Introduction

Distal Radius Fracture (DRF) can occur after a fall on an outstretched hand and is one of the most common fractures (in females and older population) [1-3] seen by orthopedic surgeons with an incidence of 195.2/100,000 persons per year [4,5]. DRF can result in an increased morbidity, with long-term functional impairment, pain, and deformity [1,6-9]. Complications (N=275 cohorts) such as Reflex Sympathetic Dystrophy (RSD) (20%), median (22%) and radial (11%) nerve compression and tendonitis (14%) [10] after DRF are often thought to be either missed or overlooked by the treating therapist [11]. Injury to the peripheral vasculature, defective vasoregulation, and nerve injury have been suggested as possible contributors to Cold Intolerance (CI) [2,12-15]. Cold intolerance is an abnormal pain after exposure to mild or severe cold, with or without discoloration, numbness, weakness, or stiffness of the hand and fingers [13,16-19]. Patients commonly report CI after hand fractures, [19] that may arise within the initial months or may have a delayed manifestation, depending on the seasonal nature of the injury [16,18,20,21]. The pathophysiology of CI is still unclear [16]. However, it is postulated that post-traumatic CI has both vascular and neural etiology among other contributing causes [22,23].

When neurovascular dysfunction exists in hands, cutaneous thermoregulation, nutritional blood flow, and autonomic functions may become impaired [24,25]. Cryotherapy is one of the
most frequent interventions provided by therapists (90%) during the mobilization phase after DRF [26]. It has also been shown to effectively reduce pain and swelling in DRF after the cast removal [27], however if an underlying neurovascular dysfunction or complication exists, then it may be contraindicated for patients to continue treatments with thermal agents or cold modalities. In addition to this, cold intolerance as reported earlier in patients with reflex sympathetic dystrophy [28], median and ulnar nerve injuries [15,29] and hand fractures can be severely disabling [12,30] and may affect their quality of life. Hence, quantitative measurements and cold provocation test [20,23,29,31,32] that are sensitive to changes in peripheral blood flow, thermoregulation and autonomic control may be important in detecting cold intolerance and neurovascular dysfunction in the hand after injury [20,21,23].

Immersion in Cold Water Evaluation (ICE) is a simple and reliable objective cold provocation measure to assess cold responses, peripheral blood flow and temperature recovery in the hand [23,31]. Sometimes, after injury the symptoms of pain due to vascular insufficiency may mimic neurologic conditions [33-37]. Previous reports on the Immersion in cold water evaluation used only skin temperature for the evaluation of thermoregulatory responses [21,23], but did not include neural and vascular measures [25,38,39]. Hand function reflects through the integration of all systems and is thought to be affected by decreased blood flow, cold hands, and loss of sensation. Hence, using baseline sensory, vascular, sympathetic and temperature responses to assess the injured and uninjured hand would be advisable to assist with early detection and monitoring of neurovascular function at important timeline (6 weeks post fracture) during the rehabilitation of DRF. This may also help to plan or modify the future care.

There is also a scarcity of published trials that have looked at the impact of cold exposure on sensory and vascular functions in patients with DRF after cast removal. Hence, the specific aim of this study is to determine whether a brief exposure to cold water immersion using ICE protocol will alter skin blood flow, skin temperature and sensation differently between the affected and unaffected hands of patients with DRF. These evaluations might also inform our understanding about the potential mechanisms behind the therapeutic effect of cold water immersion in DRF.

Methods

Participants

A sample size of 20 was considered for this research. The number needed to detect a moderate effect size for this study (ES r=0.50; two-tailed α = 0.05; 80% power) was based on Cohen’s criteria [40]. Statistical significance was considered if p<0.05.

Patients with DRF were recruited by the treating surgeon or therapist during the sixth week post fracture at the time of cast removal based on the eligibility criteria given in Table 1. Testing was done in the Hand and Upper Limb Research Lab. This study was approved by the Western University Research Ethics Board. All participants read the letter of information, had their questions answered, and signed a consent form prior to participation in this study.

Table 1: Shows inclusion and exclusion criteria used to recruit patients.

| Inclusion Criteria | Exclusion Criteria |
|--------------------|--------------------|
| Injured hand:      | Skin infection, open wound |
| Age 18 to 65 yrs.  | Pregnancy           |
| Male & female      | Pacemaker/ monitoring device |
| Stable DRF         | Malignancy           |
| Closed reduction   | Confirmed reflex sympathetic dystrophy |
| No therapy at least an hour before test | inflammatory arthritis |
| No other injury or disease to the neck, shoulder, elbow, wrist, or hand within past year | Peripheral vascular disease |
| Uninjured hand:    | Previous fractures, revision surgeries, complex fractures with neurovascular injuries |
| No recent injury or disease to neck, shoulder, elbow, wrist, or hand within the past year. | Autoimmune disorders |
|                     | Hypertension, Cardiac failure |
|                     | Diabetes              |
|                     | Internal haemorrhages |
|                     | Deficits in sensation in the area to be treated (sensory test to identify sharp and dull sensation; hot or cold) |
|                     | Deficit in circulation (Digital latency test for fingers) |
|                     | Inability to understand instructions. |
|                     | Local hot or cold sensitivity |
|                     | Cold adverse reactions |

Immersion in Cold Water Evaluation (ICE) (Traynor and Macdermid 2008) [23]:

ICE is a reliable, objective measure of cold response to assess cold intolerance in hands after injury. This protocol examines peripheral blood flow and the associated temperature recovery. A cold-provocation test is initiated by immersing hands in cold water maintained at a temperature of 12°C (+1°C) for 5 min. and the digital temperatures in the index and little fingers are measured using an infrared skin thermometer during the recovery period. All tests are performed with the patient seated comfortably in a thermo-neutral environment (20°C ± 2°C) [23].

Tivi (Tissue Viability Imager) 600 polarization spectroscopy camera (version 7.4 Wheels Bridge AB, Linköping, Sweden):

The Tivi is a reliable, [41] valid [42,43] and sensitive [44] device used for a high-resolution instantaneous imaging of Red Blood Cell (RBC) concentration in human dermal tissue (to a depth of 400-500 micrometers) [43]. This digital camera (Canon Rebel EOS model 450D, Japan) has shown many uses in drug development, burn investigations, pressure studies, and general research maneuvers due to the ease of use, portability, and low cost [43, 45].

Participants were required to keep their shoulder in neutral,
elbow in 90° flexion; forearm (s) supinated and placed somewhat lower than the heart. An outline was drawn to standardize hand position. The camera was positioned at a distance of 30 cm from the participant’s hand. One photo was taken every 5 seconds (12 photos / min) which was then uploaded into the attached computer. For each participant, one image at baseline and at each follow up points (0 min, 1 min and 10 min after Immersion in cold water evaluation; with 4 images/hand) were selected for image analysis from the computer. Regions of interest were selected and cropped over the immersed area up to 5cm proximal to the ulnar styloid process. Later these cropped images were used for further statistical analysis.

The frequency of 2000 Hz is used to stimulate the large myelinated Aβ fibers (for touch, pressure); a 250Hz to stimulate myelinated Aδ fibers (mechanoreceptive, fast pain, pressure, temperature), while a frequency of 5 Hz is used to stimulate the small unmyelinated C-polymodal nociceptive fibers (for slow pain, temperature, post ganglionic sympathetic fibers) [37, 46].

Ranged CPT (R-CPT) is a rapid sensory Perception Threshold (sPT) test in the Neurometer which is typically used to confirm or rule out sensory involvement in large samples such as screening [35,37]. In R-CPT, each frequency is repeated several times to ensure accuracy and reproducibility [37]. The Neurometer reports values (R-CPT levels) as, the normal range (6-13), hyperesthesia (1-5), and hypoesthesia (14-25) [35,37]. R-CPT was tested at two frequencies in this study (2000Hz and 5Hz) to target two different nerve fiber types. To begin 2000 Hz stimulation, the skin was cleaned with a skin paste and then the 1 cm gold electrodes coated with small amount of gel were attached to the ring finger with an adhesive tape. Then the participants were asked to press and hold the red “Test cycle” button on the remote control box and release it as soon as they begin to feel the tingling or buzzing sensation. The machine records the response when the button is released by the patient and the same process is repeated 7-10 times until a score is displayed. In total three consecutive scores were obtained at 2000Hz. The same procedure was repeated at 5Hz. These test cycles end automatically after few repetitions (7-10 times) and the Neurometer displays score for 5Hz [35,37].

**Study Protocol**

Hands of participants were assigned by concealed random allocation using sealed envelopes to indicate which of the two hands would be tested first. Testing was completed in two hands one after the other on same day according to the protocol shown in Figure 1. All the assessments and testing were provided by one physiotherapist.

Subjects were required to acclimatize to the testing room temperature upon arrival for 15 min. They were first measured on Tissue Viability imager (TiVi) over the palmar aspects up-to 10 cm proximal to ulnar styloid process, then Skin Temperature (S Temp.) was recorded from index and little finger pads using King’s infrared thermometer, and this was followed by Ranged current perception threshold test (R-CPT) measured from the tip of ring finger (median and ulnar nerve, dermatome C7, C8) to record sensory Perception Thresholds (sPT) at 2000Hz (Aβ fibers) and 5Hz ( C fibers) before starting cold water immersion. The participant subsequently underwent Immersion in Cold water Evaluation (ICE) protocol as described by Traynor and Macdermid [23]. Following a 5 min Period of Immersion (POI), the forearm and hand were quickly pat-dried and then skin blood flow, S Temp and R-CPT were measured. The TiVi measurements were taken immediately following (0 min), 1 min following and 10 min following the POI, whereas R-CPT was measured at 1 min following and 10 min following the POI. Skin Temperature was measured immediately (0 min) and 10 min following POI. The delay between the removal of hands from the water and start of the recordings on the three measures was less than 3 min. TiVi took 12 photos for 1 min (0 min to 1 min), Skin Temperature was recorded during the 5 second gap in TiVi, and R-CPT was initiated at the end of TiVi. The protocol was repeated on the subject’s opposite hand for comparison in similar order.

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TIVi software was used to calculate the mean blood flow (A.U.) over the area of immersion in both hands. The sensory perception thresholds obtained from R-CPT test at 2000Hz and 5Hz (m.A.) were recorded directly from the digital display of the Neurometer onto a separate data collection sheet along with the temperature (°C) readings.

Data Analysis

General Linear Model, repeated measures (using SPSS version 20, IBM Inc.) was used to determine if each participant’s injured and uninjured hand had different measures of skin blood flow (RBC concentration), sensory perception threshold, and skin temperature at baseline, immediately after the period of immersion (Immersion in cold water evaluation) and then 10 min following the period of immersion. A 2 x 4 (hand x time) design was used to assess changes in skin blood flow and a 2 x 3 (hand x time) design was used to assess changes in skin temperature and sensory perception thresholds at 2000 Hz and 5 Hz (Aβ, C fibers) for the injured and uninjured hands. Interactions were examined for significance between hand and time. Post hoc analyses were performed using Bonferroni correction, wherever necessary. Pair -wise comparisons were used to perform within-group comparisons wherever needed. Significance level was set at p<0.05 level.

Table 2: Shows participant demographics characteristics.

| Age in yrs. (mean± SD) | 52 ± 12.2 |
|------------------------|-----------|
| Gender:                |           |
| Females, n (%)         | 18 (90%)  |
| Males, n (%)           | 2 (10%)   |
| Side of injury:        |           |
| Right, n (%)           | 10 (50%)  |
| Left, n (%)            | 10 (50%)  |
| Type of Injury:        |           |
| Fall n (%)             | 18 (90%)  |
| Others (%)             | 2 (10%)   |

Abbreviations: SD = Standard Deviation; n = number of patients; % = Percentage of Patient

Results

Twenty patients with DRF were recruited after cast removal between November 2012 to May 2013. Table 2 shows the demographic characteristics of the patients. Table values indicate that majority of the participants were females (n=18) and those who had a fall on an outstretched hand (n=18). No data points were missing. Table 3 shows means, standard deviation and 95% confidence intervals obtained from the General Linear Models (Repeated Measures) to assess the changes in skin blood flow, skin temperature and sensory perception thresholds at 2000Hz and 5Hz. Seventeen participants volunteered to report that they felt good during cold water immersion on their injured side. No long-term discomfort was reported.

In the DRF hand, Immersion in cold water evaluation increased skin blood flow from baseline to immediately after the POI (0 min) (p=.002), then remained high for over a minute (p=.00) and returned to pre-exposure levels by 10 min (p=.45). Post hoc comparisons between baseline value and immediately (0 min) after POI (p=.00) as well as between baseline and 1 min after POI (p=.003) showed a significant difference. Post hoc comparisons between baseline and 10 min after POI (p=.94) as well as between 0 min and 1 min after POI (p=.06) were not significantly different. Please refer Table 3. Please refer Figures 2 and 3 as an example to show changes observed in the skin blood flow of a patient aged 65 years.

In the DRF hand, the skin temperature was reduced in the index finger from baseline level to immediately after POI (0 min) (p=.00) and 10min later (p=.001). A similar trend was noted in little finger from baseline to both immediately following (0 min) (p=.00) and 10min (p=.002) after POI. Post hoc comparisons (for index and little fingers) between baseline and immediately after POI (0 min) (index p=.002; little p=.01), and between (0 min) immediately after and 10 min after the POI (p=.00; p=.004), as well as between baseline and 10 min after POI (p=.002; p=.00) showed significant difference in both index and little fingers. Please refer Table 3.

In the DRF hand, the sensory perception threshold at 5 Hz remained unaltered by Immersion in cold water evaluation in both injured and uninjured hands (p=.44). Sensory perception threshold

Table 3: Shows outcome data for the injured and uninjured hand on Skin Blood Flow, Skin Temperature, Sensory Perception Threshold

| Normal side (n=20 hands) | DRF side (n=20 hands) |
|--------------------------|-----------------------|
| Skin blood flow (0-400 A.U) |                        |
| Baseline                 | 82±7.5(79,86)         |
| Post 0 min               | 106±26.0 (94,118)     |
| Post 1 min               | 104±25.0 (92,116)     |
| Post 10 min              | 84±8.9 (80,88)        |
| Skin temperature (Index °C) |                       |
| Baseline                 | 31.9±3.0 (30.4, 33.3) |
| Post 1 min               | 22.2±5.9 (19.4, 25.0) |
| Post 10 min              | 27.2±6.7 (24.0, 30.3) |
| R-CPT at 2000Hz (0-24 m.A) |                   |
| Baseline                 | 8.4±2.1 (7.4, 9.4)   |
| Post 1 min               | 9.1±1.8 (8.2, 9.9)   |
| Post 10 min              | 9.2±1.7 (8.3, 10.0)  |
| R-CPT at 5Hz (0-24 m.A)  |                       |
| Baseline                 | 12.6±3.5 (11.0-14.0) |
| Post 1 min               | 11.1±3.1 (9.6, 13.0) |
| Post 10 min              | 11.4±3.1 (9.9-12.8)  |

Abbreviations: DRF =Distal Radius Fracture; Baseline=before cold water immersion; Post 0 min = immediately after period of immersion; Post 1 min = 1 min after period of immersion; Post 10min=10 min after period of immersion; R-CPT =Ranged Current Perception Threshold Test at 2000Hz for Aβ fibers and at 5Hz for C fibers.

*All values are Mean±standard deviation (95% confidence interval)
Skin blood flow responses observed in the uninjured hand in this study are consistent with changes in normal level, indicating that the fractured hand was less responsive by an increase in threshold only on the affected side. In contrast, Aβ fibers (which carry touch and pressure sensation) operated at similar detection levels after brief exposure to cold. The extremities mitigate the detrimental effects of local cold extremes. In healthy subjects, about 5 to 10 min after the initiation of cold exposure of the hand in a 15°C or cooler environment, the blood vessels suddenly vasodilate to increase peripheral blood flow and maintain fingertip temperatures [38,50,52-54]. Others have reported that this response is stronger when cooling occurs in water [55]. This cold induced vasodilation is followed by a new phase of vasoconstriction to reduce blood flow to the peripheries in favor of a central pooling of blood in the torso and deep body core [56]. This process repeats itself and is called ‘the hunting reaction’ or the ‘Cold Induced Vasodilation’ Phenomenon (CIVD) [50]. The term hunting reaction [50] is described as the alternating periods of vasodilation and vasoconstriction during cold exposure until a steady state is reached. Maintained vasodilation without cycling has also been observed with cooling human forearms at 1°C for 15 min [51]. This reaction has implications for assessment and treatment since the clinical rationale for doing each must be consistent with the underlying physiological mechanisms. When the Immersion in cold water evaluation is used to assess abnormal physiological responses to cold, there can be a variety of indicators of this, including abnormal pain in response to cold exposure (detected by numeric pain rating and test completion), failure to achieve expected vasodilation and vasoconstriction during the test, or inability to restabilize blood flow and temperature following exposure. Similarly, the same indicators could negate the therapeutic value of cold if used as a therapeutic agent.

The responses observed in this study are consistent with ‘hunting reaction’ or the ‘Cold Induced Vasodilation’ Phenomenon (CIVD) that has been postulated to explain cold exposure responses. This study found no differences in skin perfusion and rewarming patterns between the previously fractured hand and the unaffected hand of patients presenting at sixth week following a closed reduction. Since patients with vascular injuries were not included in the study, this finding suggests that in the absence of such injury vascular function is relatively “normal.” Similarly, no difference was observed in C fiber activity after Immersion in cold water evaluation (which carries temperature, pain sensation and sympathetic signals) between the injured and uninjured hands on all measures [i.e. skin blood flow (p=.56); skin temperature of index and little fingers (p=.18; p=.97); and sensory perception thresholds at 5Hz (p=.84)]. Nor was an interaction found between hand and time (p=.28).

**Discussion**

The demonstration changes in skin blood flow immediately after cold water immersion in this study are consistent with changes in limb blood flow reported by Levy et al., [49]. These authors noted an increase in skin blood flow measured by plethysmography after hand immersion in cold water at 4°C. Even though the cold water temperatures and the methodology used in their study were different than the current protocol, the observed vasodilation in the present study is consistent with that reported by Levy et al. and the previously described “hunting reaction” phenomenon [50]. The term hunting reaction [50] is described as the alternating periods of vasodilation and vasoconstriction during cold exposure until a steady state is reached. Maintained vasodilation without cycling has also been observed with cooling human forearms at 1°C for 15 min [51]. This reaction has implications for assessment and treatment since the clinical rationale for doing each must be consistent with the underlying physiological mechanisms. When the Immersion in cold water evaluation is used to assess abnormal physiological responses to cold, there can be a variety of indicators of this, including abnormal pain in response to cold exposure (detected by numeric pain rating and test completion), failure to achieve expected vasodilation and vasoconstriction during the test, or inability to restabilize blood flow and temperature following exposure. Similarly, the same indicators could negate the therapeutic value of cold if used as a therapeutic agent.

The demonstrated changes in skin blood flow immediately after cold water immersion in this study are consistent with changes in

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in ice water. This was also observed in the injured and uninjured fingers/hands of patients with reflex sympathetic dystrophy, [57] as well as patients with median and ulnar nerve lesions [53] after an isolated cold stress test. This phenomenon is principally attributed to the opening of arterio-venous anastomoses [13] but the exact mechanism is still subject to debate [56].

The changes observed in skin temperature immediately after the cold water immersion in both index and little fingers is consistent with changes reported by Traynor et al., [23] and Smits et al., [21] in the healthy controls and patients with hand fractures [21]. These authors showed that normal active rewarming of the fingers is measurable within 50 to 80 sec after removing the hand from cold water (12°C) and lasts up to 5 or 10 min [23]. Thus, after an extensive cooling of the extremities, the thermoregulatory system increases the blood flow to the extremity to counteract the decrease in hand temperature and prevent pain and/or frostbite [31].

The current study provides new information about the response patterns in different nerve fibers to cold exposure. No alteration in small C fiber functionality was demonstrated. A small increase in threshold for the larger Aβ fibers was demonstrated in the injured hand. Since this is the first report of this finding, we cannot verify it from other studies on cold exposure. However, there are previous reports on sensory nerve conduction velocity observed after cryotherapy in healthy subjects using ice packs [56,57] and cold water immersion [58]. These studies have demonstrated that peripheral sensory nerve conduction velocity is slowed by cold application [58,59]. Because nerve conduction studies can measure sensory nerve conduction velocity of large diameter nerve fibers, [60] the increase in Aβ threshold (threshold increase corresponds to hyposensitivity or decreased sensation) observed after cold water immersion in this study is consistent with the decrease in sensory nerve conduction velocity observed by Esperanza et al.,[58]. Previous studies have demonstrated that topical cold treatment decreases the skin temperature and in underlying tissues to a depth of 2 to 4 cm, [58,61-63] decreasing the conduction velocity of pain nerve signals [57,58,63]. This result in a local anesthetic effect called cold-induced neuropraxia. We did not demonstrate evidence of this in our 5 Hz thresholds which target the small unmyelinated pain fibers (C fibers). The fact that injured and uninjured hands showed no variation in C fiber thresholds with the brief cold exposure, suggests that the cold water exposure resulted in minimal thermal, nociceptive or sympathetic physiological responses. Nerve fiber sensitivity is thus presumed to vary according to the diameter and myelination of the nerve [64]. The large diameter, myelinated nerve fibers are thought to be most responsive to cold exposure, whereas the small unmyelinated fibers are thought to be least affected by the cold [64].

The current study objectively examined thermoregulatory, sensory and vascular function after DRF by evaluating skin blood flow, skin temperature, Aβ and C fiber responses before and after a cold provocation test (Immersion in Cold water Evaluation). Normal thermo-physiological responses such as Cold Induced Vasodilation (CIVD) reaction, [19,39] and digital rewarming patterns, [31,50,52] were noted in both the injured and uninjured hands. These findings suggest that a brief exposure to cold water has a potential to induce some therapeutic effects in patients with uncomplicated DRF and needs further investigation.

Glady et al., [27] demonstrated that ice pack reduced pain, swelling and improved the range of motion in patients with DRF after cast removal. Whereas, other reports have stated that cold water immersion is preferable to ice packs [58,63,65]. Cold water immersion is thought to cause the least skin temperature reduction, possibly due to the fact that a greater area receives the treatment, leading to a faster activation of the thermoregulatory responses that protect the body from abrupt temperature changes [66] and consequently, the skin temperature is quickly stabilized and does not adequately reflect the effects of cooling on subcutaneous tissues [67-70]. The temperature reductions of approximately 10°C in both index and little fingers along with the changes in skin blood flow, perception thresholds in Aβ fibers and the possible mechanisms behind these changes led us to a conclusion that cold water immersion for 5 min. has a potential to reduce pain; and can act as a counter-irritant via pain gate mechanism through the activation of large diameter Aβ fibers which needs a further study [64,71,72]. The increase in Aβ threshold only on the DRF side after cold water immersion could be attributed to the ongoing healing process which was possibly absent in the normal tissue. Cold application helps to reduce swelling in the DRF patients after cast removal, as demonstrated by Glady et al., [27]. However, when cold is used to reduce swelling, then the position of the extremity must also be considered. Some have used contrast baths, alternating immersion in cold and hot water. A systematic review and effectiveness of contrast baths was inconclusive [71]. It might be useful to examine different approaches to cold application using the approach conducted in this study to determine potential differences in physiological effects across methods of administering thermal agents.

Limitations and Research Recommendations

There are a number of limitations in the current study that may have affected the study findings and generalizability. Results are mostly applicable to female patients and those who had a fall on an outstretched hand. Thus, these findings may not apply where complications, surgery or pre-existing co morbidities are present. Only one therapist pro-vided the testing and assessments. However minimal bias was expected with respect to the evaluation of all three measures, because sensory perception threshold was determined by the patient while the Tissue viability imaging and skin temperature were not controlled by either the patient or the therapist.

Simultaneous measurements on all measures was not possible hence, the responses at regular intervals up to 10 min after cold water immersion were not reported. Since the ring finger (test site) is innervated by median and ulnar nerves, differential effects in these nerves were not directly explored. Therefore, future research on Immersion in cold water evaluation should focus on single nerve territory.

Cold induced vasodilation is thought to vary according to age, gender, ethnicity and acclimatization to cold weather etc [22,56]; thus; future research can observe people based on these factors. A normal response to objective cold test does not prevent subjective symptoms of cold intolerance (on Cold Intolerance Symptom Severity scale or
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