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Characterizing human skin blood flow regulation in response to different local skin temperature perturbations

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ABSTRACT

Small nerve fibers regulate local skin blood flow in response to local thermal perturbations. Small nerve fiber function is difficult to assess with classical neurophysiological tests. In this study, a vasomotor response model in combination with a heating protocol was developed to quantitatively characterize the control mechanism of small nerve fibers in regulating skin blood flow in response to local thermal perturbation.

The skin of healthy subjects' hand dorsum ($n = 8$) was heated to 42 °C with an infrared lamp, and then naturally cooled down. The distance between the lamp and the hand was set to three different levels in order to change the irradiation intensity on the skin and implement three different skin temperature rise rates (0.03 °C/s, 0.02 °C/s and 0.01 °C/s). A laser Doppler imager (LDI) and a thermographic video camera recorded the temporal profile of the skin blood flow and the skin temperature, respectively.

The relationship between the skin blood flow and the skin temperature was characterized by a vasomotor response model. The model fitted the skin blood flow response well with a variance accounted for (VAF) between 78% and 99%. The model parameters suggested a similar mechanism for the skin blood flow regulation with the thermal perturbations at 0.03 °C/s and 0.02 °C/s. But there was an accelerated skin vasoconstriction after a slow heating (0.01 °C/s) (p-value < 0.05). An attenuation of the skin vasodilation was also observed in four out of the seven subjects during the slow heating (0.01 °C/s). Our method provides a promising way to quantitatively assess the function of small nerve fibers non-invasively and non-contact.

1. Introduction

Small nerve fibers (myelinated Aδ and unmyelinated C nerve fibers) carry multiple functions, such as temperature sensation, pain sensation and autonomic functions (Hoitsma et al., 2004). Small fiber neuropathy, a complication of diabetes and also seen in polyneuropathies of other origin, is a peripheral nerve disease that selectively affects small nerve fibers and their functions (Lacomis, 2002). Small fiber neuropathy has a huge negative impact on the quality of patients' daily life (Fink and Oaklander, 2006). Early diagnosis of small fiber neuropathy and, consequently, early treatment are crucial to slow down or even prevent the progress of small fiber neuropathy.

Currently, a gold standard is not always available for the diagnosis of small fiber neuropathy, as small nerve fibers are invisible in routine neurophysiological examination. Skin biopsy with an assessment of intra-epidermal nerve fiber density, compared with quantitative sensory testing and quantitative sudomotor axonal reflex test, has a higher sensitivity for the diagnosis of small fiber neuropathy (Sommer and Lauria, 2007), but the relation between the loss of intra-epidermal nerve fiber and the pathology of small fiber neuropathy is still unknown. Moreover, skin biopsy requires specialized laboratory and intensive labor.

Corneal confocal microscopy, quantitative sensory testing and laser Doppler techniques can also facilitate the diagnosis of small fiber neuropathy (Caselli et al., 2006; Cruccu et al., 2010; Illigens et al., 2013; Namer et al., 2013; Tavakoli et al., 2010; Vas and Rayman, 2013). However corneal confocal microscopy only assesses small fiber structure, not small fiber function. Quantitative sensory testing, particularly tests of temperature perception thresholds, is dependent on subject's thermal perception and cooperation, which may lead to biased results

Abbreviations: AU, arbitrary units; LDI, laser Doppler imager; LTI, linear time-invariant; ROI, region of interest; RRST, rise rate of the skin temperature; VAF, variance accounted for.

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(Freeman et al., 2003). Concerns about laser Doppler techniques include limited spatial or temporal resolution and the lack of standardization in laser-Doppler image processing.

Infrared thermography, with the advantages of being non-contact, convenient and explicit, has been frequently used to investigate skin vasomotor responses in recent studies (Gazerani and Arendt-Nielsen, 2011; Nielsen et al., 2013; Sun et al., 2006). Infrared thermography measures skin temperature which is determined not only by skin blood flow but also by many other factors, such as skin tissue thermal properties, heat transfer within tissue and at the skin-environment interface, and metabolic heat generation. Therefore, combined with thermography, a physical or mathematical model is necessary to translate skin temperature into skin vasomotor physiology. Among numerous studies in this field, Pennes made a groundbreaking contribution in 1948 known as Pennes bioheat equation (Pennes, 1948). An excellent review on recently developed bioheat models is presented by Bhowmik et al. (2013). Nitzan et al. (1988) and Raamat et al. (2002) reported a good correlation between the dynamics of skin blood flow and of skin temperature with modified thermal clearance method. Skin temperature curve can also provide information on skin blood flow as well as other tissue physiology (Bandini et al., 2013; Merla et al., 2002; Renkielska et al., 2006).

Small nerve fibers regulate local skin blood flow to control local skin temperature. The regulation process involves a number of different factors including TRPV-1 channels and the release of calcitonin-gene related peptide and/or substance P (Holzer, 1992; Wong and Fieger, 2010). A sustained heating at 42 °C induces a fast and initial increase of the skin blood flow in about 10 min, by exciting the axon reflex of small nerve fibers to release vasoactive peptides (Charkoudian et al., 2002; Minson et al., 2001; Pergola et al., 1993). The initial increase of the skin blood flow is relatively small when the local skin temperature remains below 35 °C, becomes significant for the skin temperatures above 37 °C and reaches a peak at around 42 °C (Barcroft and Edholm, 1943; Magerl and Treede, 1996).

Identification of the control mechanism of small nerve fiber for regulating skin blood flow response is a promising way to quantitatively assess the functionality of small nerve fibers. Few studies were conducted in this field. Mariotti et al. (2009) used a hypothetical control model to discriminate the presence of Raynaud's phenomenon, which is a condition with excessive reduction of skin blood flow in response to a thermal or emotional stress. Besides, small-fiber-regulated skin vasodilation is influenced by local heating rate, and a fast heating induces an increasing skin vasodilation (Hodges et al., 2009).

Nieuwenhoff et al. (2016) developed an experimental setup in which non-contact heating with an infrared lamp evokes small-fiber-mediated skin vasodilation. In this study, the same setup was used. The aim of this study was to 1) develop a quantitative control model which can characterize the mechanism of small nerve fibers for regulating the skin blood flow in response to a local thermal perturbation, and 2) test the hypothesis that the model parameters would change when different local thermal perturbations are applied, indicating a varying skin blood flow regulation mechanism.

2. Methods

2.1. Subjects

Ten healthy subjects (5 men and 5 women, age: 27.2 ± 2.8 years, height: 1.75 ± 0.13 m, weight: 68.4 ± 14.4 kg, values are mean ± standard deviation) participated in the study. All subjects were free of any conditions which may affect skin vasomotor response, such as neurological or vascular disorders. Before the experiment, the subjects were informed on the experimental protocol, and signed informed consent. The experiment was approved by Human Research Ethics Committee of Delft University of Technology, Delft, The Netherlands.

The subjects were requested to refrain from smoking, caffeine and alcohol for at least 8 h before the experiment, and to avoid the use of lotion, gel, cream or cosmetics on the left hand on the day of the experiment. The dorsum of the left hand was visually inspected to be free of skin injuries or scars. All accessories that may obstruct the experiment (such as rings, bracelets and watches) were removed.

2.2. Experimental setup

Fig. 1 gives an overview of the experimental setup. The experiment was performed in a temperature-controlled room (22–25 °C) with steady room illumination. The subject's left hand was heated with an infrared lamp approved for clinical use (Hydrosun 750 with optical filter Schott BG780; Hydrosun Medizintechnik GmbH, Mullheim, Germany). The emitted infrared wavelength ranged between 780 and 1400 nm and the axial irradiance was 4400 W/m^2. The lamp's heating field was centered at the dorsum of the subject's hand, and the distance between the hand and the lamp was varied according to the experimental protocol.

A laser Doppler imager (LDI) (PeriScan PIM3 System; Perimed AB, Jarfalla, Sweden) measured skin blood flow in arbitrary units (AU). The region of interest (ROI) of the LDI was a 5.0 × 5.0 cm area, centered at the hand dorsum, with a resolution of 3 mm and total 17 × 17 pixels. The frame rate was around 10 s per frame (i.e. a scan rate of ~35 ms per pixel).

The skin temperature was measured with a thermographic video camera (FLIR SC5600, FLIR System Inc., Wilsunville, USA) at a frame rate of 5 Hz and a resolution of 640 × 512 pixels. The skin emissivity was set at 0.98 (Steketee, 1973). The detectable temperature range was 5–57 °C with a resolution of 0.02 °C. The skin temperature at the dorsum center was monitored in real-time (Altair, FLIR System Inc., Wilsunville, USA). The ROI in the thermography was a quadrangle of which the corners were marked by four markers (Fig. 1).

2.3. Protocol

The timeline of the protocol is presented in Fig. 2. In each measurement the skin temperature and the skin blood flow were recorded simultaneously. The subjects acclimated to the room environment for at least 15 min before the start of the first measurements. The distance between the hand and the infrared lamp was set 20 cm in the first and the second measurement (M20(1) and M20(2), respectively). The increase of the skin temperature was significantly affected by the radiation flux from the infrared lamp, and the radiation flux on the skin was related to the distance between the lamp and the skin. In order to obtain different thermal perturbations, the hand-lamp distance was set 25 cm and 30 cm in the third (M25) and the fourth (M30) measurement, respectively.

In each measurement a 1 min baseline was recorded before the lamp was switched on to heat the skin (heating phase). The lamp was switched off when the skin temperature at the dorsum center reached 42 °C. Thereafter the measurement continued for 5 min to let the skin naturally cool down (cooling phase).

2.4. Data processing

Data were analyzed using custom-made scripts written in Matlab (Matlab R2013a, the Mathworks, Natrick, USA). In the following context the skin temperature and the skin blood flow respectively refer to the mean skin temperature and the mean skin blood flow over the pixels in the ROI, unless stated otherwise.

The baselines of the skin temperature and the skin blood flow were obtained by averaging the signals in the 1 min before the heating phase. Relative skin blood flow was defined as the skin blood flow normalized to the baseline. The heating time was obtained by visually inspecting the video thermography, as the start and the end of the heating were accompanied by an abrupt change in the skin temperature. The rise rate