An On-Site Thermoelectric Cooling Device for Cryotherapy and Control of Skin Blood Flow

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Cryotherapy involves the surface application of low temperatures to enhance the healing of soft tissue injuries. Typical devices embody a remote source of chilled water that is pumped through a circulation bladder placed on the treatment site. In contrast, the present device uses thermoelectric refrigeration modules to bring the cooling source directly to the tissue to be treated, thereby achieving significant improvements in control of therapeutic temperature while having a reduced size and weight. A prototype system was applied to test an oscillating cooling and heating

protocol for efficacy in regulating skin blood perfusion in the treatment area. Data on 12 human subjects indicate that thermoelectric coolers (TECs) delivered significant and sustainable changes in perfusion for both heating (increase by ($\pm SE$) $173.0 \pm 66.0\%$, $P < 0.005$) and cooling (decrease by ($\pm SE$) $57.7 \pm 4.2\%$, $P < 0.0005$), thus supporting the feasibility of a TEC-based device for cryotherapy with local temperature regulation. [DOI: 10.1115/1.4029508]

Keywords: cryotherapy, in situ cooling, oscillating cooling and heating, skin blood perfusion, thermoelectric cooling (TEC) module

Introduction

Cryotherapy has been practiced for millennia to enhance the healing of soft tissue injuries. Traditionally, tissue may be cooled via the topical application of ice [1,2], a gel pack [3], or a flexible container of small frozen particles (such as peas) [4], resulting in therapeutic episodes that are self-limited in time by the mass of the cold source and its melting/warming properties. More recently, cryotherapy devices have been widely adopted that consist of an insulated container with an immersion pump that is filled with melting ice. The remote container is connected via two lengths of insulated tubing to form a recirculating flow pathway for pumped ice water to a flexible bladder placed at the treatment site [1–3]. Cooling of the tissue can be maintained so long as the supply of ice in the container is replenished, extending the low temperature treatment for hours, days, and even weeks. These systems tend to be large, heavy, inconvenient to ambulate, and challenging to regulate the temperature applied to the tissue.

Cryotherapy is thought to have multiple mechanisms of action that contribute to its therapeutic benefit, including a slowing of the inflammatory process [5], reduced nerve conduction velocity [6,7] resulting in diminished pain [1], and induction of vasoconstriction leading to less swelling [8]. Local tissue temperatures produced by the application of a cryotherapy device are on the order of 15°C , although there can be a considerable variation under a single cryotherapy bladder [9]. Also, there is a considerable variation in the thermal performance among different cryotherapy devices [10,11]. An outcome of the an extended period of low temperature exposure in tissue may include development of a hypoxic state that can be enhanced owing to the depressed oxyhemoglobin dissociation [12] and increased blood viscosity and red cell rigidity [13] impeding the flow of blood through the nutritive microvasculature. The depression of tissue perfusion at low temperatures for the extended periods of time that can be maintained by cryotherapy units may produce a state of oxygen and nutrient deprivation as well as a local accrual of toxic metabolic byproducts, all of which may contribute to the development of nonfreezing cold injury that can manifest as neuropathy and tissue necrosis [14–18]. Since skin blood perfusion tends to be intimately linked to the local tissue temperature [19,20], the regulation of applied cryotherapy temperature both spatially and temporally may be a critical factor in deriving the desired benefits of a treatment while managing the risks of collateral tissue injury.

The present device uses TEC modules to bring the refrigeration source directly to the tissue to be treated, thereby achieving significant improvements in control of the applied therapeutic temperature while having a reduced size and weight advantage and obviating the need for a circulating heat transfer liquid in communication with a remote refrigeration source.

TECs function via the Peltier effect in which a voltage differential applied across the device generates an orthogonal temperature gradient [21]. As with all refrigeration devices, a TEC requires an energy input plus rejection of heat at a relatively high temperature to the environment in order to generate a heat flow from a relatively lower temperature system as a refrigeration effect. The energy input occurs as an electrical current flowing through the device under the action of a control voltage. The efficiency by which heat can be removed at a high temperature to the

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Manuscript received July 20, 2014; final manuscript received December 23, 2014; published online August 6, 2015. Assoc. Editor: Rupak K. Banerjee.

environment is a major factor determining the magnitude of refrigeration load that the TEC can produce.

Putra et al. utilize a cascade of TECs to generate temperatures as low as -93°C on the cold side for the purpose of thermal ablation of cancer cells [22]. Onsite application of TECs (set at 20°C) is shown beneficial in the treatment of epilepsy [23]. In the current study, onsite application of TECs was proposed to manage soft tissue injury through alternating between high and low temperatures.

The goal of this study was to design and verify the operation of a TEC device able to produce and hold stable skin temperatures resulting in a significant drop in skin blood perfusion while limiting the temperature on the hot side to no higher than a “safe touch” value (43°C) [24,25]. We hypothesize that TECs can be used to manipulate blood perfusion downward and upward from baseline values via managed excursions within this temperature range.

Materials and Methods

Experiments were performed on 12 (seven males) healthy, non-smokers with no contraindications for cryotherapy. Each subject participated in a single trial. The average age ($\pm\text{SD}$) was 19.0 ± 1.4 yr, and body mass index was 21.9 ± 3.7 ($\pm\text{SD}$). Subjects were required to refrain from the consumption of caffeine 12 hr prior to their testing. Informed consent was obtained from each subject prior to performing an experiment. This study and all related protocols were approved by the University of Texas Institutional Review Board (IRB UT #2012-07-00086).

The TEC-based cryotherapy prototype device consisted of a polyurethane sleeve onto which were mounted two $3\text{ cm} \times 3\text{ cm}$ bismuth telluride TECs (Gentherm, 21680 Haggerty Road, Northville, MI) through matching openings so that the TECs were flush with the skin. The nominal electrical resistance of the TECs was $6\ \Omega$. The sleeve maintained the TEC modules in good thermal contact with the skin surface on the anterior right thigh 5 cm above the knee. A layer of Panasonic flexible pyrolytic graphite sheet (Panasonic Electronic Components, Secaucus, NJ) having a high thermal conductivity was placed between the TEC modules and the skin to enhance the lateral distribution of heat flow to produce a more homogeneous temperature field. A forced air convection system was mounted proximal to the sleeve to dissipate waste heat conducted from the module hot side to finned aluminum heat sinks (CTS Electronic Components, Albuquerque, NM). The forced convection system was driven by a brushless delta blower fan (Delta Electronics, Inc., Alexandria, VA). Cooling airflow was directed across the heat sinks parallel to the fins by low profile shrouds. The TEC modules were powered by a DC source (HY1803D; Mastech Linear Power Supply, San Jose, CA). Figure 1 shows the physical configuration of the TEC modules mounted on the sleeve as positioned on a thigh (a) and with the blower shroud configuration (b).

Instrumentation consisted of two laser Doppler blood perfusion probes (moorVMS-LDF2; Moor Instruments, Millwey, Axminster, Devon, UK) offering a flux accuracy of 10% and an accuracy of $\pm 0.3^{\circ}\text{C}$ for temperature as specified by the manufacturers [26], multiple T-type 1 mm spherical bead thermocouples (Omega Engineering, Stamford, CN), LABVIEW signal express software (National Instruments, Austin, TX), and a National Instrument (NI) 9205 input module and a cDAQ 9174 data acquisition interface (National Instruments, Austin, TX). LABVIEW signal express software was used for real time data collection. Perfusion and temperature data were collected with a sampling rate of 12 Hz. The perfusion probes incorporated a thermistor on the detector surface so that temperature was recorded at the site of perfusion measurement. One perfusion probe was placed between the TECs on the right thigh, and the second probe was in the symmetric position on the left thigh as a control site. Thermocouples were positioned at locations to monitor temperatures on the skin and on cold and hot surfaces of the thermoelectric modules. Skin blood perfusion was measured at the midpoint between the two TECs. The applied temperature beneath the TECs will be lower/higher than peripherally during the active cooling/warming periods,

Fig. 1 Photos of a twin TEC cooling and heating device in position on a thigh. (a) Polyurethane sleeve with two TECs and a laser Doppler perfusion probe in between. Heat sinks are mounted on the heat rejection side of the TECs with the fins orientated longitudinally along the axis of the leg. (b) Enclosed shrouds through which cooling air was directed across the surface of the heat sinks.

respectively, and as a result the skin blood perfusion at the site of TEC application is expected to be affected at a correspondingly larger magnitude. The physical size, shape, and rigid properties of both the laser Doppler probe and the TEC modules precluded the measurement of blood perfusion directly under the TECs. A schematic showing the experimental setup is presented in Fig. 2.

A major design outcome of these experiments was to quantify the relationship between tissue surface temperature manipulation and the resulting skin blood perfusion during protocols consisting of alternating cooling and warming episodes. The result of a pilot study showed that the thermoelectric modules provide the best cooling to a tissue thermal load when they are operated in the power range of 8–9 W. Therefore, all trials were conducted with the TECs powered at 8.8 W during active cooling. For the warming portion of the protocol cycle, two different power levels were applied to the TECs to increase the tissue temperature and thereby to upregulate the blood perfusion rate. Thus, two sets of six trials each were conducted for heating input power levels of 2.3 W and 4.2 W. The latter was selected to ensure the subject comfort and the former was chosen high enough to increase skin temperature and blood perfusion. Subjects were randomly assigned to one of these two experimental protocols that were identical except for the TEC power level during warming.

Each trial consisted of 25 min of baseline data acquisition (15 min with cooling fans off followed by 10 min with the fans on but no power supplied to the TECs), 30 min active cooling (TECs powered in cooling mode), 5 min passive rewarming (no power to TECs, fans off), 5 min of active heating (TECs powered in heating mode, fans off), 30 min active cooling (TECs powered in cooling mode, fans on), and 40 min passive rewarming (no power to

Fig. 2 Experimental setup. P, T, and H stand for the perfusion probe, TEC, and the holder, respectively. The holder was made up of a polyurethane sleeve onto which the TECs were mounted and was used to hold the TECs and perfusion probe in place.

TECs, fans off). Developmental testing of the system identified that vibrations induced by the cooling fans caused artifacts in the laser Doppler flow probe signals. Cleaner blood flow data were obtained with the fans off. But, of course, the fans are required for the TECs to operate in active cooling mode. Therefore, to obtain the best quality data for analysis, the fans were turned off initially during baseline, following active cooling, and during active heating. Extracting blood perfusion values from data segments where the fan was turned off guaranteed the accuracy of the extracted values and ensured that it was not affected by the noise caused by the fans. Additionally, it is shown [10,11] that cold-induced reduction in skin perfusion lasts long after the cessation of cooling; therefore, we believe the extracted data are an accurate representative measure of perfusion during the cooling period. The rate of cooling was maintained at a constant power input of 8.8 W, while the active heating cycle was at an input power of either 2.3 W or 4.2 W. Temperature and perfusion data were recorded continuously throughout each trial. Four raters participated in data. Each of the raters selected a representative value for each data segment (i.e., first cooling, active heating, and second cooling) of every single experiment. The extracted values were all selected from segments of data where the fans were turned off to assure the accuracy of the extracted value as explained earlier. Intraclass correlation among the raters was measured as 1.0 for temperature and 0.90 for perfusion, with values above 0.75 considered as acceptable [27]. The average of extracted values determined by the four raters was selected as representative value for each data segment.

Wilcoxon signed-rank test was performed to quantify the magnitude of change in skin blood perfusion during active cooling, and active heating for both power input levels and to compare perfusion values between the first and second cooling episodes and to compare perfusion and temperature during different stages of experiment between the control and the treatment sites. Mann-Whitney U test was performed to compare perfusion during the heating episode between the two treatment protocols. Significance was accepted at $P < 0.05$.

Results

Data were acquired as a time series of temperature and perfusion measurements. Figure 3 shows a data set collected from a laser Doppler probe during one of the trials. Both the blood flow and thermistor temperature values are shown.

During the baseline period prior to activation of the TEC cooling fan, the standard perfusion level was defined. Note that during this time the temperature increased mildly owing the thermal insulating effect of the device placed on the skin surface, causing an associated mild rise in perfusion. When the cooling fan was turned on there was an immediate rise in the laser Doppler output that was not due to higher blood flow, but to vibrational noise transmitted from the fan. In contrast, the temperature simultaneously decreased to a new level owing to the cooling effect of the air flowing through the shroud. At 25 min, the TECs were powered into the cooling mode and the temperature dropped immediately. Perfusion also dropped with a small time lag to a state of

Fig. 3 Blood perfusion (top frame) and skin temperature (bottom frame) as acquired from the laser Doppler probe mounted between two TEC modules during one of the trials. The circles point to the general location of extracted data. Perfusion is expressed as percentage change from the baseline value measured before the cooling fans were turned on (indicated by circle 1). Circles 2 and 3 indicate the times following active cooling episodes when the fans were turned off.

vasoconstriction at about 40% of the baseline. When active cooling was terminated at 55 min and the fan was turned off, there was a downward displacement in the perfusion signal that roughly matches the increase when the fan previously was turned on. In the absence of cooling, there was a rapid rise in temperature owing to the parasitic heat gain from the environment and from the underlying tissue. In contrast, the perfusion remained essentially constant, as has been extensively documented previously [10,11]. At 60 min, the TECs were powered into the active warming mode at 4.3 W, causing an immediate gain in temperature to a value in excess of the baseline state. With a brief time lag, the perfusion followed the temperature upward to approximately three times the baseline state. At 65 min, the TECs were repowered into the active cooling mode causing an immediate drop in temperature, followed by a drop in perfusion. After 30 min, both had reached approximately the same values as at the termination of the initial 30 min cooling episode. Finally, both the TECs and the fan were turned off, allowing the device and tissue to warm passively for an additional 40 min. The temperature increased toward the initial baseline value, while the perfusion remained deeply depressed throughout this time. The foregoing data scenario is qualitatively descriptive of the system behavior for all of the trials. Changes in blood flow and temperature were noted at the completion of each stage of the trial and are reported as follows.

Table 2 A comparison of the elevations in temperature and perfusion during heating with the TECs powered at 2.3 W and 4.3 W using Mann-Whitney U test. The corresponding *P* values are presented in parenthesis. All changes are statistically insignificant (*n* = 12).

	Perfusion ($\pm$ SE)	Temperature ($\pm$ SE)
Difference for low and high power heating	86.0 $\pm$ 27.8 (<i>P</i> > 0.05)	1.3 $\pm$ 0.5 (<i>P</i> > 0.05)

Primary questions to be answered in this study are the extent to which on-site TECs can induce changes in tissue temperature and blood perfusion. Data from each of the 12 trials were analyzed to determine the values for temperature and perfusion during the baseline and at the completion of the two cooling periods and of the single intermediate heating period, and whether the changes from baseline were statistically significant.

Wilcoxon signed-rank test was applied to compare the temperatures at the completion of cooling with the baseline values. The results demonstrate statistically significant differences as shown in Table 1. Cooling episodes #1 and #2, respectively, precede and follow the intermediate heating episode that occurred at one of two TEC power levels. At the completion of the first and second

Table 1 Change in skin blood perfusion and temperature at different stages of experiment in respect to baseline for the two experimental groups. The result and power of Wilcoxon signed-rank test comparing temperature and blood perfusion for each cooling and heating episode to baseline are presented in parenthesis. Twelve subjects, equally divided between the two heating power groups, were tested one time each. All changes are statistically significant except for temperature for low power heating (*n* = 12).

	4.3 W heating power		2.3 W heating power	
	Perfusion average difference from baseline $\pm$ SE (<i>P</i> value, power)	Temperature average difference from baseline $\pm$ SE (<i>P</i> value, power)	Perfusion average difference from baseline $\pm$ SE (<i>P</i> value, power)	Temperature average difference from baseline $\pm$ SE (<i>P</i> value, power)
First cooling episode	-69.4 $\pm$ 4.1 (<i>P</i> < 0.05, 0.99)	23.6 $\pm$ 0.3 (<i>P</i> < 0.05, 0.99)	-59.6 $\pm$ 5.2 (<i>P</i> < 0.05, 0.99)	23.9 $\pm$ 0.2 (<i>P</i> < 0.050, 0.99)
Heating episode	247.4 $\pm$ 124.6 (<i>P</i> < 0.05, 0.36)	33.3 $\pm$ 0.2 (<i>P</i> < 0.05, 0.99)	85.0 $\pm$ 28.0 (<i>P</i> < 0.05, 0.67)	31.9 $\pm$ 0.4 (<i>P</i> > 0.05, 0.46)
Second cooling episode	-61.4 $\pm$ 6.1 (<i>P</i> < 0.05, 0.99)	23.2 $\pm$ 0.3 (<i>P</i> < 0.05, 0.99)	-54.3 $\pm$ 10.3 (<i>P</i> < 0.05, 0.99)	23.5 $\pm$ 0.2 (<i>P</i> < 0.05, 0.99)

Table 3 A comparison of perfusion and temperature values between control and experimental sites using Wilcoxon signed-rank test. The *P* value and power for each of the comparisons are also presented.

	Baseline		First cooling		Warming		Second cooling	
	Control	Expt.	Control	Expt.	Control	Expt.	Control	Expt.
Average perfusion ($\pm$ SE)	3.4 $\pm$ 1.4	6.8 $\pm$ 4.2	17.0 $\pm$ 6.9	-57.7 $\pm$ 4.2	34.1 $\pm$ 8.7	173 $\pm$ 66	22.8 $\pm$ 14.8	-51.1 $\pm$ 6.1
<i>P</i> value (power)	<i>P</i> > 0.5		<i>P</i> < 0.0005 (0.99)		<i>P</i> < 0.01 (0.45)		<i>P</i> < 0.0005 (0.99)	
Average temperature ($\pm$ SE)	31.2 $\pm$ 0.2	30.8 $\pm$ 0.1	31.3 $\pm$ 0.3	23.8 $\pm$ 0.3	31.7 $\pm$ 0.3	32.6 $\pm$ 0.4	31.3 $\pm$ 0.3	23.4 $\pm$ 0.3
<i>P</i> value (power)	<i>P</i> > 0.5		<i>P</i> < 0.0005 (0.99)		<i>P</i> < 0.05 (0.6)		<i>P</i> < 0.0005 (0.99)	

active cooling periods for all 12 experiments, blood perfusion had decreased from the baseline levels by an average ($\pm$ SE) of 57.7 $\pm$ 4.2% and 51.1 $\pm$ 6.1%, respectively. At the completion of the intermediate active heating period, blood perfusion increased by an average ($\pm$ SE) of 173.0 $\pm$ 66.0%.

The data were also evaluated to determine whether there was a difference in the temperature and perfusion responses to warming from a vasoconstricted state with the lower and higher TEC power levels. A Mann–Whitney U test was applied to determine whether a significant distinction exists between these two data sets, as shown in Table 2.

The analysis shows that there is not a significant difference in the tissue reaction to heating with the TEC modules operated at two power levels within the optimal range for producing therapeutic temperature and perfusion responses.

Data comparing the perfusion and temperature between the control and experimental sites are presented in Table 3. As it can be seen, there is a significant difference in temperature and perfusion between the experimental and control sites throughout the experiment with the exception of baseline period where these values are not significantly different.

Discussion

This study demonstrates clearly that thermoelectric modules applied directly at the site of treatment have the inherent capability of raising and/or lowering both temperature and local blood perfusion across ranges that may be considered as therapeutically efficacious. The performance is achieved with simple forced convection cooling to room air.

The authors' laboratory is involved in developing augmented cryotherapy protocols for which cooling is interrupted periodically by brief heating episodes to break the state of chronic vasoconstriction. The thought is to block an unabated maintenance of a deep cold-induced vasoconstriction with the potential to starve the affected tissue of oxygen and nutrients. Although there are multiple techniques by which blood flow can be reestablished during cryotherapy, raising the temperature provides the added benefit of causing a boost in the biochemical processes that drive wound healing. In this context, a TEC used for this method of cryotherapy must be able to alternately lower and raise the tissue temperature and thereby the local blood perfusion.

Among the 12 trials conducted in the manner illustrated in Fig. 2 on 12 different subjects, each and every trial demonstrated this required capability. Statistically significant excursions in temperature and perfusion were documented under the control of thermoelectric modules operating within their normal performance range. Thus, TECs present a potential upside for a practical means of embodying this technology into a medical device.

Inspection of Fig. 3 shows that the tissue responses in terms of temperature and perfusion do not occur immediately following a change in either cooling or heating power supplied to a TEC. There are finite time constants for changes in tissue properties to be realized after the TEC input changes. In general, the response time to cooling is longer than to heating. The response times are

fully consistent with those observed in other cryotherapy and thermal therapeutic devices. The time constants do not present a problem for the potential use of TEC energy sources in cryotherapy, as this type of response delay is well known, accepted, and accommodated within the field.

Another feature of the data shown in Fig. 3 is that when a change in tissue surface temperature occurs, the skin blood perfusion follows, but with a time lag. For passive warming processes this lag may be very long, as measured in hours, such as is seen in the final episode in Fig. 3. This phenomenon has been observed repeatedly in other studies with conventional cryotherapy devices [10,11]. Thus, the occurrence here is anticipated. The interdependence of temperature and perfusion during a cooling and heating cycle will result in a hysteresis effect when these properties are plotted together [28].

A well-known feature of cryotherapy systems that embody chilled water circulated through a flexible bladder placed at the treatment site is that there are often large spatial variations in the applied temperature [9]. Since the applied temperature dictates the conditions of therapy, inconsistent temperatures may be problematic in achieving desired outcomes. A direct potential advantage of practicing cryotherapy with a device consisting of an array of TECs is that each module may be monitored and controlled independently, thereby producing a therapeutic stimulus as intended.

Although the tissue surface temperature was lowered only into the mid-20 s Celsius range, that drop was well able to induce a vasoconstriction to less than half of the baseline perfusion level. This extent of vasoconstriction should be of benefit to managing the response to soft tissue injury. This outcome is consistent with our prior studies on use of skin temperature to manage blood flow for therapeutic purposes [10,11].

The insignificant difference in outcomes for TEC heating powered at 4.2 W and 2.3 W indicates that it may be possible to operate the system at relatively lower power levels, at least during heating. If this phenomenon is proven in further testing, it would provide an advantage in device energy consumption, especially for conditions in which the power is derived from a battery.

Thermoelectric modules provide the foundation for a highly tunable device that can be used to manage skin temperature over a broad spectrum of thermal states. This capability may be exploited to create a deliberate perfusion history during cryotherapy, leading to a safer technology that may have improved healing outcomes.

Conclusion

As hypothesized, thermoelectric modules may be used directly at a treatment site to affect temporal modulation of the applied therapeutic temperature. The normal operating range of typical TECs is satisfactory to produce temperatures within the range that may provide therapeutic efficacy and are effective for managing tissue blood flow throughout the treatment process. Thermoelectric modules are well adapted to affecting a new regime of cryotherapy protocols in which tissue temperature is intermittently

elevated briefly to obviate a persistent state of vasoconstriction and to reperfuse tissues with a fresh supply of blood.

Acknowledgment

This research was sponsored by National Science Foundation Grant (BET1250659) and National Institute of Health Grant (R01-EB015522), and received technical assistance and thermoelectric modules from Gentherm, Inc.

Patent applications for some aspects of this technology as applied to cryotherapy have been submitted by Dr. Khoshnevis and Dr. Diller to the United States Patent and Trademark Office. Ownership rights to this IP 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.

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