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Research report

Active skin perfusion and thermoregulatory response in the hand following nerve injury and repair in human upper extremities

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ABSTRACT

Cutaneous vasoconstriction/vasodilatation occurs in response to whole body and local cooling/heating, and the vasomotor activities play a pivotal role in thermal control of the human body. The mechanisms underlying regulation of skin blood flow involve both neurogenic and humeral/local chemical influence, contributing to the initial response to thermal stimuli and the prolonged phase of response, respectively. Previous studies have suggested the impairment of cutaneous thermal regulation after nerve injury. However, the evidence regarding how the skin perfusion and thermoregulatory response evolve after nerve injury and repair remains limited. Here we observed, by utilizing laser-Doppler perfusion imaging, baseline skin perfusion and perfusion change in response to thermal stimuli after median and ulnar nerve injury, and the results showed that baseline perfusion in autonomous skin area profoundly decreased and active rewarming after clod stress dramatically diminished before sensory recovery of the skin became detectable. In addition, baseline cutaneous perfusion was recovered as the skin regained touch sensation, and exhibited positive correlation to touch sensibility of the skin. These data indicate that both active perfusion and thermoregulatory response of the skin are markedly compromised during skin denervation and can be recovered by re-innervation. This suggests the importance of timely repair of injured nerve, especially in the practice of replantation.

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1. Introduction

The human body possesses well-controlled feedback mechanisms to maintain thermal homeostasis (Charkoudian, 2003; Flouris and Cheung, 2011). One mechanism of thermal regulation is the sudomotor and vasomotor activities of the skin in response to heating or cooling, by either vasodilatation/sweating or vasoconstriction, so that the core temperature of the body can be maintained (Charkoudian, 2003; Johnson et al., 2014; Ring, 2010). In addition to whole body heating or cooling during which the blood vessels of the body are dilated or constricted accordingly, the cutaneous vasculature is also responsive to local thermal stimulation (Johnson and Kellogg, 2010; Johnson et al., 2014). For example, cold-induced vasoconstriction, constriction of blood vessels and reduction of blood perfusion in response to cold stimuli, is recognized as active prevention of heat loss from the periphery and thereby a mechanism for maintenance of core temperature (Ruijs et al., 2011). However, when remaining in cold environment for an extended period of time, the exposed body parts are susceptible to cold injury, especially in the distal most extremities like the fingers (Kusters et al., 2010). In this case, cold-induced vasodilatation, oscillating vasodilatation during prolonged cold exposure, occurs so as to prevent frostbite injury (Ruijs et al., 2011; Smits et al., 2013). Another example of vasomotor regulation for thermal control is heat-induced vasodilatation, dilation of skin blood vessels when exposed to heat stimuli (Johnson et al., 2014; Kenney, 1988). All these responses are precisely modulated via a set of inherent and sophisticated mechanisms under physiological conditions.

The mechanisms underlying regulation of skin blood flow are complex, involving both neurogenic and humeral/local chemical influence; the former contributes to the rapid response to thermal stimuli, while the latter is thought to lead to the prolonged response (Hodges and Johnson, 2009; Johnson and Kellogg, 2010; Tew et al., 2011). Actually, in vertebrates the peripheral nerve system and the vasculature system usually travel alongside each other and follow nearly the same branching pattern and the same distribution in the skin, which are intrinsically patterned during development as evidenced by impairment of cutaneous arteriogenesis and vascular branching after genetic deletion of peripheral sensory nerves (Mukouyama et al., 2002). With regard to neurogenic control of dermal vasomotor activity, it is commonly recognized that the sympathetic nerve dominates vasoconstriction by acting on adrenergic receptors in cutaneous vasculature, whereas vasodilatation attributes mainly to the C afferent nerve (Charkoudian, 2003; Johnson et al., 2014; Ruch et al., 2003).

Although the neurogenic influence in thermoregulatory control is often studied via electric stimulation, local anesthetic block or pharmacological interventions (Chandran et al., 2010; Gazerani et al., 2009; Hornyak et al., 1990; Keller et al., 2010), nerve injuries offer a unique opportunity to address the issue due to complete loss of neural activity in autonomous skin region (Ruch et al., 2003; Ruijs et al., 2009; Smits et al., 2013). Previous clinical studies have shown that peripheral nerve injury not only leads to loss of sweating in autonomic skin territory of the nerve (Gu et al., 2012), but also results in impairment of vasomotor regulation such as active rewarming and cold-induced vasodilatation (Ruijs et al., 2009, 2011). Yet how these functional deficits evolve during re-innervation remains to be elucidated. Additionally, dystrophy and atrophy of target tissue is often seen in the case of prolonged denervation or peripheral neuropathy (Albers and Pop-Busui, 2014; Mann and Burton, 1982), suggesting a role of normal nerve activity in the maintenance of blood perfusion and nutrients supply in the target (Fu and Gordon, 1995). However, discrepancy has been seen in findings of vasomotor activity in denervated skin, with vasodilatation during first 5–8 months after injury being observed in one study (Pulst and Haller, 1981) and conversely vasoconstriction during the first 3 months in another (Ruch et al., 2003). In the present study, we set out to examine vasomotor activity in denervated and re-innervating skin in the context of resting, local cooling as well as local warming, so as to evaluate the role of innervation in cutaneous vasomotor control.

2. Results

2.1. *General findings and sensory recovery*

At 4–6 d after nerve injury (*recent injury* hereafter), the autonomous skin region did not show overt change in appearance despite numbness reported by the patients. However, at 14–74 d after injury, sensory distribution area of the injured nerve exhibited a dry and coarse appearance. The second and third finger pulps showed complete loss of touch/pressure sensibility after denervation of the median nerve at this stage. Interestingly, it is observed that during denervation after ulnar nerve injury at wrist, deep pressure sensation remained in the fifth finger pulp, which was sensitive to Semmes–Weinstein monofilament at size 6.65; by contrast, touch/pressure sensibility in the fifth finger pulp was seen in none of the 3 patients with ulnar nerve injury at the mid-forearm level. As a simple approach to monitoring axonal regeneration, Tinel's sign was elicited when tapping at the site of injury or no more than 5 cm distal to the injury during this period. A *typical denervation* stage was thus defined as complete loss of touch/pressure sensibility, or deep pressure sensibility only after ulnar nerve injury at wrist, with Tinel's sign being indicated at a level of no more than 5 cm distal to the distal wrist crease.

At 5–27 m post-injury (*re-innervating stage* hereafter), the sensory distribution area of the injured nerve(s) was found to regain luster and perspiration and significantly recover touch sensibility. At 5–13 m post-injury, median nerve injury patients regained deep pressure sensation, while the patients with ulnar nerve injury at wrist recovered overall better touch sensibility. When nerve injuries were allowed to recover for 24–27 m, the autonomous region recovered touch sensibility up to partial protective sensation, depending on the nerve involved and the level of injury. Tinel's sign was indicated up to fingertips during early re-innervation, but seemed to disappear at a later stage (over 2 years).