Deep Frostbite Treated With Hyperbaric Oxygen and Thrombolytic Therapies

Brian Higdon[1]; Laura Youngman, APN[2]; Michelle Regehr, APN[2]; Andy Chiou, MD, MPH, FACS[1,2]

Wounds 2015;27(8):215-223

From the [1]University of Illinois College of Medicine, Peoria, IL; [2]OSF Wound Healing and Hyperbaric Center, Peoria, IL

Address correspondence to:
Andy C. Chiou, MD, MPH, FACS
Peoria Surgical Group
Peoria Vein Center
Assistant Professor of Clinical Surgery and Radiology
University of Illinois College of Medicine in Peoria
8600 N. Route 91
Suite 400
Peoria, IL 61615
achiou@peoriasurgical.com

Disclosure: The authors disclose no financial or other conflicts of interest.

Abstract: The authors present a case of deep frostbite treated with both hyperbaric oxygen and thrombolytic therapies. Both of these therapies are experimental and have not yet achieved widespread clinical use. The patient described in this paper sustained frostbite after becoming intoxicated and falling unconscious in a snowy field. He was treated acutely for hypothermia and came into the authors' care for wound management. Of his 6 digits with extensive, deep frostbite, 1 digit eventually required partial amputation, and another had protracted osteomyelitis treated with intravenous antibiotics. The authors present a case history in the context of current research and provide a listing of previous case reports of hyperbaric oxygen therapy for frostbite.

Key words: clinical management, frostbite, hyperbaric oxygen, thrombolytic therapy

Frostbite is defined as the freezing of tissue, leading to the formation of extracellular ice crystals that damage cell membranes and osmotically dehydrate cells.[1] Upon rewarming, frostbite results in extensive blistering, edema, and ischemia of the affected tissues and can become necrotic and gangrenous, sometimes requiring amputation. The pathophysiological mechanisms of frostbite damage have been described as taking place in 2 phases.[1,2] The first phase is during the time of cold exposure, when cellular damage is caused by the formation of extracellular ice crystals. As crystals form, the remaining fluid becomes hyperosmotic, leading to the dehydration and shrinking of surrounding cells. Ice crystals also cause direct damage to plasma membranes and proteins. As endothelial cells shrink and are otherwise damaged, the structural integrity and function of microvasculature is compromised. Rapidly rewarming the injured tissues using warm water—a well-proven treatment for frostbite—is believed to limit the amount of damage caused by these ice crystals.[1] The second phase of the pathophysiology of frostbite is the progressive dermal ischemic damage that begins upon rewarming, as a result of the damage to endothelial cells and the resulting release of inflammatory mediators including prostaglandins and thromboxanes, leading to thromboses, edema, and other vascular sequela.[1,2] Hyperbaric oxygen (HBO) and

Table 1. Case reports of hyperbaric oxygen therapy as a treatment for frostbite.

Author, Year	No. of patients	Pressure (ATA)	Duration	No. of treatments, frequency	Delay until treatment
Ledingham, 1963*[3]	2	2.0	72 hours	1	N/A
Smith, 1964*[4]	1	NA	NA	More than 5 days	N/A
Perrin and Bossinnette, 1965[5]	1	4.0	45 min	11, more than 6 days	0 days
Trippel et al, 1966[6]	2	N/A	N/A	N/A	N/A
Ward et al, 1968[7]	4	2.0	2 hours	Up to 19, daily	5-10 days
Wilson and Wilson, 1968[8]	1	3.0	1 hour	7, more than 5 days	7 days
Cooke, 19719	3	"Standard"	N/A	N/A	
Bajrović et al, 1997**[14]	4	2.5	90 min	14 to 30, 1x-2x daily	Days to weeks
von Heimburg et al, 2001[15]	1	2.4	90 min	14, daily	7 days
Finderle and Cankar, 2002[16]	1	2.0	90 min	28, daily	14 days
McCrary and Hursh, 2005[17]	1	2.0-2.5	90 min	21, more than 35 days	22 days
Ay et al, 2005[18]	2	2.4	1 hour	30, more than 35 days; 34, more than 40 days	6 days, 14 days
Mekjavic et al, 2005**[19]	5	2.5	90 min	10-30, daily	2-4 days
Folio et al, 2007[20]	1	N/A	N/A	21, more than 90 days	2 weeks
Zanon et al, 2007[21]	4	2.5	90 min	15-20, N/A	N/A
Sever et al, 2010[22]	1	2.4	90 min	14, daily	4 days
Sever et al., 2010[23]	1	2.4	90 min	14, daily	0 days
Özkaya et al, 2011[24]	1	2.4	90 min	14, daily	0 days
Gorjanc et al, 2012**[25]	8	2.5	90 min	Average of 17.6, daily	1-7 days
Johnson-Arbor, 2013[26]	1	N/A	N/A	20, daily	2 months
Johnson-Arbor, 2013[27]	1	2.2	90 min	40, N/A	10 days
Sanders and Anderson, 2013[28]	1	2.4	90 min	17, more than 14 days; then 20, daily	1 day
Kemper et al, 2014[29]	1	2.5	60 min	19, N/A	21 days
Higdon et al, 2015	1	2.0	90 min	20, more than 28 days; then 20, more than 30 days	8 days

*, ** duplicate patients; N/A: not applicale

thrombolytics, along with prostacyclin and sympathetic nerve blocks have all been used experimentally to address dermal ischemic damage related to frostbite, but have yet to receive widespread support.

Hyperbaric oxygen therapy has been used to treat frostbite injuries for more than 50 years. Beginning in 1963, there were several case reports published that described favorable outcomes.[3-9] In response to these case reports, laboratory studies were conducted on mouse and rabbit models, but these yielded mixed results.[10-13] For 25 years, no new case reports were published. Beginning in 1997, many more case reports on HBO therapy for frostbite injuries were published, all with favorable outcomes.[14-29] In addition to these recent case reports, a laboratory study was conducted on a rabbit model that yielded favorable results.[30] There have been no controlled trials of HBO for frostbite published to date.

Thrombolytic therapy using tissue plasminogen activator (tPA) has more recently been suggested as a treatment for frostbite, and some initial clinical studies have had promising results.[31-33] One study, using a historical

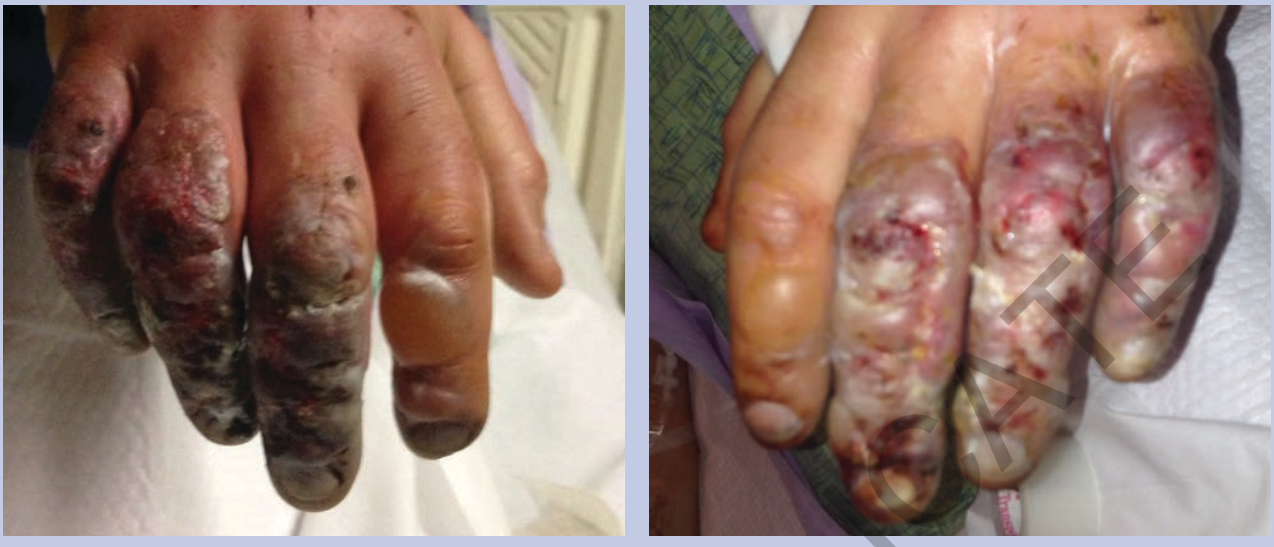

Figure 1. Right and left hands 2 days postinjury.

control group, found a significant reduction of digital amputations with use of tPA therapy.[32] Earlier studies, using frostbitten animal models, also demonstrated positive outcomes using other thrombolytic agents.[34,35]

The purpose of this report is to add a unique case to the growing literature on HBO and thrombolytic therapies for frostbite, and to provide a listing of other case reports on HBO for frostbite published to date (Table 1).

Case Report

A 33-year-old male arrived at OSF St. Francis Medical Center in Peoria, Illinois, by ambulance with hypothermia and ethanol intoxication, with altered mental status and agitation. The patient was intoxicated when he wandered outside, in temperatures of approximately 8˚F, and fell unconscious in a snowy field, where he remained for approximately 90 minutes before being found. En route to the hospital, and upon arriving at the hospital, the patient received sedatives including fentanyl and midazolam, and intravenous warmed saline. An hour after his arrival at the hospital, the patient's blood alcohol was measured to be 287 mg/dL. Ninety minutes after arriving, his rectal temperature was measured at 88.9˚F. Due to his altered mental status and agitation, the patient was sedated and intubated and remained intubated for 5 days. The patient was found to have deep frostbite injuries to nearly the full length of his third, fourth, and fifth digits on both hands. These injuries were characterized by hemorrhagic blistering, cyanosis, and moderate edema (Figure 1). There were less-severe frostbite injuries to the second digit on both hands.

The patient was an active smoker, having smoked 10 cigarettes a day for 14 years. His family reported that he was not a chronic drinker, and he did not experience any alcohol withdrawal symptoms during his hospitalization. After his injury, he stopped smoking and drinking alcohol. The patient's past medical history was otherwise unremarkable, with no history of diabetes mellitus or peripheral vascular disease.

Thirty-six hours after the patient was admitted to the hospital, he underwent an upper extremity angiogram that revealed occlusions of the digital arteries between the metacarpal phalangeal and distal interphalangeal joints and decreased soft tissue perfusion of bilateral third, fourth, and fifth digits consistent with in situ thrombosis. Bilateral intra-arterial tPA therapy was subsequently initiated at 0.5 mg/hr. After 24 hours of tPA, another angiogram was performed which showed no improvement of the occlusions but showed improved soft tissue perfusion. Clinical improvement was noted, in that there was increased warmth and color of the affected tissues. Tissue plasminogen activator therapy was continued at 0.25 mg/hr. After 24 more hours of tPA, a third angiogram again showed no improvement of the occlusions (Figure 2). Tissue plasminogen activator therapy was subsequently discontinued and a 12-hour abciximab treatment was initiated.

On his ninth day of hospitalization, 3 days after being extubated, the patient was discharged from the

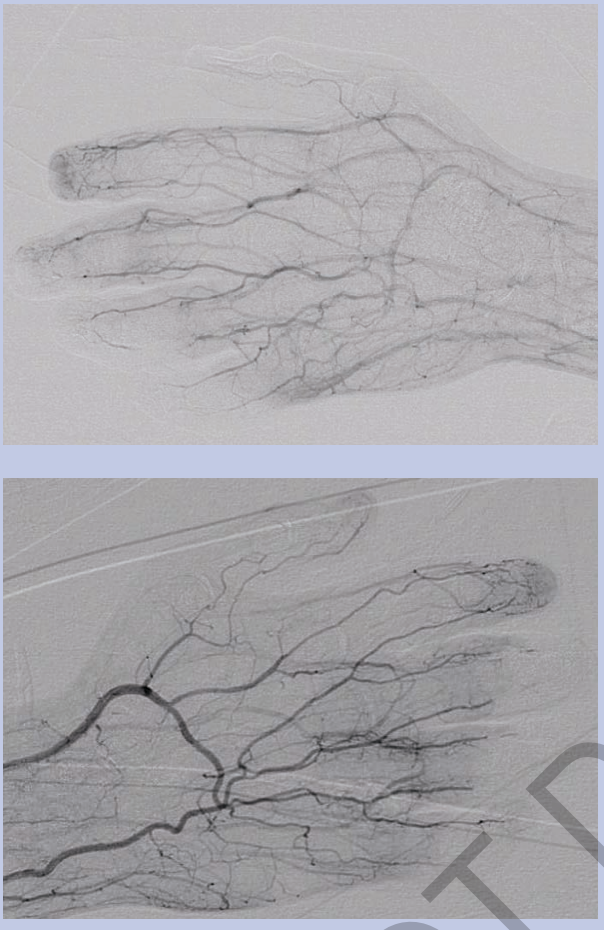

Figure 2. Angiography of right and left hands 3 days postinjury.

hospital and began HBO therapy at OSF Wound Healing and Hyperbaric Center, Peoria, IL. At presentation, the frostbite injuries were characterized by blistering and peeling skin with a minimal amount of sanguineous drainage (Figure 3). The tips of the fingers were cyanotic with no capillary refill and there was +2 edema in both hands. The patient received standard wound care, supplemented with HBO therapy. Standard wound care consisted of weekly debridements to remove any demarcated or necrotic tissue to stimulate healing, and appropriate bandaging. The patient received 20 HBO treatments over 28 days, consisting of 90 minutes at 2 atmospheres absolute (ATA) while breathing 100% O_2, which are the standard parameters used in this wound center for the treatment of nonhealing wounds. After the fourth HBO treatment, an arterial study was performed that found digit pressures were adequate for tissue viability and wound healing. After a break of 14 days, for further insurance authorization, the patient received 20 more treatments over the course of 30 days, according to the same treatment protocol as before.

During early HBO treatments, there was visible pinking of the affected tissues, and the patient reported a marked increase in pain as sensation returned to the affected fingers. Over the course of the first series of HBO treatments, all fingers, except for the fourth digit of the left hand, underwent marked improvement with continuing reepithelialization of blistered surfaces and revitalization of ischemic tissues (Figures 4 and 5). Edema in the hand was resolved, with the exception of

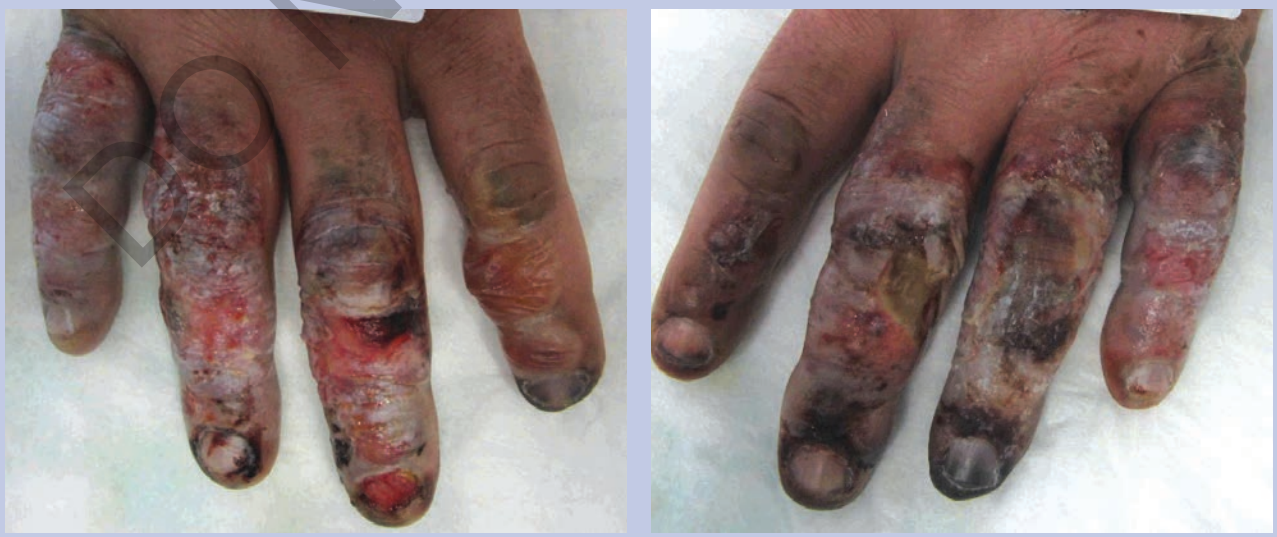

Figure 3. Right and left hands 8 days postinjury.

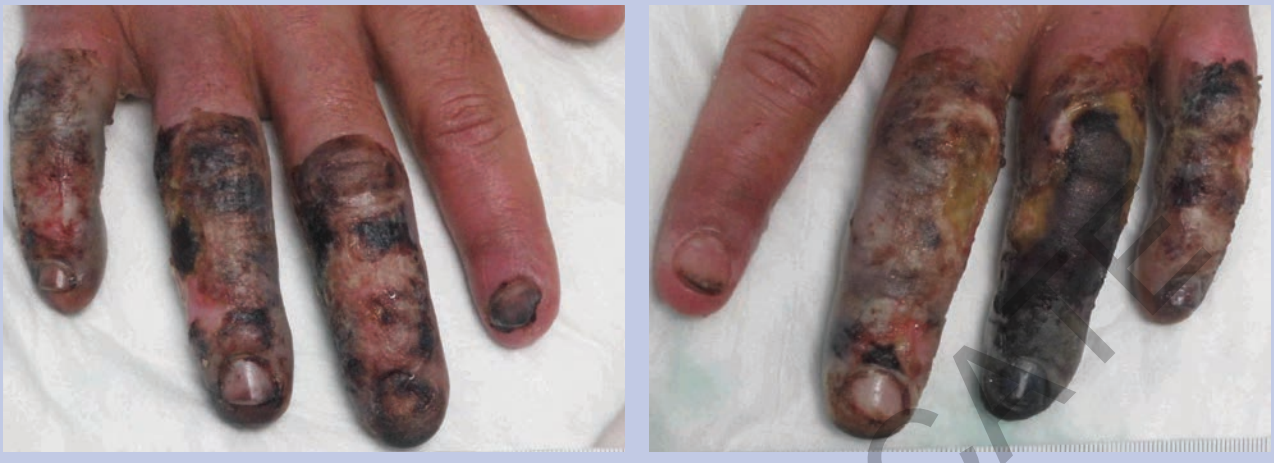

Figure 4. Right and left hands 21 days postinjury.

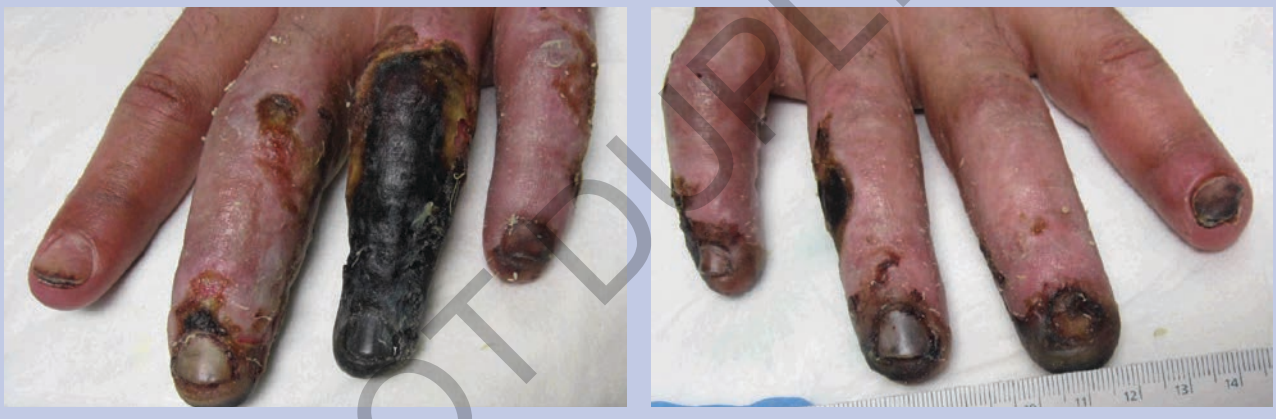

Figure 5. Right and left hands 28 days postinjury.

mild edema in bilateral fifth digits. The fourth digit of the left hand became hard and cold with dry eschar.

After completion of the second round of HBO therapy, all of the fingers on the patient's right hand had fully epithelialized, with no odor, drainage, or maceration (Figure 6). On the left hand, the third digit fingertip had a granulating base along with slough and fibrin postdebridement without drainage, odor, or maceration. The fifth digit had fully epithelialized. The fourth digit had not improved and had eschar from the distal interphalangeal joint to the tip (Figure 6). Two weeks after the final HBO treatment, surgical amputation was performed to remove the mummified portion of the distal fourth digit. The patient continued treatment at the wound clinic for the surgical wound until completion of healing (Figure 7). The patient underwent physical therapy 3 times a week to restore strength and range of motion to his fingers, enabling him to return to work in a factory without limitations. Six months after his initial injury, the patient's left third digit was found to have osteomyelitis that was treated successfully with antibiotics.

Discussion

This report describes a favorable outcome for deep frostbite after treatment with tPA and HBO, despite comorbidities of hypothermia and ethanol intoxication. The patient's grade II hypothermia put him at risk for cardiac arrhythmia and necessitated gradual rewarming, which precluded the rapid rewarming of his frostbitten fingers.[1,36] Management of his acute condition delayed management of his frostbite, including thrombolytic and HBO therapies.

Traditionally, frostbite injuries have been classified on the basis of their appearance many days after the

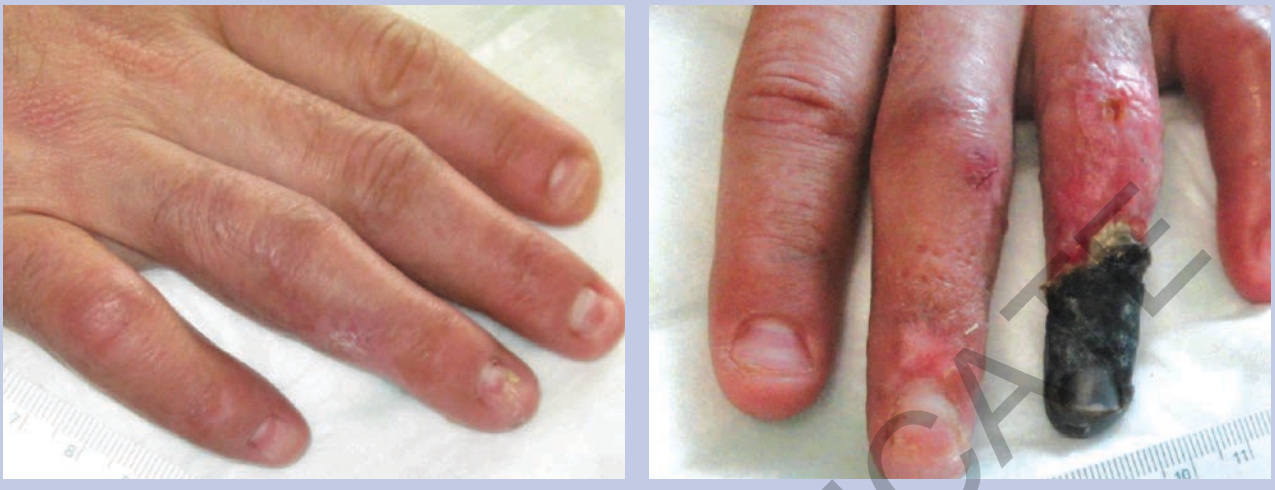

Figure 6. Right and left hands 84 days postinjury.

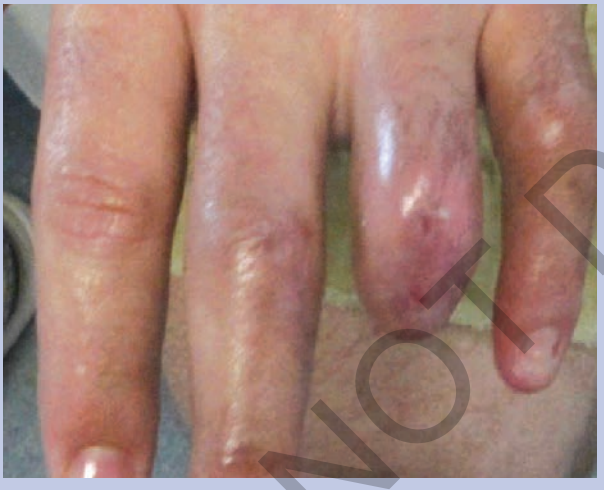

Figure 7. Left hand 126 days postinjury.

injury occurs. As such, the traditional classification scheme can neither guide clinical decisions nor predict tissue loss independent of medical intervention during the second phase of frostbite pathophysiology. More recently, Cauchy and colleagues[37] described an alternative classification scheme based on the anatomical extent of the injury soon after rewarming. According to their classification scheme, all 6 of this patient's injuries were Grade 3 frostbite, which indicates each digit carried a high risk of amputation. In the case series of Cauchy and coauthors, 83% of Grade 3 injuries to digits on the hand eventually required bone amputation with a confidence interval of 66% -100%.

In the described case, the patient's alcohol intoxication led to his prolonged exposure to the freezing temperatures that caused frostbite by affecting his judgment and level of consciousness, thereby preventing him from seeking shelter. Several epidemiological reviews have identified alcohol use as a predisposing factor for frostbite.[38-40] In addition to the behavioral effects of alcohol, a study performed on frostbitten mice tails demonstrated that alcohol has a physiologically detrimental effect on frostbite outcomes.[41] While the mechanistic effects of alcohol on frostbite have not yet been characterized, alcohol's action as a vasodilator may play a role by accelerating heat loss. Interestingly, alcohol has, in the past, been administered intravenously as a vasodilating agent as part of frostbite treatment.[8]

It is difficult to say with certainty whether this patient's prior history of smoking was also detrimental to his frostbite injury. While published frostbite treatment protocols have prudently recommended tobacco use be prohibited,[1,2] there is sparse evidence of tobacco's harmful effect on frostbite. There have been mixed epidemiological findings regarding smoking,[38,42-44] and an animal study of systemic nicotine was inconclusive.[45]

This case is unique because it is the first time in literature that a patient with frostbite has received both thrombolytic and HBO treatments. Both of these treatments for frostbite are supported by favorable research findings, but neither has attained widespread clinical use. Thrombolytic therapy, using intra-arterial tPA, has been used experimentally as a treatment for frostbite to limit the ischemic effects of frostbite by improving perfusion to affected tissues. However, there have been clinical findings that suggest this therapy is ineffec-

tive if administered more than 24 hours after rewarming.[31,32] Additionally, results from an animal study, using streptokinase, found that thrombolytic therapy begun 12 hours after rewarming is significantly more effective than thrombolytic therapy begun 24 hours after rewarming.[34] In the described case, tPA therapy was delayed until 36 hours after rewarming and it seemed to be of only minimal benefit to the patient, given that there was no substantial change in the digital artery occlusions over the course of the tPA therapy. The reported result is consistent with the previous evidence that thrombolytic therapy is less effective beyond 24 hours after rewarming the frostbitten tissue.

The apparent ability of HBO to salvage frostbitten tissue is thought to stem from a combination of physiological mechanisms related to elevated arterial oxygen concentrations. Hyperbaric oxygen therapy increases oxygen delivery to ischemic tissues directly via elevated arterial oxygen concentrations, and indirectly via angiogenesis and resolution of tissue edema. Intermittent HBO has been shown to stimulate angiogenesis, mediated by vascular endothelial growth factor.[46] Hyperbaric oxygen therapy is also able to reduce postischemic tissue edema by causing intermittent vasoconstriction,[47] which allows for improved microcirculation as interstitial pressure is reduced below capillary filling pressure. In the context of human frostbite, Finderle and Cankar[16] found moderately decreased blood flow consistent with vasoconstriction and a sixfold increase in the capillary density of injured skin immediately following HBO treatment for their patient.

A laboratory study using a frostbitten rabbit ear model demonstrated that HBO therapy, at 2.5 ATA of 100% O2 for 28 treatments over 14 days for 90 minutes each, negates some of the ischemia-causing inflammatory effects of frostbite by increasing prostacyclin—a cell mediator considered to be protective against thromboxane—and decreasing the number of neutrophils and mast cells in the treated frostbitten tissue.[30]

Research on HBO, apart from its use as a treatment for frostbite, has demonstrated additional physiological effects that may promote healing of frostbite injuries. HBO therapy has been shown to ameliorate reperfusion injuries by temporarily inhibiting neutrophil β2 integrins and inducing activity of antioxidant enzymes and anti-inflammatory proteins.[48] Hyperbaric oxygen is also capable of stimulating the synthesis of many wound healing mediators, including basic fibroblast growth factor and transforming growth factor β1, and the up-regulation of platelet-derived growth factor receptors in wounds.[48]

Ideally, HBO therapy would be initiated soon after rewarming, so that it can ameliorate the ischemic effects of frostbite that begin upon rewarming.[11,17,19] However, many case reports describe favorable results in instances where HBO therapy was initiated more than a week after the injury.[7,8,15-18,20,26-28] This report of a patient who began HBO therapy 8 days after his injury adds to the case-based evidence suggesting that HBO therapy can benefit the patient even if it is initiated many days after the injury.

Twenty-three previous case reports on HBO therapy for frostbite are tabulated, describing 38 distinct patients (Table 1). The efficacy of HBO therapy and the various parameters utilized are not amenable to direct comparison across case reports due to inconsistent reporting of wound severity, use of wound classification that is not independent of treatment efficacy, and heterogenous interventions prior to HBO therapy. Research is needed to further evaluate the efficacy of HBO therapy for frostbite and determine the optimal treatment parameters in regard to depth, duration, and frequency.

Conclusion

This case report adds further evidence that HBO can aid in salvaging tissue damaged by frostbite. As with prior case reports, the weight of the evidence is limited by a lack of a treatment control. Further research using controlled trials will be necessary to fully establish HBO as an effective treatment for frostbite and to develop optimal treatment parameters.

While HBO and thrombolytic therapies both seem to be effective adjunctive treatments for frostbite and can be used in combination with each other, HBO is advantageous in its ability to be effective for a longer period of time after the injury.

References

1. Murphy JV, Banwell PE, Roberts AH, McGrouther DA. Frostbite: pathogenesis and treatment. *J Trauma*. 2000;48(1):171-178.
2. Imray C, Grieve A, Dhillon S, Caudwell Xtreme Everest Research Group. Cold damage to the extremities: frostbite and non-freezing cold injuries. *Postgrad Med J*. 2009;85(1007):481-488.
3. Ledingham IM. Some clinical and experimental applications of high pressure oxygen. *Proc R Soc Med*.

1963;56:999-1002.
4. Smith G. Therapeutic applications of oxygen at two atmospheres pressure. *Dis Chest*. 1964;45:15-23.
5. Perrin ER, Bossinnette R. Frostbite, a new adjunct in treatment. *J Am Med Assoc*. 1965;194(1):99.
6. Trippel OH, Jurayh MN, Staley CJ, van Elk J. Surgical uses of the hyperbaric oxygen chamber. *Surg Clin North Am*. 1966;46(1):209-221.
7. Ward MP, Garnham JR, Simpson BRJ, Morley GH, Winter JS. Frostbite: general observations and report of cases treated by hyperbaric oxygen. *Proc R Soc Med*. 1968;61(8):787-789.
8. Wilson JA, Wilson AN Jr. Cold injury: report of an unusual case. *Alaska Med.* 1968;10(4):172-174.
9. Cooke JN. Hyperbaric oxygen treatment in the Royal Air Force. *Proc R Soc Med*. 1971;64(9):881-882.
10. Gage AA, Ishikawa H, Winter PM. Experimental frostbite. The effect of hyperbaric oxygenation on tissue survival. *Cryobiology*. 1970;7(1):1-8.
11. Okuboye JA, Ferguson CC. The use of hyperbaric oxygen in the treatment of experimental frostbite. *Can J Surg*. 1968;11(1):78-84.
12. Hardenbergh E. Hyperbaric oxygen treatment of experimental frostbite in the mouse. *J Surg Res*. 1972;12(1):34-40.
13. Weaver LK, Greenway L, Elliott CG. Controlled frostbite injury to mice: outcome of hyperbaric oxygen therapy. *J Hyperbaric Med*. 1988;3(1):35-44.
14. Bajrović F, Tipton MJ, Golden FSC, Mekjavic IB. HBO as an adjunct therapy in the treatment of frostbite: a progress report. In: Mekjavic IB, Tipton MJ, Eiken O, eds. *Proceedings of the 23rd Annual Scientific Meeting of the European Underwater and Baromedical Society*. Bled, Slovenia: Biomed, Ljubljana. 1997;210-212.
15. von Heimburg D, Noah EM, Sieckmann UP, Pallua N. Hyperbaric oxygen treatment in deep frostbite of both hands in a boy. *Burns.* 2001;27(4):404-408.
16. Finderle Z, Cankar K. Delayed treatment of frostbite injury with hyperbaric oxygen therapy: a case report. *Aviat Space Environ Med*. 2002;73(4):392-394.
17. McCrary BF, Hursh TA. Hyperbaric oxygen therapy for a delayed frostbite injury. *Wounds*. 2005;17(12):327-331.
18. Ay H, Yildiz S, Uzun G, Solmazgul E, Dundar K, Yildirim İ. The treatment of deep frostbite with hyperbaric oxygen. *Inj Extra*. 2005;36(11):499-502.
19. Mekjavic IB, Gorjanc J, Mekjavic PJ, Bajrovic F, Milcinski M. Hyperbaric oxygen as an adjunct treatment of freezing cold injury. *Prev Cold Injuries.* 2005;16:1-4.
20. Folio LR, Arkin K, Butler WP. Frostbite in a mountain climber treated with hyperbaric oxygen: case report. *Mil Med*. 2007;172(5):560-563.
21. Zanon V, Picchi GF, Garetto G, Bosco G. Hyperbaric oxygen therapy (HBOT) in the delayed treatment of 8000 meter peak climber frostbites [abstract]. Paper presented at: Undersea and Hyperbaric Medical Society 40th Annual Scientific Meeting; June 14-16, 2007; Kapalua, HI.
22. Sever C, Kulahci Y, Acar A, Karabacak E. Unusual hand frostbite caused by refrigerant liquids and gases. *Ulus Travma Acil Cerrahi Derg*. 2010;16(5):433-438.
23. Sever C, Kulahci Y, Acar A, Duman H. Frostbite injury of hand caused by liquid helium: a case report. *Eplasty*. 2010;10:e35.
24. Özkaya Ö, Egemen O, Bingöl D, Akan İM. Unusual both hands cryogenic burn caused by Freon gas and early treatment with hyperbaric oxygen therapy. *Inj Extra*. 2011;42(11):192-194.
25. Gorjanc J, Ahčan UG, Veselko M, Milčinski M, Mekjavić IB. Modern management of patients with frostbite [in Slovenian]. *Zdrav Vestn*. 2012;81(10):699-709.
26. Johnson-Arbor K. Hyperbaric oxygen therapy for the delayed treatment of frostbite. Poster presented at: Undersea and Hyperbaric Medical Society 46th Annual Scientific Meeting; June 13-15, 2013; Orlando, FL.
27. Johnson-Arbor K. Treatment of severe digital frostbite with hyperbaric oxygen therapy. Poster presented at: Undersea and Hyperbaric Medical Society 46th Annual Scientific Meeting; June 13-15, 2013; Orlando, FL.
28. Sanders RW, Anderson CA. A case of frostbite responds well to adjunctive hyperbaric oxygen therapy and advanced wound care techniques. Poster presented at: Undersea and Hyperbaric Medical Society 46th Annual Scientific Meeting. June 13-15, 2013; Orlando, FL.
29. Kemper TC, de Jong VM, Anema HA, van den Brink A, van Hulst RA. Frostbite of both digits of the foot treated with delayed hyperbaric oxygen: a case report and review of literature. *Undersea Hyperb Med*. 2014;41(1):65-70.
30. Uygur F, Noyan N, Sever C, Gümüs T. The current analysis of the effect of hyperbaric oxygen therapy on the frostbitten tissue: experimental study in rabbits. *Cent Eur J Med*. 2009;4(2):198-202.
31. Twomey JA, Peltier GL, Zera RT. An open-label study to evaluate the safety and efficacy of tissue plasminogen activator in treatment of severe frostbite. *J Trauma*. 2005;59(6):1350-1355.
32. Bruen KJ, Ballard JR, Morris SE, Cochran A, Edelman LS, Saffle JR. Reduction of the incidence of amputation in

frostbite injury with thrombolytic therapy. *Arch Surg*. 2007;142(6):546-553.
33. Johnson AR, Jensen HL, Peltier G, DelaCruz E. Efficacy of intravenous tissue plasminogen activator in frostbite patients and presentation of a treatment protocol for frostbite patients. *Foot Ankle Spec*. 2011;4(6):344-348.
34. Salimi Z, Wolverson MK, Herbold DR, Vas W, Salimi A. Treatment of frostbite with i.v. streptokinase: an experimental study in rabbits. *AJR Am J Roentgenol*. 1987;149(4):773-776.
35. Zdeblick TA, Field GA, Shaffer JW. Treatment of experimental frostbite with urokinase. *J Hand Surg Am*. 1983;49:619-620.
36. Brown DJ, Brugger H, Boyd J, Paal P. Accidental hypothermia. *N Engl J Med.* 2013;368(4):394.
37. Cauchy E, Chetaille E, Marchand V, Marsigny B. Retrospective study of 70 cases of severe frostbite lesions: a proposed new classification scheme. *Wilderness Environ Med*. 2001;12(4):248-255.
38. Valnicek SM, Chasmar LR, Clapson JB. Frostbite in the prairies: a 12-year review. *Plast Reconstr Surg*. 1993;92(4):633-641.
39. Koljonen V, Andersson K, Mikkonen K, Vuola J. Frostbite injuries treated in the Helsinki area from 1995 to 2002. *J Trauma*. 2004;57(6):1315-1320.
40. Antii-Poika I, Pohjolainen T, Alaranta H. Severe frostbite of the upper extremities--a psychosocial problem mostly associated with alcohol abuse. *Scand J Soc Med*. 1990;18(1):59-61.
41. Barillo DJ, Spillert CR, LoVerme PJ, Lazaro EJ. Detrimental effects of ethanol on murine frostbite. *Am Surg*. 1984;50(12):649-652.
42. Lehmuskallio E, Lindholm H, Koskenvuo K, Sarna S, Friberg O, Viljanen A. Frostbite of the face and ears: epidemiological study of risk factors in Finnish conscripts. *BMJ*. 1995;311(7021):1661-1663.
43. Hashmi MA, Rashid M, Haleem A, Bokhari SA, Hussain T. Frostbite: epidemiology at high altitude in the Karakoram mountains. *Ann R Coll Surg Engl*. 1998;80(2):91-95.
44. Ervasti O, Juopperi K, Kettunen P, et al. The occurrence of frostbite and its risk factors in young men. *Int J Circumpolar Health*. 2004;63(1):71-80.
45. Lewis RB, Moen PW. The effect of rutin, hydergine and nicotine on the extent of gangrene following experimental local cold injury. *Exp Med Surg*. 1953;11(1):9-20.
46. Hopf HW, Gibson JJ, Angeles AP, et al. Hyperoxia and angiogenesis. *Wound Repair Regen*. 2005;13(6):558-564.
47. Nylander G, Lewis D, Nordström, Larsson J. Reduction of postischemic edema with hyperbaric oxygen. *Plast Reconstr Surg*. 1985;76(4):596-603.
48. Thom SR. Hyperbaric oxygen: its mechanisms and efficacy. *Plast Reconstr Surg*. 2011;127(suppl 1):131S-141S.