Red skin re-read.

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Although relatively rare, the symptom complex of intermittent acral warmth, pain, and erythema that defines erythromelalgia (EM) has been well documented in the medical literature for over 150 years (Graves, 1838). Despite an extended awareness of this phenomenon, the cause and underlying mechanisms have until recently been completely obscure. Part of the difficulty in understanding EM has been the heterogeneity of the affected population. EM is often idiopathic or `primary,' but also has been reported to be associated with myleoproliferative and hemotologic disease, autonomicnervous system disease, pharmacologic agents, viral infections and pregnancy. It is not clear what common pathologic features in these settings produce the EM symptom complex. EM is also rare, with an estimated incidence of approximately 3 per million in the. Norwegian population (Kvernebo, 1998). Hence, there are few centers that follow a large enough population of patients to perform studies that are large enough to identify consistent physiologic features. Furthermore, as suggested by Mark et al in this issue of the JID, as well as by other authors, the underlying pathologic mechanisms are likely to involve a complex dysregulation of cutaneous blood flow that ultimately results in microvascular ischemia. Determining the nature of this dysfunction has also been challenging because the control of cutaneous blood flow is dependent on an interplay of systemic and local signals, and is not completely understood.

The cutaneous vasculature contributes critical nutritive and inflammatory functions, but the majority of blood flow through human skin serves thermoregulatory homeostasis. The distribution of the blood flow is largely regulated by two segments of the microvascular bed, the arteriovenous anastomoses and the precapillary sphincters. Arteriovenous anastomoses and the most prominent on acral skin, particularly on the palms and soles, where during vasodilatation blood is shunted away from superficial resistance vessels to increase overall flow and heat dissipation. Located at the end of the terminal arteriole, the precapillary sphincter directly regulates blood flow to capillary beds throughout the circulatory system. In the superficial dermis, the precapillary sphincter controls the flow of blood from the ascending arteriole into the capillaries of the superficial vascular plexus that provide nutrients and oxygen to the papillary dermis and the epidermis (Braverman, 2000). Both these vascular elements are responsive to multiple systemic stimuli including core temperature changes, cardiovascular homeostasis, and emotional stress, as well as local stimuli such as pain, inflammation, pressure, and heating or cooling. Vasoconstrictive signals are delivered through the sympathetic nervous system directly to vascular smooth muscle, and have most prominent effects in areas with large concentrations of arteriovenous anastomoses. Local

factors such as endothelilin-1, which is produced by vascular endothelium, may also mediate vasoconstriction. Vasodilatation is mediated by a combination of parasympathetic signals and local production of chemicals with vasomotor activity. Acetylcholine mediated parasympathetic vascular dilatation is dependent on production of nitric oxide and prostacyclin, which can also be directly induced by local stimuli.

The authors of the study in this issue of the JID have significantly contributed to our understanding of the role of dysfunction of specific elements of the cutaneous vasculature in EM. They have taken the approach of inducing symptoms in volunteers drawn from their relatively large population of affected patients, by raising core temperature, and using noninvasive methods to monitor microvascular blood flow. Laser Doppler flowmetry was previously utilized for this purpose. This technology allows the measurement of superficial perfusion, with the majority of signals arising from a depth of 200-300 Jim from the surface (Wardell et al, 1993). In areas that do not have significant numbers of AV anastomoses, areas of high flux have been mapped to individual ascending arterioles and the distal arborization of capillaries in the superficial plexus that they feed (Braverman and Schechner, 1991). Although not specifically analyzed, it is likely that in glabrous skin AV anastomoses also make a large if not dominant contribution. Mark et al (2000) confirmed that the observed erythema and warmth was in fact due to increased blood flow. Paradoxically, this increased perfusion was accompanied by local hypoxia, leading to the theory that increased blood flow was due to shunting through AV anastomoses, which resulted in hypoperfusion of the more superficial nutritive capillaries. The effects of diminished perfusion were hypothesized to be exacerbated by increased metabolic demands in response to hyperthermia, ultimately resulting in hypoxic tissue damage and pain.

The current study provides convincing evidence that despite an increased overall blood flow to the skin, the induction of erythromelalgia symptoms is accompanied by decreased perfusion of the superficial vascular plexus. This was accomplished by quantifying the density of dilated (and therefore actively perfused) capillary loops using a recently developed computer enhanced technique of capillary video microscopy. Interestingly, this observed lower capillary density was found to be most prominent in the nail folds, where there is the greatest concentration of AV anastomoses, and was less prominent on the arch of the foot, where the anastomoses are fewer. This observation supports the authors' underlying hypothesis that the dilatation of AV anastomoses is directly responsible for shunting nutritive blood flow away from the superficial vascular plexus.

The elegant monitoring techniques used in both the current and previous studies have significantly contributed to understanding the role of specific aspects of cutaneous vascular physiology in producing the symptoms of erythromelalgia. Still, several questions remain unanswered. The role dysfunction of the precapillary sphincter plays in this disease is unclear. It is unknown if shunting of blood through AV anastomoses alone is capable of inducing hypoxia severe enough to induce pain, particularly in areas that contain few AV anastomoses. Potentially inadequate compensatory dilatation, or even inappropriate constriction of the precapillary sphincter, may compound the relative hypoperfusion. In asymptomatic EM patients, decreased cutaneous perfusion has in fact

been observed (Littleford et al, 1999). The factors responsible for vascular dysfunction are also obscure. Both autonomic neuropathy (Sandroni et al, 1990; Mork et al, 2002) and endothelial injury (Drenth et al, 1996) have been observed in patients with EM, but it is not known whether this damage to critical vasoregulatory components is primary, or secondary to chronic hypoxia. Perhaps these details can be sorted out through the use of pharmacologic agents that are agonists and antagonists of specific vasomodulatory signals. Such studies are likely to identify more effective therapeutic strategies than are currently available.

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