Microvascular Responses to Skin Heating: an Introduction Issue 1.

Basic Overview

When the skin is heated, skin blood vessels dilate, more blood flows and we can detect this increase with laser Doppler. The increase in blood vessel diameter is not the only way in which blood flow increases; under normal, moderate room temperatures (20 – 24°C, not all of the smallest vessels (capillaries) have blood flowing through them. Blood flow also increases by more of the capillaries allowing blood to flow through them ('capillary recruitment').

One reason for the increase in blood flow, during local skin heating, is that it protects the skin from damage: higher blood flow conducts heat away from the surface so that a lower temperature is maintained within the skin. When the whole body is heated, during exercise for example, increased blood flow to the skin enables more efficient heat loss so that core body temperature is regulated to healthy levels.

Although it is beyond the scope of this introduction, it is interesting to note the opposite response when skin is cooled: blood flow reduces due to vasoconstriction (reduced vessel diameter) and flow through fewer capillaries. (There is also a sympathetic effect when the whole hand is cooled; blood flow in the other hand is reduced.)

Assessments that can be made with skin heating include measurements of the highest blood flow reached (recorded by laser Doppler) and the area of flare (flow increase in the skin surrounding the area actually heated).

Another reason to heat the skin is simply to standardize the temperature (e.g. 30 – 34°C) so that it is constant for laser Doppler or other measurements on different patients.

It is relatively easy to heat the skin but the mechanisms that determine microvascular responses are complex. In this Introduction we present a brief overview of ways in which heating has been used for physiological and clinical investigations. Several papers are referenced and others are added to form a useful bibliography.

Innervation

The skin is known to be innervated by two distinct branches of the sympathetic nervous system: an adrenergic vasoconstrictor system that contributes to resting cutaneous vascular tone and a cholinergic vasodilator system with an unknown neurotransmitter co-released with acetylcholine (Kellogg et al, 1995). Release of adrenergic vasoconstrictor tone contributes minimally to the overall rise in skin blood flow when the skin is directly heated (Pergola et al, 1993). The sympathetic cholinergic nerves are the primary mechanism involved in thermoregulatory vasodilation but evidence suggests that these nerves may not be involved in the vasodilation during local heating.

Local Skin Heating Response assessed by Laser Doppler Monitoring

Investigations of the cutaneous microvascular response to local heating have varied with respect to site heated, the temperature used, the duration of heating and the rate at which skin is heated. All of these factors may evoke different mechanisms and affect the cutaneous vascular response. In general, local heating evokes an initial dilator response that peaks in a few minutes, falls a little and is followed by a secondary dilation.

Minson et al (2001) describe the bi-modal skin blood flow response to skin heating and associated the initial peak to axon reflex and the much wider peak to other vasodilation mechanisms including local production of nitric oxide.
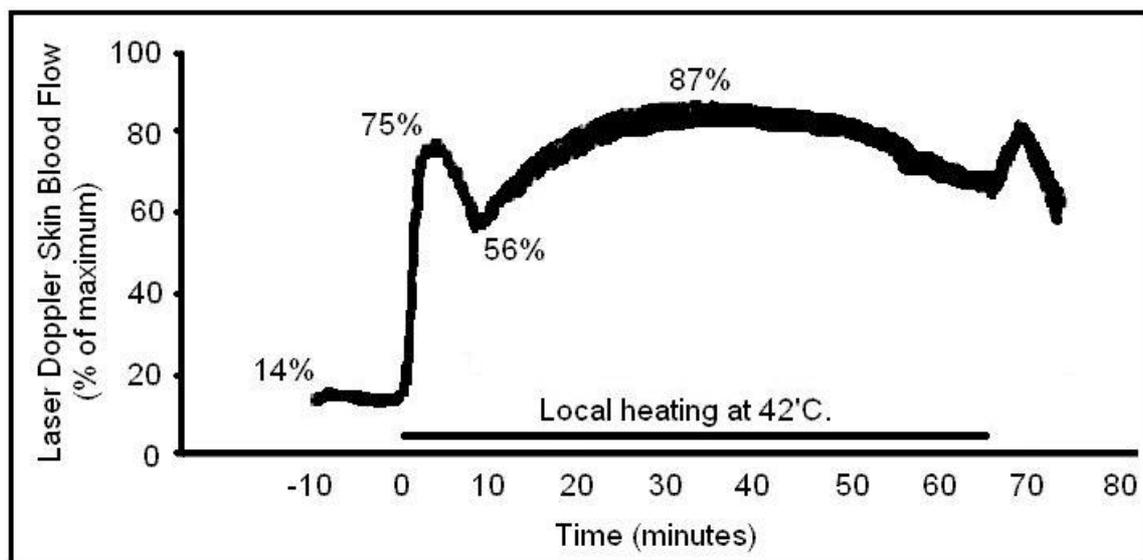

Figure 1: Skin Blood flow response to non-painful local heating (after Minson et al 2001).

Comment: The protocol for this response used a heat stimulus which evokes the axon reflex. The SH02 skin heater enables thermode temperatures to be changed in user-defined stages to enable a wide choice of protocols.

Pain and Skin Damage

Magerl and Treede (1996) observed that pain was perceived at lower temperatures as the rate of skin heating increased. To avoid pain and the additional factors that pain stimulus evokes requires careful choice of maximum temperature and rate of increase: a rate of 6°C per minute and a maximum heater temperature of 42°C (producing a skin temperature of 39.5 – 40 ° C) has been used successfully by Minson et al (2001).

Skin damage is unlikely to occur in healthy skin with a thermode at or below 44°C for 1 hour (this temperature/duration is commonly used to assess TcPO2 in neonates). However, in subjects with ischaemia or impaired microvascular response, there may be insufficient blood flow to dissipate the heat, leading to a burn. Extra care should also be exercised in subjects with neuropathy, unable to sense noxious stimuli.

Maximum Hyperaemia and Diabetes

Shore et al (1991) assessed the maximum hyperaemic response obtained with skin heating to 44°C in children with diabetes. They observed significant differences from normal before microangiopathy was clinically detectable, even in prepubertal children.

Skin Heating and Laser Doppler used in conjunction with Iontophoresis

Heating can be used as an additional stimulus or simply to maintain a constant temperature to reduce inter-subject variability (Grossman, 1995). For example, during iontophoresis of vasoconstrictors it would be difficult to assess response under some resting, baseline conditions; pre-heating will enable a larger effect to be observed.

Skin Heating and Laser Doppler used in conjunction with Micro-dialysis

Micro-dialysis has been used by Wong et al (2006) to assess the effect of various antagonists on skin blood flow: a baseline was obtained with skin temperature held constant and micro-dialysis was performed after raising the skin temperature to a stable plateau. This study pointed to the magnitude of the nadir after the initial response peak as a significant outcome measure. Gooding et al (2006) have assessed maximum skin hyperaemia in response to heating to over 42°C, and found that the hyperaemia was prolonged in the presence of sildenafil (prevents breakdown of cGMP).

Hyperaemia and Wound Healing

Early studies on patients with lower limb wounds indicated the potential for laser Doppler monitoring of heated skin to predict healing. Amputation level assessment by this technique was investigated by Gebuhr et al (1989) who found that the increase in LD blood flow was directly related to healing. The predictive value of LD for healing was found to be similar to TcPO2 by Padberg et al (1992) but did not reach clinical significance for general application at that time.

Hyperaemia and Burn Assessment

Early laser Doppler assessments of burns frequently included local heating to improve the accuracy of the technique (Micheels *et al*., 1984; Waxman *et al*., 1989; O'Reilly *et al*., 1989; Atiles *et al*., 1995; Yeong *et al*., 1996). The main reasons for its use were associated with microvascular heterogeneity; heat will also enable differentiation between deep dermal burn wounds and normal, unburned skin: blood flow increases in the latter but not the burn after skin heating. However, with the introduction of laser Doppler Imaging (Niazi et al, 1993), heating has not been found to be necessary.

Assessment of shock was one of the earliest clinical applications suggested for laser Doppler and skin heating (Micheels et al, 1984): the vasodilator response was absent in patients in shock.

Flap Monitoring

Heden and Arnander (1992) investigated the potential of skin heating and cooling to increase the accuracy of LD flap monitoring in an experimental model.

Axon Reflex Flare: Clinical Application in Diabetes using moorLDI

Krishnan and Rayman (2004) have assessed the axon reflex flare response in type 2 Diabetics with and without neuropathy. The flare area was assessed by moorLDI laser Doppler Imaging following skin heating to 44°C for 20minutes with a 9mm diameter thermode. Significant differences were found in flare area between diabetics with neuropathy (DN) and without neuropathy (p<0.0001) and between normals and DN (p<0.0001).

Furthermore, the authors noted that the group without clinical neuropathy also had significantly reduced flare response compared with normals (p<0.01) indicating that C-fibre dysfunction can be detected relatively early in type 2 diabetes, by the moorLDI technique, *before* it is detected by other currently available methods.
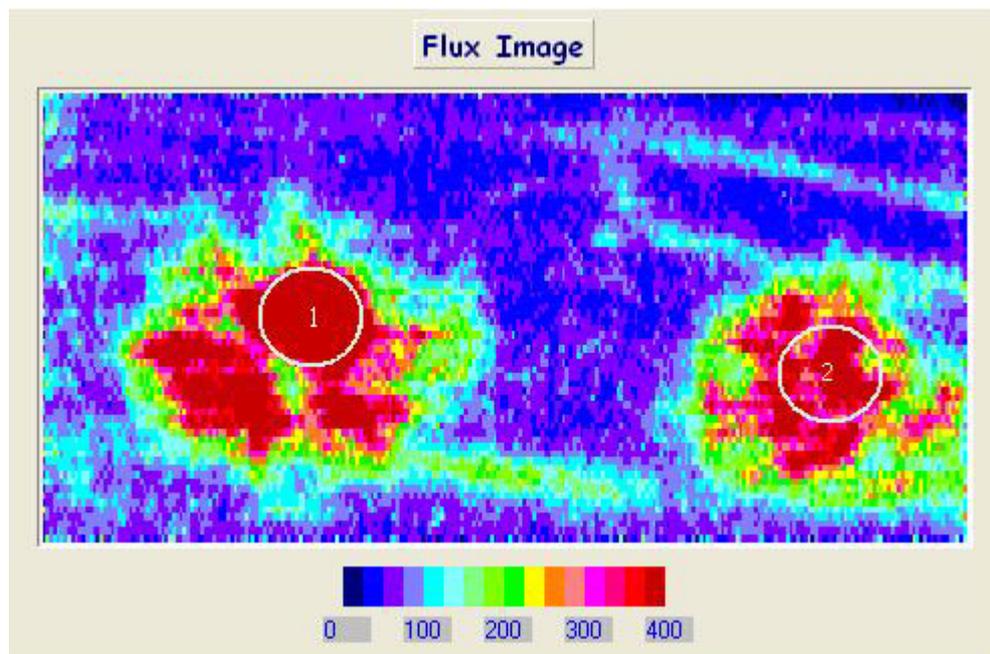

Figure 2 Flare response of forearm skin of a normal male following 20 minutes of heating to 44°C (1, left) and 42°C (2, right); positions of removed thermodes are indicated (diameter 10mm). Note the non-symmetrical flare and the greater flare area around 1 compared with 2.

Axon Reflex and Spinal Cord Injury

The initial axon reflex mediated peak was found to be impaired in patients with spinal cord injury (SCI) when measure at the foot (Nicotra et al, 2004). It was suggested that the technique could be useful to detect completeness of autonomic disruption after SCI.

Effects of Age

Weiss et al (1992) used a standard temperature of 32°C to investigate vasomotion and found that amplitudes of these oscillations in young people where more than double that found in the elderly. However vasomotion frequencies were similar. The flow differences were attributed to differences in microvascular density.

Minson et al (2002) found age related changes in both axon reflex-mediated and NO-mediated vasodilation and suggested that these contribute to attenuated cutaneous vasodilator responses in the elderly.

Whole Body Heating

Whole body heating is beyond the scope of this Introduction but a few references are included for interest: Minson et al (1998) observed that 'during direct passive heating in young men, a dramatic increase in skin blood flow is achieved by a rise in cardiac output and redistribution of flow from the splanchnic and renal vascular beds' and 'the older men had a significantly lower increase in total blood flow directed to the skin'.

The effect of exercise has been investigated by Shibasaki et al (2005) who used mean arterial pressure and LD to compute *cutaneous vascular conductance* (CVC = LD/MAP). CVC decreases during isometric handgrip exercise in heat stressed individuals.

Green et al (2005) have observed impaired skin blood flow response to environmental heating in patients with chronic heart failure.

Conclusion

Skin heating in conjunction with laser Doppler is a useful technique for clinical and physiological assessments. It is easy to apply but the underlying mechanisms are complex; much has been done over the past 20 years to better understand skin responses.

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