Topical review

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

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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 hyper-sensitivity, 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 disrupt 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 O 2) [25]. Fig. 2A shows the classic flow-diffusion equation, and how tissue oxygenation is reduced by increasing levels of CTH, at constant
increases blood–tissue concentration gradients and adrenergic fibers suppress resulting, lower Pt reperfusion [32]. If TBF responses can be suppressed, then the perfusion syndrome observed in several tissues after ischemia-hypoxia, and tissue damage, consistent with the so-called luxury failure to suppress normal vasodilatory responses under these conditions. CTH is high, this ‘oxygen loss’ may in fact exceed the benefits of vascular innervation by a under baroreceptor control for blood pressure maintenance, and vascular innervation by $\alpha_1$ and $\alpha_2$ 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 $\beta_2$-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 tetric 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 vasodilatation, 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 hyperperfusion 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, Schurrmann 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 O2/100 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 (PtO2) [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 shut 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 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 occurs 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 byCoderre 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 tadalafl alone improves muscle force (indicative of improved muscle oxygenation) and reduces pain in some CRPS patients [16]. We speculate that the recent failure of tadalafl 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

This study was supported by the Danish Ministry of Science, Innovation, and Education (MINDLab; LØ, N.B.F., S.N.J., P.S., and T.S.J.).

References