Microvascular Research 89 (2013) 40–46

Contents lists available at ScienceDirect

Microvascular Research

journal homepage: www.elsevier.com/locate/ymvre

Skin blood flow response to locally applied mechanical and thermal stresses in the diabetic foot

Yih-Kuen Jan [a,*], Sa Shen [a], Robert D. Foreman [b], William J. Ennis [c]

[a] Rehabilitation Research Laboratory, Department of Kinesiology and Community Health, University of Illinois at Urbana — Champaign, Champaign, IL, USA
[b] Department of Physiology, University of Oklahoma Health Sciences Center, Oklahoma City, OK, USA
[c] Section on Wound Healing and Tissue Repair, Department of Surgery, University of Illinois at Chicago, Chicago, IL, USA

ARTICLE INFO

Article history:
Accepted 20 May 2013
Available online 30 May 2013

ABSTRACT

Diabetic foot ulcers are one of the most common complications in diabetics, causing significant disabilities and decreasing the quality of life. Impaired microvascular reactivity contributes to the development of diabetic foot ulcers. However, underlying physiological mechanisms responsible for the impaired microvascular reactivity in response to extrinsic causative factors of foot ulcers such as mechanical and thermal stresses have not been well investigated. A total of 26 participants were recruited into this study, including 18 type 2 diabetics with peripheral neuropathy and 8 healthy controls. Laser Doppler flowmetry was used to measure skin blood flow at the first metatarsal head in response to a mechanical stress at 300 mm Hg and a fast thermal stress at 42 °C. Wavelet analysis of skin blood flow oscillations was used to assess metabolic, neurogenic and myogenic controls. Our results indicated that diabetics have significantly decreased metabolic, neurogenic and myogenic responses to thermal stress, especially in the neurogenic and myogenic controls during the first vasodilatory response and in the metabolic control during the second vasodilatory response. Diabetics have a significantly decreased myogenic response to mechanical stress during reactive hyperemia. Our findings demonstrate that locally applied mechanical and thermal stresses can be used to assess microvascular reactivity and risk of diabetic foot ulcers.

Introduction

Diabetic foot ulcers are one of the most common complications in diabetics, causing significant disabilities and decreasing the quality of life in diabetics (Burns and Jan, 2012). Fifteen percent of diabetic patients develop at least one foot ulcer during their lifetime. Diabetic foot ulcers may lead to amputations that remain the leading cause of non-traumatic lower-extremity amputations in the United States. Reducing the incidence of diabetic foot ulcers and subsequent amputations remains a top priority in healthcare (Boulton et al., 1999, 2008).

The pathogenesis of diabetic foot ulcers is multifactorial and the result of a complex interplay of a number of factors including peripheral neuropathy, high plantar pressure associated with foot deformity and stiffening plantar soft tissues, and impaired microvascular reactivity (Boulton et al., 2008; Dinh and Veves, 2005; Gefen, 2010; Jan et al., 2013). Foot ulceration does not develop spontaneously and usually follows foot trauma caused by mechanical stress on the foot during walking. Loss of protective sensation permits continuation of repetitive mechanical stresses that go undetected leading to plantar tissue ischemia and subsequent damage (Boulton et al., 1999). Abnormal temperature responses of the plantar skin during walking also increase risk of foot ulcers (Najafi et al., 2012). The most common sites of diabetic foot ulcers are on the plantar surface of the foot under the first and second metatarsal heads (Caselli et al., 2002).

The skin over the metatarsal heads is glabrous that has numerous arteriovenous anastomoses innervated by sympathetic vasoconstrictor nerves (Kellogg, 2006). In the nonglabrous skin (limb and truck), skin blood flow is regulated under sympathetic vasoconstrictor and vasodilator nerves. The differences in the vasculature and neurogenic innervation between the glabrous and nonglabrous skin result in different regulatory controls (Kellogg, 2006; Metzler-Wilson et al., 2012; Wilson et al., 2005). Although impaired microvascular reactivity in diabetics has been well documented in the literature, most studies have been conducted on the nonglabrous skin such as forearm and dorsum of the foot (Burns and Jan, 2012; Chao and Cheing, 2009; Schramm et al., 2006). Such assessment may not provide direct information on the viability and ischemia of plantar soft tissues that are subject to repetitive mechanical and thermal stresses. Newton et al. (2005) demonstrated that the plantar skin area with high pressure during walking has higher skin blood flow compared to the plantar skin with low pressure. They postulated that this may be due to a protective or maladaptive response of the plantar skin to repetitive mechanical stresses during walking. Furthermore, studying blood

* Corresponding author at: Rehabilitation Research Lab, Department of Kinesiology and Community Health, University of Illinois at Urbana — Champaign, 1206 South Fourth Street, MC-588, Champaign, IL 61820, USA. Fax: +1 2173332766.
E-mail address: yjan@illinois.edu (Y.-K. Jan).

0026-2862/$ – see front matter © 2013 Elsevier Inc. All rights reserved.
http://dx.doi.org/10.1016/j.mvr.2013.05.004

flow response to locally applied mechanical and thermal stresses may provide more direct information of soft tissue viability/ischemia (Jan et al., 2011, 2012).

Impaired microvascular reactivity has been demonstrated as a main cause of ischemia of the diabetic foot (Boulton et al., 1999; Burns and Jan, 2012; Chao and Cheing, 2009; Schramm et al., 2006). Research studies have demonstrated that diabetes causes endothelial dysfunction and autonomic nervous impairment while their effect on the impaired microvascular reactivity and pathogenesis of diabetic foot ulcers remains largely unknown. Skin blood flow is featured for variations due to vasomotion and is influenced by temporal and spatial factors (Bertuglia et al., 1996; Jan et al., 2005). Assessing the dynamics of skin blood flow has been demonstrated to be a more reliable method to study microvascular reactivity (Geyer et al., 2004; Humeau et al., 2004; Stefanovska et al., 1999). The underlying mechanism of impaired microvascular reactivity in diabetics can be quantified by using wavelet analysis of blood flow oscillations (BFO). Wavelet analysis of BFO reveals five characteristic frequencies that are associated with metabolic, neurogenic, myogenic, respiratory and cardiac activities (Jan et al., 2009; Stefanovska et al., 1999). This method may advance our understanding about underlying mechanisms responsible for impaired microvascular reactivity and be used for early detection of diabetics at risk of foot ulcers (Geyer et al., 2004; Rossi et al., 2006).

Wavelet analysis of BFO has been widely used to study blood flow regulation in various pathological conditions, but few studies have used wavelet analysis to examine microvascular reactivity in diabetics (Humeau et al., 2004; Rossi et al., 2005; Sun et al., 2012; Urbancic-Rovan et al., 2004). Furthermore, most of these studies have focused on basal skin blood flow status and only a few have investigated skin blood flow over the metatarsal heads (common sites of diabetic foot ulcers) in response to mechanical or thermal stresses (Burns and Jan, 2012). In order to understand the pathogenesis of diabetic foot ulcers, we evaluated skin blood flow at the first metatarsal head in response to mechanical and thermal stresses using wavelet analysis of BFO to characterize impaired underlying physiological mechanisms in diabetics with peripheral neuropathy. We hypothesized that diabetics with peripheral neuropathy have impaired microvascular reactivity in response to mechanical and thermal stresses and impaired metabolic endothelial control is responsible for these attenuated blood flow response in diabetics with peripheral neuropathy.

Methods

Participants

A total of 26 participants were recruited into this study, including 18 diabetics (13 males) and 8 healthy controls (4 males). The inclusion criteria included type 2 diabetes with peripheral neuropathy and a history of foot ulcers. The exclusion criteria included diagnosed peripheral arterial disease (ankle brachial index (ABI) <0.9 or >1.3), cardiovascular diseases, foot edema, hypertension, treatment using of vasoactive medicines, active foot ulcers or foot ulcer healed within 3 months, and gross foot deformities or prior foot amputations/major surgeries. This study was approved by a university institutional review board. Informed consent was obtained from each participant prior to any testing. The demographic data of the participants with diabetes were: age 48.5 ± 9.4 years, height 1.78 ± 0.1 m, weight 90.6 ± 30.4 kg, body mass index (BMI) 28.3 ± 7.1 kg/m^2, duration of diagnosed diabetes 15.2 ± 5.1 years, and HbA_1c 7.8 ± 0.9%. Peripheral neuropathy was confirmed by the inability to sense a 10 g Semmes–Weinstein monofilament at least 4 locations on the plantar surface of the right foot. The demographic data of the healthy controls were (mean ± standard deviation): age 21.8 ± 2.4 years; height 1.71 ± 0.1 m; weight 75.7 ± 11.7 kg, and BMI 25.8 ± 3.3 kg/m^2. Diabetic participants took the following medications: Glyburide, Metformin, and Neurontin.

Protocols

Room temperature was maintained at 24 ± 2 °C. All participants remained relaxed for at least 30 min in the laboratory to acclimate to the room temperature. Laser Doppler flowmetry (LDF) (PeriFlux 5001, Perimed, Ardmore, PA) and an LDF probe with heating and cooling function (Probe 415–242, Perimed) were used to measure skin blood flow at the first metatarsal head of the right foot. Skin blood flow was sampled at 32 Hz. The participant was asked to lie in a supine position and an LDF probe was taped on the first metatarsal head. There were two experimental protocols. The first protocol was used to study skin blood flow responses to mechanical stress, including a 10 min baseline, a 3 min loading at 300 mm Hg and a 17 min recovery period. The 300 mm Hg pressure was applied with an indenter (Jan et al., 2012, 2013). An example of skin blood flow at the first metatarsal head in response to mechanical stress is provided in Fig. 1. The second protocol was used to test skin blood flow response to local heating, including a 10 min baseline, a 30 min heating period at 42 °C, and a 10 min recovery period. The skin temperature was raised to 42 °C in 2 min and maintained at that temperature for the duration of the 30 min heating period. This non-painful heating protocol was designed to induce a biphasic vasodilatory response, including an axon reflex mediated vasodilation (first peak) and nitric oxide mediated vasodilation (second peak or plateau) (Jan et al., 2009; Minson et al., 2001). An example of skin blood flow at the first metatarsal head in response to thermal stress is provided in Fig. 1. A 30 min washout was allowed between two protocols.

Wavelet analysis

Wavelet analysis of BFO was performed to study underlying physiological mechanisms associated with various blood flow responses. Wavelet analysis of LDF signals in the human skin reveals five characteristic frequencies, reflecting the metabolic activity (0.0095–0.02 Hz), neurogenic activity (0.02–0.05 Hz), myogenic (vascular smooth muscle) activity (0.05–0.15 Hz), respiratory (0.15–0.4 Hz), and cardiac (0.4–2.0 Hz) origins. In this study, we focused on the local mechanisms of that are metabolic, neurogenic, and myogenic controls. Detailed wavelet analysis and related methods can be found in our previous publication (Jan et al., 2009). Here we summarize the methods. Continuous wavelet transform of a skin blood signal $x(u)$ is defined as

$$w(s,t) = \int_{-\infty}^{\infty} \psi_{s,t}(u)x(u)du, \tag{1}$$

where $\psi_{s,t}(u)$ is a wavelet function, defined as

$$\psi_{s,t}(u) = \frac{1}{\sqrt{s}}\psi\left(\frac{u-t}{s}\right), \tag{2}$$

where ψ is the mother wavelet function, t is time, and s is the scale related to the central frequency of $\psi_{s,t}(u)$. In this study, we used the Morlet wavelet, which is defined as

$$\psi_0(u) = \pi^{-1/4} e^{j\omega_0 u} e^{-u^2/2}, \tag{3}$$

where ω_0 is the nondimensional frequency. By choosing $\omega_0 = 2\pi$, the relation between s and the central frequency of $\psi_{s,t}(u)$ is $f = 1/s$ (Bracic and Stefanovska, 1998). Wavelet amplitudes of each characteristic frequency band were used to assess activities of blood flow controls. To overcome individual variations, normalized wavelet amplitudes were used in this study and were defined as the ratio of the mean amplitude of the frequency band to that of the same frequency band of the basal skin blood flow. For the heating protocol, skin blood flow around a 10 min length during the first peak and around a 10 min length during the second peak was used to calculate wavelet amplitudes. For the loading protocol, a reactive hyperemic response of