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Cold-induced sympathetic tone modifies the impact of endothelium-dependent vasodilation in the finger pulp☆

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ABSTRACT

Objective: In thermoneutral and cold subjects, the sympathetic nervous system regulates skin blood flow by adjusting frequency of the tonic vasoconstrictor impulses. However, the way these thermoregulatory impulses influence the vascular endothelium is not well known. We studied how the sympathetic nervous system influences endothelium-dependent vasodilation (EDV) caused by shear stress in skin containing arteriovenous anastomoses (AVAs) and arterioles in healthy subjects.
Methods: Thirteen healthy subjects were exposed to thermoneutral (29 °C) and cold (22 °C) ambient temperatures on separate days. EDV was induced by releasing suprasystolic pressure cuff applied to the forearm or third finger after 4 min. Bilateral laser Doppler flux from the finger pulp, dorsal finger and dorsal wrist was measured together with ultrasound Doppler from the right radial artery. Absolute EDV response (EDV peak minus baseline) and normalized relative EDV response (ratio EDV peak/baseline) were calculated (median, 95% confidence interval). The relative EDV response reflect the size of EDV response independent of the baseline level and is thus used to compare the EDV responses in the finger pulp and wrist skin in the two temperature conditions.
Results: In finger pulp (dominated by AVAs), the absolute EDV response (flux, au) in thermoneutral (137.8 (67.5, 168.8)) and cold (130.3 (97.2, 154.9)) was the same ($p = 0.85$), whereas the relative EDV response was significantly higher in cold (3.6 (2.5, 5.9)) than in thermoneutral (1.4 (1.1, 1.6), $p = 0.002$). The same patterns were found in the radial artery. In the dorsal wrist (dominated by arterioles) the absolute EDV response (flux, au) was smaller in cold (30.9 (15.91, 38.0)) than in thermoneutral (52.1 (38.4, 57.8), $p = 0.04$), whereas the relative EDV responses in cold (3.5 (2.3, 4.2)), and thermoneutral (2.3 (1.6, 2.7)) were equal ($p = 0.16$).
Conclusions: The relative EDV responses show that the impact of EDV on skin perfusion in cold conditions is significantly greater in the finger pulp than in wrist skin. However, the absolute EDV responses indicate that vascular smooth muscle relaxation during EDV is probably not affected by higher mild cold-induced sympathetic activity either in AVAs or in arterioles.

1. Introduction

Blood flow in acral skin is tightly controlled by the autonomic nervous system according to the thermoregulatory needs of the body. In the hand, 80–90% of maximum blood flow is controlled by the arteriovenous anastomoses (AVAs), which are direct links between arterioles and venules, while the arterioles control the nutritive flow (Coffman, 1972). Less is known about the influence of the vascular endothelium on the vasomotor activity of acral skin vessels and the way in which the endothelial cells respond to changes in sympathetic vasoconstrictor nerve activity. It is important to understand control of AVA blood flow, since diseases that inhibit normal AVA vasomotor activity will have a strong influence on hand blood flow.

The endothelium possesses a potent vasodilatory mechanism for lowering vascular resistance. The cellular mechanism responsible for endothelium-dependent vasodilation (EDV) in skin vessels is probably activation of endothelial nitric oxide synthase (eNOS) (Noon et al., 1996; Nohria et al., 2006).

The AVAs are located deeper in the skin than the arterioles (Grant and Bland, 1931; Molyneux, 1977). Their large lumen, high density and synchronous vasomotion enable them to conduct very large volumes of blood from the arterioles to the veins. With a diameter of up

Abbreviations: EDV, endothelium-dependent vasodilation; eNOS, endothelial nitric oxide synthase; AVA, arteriovenous anastomoses.

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to 150 μm compared to the capillary diameter of 10 μm, the AVAs provide a low-resistance pathway (Jessen, 2001). In hyperthermic conditions, venous blood is drained into the superficial veins of the extremities where heat dissipates from the skin surface (Hirata et al., 1989; Jessen, 2001). The AVAs and the superficial veins are considered to form an entity called the AVA organ (Vanggaard et al., 2012).

In thermoneutral conditions, the AVAs constrict 2–3 times per minute, causing large, rapid synchronous blood velocity fluctuations (Thoresen and Walloe, 1980; Bergersen, 1993; Lossius and Eriksen, 1995). The largest amplitude range, highest fluctuation frequency and greatest synchronicity are found at room temperatures between 24 and 32 °C (Elstad et al., 2014). The adjustments of hand blood flow to a small ambient temperature reduction in thermoneutral subjects involve slight reduction of the low, almost non-fluctuating and non-synchronous flow through the arterioles and fine-tuning of the synchronous blood flow fluctuations through the AVAs (Jessen, 2001; Elstad et al., 2014). At room temperatures below 22 °C, both AVAs and arterioles constricts (Elstad et al., 2014), and this, possibly together with constriction of superficial veins, directs blood flow to the deep veins and provides a mechanism of heat conservation in the skin of the extremities.

There has been little investigation of how EDV is related to the tight control of acral circulation by the sympathetic nervous system. Relation between the sympathetic nervous system and the vascular endothelial cells have been suggested in studies of conduit arteries (Harris and Matthews, 2004; Amiya et al., 2014). Protocols to examine EDV at different frequencies of impulses from the sympathetic nervous system are needed to investigate the hunting response, Raynaud's phenomenon and diseases involving endothelial dysfunction, such as systemic sclerosis (Heidrich, 2010). As far as we know, this is the first study of the influence of the sympathetic nervous system on EDV in the AVAs and nutritive vessels (arterioles) in the hands of healthy subjects during mild cold stress. We compared simultaneously measured EDV in the finger pulp, which is rich in AVAs, and in wrist skin, which contains mainly nutritive vessels (Grant and Bland, 1931). We hypothesised that EDV would occur in both types of vascular beds. Since AVAs have larger blood flow than arterioles, and since sympathetic nervous activity has a stronger impact on blood flow in the finger pulp than in wrist skin, we hypothesised that cold-induced sympathetic tone would influence EDV more strongly in the finger pulp than in the wrist skin. We also studied the impact of vasomotor activity of the AVAs of the dorsal finger, as there is little information on the kind of microvessels that are functionally dominant in the dorsal finger. Measurements of EDV in finger pulp using a finger cuff and a forearm cuff were also compared.

2. Material and methods

2.1. Subjects

Thirteen healthy, non-smoking students (6 males, 7 females), aged between 19 and 30 years, were recruited to the study. All subjects took part in weekly exercise (median 5 h, range 2–8 h). They were asked not to drink coffee or tea or to undertake any exercise on the experimental day. They were also asked not to eat for at least 2 h before the start of each experiment. None of the subjects had any symptoms of cardiovascular disorder and none used any medication. Informed consent was obtained from all subjects and the study protocol was approved by the regional ethical committee (REK 2014/392).

2.2. Protocol and instrumental set-up

The experiments were carried out between October and December 2014 in daytime (between 09:00 and 15:00), in a quiet climate chamber with the subject resting on a bench in a supine position, dressed in shorts and singlet. The two protocols, “thermoneutral” and “cold”, were run on two separate days. After a 30-min rest period at 24 °C during instrumentation, the room temperature was adjusted to find an individual thermoneutral temperature (room temperature: median 28.7 °C, 95% CI 27.9, 29.2) and cold temperature (room temperature: median 20.4 °C, 95% CI 18.3, 22.0) for each subject. Thermoneutral was defined as a temperature at which finger pulp flux values showed large fluctuations and 2–3 vasoconstrictions per minute (and the subject was not sweating) (Thoresen and Walloe, 1980; Elstad et al., 2014). Cold was defined as a temperature at which finger pulp flux values showed sustained vasoconstriction (and the subject was not shivering) (Thoresen and Walloe, 1980; Elstad et al., 2014). Room temperature was adjusted within the range 17–35 °C, and thermoneutral and cold were set at the first temperatures at which the individual showed the characteristic blood flow patterns. Two subjects showed no vasoconstrictions down to 17 °C and were therefore excluded from the experiment. Relative humidity was 20% in all protocols.

The following experimental set-up was used for both protocols. An arm cuff was placed below the right elbow and a finger cuff was placed on the middle phalange of the right third finger. The cuffs were inflated subsequently in a randomized order. EDV was induced by release of the automatic pressure cuff inflated to a suprasystolic pressure of 200 mm Hg (moorVMS-PRES, Moor Instruments, Devon, UK) (Nohria et al., 2006; Gaillard-Bigot et al., 2014). The control hand (left hand) rested on the bench at same level as the right hand.

2.2.1. Inflation protocol

After 15 min of baseline measurements, the first cuff was inflated for 4 min, then deflated within one heartbeat. After 25 min post-occlusion observation, baseline recordings were made for 15 min before the second cuff was inflated for 4 min (Nohria et al., 2006; Roustit et al., 2008; Lenasi and Strucl, 2010; Patvardhan et al., 2010; Gaillard-Bigot et al., 2014). The experiment was terminated after a further 25 min. Bilateral continuous recordings of laser Doppler flux were made simultaneously from both hands (DRT4 and moorVMS, Moor Instruments, Devon, UK). The probe positions were the pulps of third fingers, which are dominated by AVAs, and the dorsal wrists (2 cm proximal to the wrists), which have no or very few AVAs. The dorsal side of the middle phalange of the third fingers is designated as the dorsal finger (Fig. 1). Recordings from all 6 sites were made simultaneously using probes fastened with adhesive tape. The noise-limiting filter of the laser Doppler instrument was set at the highest level (21 kHz), and the emitted wavelength was 820 nm. The flux output signals were filtered at time constant 0.1 s. Blood velocity in the right radial artery was measured by ultrasound Doppler (SD 100 Vingmed Sound, Horten, Norway). The ultrasound transducer (10 MHz) was designed with a fixed angle of 45° between the ultrasound beam and the underlying skin surface, and was fastened 3 cm proximal to the wrist with a Velcro strap. Instantaneous arterial blood pressure was obtained from the left fourth finger (Finometer, Finapres Medical System, Amsterdam, The Netherlands).

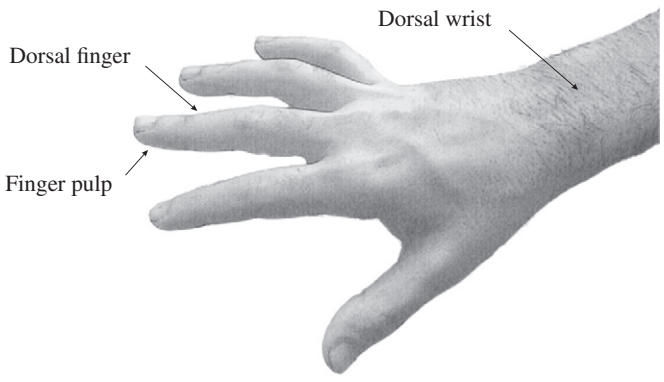

Fig. 1. Illustration of the right hand showing the position of the laser Doppler measurements.