Topical review

Capillary dysfunction and impaired tissue oxygenation in complex regional pain syndrome: A hypothesis

Leif Østergaard [a,b,*], Astrid Juhl Terkelsen [c,d], Nanna Brix Finnerup [c], Lone Knudsen [c], Kim Ryun Drasbek [a], Sune Nørhøj Jespersen [a,e], Peter Svensson [f], Jens Christian H. Sørensen [g], Troels Staehelin Jensen [c,d]

[a] Center of Functionally Integrative Neuroscience and MINDLab, Aarhus University, Aarhus, Denmark
[b] Department of Neuroradiology, Aarhus University Hospital, Aarhus, Denmark
[c] Danish Pain Research Center, Aarhus University, Aarhus, Denmark
[d] Department of Neurology, Aarhus University Hospital, Aarhus, Denmark
[e] Department of Physics and Astronomy, Aarhus University, Aarhus, Denmark
[f] Section of Clinical Oral Physiology, School of Dentistry, Aarhus University, Aarhus, Denmark
[g] Department of Neurosurgery, Aarhus University Hospital, Aarhus, Denmark

Sponsorships or competing interests that may be relevant to content are disclosed at the end of this article.

1. Introduction

Complex regional pain syndrome (CRPS) presents with severe pain in distal parts of a limb (hand or foot), typically after trauma with associated swelling and warmth of the affected limb [33]. The condition is associated with sensory abnormalities such as hypersensitivity, and with autonomic disturbances including reddening and sweating. At onset, CRPS is dominated by either a warm, hyperemic, edematous limb ('warm' CRPS) or a cold, dystrophic limb with skin atrophy ('cold' CRPS) and chronic pain [11,42]. Over time, warm CRPS can progress to cold CRPS. This complex clinical picture has led to the assumption that inflammatory, vasomotor, and maladaptive neuroplastic changes are involved in the development and maintenance of CRPS [14].

This topical review raises the hypothesis that hypoxia caused by capillary flow disturbances may play an important role in the development of CRPS and the subsequent maintenance of the condition as it progresses from the initial warm phase to the chronic cold phase.

2. Is tissue oxygenation impaired in CRPS?

Histological examination of muscle tissue from CRPS patients who underwent amputation revealed gross thickening of capillary basement membranes, pericyte loss, and, in some cases, capillary necrosis [47] (Fig. 1). Such changes would be expected to disturb capillary flow patterns, and possibly muscle ischemia (low blood flow). The latter is supported by the cold and dystrophic appearance of limbs in 'cold' CRPS [42], by magnetic resonance spectroscopy studies that reveal muscle hypoxia [17], and by findings of reduced skin oxygenation in CRPS [27]. However, other observations are difficult to reconcile with ischemia being the sole cause of CRPS. First, capillary changes and edema pressure have not been shown to impair tissue blood flow [41], and skin hypoxia cannot be explained by edema alone [27]. Second, limb hyperperfusion has been demonstrated in mixed populations of 'warm' and 'cold' CRPS patients [34,41,43], although skin oxygenation is low in both groups [27]. Third, oxygen extraction fraction is dramatically reduced in CRPS [34,43], not elevated as one would expect in limb ischemia. Taken together, these observations suggest that impaired tissue oxygenation, rather than ischemia, is central to the etiopathogenesis of CRPS.

3. Relation between tissue blood flow and tissue oxygenation revisited

We recently uncovered a fundamental limitation in the assumed one-to-one correspondence between tissue blood flow (TBF) and tissue oxygenation [25]. The assumption is rooted in the classic flow-diffusion equation [38], which assumes that all tissue capillaries are equally perfused. Normal tissue, however, displays considerable capillary transit time heterogeneity (CTH). We generalized the flow-diffusion equation to express tissue oxygenation in terms of TBF, CTH, and tissue oxygen tension (P_tO_2) [25]. Fig. 2A shows the classic flow-diffusion equation, and how tissue oxygenation is reduced by increasing levels of CTH, at constant

* Corresponding author at: Aarhus University Hospital, Department of Neuroradiology, Center of Functionally Integrative Neuroscience and MINDLab, Building 10G, 5th floor, Nørrebrogade 44, Aarhus C 8000, Denmark. Tel.: +45 7846 4091; fax: +45 7846 1622.

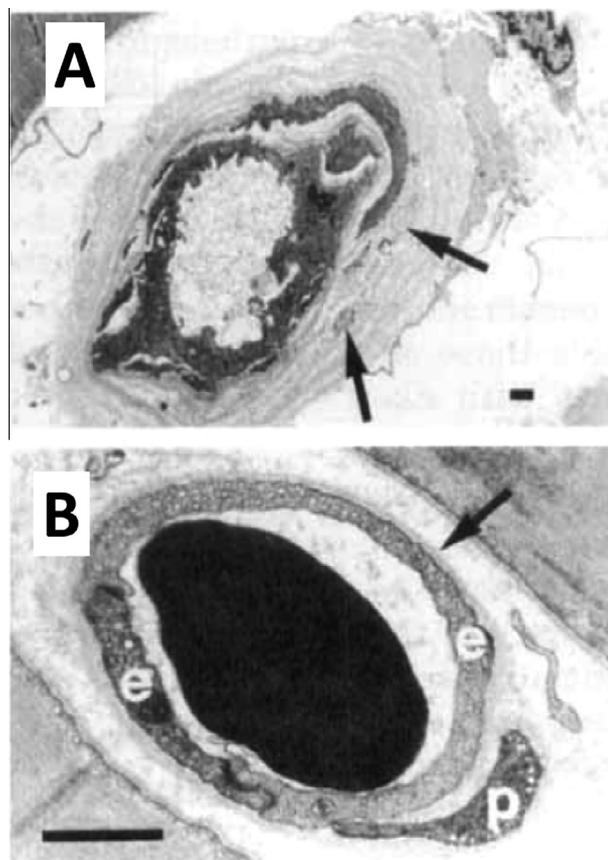E-mail address: leif@cfin.dk (L. Østergaard).

Fig. 1. (A) Gross thickening of the basal membrane in a capillary from the soleus muscle of a 46-year-old male CRPS patient [47]. Note the multiple basal membrane layers with cell debris from pericytes between the laminae (arrows). (B) Normal muscle capillary with a red blood cell, obtained from a 41-year-old female control subject. Note the endothelial cell (e), pericyte (p), and thin surrounding basal membrane (arrow). Although all patients in the study by van der Laan et al. [47] revealed severe changes in capillary and basement membrane morphology, it should be kept in mind that biopsy material from amputations invariably represents tissue from severe cases of CRPS. Figure from van der Laan et al. [47], reproduced with permission from the publisher.

P_tO_2. Accordingly, tissue oxygenation during vasodilation depends on both TBF and the parallel homogenization of capillary flows. If capillary flow patterns are poorly regulated, a condition called capillary dysfunction, blood passes through capillaries at transit times too short to permit efficient extraction of oxygen by the tissue. If CTH is high, this 'oxygen loss' may in fact exceed the benefits of vasodilation—a phenomenon called malignant CTH. Paradoxically, failure to suppress normal vasodilatory responses under these conditions is predicted to result in uncontrolled hyperemia, tissue hypoxia, and tissue damage, consistent with the so-called luxury perfusion syndrome observed in several tissues after ischemia-reperfusion [32]. If TBF responses can be suppressed, then the resulting, lower P_tO_2 increases blood–tissue concentration gradients and oxygen extraction so that some level of tissue function (eg, muscle work) can be maintained [25].

4. Blood flow regulation in normal muscle and skin

The sympathetic nervous system is involved in the regulation of resting blood flow in skin and muscle. In muscle, vessel tone is under baroreceptor control for blood pressure maintenance, and vascular innervation by α_1 and α_2 adrenergic fibers suppress resting blood flow so that sudden removal of sympathetic tone increases muscle blood flow 2- to 3-fold [22]. Meanwhile,

stimulation of β_2-adrenoreceptors causes vasodilation. During muscle work, tissue hypoxia, low pH, and the release of adenosine and nitric oxide increases blood flow. Muscle blood flow is interrupted by muscle contractions, and sustained tetanic contractions such as those used in an animal model of chronic pain [48] are thus likely to result in muscle hypoxia. In skin, stimulation of adrenergic fibers causes vasoconstriction, and stimulation of cholinergic fibers causes vasodilation and an increase in blood flow [26], although the extent of active cholinergic vasodilation, especially on distal body parts, remains under debate [39]. CRPS is localized to the limbs where muscle and overlying skin most often receive their blood supply from different vascular branches [44].

5. Blood flow regulation and oxygen extraction fraction in CRPS

Skin blood flow in CRPS can be subdivided according to three distinct phases [15,30]. In the acute or 'warm' phase of CRPS, the affected limb is usually warmer than the contralateral limb. This has been ascribed to functional inhibition of the sympathetic vasoconstriction of the dermal arterioles involved in thermoregulation [50,51], to ongoing inflammation, and to increased blood flow in underlying muscle and soft tissue (see below) [41]. The acute phase is often followed by an intermediate phase in which skin blood flow and temperature alternate between warm and cold [15,30]. Then, some patients develop a cold or chronic phase of CRPS [15,30], in which both nutritional and thermoregulatory skin flow is reduced. This hypoperfusion has been interpreted as catecholamine hypersensitivity [15], but this hypothesis is not supported by recent results [45]. Instead, increasing evidence suggests that endothelium-dependent vasodilation is suppressed, a condition called endothelial dysfunction [9,40]. Endothelial dysfunction is associated with increased levels of reactive oxygen species (ROS) in the arteriolar vessel walls, and reduced levels of nitric oxide (NO), which relaxes vascular smooth muscle cells. Long-term exposure of artery and arteriole walls to ROS and low NO causes remodeling and thickening of the vessel walls, which become more rigid and develop abnormal focal constrictions. Such morphological changes are indeed observed in CRPS patients [10].

Muscle or whole-limb blood flow regulation is difficult to study in CRPS. In patients with 'warm' CRPS, Matsumura et al. found reduced pH and high venous oxygen saturation (low oxygen extraction fraction) in the affected limb, and radiographic signs consistent with fast blood transits and AV shunting [34]. In chronic CRPS patients, Tan et al. reported reduced venous oxygen saturation (high oxygen extraction fraction), profound thickening of capillary endothelium and basement membranes in muscle, and evidence of severe hypoxia [43]. In a mixed population of individuals with 'warm' and 'cold' CRPS, of whom >90% showed severe tissue edema, Schurmann et al. found elevated blood flow in the affected arm, but no correlation between skin temperature and limb blood flow [41].

6. Inflammation and edema in CRPS

CRPS is associated with exaggerated inflammatory responses [3] and increased vascular permeability to macromolecules in the affected extremity [36]. It is generally assumed that the inflammation is neurogenic, mediated by the depolarization of small sensory afferents, mainly nociceptive C-fibers, in the skin. These depolarizations trigger the release of neuropeptides such as CGRP and substance P (SP), which induce local inflammation, protein extravasation, vasodilatation, and the release of cytokines [18]. Accordingly, skin levels of SP, CGRP, and inflammatory cytokines are elevated in CRPS [2,20,23,28]. Tissue hypoxia in itself may also elicit inflammation by up-regulating nuclear factor–κB transcription
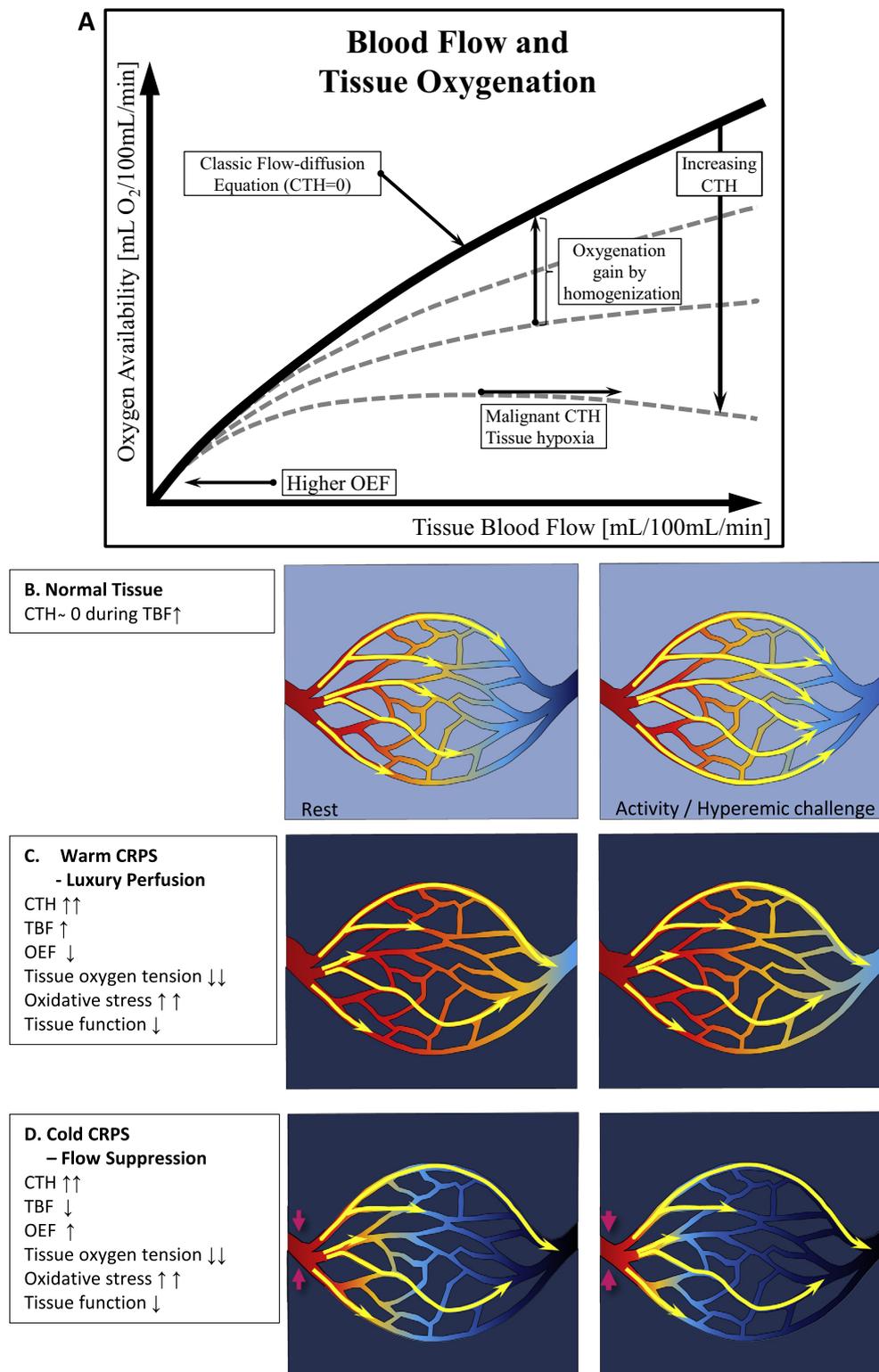
Fig. 2. (A) Relation between tissue blood flow (TBF; measured in mL/100 mL tissue/min), and tissue oxygenation, expressed as the maximum metabolic rate (mL O_2/100 mL tissue/min) that can be supported by the blood, according to the classic flow-diffusion equation [38], which assumes negligible capillary transit time heterogeneity (CTH) (full black curve). Dashed grey lines schematically show the effects of increasing levels of CTH, at fixed tissue oxygen tension (P_tO_2) [25]. In normal tissue, CTH is high during rest, but CTH is reduced in parallel with increases in TBF (B). This gives rise to efficient oxygen extraction at higher TBF values, despite the decreasing slope of the classical flow-diffusion equation. Conversely, failure of CTH to fall during vasodilation, so-called capillary dysfunction, renders vasodilation inefficient as a means of increasing tissue oxygenation. Note how the grey curves increase little towards high TBF. The lower grey curve illustrates the malignant CTH phenomenon. Eventually, TBF can reach a limit beyond which further vasodilation would reduce tissue oxygenation. Failure to suppress normal vasodilation during elevated metabolic needs would therefore lead to a condition of uncontrolled hyperemia, tissue hypoxia, and severe tissue damage. This phenomenon resembles the luxury perfusion syndrome [32] observed in some organs after tissue reperfusion. We hypothesize that this hemodynamic abnormality is present in 'warm' CRPS (C). If TBF responses can be suppressed, then the resulting reduction in tissue oxygen tension will increase blood–tissue concentration gradients, and increase the oxygen extraction fraction. Suppression of normal flow responses, for example, by endothelial dysfunction, permits better oxygen extraction and some level of tissue function, for example, muscle work. We hypothesize that 'cold' CRPS is characterized by suppression of resting and activity-related blood flow (D).

factors, which act as regulators of inflammation and orchestrate immune responses to protect the host, including the production of tumor necrosis factor, a key pro-inflammatory cytokine [13].

7. Capillary dysfunction hypothesis of CRPS

We hypothesize that CTH is elevated in tissue injury and acute inflammation as a result of the following: capillary compression by increased interstitial pressure (which occurs at only half the pressure needed for arteriolar compression) caused by local hemorrhage and edema [49]; capillary constriction due to vasoactive blood break-down products [29]; and disturbed blood rheology due to abnormal adhesion of erythrocytes and white blood cells to the capillary wall in inflammation [35]. These factors have been shown to disturb capillary flow patterns and effectively shunt blood through the capillary bed [35,49]. We hypothesize that the increased blood flow and reduced oxygen extraction in both skin and muscle in 'warm' CRPS reflect failure to suppress TBF in the presence of malignant CTH, that is, 'luxury perfusion'. We further speculate that that the high oxygen extraction fraction [43] found in chronic 'cold' CRPS represents suppression of resting blood flow and blood flow responses by endothelial dysfunction [40] to maintain tissue oxygenation. Vasospasms, rather than being the source of ischemia CRPS and CRPS models [6,7], are thus predicted to compensate for downstream capillary dysfunction by attenuating the 'oxygen loss' that occur as blood is shunted through the capillaries at high flow rates. We believe that the intrinsic ROS production throughout these phases causes permanent capillary wall damage, propagating the condition [43,47]. These scenarios are illustrated in Fig. 2B to E.

The key events in the hypothesized CRPS etiology are prolonged disturbances of CTH by the factors above, and oxidative damage to capillary walls and tissue (Fig. 2). Nicotine up-regulates the expression of adhesion molecules in the capillary endothelium [1] and increases leukocyte rolling [54]. Smoking would therefore be expected to worsen capillary flow disturbances and increase the risk of developing CRPS, whereas prompt reduction of the tissue swelling and inflammation would be expected to reduce the risk. We speculate that these mechanisms may contribute to the increased prevalence of smokers among CRPS patients [21] and the benefits of corticosteroid treatment in preventing CRPS [5]. Meanwhile, we speculate that administration of vitamin C (a ROS scavenger) reduces the risk of developing CRPS [55] by attenuating oxidative capillary wall damage.

8. Origin of pain in CRPS

The mechanisms by which ischemia might create pain have been reviewed by Coderre et al. [7,37]. Briefly, tissue hypoxia would be expected to result in elevated lactate levels and acidosis secondary to energy depletion, as observed in the muscle and skin of CRPS patients [4,17,27]. Indeed, exercise increases pain in CRPS patients [7], and increased lactate levels correlate with the degree of pain in animal models [7]. Both nociceptor discharges in relation to the initial injury, and ectopic discharges thought to occur in C-fibers in animal models of hypoxia and inflammation [7], are likely to initiate and maintain central sensitization [53]. Meanwhile, tissue hypoxia and inflammation are also known to increase the levels of pro-inflammatory cytokines thought to produce neuropathic pain [12,52].

9. Conclusion and perspectives

Based on a chronic postischemic pain model [8] and earlier observations of vascular abnormalities in CRPS [6], Coderre et al.

have proposed that CRPS is initiated by a compartment-like syndrome, during which injury-related edema compresses tissue microvessels and causes severe ischemia [7] and that subsequent reperfusion causes microvascular injury and a permanent state of vasospasm, slow flow, and deep tissue ischemia [6,7]. We have extended this notion by proposing that capillary flow disturbances, rather than arteriolar compressions or vasospasms, and tissue hypoxia rather than ischemia, may be central disease entities in CRPS.

Direct demonstration that a reduction of tissue CTH alleviates CRPS symptoms and improves TBF would support the prediction that capillary dysfunction is central to CRPS etiopathogenesis. Phosphodiesterase (PDE) inhibitors reduce platelet aggregation [19], decrease blood viscosity [24], and increase the flexibility of erythrocytes [24]. By these hemorheologic effects, PDE inhibitors would therefore be expected to reduce CTH, and hence improve tissue oxygenation. The PDE inhibitor tadalafil indeed improves muscle force (indicative of improved muscle oxygenation) and reduces pain in some CRPS patients [16]. We speculate that the recent failure of tadalafil to elevate limb temperature [37] is the result of capillary dysfunction, which causes a dissociation between tissue oxygenation on one hand, and limb blood flow/ temperature on the other. Studies in a post-ischemic pain model confirm that systemic PDE [46], as well as topical PDE application either alone or in combination with vasodilators [37], relieve allodynia while reversing the suppression of flow responses [31], consistent with a role of elevated CTH and tissue hypoxia in this model.

Conflict of interest statement

The authors declare no conflicts of interest.

Acknowledgements

References

[1] Albaugh G, Bellavance E, Strande L, Heinburger S, Hewitt CW, Alexander JB. Nicotine induces mononuclear leukocyte adhesion and expression of adhesion molecules, VCAM and ICAM, in endothelial cells in vitro. Ann Vasc Surg 2004;18:302–7.
[2] Bernateck M, Karst M, Gratz KF, Meyer GJ, Fischer MJ, Knapp WH, Koppert W, Brunkhorst T. The first scintigraphic detection of tumor necrosis factor-alpha in patients with complex regional pain syndrome type 1. Anesth Analg 2010;110:211–5.
[3] Birklein F, Schmelz M. Neuropeptides, neurogenic inflammation and complex regional pain syndrome (CRPS). Neurosci Lett 2008;437:199–202.
[4] Birklein F, Weber M, Neundorfer B. Increased skin lactate in complex regional pain syndrome: evidence for tissue hypoxia? Neurology 2000;55:1213–5.
[5] Christensen K, Jensen EM, Noer I. The reflex dystrophy syndrome response to treatment with systemic corticosteroids. Acta Chir Scand 1982;148:653–5.
[6] Coderre TJ. Complex regional pain syndrome: what's in a name? J Pain 2011;12:2–12.
[7] Coderre TJ, Bennett GJ. A hypothesis for the cause of complex regional pain syndrome-type I (reflex sympathetic dystrophy): pain due to deep-tissue microvascular pathology. Pain Med 2010;11:1224–38.
[8] Coderre TJ, Xanthos DN, Francis L, Bennett GJ. Chronic post-ischemia pain (CPIP): a novel animal model of complex regional pain syndrome-type I (CRPS-I; reflex sympathetic dystrophy) produced by prolonged hindpaw ischemia and reperfusion in the rat. PAIN® 2004;112:94–105.
[9] Dayan L, Salman S, Norman D, Vatine JJ, Calif E, Jacob G. Exaggerated vasoconstriction in complex regional pain syndrome-1 is associated with impaired resistance artery endothelial function and local vascular reflexes. J Rheumatol 2008;35:1339–45.
[10] Derenthal N, Maecken T, Krumova E, Germing A, Maier C. Morphological macrovascular alterations in complex regional pain syndrome type I demonstrated by increased intima-media thickness. BMC Neurol 2013;13:14.
[11] Eberle T, Doganci B, Kramer HH, Geber C, Fechir M, Magerl W, Birklein F. Warm and cold complex regional pain syndromes: Differences beyond skin temperature? Neurology 2009;72:505–12.

[12] Eliav E, Herzberg U, Ruda MA, Bennett GJ. Neuropathic pain from an experimental neuritis of the rat sciatic nerve. PAIN® 1999;83:169–82.

[13] Eltzschig HK, Carmeliet P. Hypoxia and inflammation. N Engl J Med 2011;364:656–65.

[14] Goebel A. Complex regional pain syndrome in adults. Rheumatology (Oxford) 2011;50:1739–50.

[15] Groeneweg G, Huygen FJ, Coderre TJ, Zijlstra FJ. Regulation of peripheral blood flow in complex regional pain syndrome: clinical implication for symptomatic relief and pain management. BMC Musculoskelet Disord 2009;10:116.

[16] Groeneweg G, Huygen FJ, Niehof SP, Wesseldijk F, Bussmann JB, Schasfoort FC, Stronks DL, Zijlstra FJ. Effect of tadalafil on blood flow, pain, and function in chronic cold complex regional pain syndrome: a randomized controlled trial. BMC Musculoskelet Disord 2008;9:143.

[17] Heerschap A, den Hollander JA, Reynen H, Goris RJ. Metabolic changes in reflex sympathetic dystrophy: a 31P NMR spectroscopy study. Muscle Nerve 1993;16:367–73.

[18] Holzer P. Neurogenic vasodilatation and plasma leakage in the skin. Gen Pharmacol 1998;30:5–11.

[19] Horlington M, Watson PA. Inhibition of 3'5'-cyclic-AMP phosphodiesterase by some platelet aggregation inhibitors. Biochem Pharmacol 1970;19:955–6.

[20] Hou Q, Barr T, Gee L, Vickers J, Wymer J, Borsani E, Rodella L, Getsios S, Burdo T, Eisenberg E, Guha U, Lavker R, Kessler J, Chittur S, Fiorino D, Rice F, Albrecht P. Keratinocyte expression of calcitonin gene-related peptide beta: implications for neuropathic and inflammatory pain mechanisms. PAIN® 2011;152:2036–51.

[21] Hsu C, Harden RN, Houle T. Nicotine and caffeine intake in complex regional pain syndrome. J Back Musculoskelet Rehabil 2002;16:33–8.

[22] Hudlicka O. Regulation of muscle blood flow. Clin Physiol 1985;5:201–29.

[23] Huygen FJ, De Bruijn AG, De Bruin MT, Groeneweg JG, Klein J, Zijlstra FJ. Evidence for local inflammation in complex regional pain syndrome type 1. Mediators Inflamm 2002;11:47–51.

[24] Jacoby D, Mohler 3rd ER. Drug treatment of intermittent claudication. Drugs 2004;64:1657–70.

[25] Jespersen SN, Østergaard L. The roles of cerebral blood flow, capillary transit time heterogeneity and oxygen tension in brain oxygenation and metabolism. J Cereb Blood Flow Metab 2012;32:264–77.

[26] Kellogg Jr DL. In vivo mechanisms of cutaneous vasodilation and vasoconstriction in humans during thermoregulatory challenges. J Appl Physiol 2006;100:1709–18.

[27] Koban M, Leis S, Schultze-Mosgau S, Birklein F. Tissue hypoxia in complex regional pain syndrome. PAIN® 2003;104:149–57.

[28] Kramer HH, Eberle T, Uceyler N, Wagner I, Klonschinsky T, Muller LP, Sommer C, Birklein F. TNF-alpha in CRPS and 'normal' trauma—significant differences between tissue and serum. PAIN® 2011;152:285–90.

[29] Kranc KR, Pyne GJ, Tao L, Claridge TD, Harris DA, Cadoux-Hudson TA, Turnbull JJ, Schofield CJ, Clark JF. Oxidative degradation of bilirubin produces vasoactive compounds. Eur J Biochem 2000;267:7094–101.

[30] Kurvers HA, Jacobs MJ, Beuk RJ, Van den Wildenberg FA, Kitslaar PJ, Slaaf DW, Reneman RS. Reflex sympathetic dystrophy: evolution of microcirculatory disturbances in time. PAIN® 1995;60:333–40.

[31] Laferriere A, Abaji R, Tsai CY, Ragavendran JV, Coderre TJ. Topical combinations to treat microvascular dysfunction of chronic postischemia pain. Anesth Analg 2014;118:830–40.

[32] Lassen NA. The luxury-perfusion syndrome and its possible relation to acute metabolic acidosis localised within the brain. Lancet 1966;2:1113–5.

[33] Marinus J, Moseley GL, Birklein F, Baron R, Maihofner C, Kingery WS, van Hilten JJ. Clinical features and pathophysiology of complex regional pain syndrome. Lancet Neurol 2011;10:637–48.

[34] Matsumura H, Jimbo Y, Watanabe K. Haemodynamic changes in early phase reflex sympathetic dystrophy. Scand J Plast Reconstr Surg Hand Surg 1996;30:133–8.

[35] Mazzoni MC, Schmid-Schonbein GW. Mechanisms and consequences of cell activation in the microcirculation. Cardiovasc Res 1996;32:709–19.

[36] Oyen WJ, Arntz IE, Claessens RM, Van der Meer JW, Corstens FH, Goris RJ. Reflex sympathetic dystrophy of the hand: an excessive inflammatory response? PAIN® 1993;55:151–7.

[37] Ragavendran JV, Laferriere A, Xiao WH, Bennett GJ, Padi SS, Zhang J, Coderre TJ. Topical combinations aimed at treating microvascular dysfunction reduce allodynia in rat models of CRPS-I and neuropathic pain. J Pain 2013;14:66–78.

[38] Renkin EM. B. W. Zweifach Award lecture. Regulation of the microcirculation. Microvasc Res 1985;30:251–63.

[39] Roddie IC. Sympathetic vasodilatation in human skin. J Physiol 2003;548:336–7.

[40] Schattschneider J, Hartung K, Stengel M, Ludwig J, Binder A, Wasner G, Baron R. Endothelial dysfunction in cold type complex regional pain syndrome. Neurology 2006;67:673–5.

[41] Schurmann M, Zaspel J, Gradl G, Wipfel A, Christ F. Assessment of the peripheral microcirculation using computer-assisted venous congestion plethysmography in post-traumatic complex regional pain syndrome type I. J Vasc Res 2001;38:453–61.

[42] Schwartzman RJ, McLellan TL. Reflex sympathetic dystrophy. A review. Arch Neurol 1987;44:555–61.

[43] Tan EC, Ter Laak HJ, Hopman MT, van Goor H, Goris RJ. Impaired oxygen utilization in skeletal muscle of CRPS I patients. J Surg Res 2012;173:145–52.

[44] Taylor GI, Palmer JH. The vascular territories (angiosomes) of the body: experimental study and clinical applications. Br J Plast Surg 1987;40:113–41.

[45] Terkelsen AJ, Gierthmuhlen J, Petersen LJ, Knudsen L, Christensen NJ, Kehr J, Yoshitake T, Madsen CS, Wasner G, Baron R, Jensen TS. Cutaneous noradrenaline measured by microdialysis in complex regional pain syndrome during whole-body cooling and heating. Exp Neurol 2013;247:456–65.

[46] Vaigunda Ragavendran J, Laferriere A, Khorashadi M, Coderre TJ. Pentoxifylline reduces chronic post-ischaemia pain by alleviating microvascular dysfunction. Eur J Pain; 2013, in press.

[47] van der Laan L, ter Laak HJ, Gabreels-Festen A, Gabreels F, Goris RJ. Complex regional pain syndrome type I (RSD): pathology of skeletal muscle and peripheral nerve. Neurology 1998;51:20–5.

[48] Vatine J, Tsenter J, Raber P, Seltzer Z. A model of CRPS-1 produced by tetanic electrical stimulation of an intact sciatic nerve in the rat: genetic and dietary effects. In: Harden RN, Baron R, Janig W, editors. Complex regional pain syndrome. Progress in pain research and management. Seattle: IASP Press; 2001. p. 53–74.

[49] Vollmar B, Westermann S, Menger MD. Microvascular response to compartment syndrome-like external pressure elevation: an in vivo fluorescence microscopic study in the hamster striated muscle. J Trauma 1999;46:91–6.

[50] Wasner G, Heckmann K, Maier C, Baron R. Vascular abnormalities in acute reflex sympathetic dystrophy (CRPS I): complete inhibition of sympathetic nerve activity with recovery. Arch Neurol 1999;56:613–20.

[51] Wasner G, Schattschneider J, Heckmann K, Maier C, Baron R. Vascular abnormalities in reflex sympathetic dystrophy (CRPS I): mechanisms and diagnostic value. Brain 2001;124:587–99.

[52] Watkins LR, Maier SF. Beyond neurons: evidence that immune and glial cells contribute to pathological pain states. Physiol Rev 2002;82:981–1011.

[53] Woolf CJ, Thompson SW. The induction and maintenance of central sensitization is dependent on N-methyl-D-aspartic acid receptor activation; implications for the treatment of post-injury pain hypersensitivity states. PAIN® 1991;44:293–9.

[54] Yong T, Zheng MQ, Linthicum DS. Nicotine induces leukocyte rolling and adhesion in the cerebral microcirculation of the mouse. J Neuroimmunol 1997;80:158–64.

[55] Zollinger PE, Tuinebreijer WE, Kreis RW, Breederveld RS. Effect of vitamin C on frequency of reflex sympathetic dystrophy in wrist fractures: a randomised trial. Lancet 1999;354:2025–8.