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LOCAL SKIN COOLING AS AN AID TO THE MANAGEMENT OF PATIENTS WITH BREAST CANCER RELATED LYMPHEDEMA AND FIBROSIS OF THE ARM OR BREAST

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ABSTRACT

Based on preliminary observations that topical cooling appeared to soften lymphedematous and fibrotic tissue, our goal was to systematically and quantitatively evaluate this effect. For this purpose, topical cooling was used as part of treatment of lymphedematous and fibrotic skin of women with breast cancer related lymphedema (BCRL) and localized fibrosis. Skin tissue hardness was assessed via the force required to indent skin to 4 mm ($F_{4.0}$) and 1.3 mm ($F_{1.3}$) and skin water was assessed by measurements of tissue dielectric constant (TDC). Measurements were done before cooling, after cooling, and after a single treatment session in 20 women with arm involvement and in 12 women with breast involvement. Pre-cooled arm and breast skin temperatures (mean ± SD) of 32.4 ± 1.4 °C and 33.8 ± 1.0 °C were reduced to 23.7 ± 2.0 °C and 24.7 ± 1.6 °C respectively via application of cold washcloths. Cooling was associated with a significant ($p<0.001$) decrease in $F_{4.0}$ and $F_{1.3}$ at arm and breast sites. At arm sites, force reductions ranged from 24% to 28% depending on indentation depth. Although the precise mechanism linking cooling to softening is as yet not fully understood, the fact that tissue is softened carries with it many potential benefits to patient and therapist. The near immediate tissue softening is associated with less pressure on underlying nerve endings and less input to sensory nerves thereby interrupting the pain cycle resulting in rapid pain relief. The rapidly softened tissue and decreased perception of pain offers the patient hope and encouragement in their therapeutic journey to reclaiming functional use of their affected body. Further, because softer tissue becomes more pliable, myofascial lengthening, scar tissue releasing, and other aspects of treatment are easier to perform thereby reducing treatment time and effort while achieving improved functional mobility.

Keywords: lymphedema, fibrosis, skin hardness, breast cancer, tissue dielectric constant, tissue mechanical properties, skin cooling, cryotherapy

Topical cooling of skin causes an initial local vasoconstriction that persists beyond the time of skin temperature normalization (1) and reduces the normal post-ischemic hyperemic response caused by tissue indentation loading (2). Skin cooling also causes systemic vasoconstriction (3-5) which, together with local vasoconstriction, decreases capillary-to-interstitium fluid filtration and promotes post-capillary fluid reabsorption. These enhanced processes tend to reduce interstitial fluid volume. Further, given the

almost universal acceptance of cooling as a modality to help treat and blunt various forms of edema (6), and the reported effects of elevated environmental temperatures on lymphedema (7), it was surprising to us that cooling has not been suggested as a potential therapeutic modality for lymphedema. Moreover, lymphedema is often associated with co-present inflammation and fibrosis (8) so that skin surface cooling, which can produce cooling to a depth of 2 cm (9), might be a way to have positive impacts on these conditions. In treating patients who have developed breast cancer treatment related lymphedema (BCRL), it was noted that skin tissue regions most bothersome to patients were often regions with elevated skin temperatures suggesting underlying inflammatory processes often in conjunction with palpated fibrosis. In an effort to provide relief to these patients topical cooling was integrated into their physical therapy session which included lymphatic drainage techniques. An unforeseen yet welcome observation associated with that topical cooling was the apparent reduction in tissue firmness as judged by palpation and effort expenditure experienced during treatment. The purpose of this research was to systematically and quantitatively evaluate the impact of skin tissue cooling on skin tissue water content and skin firmness via measures of indentation resistance in women with documented BCRL.

METHODS

Subjects

Women participating in this study all had prior breast cancer-related surgery and were referred to clinic for lymphedema therapy. Prior to assessments, the nature of the research was explained to each woman and they each signed a university institutional review board approved consent form. Eligible for participation were women at least 18 years of age who were referred to clinic for treatment of either arm or breast related lymphedema issues and who had lymphedema-related tissue hardening or fibrosis as judged initially by clinical evaluation. Patients were excluded from participation if they had active cancer or were pregnant. Decreased sensation to the breast secondary to breast surgery was considered a precaution. A total of 32 women were included in the present study, 20 of whom had unilateral arm lymphedema and localized fibrosis and 12 of whom had breast lymphedema and localized fibrosis. Average age (mean ± SD) of the studied group was 61.0 ± 12.1 years (range 38-88 years). The time from their initial surgery was 6.9 ± 7.2 years (range 1 to 40 years) and the duration of their lymphedema was 41.6 ± 35.1 months (range 3 to 132 months). Surgery was associated with the removal of 15.1 ± 8.6 nodes (range 3 - 40) with 4.1 ± 5.7 being cancer positive (range 0 to 18). Of the patients evaluated, 70% had received radiation therapy and 78% had received chemotherapy.

Initial Procedures

As part of the standard pre-treatment assessment, all potential subjects received a full physical therapy evaluation that included the collection of subjective complaints and current reason for seeking care along with objective measures such as range of motion, muscle strength, sensation, as well as a functional assessment of affected areas. If compression garments were utilized, the integrity and fit of the garments were also evaluated. In addition, arm girths were measured using a Gulick tape measure at wrist, elbow, mid upper arm, and axilla of both arms. Lower and upper arm volumes were calculated based on the frustum model and the ratios of affected to control arm ratios determined. For the present data set, patients referred for arm lymphedema had lower arm (wrist to elbow) volume ratios of 1.139 ± 0.119 and upper arm (elbow to axilla) volume ratios of 1.114 ± 0.088 representing edema volumes of 13.9% and 11.4%,

respectively. For the patients referred for breast lymphedema, similar arm measurements were made with lower arm and upper arm ratios of 1.047 ± 0.084 and 1.039 ± 0.076, respectively. Thereafter a single location on the arm or breast was identified as the research target measurement site. This was achieved using palpation and patient interview to locate the most swollen and firmest area on breast or arm.

Measurements

Prior to cooling and also after cooling, measurements were done at the selected lymphedematous target site on the arm or breast and also on the contralateral arm or breast region at an anatomically similar site. After the treatment session measurements were repeated, but done only on the lymphedematous target site.

Indentation Force: The force needed to indent skin tissue to a depth of 1.3 mm ($F_{1.3}$) was measured with a hand-held device (SkinFibroMeter, Delfin Technologies, Kuopio, Finland). In use, skin is lightly touched causing a 2 mm diameter indenter to deform skin inwardly with the resultant force recorded and displayed on the front of the device. The device has internal sensors that accept measurements only within prescribed limits on applied force and velocity such that if an applied force is too large or applied too slowly or rapidly the device's software prompts to repeat the measurement. A single recorded value is obtained as the average of five acceptable sequential measurements made rapidly in succession and requiring about five seconds overall. Each site was measured five times. The force needed to indent skin tissue to 4.0 mm ($F_{4.0}$) was determined using a custom built hand held indentor device referred to as the Tiss-U-Press with specifications and validation data previously described (10). In brief, the device has a force indicator rigidly coupled to a penetration depth indicator (PDI). The PDI has a circular 29.5 mm diameter base plate attached at the bottom with a central 10.5 mm diameter opening through which a 10 mm diameter indentor passes to indent the tissue. Contact areas for the base plate and indentor are 601 mm^2 and 78.5 mm^2, respectively. Force and PDI accuracies are ± 5 g and ± 0.1 mm. The relationship between indentation force (F) and depth (δ) for soft tissues with an overall thickness H is expressible as $F = \delta E D \kappa / (1-\nu^2)$, in which E is the tissue elastic modulus, an index of tissue hardness, D is the indentor diameter, is the tissue Poisson ratio and is a factor that depends on the ratio of δ/H and D/H (11-13). Thus, measured force depends directly on penetration depth and soft tissue elastic modulus. If penetration depth is fixed as herein, then changes in force depend directly on changes in tissue elastic modulus.

Tissue Dielectric Constant: The tissue dielectric constant (TDC) is the ratio of skin tissue dielectric constant to that of vacuum. It was measured at 300 MHz with a hand-held battery operated device (MoistureMeter DCompact, Delfin Technologies, Kuopio, Finland). The device functions as an open-ended coaxial transmission line (14-16). At 300MHz TDC values are sensitive to both free (mobile) and bound water (17,18). Many reports regarding the physics (15,19-22) and use of TDC measurements are available (23-28) but the compact device herein used is relatively newer but values obtained are similar with those previously reported (23). TDC values are routinely tested against known values for various ethanol-water concentrations to insure intrinsic accuracy. All such measurements agreed with published values within ± 2.5%. In use, the device is applied to skin for about 5 seconds and a 300-MHz internal signal is transmitted to tissue with a portion of the incident electro-magnetic wave reflected in an amount that depends on the TDC. In its current form the device internally converts the actually

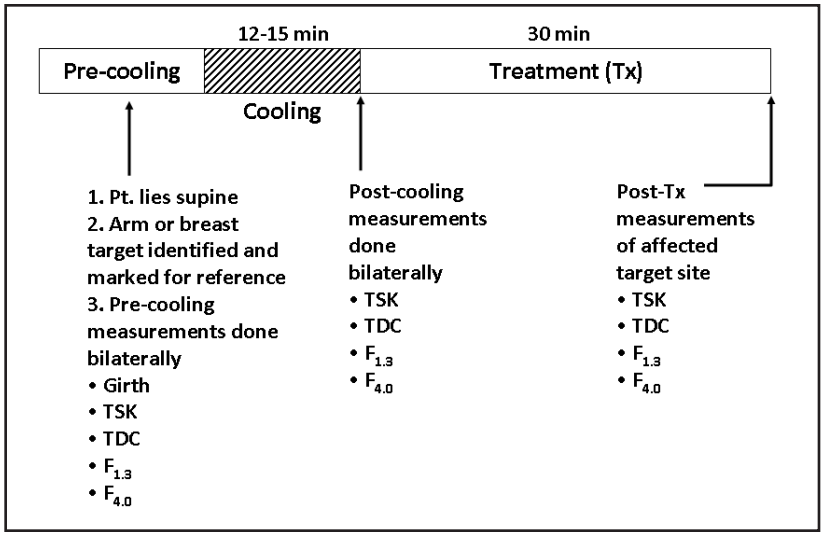

Fig. 1. Sequential Procedures. During the pre-cooling interval, the target site was chosen and pre-cooling measurements done. During the cooling interval, cold towels were placed over the affected region and repeated 3-4 times. Immediately after the cooling interval, post-cooling measurements were made and a treatment session was then begun which varied dependent on whether the target was arm or breast. At the end of the treatment (Tx) interval, a final set of post-Tx measurements was done.

measured TDC value into a percentage of water at a fixed temperature. However, since TDC varies with temperature, we report baseline pre-cooling true TDC values (dimensionless) as measured on the skin and also the percentage skin water under all conditions (e.g., pre-cool, post-cool and post-MLD). These percentages are determined using the ratio of measured TDC value to the TDC value of pure water at the measured temperature. For reference the TDC of water at 32 °C is about 76 with a value that increases with decreasing temperature. All TDC measurements were done in triplicate at each site and time point with the average values used to characterize TDC.

Arm Girth and Skin Temperature: Arm girths at target sites were measured using a Gulick type tape measure pulled to a constant tension and skin temperatures at target sites were measured using a non-contact infrared thermometer with a stated accuracy of ± 1 °C.

Procedure Sequence: *Fig. 1* summarizes the measurement sequence. After identifying the target area the pre-cooling measurements were done at the target site as indicated in the figure. These measurements were girth (arm patients only), skin temperature (TSK), TDC from which % H_2O was determined, and indentation forces to 4.0 mm ($F_{4.0}$) and 1.3 mm ($F_{1.3}$). Steps for cooling consisted of preparing an ice water bath in a large bowl and allowing the ice-water bath to temperature equilibrate. Washcloths were then immersed into the cold bath for about five seconds then removed, wrung out and laid over the affected area. Depending on size of the area to be covered 2-4 washcloths were utilized for optimal coverage with an overall cooling time of about 12-15 minutes. The patient was asked to touch the cold washcloths prior to first-time draping of the affected area to prepare for placing of the cold washcloth and decrease the impact of the cold sensation on initial skin contact. If requested by the patient, the temperature of the water into which the washcloths were dunked was adjusted with room temperature

TABLE 1
Baseline Pre-Cooling Parameters

	Arm Patients			Breast Patients		
	Control Arm	Affected Arm	p-value	Control Breast	Affected Breast	p-value
$F_{4.0}$ (N)	2.16 ± 0.70*	3.92 ± 1.04	< 0.0001	1.46 ± 0.47	3.54 ± 0.72	< 0.0001
$F_{1.3}$ (mN)	54.9 ± 14.4	111.6 ± 53.1	< 0.0001	47.2 ± 19.5	92.7 ± 40.7	< 0.0001
$\%H_2O$	43.3 ± 9.5**	76.0 ± 19.5	< 0.0001	58.9 ± 12.4	75.2 ± 20.2	0.022
TDC	32.8 ± 7.2**	57.5 ± 14.7	< 0.0001	44.3 ± 9.4	56.6 ± 15.2	0.022
TSK °C	32.5 ± 1.3	32.4 ± 1.4	0.251	33.5 ± 1.0	33.8 ± 1.0	0.230
Girth (cm)	23.6 ± 4.0	28.8 ± 4.9	< 0.0001			

Data entries are mean ± SD for 20 arm patients and 12 breast patients. $F_{4.0}$ and $F_{1.3}$ are resultant forces when skin tissue is indented to 4.0 and 1.3 mm expressed in Newtons (N) and mN respectively. The $\%H_2O$ is the percentage water of skin tissue to an effective depth of between 2.0-2.5 mm at the site of force measurements. TDC is tissue dielectric constant (dimensionless), TSK is skin temperature, and girth is the circumference of the arm at the site of arm force measurements (not measured for breast patients). All measured parameters are significantly greater on affected sides. * $p < 0.01$, ** $P < 0.001$ compared to breast value.

water to accommodate varying patient sensitivities to cold water. This process was repeated 3-4 times until a drop in skin temperature of 7-9 °C was achieved. At the end of the cooling interval all measurements except girth were repeated. The patient was asked to palpate the cooled area with her own hand prior to and post cooling to note any changes in tissue firmness. Following post-cooling measurements, the patient received treatment consisting of physical therapy and lymphatic drainage per individual patient care plan. After treatment, the post-treatment measurements were made.

RESULTS

Baseline Comparisons (Pre-Cooling)

As summarized in *Table 1*, baseline indentation forces ($F_{4.0}$ and $F_{1.3}$), TDC and skin water percentages were each significantly greater on affected arms and breasts as compared to contralateral (control) sides. Lymphedematous arm girths were also significantly greater but skin temperatures did not differ between affected and control sides for either arms or breasts. Combined average skin temperature of breasts (33.7 ± 0.9 °C) was about 1 °C greater than for arms (32.4 ± 1.3 °C, $p<0.01$). Comparisons between arms vs. breasts showed that for control sides, except for skin temperatures, all other measured parameters were significantly different on arms vs. breasts. Notably, arms had a significantly greater $F_{4.0}$ indentation force ($p<0.01$) and significantly lower values for TDC and $\%H_2O$ ($p<0.001$). In contrast, affected side arms did not significantly differ from affected side breasts in any measured parameter.

Arm Skin Cooling and Treatment Effects

Fig. 2 shows the arm indentation force and skin tissue water pattern of changes due to skin cooling and treatment. Arm cooling caused a reduction in skin temperature from a pre-cooling level of 32.4 ± 1.4 °C to a post-cooling level of 23.7 ± 2.0 °C. This temperature drop caused a significant decrease in $F_{4.0}$ from a pre-cooling level of 3.92 ± 1.0 N to a post-cooling level of 3.00 ± 1.04 N, $p<0.0001$. A small further decrease to 2.55 ± 0.84 N was measured after treatment. A similar but less dramatic pattern was observed for the cooling

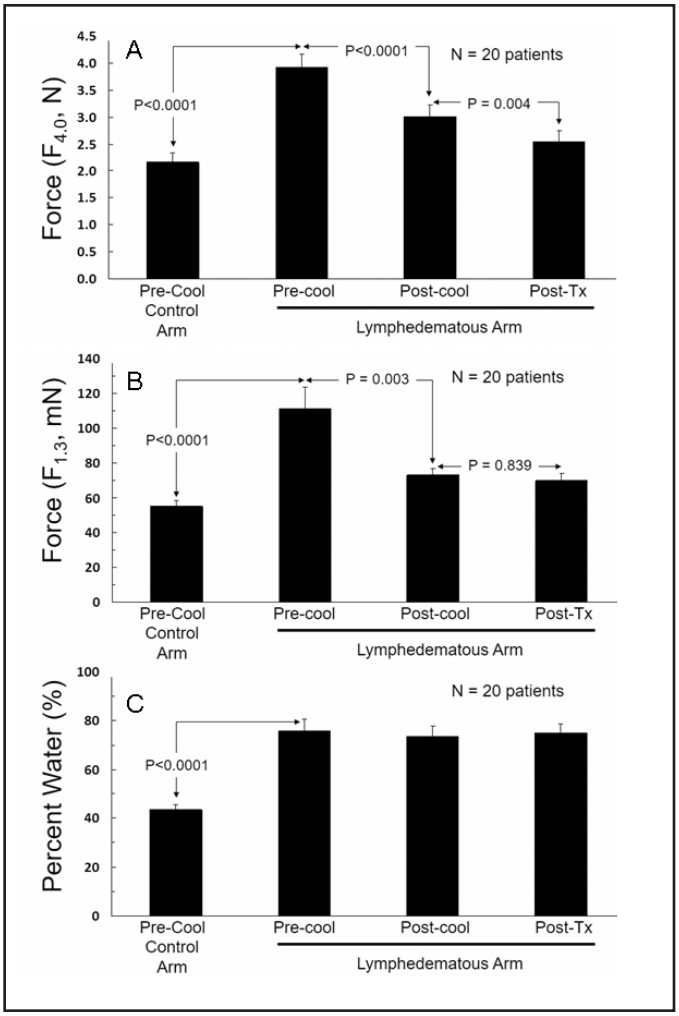

Fig. 2. Cooling Effects on Lymphedematous Arms. Data show effects on indentation forces to A) 4.0 mm ($F_{4.0}$) and B) 1.3 mm ($F_{1.3}$) and C) skin percentage water associated with treatment of 20 arm patients with contralateral control arm as reference. Main observable effect is a significant reduction in indentation forces with small or no additional effects of treatment (Tx). Cooling showed essentially no effect on skin water percentage as assessed by TDC.

related decrease in $F_{1.3}$ with cooling causing a decrease from 111.6 ± 53.1 to 74.1 ± 17.1 mN, p=0.003. No further reduction was seen after treatment. Neither cooling nor treatment caused a change in skin water percent.

Breast Skin Cooling and Treatment Effects

Fig. 3 shows the breast indentation force and skin tissue water pattern of changes associated with skin cooling and then treatment that is similar to that seen in the arm. Cooling from a breast skin temperature of 33.8 ± 1.0 °C to 24.7 ± 1.6 °C caused a significant decrease in $F_{4.0}$ from 3.54 ± 0.72 N to 2.79 ± 0.81 N, p<0.001, with a small further decrease to 2.25 ± 0.52 N measured after treatment. As with the arm pattern a similar but less dramatic pattern was observed for the cooling-related decrease in $F_{1.3}$. Cooling caused $F_{1.3}$ to decrease from 92.7 ± 40.7 to 76.0 ± 21.0 mN, p=0.008 but treatment did

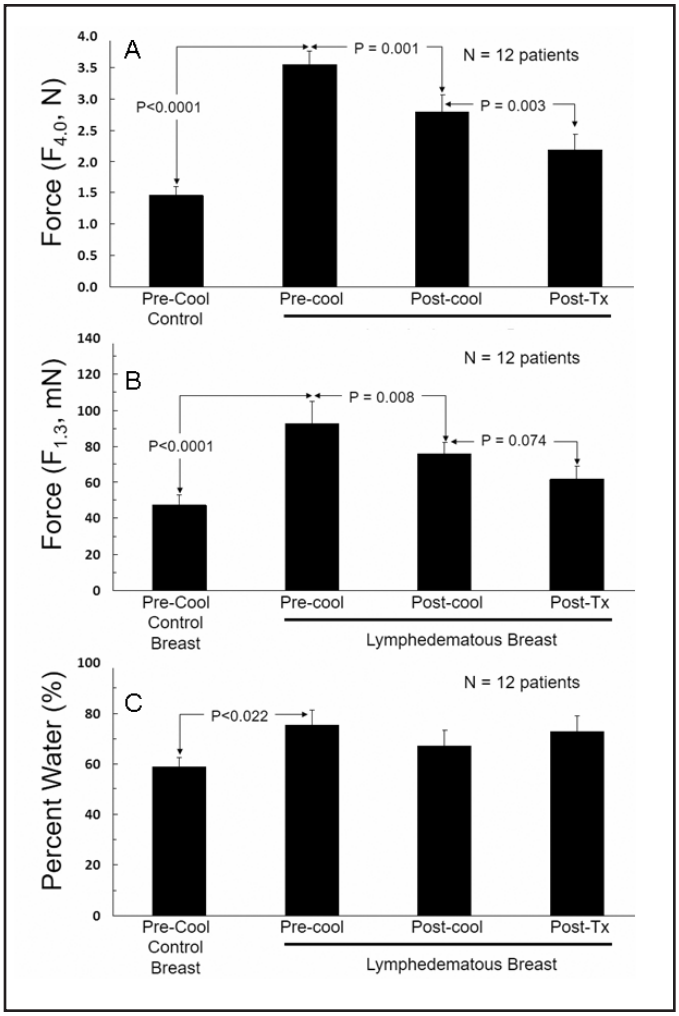

Fig. 3. Cooling Effects on Lymphedematous Breasts. Data show effects on indentation forces to A) 4.0 mm ($F_{4.0}$) and B) 1.3 mm ($F_{1.3}$) and C) skin percentage water associated with treatment of 12 breast patients with the contralateral control breast as reference. Main observable effect is a significant reduction in indentation forces with small or no additional effects of treatment. Cooling showed essentially no effect on skin water percentage as assessed by TDC.

not further significantly reduce this value. As for the case of arm cooling, neither breast cooling nor treatment was associated with significant skin water changes.

Skin Wetting Effects

Effects of wetting the skin prior to cooling was evaluated in 10 patients to assess the possible tissue indentation effects of simple wetting. The procedure used was similar to that used for cooling except the water used to soak the washcloths was first heated to between 35-37 °C. This was done on 5 arm and 5 breast patients during a subsequent therapy visit, and these data are separate from that included in the main study. The results, summarized in *Fig. 4*, show no significant effect of skin wetting per se on $F_{4.0}$ but significant reduction subsequent to cooling.

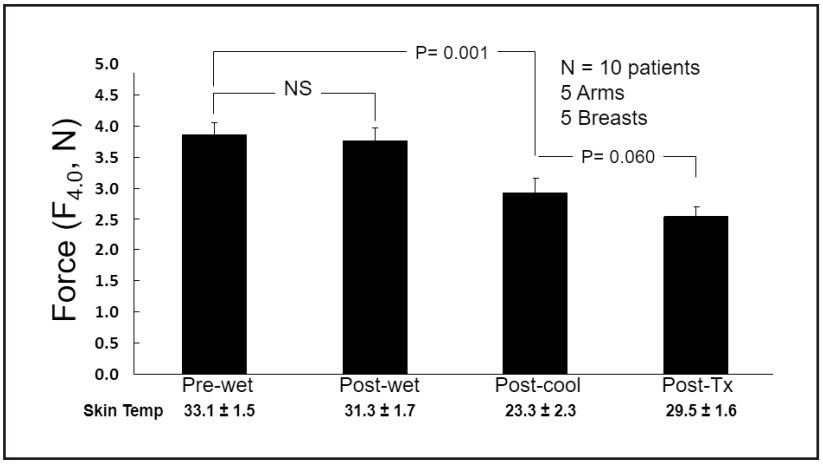

Fig. 4. Skin Wetting Effects. Data show effects on indentation force to 4.0 mm ($F_{4.0}$) associated with skin wetting in 5 arm and 5 breast patients. Skin temperatures shown are those measured at the end of the wetting, cooling, and treatment intervals. Main observable effect is a non-significant (NS) change in $F_{4.0}$ due to simple wetting but a significant reduction due to cooling.

DISCUSSION

The major result of the present study was the finding that topical surface cooling of lymphedematous and fibrotic regions led to a reduction in tissue hardness as judged by reduced local indentation forces. In discussing this finding there are two major considerations: 1) what explains the hardness reduction and 2) what is its clinical significance. Trying to isolate the specific cooling-related mechanism is made difficult due to the range of effects associated with tissue cooling that include hemodynamic, neuromuscular, and metabolic.

Possible Cooling-Related Tissue Hardness Reduction Processes

The main hemodynamic affect is a blood flow reduction attributable to cold-induced vasoconstriction (3) and to a lesser degree to increased blood viscosity (29). Such pre-capillary vasoconstriction tends to reduce fluid transport from capillary to interstitium and also promotes post-capillary fluid reabsorption due to an associated decrease in venous intravascular pressure. This cooling-related reduction in tissue water could potentially account for the measured reduction in indentation resistance. However, this possibility could not be confirmed since TDC measurements did not show a significant cooling-related reduction in skin water percentage. However, since the TDC effective measurement depth of the compact device used in this study was between 2 to 2.5 mm, it is possible that undetected reductions in water content below this depth occurred and contributed to the net tissue softening. It is noteworthy that treatment following the cooling phase also did not significantly reduce tissue water percentages. In contrast, prior work has shown a treatment-related reduction when only MLD was used in lymphedematous but non-fibrotic limbs (30). The absence of a significant treatment-related reduction in the present study may be due to a combination of tissue fibrosis presence in all cases and to the lesser reliance on strictly MLD as a treatment modality.

Another possible mechanism whereby tissue hardness may have been reduced is via a direct cooling effect on skeletal muscle contractile state. Such changes have been reported to occur (31) although others have

indicated no change in muscle contractile properties associated with cooling (32). It is also possible that there was an indirect skeletal muscle relaxation mediated by a rapid pain-reducing effect of cooling (33-35). However, if either of these were operative mechanisms, it would apply only to arms since breast tissue is essentially devoid of functional skeletal muscle. Since the cooling-related findings for arm and breast were very similar, a major role for cooling-induced skeletal muscle relaxation accounting for the present findings is in our opinion unlikely.

Average cooling-induced temperatures achieved on the arm (23.7 °C) and breast (24.7 °C) would have caused altered sensory nerve activity via effects mediated by transient receptor potential (TRP) channels located in the sensory nerve endings (36). Cooling to temperatures of 30 °C to 15 °C, as with the present case, cause specific voltage-gated TRP channels (TRPM8) to open in relation to the amount of the temperature decrease causing increased inward calcium current. This causes an increase in the tonic firing rate of cold-sensitive A afferent nerve fibers (37). Although the altered nerve firing rate is mainly providing sensory feedback, the possibility that there could be a mechanical effect on tissue via other potential pathways cannot be fully excluded although no specific mechanisms have been uncovered to support this connection.

Clinical Relevance of Cooling-Related Tissue Hardness Reduction

Topical skin cooling is commonly used to treat swelling post trauma, but has not found a place in the management of lymphedema. A possible reason for this is that breast tissue is sensitive to extreme temperature and damage to microvascular vessels would be contraindicated. In fact, persons with lymphedema are commonly instructed to avoid extremes of temperature. However, application of cooling where due care has been taken to not cause discomfort or microvascular damage has not been previously studied.

When tissue is softened by local cooling as has been observed in the present study, there are a number of positive benefits that accrue to both patient and therapist or treating clinician. The tissue becomes more pliable and the clinician can facilitate deeper levels of myofascial lengthening and scar tissue releasing that result in the release of restricted lymphatic structures and improved lymphatic flow. The cooling-related tissue softening that occurs during the session also provides a setting in which the clinician can more effectively utilize therapy time for fibrosis management and for other therapeutic activities. Further because of the rapid cooling-related tissue softening, pressure on sensory nerve endings is likely partly or fully relieved. This manifests itself as a rapid reduction in pain in those patients presenting with fibrosis-related nerve compression pain. Such pain reduction is achieved without the use of pharmaceuticals and had an immediate positive reaction from those patients so treated. In addition, the tissue softening likely reduces pressure on muscles and muscle spindles in those areas in which the fibrosis is impacting muscle. This serves to help normalize sensory nerve communicated muscle-length feedback to the central nervous system that in turn helps with the stretching therapy during the treatment session. Perhaps equally important to the various physical and physiological effects is the psychological impact of rapid tissue softening and the associated decrease in pain that improves the patient's outlook for recovery.

Tissue softening by means of topical skin cooling holds potential as a cost effective and accessible treatment option for management of patients with lymphedema worldwide. Topical skin cooling can easily be carried over in the home and gives patients more independence in managing symptoms. The suitability of cooling and its optimal treatment parameters as a standard component to lymphedema therapy and self-management

needs to be prospectively determined by further research.

SUMMARY AND CONCLUSION

Results show that arm skin cooling softens lymphedematous and fibrotic tissue by about 24% to 28% depending on indentation depth. This appears to occur without a significant change in skin fluid content at least to a depth of about 2.5 mm. Although the precise mechanism linking cooling to softening is as yet not fully understood, the fact that tissue is softened carries with it many potential benefits to patient and therapist. The near immediate tissue softening is associated with less pressure on underlying nerve endings and less input to sensory nerves thereby interrupting the pain cycle resulting in rapid pain relief. The rapidly softened tissue and decreased perception of pain offers the patient hope and encouragement in their therapeutic journey to reclaiming functional use of their affected body. Further, because softer tissue becomes more pliable, myofascial lengthening, scar tissue releasing and other aspects of treatment are easier for the therapist to perform, thereby reducing treatment time and effort while achieving improved functional mobility.

CONFLICT OF INTEREST AND DISCLOSURE

All authors declare that no competing financial interests exist.

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