Percutaneous Image-Guided Cryoablation in Vascular Anomalies

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Semin Intervent Radiol 2017;34:280–287

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Abstract

Understanding and management of vascular anomalies has always been intriguing. These disorders exhibit an expected pattern of clinical presentation and progression, and characteristic imaging findings. Significant progress in understanding and treating patients with vascular anomalies has been made in the past quarter century. Newer multidisciplinary domains for treating these disorders with medical drugs and less invasive image-guided or surgical procedures are constantly evolving. Vascular anomalies can exhibit aggressive tumor-like behavior resulting in recurrence or persistent symptoms after treatment. Thermal ablation has been widely used in tumor treatment. This has generated interest on using thermal ablation for treating vascular anomalies. Percutaneous image-guided cryoablation is increasingly used for this purpose as compared with other ablation technologies. Availability of small caliber cryoprobes and the ability to monitor the freeze zone in real time have made this an attractive option to interventional radiologists. These experiences are relatively new and limited. It is helpful to understand the emerging role of this technology in the treatment of vascular anomalies.

Keywords

- vascular malformations
- vascular anomalies
- percutaneous image-guided cryoablation
- cryotherapy
- interventional radiology

Objectives: Upon completion of this article, the reader will be able to describe the indications and technique of safely performing cryoablation in patients with vascular anomalies. Essential technical details about cryoablation are also discussed.

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The management of vascular malformations is challenging and requires an interdisciplinary approach. Treatment typically focuses on reducing the disease burden, preventing

complications, improving quality of life, and providing cure whenever possible. The role of interventional radiology has traditionally been to perform image-guided percutaneous sclerotherapy and endovascular embolization to obliterate the vascular component of the malformations.¹ These lesions tend to recur or continue to grow, necessitating repeated endovascular treatments to achieve a reasonable control. Additionally, these malformations are frequently associated with variable bulk of soft-/solid-tissue component that does not respond to endovascular treatment alone and may be the cause of treatment failure.² The soft-tissue portion of the malformation can be a dormant source of the malformation, allowing it to recur over time. Occasionally, it may be the cause of residual pain and functional impairment in malformations.³ Surgical resection of the residual soft-tissue abnormality following endovascular closure of vessels may be required to prevent recurrence and improve the overall response. Image-guided thermal ablation techniques, such as cryoablation, radiofrequency ablation, microwave ablation, are being increasingly used in the treatment and pain

palliation of solid tumors.⁴ These provides tumor shrinkage and pain control by direct and indirect effects. Based on this experience, ongoing attempts are being made, especially by interventional radiologists, to use these techniques for treating vascular malformations.^{5,6} Percutaneous cryoablation has been the most commonly used ablation modality with limited early experiences still emerging.⁷⁻¹⁰

Strategies for Percutaneous Image-Guided Cryoablation in Vascular Anomalies

Patient Selection and Informed Consent

At our institution, we offer cryoablation in patients with vascular malformations presenting with focal pain, especially in patients with fibro-adipose vascular anomaly (FAVA). All patients are initially evaluated in the interdisciplinary vascular anomaly clinic. A detailed clinical examination and review of all available imaging is performed. An on-site ultrasound (US) examination is performed by the interventional radiologist to document the lesion characteristics. Magnetic resonance imaging (MRI), which includes T2-weighted fat-suppressed/inversion recovery images (►Fig. 1a) and T1-weighted (►Fig. 1b) and postgadolinium images (►Fig. 2a), is preferred and routinely requested when no prior cross-sectional images

are available. A decision to use cryoablation for treatment is reached by consensus among the involved specialists. The interventional radiologist and the orthopedician are especially involved in formulating the treatment and follow-up plan. Patients with vascular malformation whom we consider as poor candidates to cryoablation have one or more of the following features:

1. Diffuse involvement of the malformation.
2. Pain or symptoms discordant to location of the malformation.
3. Significant muscle contracture.
4. Malformation wrapping around or extending into nerves.
5. Intra-articular involvement.
6. Acral (hand and foot) lesions (►Fig. 1a-d).

It is essential to understand the expectations of the patients and discuss with them the anticipated goals or end points of the treatment. A thorough preprocedural discussion is necessary with the parents/legal guardians of pediatric patients to educate them of the outcome expectations, follow-up, other treatment options, and possible complications. Since the procedure is relatively new, many parents are anxious and nervous about subjecting their children to this technique. A simple, clear conversation to

Fig. 1 (a) Coronal T2-weighted fat-suppressed MR image demonstrates an extensive hyperintense painful vascular malformation involving the intrinsic muscles of the foot (arrows). (b) Sagittal T1-weighted MR image reveals the infiltrative nature of the malformation wrapping around the neurovascular structures (arrow). (c) Ultrasound image demonstrates ill-defined hyperechoic malformation extending close to the skin. (d) Ultrasound image during cryoablation shows the ice ball margin (wide arrow) growing close toward the skin (narrow arrow).

Fig. 2 (a) Axial T1-weighted fat-suppressed postgadolinium MR image reveals significant enhancement of the intramuscular (semimembranosus) vascular malformation (wide arrow). The sciatic nerve is located adjacent to the malformation seen as oval nonenhancing structure (narrow arrow). (b) Axial dyna-CT image demonstrates a thermocouple (wide arrow) placed between the sciatic nerve (narrow arrow) and the malformation. Diluted contrast was injected to hydrodissect and displace the nerve away from the malformation prior to ablation. (c) Axial dyna-CT image during cryoablation demonstrates the two parallel cryoprobes in the center of the malformation (arrow). The ice ball is seen as hypodensity around the cryoprobes.

make them comfortable without inducing unwarranted fear of the procedure risks is supportive. Most adolescent patients are able to participate actively in the decision-making process and ask questions regarding symptom relief, degree of cosmetic correction and resumption of full activity postprocedure.

Anesthesia

Almost all children will need general anesthesia or higher levels of sedation to minimize motion, tolerate pain better, and allow positioning during the procedure. Deep sedation or general anesthesia in children can provide some postprocedure amnesia unlike in adults who can tolerate most procedures under mild sedation and local anesthesia. Vascular malformations can be painful due to underlying inflammation, pressure symptoms, or involvement of nerves. Cryoablation also produces inflammatory response aggravating postrecovery pain and swelling. Patients with lower extremity lesion may have a limp during the recovery phase. High-dose steroids and narcotic analgesics can be administered periprocedurally to curtail the inflammation and provide postablation pain control. We routinely use regional nerve block for postablation pain control. The regional block anesthesiologist places a nerve block catheter prior to the procedure in the interventional radiology suite. All nerve blocks are done with continuous US guidance with in-plane visualization of needle (→ Fig. 3). Occasionally, nerve stimulation is used as a tool for nerve localization in conjunction with US. Bupivacaine (0.25 and 0.5%) and Ropivacaine (0.2 and 0.5%) are the most often used agents, as they are the longest acting local anesthetics available. Typical dose is usually 0.25 to 1 mL/kg depending on site, patient's weight, and local anesthetic being used. It is imperative to have treatment for local anesthetic systemic toxicity (LAST) readily available in the suite.¹¹ For upper extremity lesions, an interscalene block for shoulder, proximal humeral lesions and infraclavicular/supraclavicular block for mid

humerus, forearm, and hand lesions is performed.¹² In lower extremity, a lumbar plexus block for lesions near the hip and upper femur, a femoral block for anterior thigh lesions, and a sciatic block for posterior thigh and below knee lesions are often performed.¹³ An initial bolus dose of a local anesthetic is administered prior to ablation. Additional infusion dosing is determined based on any residual discomfort or pain when patient is in the recovery unit. Regional nerve block has been exceedingly helpful for a smooth recovery in the immediate postablation period. Typically, most patients stay overnight and get discharged the following day. Narcotic analgesics are routinely prescribed for approximately 5 days thereafter. Patients who have cryoablation for lower extremity lesions may need crutches for few days to limit weight bearing and accomplish an easier recovery.

Fig. 3 In-plane ultrasound image during regional nerve block demonstrates the sciatic nerve (wide arrow) and the needle (narrow arrow) tracking toward the nerve.

Equipment

The availability of smaller 17-gauge vacuum-insulated cryoprobe has made cryoablation possible as a percutaneous treatment rather than an open surgical procedure. Currently, in the United States, there are two commercially available cryoablation devices. Endocare produces the Percryo system (Endocare/HealthTronics, Austin, TX), which allows placement of up to eight individually controlled cryoprobes. Needle sizes range from 1.7 to 2.4 and to 3.8 mm in diameter. The size and shape of the resultant ice balls are the function of cryoprobe size and Joule-Thompson chamber configuration. Galil Medical's cryoablation system (Galil Medical, Arden Hills, MN) offers 1.5-, 2.1-, and 2.4-mm-diameter probes that are MR compatible. Both systems allow real-time monitoring of temperature using thermocouples.¹⁴ Argon gas is used for freezing and helium gas is used for thawing, both being colorless, odorless, and nontoxic. To achieve a complete and uniform treatment, the critical temperature lies between -20 and -40°C . No further tissue damage is caused by dropping lower than -40°C .¹⁵ The ice ball has at least three variable zones of freeze temperatures which are -40°C at the core surrounded by a zone of -20°C and a peripheral zone of -0°C . Accordingly, most cell death occurs within the two inner zones. The generator has a capacity to connect to eight cryoprobes to be used simultaneously, with equivalent number of ports for temperature sensors. The temperature sensors which are typically 17 gauge in size have thermocouples at the tips for temperature monitoring. Both straight and angled shaft cryoprobes are available. It is recommended to test the cryoprobes to detect for gas leaks or any aberrations in the ice ball configuration before placement in vivo.

Imaging

Prior to the procedure, all available imaging techniques especially the cross-sectional imagings such as MRI, US, and computed tomography (CT) are carefully reviewed to correlate the symptomatic sites and localize critical structures prone to injury during ablation. We extensively use US (Logiq E9; GE Healthcare, Waukesha, WI) both for placement of the cryoprobes and to monitor the ice ball growth in real

time ($\rightarrow$ Fig. 4). Occasionally, we also use intermittent DynaCT (Siemens AG, Forchheim, Germany) imaging to confirm appropriate probe placement and estimate if the isotherm of the ice ball encompasses the entire malformation ($\rightarrow$ Fig. 2c). Optimal use of US precludes the need for unnecessary ionizing radiation and its stochastic effects, which is a concern in pediatric patients.¹⁶

Anatomical Considerations

Children have a smaller body mass index which can limit the accessibility. Due to the smaller volume of the subcutaneous fat and muscle bulk, the skin can be vulnerable to injuries during ablation of tumors. It is critical to embed the active tip of the probe entirely into the malformation away from the skin. The ice can quickly propagate toward the skin along the shaft resulting in injury at the entry site. Therefore, the skin, not only at the ablation site but also at the entry site of the cryoprobe, should be constantly monitored and protected from cold burns. Unlike sedation used for most procedures in adults, in children these are done under general anesthesia, which may obscure any immediate signs of nerve injury. As we use regional nerve blocks in our patients, nerve injuries can be masked until the block wears off. Therefore, we take extreme care to protect any adjacent nerves during ablation. These facts need to be carefully considered during pre-procedure planning.

Technique

Patient preparation: On the day of the procedure, the painful sites are outlined by the patient using a skin marker in the presence of the interventional radiologist. When several painful spots are present in a large or extensive malformation, the sites to be treated are prioritized based on severity of symptoms. Patients also complete a brief pain inventory (BPI) form that also includes quality-of-life questionnaire.¹⁷⁻¹⁹ We also document the presence of concurrent symptoms such as swelling, functional restriction (mobility, weight bearing, range of motion, weakness, and gait abnormalities), and skin hyperesthesia.

Fig. 4 (a) Ultrasound image during cryoprobe placement reveals the probe centered within the malformation with its tip extending slightly beyond the margin (arrow). (b) Ultrasound image during cryoablation shows contour of ice balls from two parallel cryoprobes (arrows).

Anesthesia and patient positioning: A regional nerve block is initially placed after complete general anesthesia. Patient positioning is critical and depends on factors such as anticipated imaging to be used during the procedure, ease of accessibility to the malformation, any additional procedures such as sclerotherapy/embolization to be performed concurrently, and positioning of the cryoablation system especially the long redundant cables to the probes. It is important to be able to move/rotate the extremity to correctly place or direct the applicator probes when the malformation extends across curved anatomical regions. These details should be carefully considered prior to the procedure.

Intraprocedural details: US guidance is used for initial probe placement. A careful US examination is performed to accurately localize the margins of the lesion, measure the lesion in two planes, and to identify and mark the nearby nerves when possible. One or more Endocare Perc-17 or Perc-24 cryoprobes (HealthTronics/Endocare Incorporated, Irvine, CA) are selected by referring to the vendor-supplied reference chart showing isotherm ice ball dimensions. For smaller and superficial lesions, a single cryoprobe is placed centrally along the long axis of the lesion (►Fig. 4a). When more than one cryoprobe is employed, these are generally placed within 1.5 to 2 cm of one another and 1 cm of the lesion to allow complete coverage (►Fig. 2c). It is essential to slightly advance the tip beyond the distal margin to ensure adequate coverage. When the malformation is in close apposition to a nerve, hydrodissection, or even carbon dioxide dissection, can be used to displace the nerve.²⁰ Additionally, temperature or evoked potential monitoring may be used for intraprocedural monitoring of peripheral nerves with higher risk of injury during cryoablation.^{20–22} We also place one or more thermocouples in the intervening plane just next to the nerve (►Fig. 2b). US is continuously used for cautious and safe placement of the thermocouple needles without causing direct trauma to the nerve. Ice ball growth is monitored with US, and/or with DynaCT images every 2 to 5 minutes for deeper lesions that are difficult to visualize with US. Two freeze cycles are performed with an intervening passive thaw. Freeze times are adjusted based on real-time monitoring of the ice ball growth to cover the entire lesion and avoid inadvertent freezing of adjacent critical structures like nerves and skin. Final active thaw is performed with helium before probe removal. For extensive lesions, the far end and the deeper aspect of the lesion are targeted first, and the near portions are then ablated by retracting the probes. For superficial lesions, the overlying skin can be protected with prewarmed fluid bags or warm saline filled in sterile gloves (►Fig. 2b). Ablation is normally stopped when the ice ball reaches approximately 5 mm from the skin or when blanching of the skin starts to appear. With any initial blanching of the skin, the ablation should be immediately stopped and redirection of the probe into a relatively deeper plane should be considered whenever possible. Hydrodissection can also be used to displace the

skin away from the ice ball in superficial lesions. Early skin blanching can be reversed with careful rewarming of the skin using the warm saline bag. Additional sclerotherapy or embolization to close anomalous vessels is then performed.

Postprocedure recovery: The patients are monitored in the recovery unit for 2 to 3 hours following the procedure and then admitted overnight for observation. The degree of any residual pain or discomfort can be assessed and addressed in the recovery unit. The nerve block is discontinued the following morning. Before being discharged, the patients are reevaluated for any new symptoms or concerns, especially for nerve injuries. For lower extremity lesions, patients obtain appropriate physiotherapy evaluation and recommendations. Patients are discharged with anti-inflammatory medication for 3 to 5 days.

Assessment and Follow-up

Patients fill a BPI prior to the procedure (on the day of the procedure) and on follow-up clinic visits.^{17,18} A general evaluation of overall pain, swelling, functional restriction (mobility, weight bearing, range of motion, weakness, and gait abnormalities), and skin hyperesthesia are also documented. Patients are again seen in the clinic at 10 days to assess for any emerging complications. A response follow-up is usually performed at 1 month, 3 months, and every 2 months up to 6 months. Clinical examination and US examination, if needed, are performed at follow-up. The clinical response, patient satisfaction, and complications are documented.

Mechanism of Action of Cryoablation

Vascular malformations are made up of dysmorphic and disorganized tissue with little or no function. Targeted cryoablation destroys the malformation by causing effective cell death within the malformation. With argon-based cryoablation systems, the Joule-Thomson effect of expanding gases is utilized to cause rapid freezing. Sudden expansion of the pressurized cryogen at the needle tip produces a heat sink near the antenna tip that cools the probe to temperatures of -140°C . This can cause cell death by both direct and indirect mechanisms. Rapid freezing causes formation of interstitial ice crystals and hyperosmotic environment which dehydrates the cells and compromises cell membranes. This allows for intracellular ice formation which irreversibly damages cell membranes and cell organelles promoting cell death.^{23,24} Five to 10 minutes of rapid freezing causes sustained cellular death.²⁵ The thawing process, which is a prime factor in cell death, reverses the osmotic gradient driving additional water into the viable cells and rupturing the membranes.²⁶ The indirect cytotoxic effect is caused by cold-induced vasoconstriction of vessels leading to ischemia. Slow thawing causes crystallization of water in the vascular endothelium causing ice formation within the microvasculature and further ischemic changes.²⁷ Due to leakage of intravascular contents into the interstitium, an inflammatory reaction ensues which leads to cellular anoxia and infarction.^{26,28} Additionally, apoptotic cell death is seen

at the periphery of the ablation zones.^{29,30} Cryotherapy has also shown evidence of downregulation of vascular endothelial growth factor, which is a critical component in growth of malformations.^{3,31}

Advantages and Limitations of Cryoablation

The major advantage of cryoablation is the visualization and control of the aggregated ice ball with US, CT, and MRI, although only the leading edge of the ice ball is seen with US as a hyperechoic rim with intense acoustic shadowing.³² On CT, the ice ball appears hypodense around the dense probe, and as signal void on T1- and T2-weighted MR sequences.³³ Cryoablation devices typically do not cause interference with CT or MRI machines, as the mechanism of cooling is mechanical and not electronic.¹⁴ Multiple probes can be used simultaneously to create an ablation zone that conforms to the diffuse or infiltrative shape of the malformation. As cryoablation has local anesthetic effect, it is also less painful as compared with other ablation techniques such as radiofrequency and microwave during the procedure.¹⁴ However, it can also produce a vigorous inflammatory response.³⁴ This can cause additional pain during recovery in inflamed and painful malformations such as in FAVA.³⁵ Because the ablation zone is reperfused after the ice ball melts, the result is a rapid release of cellular debris into the systemic circulation, causing a systemic inflammatory response syndrome known as cryoshock.³⁶ This is typically seen with large volume ablation. The higher isotherm temperatures at the periphery of the ice ball may result in unreliable cell death and ineffective treatment of the entire malformation. Although this is not strictly necessary while treating pain alone in malformations, this may be the cause of recurrent symptoms or interval growth of the malformation. Cryoablation does not provide inherent cautery effect which can exacerbate hematoma or incessant oozing within the vascular malformation. A particular concern with cryoablation is the risk of causing nerve injury. All necessary precautions to protect the nerves should be appropriately planned and implemented during the procedure.^{20–22} Most nerve injuries are mild and transient. If any nerve damage is suspected or anticipated, an early follow-up, typically at 10 to 14 days, is helpful to reassess and intervene earlier to prevent any long-term sequelae. If neurapraxia does occur, steroids may be considered for treatment.³⁷ However, in cryoablation-related nerve injury, the epineurium and perineurium are preserved, which allows for nerve regeneration over time.^{38,39} For superficial lesions close to the skin, cryoablation can cause skin burns and rarely skin necrosis.⁴⁰ Similar adjunctive steps like carbon dioxide dissection or hydrodissection and constant local warming can be used to prevent skin injury.

Cryoablation in Low-Flow Malformations

The initial experience of using cryoablation was in venous malformations. Cornelis et al reported ablating focal venous malformations in four patients.⁷ Only one session was performed in each patient. They used two to four cryoprobes to over the entire lesion with two alternate rounds of 10-minute

freeze. All patients experienced complete resolution of pain in 2 weeks and 75 to 95% shrinkage of the malformation over 3 to 6 months. There was also resolution of contrast enhancement on follow-up MRI study. No complications were seen. We first described the largest experience of using cryoablation in patients with FAVA. FAVA, a recently recognized type of venous malformation, exhibits fibro-fatty infiltration of the muscles, unusual pain and phlebectasia, and contracture of the affected limb.⁹ Conventional treatments like sclerotherapy and local injection of steroid offer none or very transient relief. Surgical resection can be effective but has a longer recovery and increased risks. Cryoablation was performed in 26 FAVA lesions (focal and infiltrative types). An in-depth analysis of the response was performed using a modified BPI for pain and quality of life, in addition to evaluating concurrent symptoms and patient satisfaction. There was significant improvement in almost all the response parameters. Only one lesion in the foot required a repeat session after 3 months due to persistent pain. Surgical resection was performed for one lesion, 15 months after cryoablation for recurrent symptoms and patient preference. There was mild numbness overlying the area of ablation and along the nerve distribution at 4 of the 26 (15%) sites, which improved in 6 to 8 weeks. Another series described using cryoablation in three patients with venous malformations.² There was complete resolution of symptoms in two patients, and partial resolution in one patient. A minor complication occurred in the form of localized regional numbness.

Cryoablation in High-Flow Malformations

Woolen and Gemmete recently described their preliminary experience of treating residual facial AVMs with cryoablation.¹⁰ Four patients who had prior embolization procedures to obliterate the AVM until the arterial feeders or nidus vessels were too small to be safely accessed for further embolization were treated with cryoablation. This was performed at an average of 15 weeks after the last embolization. Two patients required additional session at 3 months. The rationale of using cryoablation over further embolization or surgery was for the following reasons: (1) AVM vessels too small to safely inject ethanol or NBCA with increased risk of causing injury to normal tissues and skin and (2) potential risks like hemorrhage, inability to assess extent of disease, and prolonged healing with surgical excision. In all patients, they were able to significantly reduce the residual component and the swelling at 1 year, precluding the need for further surgery. Minor complications such as angioedema, skin breakdown, and facial numbness were encountered which resolved between 3 days to 8 weeks.

Cryoablation in Vascular Tumors

Cryotherapy has been used to treat hemangiomas. There are case reports describing its use in oral hemangiomas and vascular lesions.^{41–43} A noninvoluting congenital hemangioma of the buccal space and maxillary tuberosity in an 18-year-old patient, presenting with recurrent and refractory bleeding,

was successfully treated with percutaneous cryoablation. Sebastian et al described a novel technique of using cryoablation for painful epithelioid hemangioendothelioma of a lumbar vertebra. Preoperative cryoablation of the L2 lumbar vertebral lesion was performed followed by staged surgery, also using image-guided minimally invasive approach. The patient did not require a spinal fusion and there was no recurrence on 3.5-year follow-up. The authors hypothesized that cryoablation killed the tumor cells likely preventing the lesion from recurring.⁴⁴ Thompson et al used cryoablation in two patients with hemangioendothelioma with complete resolution of pain and bleeding.² They propose that percutaneous ablation could be used as an alternative treatment option to surgical debulking in symptomatic vasoproliferative neoplasms and serves as an adjunct to medical therapy.

Conclusion

It is becoming increasingly clear that minimally invasive ablation techniques are emerging as alternative tools in the management of difficult and complex vascular anomalies. Cryoablation is one of the most accepted and attractive approaches, given its advantages. Moreover, it can be used to treat even large lesions and effectively control pains, and is relatively simple to perform percutaneously with image guidance. Future directions include expanding its use in the treatment of other vascular anomalies, and its possible adjunct to use with medical therapy and targeted drug delivery. At present, the high cost and limited availability of this modality continue to be its main limiting factors.

Acknowledgment

We thank Dr. Beth Eastburn, MD for contributing to the anesthesia section of the manuscript.

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