Journal of Tissue Viability (2014) 23, 69–77

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JOURNALOF tissueviability

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Basic research

# Effect of local cooling on pro-inflammatory cytokines and blood flow of the skin under surface pressure in rats: Feasibility study

Bernard Lee [a], Siribhinya Benyajati [a], Jeffrey A. Woods [b], Yih-Kuen Jan [b,*]

[a] *Department of Physiology, University of Oklahoma Health Sciences Center, Oklahoma City, OK, USA*
[b] *Rehabilitation Engineering Laboratory, Department of Kinesiology and Community Health, University of Illinois at Urbana-Champaign, Champaign, IL, USA*

**KEYWORDS**
Cooling;
Cytokines;
Inflammation;
Laser Doppler;
Pressure ulcers

**Abstract** The primary purpose of this feasibility study was to establish a correlation between pro-inflammatory cytokine accumulation and severity of tissue damage during local pressure with various temperatures. The secondary purpose was to compare skin blood flow patterns for assessing the efficacy of local cooling on reducing skin ischemia under surface pressure. Eight Sprague–Dawley rats were assigned to two protocols, including pressure with local cooling ($\Delta t = -10$ °C) and pressure with local heating ($\Delta t = 10$ °C). Pressure of 700 mmHg was applied to the right trochanter area of rats for 3 h. Skin perfusion quantified by laser Doppler flowmetry and TNF-* and IL-1β levels were measured. Our results showed that TNF-α concentrations were increased more significantly with local heating than with local cooling under pressure whereas IL-1β did not change. Our results support the notion that weight bearing soft tissue damage may be reduced through temperature modulation and that non-invasive perfusion measurements using laser Doppler flowmetry may be capable of assessing viability. Furthermore, these results show that perfusion response to loading pressure may be correlated with changes in local pro-inflammatory cytokines. These relationships may be relevant for the development of cooling technologies for reducing risk of pressure ulcers.


* Corresponding author. Rehabilitation Engineering Laboratory, Department of Kinesiology and Community Health, University of Illinois at Urbana-Champaign, 1206 South Fourth Street, Room 2009, Huff Hall, MC-588, Champaign, IL 61820, USA.
*E-mail addresses:* yjan@illinois.edu, yjan@uiuc.edu (Y.-K. Jan).

0965-206X/$36 
http://dx.doi.org/10.1016/j.jtv.2014.01.002

## Introduction

A pressure ulcer is a localized injury to the soft tissues usually over a bony prominence as a result of pressure, shear moisture and temperature [1]. Pressure ulcers are one of the most prevalent secondary conditions faced by people with impaired mobility [2,3]. Pressure ulcers may lead to infection, increased medical costs and even threaten the life of the person. A total of 503,300 hospital stays was required for all people with pressure ulcers as a diagnosis in 2006 [4]. This is 80% increase from 1993 amounted to over $11 billion in hospital costs. In the United States alone, 1—3 million people develop pressure ulcers each year despite the research toward prevention and the rapidly expanding knowledge on pressure ulcer etiology. These numbers are expected to continue rising.

Limited data exist on how direct pressure is transferred through soft tissues and how it mechanistically leads to ulceration [5]. Theories on contributing factors include prolonged tissue ischemia, direct cell death by mechanical pressure, excessive interstitial fluid pressure, and ischemia—reperfusion injury [6,7]. The lack of precise etiology besides the insurmountable challenge imposed by gravity increases the importance of exploring the influences of secondary factors such as moisture and temperature to address the prevention of pressure ulcers [8]. Pressure ulcer prevention logically centers on reducing the magnitude and duration of peak pressures by using support surfaces and repositioning [9]. While it is common clinical practice to try to prevent pressure ulcers by these strategies, no currently proven link exists between a particular intensity of pressure and pressure ulcer development [8,10]. Exploring alternative aspects of pressure ulcer etiology to produce improved preventative techniques and tissue viability assessment tests are needed [8,11].

Lachenbruch made the case that local cooling of 5 °C is equivalent to peak pressure reduction between the highest cost and lowest cost support surfaces on the market [12]. His calculations estimated that a temperature reduction from 36 °C to 28 °C is like reducing the interface pressure from one support surface from 56 mmHg (7.5 kPa) to 40 mmHg (5.3 kPa). Though temperature change will not prevent occlusion of blood vessels of weight-bearing soft tissues, his argument implies that local cooling may be able to attenuate the consequences of pressure on weight-bearing soft tissues and increase the length of time soft tissues can withstand. This increase in tissue tolerance is measureable through tissue responses at different temperatures and is a clinically feasible mechanism for functionally investigating viability of weight-bearing soft tissues. Previous work on the effect of local cooling has shown qualitative benefits on reducing ischemic damage of weight-bearing tissues [11,13—16]. Reducing normal skin temperature by 5 °C—10 °C may lessen or completely prevent full thickness tissue damage at the same loading pressure condition [13,16]. In contrast, incrementally increasing the temperature may accelerate deterioration that causes epidermal necrosis and subdermal as well as underlying muscle damage [13,16].

Presently, there is no adequate metric for assessing the effectiveness of pressure ulcer preventative strategies [9,17,18]. Although randomized controlled trials may determine the effectiveness of a preventive intervention, the trials cannot quantify the functional status of soft tissues that may be important to optimize the regimens of preventive interventions [8,19]. Skin blood flow studies in rats and other animals have demonstrated the feasibility of using non-invasive instruments such as laser Doppler flowmetry (LDF) to examine the effects of loading pressure before the onset of pressure ulcers [11,20—22]. Jan et al. demonstrated that local cooling preserves metabolic and myogenic activities in the skin under surface pressure based on spectral analysis of blood flow oscillations [11]. They suggested that local heating aggravates ischemia in weight-bearing tissues, whereas local cooling provides a protective effect. The accumulated knowledge from these experiments leads to the suggestion that measuring patterns of blood flow changes to discern the effects of local cooling on tissue viability and therefore pressure ulcer development is practical [14]. Although LDF is a useful tool to assess the impairment of skin blood flow, LDF technology cannot measure muscle blood flow that is particularly important in deep tissue injury [7].

Inflammation measurements may supply a quantitative bridge between blood flow measurements and soft tissue damage from loading pressures [11,23—26]. From the positive relationship between the tissue temperature and severity of soft tissue damage [13,16], it was assumed that local cooling may reduce the noninfectious inflammatory response as it reduces damage of weight bearing tissues. Limiting metabolic distress and cell death in tissues through cooling may reduce the release of a variety of pro-