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Skin perfusion responses under normal and combined loadings: Comparisons between legs with venous stasis ulcers and healthy legs

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ABSTRACT

Background: Venous ulcers, also known as stasis ulcers, are skin wounds often found at the medial surface of the lower leg. These wounds are related to chronic venous insufficiencies and affect almost 2.5 million patients every year in the United States.

Method: Eighteen participants with venous stasis ulcers on at least one leg and twenty healthy participants were tested. Normal and combined normal and shear loadings were applied to each lower leg and local blood perfusion was monitored. Basal perfusion, post-occlusive reactive hyperemia as well as changes in perfusion due to different loadings were compared.

Findings: Legs with existing venous stasis ulcers ("wounded legs") had the highest reactive hyperemia and basal perfusion values. Legs without ulcers but from participants with venous stasis ulcers ("non-wounded legs") had intermediate reactive hyperemia, and healthy legs exhibited the lowest values. Wounded legs also exhibited the largest decrease in blood perfusion under both normal and combined loadings. Non-wounded legs decreased perfusion similarly to healthy legs under normal loadings; however, non-wounded legs exhibited larger decreases in blood flow than healthy legs in response to shear and normal loading together.

Interpretation: These results suggest that patients with venous stasis disease have abnormal responses to tissue loading and raise the possibility that this technique may have the potential to identify patients at risk for developing a venous stasis ulcer. Moreover, they emphasize the importance of studying shear loading in addition to normal loading in attempting to understand the pathophysiology of this disease.

1. Introduction

Venous ulcers, also known as stasis ulcers, are skin wounds that occur most commonly on the lower leg. These wounds are due to chronic venous insufficiency and are the most common ulceration in the lower extremities, affecting almost 2.5 million patients every year in the United States (Arnold et al., 1994; Brem et al., 2004; Milic et al., 2009). Gravity makes the lower legs the most vulnerable to venous blood reflux for patients with insufficient venous function (Kramer, 1999; Partsch, 2013; Sieggreen, 2005; Villavicencio, 2013). Pooled blood in the lower legs induces high intravascular pressure, leakage of plasma proteins, and fluid into the surrounding tissues, which causes increased interstitial pressure, tissue breakdown, and ulcer formation (Burton, 1991; Collins and Seraj, 2010). Poor perfusion related to arterial insufficiency is a common cause of poorly healing leg wounds (Douglas and Simpson, 1995; Valencia et al., 2001). However, circulatory problems may be arterial or venous. Patients with venous insufficiency (including those with venous vascular dysfunction, venous thrombosis, and large "perforators" that connect the deep and superficial venous system) are at high risk for what are called venous stasis ulcers, which are also difficult to heal. Demographically, these patients are frequently elderly, diabetic, inactive, or have a history of leg trauma (Kolluri, 2014; Margolis et al., 2002; Markova and Mostow, 2012; Valencia et al., 2001). Although the genetics are unclear, there is some propensity of the disease to cluster in families (Ontario, 2011; Suehiro et al., 2014).

Treatment for venous ulcers in current clinical practice tends to focus more on treating the ulcer than on prevention or avoiding recurrence (Alvarez et al., 1998; Ghatnekar et al., 2011; Omar et al., 2004; Poblete and Elias, 2009; Thomas, 2013). Stasis ulcers, however, have high recurrence rates; 33% recur after traditional compression treatment and 15% after surgical intervention (Howard et al., 2008). Such recurrences result in multiple visits to wound clinics or hospitals, substantial costs for the patient and/or health care system, and frustration and stress for patients (George et al., 2014; Lamel and Kirsner, 2013; Ma et al., 2014). Many employed patients must take time off from work for leg elevation or wound care, creating an additional financial burden. In addition, since venous disease is often bilateral, patients with venous ulcers on one leg are likely to develop ulcers on the other leg within 3 to 5 years if no preventive measures are taken (Abbade and Lastória, 2005; Kunimoto et al., 2001). Patients with healed ulcers

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may be advised to wear compression stockings, but the discomfort these engender leads to poor compliance. Interestingly, a recent meta-analysis found insufficient evidence to support the prophylactic efficacy of such compression stockings (Shingler and Robertson, 2013).

Ablative venous surgical procedures may be more effective in preventing recurrence (Ontario, 2011), but it is difficult to decide which patients require such therapy. Indeed, at least in the United States, most insurers will not pay for venous ablative procedures unless patients have failed medical therapy for their acute ulceration over a prolonged period; this creates a large subgroup of patients who recur frequently even though they are healed each time with aggressive non-surgical therapy. Thus, more information is needed on how to decrease the recurrence rate and reduce the burden of venous ulcer disease (Langemo, 1999; Palfreyman and Stone, 2015). One approach would be the identification of physical characteristics of the patient's leg that might predict venous ulceration and/or recurrence.

Prolonged external loads on the skin impair blood circulation and can cause ulceration. Although much attention has been paid to pressure from normal loads (perpendicular to the skin) (Bliss and Schofield, 1996; Kramer, 1999; Lewis and Towne, 2011; Reeder, 2013), increasing attention has been paid to the influence of shear loads (loads parallel to the skin) and their relationship to decreased blood flow and ulcer formation (Manorama et al., 2010, 2013). Additionally, the high blood flow during reperfusion after the loads are removed leads to ischemia-hyperemia injury, which may contribute to venous ulceration (Capp et al., 2004; Liao et al., 2013; Loerakker et al., 2011; Morales et al., 2005; Rendell and Wells, 1998).

Despite the importance of loading, little is known about how responses to loading in healthy legs compare to the responses of legs with wounds. In particular, the possibility that blood flow response may differ with respect to different loading conditions between ulcerated skin and healthy skin is important, as legs are subjected to both normal loading (perpendicular to the skin) and shear loading in common daily postures. In this study, differences in lower leg skin perfusion responses to various types of loading were investigated among patients with venous ulcers and healthy individuals. Understanding differences in skin blood flow during ischemia and between patients with venous ulcers compared to healthy individuals will lay a foundation for establishing a tissue injury model for ulcer formation and has the potential to provide preventive indicators and measures for venous ulcer treatment.

2. Methods

2.1. Equipment

Load was applied using a custom-built device. The device included a six-axis load cell (MC3A, AMTI, USA) mounted on its side in a vertical frame (Fig. 1) that was calibrated prior to each use. The load cell was constrained to two degrees of freedom in this study, allowing force to be measured in the X and Z directions. The normal loading was applied on the lateral portion of the calf; approximately 25 cm above the ankle with the force vector directed medially (X direction) (Fig. 1). The load cell also was free to move vertically (Z), allowing for shear load application to the skin. For participants with existing leg wounds, loads were applied at least 24.5 mm away from the wound to avoid any potential deleterious effect on the wound itself. Thus, in some cases, the load application was adjusted superiorly or inferiorly slightly to accommodate the wound. The contralateral leg was tested at the corresponding height. Since blood perfusion is measured at the capillary level, homogeneity of the regional blood flow near the region can be assumed and this slight adjustment does not affect group comparisons (Jakobsson and Nilsson, 1993; Mayrovitz and Larsen, 1994)

To mimic loading that participants would see in everyday living, the loads applied were subject-specific. The magnitude of normal loading equaled 75% of the subject's lower leg weight, which was 4.5% of the subject's whole body weight (Chaffin and Andersson, 1991); shear loading, in the combined loading condition, was 50% of the applied normal loading. The forces used were clinically relevant because they are comparable to those that the leg might experience intermittently during normal living, such as crossing one's legs or resting one's leg on a couch or ottoman while sitting (Bush and Hubbard, 2007; Douglas and Simpson, 1995; Goossens et al., 1997; Kohnle, 2000).

A laser Doppler perfusion monitor (PF 5010 LDPM Unit, Perimed, Sweden) was used to monitor and record the blood perfusion of the skin during the entire test period (Nilsson, 1984). The laser Doppler sensor was attached to the leg via a hypoallergenic adhesive such that the customized device surrounded the sensor; loading was then applied around the region of the sensor. The laser Doppler system is non-invasive; it is mounted to the surface of the skin and no skin penetration occurs. Temperature consistency was maintained through the heated sensor, which was set at 37 °C.

Both the load cell and the perfusion monitor have been shown to be valid and reliable (Bartlett et al., 2014; Chen and Bates, 2000; Manorama et al., 2010).

2.2. Test procedure

Two groups of test participants were recruited for this research. Eighteen individuals were in the wounded group and twenty were in the healthy group. Individuals were included in the wounded group if they were over the age of 18 years old, had stasis ulcers on at least one leg, were able to sit for at least one hour, and had no mental health issues. Additionally, healthy participants were over the age of 18 and

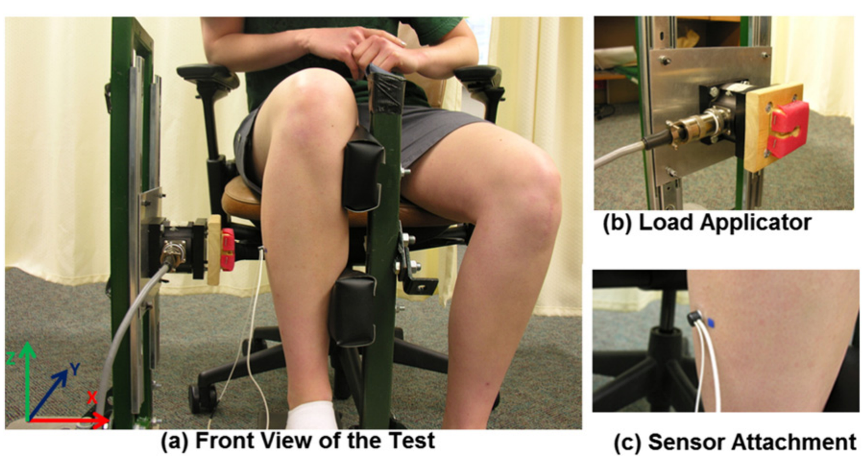

Fig. 1. Perfusion test apparatus with a healthy participant. (a) Front view of the apparatus with the perfusion sensor and load applicator located to the right of subject's right leg. (b) Load applicator with customized slot cut to fit in the laser Doppler perfusion sensor. (c) Sensor attached to the skin of a healthy lower leg is surface-mounted and non-invasive.