefaction occurs early in the course of arterial hypertension and may not be a secondary phenomenon but a primary pathology. This consideration is supported by the studies of Ciuffetti et al., who demonstrated that capillary rarefaction occurs in parallel with hypertension and is not secondary to long-standing hypertension.[64–66]

This could be used in the future as a predictive marker for the development of arterial hypertension.

SUMMARY

Understanding microcirculatory disorders of the skin is crucial both diagnostically and therapeutically.

In the case of connective tissue diseases, the morphological changes of the nailfold capillaries are of particular importance for confirming the diagnosis and assessing the severity. Similarly, therapeutic effects can be inferred from changes in dynamic parameters (e.g., erythrocyte flow velocity in nailfold capillaries).

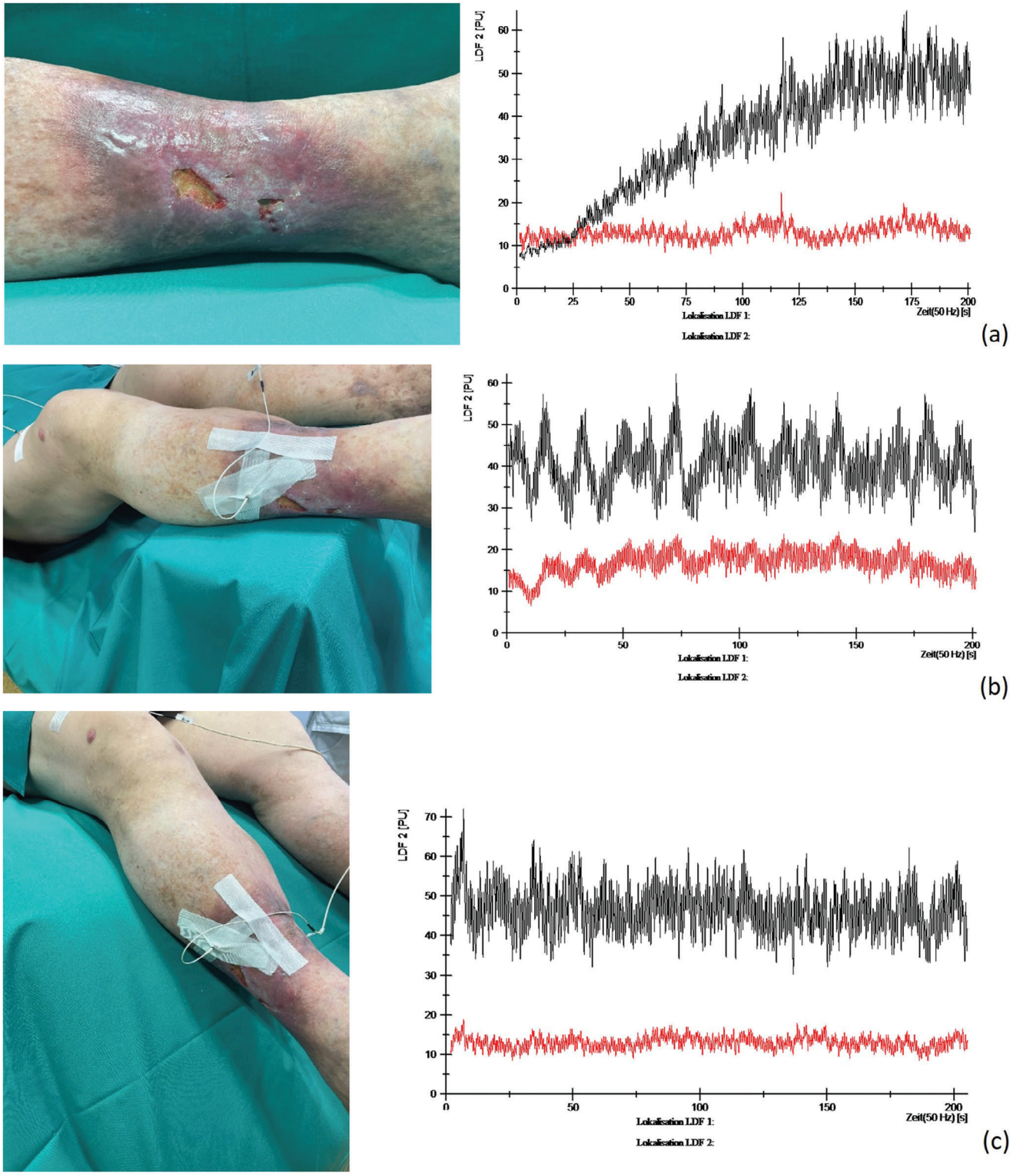

FIGURE 29 (a) Ulcers of mixed genesis, there is a peripheral arterial disease (PAD) stage II according to Fontaine, a postthrombotic syndrome with a deep vein insufficiency and a polyneuropathy in the context of a diabetes mellitus (tuning fork test 2/8). (b) The functional examination shows that, as a reflection of the existing PAD, no increase in perfusion is possible with elevation, as the arterioles are already maximally dilated. (c) As an expression of the existing polyneuropathy in the context of an existing diabetes mellitus (tuning fork test 2/8) and the arterial perfusion disorder (PAD), there is also a lack of decrease in flux when the limb is lowered below the level of the heart.

In hemodynamically effective disorders, it is the functional changes that significantly affect the microcirculation. Chronic venous insufficiency, due to impaired venous function, leads to congestion in the capillary bed, which, if prolonged, affects the arterial vascular limb to such an extent that the skin suffers functional ischemia similar to PAD and ulceration develops. In addition to addressing the underlying cause of CVI, a complex skin decongestion through compression and lymphatic drainage significantly contributes to the healing process.

In peripheral arterial disease, it is significant that critical nutritional microcirculatory disorders typically occur only at far advanced stages. This means that when necrosis occurs, the entire compensatory reserve of the nutritive microcirculation is depleted. Therefore, it is important to treat existing PAD before necrosis and ulceration occur (vascular intervention). Chronic dilation of the arterial vasculature distal to the occlusion results in permanent hydrostatic pressure effects on the capillaries. This leads to endothelial damage with increased permeability, leading to tissue edema, which exacerbates tissue ischemia. These relationships make it clear that patients with PAD can benefit from complex decongestive therapy, of course, taking into account preserved perfusion.

Tissue edema is also a parameter for more severe and adverse outcomes in diabetic plantar ulcers and is a therapeutic target in these cases as well.

In mixed ulcers, PAD is responsible for ulcer growth, making intervention a priority. Both chronic venous insufficiency and PAD benefit from complex decongestive therapy. In ulcers with different causes, functional microcirculation tests (LDF measurements with positioning maneuvers) can help differentiate.

Microcirculatory disorders may also serve as predictive markers; in arterial hypertension, nailfold capillary density and morphology may indicate the presence or development of this condition.

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CONFLICT OF INTEREST

None.

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[CME Questions / Lernerfolgskontrolle]

1. Die Mikrozirkulation der Haut ist aus einem komplexen Gefäßsystem aufgebaut mit entsprechenden Regulationsmechanismen. Welche Aussage ist richtig?
   a. Der Anteil des nutritiven Blutflusses macht etwa 80% der Mikrozirkulation aus.
   b. Der für die Nutrition notwendige Blutfluss beträgt etwa 15% der Mikrozirkulation.
   c. Nutritiver und thermoregulatorischer Blutfluss machen jeweils 50% aus.
   d. Der nutritive und thermoregulatorische Blutfluss beeinflusst sich nicht gegenseitig.
   e. Fällt der nutritive Blutfluss aus, übernimmt der thermoregulatorische Blutfluss diese Funktion.

2. Welche der nachfolgenden Aussagen ist richtig? Die Dermatoskopie von Kapillargefäßen …
   a. ist das Mittel der Wahl zur bildgebenden dynamischen Bilddokumentation.
   b. ist eines der am besten standardisierten Verfahren in der Diagnostik von Kollagenosen.
   c. kann eine vergrößerte Darstellung der Kapillargefäße um das 10–15fache erzielen.
   d. stellt den nichtinvasiven bildgebenden Standard in der Routinediagnostik von Kollagenosen dar.
   e. ermöglicht in der Regel aussagekräftige kontraktfreie Untersuchungen mit normalem oder polarisiertem Licht an dem Nagelfalz.

3. Marisq et al. definierten bereits 1980 für die systemische Sklerose typische kapillarmikroskopische Muster. Welche Aussage zur Untersuchung und hinsichtlich charakteristischer morphologischer Parameter ist richtig?
   a. Die Beurteilbarkeit der Kapillaren ist an Finger II und III am besten.
   b. Thrombotisch verursachte Mikroangiopathien spielen für die Kapillarveränderungen keine Rolle.
   c. Eine Kapillardichte im Bereich des Nagelfalz von > 3/mm gilt als physiologisch.
   d. Torquierte Kapillarschlingen sind diagnostisch beweisend für die systemische Sklerose.
   e. Megakapillaren sind ein typischer kapillarmikroskopischer Aspekt bei der systemischen Sklerose.

4. Welche der nachfolgenden Aussagen ist richtig? Die Laser-Doppler-Fluxmetrie (LDF) …
   a. ist ein geeignetes Verfahren zur Beurteilung der Kapillarmorphologie.
   b. nutzt das Laserlicht eines Argon-Neon-Lasers.
   c. erreicht sinnvolle Messtiefen von circa 3 mm.
   d. misst in stochastischer Darstellung die Anzahl der Erythrozyten im untersuchten Gewebeabschnitt multipliziert mit ihrer Geschwindigkeit.
   e. lässt keinen Rückschluss auf die kutane vaskuläre Reserve bei arteriellem Zuflusshindernis zu.

5. Welche der nachfolgenden Aussagen ist richtig? Bei der systemischen Sklerose …
   a. steht zum Beginn der Erkrankung eine kapilläre Endothelschädigung im Vordergrund.
   b. spielt eine Thrombophilie in der Genese keine Rolle.
   c. sind Makro - und Mikroangiopathie zumeist in gleicher Ausprägung am pathologischen Geschehen beteiligt.
   d. wird die Vasokonstriktion in den betroffenen Arealen vor allem über Stickstoffmonoxid (NO) vermittelt.
   e. führt Endothelin-1 zu einer Vasodilatation und hemmt die Proliferation glatter Muskelzellen sowie Fibrose und Entzündung.

6. Welche der nachfolgenden Aussagen ist richtig? Bei der Dermatomyositis zeigen sich folgende Veränderungen der Mikrozirkulation:
   a. Als Folge der Entzündung ist der kapilläre Blutfluss erhöht.
   b. Es zeigt sich eine Abnahme der Gefäßpermeabilität.
   c. Es zeigen sich oft erhöhte Fibrinogenwerte.
   d. Die Viskosität ist vermindert.
   e. Erythrozyten- und Thrombozytenaggregation sind vermindert.

7. Welche der nachfolgenden Aussagen ist richtig? Bei der CVI sind folgende Veränderungen in der Kapillarmikroskopie typisch:
   a. Mikrothromben in den Kapillaren

b. Manschettenartige Fibrinablagerungen in den Kapillaren treten selten auf.
c. In Hautarealen mit floriden Ulzera nimmt die Kapillardichte kompensatorisch zu.
d. Typisch sind verengte Kapillaren.
e. In der Laser-Doppler-Fluxmetrie (LDF) ist der mittlere Flux deutlich vermindert.

8. Welche der nachfolgenden Aussagen ist richtig? Bei der pAVK kommt es zu komplexen Veränderungen im Bereich der Mikrozirkulation:
   a. Es kommt zu einem Druckverlust im postkapillären venösen Bereich.
   b. Der nutritive Blutfluss ist im Vergleich mit gesunden Probanden frühzeitig vermindert.
   c. Der totale Blutfluss ist bei Patienten mit einer pAVK im Vergleich zu gesunden Personen gesteigert.
   d. Im postkapillären venösen Bereich ist der Druck vermindert.
   e. Das Verhältnis zwischen Blutfluss in den nutritiven Kapillaren und Gesamtdurchblutung der Haut bleibt etwa gleich.

9. Die chronisch venöse Insuffizienz ist eine komplexe Erkrankung, welche schwere hämodynamische Störungen mit sich bringt. In fortgeschrittenen Stadien treten Ulzerationen auf. Diese sind Folge der fortgeschrittenen Störung der Mikrozirkulation. Welche Aussage trifft zu?
   a. Es kommt zu einem venösen Rückstau auf Kapillarebene, sodass es sich in den arteriellen Schenkel zurückstaut, eine Gewebeischämie ist die Folge.
   b. Der venöse Rückstau auf Kapillarebene führt dazu, dass der thermoregulatorische Plexus den nutritiven Plexus umgeht.
   c. Der venöse Rückstau verursacht ein disseminiertes Rupturieren der Kapillaren wodurch es zu Ulzerationen an der Haut kommt.
   d. Es kommt zu einem venösen Rückstau, der das thermoregulatorische Gefäßsystem außer Funktion stellt.
   e. Es kommt zu einem venösen Rückstau, der zum Öffnen der arteriovenösen Anastomosen führt.

10. Für die Störung der Mikrozirkulation im Rahmen des Diabetes ist folgende Aussage richtig?
    a. Bereits in der einfachen Nagelfalz-Kapillarmikroskopie zeigen sich auffällige morphologische Veränderungen.
    b. Eine über längere Zeit bestehende Hyperglykämie führt zu nichtenzymatischer Glykosylierung von Proteinen und Akkumulation in den Gefäßwänden.
    c. Die Veränderungen der kontraktilen Eigenschaften der Gefäßwände sind als Besonderheit primär irreversibel.
    d. Die Basalmembran der Kapillaren bleibt bei der diabetischen Mikroangiopathie weitgehend unverändert.
    e. Durch Akkumulation von Proteinen und die damit verbundene Perfusionsminderung sinkt der hydrostatische Druck in den Kapillarbetten.

Liebe Leserinnen und Leser, der Einsendeschluss an die DDA für diese Ausgabe ist der 30.April 2024.

Die richtige Lösung zum Thema "Wirkweise, Indikationen und Therapieempfehlungen der extrakorporalen Photopherese (ECP)" in Heft 11/2023:
1c, 2a, 3d, 4e, 5a, 6b, 7d, 8c, 9a, 10d

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