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Assessment of Microcirculation and the Prediction of Healing in Diabetic Foot Ulcers

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1. Introduction

Globally, diabetes mellitus has grown to pandemic proportions, affecting 194 million people worldwide and is expected to increase in prevalence to 344 million by the year 2030 (Wild, et al., 2004). Of these patients, between 2 and 6% will develop a diabetic foot ulcer (DFU) yearly (Ramsey, et al., 1999). The onset of a DFU often precipitates a complex chain of events that may lead to limb loss. Infected DFUs account for 20% of hospital visits for this patient population (Bouter, et al. 1993) and precede roughly 85% of lower extremity amputations in patients with diabetes (Pecoraro, et al. 1990). The long-term outcome for a diabetic patient after a major limb amputation is grave with 50% of these patients deceased at 5 years (Moulik, et al. 2003). Additionally, the cost to treat this disease places a significant strain on the health-care system. The cost to manage these foot disorders is estimated at several billion dollars annually (Wild, et al. 2004), while the individual cost of a major limb amputation is estimated at almost \$45,000 (Apelqvist, et al. 1994). With the combination of excessive cost to treat diabetes complications coupled with the major detrimental health effects on individual patients, it is necessary to develop and employ new technological methods to predict healing of diabetic foot ulcers.

Once a diabetic patient develops a pedal ulceration it becomes incumbent on the physician to evaluate the ulcer's healing potential. Much research has focused on the prediction of diabetic foot ulcer healing. Clinically, it has been shown that a 50% decrease in area over a 4-week period with standard wound care adequately predicts ulcer healing at 12 weeks (Sheehan, et al., 2003). The disadvantage of this method, however, is the delay in treatment that occurs as a result of the natural time deferment in this process. As such, newer technologies have utilized the determination of microcirculation to predict ulcer healing. This chapter focuses on the application of these new technologies to determine microvascular circulation and predict diabetic foot ulcer healing.

Large artery (macrocirculatory) disease has been well documented elsewhere with disease at the infrapopliteal region (Bembi, et al. 2006) causing loss of tissue perfusion and critical limb ischemia and gangrene. Various noninvasive vascular testing modalities exist to determine large vessel luminal disease. These include dual mode ultrasound, segmental leg pressures, ankle brachial indices, pulse volume recordings, toe pressures, and toe brachial indices. The above tests have been found to yield useful clinical data regarding large vessel disease and often function as safe precursors to more advanced imaging techniques such as magnetic resonance arteriography. These methods also assist with surgical revascularization

planning. However, the options for assessment of microvascular disease are comparatively sparse. This chapter will focus on the following noninvasive modalities to evaluate microvascular disease and predict ulcer healing: Transcutaneous Oxygen Pressure, Skin Perfusion Pressure, Laser Speckle Perfusion Imaging, and Hyperspectral Imaging.

2. Peripheral arterial disease and the pathophysiology of microvascular disease in diabetes

The pathogenesis of macrocirculatory disease has been discussed in depth elsewhere. Microcirculation includes the capillaries, arterioles, and venules. These microvessels are arranged in two horizontal network patterns with a superficial subpapillary plexus and a deeper cutaneous plexus with capillary blood flow providing nutrition and arteriovenous shunts that serve a thermoregulatory function (Chao & Cheing, 2009). The nutritional capillaries are organized into functional units within the papillary layer of the dermis. A precapillary sphincter is situated just upstream of the capillary which controls vasodilation and constriction (LaFontaine, et al., 2006). Arteriovenous anastomoses exist between the arterioles and venules to allow normal shunting of blood under physiologic conditions. The internal vessel lumen is lined with a single-layer-thick endothelium. This endothelium lies on a basement membrane which is normally thicker in the foot than other body locations due to the increased hydrostatic pressure associated with stance (LaFontaine, et al., 2006). Blood flow to the skin runs through this arteriovenous system supplying nutrition, oxygen, and regulating temperature through an increase or decrease of blood flow to the dermal papilla.

Blood flow to the skin is controlled by the peripheral sympathetic nervous system via vasodilatory cholinergic and vasoconstrictor adrenergic nerve fibers (Chao & Cheing, 2009) as well as vasoactive substances such as nitric oxide. Additionally, the endothelial basement membrane regulates blood flow and the local inflammatory response via vasoactive substances (Guerici, et al. 2001).

The pathogenesis of microvascular disease in diabetics is complex and multifactorial. Hyperglycemia is considered the most important risk factor (LaFontaine, et al., 2006) and is noted to occur in two stages, a reversible functional stage and a structural adaptation and remodeling stage leading to a thickened basement membrane and capillary failure (LaFontaine, et al., 2006). The hemodynamic hypothesis of microangiopathic disease was first described by Parving, et al (Parving, et al. 1983). Blood flow dysregulation, caused by neuropathic changes to the sympathetic nerve fibers, is mediated by hyperglycemia. The resulting stimulation of the polyol pathway decreases nitric oxide production, increasing blood flow and capillary pressure. This increased pressure leads to thickening of the basement membrane which resists vasodilation and increases capillary permeability with ensuing chronic edema.

A second mechanism that has gained experimental support is the “capillary steal syndrome” (Uccioli, et al. 1992). This is thought to result from sympathetic denervation with chronic vasodilation, resulting in an increased blood flow through the arteriovenous shunt away from the arterioles in the papillary dermis. As blood moves more rapidly toward the postcapillary venule, nutrition, metabolite, and oxygen exchange are significantly reduced (Boulton, et al, 1982).

It is unknown which pathway is dominant or if another mechanism is responsible, though there is most likely a combination of both pathogenic pathways that end with functional

ischemia, reduced nutritional capacity, and increased metabolic end products that function together to limit healing capacity in the face of skin ulceration.

3. Current methods to assess healing potential in diabetic foot ulcers

Large vessel disease is evaluated through several noninvasive methods including dual mode ultrasound, segmental leg pressures, ankle brachial indices, pulse volume recordings, toe pressures, toe brachial indices, magnetic resonance angiography, and computed tomographic angiography. However, these modalities only characterize blockages of large arteries and do not assist with prediction of direct wound healing on the lower extremity. Contemporary microvascular technologies utilize the above pathogenic principles to evaluate microangiopathic changes and predict ulcer healing. The following discussion will review the currently available methods to clinically assess microvascular blood flow and predict the healing potential of diabetic foot ulcers.

4. Transcutaneous oxygen pressure

Physiology of test. Transcutaneous oxygen pressure (TcPO₂) measures excess oxygen diffusion from red blood cells as they pass through the capillary circulation. This pressure reflects the metabolic state of the adjacent interstitial spaces. TcPO₂ is measured via electrochemical reduction at a cathode placed against the skin.

Method. Transcutaneous oxygen pressures are measured by placing a heated probe against the skin. The standard 44 degrees Celsius causes vasodilation and a local reactive hyperthermia (Figures 1 and 2). Oxygen diffusing across the skin and toward the cathode in the probe is reduced. This reduction is proportional to the number of oxygen molecules (Mathieu and Mani 2007) and is measured as oxygen pressure. Common locations of measurement include the dorsum of the foot, anteromedial calf approximately 10 cm below the patella, and the thigh 10 cm above the patella. The subclavicular region is often used as a reference point due to its close anatomic location to coronary perfusion and low likelihood of arterial insufficiency. Pressure measurements may be enhanced by having the patient exercise, increasing the metabolic demand and need for oxygen. Placing the leg in a dependent position additionally augments oxygenation, providing further information about the arterial reserves available. TcPO₂ measurement may also be performed in patients in which arterial claudication is suspected. In this situation normal oxygen metabolic demands are sufficiently supplied. However, when stress is applied to the extremity, oxygen demands increase and exceed the oxygen supplied by the now insufficient arterial flow (Franzeck, et al. 1982). To test this, transcutaneous oxygen tension measurements may be performed while the patient exercises. It is also important to consider that resting TcPO₂ measurement is more likely to diagnose disease in more severe occlusions due to the lack of metabolic demand when the patient is at rest during the examination. Byrne, et al. compared transcutaneous oxygen measurement with angiography. They found TcPO₂ to have a sensitivity of 100% following exercise but falling to 77% at rest (Byrne, et al. 1984). This striking drop in sensitivity argues for standard exercise TcPO₂ testing.

Interpretation of Findings. Normal limb TcPO₂ values are 50- 60mmHg, though values greater than 55mmHg at any site regardless of age are considered normal (Cina, et al, 1984). Wound healing is considered unimpaired at pressures less than 40mmHg (White, et al. 1982). Pressures of 20mmHg are seen in legs with rest pain, ischemic ulcers, and/or gangrene, while pressures below 20mmHg usually require amputation (Oh, et al. 1987) (Table 1).



(a)



(b)

Fig. 1. Transcutaneous oximetry measurement technique. (a) chest and (b) foot. Courtesy of Casa Colina Centers for Rehabilitation Wound Care and Hyperbaric Medicine Program.

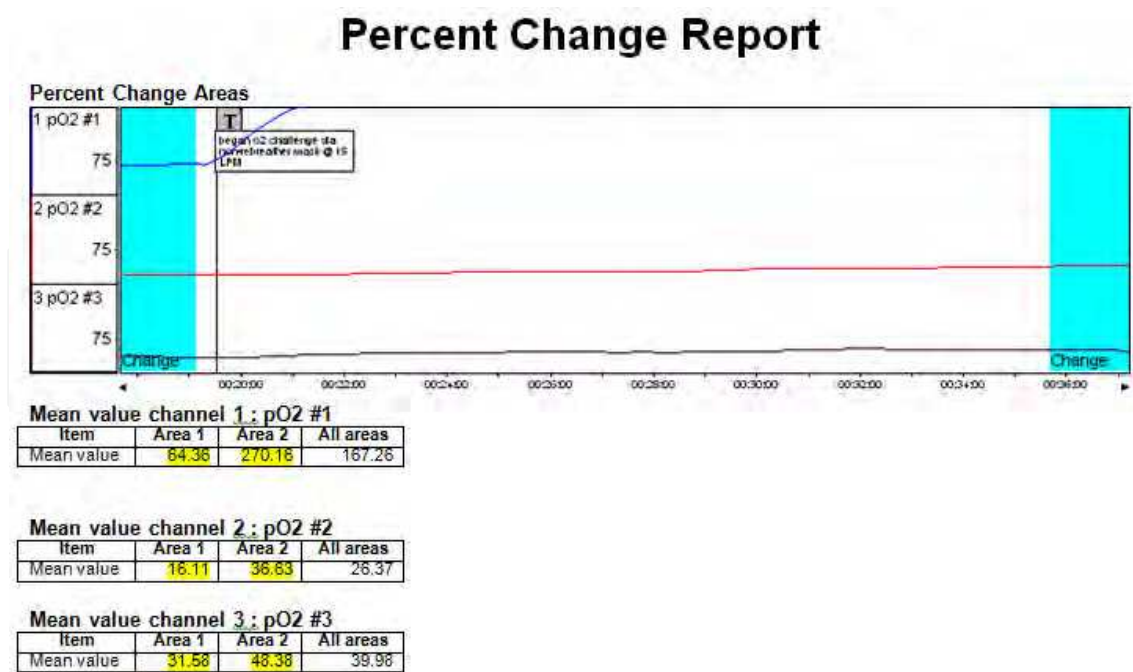


Fig. 2. Standard TCPO2 report. Courtesy of Casa Colina Centers for Rehabilitation Wound Care and Hyperbaric Medicine Program.

TcPO2 Value	Interpretation
>50 mmHg	Normal
40mmHg	Unimpaired wound healing
<30 mmHg	Impaired wound healing
20mmHg	Predicted rest pain, ischemic ulceration, gangrene.
<20mmHg	Amputation likely

Table 1. Transcutaneous oxygen values and associated clinical interpretation.

As noted above, TcPO2 measurement is most clinically relevant for assessing oxygenation in patients with more advanced arterial occlusion or performing the test with exercise. Additionally, since the results are not affected by sclerosis of the tunica media of arteries this is a viable test in patients with diabetes and renal disease (Hauser, et al. 1984). TcPO2 may also be used in conjunction with hyperbaric oxygen therapy.

Several limitations exist with the use of TcPO2. TcPO2 cannot be measured under certain physical conditions (edema, dry flaky skin, maceration, callused or plantar skin, cellulitis, or skin over bones and tendons) (Dooley, et al. 1996). These conditions tend to decrease the sensitivity of the probe to detect skin perfusion. Since the electrode probe is placed on intact adjacent skin rather than directly on the wound itself this method does not measure oxygen tension within the wound. The need to warm the extremity causes temperature differences between sites and subjects leading to false readings. TcPO2 is reliable in the normal but not in the low range, resulting in a high false positive rate for critical limb ischemia (Byrne, et al. 1984). Mechanical pressures on the electrode alter the TcPO2 value. Additionally, a significant amount of time is necessary to obtain pressure measurements with calibration,

sensor maintenance and skin preparation delaying a reliable reading upwards of 45 minutes. TcPO₂ is therefore site restrictive and operator sensitive.

Ulcer healing predictive value. TcPO₂ has a wound healing predictive accuracy of 83% and is unaffected by diabetic status or chronic renal failure (Padberg, et al., 1996). In reference to the appropriate time to perform lower extremity salvage surgery using TcPO₂ measurements after surgical intervention for arterial occlusion, Arroyo et al. found an optimal waiting period of at least three days and preferably one week before intervention (Arroyo, et al. 2002). In regards to predicting amputation healing Katsamouris and colleagues found that a level of 40mmHg at the anterior skin surface was predictive of successful healing after partial foot and lower leg amputations (Katsamouris, et al. 1984). Similarly, Ballard and colleagues successfully used TcPO₂ measurements to determine the severity of foot ischemia and guide treatment. They found that a transmetatarsal TcPO₂ level of 30mmHg or greater successfully predicted healing with conservative care in 31/36 (86%) of diabetic patients (Ballard, et al. 1995).

5. Skin perfusion pressure

Physiology of test. Skin perfusion pressure (SPP) utilizes a laser doppler and pressure cuff to evaluate reactive hyperemia. SPP measures the pressure at which blood flow first returns to the capillary during the controlled release of occlusive pressure.

Method. A laser sensor is placed on the desired location while a pressure cuff is placed at the ankle. The cuff is inflated until occlusion of the arterial flow to the extremity occurs and is then released. As arteriolar flow is restored and the subsequent reactive hyperemia occurs, the laser sensor reads the resulting arteriolar pressures.

Interpretation of Findings. Skin perfusion pressures greater than 40mmHg are considered non-ischemic while marginal ischemia is noted between 30 and 40mmHg. The wound is unlikely to heal below a pressure of 30mmHg (Castronuovo, et al., 1997).

The advantages of SPP are the following: it can be used in the presence of edema and in the plantar foot, no calibration is needed, no maintenance is required, no skin warming is necessary, and it is faster than TcPO₂ measurement (2-3 minutes per site).

The limitations of SPP are that it provides data regarding the limited area of skin under the sensor. Multiple separate readings are necessary to obtain a global understanding of pedal microvasculature.

Ulcer healing predictive value. SPP predicts a 90% healing ability above 30mmHg (Castronuovo, et al., 1997) and has a 100% negative predictive value (Adera, et al. 1995). In patients with critical limb ischemia SPP was 80% accurate in diagnosing this condition (Castronuovo, et al., 1997). Similarly, Faris and colleagues found SPP was useful in predicting healing of ulcers or gangrene of the feet in 35 of 40 diabetic patients with levels above 40mmHg. Conversely healing was unlikely if the SPP was less than 40mmHg (Faris, et al. 1985). Yamada, et al. studied a larger cohort of 211 patients with ischemic limbs. However, this cohort was not restricted to diabetic patients alone. As with the above mentioned studies, this group also found a threshold of 40mmHg as predictive of healing ulceration or gangrene but with a slightly lower sensitivity and specificity (72% and 88%, respectively) (Yamada, et al. 2008). In 85 limbs of 71 patients referred to a vascular laboratory, skin perfusion pressure measurement was found to correlate closely with toe pressure measurements (Tsai, et al. 2000), allowing substitution of SPP for toe pressures. This is a significant benefit in certain circumstances since it may be impractical to determine toe pressures due to the commonality of wounds on the toes.

6. Hyperspectral Imaging (HSI)

Physiology of test. Skin with wounds requires a greater amount of oxygen, without which healing will not occur. Hence, both oxygen delivery (measured by oxyhemoglobin) and oxygen extraction (measured by deoxyhemoglobin) into the wounded tissue can function as indicators of a wound's capacity to heal. This is done with the use of hyperspectral imaging (CombiVu-R System, HyperMed, Waltham, MA) which uses a spectral separator to vary the wavelength of light admitted to a detector. Red blood cells in the skin are struck with this variable light which is reflected back toward the detector. Since the wavelengths of light absorbed and emitted by oxygenated red blood cells (RBCs with oxyhemoglobin) differs by that emitted by deoxygenated red blood cells (RBCs with deoxyhemoglobin) the machine is able to detect the respective levels of these molecules with a high level of accuracy (Gillies, et al 2003, Greenman, et al. 2005). The data is then compared using a computer with standardized data for these molecules, and an image is provided with a color bar legend for comparison, and colored scans are used to demonstrate levels of oxygenation (Gilles, et al. 2003).

Method. Patients are placed supine, and scans are obtained from various areas of the lower extremity, including the wound site. The imaging technology does not require contact with the skin. An approximately 30 second scan is obtained at a 12 inch distance from the site in question. Images are displayed on a computer screen with a color bar for comparison. Oxyhemoglobin levels are associated with varying colors while deoxyhemoglobin is demonstrated by varying levels of brightness. Numerical values are also placed on the color bar, measured in AUs (astronomical units) (Figures 3 and 4).

Interpretation of Findings. A healing index has been suggested for the use of ulcer healing prediction based on the ratio of oxyhemoglobin to deoxyhemoglobin. Higher levels of both molecules correlate with a greater potential for healing (Khaodhiar, et al., 2007). In general a healing index greater than zero predicts an ulcer will heal while a negative healing index demonstrates an ulcer that is unlikely to heal.

Hyperspectral imaging provides multiple advantages including the lack of contact with skin, global examination of lower extremity microvascular supply, immediate accurate ulcer healing prediction, use on glabrous and nonglabrous skin, and ease of use and interpretation with a healing index.

Disadvantages of HSI are that few studies currently exist to fully validate the use of this modality. A thicker border surrounding the wound decreases the ability of HSI to discriminate well from poorly vascularized tissues. It is currently recommended to use a border thickness of 0.5 to 1 cm (Nouvong, et al., 2009).

Ulcer healing predictive value. Khaodhiar and colleagues found the following ulcer healing predictive values in a pilot study of HSI: sensitivity 93%, specificity 86%, positive predictive value 93%, and negative predictive value 86% (Khaodhiar, et al., 2007). A larger prospective clinical study by Nouvong, et al. found similar prediction values of 86% sensitivity, 88% specificity, and 96% positive predictive value (Nouvong, et al., 2009). This modality compares strongly with clinical observations to predict wound healing. Sheehan and colleagues in their study of clinical healing indicators found a 91% sensitivity, 58% specificity, 58% positive predictive value, and 91% negative predictive value using the percent change in area over a four week time period to predict ulcer healing (Sheehan, et al., 2003). Comparing HSI with clinical indicators demonstrates hyperspectral imaging is superior to following the clinical course in predicting the potential healing and nonhealing of diabetic foot ulcers.



Fig. 3. Hyperspectral imaging system.

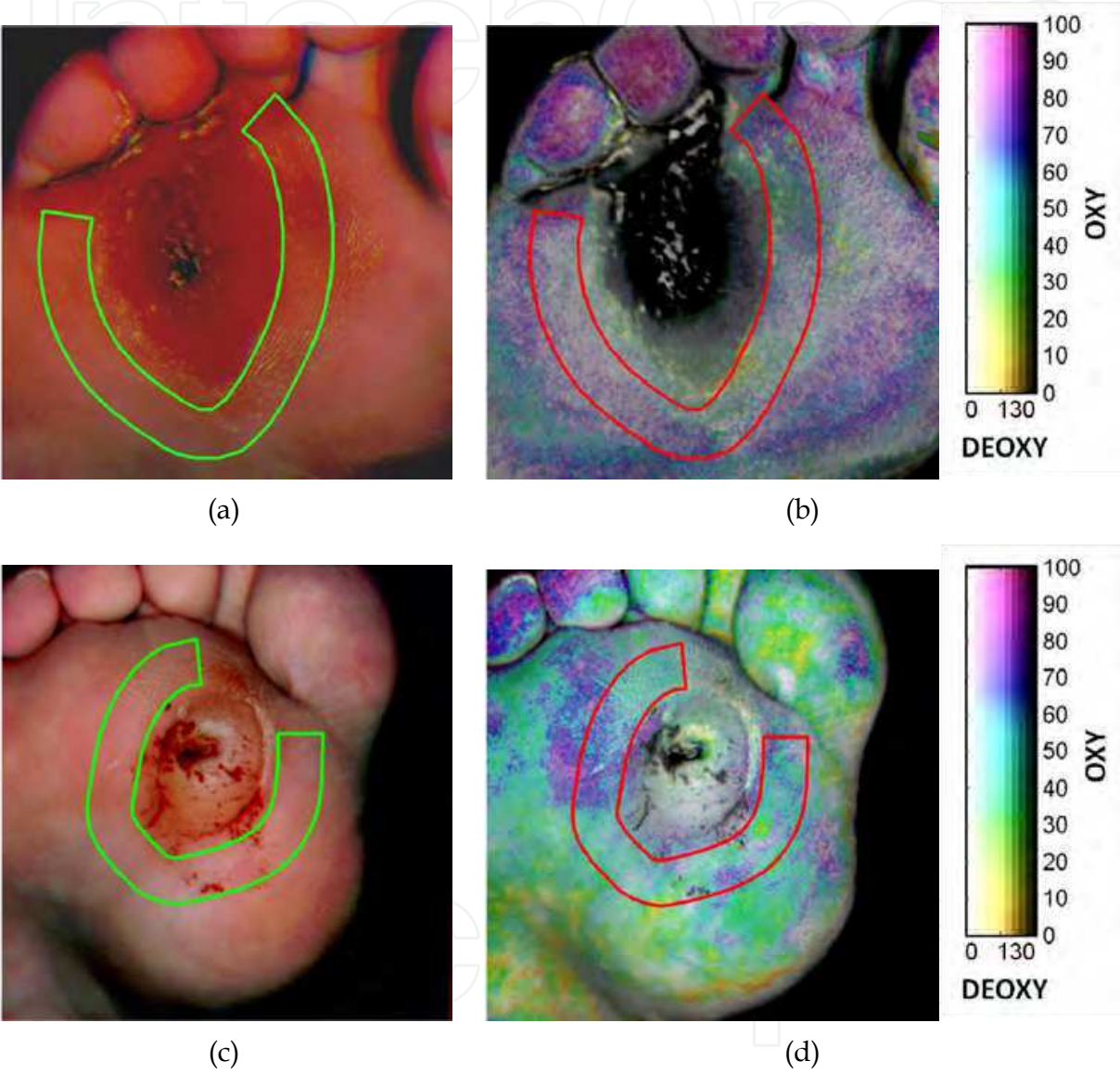


Fig. 4. (a) visible and (b) hyperspectral images of a healing diabetic foot ulcer and (c) visible and (d) hyperspectral images of non-healing diabetic foot ulcer.

7. Future directions for microcirculation testing

The assessment of microangiopathic disease is a new science with early clinical applications. As new technologies are developed physicians will increasingly be able to extract information about the vascular status of potentially ischemic areas while providing a greater understanding of the pathophysiology of the diabetic lower extremity.

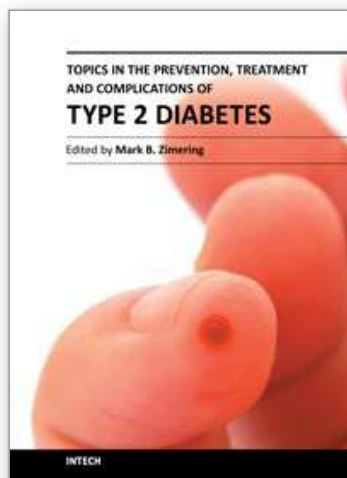
Laser Speckle Perfusion Imaging. This new technology employs the principle of laser scatter contrast imaging. In this technique a laser illuminates an area of tissue which produces a backscattered light. This light forms a pattern of light and dark areas called a speckle pattern (Draijer, et al. 2009). In 2007 a new device, the Full-Field Laser Perfusion Imager (FLPI) (Moor Instruments, Essex, UK), was released for commercial use (McGuire & Howdieshell, 2010). This device images skin to a depth no greater than 1 mm and results in images of blood flow within the skin (McGuire and Howdieshell 2010). The presence or absence of blood in the microvasculature indicates the ability to heal. This new technology is advantageous in providing real-time video images of microvascular blood flow (Thompson and Andrews 2010) and represents the potential future ability to view the dynamic microvascular environment within the skin. Future research is necessary to determine the predictive value of laser speckle perfusion imaging in wound healing and amputation level prediction.

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Type 2 diabetes is estimated to affect 120 million people worldwide- and according to projections from the World Health Organization this number is expected to double over the next two decades. Novel, cost-effective strategies are needed to reverse the global epidemic of obesity which is driving the increased occurrence of type 2 diabetes and to less the burden of diabetic vascular complications. In the current volume, Topics in the Prevention, Treatment and Complications of Type 2 Diabetes, experts in biology and medicine from four different continents contribute important information and cutting-edge scientific knowledge on a variety of topics relevant to the management and prevention of diabetes and related illnesses.

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