

## Peripheral Vasodilation Responses to Prevent Local Cold Injuries

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One of the earliest responses to cold exposure is decreased blood flow to the extremities. This can occur simply with facial cooling or by direct cooling of the hands and feet. The sympathetic response that drives this decrease in blood flow is maximal with whole-body cooling. This decreased blood flow limits the heat delivery to the extremities, and subsequent tissue cooling is associated with a decrease in thermal comfort and physical performance and an increased risk of peripheral cold injury. Methods are needed to increase extremity blood flow to minimise these adverse effects. Peripheral blood flow can be altered several ways. These can be classified into 3 broad categories, physiological (cold-induced vasodilation, CIVD), behavioural (increased exercise intensity), and technological (external heating). The purpose of this review is to summarise the role of CIVD, exercise, and external heating on dilating peripheral tissues and preventing injury during cold exposure.

### COLD-INDUCED VASODILATION

CIVD is a cyclic fluctuation in blood flow that occurs upon cold exposure which commonly occurs in the extremities (hands, feet) and face (cheeks, nose, ears). The initial response to cold exposure is a sympathetically-mediated peripheral vasoconstriction, resulting in reduced local tissue temperature. With continued cold exposure, this vasoconstriction may be interrupted, resulting in periods of vasodilation, which correspond to an increase in tissue temperature. The vasodilation is typically transient, followed after several minutes by another vasoconstriction, and a characteristic cyclic pattern of increasing and decreasing blood flow may be displayed (29). By maintaining higher tissue temperatures, CIVD is associated with improved dexterity (20) and less pain (1; 26) when working in the cold, and is also believed to have a protective role against peripheral cold injury (44).

Several hypotheses have been postulated on the mechanism of CIVD (7). These include an axon reflex, decreased norepinephrine (NE) release from nerve endings, release of a vasodilatory substance in the blood, and cold directly reducing smooth muscle contractility (18). The axon reflex is simply the stimulation of sensory cutaneous receptors transmitting signals back toward the spinal cord and also along branches that terminate near blood vessels in the fingers (30). These nerves release an unknown substance that causes vasodilation. The reflex can be caused by painful stimuli, which cold certainly can trigger (7). Daanen and

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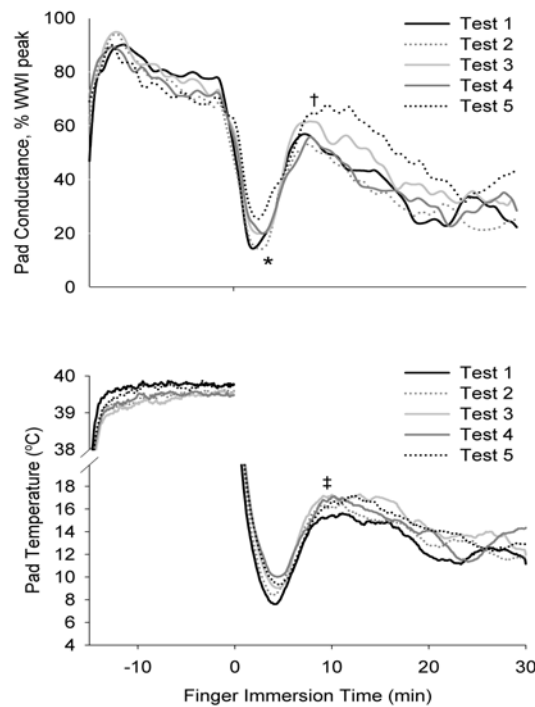
Ducharme recently tested the axon reflex hypothesis as a mechanism for CIVD by evoking pain using electrical stimulation during cycles of CIVD (9). They found that these stimuli had no effect on the CIVD response. If a decrease in norepinephrine release causes the CIVD response, then exogenous administration of norepinephrine would abolish the vasodilatory response. However, Keatinge found that iontophoresis (explain this term) of NE did not completely abolish CIVD, but decreased the response to 33% of the normal response (23). To date, no vasodilator substance has been implicated in CIVD. Gomez et al. (18) found that cooling of isolated cutaneous arteries reduced maximal contractility when stimulated by alpha-adrenergic agonists. However, the evidence supporting direct cooling causing vasodilation is not strong (7).

Evidence for the link between CIVD and frostbite susceptibility is provided by a study conducted by Wilson and Goldman (44). They subjected the fingertips of volunteers to various combinations of air temperature and wind speed and observed whether frostnip or CIVD occurred. Note that there was no frostbite at  $-5^{\circ}\text{C}$  and 100% frostbite at  $-25^{\circ}\text{C}$ . At  $-15^{\circ}\text{C}$ , more frostbite occurred as the wind speed increased. If CIVD occurred, frostbite did not occur. Table 1 summarises their results with the number of frostnip and CIVD observations.

**Table 1: Number of observations of frostnip and CIVD during finger exposure to various combinations of ambient temperature and wind speed. CIVD in all cases prevented frostnip from occurring. Data from Wilson and Goldman (44)**

Temperature	Wind Speed		
	$5 \text{ m}\cdot\text{s}^{-1}$	$10 \text{ m}\cdot\text{s}^{-1}$	$15 \text{ m}\cdot\text{s}^{-1}$
$-5^{\circ}\text{C}$			0 frostnip 3 CIVD
$-15^{\circ}\text{C}$	1 frostnip 6 CIVD	6 frostnip 4 CIVD	9 frostnip 5 CIVD
$-25^{\circ}\text{C}$	11 frostnip 0 CIVD	11 frostnip 0 CIVD	

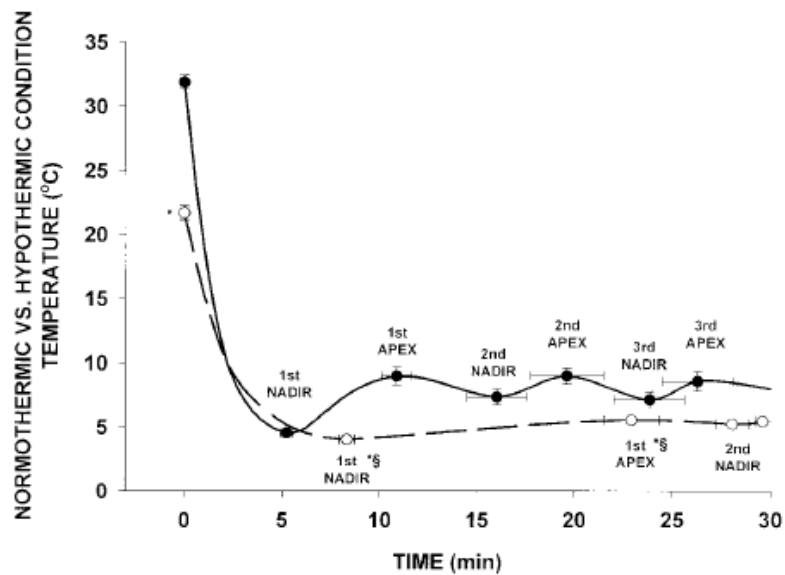
An important aspect to consider when understanding the CIVD response is that the day-to-day variability must be overcome/understood before meaningful treatment effects can be observed. This is important not only for controlled laboratory conditions (“best case”), but also for field studies where reproducibility of the response is expected to be poorer. However, the reproducibility of the CIVD response has not been extensively studied. O’Brien (35) recently evaluated the reproducibility of the CIVD response under standard conditions over 5 separate test days controlling for factors known to modify CIVD including ambient temperature, time of day, posture, body heat content, exercise, food intake, nicotine, and alcohol intake. Figure 1 presents the data for blood flow and finger temperature during finger immersion in  $4^{\circ}\text{C}$  water averaged over all 21 subjects for each of the 5 test days. The data show that under well-controlled conditions, finger skin temperatures (nadir, apex, mean) are reproducible in the nailbed (9-12% CV), but not in the pad (15-21% CV). The time course of the CIVD response (onset and apex time) was reproducible for blood flow (5-9% CV), but not skin temperature (18-24% CV). These findings are important in that they indicate how much of a change in the magnitude of CIVD must be observed to determine whether a treatment effect is meaningful, the number of subjects needed to detect differences between treatments, and in choosing the appropriate methodology and site of measurement for future experiments.



**Figure 1: Finger pad cutaneous vascular conductance (CVC) expressed as percent change from peak during warm water immersion (upper panel) and finger skin temperature (lower panel) averaged over 21 subjects on each of the five cold water (4°C) tests. \* P = 0.051, onset of CVC on Test 1 vs. Tests 4 or 5. † P = 0.03 apex CVC Test 1 vs. Test 5, and P = 0.015 Test 2 vs. Test 5. ‡ P = 0.027, apex temperature Test 1 vs. Test 3. Graph from O'Brien (35)**

The dramatic influence that a change in body heat content can have on the magnitude of CIVD is illustrated in Figure 2 (37). The figure shows the CIVD response during normothermia ( $T_{\text{core}} = 37^{\circ}\text{C}$ ) compared to hypothermia ( $36^{\circ}\text{C}$ ). Clearly, the CIVD response is blunted when body core temperature is lowered. Daanen further observed that both core and skin temperature independently influence CIVD (8; 10). This response illustrates the clinical finding that exposed persons commonly suffer from both hypothermia and frostbite.

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**Figure 2: Finger temperature during cold-water immersion (4°C) when normothermic (37°C) and hypothermic (36°C). \*** initial finger temperature was significantly lower ( $P < 0.05$ ) at min 0 in the hypothermic condition; **§**, first nadir and first apex significantly longer ( $P < 0.05$ ) in hypothermic condition compared to normothermic. Graph from O'Brien et al. (37)

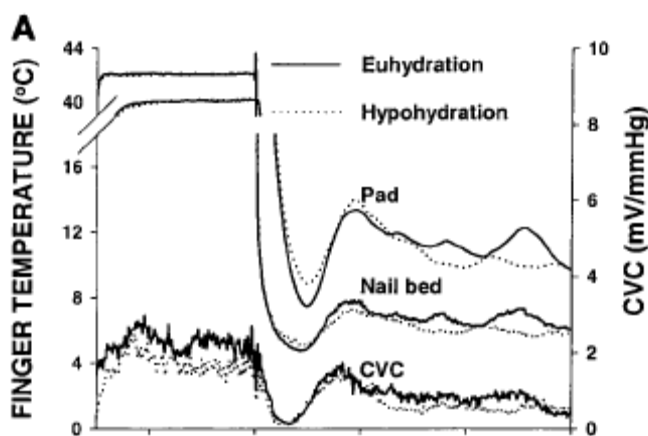
Table 3 lists other environmental and individual factors that are commonly cited as modulators of the CIVD response. It is important to consider that many of the early CIVD studies did not control for skin temperature, core temperature, activity, etc. that we now know impact CIVD.

**Table 3: Effects of environmental and individual factors on CIVD response and increased frostbite risk.**

Factor	CIVD Response	Reference	Epidemiological Support for Increased Frostbite Risk (Reference)
Hypoxia	Lower mean finger at high altitude	(11)	> 5100 meters (19)
Age	Later onset with increasing age	(39; 41)	Higher after age 60 (24; 25)
Gender	?	(45)	Women have increased frostbite in Army & Marines (3)
Race	Blacks have lower mean finger and later onset	(21)	Frostbite risk higher in Blacks (12)
Cold Acclimatization	Higher mean finger, earlier onset	(31; 38)	
Alcohol	No deleterious effect of alcohol	(33)	Higher with increased alcohol intake (24)

Smoking	decrease # of CIVD cycles, but not abolished	(6) (17)	Increased with heavy smoking (14)
Raynaud's Phenomenon	Later onset in RP	(22)	
Vibration-Induced White Finger	?		Increased in those with VIWF (14)

Dehydration is commonly cited as a factor that pre-disposes individuals to frostbite, although there is little data to support this. O'Brien and Montain examined the effect of 4% hypohydration on skin temperature and blood flow responses during a 30 minute cold water finger immersion (36). The data (Figure 3) indicate that 4% hypohydration had no effect on the CIVD response for either finger temperature or cutaneous vascular conductance.



**Figure 3: Finger nailbed and pad temperatures and cutaneous vascular conductance (CVC) for 15-min warm water (42°C) and 30-min cold water (0°C) immersion during euhydration and 4% hypohydration. Graph from O'Brien et al. (36)**

Using CIVD as part of a larger strategy to prevent cold injuries is rather limited. In the field, maintaining body heat content is the most important measure. Tactics could also include inducing local cold acclimatisation so that fingers remain warmer when exposed to the cold. The importance of having soldiers train outside should not be underestimated. Livingstone found that CIVD was enhanced after 100 days of skiing in the Arctic (31). Positive changes included an increase in the finger temperature when the first dilatory period occurred and an increase in the mean finger temperature when the finger was exposed to 0°C water. Many other studies have also generally observed warmer hands and fingers (though not enhanced CIVD responses per se) when exposed to cold air after cold acclimatisation (46). Enhanced CIVD responses have been observed in fisherman (27) and fish filleters (34) who continually had their hands in cold water as part of an occupational exposure. Experimental studies have been used to induce local cold acclimatisation. Using various combinations of water temperatures and acclimation periods, the hands and fingers have been observed to be warmer following cold acclimation (1; 13; 28), although not always (16). Although it may be physiologically possible to induce enhanced CIVD responses before the onset of the winter season, it may not be practical. Successful acclimation programs require daily cold exposure for at least 30 days to produce a measurable effect.

**EXERCISE**

Cutaneous vasodilation occurs during exercise in hot and temperate environments as core body temperature increases and heat dissipation is required. The ability of exercise to significantly raise skin temperature during cold exposure below 0°C, especially for the finger, toes, and face, has only been recently described. Mäkinen et al. (32) and Gavhed et al. (15) examined the role of exercise intensity on finger, toe, and face temperatures during still and windy conditions. Increasing the exercise intensity from 220 to 350 Watts in still and low wind conditions (Figure 4) raised finger temperatures well above levels (20°C) associated with pain and decrements in manual dexterity (15°C). This increase in finger temperature was attenuated when conditions were much windier. Similar interactions between exercise intensity and wind were also observed for the toe. Nose temperature also increased at the higher workload for the low wind conditions, but unlike the finger and toe, an increase in exercise intensity was associated with higher nose temperatures, even in 5 m·s<sup>-1</sup> wind (Figure 5). Finally, cheek temperatures progressively became lower as the wind velocity increased, but, unlike the nose and similar to the finger, exercise at 350 Watts during a 5 m·s<sup>-1</sup> wind did not raise these temperatures (15).

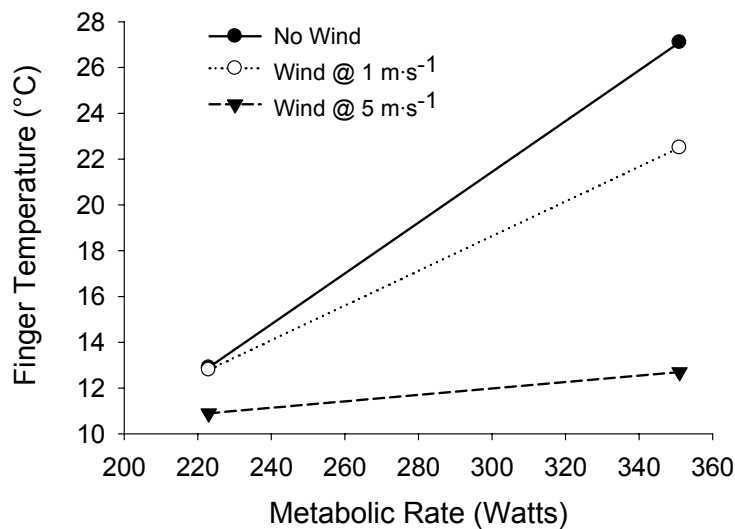
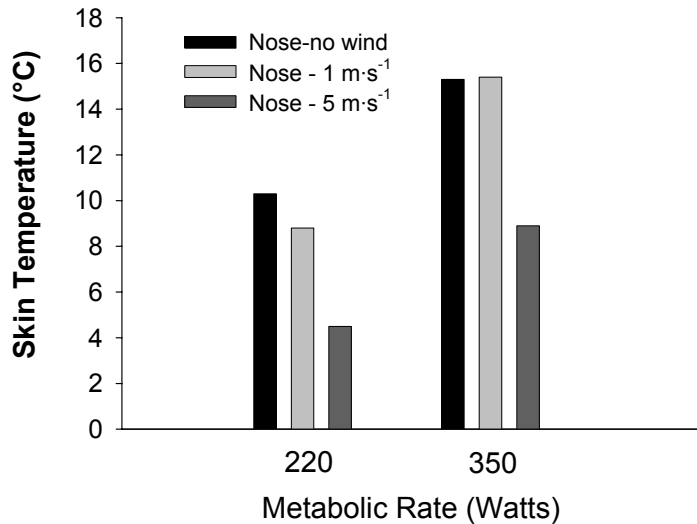


Figure 4: Finger temperatures during treadmill walking at two metabolic rates in -10°C air in three different wind conditions. Data from Mäkinen et al. (32)



**Figure 5: Nose temperatures during treadmill walking at 220 and 350 Watts in -10°C air in three different wind conditions. Data from Gavhed et al. (15)**

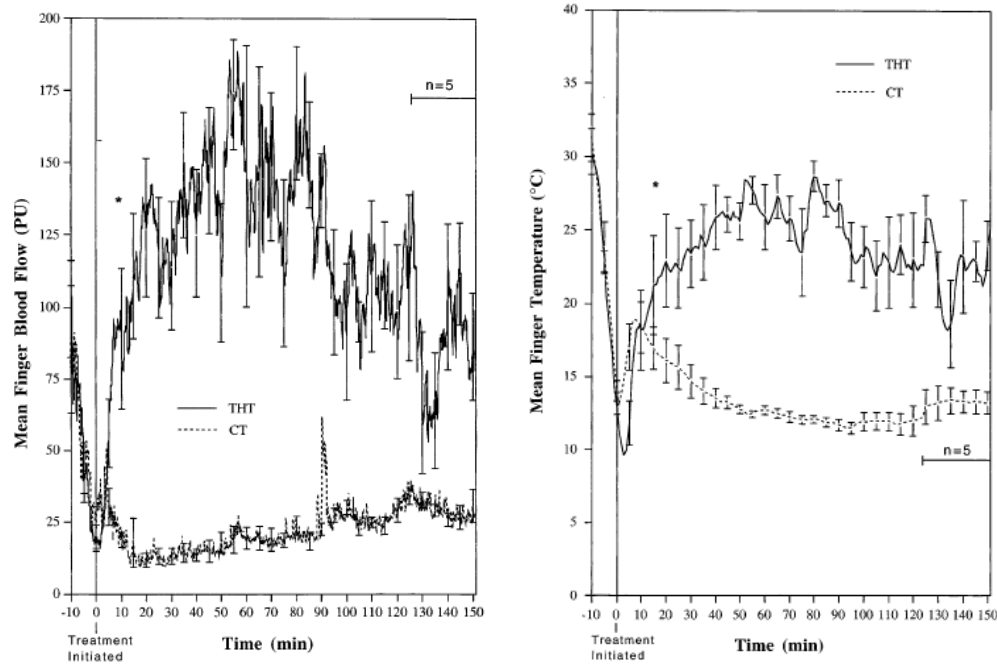
Acclimatisation may also be a factor in the finger response to exercise. Outdoor workers in Norway (lumberjacks, fish filleters) who consistently are exposed to local cold (hands, face) increase their finger pad temperature at low external workloads (50 Watts) compared to controls (42). Only when exercise was doubled to 100 Watts did control subjects increase finger pad temperatures. Another study demonstrated that Eskimos re-warmed their hands sooner during cycle ergometer exercise at 100 Watts in 5°C air compared to Caucasian controls (2). In that study, hand temperature increased after 10 minutes of exercise (100 Watts external load) and reached 33-34°C after 30 minutes of work for the Eskimos, whereas the Caucasians' hand temperatures fell to 23-24°C and did not begin to increase until after 30 minutes of exercise had been performed.

## EXTERNAL HEAT

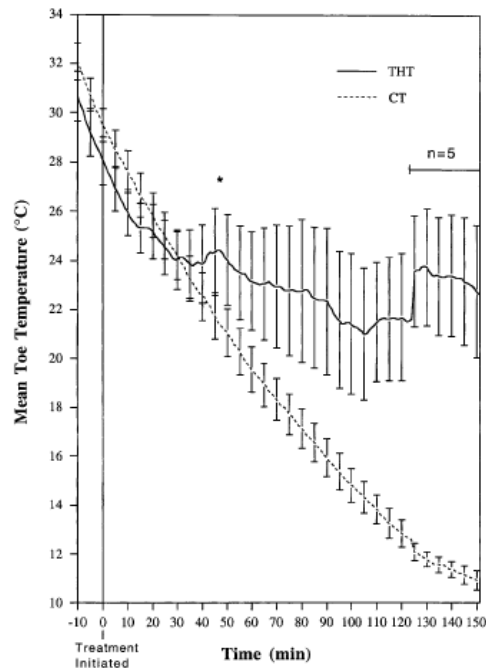
The concept of using an exogenous heat source to increase extremity temperatures has been tested for decades. Many methodologies have been utilized, including hand, forearm, torso, or whole-body heating. Recently, the use of torso heating has been used by DRDC-Toronto to examine more extensively the relationships between heat storage, body heat content, peripheral skin temperatures, and dexterity.

Brajkovic et al. completed a series of studies using a heated vest to raise the skin temperature on the torso (0.366 m<sup>2</sup>) to 42°C, which required a power output of ~ 108 Watts. The first study examined the efficacy of this treatment on finger and toe temperatures while subjects sat in -15°C air with bare hands (5). The experiment was designed to have the finger decline until it reached 15°C and then the external heating device was turned on. External heating caused vasodilation and raised finger temperatures (Figure 6) to comfortable levels (> 20°C), despite the low initial temperatures. Toe temperatures declined even with heating (Figure 7), but were maintained at higher, more comfortable temperature (22°C) with heating, compared to no heat (11°C). These changes occurred despite a negative body heat storage.

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**Figure 6: Finger blood flow and finger temperature during sedentary exposure to  $-15^{\circ}\text{C}$  during no torso heating (CT) and torso heating to  $42^{\circ}\text{C}$  (THT). \*, significant difference ( $P < 0.05$ ) from \* to min 151 between THT and CT. Graph from Brajkovic et al. (5)**



**Figure 7: Toe temperatures during sedentary exposure to  $-15^{\circ}\text{C}$  during no torso heating (CT) and torso heating to  $42^{\circ}\text{C}$  (THT). \*, significant difference ( $P < 0.05$ ) between THT and CT from \* to min 151. Graph from Brajkovic et al. (5)**



Brajkovic et al. followed this study up by examining the relationships among finger and toe temperature, heat storage, and total body heat content during sedentary exposure to  $-25^{\circ}\text{C}$  air (4). Four treatments were used to experimentally manipulate heat storage. These treatments were high clothing insulation (3.6 clo) and bare hands with heating (HI-bare), low clothing insulation (2.6 clo) and bare hands with heating (LI-bare), high clothing insulation, gloves and mittens with heating (HI-g+m), and high clothing insulation, gloves and mittens with no heating (HI-g+m-NP). They found that finger and toe temperatures were not related to heat storage (which reached a steady-state value) but were strongly related to total body heat content (integration of heat storage over time). Figure 8 depicts the relationship of heat content and finger temperature. Finger temperature was  $> 23^{\circ}\text{C}$ , up to a heat content loss of 250 kilojoules. These studies demonstrate that: a) external torso heating combined with 3.6 clo insulation can maintain warm fingers despite being bare-handed at air temperatures of  $-25^{\circ}\text{C}$  and b) body heat content will fall and fingers will get cold despite wearing 3.6 clo of insulation along with contact gloves and mittens, i.e., external heat is necessary to maintain finger temperature in these conditions even with handwear.

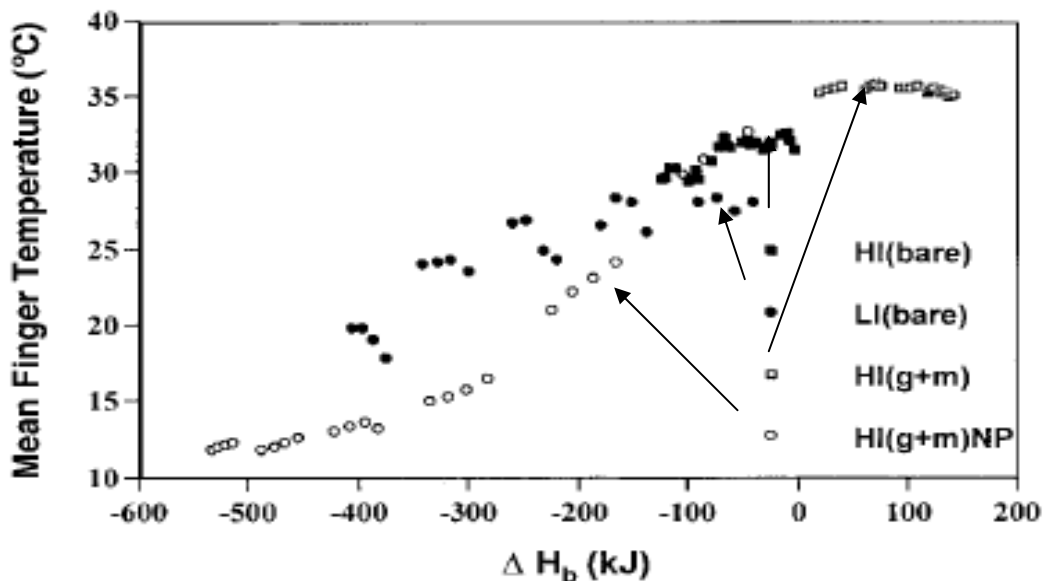


Figure 8: Relationship between finger temperature and change in body heat content ( $\Delta H_b$ ) for 4 different conditions during sedentary exposure to  $-25^{\circ}\text{C}$  air. See text for description of the 4 glove, insulation, and heating conditions. Graph from Brajkovic et al. (4)

## PRE-SCREENING STRATEGIES

Certain populations have been shown to have a higher incidence of cold injury that extends beyond the exposure conditions. Identification of these groups will a) allow increased vigilance for early signs of cold injury, b) highlight conditions where greater risk of injury exists, and c) may allow identification of markers associated with these groups (genetic markers).

Pre-screening strategies include the medical history and epidemiological evidence. Table 4 lists several factors that increase the risk of peripheral cold injury. The medical history can be used not only to diagnose conditions that will place a person at a greater risk, but also determine if someone has suffered occupational exposures (e.g., vibration-induced white finger) that will decrease the CIVD response. Epidemiological evidence can be used to identify groups who have a blunted CIVD response and may be at

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higher risk (Table 3), which allows leaders to more carefully monitor these individuals. For example, DeGroot et al. (12) reported that African-Americans in the U.S. Army were about 3.3 times more likely to suffer a cold injury than Caucasians, and this was evident across all military occupations.

**Table 4: Predisposing factors for frostbite and peripheral cold injury.**

<b>Environmental</b>	<b>Mechanical</b>	<b>Physiologic</b>	<b>Psychologic</b>	<b>Medical</b>
<ul style="list-style-type: none"> <li>• Temperature</li> <li>• Wet skin</li> <li>• Exposure duration</li> <li>• Wind-chill</li> <li>• POLs (petroleum, oil, lubricants)</li> <li>• Contact with metals</li> </ul>	<ul style="list-style-type: none"> <li>• Constrictive clothing</li> <li>• Wet clothing</li> <li>• Inadequate clothing and shelter</li> <li>• Tight boots</li> <li>• Vapor barrier boots</li> <li>• Cramped and prolonged stationary posture</li> </ul>	<ul style="list-style-type: none"> <li>• Race</li> <li>• Women</li> <li>• Hypothermia</li> <li>• Prior peripheral cold injury</li> <li>• Trauma</li> <li>• Erythrodermas</li> <li>• Hyperhidrosis</li> <li>• Hypoxia</li> <li>• Smoking</li> <li>• Energy depletion</li> <li>• Poor physical conditioning</li> </ul>	<ul style="list-style-type: none"> <li>• Severe mental stress</li> <li>• Poor training</li> <li>• Poor leadership</li> <li>• Drug and alcohol abuse</li> </ul>	<ul style="list-style-type: none"> <li>• Hypotension</li> <li>• Atherosclerosis</li> <li>• Arteritis</li> <li>• Raynaud Syndrome</li> <li>• Vasospastic disorders</li> <li>• Anaemia</li> <li>• Sickle cell disease</li> <li>• Diabetes</li> <li>• Shock</li> <li>• Vasoconstrictors</li> </ul>

Another possible pre-screening strategy is to evaluate the CIVD response of each soldier. Cold water tests have the advantage of eliciting CIVD in a relatively short time period (5-10 minutes in most subjects). However, even though CIVD responses are likely protective against frostbite, it is not known whether a “good responder” during a cold water test would also be a good responder during cold air exposure, i.e. the relationship between CIVD responses during cold-water immersion and cold air exposure has not been delineated. Furthermore, what is a “good responder?” Is it a higher overall finger temperature? Early onset? Higher apex? A particular pattern of response? Finger re-warming following cold exposure has been used to characterize subjects with vasomotor disorders such as Raynaud’s Phenomenon and Vibration-Induced White Finger, who have a delayed increase in finger temperature compared to controls. Perhaps this would be more predictive than the CIVD response itself. It is also important to determine the purpose of a CIVD pre-screening. Will it be used for non-deployment to cold regions if the response is blunted or will it be used by leadership to monitor poor responders more closely? If so this leads to further questions such as: Is it practical to test everyone? How strong is the link between a “good” responder and decreased cold injury? Answering the basic questions about what constitutes a good response and the linkage to cold injury is an exciting area for future research.

Identifying genetic markers for multiple purposes (e.g. disease prediction, exercise performance) has become increasingly widespread and could potentially be used to screen populations. Whether such a genetic marker exists for predicting susceptibility to cold-weather injuries is unknown. Several studies have examined whether there is a genetic marker for those who suffer from primary Raynaud’s Phenomenon. In one study (40), the candidate genes examined in a case-control study were those associated with mediating vasoaction and included bradykinin receptor genes, endothelin-1, endothelin receptors, and endothelial nitric oxide synthase. No association was observed between these genes and Raynaud’s. Another study suggested potential candidate genes of muscle acetylcholine receptor, and serotonin 1B and 1E receptors (43), but these markers still need to be confirmed with rigorous case-control experiments.

## SUMMARY

- 1) CIVD acclimation is perhaps not practical. This may occur during repeated training for extended periods in cold weather.
- 2) Exercise is both practical and effective, yet may not be able to be sustained long-term.
- 3) External heating is effective, but providing an energy source is an obstacle due to weight, type, portability, and reliability of a power supply.
- 4) Pre-screening is valuable for increased vigilance and for possible preventive and protective measures.
- 5) Training in the cold, education, leadership, and early recognition of injuries are the most important methods to decrease peripheral cold injury and these apply to all groups, even those with greater risk factors for cold injury.

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