CRYOABLATION TOOLKIT

Nicole A. Wilson, PhD, MD; Edmund Yang, MD PhD

on behalf of the APSA New Technology Committee

BACKGROUND

Currently, there are two primary methods used to correct pectus excavatum: the open Ravitch procedure[1] and the minimally-invasive "Nuss" procedure[2]. Traditionally, pain control after pectus excavatum repair has been challenging. In particular, the sudden remodeling of the chest wall inherent in the minimally invasive Nuss procedure is associated with significant postoperative pain. Pain after pectus excavatum repair is caused by several factors including incisional pain, interruption of cartilaginous, muscular, and ligamentous structures in the chest wall, alteration of chest wall mechanics due to the presence of a bar, and pain of pleural irritation from the bar. Inadequately controlled pain can result in poor pulmonary "toilet", and result in sputum retention, atelectasis, pneumonia, lack of participation in physical therapy, and other postoperative complications. Therefore, it is critical that pain be adequately addressed in the immediate postoperative period.

Historically, analgesia was achieved with opiates administered parenterally and transitioned to enteral administration after the first few postoperative days. More recently, multimodal therapies including thoracic epidurals, patient-controlled parenteral opiate administration (PCA), anti-inflammatories, gabapentinoids, and muscle relaxants, have become the gold standard[3]. However, despite development of extensive multimodal analgesic regimens, the mainstay of postoperative pain management remains opioid pain medications. Concerns regarding increased risk of long-term opioid use after postoperative opioid therapy[4] and management of the side effects of opioid administration (respiratory depression, itching, nausea, sedation, and constipation) continue to drive the search for alternative pain management strategies.

CRYOABLATION

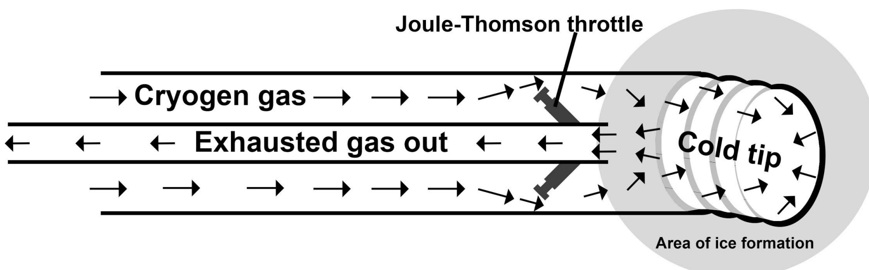
One of the first descriptions of the clinical application of cryotherapy to produce local blocking of peripheral nerves was in 1976 by LLoyd, Barnard, & Glynn[5]. Cryotherapy techniques have since been applied to the treatment of various neuralgias[6,7] and chronic pain[8]. Cryoablation has been shown to improve respiratory mechanics and to decrease opioid use when used for postoperative pain control after thoracotomy[9,10]. Given the success with cryoablation in adult patients after thoracic surgery, there has been recent interest in using cryoablation in pediatric patients undergoing repair of pectus excavatum[3,11-14].

Physiology

Cryoablation of intercostal nerves can offer both short- and long-term analgesia. A cryoprobe makes use of the Joule-Thomson (or Joule-Kelvin) effect, which describes the cooling effect that occurs with expansion of a gas that passes from an area of higher pressure to a lower pressure area[15]. The gas, typically carbon dioxide or nitrous oxide, is released at high pressure and allowed to rapidly expand within the bulb of the cryoprobe, resulting in cooling of the probe tip to approximately -50°C to -70°C[10] (Figure 1).

The cryoprobe is applied directly (or immediately adjacent) to the peripheral nerve of interest and creates a localized freezing, which induces axonotmesis, in which Wallerian degeneration of the axon and myelin sheath occurs distal, and to a lesser extent proximal, to the lesion[10]. This disrupts axonal continuity between the sensory nerve endings and the central nervous system (CNS). The perineurium and epineurium are relatively resistant to freezing, so they remain intact, maintain continuity, and provide a scaffold between the sensory nerve endings and the CNS[10]. Recovery (and restoration of sensation) is accomplished via axonal regeneration through the perineurial canal, which takes place at a rate of 1-3 mm/day.

Figure 1: Diagram of a Cryoprobe (Adapted from Smiley 2018[16])



Moorjani et al., (2001) investigated the histologic changes after direct application of a cryoprobe to intercostal nerves for 60 seconds[10]. Immediate histologic changes included axonal degeneration, accumulation of edema fluid, capillary stasis, and that the endoneurium remained intact. They also showed that one week after cryoablation axonal swelling gradually resolved. Histologically, there were signs of Schwann cell proliferation and axonal segments had reappeared in some nerve fibers indicating partial recovery of the ablated nerve tissue. This partial recovery was progressive and complete by one month after cryoablation. Furthermore, they demonstrated that longer applications of the cryoprobe caused the same changes, but the time taken for complete recovery was proportionally increased[10]. After a standard 90-120 second application of a cryoprobe, complete axonal regeneration can be expected by 4-6 weeks[13].

STEPS OF THE PROCEDURE

Use in the Nuss Procedure:

Since the use of cryoablation in the Nuss procedure is relatively novel, the surgical steps are somewhat variable and surgeon-dependent. Many surgeons use the cryoICE cryoprobe (Cryo2 or 3, https://www.atricure.com/cryo, AtriCure, Inc., Mason, OH, USA) which is a wand-shaped probe that can be placed into the chest under thoracoscopic guidance. It has an insulated shaft, allowing minimal exposure of the cryoablation tip. The probe is used with a preprogrammed freeze/thaw cycle for 120 seconds. It cools to -60°C and effective ablation is visualized as ice crystal formation on the chest wall. The probe initially adheres to the tissues, but releases from the area of ablation with warming (3-5 seconds. The probe is commonly bent at the tip to facilitate longitudinal application along the inferior aspect of the rib.

Cryoablation is performed posterolaterally at the same interspace in which the pectus bar is located, two intercostal spaces above the bar and two below the bar[13,14,17]. This usually ends up being intercostal nerves 4 through 8, although some authors extend ablation to include the 9th intercostal nerve. Care should be taken to count the interspaces, since Horner's syndrome and abdominal wall laxity are potential complications from ablating the T1-2 and T11-12 intercostal nerves, respectively. Though initial publications described subcutaneous dissection using the cryoprobe to reach the intercostal nerves[3], recent studies describe intrathoracic use of the probe bilaterally with thoracoscopic guidance. Single-lung ventilation can assist by providing better exposure of the intercostal nerves. Some authors elevate and dissect the mediastinum, then extend the thoracoscope and cryoprobe across the mediastinum to ablate the contralateral nerves[11,12], whereas some insert the thoracoscope and probe into each side for ipsilateral cryoablation[18].

Use in the Ravitch Procedure:

There is only a single study involving the use of cryoablation for analgesia in patients undergoing modified Ravitch procedure[19]. The cryoablation was performed thoracoscopically to the pertinent intercostal spaces. This was done either before or after the Ravitch procedure.

Use in Thoracotomy:

A posterolateral thoracotomy incision may be used to gain access to the thorax for a number of operations. Either upon gaining access to the chest, or before closure of the thorax, the intercostal nerves (one at the level of the incision, one cranial, and two caudal) are identified and exposed by peeling off the parietal pleura[10]. The cryoprobe is then placed on each nerve to be ablated, under direct vision, and ablation proceeds according to steps similar to those outlined above. The same equipment used for thoracoscopic cryoablation can be used under direct vision with a thoracotomy incision.

Use in Non-adolescent Children:

The successful use of cryoablation in adolescent patients undergoing the Nuss procedure begs the question of use in younger pediatric patients during thoracotomy. Unfortunately, there have been no documented studies involving thoracotomy nerve cryoablation for analgesia in this age group. However, cryoablation has been used in younger patients for ablation of tumors[20], vascular malformations[21], and foci of cardiac arrythmias[22].

REVIEW OF EVIDENCE FOR SAFETY AND EFFECTIVENESS:

There have been a number of studies investigating the use of intercostal nerve cryoablation in patients undergoing thoracotomy and Nuss procedure (Table 1). These studies show that use of cryoablation, in conjunction with a multimodal approach to postoperative pain control, results in a decreased length of hospital stay and decreased usage of opioid analgesics both as an inpatient and after discharge.

Table 1: Review of Literature

Study	Prospective vs. Retrospective	Number of patients (adult vs. pediatric)	Procedure	Length of stay (days)	Analgesia
Moorjani (2001)[10]	Randomized prospective	200 (adult)	Thoracotomy	NR	***Opioid: 7 days** **Cryo: 6 days**
Keller (2016)[3]	Retrospective	52 (pediatric)	Nuss	**Epidural: 5.8** **Cryo: 3.5**	***Epidural: 3.96 days** **Cryo: 3 days**
Sujka (2018)[18]	Retrospective	28 (NR)	Nuss	**Epidural/PCA: 4.0** **Cryo: 1.4**	**†Epidural/PCA: 2.6 days** **Cryo: 1.2 days**
Harbaugh (2018)[17]	Retrospective	31 (pediatric)	Nuss	**Epidural: 6** **Cryo: 3**	‡Epidural: 1.82 OME/kg Cryo: 1.78 OME/kg
Graves (2019)[13]	Randomized prospective	20 (adult & pediatric)	Nuss	**Epidural: 5** **Cryo: 3**	**§Epidural: 684 mg** **Cryo: 268 mg**
Dekonenko (2020)[23]	Prospective	100 (pediatric)	Nuss	**Epidural/PCA: 4** **Cryo: 1**	**†Epidural/PCA: 3.0 days** **Cryo: 0.9 days**
Pilkington (2020)[19]	Retrospective	29 (pediatric)	Ravitch	**Epidural: 6** **Cryo: 4**	†Epidural: 2 days Cryo: 1.5 days

NR: not reported; Cryo: cryoablation; **Bold text** indicates a significant difference between groups; * Days to cessation of use of opioid analgesics; † Days to only oral pain medication; ‡ Post-operative inpatient oral morphine equivalents (OME/kg), not significantly different; § Reported as oral morphine equivalents

The studies of cryoablation in pectus excavatum repair reviewed above are limited by their retrospective nature, rapidly evolving pain control protocols, and small sample sizes. However, despite these limitations, results are promising, suggesting improved patient outcomes with cryoablation compared to other pain control modalities.

While cryoablation is certainly promising as an additional therapy in our armamentarium, these studies demonstrate that cryoablation alone is not sufficient for postoperative pain control as it can take 24-36 hours to become fully effective[13,18]. In addition, its use is not without complications, side effects, and associated difficulties.

COMPLICATIONS / SIDE EFFECTS

As would be expected, cryoablation increases operative times. A single nerve ablation takes 2 minutes and typically 5 nerves are ablated on each side, the minimum length of time for a full cryoablation procedure is 20 minutes. Longer operative times (range: 40-60 minutes, mean 30 minutes) have been reported in the most recent literature[3,13,17,18,23]. One study did not demonstrate an increase in operative time for the modified Ravitch procedure when comparing cryoablation to thoracic epidural anesthesia[19].

Potential long-term complications following cryoablation include chronic neuropathic pain and persistent chest wall numbness. A recent study which included 43 adult and pediatric patients, demonstrated neuropathic pain in 38.5% of adults (age > 21 years), but an incidence of 0% in pediatric patients (age < 21 years)[24]. In this study, pediatric patients also had faster resolution of chest wall numbness (3.4 months vs. 10.8 months) compared to adult patients. In addition, there have been previous reports of neuralgia (e.g., burning, electrical, or tingling sensations) after cryoablation, with an incidence reported between 20-30% in adult series using cryoablation after thoracotomy[25]. The Graves et al. (2019) study included no reports of neuralgia in the group that underwent cryoablation. All patients had anterior chest wall numbness at initial follow-up and sensation returned to normal in all patients (6/10 at 3 months, 10/10 with one year)[13].

CAPITAL INVESTMENT AND COST ESTIMATES

The cryoICE Probe (cryoICE Probe for Cryo Nerve Block, CRYO2, AtriCure, Inc., Mason, OH, USA) is the most common probe used for peripheral nerve ablation. The probe itself is a single-use piece and is designed to be used with the AtriCure Cryo Module (ACM; cryoICE BOX V6, AtriCure, Inc., Mason, OH, USA) and the AtriCure Cryo1 Accessory Kit (composed of a Nitrous Oxide tank heater, a pressure regulator unit, and a temperature display unit). The ACM and Accessory Kit represent capital investments. Pricing for all components are negotiated at the hospital level.

This is the link to the website: http://https://www.atricure.com/cryo. There are video clips on the website demonstrating some uses of the cryoICE Probe (https://www.atricure.com/cryoice-probe-cryo-nerve-block) and additional information.

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