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# Skin blood flow dynamics and its role in pressure ulcers

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## Abstract

Pressure ulcers are a significant healthcare problem affecting the quality of life in wheelchair bounded or bed-ridden people and are a major cost to the healthcare system. Various assessment tools such as the Braden scale have been developed to quantify the risk level of pressure ulcers. These tools have provided an initial guideline on preventing pressure ulcers while additional assessments are needed to improve the outcomes of pressure ulcer prevention. Skin blood flow function that determines the ability of the skin in response to ischemic stress has been proposed to be a good indicator for identifying people at risk of pressure ulcers. Wavelet spectral and nonlinear complexity analyses have been performed to investigate the influences of the metabolic, neurogenic and myogenic activities on microvascular regulation in people with various pathological conditions. These findings have contributed to the understanding of the role of ischemia and viability on the development of pressure ulcers. The purpose of the present review is to provide an introduction of the basic concepts and approaches for the analysis of skin blood flow oscillations, and present an overview of the research results obtained so far. We hope this information may contribute to the development of better clinical guidelines for the prevention of pressure ulcers.

### Keywords

complexity; nonlinear analysis; pressure ulcers; skin blood flow; wavelet

## 1. Introduction

Pressure ulcers are a significant healthcare problem affecting the quality of life in persons who use wheelchairs and are a major cost to the healthcare system [1]. Pressure ulcer management is extremely difficult and presence of a pressure ulcer often prolongs hospitalization [2], which can contribute to further deterioration of a patient's general health condition [3]. In clinical practice, early prevention of pressure ulcers requires an effective method for identifying people at the highest risk of pressure ulcers [4]. Various assessment tools such as the Braden scale have been developed to quantify the risk level of pressure



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ulcers [5]. These scales have provided an initial guideline on preventing pressure ulcers while additional assessments are needed to improve the outcomes of pressure ulcer prevention [6, 7].

Pressure ulcers are caused by prolonged mechanical loading of the soft tissues, while the detailed mechanisms remain largely unknown [1, 8, 9]. Several theories have been developed pertaining to the link between mechanical loading and tissue necrosis, including localized ischemia [10–12], sustained deformation of cells [13, 14], impaired interstitial fluid flow and lymphatic drainage [15], and reperfusion injury [16]. Among these theories, local ischemia is widely accepted as the primary etiology of pressure ulcers [1, 8, 9]. The ischemia theory proposes that tissue ischemia induced by the occlusion of blood vessels by externally applied pressure causes ischemic damage of weight bearing tissues. Aligned with the ischemia theory, skin blood flow function that determines the ability of the skin in response to ischemic stress has been proposed to be a good indicator for identifying people at risk of pressure ulcers [8, 12].

The skin serves a number of vital functions. The majority of skin blood flow (~85%) regulates body temperature, and the remaining portion (~15%) is for the metabolic needs of the skin [17, 18]. Skin microcirculation is thought to reflect the microcirculation of other vascular beds [19]. For instance, endothelial dysfunction is a systemic disease process that occurs simultaneously in multiple vascular beds [20]. Skin microcirculation can be studied using minimally invasive methodologies so it has been used as a model circulation for investigating vascular disease mechanisms and the state of microcirculatory function in high-risk populations [6, 21–23].

Skin microcirculation can be assessed by quantifying changes in skin blood flow response to a variety of stimuli such as pressure [11, 24], local heating [25, 26], local cooling [12, 27], and specific vasoactive pharmacological agents delivered via iontophoresis or intradermal microdialysis [28]. Blood flow over large areas of skin can be measured using laser Doppler imaging [29], and rapid dynamic changes in flow over a small area can be measured using laser Doppler flowmetry (LDF) [4, 28]. In addition, spectral and nonlinear complexity analyses of blood flow oscillations (BFO) have been performed to investigate the influences of the metabolic, neurogenic, and myogenic activities on cutaneous microvascular regulation [6, 30–32]. To date, impaired mechanisms for skin blood flow regulation have been found in the normal aging process [6, 33], as well as a variety of pathological conditions such as hypertension [21, 34], diabetes [23, 35, 36], and spinal cord injury [27, 37, 38].

The purpose of the review is to provide an introduction of the basic concepts and approaches for the analysis of BFO, and present an overview of the results obtained so far. We hope this information will contribute to the understanding of the role of soft tissue ischemia on the development of pressure ulcers.

## 2. Dynamics of skin blood flow oscillations

### 2.1. Skin vasculature

Skin consists of the dermis and the epidermis (Figure 1). The epidermal layer of the skin contains no blood vessels, whereas the dermis has a rich blood supply. The vasculature of the dermis consists of two interconnected systems, the superficial vascular plexus in the capillary dermis and the deep vascular plexus at the dermal-subcutaneous interface, which represent the physiologically important areas in the skin [39]. The superficial plexus is comprised of paired arterioles and venules, with capillaries arising from these arterioles, extending upward within the papillary dermis and then looping back down to the venules. The deep vascular plexus contains arterioles and venules of larger diameter that arise from

the underlying muscles and subcutaneous fat [39, 40]. The two plexus are connected by paired ascending arterioles and descending venules, which supply the hair bulbs and sweat glands [39]. Sphincter-like smooth muscle cells are located at the point where the ascending arterioles divide to form the arteriolar component of the upper horizontal plexus [39].

Vessels in the papillary dermis are composed of terminal arterioles, arterial and venous capillaries, and postcapillary venules. The terminal arterioles, typically 17 to 26 μm in diameter, function as a part of the resistance vessels in the skin [39, 40]. In these arterioles, smooth muscle cells are lined with endothelial cells, capable of releasing vasodilators and vasoconstrictors such as nitric oxide (NO), prostanoids, and endothelium-derived hyperpolarizing and constricting factors [41]. There are abundant sympathetic nerve fibers in arterioles, which are adjacent to smooth muscle cells [42]. In the nonglabrous skin, blood vessels contain both adrenergic and sympathetic cholinergic nerves, whereas blood vessels in the glabrous skin are primarily innervated by sympathetic adrenergic nerves [36, 41]. In both the nonglabrous and glabrous skin, sensory nerves release vasoactive agents in response to thermal, chemical, and mechanical stimuli, which influence cutaneous vascular tone. In addition, these nerves serve to provide feedback to the central nervous system for local blood flow regulation [41].

Capillaries, usually 5–10 μm in diameter, are simple endothelial tubes surrounded by a basement membrane [42]. Capillaries permit the exchange of water, oxygen, carbon dioxide, and other nutrient and waste chemical substances between blood and surrounding tissues. Although capillaries cannot actively dilate or contract, the surface area available for exchange may be regulated to a degree by precapillary sphincters, rings of smooth muscle regulated by the sympathetic system, or by terminal arterioles. The capillary bed is an interwoven network of two types of vessels, including true capillaries which provide for the exchange of oxygen, carbon dioxide and nutrients, and a vascular shunt, a short vessel which directly connects the arterioles and venules in the bed.

### 2.2. Mechanisms of skin blood flow regulation

Skin blood flow regulation is based on the relationship between vascular resistance and vessel diameter [42, 43]. Blood vessels, specifically arterioles, can change their diameter passively or actively by altering the contractile state of smooth muscles in the vascular wall. Changes in diameter lead to changes in resistance within the vascular segment, which varies in approximately inverse proportion to the fourth power in vessel diameter [42]. Thus, a small increase in diameter would lead to a large increase in blood flow; conversely, a decrease in diameter would greatly decrease blood flow [43]. Transmural pressure, vessel wall shear stress, neurogenic stimuli, and metabolic stimuli are factors that induce active changes in the contractile state of vascular smooth muscles [44]. When smooth muscles are physiologically active, cutaneous arterioles constrict when pressure increases and dilate when pressure decreases. Arterial vessels respond to changes in wall shear stress via endothelial release of NO, leading to an increase in skin blood flow [26, 42]. Sensory nerves respond to thermal, chemical, and mechanical stimuli and so provide feedback to the central nervous system. They also release local neuropeptides and other vasoactive agents that influence vascular tone.

Postocclusive reactive hyperemia refers to the increase in skin blood flow that occurs following release of an arterial occlusion [24, 28] (Figure 2a). It is characterized by an initial peak in flux followed by a sustained hyperemia. This response has been used in the investigation of endothelial dysfunction [45] and changes in microvascular function following pharmacological intervention [46]. Despite its usefulness as a clinical tool in the assessment of microvascular reactivity, the exact mechanisms responsible for reactive hyperemia remain unclear. Several studies suggest that the hyperemic response could

involve endothelial vasodilators, myogenic response, and sensory nerves [28]. Of the endothelial vasodilators, there is evidence to suggest at least part of the response is mediated by prostanoids [46] and that NO does not play a significant role in the development or maintenance of reactive hyperemia [47, 48].

Local heating of the skin causes a vasodilation dependent on the degree and rate of heating [25, 26]. When local temperature is rapidly increased to 42°C and maintained at that level, the vasodilation is typically biphasic, including an initial peak followed by a moderate decrease leading to a prolonged plateau phase (Figure 2b). The initial vasodilatory phase is predominantly mediated by local sensory nerves whereas the plateau phase is predominantly mediated by NO. Results from a series of studies suggest that the NO is generated from the endothelial NO synthase isoform [49]. There is evidence suggesting the sympathetic neurotransmitters norepinephrine and neuropeptide Y are involved in both the initial peak and plateau phases [50].

Local cooling of the skin typically causes an initial decrease in skin blood flow followed by a transient vasodilation, and a progressive vasoconstriction [12, 41, 51] (Figure 2c). The rate of change in temperature, and the extent of temperature change influence the pattern of blood flow response [41]. The underlying mechanisms thought to be responsible for alterations in blood flow in response to local cooling include local activation of adrenergic nerves and an increase in the affinity of postsynaptic α-receptors (especially $\alpha_2$-receptors) with decreasing temperature [27, 52]. Local cooling prompts a vasoconstrictive effect via inhibition exerted by the NO system [53], in part at the level of the NO synthase enzyme and in part at steps downstream from the production of NO [51]. Adrenergic nerve components are involved in norepinephrine-mediated vasoconstriction triggered by the cooling stimulus.

### 2.3. Skin blood flow oscillations

Blood flow in microvessels is well known for oscillatory as opposed to steady. In the early 1920's, Nobel Prize winner August Krogh noted the heterogeneity of blood flow in the webbed feet of frogs [54]. He found that flow in capillaries may become retarded or accelerated and that the direction of flow in capillary anastomoses may change periodically. In the 1960's, measurements of red cell velocity in individual capillaries showed that fluctuations virtually always occur in microvessels [55]. Fung [56] suggested the dynamics of capillary blood flow could be attributed to the random statistical distribution of red blood cell sizes, blood vessel geometry, and the multiloop system. Griffith et al. [57] suggested spontaneous fluctuations in vascular diameter (vasomotion) and the nonlinear rheological properties of blood contributed to temporal heterogeneity in microvascular perfusion. Colantuoni et al. [58] studied vasomotion and flux motion in skeletal muscle microcirculation and proposed that flux motion is fundamentally dependent on the type of vessel from which it originates and is directly related to the vasomotion of the arterioles. Findings from numerous studies suggested that vasomotion and the consequent skin blood flow oscillations may play a critical role in determining the optimal distribution of blood flow in the microvascular bed [59–61].

### 2.4. Measurement of skin blood flow

A number of methodologies have been utilized to develop indices of skin blood flow [4, 28]. Skin blood flow over large areas can be measured using laser Doppler imaging. This technique is useful for examining spatial distribution of microvessel reactivity [29] while laser Doppler flowmetry (LDF) can be used to measure dynamic changes in skin blood flow over a small area [17]. The laser Doppler technology is based on the Doppler effect, first described by Johan Christian Doppler (1803–1853), which occurs when a shift in frequency is created when there is relative motion between the wave source and its observer. When a

laser beam strikes the skin surface, about 4 to 5% of the incident light is reflected back from the outer skin layer [17]. The remaining light beam is then scattered and partly absorbed by the tissue. Light hitting moving blood cells undergoes a frequency shift that is proportional to the velocity of the moving object while the frequency of light waves hitting static objects is unchanged. The magnitude and frequency distribution of these changes in wavelength are picked up by a receiving fiber, and analyzed to yield an indirect measure of red blood cell velocity and the concentration of blood cells. The measurement depth depends on tissue properties, the wavelength of the laser light, and the distance between the sending and receiving fibers in the laser Doppler probe [4]. For instance, in normal skin, using a probe with a fiber separation of 0.25 mm, and a 780 nm wavelength laser, the measuring depth is about 1mm. This depth is sufficient to reach the superficial vascular plexus but not the deep vascular plexus residing below the dermis [39].

LDF performance compares favorably to other measures of tissue perfusion including radioisotropic clearance, the most accurate measurement of skin perfusion, with correlation coefficients up to 0.98 [62]. The major advantage of this technique is its sensitivity in detecting and quantifying changes in skin blood flow in response to stimulus [28]. In the case of identifying people at risk of pressure ulcers, impaired vascular reactivity has been shown to be a better index that can overcome the temporal and spatial variations of skin blood flow [18, 28, 63]. Vascular reactivity is usually used to investigate the mechanisms involved in the regulation of skin blood flow, to detect functional changes associated with the development of diseases, or to evaluate the efficiency of disease treatment.

## 3. Linear analysis of blood flow oscillations

Skin blood flow signals have been analyzed using linear and nonlinear approaches in order to obtain information about impaired microcirculatory mechanisms. Linear analysis includes time domain analysis and spectral analysis. The former usually quantifies the overall variation in blood flux in response to a given stimulus, while the later quantifies the influences of the control mechanisms of BFO [24, 25, 30, 64]. Spectral analysis of skin BFO in human beings has revealed six characteristic frequencies which represent the influence of heart beat (~1 Hz), respiration (~0.3 Hz), myogenic activity of the vascular smooth muscle (~0.1 Hz), neurogenic activity in the vessel wall (~0.04 Hz), and two different mechanisms of vascular endothelial function (0.01 as nitric oxide dependent and 0.007 Hz as nitric oxide independent), respectively [30]. NO and endothelium-derived hyperpolarizing factor are hypothesized to be involved in the two mechanisms, respectively. The power within each frequency interval has been used to characterize the activity of the corresponded mechanism [25, 30, 64].

### 3.1. Time domain analysis of blood flow

The time dependent characteristics of reactive hyperemia include peak hyperemia, time to peak, and area under the curve of hyperemic response [28, 45] [12]. It is suggested that peak hyperemia may be related to how fast and how extensively the vessels react to ischemia [65] and time to peak may be related to vascular resistance [66]. As the duration of arterial occlusion in the human forearm increases, total hyperemic response also increases [47], the area under the curve of hyperemic response is considered as a measure of the need for metabolic repayment following tissue ischemia [67]. It was reported that peak hyperemia expressed as raw value or raw value minus baseline was highly reproducible, whereas it was less reproducible when expressed as raw value normalized to baseline [66]. However, the reproducibility of reactive hyperemia also depends on the skin site and baseline skin temperature [68]. Studies investigating the reproducibility of reactive hyperemia performed on the volar surface of the forearm showed that when the same skin site was studied, excellent reproducibility was observed [66]. It is therefore suggested that variations in

reactive hyperemia are mainly attributed to the variation in capillary density between different skin sites [46]. Blood flow response can be normalized to the maximal skin blood flow [41] or to the baseline [63]. In addition, since skin temperature plays an important role in baseline flux, maintaining skin temperature at an appropriate level can improve reproducibility of reactive hyperemia, especially when data are expressed as a function of baseline. Taken together, if skin sites are well chosen and baseline skin temperature is maintained at an appropriate level, results reported in different studies could be directly compared.

### 3.2. Spectral analysis of blood flow oscillations

**3.2.1. Fourier spectral analysis—**Spectral analysis, usually including Fourier spectral analysis or wavelet analysis, has been utilized to study activities of the regulatory mechanisms of skin blood flow [6, 30]. The Fourier spectral analysis is based on the assumption that a time series can be decomposed into a finite number of periodic sinusoidal functions with different frequencies and phases. Periodic oscillations of skin blood flow can be quantified directly by Fourier spectral analysis, which reveals the amplitude (energy) of the whole signal at given frequencies. Figure 3 shows an example of Fourier spectrum of the LDF signal shown in Figure 2b during 1–10 min Fourier transform bears no information about the time. Because characteristics of skin blood flow signals change continuously, they are better analyzed using wavelet transform, which is able to reveal both the dominant modes of variability and how those modes vary in time.

**3.2.2. Wavelet analysis—**Because characteristics of blood flow signals change continuously, it is better to perform spectral analysis using the wavelet transform. A wavelet is a function with zero mean and that is localized in both time and frequency domain [69]. This feature allows us to determine both the dominant modes of BFO and how those modes vary in time. Wavelet transform of a signal yields a three-dimensional structure above the time-frequency plane. Usually, the wavelet amplitude and power spectrum can be defined as the absolute values of the wavelet transform and their squares, respectively [69]. For skin blood flow signals, Morlet wavelet is a good choice, since it provides a good balance between time and frequency localization. Figure 4 shows an example of wavelet analysis of LDF signals. Because the characteristic frequencies vary with time (Figure 4a), some peaks of amplitude spectrum therefore are broadened (Figure 4b).

**3.2.3. Characteristic frequencies of BFO and their physiological origins—**Time frequency analysis of LDF signals has revealed a number of oscillatory components in the 0.005–2 Hz frequency interval [70, 71]. The oscillations at around 1 and 0.3 Hz correspond to heart beat and respiration, respectively. The low frequency oscillations around 0.1, 0.04, 0.01, and 0.007 Hz have been associated with the myogenic activity of vascular smooth muscle, the neurogenic activity of the vessel wall, and two different mechanisms of vascular endothelial activities, respectively [72–74]. Söderström et al. [74] found that spectral amplitude and power in the frequency interval 0.02–0.05 Hz normalized by the mean amplitude and total power in the interval from 0.0095 to 2 Hz were significantly lower in free skin flaps deprived of sympathetic nerve activity compared to intact skin in humans. They concluded that sympathetic nerve activity influences BFO at frequencies of 0.02–0.05 Hz. Because the amplitude of 0.01 Hz frequency increases when stimulated by acetylcholine rather than sodium nitroprusside, it is suggested that this frequency is associated with endothelial activity [75]. These mechanisms of low frequency oscillations are involved in the regulation of the vessels' resistance [76], but the exact mechanisms of skin blood flow regulation remain elusive [41, 51].

It has been found that the amplitudes and frequencies of the oscillatory components are not constant but vary with time [76]. Stefanovska [76] proposed explanations of the oscillatory nature of the cardiovascular system. One explanation is that each of the observed oscillatory components is a result of an ensemble of oscillators that are spatially distributed and not fully synchronized [76]. Another explanation holds that these variations come from interactions between the oscillators [76]. Since the low frequency BFO are generated locally, the variations in their amplitudes and frequencies may be due to interactions among the control mechanisms of blood flow [32, 63].

### 3.3. Applications of linear analysis

A variety of patho-physiolological conditions have been investigated using linear analysis techniques and abnormalities of BFO have been observed in hypertension, diabetes, congestive heart infarction, spinal cord injury, primary aging, and risk of pressure ulcers. Table 1 summarizes the major recent findings. These studies have shown the promise of using nonlinear analysis of BFO to further classify people at the highest risk of pressure ulcers and better understand the role of ischemia and viability on the development of pressure ulcers.

## 4. Nonlinear analysis of blood flow oscillations

BFO are directly related to vasomotion [42, 44] and vasomotion patterns have been found to change from sinusoidal to highly irregular/chaotic [57]. When stimulated by constrictor agonists, isolated arteries exhibit complex oscillations in tone/diameters, including transitions from periodic to quasiperiodicity, period-doubling intermittency [77, 78]. The sources and physiological benefits of chaotic vasomotion have been extensively discussed in recent reviews [79, 80]. It has been speculated that nonlinear analysis of BFO might provide valuable information about blood flow patterns in pathological conditions [31, 32, 81–83]. The rationale for using fractal and chaotic approaches to describe the dynamics of microflow fluctuations is twofold. On one hand, it is known that multiple local events affect blood flow in the microvascular network; but on the other hand, there is increasing evidence of chaotic dynamics of vasomotion in isolated segments of these vascular networks [80].

### 4.1. Fractal analysis

The fractal concept is often associated with objects that display self-similarity [84]. This concept has also been applied to quantify complex processes that exhibit irregular fluctuations across multiple time scales when such temporal variability is statistically self-similar [84]. A typical example of such processes is healthy heart rate regulation. Research studies have demonstrated that BFO can be viewed as a fractal process [81, 85]. Figure 5 shows a skin blood flow signal on three time scales. The fluctuations seen on different scales are not visually distinguishable, suggesting a statistical self-similar (scaling) property.

Fractal analysis aims to detect and quantify the scaling properties of time series. The most commonly used indexes include Hurst exponent [86], $1/f$ slope [87], fractal dimension [88], detrended fluctuation analysis (DFA) [89], and multifractal analysis [90]. DFA was introduced by Peng et al. [89] to quantify the long-range power law correlations of nonstationary time series. The root-mean-square fluctuation of the integrated and detrended data are measured within observation windows of various sizes and then plotted against window size on a log-log scale. A linear relationship between *log* (fluctuation) and *log* (window size) indicates the presence of scaling (self-similarity) and the slope gives the scaling exponent $\alpha$, which actually represents the correlation properties of the signal. An uncorrelated signal (white noise) yields $\alpha = 0.5$; a scaling exponent $\alpha > 0.5$ indicates the presence of positive correlations in the signal; and $0 < \alpha < 0.5$ indicates anti-correlations in the

signal [91]. For LDF signals, the log-log plot may exhibit more than one scaling region [32, 81]. For instance, local heating-induced vasodilatory blood flow shows three scaling regions with two crossovers [32, 81] (Figure 6). These regions are related to the frequency bands for different control mechanisms of skin blood flow [33, 81, 92].

### 4.2. Nonlinear dynamical analysis

A dynamical system is a model that determines the evolution of the system given only the initial state [93]. The evolution of the system corresponds to a series of consecutive points in its phase (state) space, which is called a trajectory of the system. The most commonly used nonlinear measures are correlation dimension (CD), Lyapunov exponents (LEs), and approximate entropy (ApEn) or sample entropy (SampEn) [93]. CD can be considered as a measure of the number of independent variables needed to define the system in phase space [94]. It quantifies the space-filling properties of the trajectories and thus reflecting the complexity of underlying dynamics [95]. LEs quantify the exponential divergence of initially close trajectories [96]. In principle, a positive largest exponent indicates the presence of chaos [96]. However, noise time series can also give rise to spurious positive exponents [97]. ApEn and SampEn reflect the conditional probability that any two sequences of length $m$+1 in the time series are similar given that they are similar for the first $m$ elements of the sequences [98]. A higher value of ApEn or SampEn indicates more regular structures of the time series. An effective way to check the nonlinearity of the data is the use of surrogate data [99]. One commonly used approach for construction of surrogate data is to perform a Fourier transform, randomize the phases, and then perform an inverse Fourier transform. This procedure preserves the power spectrum of the original data but destroys its nonlinear structures [100]. Thus, if a nonlinear measure of surrogate data is clearly different from that of the original data, it can be concluded that the original data contain some nonlinear structures.

Nonlinear measures are not designed to assess the magnitude of variability but the structures of time series. This makes nonlinear analysis particularly useful in characterizing the dynamics of BFO. However, one should be careful when interpreting the results of nonlinear techniques applied to BFO. First, no single statistical measure is able to assess the complexity of physiologic systems [101]. Fractal complexity of BFO refers to a multiscale, fractal-type of oscillations. ApEn and SampEn are fundamentally measures of regularity, not direct measures of complexity [101]. CD is actually equivalent to the randomness or degrees of freedom of the functional source and does not provide information on the evolution of trajectories over time [93]. Second, DFA can be used to separately quantify the correlation properties of the characteristic frequency components of BFO, whereas ApEn, SampEn, CD, or largest LE, reflects specific properties of the whole signal.

### 4.3. Applications of nonlinear analysis

Currently, assessment of BFO is largely based on statistical or spectral analysis, whereas nonlinear features are neglected. This is likely due to the difficulty in obtaining an explicit interpretation of results from the nonlinear analysis. Nevertheless, several authors have provided evidence for the potential ability of nonlinear methods to identify abnormal patterns of BFO [33, 82, 92, 102]. The major recent findings are summarized in Table 2. These findings have complemented the studies of nonlinear analysis of BFO on the understanding of pressure ulcer risk in various pathological conditions.

## 5. Conclusion

Although the etiology of pressure ulcers is multifactorial, tissue ischemia caused by mechanical loading is widely accepted as the primary factor [1, 9, 24]. Because skin blood

flow can be monitored non-invasively using LDF, evaluation of skin blood flow response to causative factors of pressure ulcers, e.g. surface pressure with thermal stress, may be a good indicator for identifying people with impaired microvascular function and at risk of pressure ulcers. Traditionally, clinicians rely primarily on the use of mean skin blood flow in the assessment of microvascular function. Such analyses are valuable in certain aspects such as local heating-induced maximal vasodilation, which may provide a reliable test of endothelial function [103].

Using spectral analysis of BFO, the underlying physiological mechanisms and the degree of impairment associated with various diseases can be further quantified. Such information may be used to further classify people at the highest risk of pressure ulcers. To sum up, the study of skin blood flow oscillations has shown the promise to characterize the microvascular impairments and its influence on the response to ischemic stresses in people at risk of pressure ulcers. Such information may be important to identify people at the highest risk of pressure ulcers.

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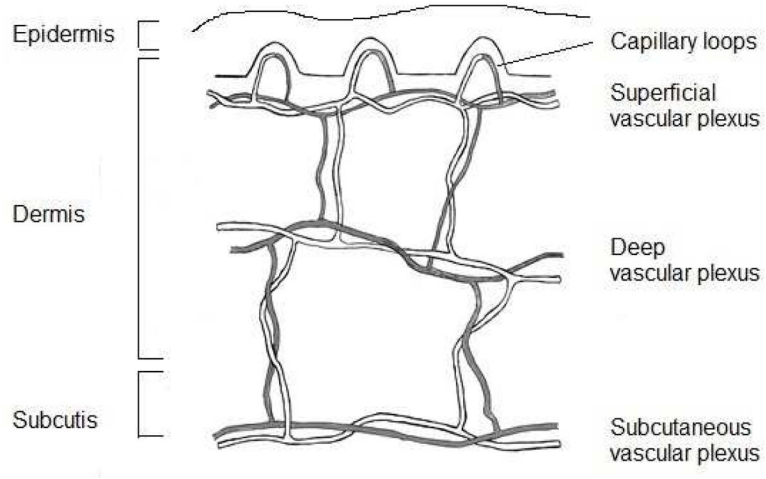


**Figure 1.**
Schematic diagram of the architecture of the skin vasculature.

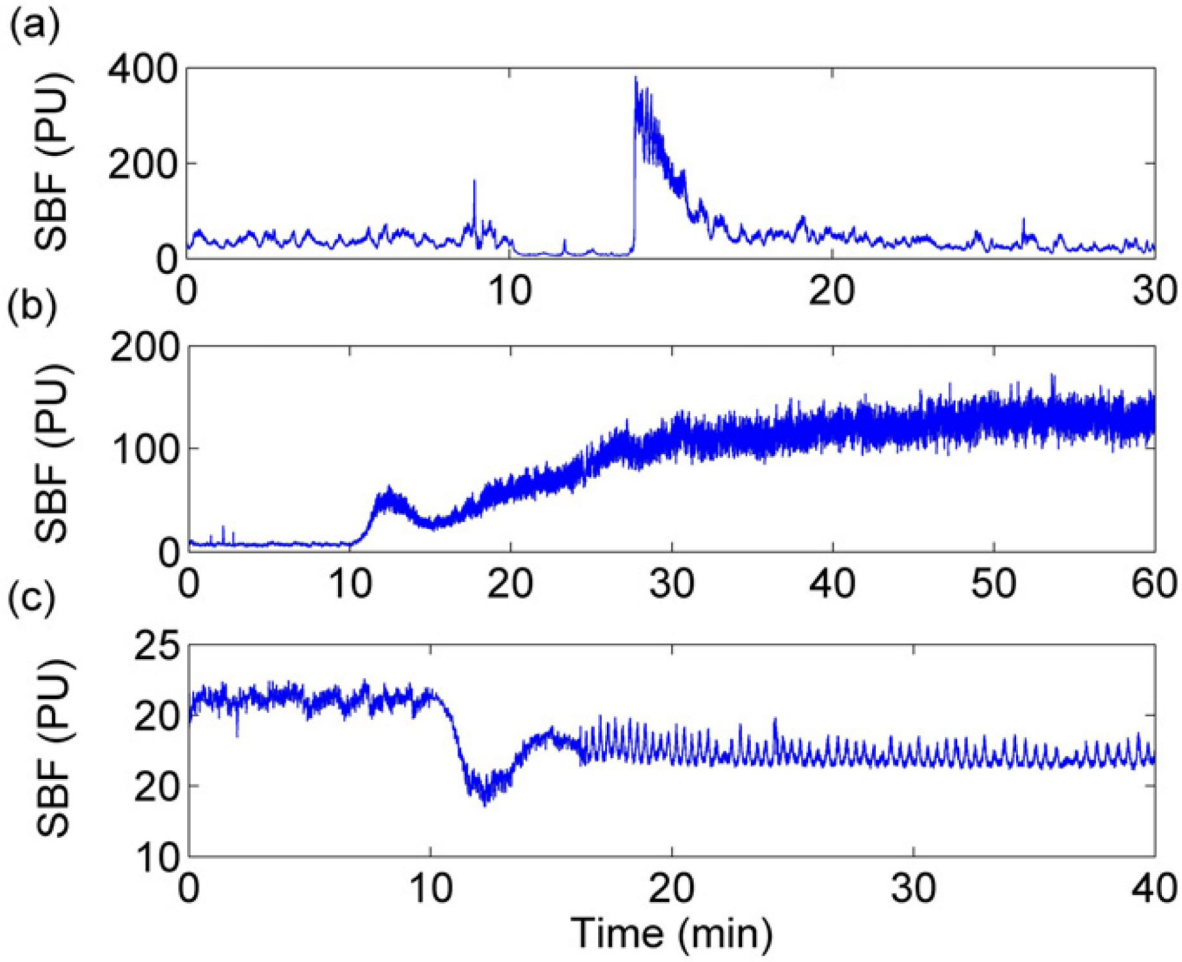


**Figure 2.**

Skin blood flow (SBF) response in the sacral skin of a heathy subject. (a) Skin blood flow under externally pressure shows a decrease between 10$^{th}$ and 14$^{th}$ min. After the removel of the pressure, skin blood flow shows an increase (reactive hyperemia). (b) SBF response to a rapid local heating to 42 °C shows a biphasic vasodilation. The first peak is mediated by axon relfex and the second pleateau is mediated by nitric oxide. (c) SBF response to local cooling to 25 °C. Skin blood flow decreaes in response to cooling. PU, perfusion unit.

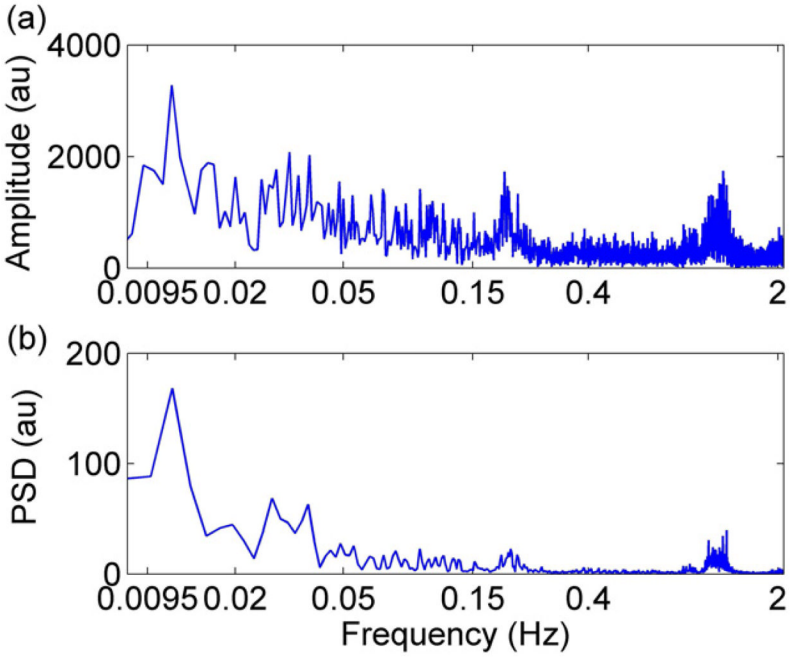


**Figure 3.**
Fourier spectrum of the LDF blood flow signal shown in Figure 2b during 1–10min. (a) The wavelet amplitude spectrum of the signal. (b) The power spectrum of the signal. PSD, power spectral density.

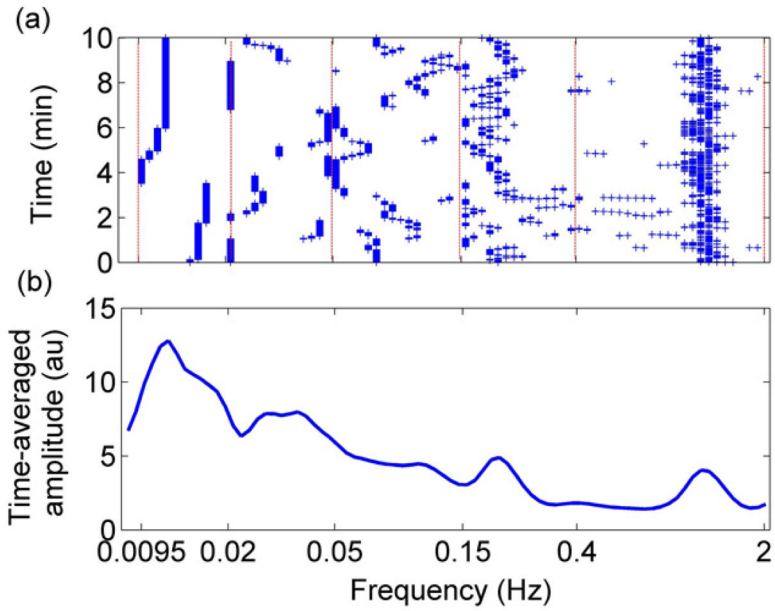


**Figure 4.**
An example of wavelet analysis of the LDF blood flow signal shown in Figure 2a. (a) Instantaneous frequencies corresponding to the local maxima of absolute wavelet coefficients. (b) Wavelet amplitude spectrum.

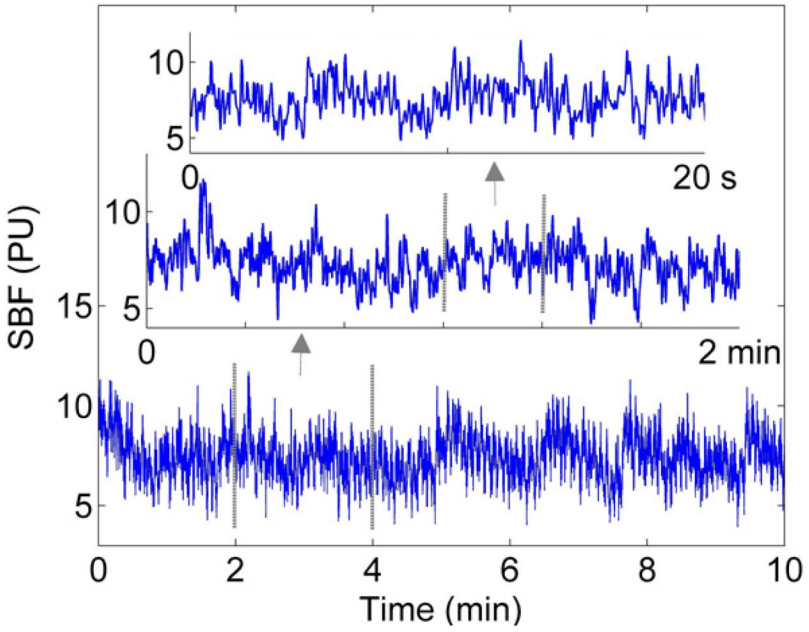


**Figure 5.**
Schematic representation of self-similar BFO on different time scales. The bottom panel shows a 10 min SBF signal (Figure 2b during 1–10 min), the middle panel shows a 2 min segment of the signal, and the top panel shows a 20 sec segment of the signal. SBF, skin blood flow; PU, perfusion unit.

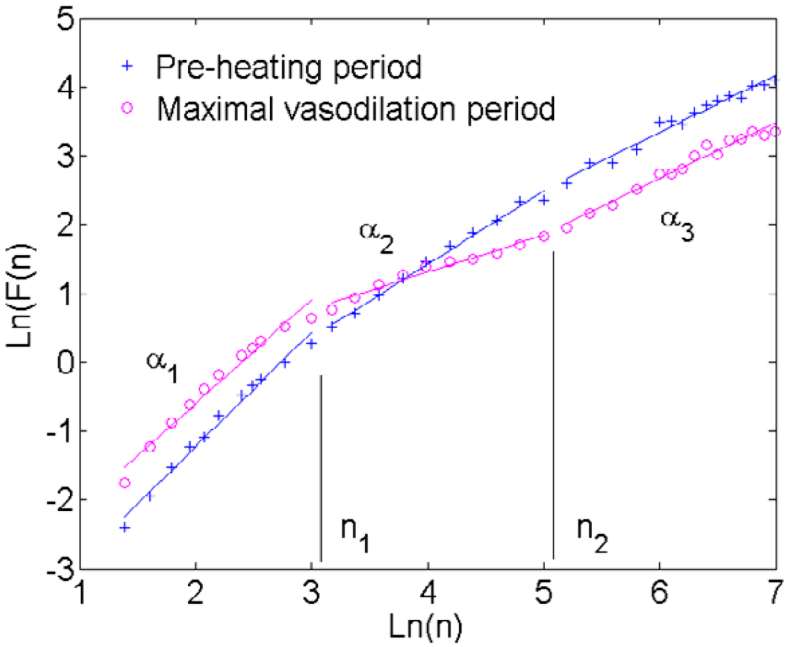


**Figure 6.**

Illustration of detrended fluctuation analysis of LDF blood flow signals. For the signal shown in Figure 2b during the pre-heating period (1–10 min), the scaling regions $n_1 < n < n_2$ and $n > n_2$ are not distinguishable (blue line), whereas the LDF signal during the maximal vasodilation period (51–60 min) exhibited three distinct scaling regions with two crossovers (pink line). In this figure, represents the observation window size, represents the corresponded fluctuation of BFO, and $\alpha_1$,$\alpha_2$, and $\alpha_3$ represent the scaling exponents.

## Table 1

Major recent findings of linear analysis of skin blood flow oscillations (BFO).

| Patho-physiological condition | Findings [Reference] |
|---|---|
| Pressure ulcer risk | Lower first peak and second peak during local heating to 42°C in the elderly [6]<br>Local cooling reduces ischemia of the weight-bearing soft tissues [12, 27]<br>Efficacy of wheelchair tilt-in-space and recline on improving viability of weight-bearing soft tissues in people with spinal cord injury [8, 104, 105]<br>Impaired blood flow response to alternating pressure in people with spinal cord injury [24]<br>Impaired blood flow response to postural changes in people with spinal cord injury [38]<br>Skin blood flow response to causative factors (mechanical stress, heating) in healthy people [25, 43, 63, 106] |
| Aging | Attenuated vasoconstrictor response to Norepinephrine [107]<br>Attenuated reflex cutaneous vasodilation [108] |
| Diabetes | Reduced 0.1 Hz BFO [35, 109]<br>Impaired neurogenic and myogenic BFO during the first peak of thermally induced maximal vasodilation and impaired metabolic BFO during the plateau phase; impaired myogenic BFO during reactive hyperemia [36] |
| Hypertension | Reduced postocclusive hyperemia [110]<br>Attenuated myogenic and neurogenic components in newly diagnosed essential hypertension; attenuated endothelial and neurogenic components in chronic essential hypertension [111] |
| Spinal cord injury | Diminished axon-reflex vasodilatation below the level of lesion in complete SCI [112]<br>Lower neurogenic BFO [113] |

## Table 2

Major recent findings of nonlinear analysis of skin blood flow oscillations (BFO).

| Patho-physiological condition | Findings [Reference] |
|---|---|
| Pressure ulcer risk | Decreased complexity of metabolic BFO in response to local heating in the elderly [32, 33]<br>Lower degree of complexity of metabolic BFO in people with spinal cord injury; lower degree of complexity of neurogenic BFO in people with complete spinal cord injury [37, 92]<br>Enhanced phase synchronization between heated and adjacent non-heated skin sites [114] |
| Aging | More monofractal and decreased sample entropy [31] |
| Diabetes | Loss of deterministic structure of 0.1Hz BFO in diabetic patients with neuropathy [82] |
| Endothelial dysfunction | Decreased DFA coefficient in the scale range related to endothelial activity Basal state [102] |