Published in final edited form as:

Knee Surg Sports Traumatol Arthrosc. 2015 September ; 23(9): 2475–2483. doi:10.1007/s00167-014-2911-y.

Cold-induced vasoconstriction may persist long after cooling ends: an evaluation of multiple cryotherapy units

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Abstract

Purpose—Localized cooling is widely used in treating soft tissue injuries by modulating swelling, pain, and inflammation. One of the primary outcomes of localized cooling is vasoconstriction within the underlying skin. It is thought that in some instances, cryotherapy may be causative of tissue necrosis and neuropathy via cold-induced ischaemia leading to nonfreezing cold injury (NFCI). The purpose of this study is to quantify the magnitude and persistence of vasoconstriction associated with cryotherapy.

Methods—Data are presented from testing with four different FDA approved cryotherapy devices. Blood perfusion and skin temperature were measured at multiple anatomical sites during baseline, active cooling, and passive rewarming periods.

Results—Local cutaneous blood perfusion was depressed in response to cooling the skin surface with all devices, including the DonJoy (DJO, $p = 2.6 \times 10^{-8}$), Polar Care 300 (PC300, $p = 1.1 \times 10^{-3}$), Polar Care 500 Lite (PC500L, $p = 0.010$), and DeRoyal T505 (DR505, $p = 0.016$). During the rewarming period, parasitic heat gain from the underlying tissues and the environment resulted in increased temperatures of the skin and pad for all devices, but blood perfusion did not change significantly, DJO (n.s.), PC300 (n.s.), PC500L (n.s.), and DR505 (n.s.).

Conclusions—The results demonstrate that cryotherapy can create a deep state of vasoconstriction in the local area of treatment. In the absence of independent stimulation, the condition of reduced blood flow persists long after cooling is stopped and local temperatures have warmed towards the normal range, indicating that the maintenance of vasoconstriction is not directly dependent on the continuing existence of a cold state. The depressed blood flow may dispose tissue to NFCI.

Keywords

Cryotherapy; Vasoconstriction; Tissue blood perfusion; Tissue cooling; Nonfreezing cold injury

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Conflict of interest A patent application has been submitted by Dr. Khoshnevis and Dr. Diller to the United States Patent and Trademark Office under the title *Improved Cryotherapy Devices and Methods to Limit Ischaemic Injury Side Effects*. Ownership rights to this patent reside with The University of Texas System. Dr. Diller has served as an expert witness for both plaintiff and defendant counsel since 2000 in numerous legal cases regarding the safety and design of existing cryotherapy devices.

Introduction

This paper presents new and novel data for the magnitude and duration of local blood flow depression in conjunction with the application of common cryotherapy devices. Localized cooling is used with benefit following orthopaedic surgery and in sports medicine to reduce swelling, pain, inflammation, metabolism, muscle spasm, and bleeding [6, 37]. The practice of cold therapy for soft tissue injury has been widely documented in the literature [1, 23, 26]. Nonetheless, there remains to the present time controversy over the appropriate protocols for application of cryotherapy devices and the risk factors associated with their use [28]. Some practitioners advocate continuous application of cryotherapy to a treatment site with no break in cooling for days or even weeks [4, 10, 38, 39], whereas others recommend alternating cycles of short-term active cooling followed by passive rewarming, with cooling periods limited to 10–30 min [7, 27, 30]. Although therapeutic cooling is tolerated by most patients, there are incidences in which application of a cryotherapy device may lead directly to functional impairment or even to tissue necrosis and/or nerve injury in the treatment area, sometimes with dire medical consequences [5, 8, 27].

There are many alternative schemes for effecting cold therapy to soft tissue, such as crushed ice [3], ice bags [7], cold gel packs [2], and, in particular, cryotherapy units (CTU) that can provide a continuous or intermittent circulation of ice water from an insulated container to a pliable cooling pad placed onto the treatment area [3, 8, 24, 29, 39, 43, 44]. Local cooling is sometimes combined with complementary therapeutic modalities such as transient tissue compression [24, 25]. Powered CTUs that feature the capability for continuous circulation of cold water have facilitated the ability to sustain extended periods of cold therapy measured in hours and days.

A primary consequence of the prolonged local cooling of tissue is induction of vasoconstriction [19, 22, 31, 33] which may lead to ischaemia. Extended exposure to cold-induced vasoconstriction may cause injuries that typically fall within the domain termed nonfreezing cold injury (NFCI) [16–18, 20, 40]. In addition, a prolonged state of vasoconstriction can lead to the occurrence of reperfusion injury when blood flow is reestablished to the affected tissue [21].

The aim of this study was to measure the extent of vasoconstriction produced by various CTUs and its persistence following the termination of active cooling. Data are presented to document that assorted makes and models of CTUs produce deep depression of skin blood flow during active cooling which continues during subsequent passive parasitic rewarming of tissue. Some implications of this phenomenon on the use of cryotherapy are discussed.

The *hypothesis* of this study is that the vasoconstriction caused by local cooling of skin may persist during subsequent passive rewarming of tissue.

Materials and methods

Experiments were conducted on FDA approved, commercially available cryotherapy devices, namely: BREG Polar Care 300 (PC300; BREG, Carlsbad, CA), BREG Polar Care 500 Lite (PC500L; BREG, Carlsbad, CA), DeRoyal T505 (DR505; DeRoyal Industries,

Powell, TN), and DonJoy Ice man 1100 (DJO; DonJoy Global, Vista, CA). Similar tests were conducted on other CTUs issuing in consistent results, although not in statistically significant numbers to warrant reporting herein: BREG Polar Care 500 (BREG, Carlsbad, CA), DeRoyal T600 (DeRoyal Industries, Powell, TN), Game Ready (Game Ready, Concord, CA), Artic Ice System (Pain Management Technologies, Akron, OH), Aircast Cryo/Cuff (DonJoy Global, Vista, CA), EBice Controlled Cold Therapy 10D (EBI, LLC., Parsippany, NJ), Bledsoe bMini (BledsoeBrace Systems, Grand Prairie, TX), Bledsoe bPro (BledsoeBrace Systems, Grand Prairie, TX), and Bledsoe Cold Control (Bledsoe-Brace Systems, Grand Prairie, TX).

The CTUs tested in this study were available only on a temporary basis that we did not control and that therefore dictated the scheduling of specific trials. Subjects were assigned to trials as a function of the CTU time-wise availabilities. Accordingly, the study was conducted in three sequential phases. In the first phase, three subjects each underwent three single trials using three different CTUs (DJO, PC300, and PC500L). The resulting data were subjected to repeated measure analysis using the Friedman test. Nine subjects were recruited for the second phase and randomly assigned to a single trial on one of three different CTUs (DJO, PC300, and DR505) so that each CTU was tested three times. The data were assessed via independent study analysis using the Kruskal–Wallis test. For the third phase, seven subjects were assigned to a single trial with a DJO CTU and a test site at either the knee or the foot/ankle. The data from these experiments were analysed using the independent *t* test. Some subjects participated in multiple phases of the study. No more than one trial was conducted per week on any given subject. Individual subjects were included in various specific trials as a function of their shared time-wise availability with the various CTUs to be tested, in combination with the need for distribution of the subjects among different trials to satisfy the requirements for statistical analysis of data.

Subjects were recruited from the University of Texas at Austin faculty and student body and were screened for contraindications of cryotherapy described by Rheinecker [35] and Lee et al. [27], including use of vasoactive medications, pregnancy, or a fresh wound at the site of cooling. The demographic data and assignment of protocols are presented in Table 1.

The basic research protocol consisted of applying CTUs to human subjects and measuring changes in the skin temperature and blood perfusion in a targeted treatment area before, during, and following a period of active cooling. The protocols were designed and implemented to mimic typical prescribed uses of the devices.

Instrumentation

The data presented in this paper were collected using MoorVMS-LDF2 laser Doppler blood perfusion and temperature probes (Moor Instruments, Millwey, Axminster, Devon, UK) with a flux accuracy of 10 % of magnitude for perfusion and an accuracy of ± 0.3 °C for temperature, based on manufacturers' specifications [45]. The Moor probes measure perfusion within the superficial 0.5 mm of tissue [32]. Thin ribbon or small bead thermocouples (Omega Engineering, Stamford, CT) were used to monitor temperature (± 0.1 °C) at multiple sites. Each sensor was mounted directly onto the skin beneath the site of the cooling pad. Blood pressure was monitored intermittently with a sphygmomanometer, and

the values were applied to calculate cutaneous vascular conductance (CVC) to represent skin perfusion [9].

National Instruments (NI) input modules 9201, 9205, 9211, and 9213 (National Instruments, Austin, TX) were used to acquire blood perfusion and temperature data from the sensors, and NI DAQ 9172 and 9174 were used as a computer interface. Data were collected with a sampling rate of 12 Hz. Temperature data were subsequently down sampled to 4 Hz, a rate that prevented aliasing.

Figure 1 shows sequential stages of the subject preparation, including placement of sensors, application of an ACE wrap as a thermal barrier, and positioning of the cooling pad. Additional thermocouples measured temperature on the cooling pad surface, ice water bath, and room air. In some instances, temperatures of the ice water flowing at the pad inlet and outlet were monitored with inline thermocouples.

Experimental protocol

Each experiment was composed of three instrumented sequential segments: (1) baseline, (2) active CTU cooling, and (3) passive rewarming with the CTU pump off. Subjects were in a semi-recumbent position during the experiments and were asked to minimize physical movements of the test site to avoid creating motion artefacts in the laser Doppler perfusion data. All experiments were performed at a fixed room temperature (22 ± 0.5 °C) and humidity (50 % r.h.) environment. At least 1 h was provided to acclimate to ambient conditions while being instrumented. A blanket was applied at subject request to prevent global vasoconstriction from ambient air exposure.

Data extraction

Data were grouped into 5 min segments beginning with the start of the rewarming period. Perfusion data were represented by the median value for the associated time segment. The baseline value was calculated over the last 5 min of that period. All perfusion values were normalized to the baseline. When data were available, the perfusion measurements at multiple different locations were averaged.

Extraction of data was performed by a single researcher who is not an author using a MATLAB (MATLAB7.10, The MathWorks Inc., Natick, MA) program that automatically isolated all necessary data, with the exception of manually marking the start and end points of the cooling period. To independently verify the integrity and accuracy of this process, extraction from the same data sets was repeated by two additional researchers within the laboratory, one of whom is not an author, and intraclass correlation (ICC) was used to compare their findings using Statistical Package for Social Science (SPSS, IBM SPSS version 20.0 for Windows; IBM Corp, Armonk, NY) software.

This study and all related protocols were approved by the University of Texas Institutional Review Board (IRB UT #2011-05-0106).

Statistical analysis

A major challenge for statistical analysis was the small sample size ($n = 3$) of the data. Among various available tests for normality, the Shapiro–Wilk [36] is the most suitable for small samples. However, it carries a very low power for small n , such as $p < 20\%$ for $n = 10$ [34]. The same limitation is true for the Kolmogorov–Smirnov, Lilliefors and Anderson–Darling tests. Therefore, for data analysis, we chose to use nonparametric tests which do not require the assumption of normality. Nonparametric tests, such as Friedman and Kruskal–Wallis, were used whenever possible. Since there is no accepted nonparametric equivalent for a t test, it was used as needed.

The DonJoy cryotherapy experiments consisted of four to the foot and ankle, three to the knee, and one to the shoulder. The minimum perfusions achieved during cooling were compared between the foot/ankle and knee experiments through unpaired t tests (Matlab) to evaluate the effect of these anatomical locations on the vascular response to cold exposure.

Friedman and Kruskal–Wallis tests were performed to evaluate minimum perfusion values for all devices on the knee to determine whether significant differences existed. Pairwise comparison using paired t tests was also performed between the perfusion values for adjacent time points to evaluate transient changes in blood flow.

One-sample t tests were used to quantify the significance of changes in perfusion during cooling relative to baseline. G*Power version 3.1 was used to calculate sample size for a significance of 0.05 and power of 0.95 [12, 13], which was $n = 3$.

Dunnett’s test was applied in SPSS to evaluate the extent of perfusion change during rewarming. Values from the first 5 min of rewarming for each trial were compared to those at subsequent times in a case–control fashion. This same analysis was also performed to evaluate changes in temperature during rewarming.

Plots of standard error were used to determine the degree of overlap among perfusion values during the rewarming period, and a linear mixed-model regression analysis was applied to evaluate the general trends. This type of analysis was used since the data included measurements involving different rewarming durations for subjects. Unlike general linearized regression analysis, linear mixed-model regression does not stipulate independence and allows for missing data at later time points. Time was assigned to be a fixed effect in this analysis to determine whether a perfusion trend occurred. Time was assigned to be a random effect to check for nonindependence.

Results

Cooling pad and skin surface temperatures and skin blood flow data for an exemplar protocol are shown in Fig. 2 to illustrate the temporal characteristics of the data. Notice how the perfusion falls with decreasing temperature but does not follow the subsequent trend of increasing temperature.

Effect of anatomical location

An independent t test performed between the DJO data for the knee ($n = 3$), and foot/ankle ($n = 4$) revealed no significant difference in the extent of vasoconstriction between these locations (n.s.).

Comparison among CTU devices

Both dependent and independent statistical analyses were applied to analyse the degree of vasoconstriction induced by different CTU devices. A Friedman test was performed to compare the vasoconstriction in subjects ($n = 3$) who all used the DJO, PC300, and PC500L. A Kruskal–Wallis test was performed to compare the extent of vasoconstriction among independent groups ($n = 3$) who used the DJO, PC300, or DR505. No significant differences were found ($\alpha = 0.05$, n.s.). Table 2 presents a summary of statistics comparing the various CTU and anatomical combinations.

Effect of cooling on depression of blood perfusion

One-sample t tests confirmed that a significant difference existed between baseline and minimum perfusion values caused by cooling (Table 3).

Transient gradients in perfusion during rewarming

Pairwise comparison for all devices between perfusion at adjacent 5-min periods during rewarming showed that no significant differences ($\alpha = 0.05$) except for single points on DJO for 5 and 10 min ($p = 0.033$) and PC300 for 10 and 15 min ($p = 0.045$).

Persistence of vasoconstriction during rewarming

A case–control study for all devices used Dunnett’s test to compare current and subsequent perfusion values and showed that there was no significant increase in blood perfusion during the observed rewarming period for any of the cryotherapy devices. The mean and standard deviation of perfusion were calculated for the PC300 and DJO data over each 5-min rewarming interval showing that there was no net accrued increase in perfusion. Figure 3a, b, respectively, shows the aggregate calculated PC300 and DJO data that document the absence of change in perfusion during rewarming.

Mixed-model linear regression analysis was performed on this rewarming data to derive the regression equations presented in Table 4.

Increase in temperature during rewarming

A case–control analysis via Dunnett’s test compared the temperature at the start of rewarming and subsequently. It showed a significant increase after 15 and 30 min for DJO and PC300, respectively. Although temperature showed an increasing trend for both DR505 (5.5 °C in 20 min) and PC500Lite (3.5 °C in 15 min), the increase was not significant by this measure. The results are in Table 5.

Data extraction reliability

A single rater (who is not an author) performed the extraction for all data reported herein. This work was verified via partial replication by two other raters (one not an author) and compared by ICC analysis. The ICC values were 0.97 for the minimum perfusion data, 0.97 at 5 min, and 0.99 at 30 min later. Fleiss ranks ICC values over 0.75 as excellent [15]. Flack et al. and Walter et al. associate our ICC values and number of trials with a power of at least 0.98 [14, 41, 42].

Discussion

The most important finding of the present study was that following the large drop in blood perfusion caused by surface cooling of soft tissue, in the absence of an imposed stimulation the perfusion will remain depressed for an extended time even while the tissue temperature is returning towards baseline. To our knowledge, this phenomenon has not been identified in prior studies of the effects of cryotherapy.

No obvious anatomical differentials in the response to cryotherapy were detected. There would appear to be a common local vasomotive control mechanism. The vasoconstriction response to surface cooling appears to be ubiquitous. Thus, the site of cooling application is not considered as a distinguishing factor in this data set.

There was no significant difference in the extent of vasoconstriction induced by the different devices tested: DJO, PC300, PC500L, and DR505. These statistical results suggest that device type does not significantly affect the level of vasoconstriction induced by cryotherapy. The response to other ice water circulating CTUs that we have measured, but not reported herein, is fully consistent with these results.

Primary limiting factors in the present study are that blood perfusion and temperature measurements were performed only at singular locations, inherently missing the two-dimensional distributions of these properties across the entire treatment area. We have casually observed that anatomical structures such as the knee patella may influence both temperature and perfusion, but explicit data that document this effect remain to be acquired owing to limitations of our current instrumentation. We have made two-dimensional temperature measurements via IR thermography at a single time point that will be included in subsequent publications. Also, the blood perfusion probes have an approximately 1 cm vertical height, meaning that where they are positioned, the cooling pad is locally held away from the skin surface, resulting in a reduced cooling effect. The temperatures measured with the perfusion probe thermal sensor are approximately 2–3 °C warmer during cooling than sensed by thermocouples at peripheral sites directly below the pad. Thus, the dose–response effect of cryotherapy on blood flow is compromised. This phenomenon has been quantified and will be reported in a subsequent publication under preparation.

There are few published studies that have systematically analysed the microcirculatory modification effects of cryotherapy and still fewer that have been conducted on human subjects. One such human subject study concluded that cryotherapy results in a significant decrease in superficial (2 mm depth) and deep (8 mm depth) microcirculatory blood flow

during a 30-min cooling period [25], consistent with our findings. But, post-cooling perfusion measurements were not recorded.

Another study in rats showed that 20 min of cryotherapy caused a significant decrease in perfusion [11]. Contrary to our findings, the blood flow depression did not persist following the cessation of active cooling. However, this study measured perfusion in deeper skeletal muscular and only at relatively infrequent intervals.

The data from this study indicate that it is likely that a long acting humoral agent is released locally with a continuing vasoconstrictive effect that persists, while tissue temperatures rewarm towards the baseline values. We are pursuing further research to confirm, identify, and characterize the action of local vasoactive agents with the objective being able to better control cryotherapy-induced tissue ischaemia.

A focal message delivered by this study is that many commercially available cryotherapy devices have inherent operating conditions that produce a significant degree of vasoconstriction that may last long after cessation of active cooling. The experimental results show an uncoupling between skin perfusion and temperature during the passive rewarming period. The extent of vasoconstriction and its prolongation are sufficient to possibly lead to an equivalent ischaemic state and then to NFCl.

Conclusion

The results demonstrate that standard cryotherapy methods produce a significant and persistent state of vasoconstriction in the local area of treatment during both active cooling and subsequent passive rewarming. The data presented in this paper that extend the understanding of the response in blood perfusion to cryotherapy may be embodied in improved therapeutic schemes to reduce the risk of ischaemic injury.

Acknowledgments

This research was sponsored by National Science Foundation Grants CBET 0828131, CBET 096998, and CBET 1250659, National Institutes of Health Grant R01 EB015522, and the Robert and Prudie Leibrock Professorship in Engineering at the University of Texas at Austin. We would also like to thank Ms. Natalia Mejia for investing long hours of careful and conscientious work in her critical role in extracting data for this publication, and Dr. Michael Mahometa of the Division of Statistics and Scientific Computation, College of Natural Sciences at the University of Texas at Austin for his help and guidance in statistical analysis of data. Comments by the reviewers have been very helpful.

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Fig. 1.

a Placement of instrumentation consisting of thermocouples (*T*), heat flux gauge (*HFG*), and LDF2 probes (*P*) to the ventral aspect of the right knee. Heat flux data are not reported in this paper. **b** Same location after application of a single thermal insulation layer (ACE bandage wrap) with no elastic stretching. **c** After application of a PC300 cooling pad over the insulation layer

Fig. 2.

Data for a trial with a BREG Polar Care 300 cryotherapy unit applied to the knee, consisting of 30 min of baseline data, followed by 60 min of active cooling, and 84 min of passive rewarming. **a** Temperature histories measured at two locations on the skin surface under the cooling pad (red and green) and on the surface of the pad (blue). **b** Perfusion histories at the two sites in the skin under the cooling pad

Fig. 3. Mean and standard errors of perfusion values from the **a** PC300 and **b** DJO cryotherapy devices during 90 and 95 min of rewarming, respectively. The overlap among the *error bars* shows that there is no overall significant change in perfusion during rewarming

Table 1

Demographic data and experimental protocols by device type

Device type	DonJoy (DJO)	Polar Care 300 (PC300)	DeRoyal T505 (DR505)	Polar Care 500 Lite (PC500L)
Number of subjects	$n = 8$	$n = 4$	$n = 3$	$n = 3$
Subjects IDs	S1, S2, S3, S6, S7, S8, S9, S12	S1, S3, S4, S7	S3, S6, S11	S1, S3, S7
Site of cooling	Knee ($n = 3$), foot/ankle ($n = 4$), shoulder ($n = 1$)	Knee ($n = 4$)	Knee ($n = 3$)	Knee ($n = 3$)
Cooling duration (min)	55.3 ± 8.4	59.4 ± 3.0	92.8 ± 24.1	61.0 ± 1.2
Gender	F (3) M (5)	F (2) M (2)	F (2) M (1)	F (2) M (1)
Age (years)	33.0 ± 17.4	38.8 ± 21.6	36.0 ± 14.0	44.3 ± 22.6
BMI (kg/m^2)	22.7 ± 3.3	22.8 ± 4.7	20.8 ± 3.0	22.5 ± 5.7

Table 2

Statistical tests used to analyse data for each experimental set

Phase	Device 1	Device 2	Device 3	Test type	p value	Body part	Subject assignment
1	DJO	PC300	PC500L	Friedman	n.s.	Knee	S1, S3, S7
2	DJO	PC300	DR505	Kruskal–Wallis	n.s.	Knee	S2, S6, S8 S1, S3, S4, S7 S3, S6, S11
3	DJO	DJO	N/A	Independent t test	n.s.	Knee Foot/ankle	S3, S7, S9 S1, S2, S8, S12

Subject assignments are indicated by common alignment with the device identifier

Table 3

One-sample *t* test values for the significance of the drop in perfusion in response to localized cooling

CTU	<i>p</i> value	<i>n</i>
DJO	2.6×10^{-8}	8
PC300	0.0011	4
PC500L	0.01	3
DR505	0.016	3

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Table 4

Linear regression equations for perfusion as a function of time during passive rewarming

CTU	Regression equation	<i>p</i> value	Duration (min)
DJO	$y = 0.00017x + 37$	n.s.	95
PC300	$y = -0.024x + 50$	n.s.	90
DR505	$y = -0.036x + 44$	n.s.	20
PC500L	$y = -2.6x + 98$	n.s.	15
PC500L	$y = -0.20x + 52$	n.s.	120

Table 5

The persistence of vasoconstriction and reduced temperature during rewarming period based on a case-control study using Dunnett's test

CTU	Metric	5	10	15	20	25	30	35	40	45	50	55	60	65	70	75	80	85	90	95
DIO	Perfusion																			
	Temperature																			
PC300	Perfusion																			
	Temperature																			
DR505	Perfusion																			
	Temperature																			
PC500L	Perfusion																			
	Temperature																			

The metric numbers define the time in minutes from the start of rewarming period. The shaded areas show the region where no significant increase in either skin perfusion or temperature occurred. For PC300, DR505, and PC500L, rewarming data were measured for only 90, 20, and 15 min, respectively