Non-freezing cold-induced injuries (NFCI) is the Cinderella of thermal injuries and is a clinical syndrome that occurs when tissues are exposed to cold temperatures close to freezing point for sustained periods. NFCI is insidious in onset, often difficult to recognize and problematic to treat, and yet the condition accounts for significant morbidity in both military and civilians who work in cold conditions. Consequently recognition of those at risk, limiting their exposure and the appropriate and timely use of suitable protective equipment are essential steps in trying to reduce the impact of the condition. This review addresses the issues surrounding NFCI.
Nonfreezing Cold–Induced Injuries

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Abstract

Non-freezing cold injury (NFCI) is the Cinderella of thermal injuries and is a clinical syndrome that occurs when tissues are exposed to cold temperatures close to freezing point for sustained periods. NFCI is insidious in onset, often difficult to recognize and problematic to treat, and yet the condition accounts for significant morbidity in both military and civilians who work in cold conditions. Consequently recognition of those at risk, limiting their exposure and the appropriate and timely use of suitable protective equipment are essential steps in trying to reduce the impact of the condition. This review addresses the issues surrounding NFCI.

Introduction

Nonfreezing cold-induced injury (NFCl) is a clinical syndrome that occurs when tissues are exposed to cold temperatures close to freezing point (0-15°C) for sustained periods. NFCl does not involve tissue freezing, which distinguishes it both clinically and pathologically from frostbite [1]. Baron Dominique Jean Larrey, Napoleon’s chief surgeon, described the “congelation” amongst the non-freezing and frostbite casualties during the 1812 retreat from Moscow [2]. Historically, infantry regiments have been seriously affected by cold and wet conditions [3,4], and although our understanding of the aetiology of NFCI has improved, the treatment of those affected continues to present a serious challenge.

Physiology

Skin - a thermoregulatory organ

The metabolic requirements of skin are fixed and relatively modest, and the observed large fluctuations in cutaneous blood flow are primarily determined by the individual’s thermoregulatory needs. Heat is dissipated by four processes: radiation, conduction, convection and evaporation. The large numbers of arterio-venous (A-V) anastomoses found in the extremities are under dual neural control. Firstly, under cold conditions, the hypothalamus increases sympathetic tone which results in local A-V vasoconstriction. Secondly there is a direct local control which causes A-V dilatation in warm conditions and constriction in the cold. Under basal conditions, a 70-kg human has a total cutaneous blood flow of 200 - 500 mL/min. With external heating to maintain skin temperature at 41°C, this may increase to 7000 - 8000 mL/min, while cooling the skin to 14°C may diminish it to 20 - 50 mL/min.

Veni-arteriolar response

Orthostasis or lowering a limb below heart level causes an immediate two third reduction in the peripheral blood flow as a result of the veni-arteriolar response. The response probably helps maintain central arterial pressure during standing and reduces dependent oedema formation. The response is thought to be exacerbated by long periods of sitting or standing and warmth, but there seems to be little difference in its intensity once skin temperature is normal or lower.

Cold Induced Vasodilation

When the hand or foot is cooled to 15°C, maximal vasoconstriction and minimal blood flow occurs. If cooling continues to 10°C, vasoconstriction is interrupted by periods of vasodilation and an associated increase in blood and heat flow. This cold-induced vasodilation (CIVD), or “hunting response,” recurs in 5 to 10 minute cycles to provide some protection from the cold. Prolonged repeated exposure to cold increases CIVD and offers some degree of acclimatization. Eskimos, Lapps, and Nordic fishermen have a very strong CIVD response and very short intervals between dilations [5], which may help to maintain hand function in cold environments, similar findings were found in British fish filleters [6]. CIVD responses are more pronounced when the body core and skin temperatures are warm (hyperthermic state) and suppressed when they are cold (hypothermic state), when compared to normothermia [7-9]. Subjects with a weak CIVD to experimental cold-water immersion of the fingers in a laboratory setting have been shown to have a higher risk for local cold injuries when exposed to cold in real life [10]. Felicijan et al found evidence for a significant enhancement of the CIVD response after brief high altitude acclimatization, and that these changes were especially prominent in the mountaineers feet when compared to controls [11]. However, whilst CIVD is well demonstrated in fingers - given the right experimental conditions - it is much harder to elicit reliably in the feet. So whilst CIVD may have a role in preventing the development of cold injury in the hands the relevance to the feet is more questionable.

Epidemiology

Exposure to cold wet conditions is most common, but by no means a pre-requisite for NFCI. It appears to be part of a spectrum of conditions resulting from vascular stasis and ischaemia, followed by hyperaemia and pain [12]. Historically, NFCI was observed most commonly when temperatures were close to freezing and when the ground was muddy rather than...
frozen [13,14]. Standing or sitting for long periods, wearing constrictive footwear, malnutrition, fatigue, or the blunt trauma of marching on cold, wet feet all added to the severity of injury [15]. Original animal studies that modelled NFCI, demonstrated that cold temperatures near the freezing point were more likely to cause injury when the extremities were wet than when they were dry [14]. Established NFCI is associated with histological and/or clinical evidence of nerve damage [16,17].

Military

During the Crimean War, cold injury was documented among "men in the trenches who were so restricted in their movements. Frequently this position happened to be the bottom of a trench knee-deep in mud and water or half-filled with snow [14]." In November 1944, American forces sustained 11,000 cases of trench foot [18]. An evaluation of possible risk factors for cold injury during the war in the Falkland Islands 1982 found no evidence of abnormal circulating proteins, plasma hyper viscosity or indicators of alcohol abuse in those injured [19]. Interestingly in the 1990s, both the United States Army and the Israeli Defence Forces recorded that the majority of cold injuries (hypothermia and NFCI) occurred during routine training exercises rather than combat operations [20-22].

NFCI covers a range of clinical syndromes including trench foot, immersion foot, shelter limb and paddy foot. They are clinically and pathologically indistinguishable, but they have different aetiologies. Trench foot was described during the trench warfare of World War I [18], when soldiers wore wet boots and socks for prolonged periods [23]. Immersion foot was first described in World War II in shipwreck survivors whose feet had been continuously immersed in cold water [24]. Both injuries occur when tissue is exposed to cold and wet conditions at temperatures ranging from 0°-15°C. Colder temperatures reduce the time required to induce NFCI [25]. Severe nerve damage from immersion foot has been seen after exposure periods of 14-22 hours [26-29]. Immersion foot injury may extend proximally and involve the knees, thighs, and buttocks, depending on the depth of immersion [30]. In shelter limb (dependency without cold) and paddy foot (wet but not cold), the injury appears to be very similar to NFCI. As a result neither cold nor wet is an absolute requirement to developing the injury. NFCI appears to be a reperfusion injury which develops after a sustained period of peripheral vasoconstriction [12].

Ethnicity

Historically, the first reports of increased susceptibility in certain ethnic groups (Afro-Americans) to cold weather injury came from the American Civil War [31]. An increased incidence of cold injuries amongst African Americans in the cold winter conflict in the Ardennes in 1944 was also reported [18]. A major retrospective study looking at 2,143 US Army cold weather injury hospital admissions between 1980-1999 found the injury rate for men and women was very similar, 13.9 and 13.3/100,000 soldiers respectively [20]. Increased rank and experience was associated with a decrease in old weather injuries. There were 3.3 times more African-Americans hospitalised than Caucasians (95% CI 3.1-3.7), and infantry and gun crews appeared to be at greater risk. There was also a marked reduction in the number of soldiers admitted to the hospital between 1980 and 1999 from greater than 30 cases per 100,000 soldier years to almost zero. Young male Afro-Caribeans in the British Army have been found to have a 30 times greater chance of developing peripheral cold injury and are more severely affected than their Caucasian counterparts following similar climatic exposure, using similar clothing and equipment. Pacific Islanders are at a 2.6 times increased risk, while being a Guurkha appeared protective [32]. It should be noted there may be cultural differences in reporting, and the study has yet to be corroborated. Furthermore, peripheral vascular responses to a local cold stress were studied in four groups of Indians: South Indians, North Indians, Guurkhas and High Altitude Natives (HAN) of 3,500m. The heat output and cold induced vasodilatation (CIVD) were highest in HAN, with the lowest observed in South Indians [33].

Prevalence

The exact prevalence remains problematical in part because there is no clear ICD-9 (International Statistical Classification of Disease) code for NFCI, and most reported figures are not actually prevalence but referral rates to secondary care. In most NATO countries, the reported prevalence of NFCI injuries appears to be static or decreasing amongst their military personnel. However amongst British forces, there appears to be a marked increase in the incidence of reported cold weather injury. Over a four year period the reporting rate increased from 9 per 1000 to 30 per 1000 recruits, with the majority of cases (90%) being reported during field-based training. Independent factor analysis demonstrated that Afro-Caribbeans were 13.2 (95% CI 9.5-18.4, P<0.01) times more likely to report cold injury and 27.3 (95% CI 16.3-45.9, P<0.01) times more likely to be medically discharged compared to Caucasians [34]. Clearly an important question is why does there appear to be this isolated observed rise in NFCI in British forces? This might be a true rise due to factors such as increased exposure, or increased awareness, or a lower threshold to diagnose the condition, or it could be due to the recruiting of a different and more sensitive population.

NFCI is a clinical syndrome, diagnosed on a history of exposure and the subsequent development of specific symptoms. Any clinical condition which uses a biochemical or physiological test to diagnose or quantify the severity of the syndrome is open to potential methodological errors. An observed rise in such a condition may be due to a Type 1 error (poor specificity of the diagnostic tests or excessive credulity) or a Type 2 error (poor sensitivity of the tests used to diagnose the condition). Finally are other countries failing to diagnose and report the condition [35]?

Civilian

The environmental conditions that can produce NFCI in military settings can also be found in the context of wilderness medicine. Outdoor recreation may lead to cold, dehydrated, exhausted, and wet hikers exposed to the elements for an extended period. These individuals may be unwilling or unable to take the time and effort to care for their wet boots and socks, and they may be unaware of the risks inherent to the situation. Other civilian populations at risk for NFCI include the homeless [36], older adults [37], and alcoholics.

Personal administration

Proper protective equipment and appropriate usage are important factors reducing the incidence of NFCI. Factors affecting the incidence of frostbite are closely related to those affecting NFCI. A surprisingly high incidence of frostbite has been reported in
mountaineers. In one study the mean incidence was 366/1000 population per year. Mild (Grade 1) injury (83.0%) and hands (26.4%) and feet (24.1%) involvement were most common. There was a significant relationship between lack of proper equipment (odds ratio 14.3) or guide (p<0.001) and the injury. Inappropriate clothing, lack or incorrect use of equipment and lack of knowledge of how to deal with cold and severe weather were claimed to be the main reasons for the injury [38].

Pathophysiology
NFCl is primarily caused by prolonged vasoconstriction, which in turn may cause direct injury to the vessels (and endothelium) that supply blood to nerve, fat, and muscle cells. Pain, fear, constrictive footwear, and immobility interact in maintaining vasoconstriction through a heightened sympathetic nervous system response or mechanically limiting blood flow. Nerve cooling has been suggested as contributory to the aetiology of NFCl. Large myelinated fibers (C fibers) are most susceptible to prolonged cold exposure [39-42]. In severe non-freezing cold injury there is characteristic peripheral nerve damage and tissue necrosis [43]. Clinical sensory tests indicated damage to both large and small diameter nerves. Prolonged cold injury affects blood vessels serving these large myelinated fibers with subsequent ischemia causing a decrease of oxygen to the nerve, resulting in the appearance of a primary nervous system injury [44,45].

The prolonged decrease in blood flow caused by vasoconstriction causes direct injury to capillary endothelium. Studies indicate that the endothelial lining separates from the underlying cells leaving “gaps” [46]. Leukocytes and platelets fill in these gaps and accumulate to further decrease capillary blood flow, leading to ischemia and eventual tissue hypoxia. It is the degree and duration of the cold exposure that determine the severity of the injury.

Animal models have been developed to understand the underlying pathophysiology of NFCl. Thomas et al developed a rat model of NFCl by immersing the tail in 1°C water for 6-9 hours and characterized the loss of cold-induced vasodilation (CIvD), a prolonged decrease in tail blood flow, followed by an increase in blood flow above baseline. This pattern is similar to that clinically observed in humans during the pre-hyperaemic phase followed by the hyperaemic phase [47]. Also, the absence of CIvD with prolonged cold exposure is a prominent and consistent finding of NFCl in humans. Stephens et al. recently used the rat tail model in an attempt to elucidate possible mechanisms that cause vascular endothelial damage [48]. Their preliminary data suggest that acute cold-water exposure causes a loss of nitric oxide-dependent endothelial function and possibly a change in smooth muscle contractility. Irwin, using a rabbit hind limb model, demonstrated that cold water immersion damaged large myelinated fibers while sparing small myelinated and unmyelinated fibers [41].

One of the major pathological processes in cold injury is the progressive microvascular thrombosis following reperfusion of the ischaemic limb, with the cold-damaged endothelial cells playing a central role in the outcome of these cold injured tissues [49]. Reperfusion of previously ischemic tissues causes free radical formation, leading to further ischaemic endothelial damage and subsequent oedema. With restoration of blood flow there is a reintroduction of oxygen species within cells that further damages cellular proteins, DNA, and the plasma membrane. Free radical species may also act indirectly in redox signalling to turn on apoptosis. Leukocytes may also build up in small capillaries, obstructing them and leading to more ischemia [44,45].

Clinical Presentation of NFCI
Clinically, NFCI is insidious in onset, with a progression from initial exposure through four distinctive phases (pre-hyperaemic, cyanotic, hyperaemic, post-hyperaemic). These phases have variable time courses and may overlap.

Pre-hyperaemic Phase
During the pre-hyperaemic phase, the affected limb appears blanched, yellowish white, or mottled but at this stage seldom blistered [29]. Loss of sensation is the characteristic feature, and there is often a complete loss of proprioception, resulting in gait disturbance. This has been described as “walking on air” or “walking on cotton-wool” [29]. Capillary refill is sluggish and foot pulses can usually only be found with Doppler examination [50]. Intense vasoconstriction is the predominant feature of this stage [51].

Cyanotic Phase
This is a fleeting phase lasting minutes at most, with cyanosis, and is the start of pain and hyperaemia during early re-warming.

Hyperraemic Phase
Within several hours after rewarming, the extremities become hot, erythematous, painful, and swollen, with full bounding palpable pulses [52]. The microcirculation is impaired with delayed capillary refill [12] and petechial haemorrhages [30]. Sensation returns rapidly progressing to a severe, burning, or throbbing pain, peaking at 24 to 36 hours [27,29]. This pain is aggravated by heat and dependent positioning and may be worse at night [51]. Vibratory sensation is reduced or lost, whereas proprioception is usually retained. Anhidrosis coincides with the extent of sensory loss [12]. On lowering the affected limb there is blood pooling with associated changes in colour (deep purple-red) which is likely to be due to loss of the veno-arteriolar response. There is often an associated oedema with haemorrhagic blister formation [12].

Post-hyperaemic Phase
The post-hyperaemic phase lacks obvious physical signs to the extent that in milder cases, this phase may be absent [29]. However in the more severe cases, it may last for weeks to months [27,50]. The affected extremities have an abnormal response to cold, becoming unduly sensitive. There is often an increase in sweating even in cold weather [27] and the hyperhidrosis increases the risk of fungal infections [29].

In the most severe cases gangrene can develop and ablative surgery in the form of amputations of digits or occasionally major lower limb amputation is necessary. The neuropaethic tissue is susceptible to local trauma, ulceration and eventually local osteomyelitis and sinus development. Partial foot amputations result in significant alterations in the functional biomechanics of the foot [53].

Initial Management
Hypothermia
The management of hypothermia differs from localized NFCI, and it is has been suggested core temperature must be raised
while the extremities are kept cool [18,30,52]. Injured feet should be elevated and exposed to steady cool air from a fan [30,52]. Rewarming of injured tissues increases metabolic demand of damaged cutaneous cells above the supply capability of the injured subcutaneous blood vessels [30]. Continuous cooling is said to bring a rapid improvement in pain, oedema, and vesiculation [30,52].

**Drugs**

The diagnosis of NFCI is often difficult or delayed. Since painful re-warming and persisting pain are features of NFCI it is important to attempt to alleviate pain at an early stage. Pain is often severe and as with post-herpetic neuralgia, if treatment is not instituted promptly, there is a significant risk of chronic pain that is resistant to all treatment modalities. The pain is often most prominent at night, and typically occurs in the soles of the feet and at the base of the toes. Since 1982, the standard treatment in the British military, first proposed by Riddell [54], has been amitriptyline hydrochloride. The standard regime is 10-25 mg nocte initially, increasing the dose by 25 mg every 3 nights or so to a maximum of 100 mg until the pain subsides. The dose often requires adjusting. Incremental increases in dosage may be required if pain “breaks through” after initial relief [55]. Gabapentin may offer an alternative approach, but requires further study.

**More severe injuries**

In severe cases, the cold sensitisation may be so severe that individuals are unable to work outside. There is often persisting oedema and hyperhidrosis making the individual susceptible to fungal infections. Chronic pain resembling causalgia or reflex sympathetic dystrophy is reported. The neuropathic foot can develop ulceration and tissue loss, ultimately resulting in either minor or major lower limb amputation. On-going care within a specialist foot clinic using custom made shoes and insoles appears to improve functional outcome. Multidisciplinary team approaches such as healing of the ulcerated neuropathic foot using patella bearing orthoses has been described [56]. It has been reported that the pain of NFCI can be so severe as to require tricyclic antidepressants, and this should be instituted at an early stage [55]. Failure to do so increases the risk of developing severe chronic pain resistant to all subsequent treatment modalities. Early involvement of pain specialists is important.

**Assessing the severity of NFCI**

Following the initial injury an increased sensitivity to cold develops. There are often surprisingly few objective clinical signs. A careful history of appropriate cold exposure, a clear history of the typical rewarming symptoms and signs, detailed examination and special investigations all tend to build up a picture consistent with an NFCI. Corroborative evidence from medical records is vital.

**Special investigations**

Infra-red thermography can be used to assess the individual's response to a standardised cold stress, and may be helpful in confirming the diagnosis, assessing the severity of the injury, and finally monitoring the recovery or otherwise from the NFCI, however, it not widely used elsewhere [53,57]. There may be a significant variability in the response of some individuals to current infra-red thermography test although this is currently being assessed, and in normal individuals there appears to be a very good co-efficient of variation [58]. Interest is being shown in the use of gentle exercise before the cold sensitivity test, and also in the use of laser Doppler flowmetry (a non-invasive real time measurement of red cell perfusion to tissues) to try to improve the assessment used to classify non-freezing cold injury [59]. However careful experimental design to validate any potential new tests against suitable controls both pre- and post- exposure will be required. Currently, there are no validated, reliable clinical tests to diagnose NFCI.

**Prevention**

The simplest way to prevent NFCI is to avoid prolonged exposure to cold-wet environments. This can be quite difficult to implement bearing in mind the variable conditions and variable susceptibility of each individual. Prevention is best achieved by encouraging people to remain active and increase blood flow to the feet, rotating personnel out of cold-wet environments on a regular basis, keeping feet dry by early changing of wet socks, maintaining body core temperature by limiting sweat accumulation into clothing and dressing in layers, and by educating personnel about the early signs and symptoms of NFCI [60]. Changing socks two to three times throughout the day is mandatory in cold-wet environments. The military suggests that optimal care entails air drying feet for at least 8 hours out of every 24 [61]. Vapour barrier boots do not allow sweat from the foot to evaporate, and in some situations this increases maceration [62] possibly exacerbating the risk of NFCI. Footwear should not constrict blood flow; therefore sizing is important as is educating the user not to tie shoelaces too tight.

As a consequence of the apparent increasing incidence of NFCI in the British Military, a number of additional preventative steps have been taken including the improved education of recruits, serving personnel and training staff about additional preventative measures and equipment and early recognition. Well designed, protective equipment, supplied to the appropriate personnel, used in a timely and appropriate way, with due support and flexibility being shown by superiors who understand the variability in the individual susceptibility to NFCI should all reduce the risk of developing an injury. Despite this, or possibly as a result of the increased recognition, there is now a significant litigation issue facing the Ministry of Defence [35]. Interestingly the severity of the injuries appears to be relatively mild in comparison to civilian NFCI injuries and military historical controls. This raises the question as to whether a) there is either a continuous spectrum of disease, or b) whether there is a bi-modal distribution of the disease with milder and more severe forms of NFCI or c) whether the commonly presenting form now seen is the actually same disease process that has been investigated in the past [35].

One approach to reducing the high levels of NFCI observed, would be to consider screening potential recruits. However this requires a test with high sensitivity and specificity and individual variation in the control of peripheral blood flow is so great that none of the assessments currently available [7,8,10,55,63] meet these requirements.

With the likelihood of chronic sequelae and limited potential for treatment, the only effective approach to NFCI is to try to prevent its occurrence. This requires the enthusiastic engagement of commanders at every level, training staff, and all those at risk of sustaining injury. Reducing the incidence of cold injury in military training requires striking a delicate balance between training realism, and safety. Whilst training in demanding environments runs real risks of injuring personnel, the benefits to
them in the development of field craft skills are vital if they are to avoid NFCI in the future [55].

Summary
NFICI is a potentially serious thermal injury which can have serious long term consequences. The diagnosis is based upon a history of exposure and the development of subsequent clinical sequelae. Treatment is problematical avoidance of further cold exposure is important. With only limited treatment options avoidance of the initial injury is crucial. A combination of recognising the potential risks and the timely and effective use of the appropriate equipment is vital.

However, in spite of preventive measures such as better protective equipment and education of commanders, the number of cases continues to rise. More work is needed to develop understanding of the condition, diagnosis, grading of severity, and long term implications.

Patient and GP information
http://www2.armynet.mod.uk/armysafety/features/nfci.htm
http://www.nhsinform.co.uk/health-library/articles/n/non-freezing-cold-injury/introduction.aspx

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