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Topical Menthol, Ice, Peripheral Blood Flow, and Perceived Discomfort

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Context: Injury management commonly includes decreasing arterial blood flow to the affected site in an attempt to reduce microvascular blood flow and edema and limit the induction of inflammation. Applied separately, ice and menthol gel decrease arterial blood flow, but the combined effects of ice and menthol gel on arterial blood flow are unknown.

Objectives: To compare radial artery blood flow, arterial diameter, and perceived discomfort before and after the application of 1 of 4 treatment conditions.

Design: Experimental crossover design.

Setting: Clinical laboratory.

Participants or Other Participants: Ten healthy men, 9 healthy women (mean age = 25.68 years, mean height = 1.73 m, mean weight = 76.73 kg).

Intervention(s): Four treatment conditions were randomly applied for 20 minutes to the right forearm of participants on 4 different days separated by at least 24 hours: (1) 3.5 mL menthol gel, (2) 0.5 kg of crushed ice, (3) 3.5 mL of menthol gel and 0.5 kg of crushed ice, or (4) no treatment (control).

Main Outcome Measure(s): Using high-resolution ultrasound, we measured right radial artery diameter (cm) and blood flow (mL/min) every 5 minutes for 20 minutes after the treatment was applied. Discomfort with the treatment was documented using a 1-to-10 intensity scale.

Results: Radial artery blood flow decreased ($P < .05$) from baseline in the ice (–20% to –24%), menthol (–17% to –24%), and ice and menthol (–36% to –39%) treatments but not in the control (3% to 9%) at 5, 10, and 15 minutes. At 20 minutes after baseline, only the ice (–27%) and combined ice and menthol (–38%) treatments exhibited reductions in blood flow ($P < .05$). Discomfort was less with menthol than with the ice treatment at 5, 10, and 20 minutes after application ($P < .05$). Arterial diameter and heart rate did not change.

Conclusions: The application of 3.5 mL of menthol was similar to the application of 0.5 kg of crushed ice in reducing peripheral blood flow. Combining crushed ice with menthol appeared to have an additive effect on reducing blood flow.

Key Words: rehabilitation, modalities, cryotherapy

Key Points

- The ice, menthol, and ice-plus-menthol treatments all resulted in reduced blood flow compared with the control condition and with baseline.
- The ice-plus-menthol treatment resulted in a more rapid and greater reduction in blood flow.

Soft tissue injuries are the most common injuries encountered in a primary care practice and account for up to 55% of all sport-related injuries.¹ The standard acute care management protocol of soft tissue injuries involves cryotherapy. The physiologic effects of localized cryotherapy are thought to be mediated by reducing metabolic demands on the tissue and blood flow around the injured tissue. This reduction in blood flow to injured tissue in turn reduces edema and hemorrhaging into the tissue and limits the induction of inflammation.^{2–5}

Topical application of either menthol or ice appears to be effective in decreasing arterial perfusion. Ice has a vasoconstrictive effect: it lowers the temperature of the tissues, which stimulates the thermoreceptors and local chemical reactions that result in vasoconstriction.^{6–9} Menthol does not lower tissue temperature but rather stimulates thermoreceptors in the skin through a chemical reaction, which results in local vasoconstriction and decreases in blood flow.^{10–12} Thus, it seems logical to examine the combined effects of topical menthol and ice to determine whether the vasoconstrictive properties of these treatments are complementary or additive. The purpose of our study was to compare radial artery blood flow, arterial

diameter, and perceived discomfort before and at 5, 10, 15, and 20 minutes after the application of 1 of 4 conditions: (1) 3.5 mL of 3.5% menthol gel, (2) 0.5 kg of crushed ice, (3) 3.5 mL of 3.5% menthol gel and 0.5 kg of crushed ice, or (4) no treatment (control). Our hypotheses were as follows:

- H1: The application of 3.5% menthol, crushed ice, or a combination of menthol and crushed ice to the right forearm will result in a reduction in radial artery blood flow compared with the no-treatment (control) condition.
- H2: The application of 3.5% menthol, crushed ice, or a combination of menthol and crushed ice to the right forearm will result in a reduction in radial artery diameter compared with the no-treatment (control) condition.
- H3: The application of 3.5% menthol, crushed ice, or a combination of menthol and crushed ice to the right forearm will result in different perceptions of discomfort.

METHODS

This research protocol was submitted to and approved by the institution's Human Subjects Review Board. Partici-

pants provided written consent before the four 30-minute data-collection sessions in the laboratory. Ordering of the treatment conditions was randomly assigned by asking each participant to select 1 envelope from 20 sealed envelopes that listed the treatment conditions in different orders. A number of potential contaminating variables were controlled by recruiting a homogeneous sample that was young, seemingly healthy, and nonsmoking and did not report any health condition that could affect peripheral blood flow.

DESIGN

An experimental crossover design was used with repeated-measures analysis to determine whether the dependent variables of arterial blood flow, arterial diameter, and perception of discomfort differed on 4 days under 4 different treatment conditions. The treatment conditions, or independent variables, included 3.5 mL of 3.5% menthol gel, 0.5 kg of crushed ice, 3.5 mL of 3.5% menthol and 0.5 kg of crushed ice, and a no-treatment (control) condition. The data-collection protocol on each day was the same and conducted by the same 2 investigators, except for the treatment intervention. After they provided informed consent, all participants completed a brief demographic questionnaire, and we measured their height and weight. Treatment order was randomly assigned during each data-collection session, and sessions were separated by at least 24 hours in order to provide a washout period between treatments. Each data-collection session included blood-flow measurements at 5 time points: baseline after sitting quietly for 5 minutes and then at 5, 10, 15, and 20 minutes following the application of the treatment condition.

Participants

A convenience sample of 10 healthy men and 9 healthy women (mean age = 25.68 years, mean height = 1.73 m, mean weight = 76.73 kg) was recruited for the study. Volunteers were excluded if they reported health conditions that might have altered the blood flow in the right arm (eg, diabetes, Raynaud disease, peripheral vascular disease, previous vascular surgery). None smoked, and all refrained from caffeine consumption and vigorous physical activity for 8 hours before data collection.

Procedures

Upon arrival in the laboratory, participants were asked to sit quietly and relax for 5 minutes. After this relaxation period, baseline data collection took place, and then 1 of 4 randomly selected treatments was applied to the right forearm for 20 minutes. During the treatment application, additional blood flow and discomfort data were collected at 5, 10, 15, and 20 minutes. The laboratory environment remained stable during all data collection at 22°C to 23°C with relative humidity between 45% and 55%.

The ice treatment involved 0.5 kg of crushed ice obtained from a commercial ice machine. This crushed ice was captured in a 2-L plastic bag and applied without compression to the anterior surface of the forearm; the position of the plastic bag was maintained without active tissue compression by using nonelastic hook-and-loop

straps. The ice treatment was applied for 20 minutes immediately after the collection of baseline data.

The 3.5-mL dose of 3.5% menthol gel was based on previous pilot testing and the amount typically applied in an athletic training facility (1 mL of gel for every 200 cm² of surface area). The dose of menthol gel was standardized from a sample of 10 adult forearms at approximately 700 cm² of surface area. This standard amount (3.5 mL) of menthol gel was applied by a gloved technician from the participant's wrist to elbow and included the entire surface of the right forearm.

During the combined application of ice and menthol, the menthol gel was applied to the right forearm in the same way. Plastic wrap was then placed over the forearm so that condensation from the ice bag did not wash away the menthol gel. A plastic bag containing 0.5 kg of crushed ice was placed over the plastic wrap on the anterior surface of the right forearm and secured with minimal to no tissue compression with nonelastic hook-and-loop straps.

On each day of data collection, the participants reported to the same laboratory and were placed in a seated position and told to rest quietly for 5 minutes before data collection. Heart rate (beats/min) was palpated on the left side in the radial artery for 1 minute immediately before all blood-flow measures. Blood pressure (mm Hg) was assessed using a manual mercury sphygmomanometer on the left arm immediately before baseline data collection only to confirm that participants were normotensive (diastolic < 85 mm Hg, systolic < 135 mm Hg). Blood pressure was not assessed in the right or left arm after baseline data collection because this procedure could affect blood flow in the right radial artery. Blood flow was measured noninvasively in the right radial artery, proximal to the carpus between the radial collateral ligament of the wrist and the tendons of the abductor pollicis longus and extensor pollicis brevis using high-resolution ultrasound (model HDI 5000; Philips Ultrasound, Inc, Seattle, WA). The radial artery was imaged longitudinally by B-mode ultrasound using a 12 to 5 MHz linear array transducer. This method of estimating blood flow was reported to be highly valid ($r = 0.96-0.98$) when calculating blood flow in different vessel compartments.¹³ We collected a video file of the ultrasound over 5 pulsations (or heartbeats) at the specified data-collection intervals in the vessel to allow data analysis after the test. The vessel diameter was also averaged over these 5 pulsations to arrive at a measure of the radial artery diameter (cm). Custom software (LabVIEW, version 7.1; National Instruments Corporation, Austin, TX) measured the changes in the radial artery diameter beat by beat and calculated the volume of blood through the vessel per minute (mL/min).

Each participant reported his or her perceived discomfort intensity of 3 treatments (ice, menthol, and ice plus menthol) at 5, 10, 15, and 20 minutes after application of the treatment. These data were not collected during the control condition or during baseline data collection because we assumed participants would report no discomfort when no treatment was applied. Perceived intensity of discomfort was quantified by asking each participant to respond to the question, "On a scale of 1 to 10, with 1 being *no discomfort* and 10 being *extreme discomfort*, how intense is the discomfort you are experiencing to your forearm at this time?" The numerical response was considered the

Table 1. Heart Rate (beats/min) by Treatment Over Time (Mean ± SD)

Treatment	Time, min				
	Baseline	5	10	15	20
Control	73.89 ± 13.86	76.74 ± 13.20	75.16 ± 13.17	75.47 ± 11.54	77.05 ± 13.46
Menthol	78.63 ± 11.47	74.84 ± 9.67	77.68 ± 14.63	76.74 ± 11.76	76.95 ± 11.88
Ice	76.74 ± 12.10	76.11 ± 12.01	76.74 ± 11.59	77.80 ± 8.46	76.74 ± 9.50
Menthol and ice	78.95 ± 9.85	75.47 ± 9.02	78.32 ± 12.72	77.05 ± 9.44	76.42 ± 9.56

participant's perceived intensity of discomfort of the treatment at the specified data-collection point.

Statistical Analysis

We conducted a 4 × 5 (treatment × time) repeated-measures analysis of variance using SPSS (version 19.0; IBM Corporation, Armonk, NY) to test for the effects of time, treatment, and interaction (time × treatment) to address hypotheses 1 and 2. A 3 × 4 (treatment × time) statistical design was used to assess changes in perceived intensity of discomfort predicted in hypothesis 3. Significant main or interaction effects were further evaluated by calculating the Tukey least significant post hoc differences to determine differences between treatment and time means. All analyses were considered statistically significant at the $P < .05$ level. Percentage changes in arterial blood flow from baseline were also calculated for each treatment condition to determine the clinical significance of the findings.

RESULTS

Heart rate did not change within or between treatment conditions over the duration of the trial ($P < .05$; Table 1). A treatment × time interaction effect on blood flow through the radial artery was noted ($F = 3.22$, $P < .001$). Post hoc analysis indicated that radial artery blood flow was lower at 5, 10, 15, and 20 minutes after the menthol, ice, and menthol-and-ice treatments compared with baseline measurements within each of these 3 treatment conditions (all P values $< .05$; Table 2). Also, radial artery blood flow was lower during the menthol, ice, and menthol-and-ice treatments than during the control condition at 5, 10, and 15 minutes after treatment application (all P values $< .05$). At 20 minutes after the application of the treatments that contained ice (ice alone or menthol and ice), arterial blood flow in the radial artery was reduced compared with the control condition ($P < .05$). Only at the 15-minute data-collection point did the ice-and-menthol treatment demonstrate less blood flow than in the control and the other 2 treatment conditions ($P < .05$). At 20 minutes after

application of the menthol-alone treatment, arterial blood flow was not different than in the control condition ($P > .05$).

Although not part of the original purpose, the time to peak reduction in arterial blood flow from baseline was calculated (Table 2). The menthol-alone application resulted in peak reduction in blood flow at 10 minutes after baseline (23.69%). The menthol-and-ice application demonstrated a peak reduction in blood flow at 15 minutes after baseline (39.34%), whereas the most protracted time to peak reduction in blood flow of the 3 treatments occurred at 20 minutes after the ice-alone application (26.57%).

No significant time, treatment, or treatment × time interaction effects on radial artery diameter were noted during the trial (all P values $> .05$, Table 3). A treatment × time interaction ($F = 3.56$, $P < .001$) for the participants' perceptions of discomfort among 3 treatment conditions (menthol, ice, menthol and ice) is presented in Table 4. Post hoc analysis indicated that at 5 minutes after the treatment application, perceived discomfort was different among all 3 treatments, with the ice-alone treatment resulting in the greatest perceptions of discomfort and the menthol-alone treatment resulting in the lowest ($P < .05$). At 10 minutes after application, the ice-alone treatment yielded greater perceptions of discomfort than either the menthol-alone or the menthol-and-ice treatments ($P < .05$). At the 15-minute data-collection point, perceived discomfort was similar for all 3 treatments. Finally, at 20 minutes after application, the menthol treatment produced less perceived discomfort than did the ice or the menthol-and-ice treatments ($P < .05$).

DISCUSSION

Our results supported research hypotheses 1 and 3 and fell short of supporting hypothesis 2. The application of 3.5% menthol, ice, or a combination of menthol and ice to the right forearm appeared to reduce radial artery blood flow compared with a no-treatment (control) condition. None of these treatments reduced radial artery diameter compared with a no-treatment condition. The application of 3.5% menthol, ice, or a combination of menthol and ice to

Table 2. Change From Baseline in Radial Artery Blood Flow (mL/min) by Treatment Over Time (Mean ± SD, %)

Treatment	Time, min				
	Baseline	5	10	15	20
Control	28.72 ± 15.92	31.36 ± 17.50 (9.19%)	28.87 ± 15.79 (0.52%)	29.64 ± 18.23 (3.20%) ^a	26.47 ± 13.56 (-7.83%)
Menthol	29.51 ± 17.60	23.13 ± 14.51 (-21.62%) ^b	22.52 ± 13.64 (-23.69%) ^b	24.58 ± 15.79 (-16.71%) ^b	24.47 ± 15.26 (-17.08%) ^b
Ice	27.22 ± 16.18	20.73 ± 12.31 (-23.84%) ^b	20.94 ± 13.58 (-23.07%) ^b	21.67 ± 12.19 (-20.39%) ^b	19.99 ± 13.42 (-26.56%) ^b
Menthol and ice	28.29 ± 13.35	18.06 ± 9.77 (-36.18%) ^b	17.61 ± 11.69 (-37.75%) ^b	17.16 ± 9.44 (-39.34%) ^c	17.65 ± 9.90 (-37.61%) ^b

^a At the 15-minute point, the control treatment resulted in greater blood flow than all other treatments ($P < .05$).

^b Different from baseline within treatment ($P < .05$).

^c At the 15-minute point, the menthol-and-ice treatment resulted in less blood flow than all other treatments ($P < .05$).

Table 3. Radial Artery Diameter (cm) by Treatment Over Time (Mean ± SD)

Treatment	Time, min				
	Baseline	5	10	15	20
Control	0.287 ± 0.047	0.298 ± 0.049	0.295 ± 0.053	0.297 ± 0.048	0.295 ± 0.056
Menthol	0.300 ± 0.052	0.288 ± 0.053	0.293 ± 0.048	0.288 ± 0.051	0.301 ± 0.048
Ice	0.305 ± 0.049	0.292 ± 0.053	0.286 ± 0.042	0.297 ± 0.046	0.295 ± 0.049
Menthol and ice	0.302 ± 0.044	0.285 ± 0.032	0.282 ± 0.050	0.277 ± 0.033	0.286 ± 0.036

the right forearm resulted in different perceptions of discomfort. Finally, the effect of these treatments on local blood flow did not appear to be attributable to differences in heart rate during treatment application because heart rate did not change within or between treatment conditions over the duration of the trial.

On first review of the data, the time to peak effect in reducing blood flow appeared different among the 3 treatment conditions, but this observation must be interpreted cautiously. Although the peak effect of menthol may seem to be more proximal to the application compared with the peak effect of the ice treatment, the percentage reduction of blood flow between these treatments appeared clinically indistinguishable at 5 minutes (21.62% versus 23.84%) and 10 minutes (23.69% versus 23.07%) after application. At 15 minutes (16.71% versus 20.39%) and 20 minutes (17.08% versus 26.56%) after the treatment application, the effect of the menthol alone appeared to wane, whereas the effect of the ice was sustained. A variety of explanations are possible for these findings, which indicate the need for further study. The menthol-alone and ice-alone treatments had a statistically indistinguishable effect in reducing blood flow over the first 15 minutes after application, although the menthol may exert a peak effect more quickly, with a more rapid sensitization than seen with the ice treatment. The different times to peak effect in reducing blood flow between menthol and ice have been reported by previous authors.^{10,14} The short-acting effect of menthol compared with ice may be attributable to different mechanisms of action in decreasing blood flow. Previous investigators¹⁵⁻¹⁷ have reported that topical menthol stimulates cutaneous cold receptors, which have been postulated to reduce blood flow through a neuronal reflex mechanism.¹⁵ Haeseler et al¹⁸ and Ragan et al¹⁹ concluded that the application of topical menthol attenuated blood pressure through an increase in peripheral resistance in the muscle, thus leading to a reduction in overall blood flow to the area. The reduction in the pressor response is thought to be due to inhibition of the small-diameter sensory nerve

fibers (group III and IV afferents) that synapse with the spinoreticular tract neurons in the dorsal horn of the spinal cord.¹⁹

Topical application of ice also stimulates cold receptors and results in reduced blood flow to the area through the neuronal reflex mechanism. In addition, the reduction in tissue temperature that accompanies the topical application of ice produces a local increase in Rho kinase activity²⁰ and decreased endothelial nitric oxide production. Both local chemical mechanisms resulting from declines in tissue temperature increase translocation of the α_2 -adrenergic receptors to the smooth muscle of the local arterial system^{20,21} and increase calcium sensitization,^{20,22} which results in reduced blood flow. Menthol appears to reduce blood flow through a spinal reflex, whereas ice also stimulates this spinal reflex and has a local effect on the tissue vasculature²³ to reduce blood flow.

These different mechanisms of action of menthol and ice that result in decreased blood flow may explain other findings of our study. Menthol's influence is believed to be mediated through nervous system mechanisms, which may account for the relatively rapid deterioration of effect resulting from this treatment. This reduction in blood flow may be short lived because the nervous mechanism quickly sensitizes or adapts to the stimulating effect of the menthol. Ice likely stimulates the same nervous mechanism as the menthol treatment, although the ice in this trial was not applied to the same surface area as the menthol, which may have attenuated the initial nervous response to stimulating the cold receptors. By lowering local tissue temperature, ice might have also stimulated local tissue mechanisms to reduce blood flow. These local mechanisms respond to decreases in tissue temperature and may be slower than the nervous system mechanism. The protracted time required to cool the tissues may have also been compounded by the limited surface area exposed to the ice compared with the menthol treatment. Finally, this delayed effect of tissue cooling is mediated through local mechanisms, which did not appear to be sensitized over the 20 minutes after the treatment application. This hypothesis is consistent with our previous conclusion that ice therapy requires 15 to 20 minutes to evoke a maximum effect in reducing blood flow to the area being treated.^{10,14}

Another interesting finding of the study was the observation that the menthol-and-ice treatment resulted in the greatest decline in blood flow. Although beyond the hypotheses of this study, secondary analysis indicated that at the 15-minute data-collection point, blood flow under the menthol-and-ice condition was less than under any of the other treatment conditions. This observation supports the idea that menthol and ice result in reduced blood flow via different mechanisms; when combined, these treatments can have additive effects in decreasing blood flow.

Table 4. Perceptions of Discomfort^a by Treatment Over Time (Mean ± SD)

Treatment	Time, min			
	5 ^b	10	15 ^c	20
Menthol	2.89 ± 1.73	3.37 ± 1.67	3.26 ± 1.70	2.53 ± 1.93
Ice	5.11 ± 1.76	4.32 ± 2.00 ^d	3.63 ± 2.11 ^d	3.58 ± 1.92 ^d
Menthol and ice	3.95 ± 1.62	3.47 ± 1.81	3.89 ± 2.18	3.89 ± 2.33

^a 1 = no discomfort, 10 = extreme discomfort.

^b All treatment groups were different ($P < .05$).

^c All treatment groups were equal ($P > .05$).

^d Only the ice group experienced a decline from the 5-minute point ($P < .05$).

The differences in perceived discomfort may also support the hypothesis that menthol and ice result in different types of nervous system activity at the site of application. At the 5-minute data-collection point, ice yielded the greatest perceptions of discomfort. This finding is likely attributable to the initial application of ice resulting in intense stimulation of the thermoreceptors and pain receptors.²⁴ As the tissue cools with sustained ice application, pain perceptions are reduced via slowing of nerve conduction velocity, inhibiting of nociceptors, or a reduction in metabolic enzyme activity within the nerves (or a combination of these).^{25,26} Prolonged tissue cooling results in a numbing sensation and the pain-relieving effect of ice. This initial effect of ice as painful and then numbing was demonstrated by the participants in our study, who reported less intensity of sensation with sustained application of ice. Algaftly and George²⁵ concluded that sustained application of ice can increase the pain threshold and pain tolerance, perhaps due to declines in nerve conduction velocity. Menthol does not appear to lower tissue temperature but instead stimulates cold thermoreceptors^{27–30} through a chemical reaction and seems to result in pain relief³¹ through a counterirritant effect.¹⁸ Similar to the reductions in blood flow from the application of menthol, this counterirritant effect appears short lived (less than 20 minutes).

These findings may have important clinical implications but must be interpreted cautiously due to a number of possible threats to internal validity. Adipose tissue thickness at the treatment site was not measured and may have affected the treatments. However, all treatments were applied to all participants, so this contaminating effect was likely minimized by the repeated-measures crossover design. Decreasing blood flow to a soft tissue injury may reduce edema, hemorrhaging into the tissue, and the onset of inflammation.^{2–5} All experimental conditions decreased blood flow when compared with the control condition. Combined menthol and ice appeared to have the greatest effect in decreasing blood flow.

This trial was conducted on a small sample of uninjured healthy young adults; thus, the findings are not generalizable to other groups. None of the interventions affected arterial diameter, although the method we used to measure arterial diameter may not have been sensitive enough to detect a vasoactive effect of any of the treatment conditions. A next possible step in this area of inquiry is to examine the separate and combined effects of menthol and ice on the progression of soft tissue injuries, including secondary injury related to inflammation, and return to normal activity. The combined effects of menthol and tissue cooling, or cryotherapy, may be of particular interest to practitioners who are attempting to maximize reduction in blood flow to a particular area.

CONCLUSIONS

Our results indicate that all 3 experimental conditions decreased blood flow when compared with the control condition and with baseline. The addition of menthol to cryotherapy may offer a number of advantages over cryotherapy alone. Practitioners may wish to combine menthol with ice to enhance the reductions in arterial perfusion. The maximum reductions in blood flow with ice

occurred after a longer duration of time compared with menthol treatments alone. Yet incorrectly sustained tissue cooling to achieve maximum decreases in blood flow from the application of ice has the potential for tissue damage from frostbite.³² Combining menthol and ice results not only in a greater reduction in blood flow but also in a more rapid onset of the maximum effect in reducing blood flow, thereby limiting the risk of frostbite from sustained ice application. Menthol gels can be applied to athletes' injuries on the field when ice is not available in order to initiate reductions in blood flow, which can be enhanced when ice is added. Finally, cryotherapy alone has been associated with declines in neuromuscular functioning, including reduced proprioception,³³ nerve conduction,³⁴ and muscle strength.¹¹ Future researchers should determine whether menthol alone or in combination with cryotherapy has similar deleterious effects on functioning.

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