Microvascular Responses to Skin Heating: an Introduction

Basic Overview

When the skin is heated, skin blood vessels dilate, more blood flows and oxygenation increases; we can detect these increases with laser Doppler and white light spectroscopy, respectively. The increase in blood vessel diameter is not the only way in which blood flow increases; under normal, moderate room temperatures (20 – 24ºC), 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').

The increase in blood flow, during local skin heating 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 one hand is cooled, blood flow in the other hand reduces.)

Assessments that can be made with skin heating include measurements of the highest blood flow reached (recorded by laser Doppler or laser speckle contrast) and the area of flare (flow increase in the skin surrounding the area actually heated). Changes in microvascular oxygenation can also be assessed by white light spectroscopy (WLS). 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 occasions and for different patients; e.g. to improve reproducibility of PORH tests (Barwick et al, 2015).

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 a neurotransmitter co-released with acetylcholine, Kellogg et al, 2011, found that soluble guanylyl cyclase (sGS) inhibition had a large effect on the vasodilation induced by local skin warming suggesting that NO mediation of the local warming response is more reliant on heme-dependent sGC activation. Contributors to the sympathetic active vasodilator system include: cholinergic co-transmission, nitric oxide, substance P, histamine, prostoglandins and possibly vasoactive intestinal peptide; negative modifiers include: acute exercise, orthostasis, dehydration, progesterone, primary aging, diabetes, heart failure and hypertension; and positive modifiers: oestrogen and exercise training (Charkoudian, 2010).

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.

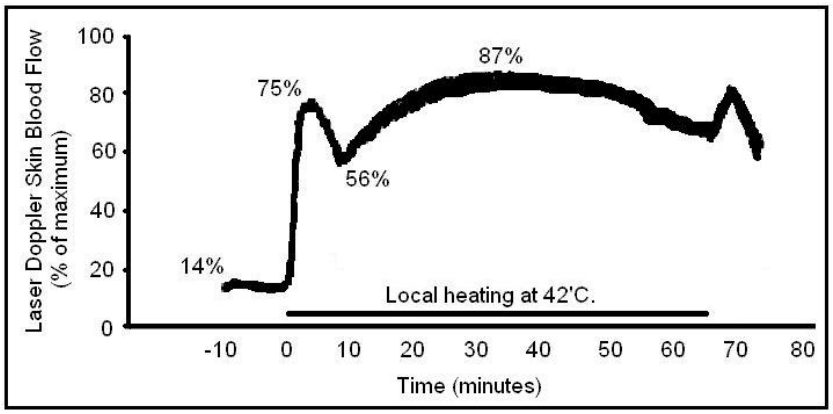


Figure 1: Skin Blood flow response to non-painful local heating (after Minson et al 2001).

Comment: The protocol for this response used a heat stimulus which evokes the axon reflex (see Axon Reflex, LDI-Flare and Small Fibre Neuropathy, below)

The moorVMS-HEAT skin heater enables thermode temperatures to be changed in user-defined stages to enable a wide choice of protocols. The reproducibility with use of various heating protocols has been assessed by Roberts et al, 2017.

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 responses during local anaesthesia were studied by Cracowski et al, 2007.

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. The mechanisms of maximal skin hyperaemia induced by local heating have been studied by Minson et al, 2002, and Gooding et al, 2006. Heating for maximum hyperaemia has been used by Heimhalt-El Hamriti et al, 2013 to assess endothelial function in 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. A constant raised temperature is also an appropriate starting point to investigate vasoconstrictor drugs iontophoresed; e.g. norepinephrine, Beed et al, 2009.

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 microdialysis 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. Also see Holowatz et al, 2007 and Kellogg et al, 2011. Gooding et al (2006) have assessed, using microdialysis, mechanisms of maximum skin hyperaemia in response to local heating, finding 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. The significant effect of ischaemic preconditioning on microvascular function, by LDF response to heating, has been assessed Kim et al, 2019.

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 (Pape et al, 2012; Monstrey et al, 2011) for accurate burn assessment.

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 for 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, LDI-Flare and Small Fibre Neuropathy

Vas et al, 2012 & 2013, have assessed the axon reflex flare response (LDI-Flare) in type 1 diabetes of moderate duration. The aim of this study was to determine the influence of microvascular disease (MV) on C-fibre function. LDI-Flare was assessed by moorLDI laser Doppler Imaging following skin heating, heating stepwise: 44°C for 2 min, 46°C for 1 min and finally 47°C for 3 min. Disease duration-averaged HbA1c was higher in the MV+ group (8.6±0.9% [70±9 mmol/mol] vs 7.6±0.6% [60±7 mmol/mol], p<0.001) and correlated with LDI-Flare size (r0–0.50, p<0.001. LDI-Flare was reduced in MV+ (5.1±1.8 cm2) compared with Healthy controls (10.0±3.1 cm2) , p<0.0001 and MV– (9.9±2.9 cm2), p<0.0001. In an earlier study, with a slower protocol, Krishnan et al, 2004, found significant differences 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.

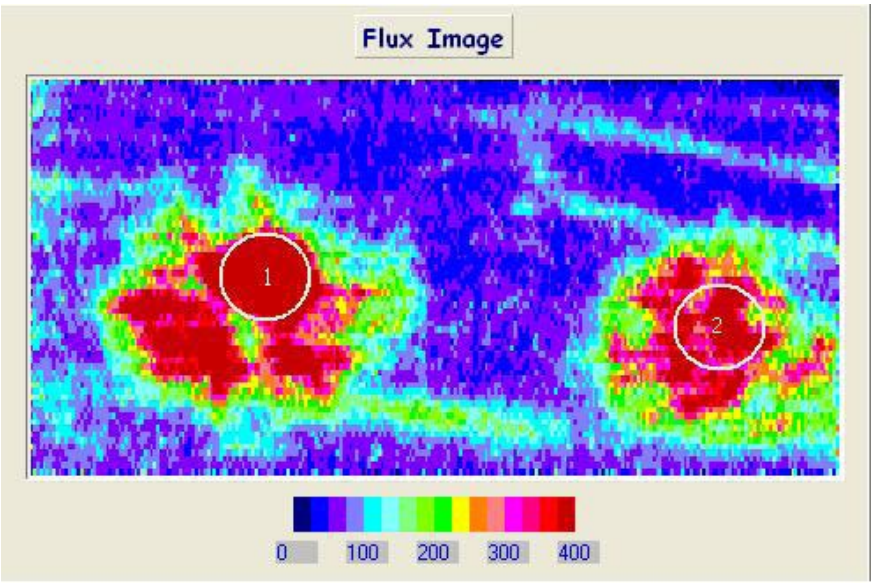


Figure 2 Flare response of forearm skin of a normal male following 20 minutes of heating to 44°C (1, left) and 42°C (2, right); positions of removed thermodes are indicated. Note the non-symmetrical flare and the greater flare area around 1 compared with 2.

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. Functional electrostimulation did not alter responses to local heating below (leg) or above (forearm) the spinal cord lesion (Van Duijnhoven et al, 2009).

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. Vasomotion oscillations during heating to 33°C and 43°C have been assessed by Thanaj et al, 2018 by multi-scale analysis of laser Doppler blood flow and WLS oxygenation.

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. Response to local heating of skin was found, by Agarwal et al, 2012, to better discriminate coronary artery disease than other tests.

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.

References and Bibliography

Sharad C Agarwal, John Allen, Alan Murray, Ian F Purcell (2012).
Laser Doppler assessment of dermal circulatory changes in people with coronary artery disease.
Microvasc Res. 2012 Jul;84(1):55-9.
https://doi.org/10.1016/j.mvr.2012.02.002

S Arora, P Smakowski, R G Frykberg, L R Simeone, R Freeman, F W LoGerfo, A Veves (1998).
Differences in foot and forearm skin microcirculation in diabetic patients with and without neuropathy.
Diabetes Care. 1998 Aug;21(8):1339-44.
https://doi.org/10.2337/diacare.21.8.1339

L Atiles, W Mileski, G Purdue, J Hunt, C Baxter (1995).
Laser Doppler Flowmetry in Burn Wounds.
J Burn Care Rehabil. Jul-Aug 1995;16(4):388-93.
https://doi.org/10.1097/00004630-199507000-00003

Alex Barwick, Sean Lanting, Vivienne Chuter (2015).
Intra-tester and inter-tester reliability of post-occlusive reactive hyperaemia measurement at the hallux (2015).
Microvasc Res. 2015 May;99:67-71.
https://doi.org/10.1016/j.mvr.2015.03.001

M Beed, M B O'Connor, J Kaur, R P Mahajan, I K Moppett (2009).
Transient hyperaemic response to assess skin vascular reactivity: effects of heat and iontophoresed norepinephrine.
Br J Anaesth. 2009 Feb;102(2):205-9.
https://doi.org/10.1093/bja/aen349

Aude Boignard, Muriel Salvat-Melis, Patrick H Carpentier, Christopher T Minson, Laurent Grange, Catherine Duc, Françoise Sarrot-Reynauld, Jean-Luc Cracowski (2005).
Local hyperemia to heating is impaired in secondary Raynaud's phenomenon.
Arthritis Res Ther. 2005;7(5):R1103-12.
https://doi.org/10.1186/ar1785

S D Brain, S R Hughes, H Cambridge, G O'Driscoll (1993).
The contribution of calcitonin gene-related peptide (CGRP) to neuro-genic vasodilator responses.
Agents Actions. 1993;38 Spec No:C19-21.
https://doi.org/10.1007/bf01991124

David M Brienza, Mary Jo Geyer, Yih-Kuen Jan (2005).
A comparison of changes in rhythms of sacral skin blood flow in response to heating and indentation.
Arch Phys Med Rehabil. 2005 Jun;86(6):1245-51.
https://doi.org/10.1016/j.apmr.2004.11.038

H A Bull, J Hothersall, N Chowdhury, J Cohen, P M Dowd (1996).
Neuropeptides induce release of nitric oxide from human dermal microvascular endothelial cells.
J Invest Dermatol. 1996 Apr;106(4):655-60.
https://doi.org/10.1111/1523-1747.ep12345471

P A Carberry, A M Shepherd, and J M Johnson (1992).
Resting and maximal forearm skin blood flows are reduced in hypertension.
Hypertension. 1992;20:349–355.
https://doi.org/10.1161/01.HYP.20.3.349

N Charkoudian, D P Stephens, K C Pirkle, W A Kosiba, J M Johnson (1985).
Influence of female reproductive hormones on local thermal control of skin blood flow.
J Appl Physiol (1985). 1999 Nov;87(5):1719-23.
https://doi.org/10.1152/jappl.1999.87.5.1719

Nisha Charkoudian (1985).
Mechanisms and modifiers of reflex induced cutaneous vasodilation and vasoconstriction in humans.
J Appl Physiol (1985). 2010 Oct;109(4):1221-8.
https://doi.org/10.1152/japplphysiol.00298.2010

M K Church, S el-Lati, J P Caulfield (1991).
Neuropeptide-induced secretion from human skin mast cells.
Int Arch Allergy Appl Immunol. 1991;94(1-4):310-8.
https://doi.org/10.1159/000235393

Geraldine F Clough (1999).
Role of nitric oxide in the regulation of microvascular perfusion in human skin in vivo.
J Physiol. 1999 Apr 15; 516(Pt 2): 549–557.
https://dx.doi.org/10.1111%2Fj.1469-7793.1999.0549v.x

G F Clough, A R Bennett, M K Church (1998).
Measurement of nitric oxide concentration in human skin in vivo using dermal microdialysis.
Exp Physiol. 1998 May;83(3):431-4.
https://doi.org/10.1113/expphysiol.1998.sp004126

Jean-Luc Cracowski, Santiago Lorenzo, Christopher T Minson (2007).
Effects of local anaesthesia on subdermal needle insertion pain and subsequent tests of microvascular function in human.
Eur J Pharmacol. 2007 Mar 22;559(2-3):150-4.
https://doi.org/10.1016/j.ejphar.2006.11.069

Jennifer L Davison, Daniel S Short, Thad E Wilson (2004).
Effect of local heating and vasodilation on the cutaneous venoarteriolar response.
Clin Auton Res. 2004 Dec;14(6):385-90.
https://doi.org/10.1007/s10286-004-0223-x

E Evans, M Rendell, J Bartek, S Connor, O Bamisedun, D Dovgan, M Giitter (1993).
Thermally-induced cutaneous vaso-dilation in aging.
J Gerontol. 1993 Mar;48(2):M53-7.
https://doi.org/10.1093/geronj/48.2.m53

P Gebuhr, J P Jørgensen, B Vollmer-Larsen, S L Nielsen, B Alsbjørn (1989).
Estimation of Amputation Level with a Laser Doppler Flowmeter
J Bone Joint Surg Br. 1989 May;71(3):514-7.
https://doi.org/10.1302/0301-620x.71b3.2656723

Sandrine Golay, Christian Haeberli, Anne Delachaux, Lucas Liaudet, Paul Kucera, Bernard Waeber, François Feihl (2004).
Local heating of human skin causes hyperemia without mediation by muscarinic cholinergic receptors or prostanoids.
J Appl Physiol (1985). 2004 Nov;97(5):1781-6.
https://doi.org/10.1152/japplphysiol.00814.2003

P C Goldsmith, T A Leslie, N A Hayes, N J Levell, P M Dowd, J C Foreman (1996).
Inhibitors of nitric oxide synthase in human skin.
J Invest Dermatol. 1996 Jan;106(1):113-8.
https://doi.org/10.1111/1523-1747.ep12328204

Kim M Gooding, Michael M Hannemann, John E Tooke, Geraldine F Clough, Angela C Shore (2006).
Maximum Skin Hyperaemia Induced by Local Heating: Possible Mechanisms.
J Vasc Res. 2006;43(3):270-7.
https://doi.org/10.1159/000091736

Daniel J Green, Andrew J Maiorana, Jeffrey Ha Jin Siong, Valerie Burke, Matthew Erickson, Christopher T Minson, William Bilsborough, Gerry O'Driscoll (2006).
Impaired skin blood flow response to environmental heating in chronic heart failure.
Eur Heart J. 2006 Feb;27(3):338-43.
https://doi.org/10.1093/eurheartj/ehi655

M Grossmann, M J Jamieson, D L Kellogg Jr, W A Kosiba, P E Pergola, C G Crandall, A M Shepherd (1995).
The effect of iontophoresis on the cutaneous vasculature: evidence for current-induced hyperemia
Microvasc Res. 1995 Nov;50(3):444-52.
https://doi.org/10.1006/mvre.1995.1070

Mirjam Heimhalt-El Hamriti, Corinna Schreiver, Anja Noerenberg, Julia Scheffler, Ulrike Jacoby, Dieter Haffner, Dagmar-C Fischer (2013).
Impaired skin microcirculation in paediatric patients with type 1 diabetes mellitus.
Cardiovasc Diabetol. 2013 Aug 12;12:115.
https://doi.org/10.1186/1475-2840-12-115

A A Hassan, J E Tooke (1988).
Mechanism of the postural vasoconstrictor response in the human foot.
Clin Sci (Lond). 1988 Oct;75(4):379-87.
https://doi.org/10.1042/cs0750379

P Hedén, C Arnander (1992).
Temperature Load Test to Increase the Accuracy of Laser Doppler Monitoring of Flaps
Scand J Plast Reconstr Surg Hand Surg. 1992;26(1):29-32.
https://doi.org/10.3109/02844319209035179

Lacy A Holowatz, W Larry Kenney (2007).
Up-regulation of arginase activity contributes to attenuated reflex cutaneous vasodilatation in hypertensive humans.
J Physiol. 2007 Jun 1;581(Pt 2):863-72.
https://doi.org/10.1113/jphysiol.2007.128959

D L Kellogg Jr, P E Pérgola, K L Piest, W A Kosiba, C G Crandall, M Grossmann, J M Johnson (1995).
Cutaneous active vasodilation in humans is mediated by cholinergic nerve cotrans-mission.
Circ Res. 1995 Dec;77(6):1222-8.
https://doi.org/10.1161/01.res.77.6.1222

Dean L Kellogg Jr 1 , Joan L Zhao, Yubo Wu, John M Johnson (2011).
Antagonism of soluble guanylyl cyclase attenuates cutaneous vasodilation during whole body heat stress and local warming in humans.
J Appl Physiol (1985). 2011 May;110(5):1406-13.
https://doi.org/10.1152/japplphysiol.00702.2010

W L Kenney, A L Morgan, W B Farquhar, E M Brooks, J M Pierzga, J A Derr (1997).
Decreased active vasodilator sensitivity in aged skin.
Am J Physiol. 1997 Apr;272(4 Pt 2):H1609-14
https://doi.org/10.1152/ajpheart.1997.272.4.h1609

F Khan, T A Elhadd, S A Greene, J J Belch (2000).
Impaired skin microvascular function in children, adolescents, and young adults with type 1 diabetes.
Diabetes Care. 2000 Feb;23(2):215-20.
https://doi.org/10.2337/diacare.23.2.215

Jahyun Kim, Warren D Franke, James A Lang (2020).
Improved endothelial-dependent and endothelial-independent skin vasodilator responses following remote ischemic preconditioning.
Am J Physiol Heart Circ Physiol. 2020 Jan 1;318(1):H110-H115.
https://doi.org/10.1152/ajpheart.00467.2019

Monika Klede, Geraldine Clough, Grischa Lischetzki, Martin Schmelz (2003).
The effect of the nitric oxide synthase inhibitor N-nitro-L-arginine-methyl ester on neuropeptideinduced vasodilation and protein extravasation in human skin.
J Vasc Res. Mar-Apr 2003;40(2):105-14
https://doi.org/10.1159/000070707

Singhan T M Krishnan, Gerry Rayman (2004).
The LDIflare: a novel test of C-fiber function demonstrates early neuropathy in type 2 diabetes
Diabetes Care. 2004 Dec;27(12):2930-5.
https://doi.org/10.2337/diacare.27.12.2930

W Magerl, R D Treede (1996).
Heat-evoked vasodilation in human hairy skin: axon reflexes due to low-level activity of nociceptive afferents.
J Physiol. 1996 Dec 15;497 (Pt 3)(Pt 3):837-48.
https://doi.org/10.1113/jphysiol.1996.sp021814

H L Martin, J L Loomis, W L Kenney (1985).
Maximal skin vascular conductance in subjects aged 5-85 yr.
J Appl Physiol 79: 297–301, 1995.
https://doi.org/10.1152/jappl.1995.79.1.297

Gregg R McCord, Christopher T Minson (1985).
Cutaneous vascular responses to isometric handgrip exercise during local heating and hyperthermia.
J Appl Physiol (1985). 2005 Jun;98(6):2011-8.
https://doi.org/10.1152/japplphysiol.00888.2004

J Micheels, B Alsbjörn, B Sørensen (1984).
Clinical Use of Laser Doppler Flowmetry in a Burns Unit.
Scand J Plast Reconstr Surg, 1984, 18, 65-73.
https://doi.org/10.3109/02844318409057405

J Micheels, B Alsbjorn, B Sorensen (1984).
Laser Doppler flowmetry. A new non-invasive measurement of microcirculation in intensive care?
Resuscitation. 1984 May;12(1):31-9.
https://doi.org/10.1016/0300-9572(84)90056-x

C T Minson, S L Wladkowski, A F Cardell, J A Pawelczyk, W L Kenney (1985).
Age alters the cardiovascular response to direct passive heating.
J Appl Physiol (1985). 1998 Apr;84(4):1323-32.
https://doi.org/10.1152/jappl.1998.84.4.1323

C T Minson, L T Berry, M J Joyner (1985).
Nitric Oxide and Neurally Mediated Regulation of Skin Blood Flow during Local Heating.
J Appl Physiol (1985). 2001 Oct;91(4):1619-26
https://doi.org/10.1152/jappl.2001.91.4.1619

Christopher T Minson, Lacy A Holowatz, Brett J Wong, W Larry Kenney, Brad W Wilkins (1985).
Decreased nitric oxide- and axon reflex-mediated cutaneous vasodilation with age during local heating.
J Appl Physiol (1985). 2002 Nov;93(5):1644-9.
https://doi.org/10.1152/japplphysiol.00229.2002

S M Monstrey, H Hoeksema, R D Baker, J Jeng, R S Spence, D Wilson, S A Pape (2011).
Burn wound healing time assessed by laser Doppler imaging. Part 2: Validation of a dedicated colour code for image interpretation.
Burns. 2011 Mar;37(2):249-56.
https://doi.org/10.1016/j.burns.2010.08.013

Z B Niazi, T J Essex, R Papini, D Scott, N R McLean, M J Black (1993).
New Laser Doppler Scanner, a Valuable Adjunct in Burn Depth Assessment.
Burns. 1993 Dec;19(6):485-9.
https://doi.org/10.1016/0305-4179(93)90004-r

A Nicotra, M Asahina, C J Mathias (2004).
Skin vasodilator response to local heating in human chronic spinal cord injury.
Eur J Neurol. 2004 Dec;11(12):835-7.
https://doi.org/10.1111/j.1468-1331.2004.00889.x

T J O'Reilly, R J Spence, R M Taylor, J J Scheulen (1989).
Laser Doppler Flowmetry Evaluation of Burn Wound Depth.
J Burn Care Rehabil. Jan-Feb 1989;10(1):1-6
https://doi.org/10.1097/00004630-198901000-00001

F T Padberg Jr, T L Back, L C Hart, C D Franco (1992).
Comparison of heated-probe laser Doppler and transcutaneous oxygen measurements for predicting outcome of ischemic wounds.
J Cardiovasc Surg (Torino). Nov-Dec 1992;33(6):715-22.

A Pape, R D Baker, D Wilson, H Hoeksema, J C Jeng, R J Spence, S Monstrey (2012).
Burn wound healing time assessed by laser Doppler imaging. Part 1: Derivation of a dedicated colour code for image interpretation.
Burns. 2012 Mar;38(2):187-94.
https://doi.org/10.1016/j.burns.2010.11.009

P E Pérgola, D L Kellogg Jr, J M Johnson, W A Kosiba, D E Solomon (1993).
Role of sympathetic nerves in the vascular effects of local temperature in human forearm skin.
Am J Physiol. 1993 Sep;265(3 Pt 2):H785-92.
https://doi.org/10.1152/ajpheart.1993.265.3.h785

Kirsty A Roberts, Thijs van Gent, Nicola D Hopkins, Helen Jones, Ellen A Dawson, Richard Draijer, Howard H Carter, Ceri L Atkinson, Daniel J Green, Dick H J Thijssen, David A Low (2017).
Reproducibility of four frequently used local heating protocols to assess cutaneous microvascular function.
Microvasc Res. 2017 Jul;112:65-71.
https://doi.org/10.1016/j.mvr.2017.03.005

D D Sandeman, C A Pym, E M Green, C Seamark, A C Shore, J E Tooke (1991).
Microvascular vasodilation in feet of newly diagnosed non-insulin dependent diabetic patients.
BMJ. 1991 May 11;302(6785):1122-3.
https://doi.org/10.1136/bmj.302.6785.1122

Manabu Shibasaki, Niels H Secher, John M Johnson, Craig G Crandall (2005).
Central command and the cutaneous vascular response to isometric exercise in heated humans.
J Physiol. 2005 Jun 1;565(Pt 2):667-73.
https://doi.org/10.1113/jphysiol.2005.083535

A C Shore, K J Price, D D Sandeman, E M Green, J H Tripp, J E Tooke (1991).
Impaired microvascular hyperaemic response in children with diabetes mellitus.
Diabet Med. Aug-Sep 1991;8(7):619-23.
https://doi.org/10.1111/j.1464-5491.1991.tb01667.x

K B Stansberry, M A Hill, S A Shapiro, P M McNitt, B A Bhatt, A I Vinik (1997).
Impairment of peripheral blood flow responses in diabetes resembles an enhanced aging effect.
Diabetes Care. 1997 Nov;20(11):1711-6.
https://doi.org/10.2337/diacare.20.11.1711

K B Stansberry, H R Peppard, L M Babyak, G Popp, P M McNitt, A I Vinik (1999).
Primary nociceptive afferents mediate the blood flow dysfunction in non-glabrous (hairy) skin of type 2 diabetes: a new model for the pathogenesis of microvascular dysfunction.
Diabetes Care. 1999 Sep;22(9):1549-54.
https://doi.org/10.2337/diacare.22.9.1549

Julian Stewart, Adam Kohen, Daniel Brouder, Fahim Rahim, Stephen Adler, Renee Garrick, Michael S Goligorsky (2004).
Noninvasive interrogation of microvasculature for signs of endothelial dysfunction in patients with chronic renal failure.
Am J Physiol Heart Circ Physiol. 2004 Dec;287(6):H2687-96.
https://doi.org/10.1152/ajpheart.00287.2004

W F Taylor, J M Johnson, D O'Leary, M K Park (1984).
Effect of high local temperature on reflex cutaneous vasodilation.
J Appl Physiol Respir Environ Exerc Physiol. 1984 Jul;57(1):191-6.
https://doi.org/10.1152/jappl.1984.57.1.191

P R J Vas, A Q Green, G Rayman (2012).
Small fibre dysfunction, microvascular complications and glycaemic control in type 1 diabetes: a case-control study.
Diabetologia. 2012 Mar;55(3):795-800.
https://doi.org/10.1007/s00125-011-2417-9

Prashanth R J Vas, Gerry Rayman (2013).
Validation of the modified LDIFlare technique: a simple and quick method to assess C-fiber function.
Muscle Nerve. 2013 Mar;47(3):351-6.
https://doi.org/10.1002/mus.23532

A Veves, C M Akbari, J Primavera, V M Donaghue, D Zacharoulis, J S Chrzan, U DeGirolami, F W LoGerfo, R Freeman (1998).
Endothelial dysfunction and the expression of endothelial nitric oxide synthetase in diabetic neuropathy, vascular disease, and foot ulceration.
Diabetes. 1998 Mar;47(3):457-63.
https://doi.org/10.2337/diabetes.47.3.457

J Wallengren (1997).
Vasoactive peptides in the skin.
J Investig Dermatol Symp Proc. 1997 Aug;2(1):49-55.
https://doi.org/10.1038/jidsymp.1997.11

David O Warner, Michael J Joyner, Nisha Charkoudian (2004).
Nicotine increases initial blood flow responses to local heating of human non-glabrous skin.
J Physiol. 2004 Sep 15;559(Pt 3):975-84.
https://doi.org/10.1113/jphysiol.2004.062943

K Waxman, N Lefcourt, B Achauer (1989).
Heated Laser Doppler Flow Measurements to Determine Depth of Burn Injury.
Am J Surg. 1989 Jun;157(6):541-3.
https://doi.org/10.1016/0002-9610(89)90694-6

M Weiss, B Milman, B Rosen, Z Eisenstein, R Zimlichman (1992).
Analysis of the diminished skin perfusion in elderly people by laser Doppler flowmetry.
Age Ageing. 1992 Jul;21(4):237-41.
https://doi.org/10.1093/ageing/21.4.237

Diane E Wick, Shelly K Roberts, Ananda Basu, Paola Sandroni, Robert D Fealey, David Sletten, Nisha Charkoudian (1985).
Delayed threshold for active cutaneous vasodilation in patients with Type 2 diabetes mellitus.
J Appl Physiol (1985). 2006 Feb;100(2):637-41.
https://doi.org/10.1152/japplphysiol.00943.2005

Brad W Wilkins, Linda H Chung, Nathan J Tublitz, Brett J Wong, Christopher T Minson (1985).
Mechanisms of vasoactive intestinal peptide-mediated vasodilation in human skin.
J Appl Physiol (1985). 2004 Oct;97(4):1291-8.
https://doi.org/10.1152/japplphysiol.00366.2004

S B Wilson, P E Jennings, J J Belch (1992).
Detection of microvascular impairment in type I diabetics by laser-Doppler flowmetry.
Clin Physiol. 1992 Mar;12(2):195-208.
https://doi.org/10.1111/j.1475-097x.1992.tb00306.x

Brett J Wong, Sarah J Williams, Christopher T Minson (2006).
Minimal role for H1 and H2 histamine receptors in cutaneous thermal hyperemia to local heating in humans.
J Appl Physiol (1985). 2006 Feb;100(2):535-40.
https://doi.org/10.1152/japplphysiol.00902.2005

E K Yeong, R Mann, M Goldberg, L Engrav, D Heimbach (1996).
Improved Accuracy of Burn Wound Assessment using Laser Doppler.
J Trauma. 1996 Jun;40(6):956-61; discussion 961-2.
https://doi.org/10.1097/00005373-199606000-00015