Title

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Forgotten Branch of the Intercostal Nerve: Implication for Cryoablation Nerve Block for Pectus Excavatum Repair

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Abstract

Background: We first utilized and reported on the use of cryoanalgesia for postoperative pain control for Nuss procedure in 2016. We hypothesized that postoperative pain control could be optimized if the intercostal nerve anatomy is better understood. To test this hypothesis, human cadavers were dissected to elucidate the intercostal nerve anatomy. Cryoablation technique was modified.

Methods: Cadaver Study: Adult cadavers were used to visualize the branching patterns of the intercostal nerves. Cryoablation: Posterior to the mid-axillary line for intercostal nerves 4,5,6 and 7, main intercostal nerve, lateral cutaneous branch and collateral branch were cryoablated under thoracoscopic view. Verbal pain scores were obtained from patients one day after the procedure.

Results: The study results were obtained during the years 2021 and 2022. Eleven cadavers were dissected. The path of the main intercostal and lateral cutaneous branch lie on the inferior rib surface of the corresponding intercostal nerve. Total of 92 lateral cutaneous branches of the intercostal nerve were dissected and measured as they pierced the intercostal muscle. Most lateral cutaneous branches of the intercostal nerve pierced the intercostal muscle anterior to midaxillary line 78.3%, posterior to midaxillary line 18.5% or on the midaxillary line 3.3%. The collateral branch of the intercostal nerve separated near the spine and traveled along the superior surface of the next inferior rib. Cryoablation: 22 male patients underwent Nuss procedure with cryoanalgesia. Median age of the patients was 15 years (IQR: 2), median Haller index was 3.73 (IQR:0.85), median pain score (0 to 10 maximum pain) was 1(IQR:1.75)**.**

Conclusion: Cryoablation of the intercostal nerve and its two branches improves pain control after a Nuss procedure.

Keywords: intercostal nerve, collateral branch, lateral cutaneous branch, cryoanalgesia, cryoablation, pectus excavatum, Nuss procedure

Level of Evidence: Level 4, Observational study

Abbreviations*:* IQR: interquartile range

Highlights:

1. *What is currently known about this topic?*

   The main intercostal nerve is cryoablated to achieve postoperative pain control after Nuss procedure.

2. *What new information is contained in this article?*

   Intercostal nerve anatomy dissection confirmed the course of the collateral branch is different from the main branch. The divergence of the lateral cutaneous branch from the main intercostal nerve tended to occur anterior to the mid-axillary line. Cryoablation of all three branches of the intercostal nerve produced complete regional chest block. The main patient complaint after Nuss procedure with cryoablation was anterior chest wall pressure sensation which resolved typically after two weeks.

Introduction

The first major report showing the benefits of cryotherapy or cryoanalgesia to block peripheral nerve pain was first reported in 1976 [1]. This method was used to treat thoracotomy pain, which was reported four years later [2]. Despite good initial results, the method did not become popular due to reports of post cryoablation neuralgia [3]. The reasons for neuralgia were later assigned to imprecise contact between the cryoprobe and the target nerve, inefficient equipment, differential cold effect on large myelinated nerve fibers compared to small fibers which are more susceptible to cold [4]. With improvement in equipment design, the method of cryoanalgesia managed to maintain a small niche in thoracotomy pain control. The use of cryoanalgesia for pediatric procedures has been nonexistent.

The use of cryoablation for adult patient thoracotomy pain control received a boost with our reporting of its use in 2016 for Nuss procedure, minimally invasive repair for pectus excavatum in pediatric patients [5,6]. Although often labeled minimally invasive, Nuss procedure is one of the most painful operations that pediatric surgeons inflict on children. Since its first report in 1998, Nuss procedure has become the gold standard surgical treatment for the repair of pectus excavatum by fulfilling its goal: to reconstruct the chest without tissue destruction [7]. Despite the success, the Achilles heel of the operation remained, which has been extreme postoperative pain that can last for months. The use of cryoanalgesia for Nuss procedure has been fitting since cryoanalgesia not only blocks the immediate postoperative pain but the smoldering chronic pain.

One unexpected observation of intercostal nerve cryoablation for Nuss procedure has been the apparent one day delay for the full regional block of anterior chest to take effect. This observation prompted us to investigate the anatomy of the intercostal nerve to elucidate this observation, since the course of the intercostal nerve and its branches cannot be

thoracoscopically visualized. In this report, we resurrect the forgotten branch of intercostal nerve, the collateral branch, which was named by anatomists from King's College of England in 1932 [8], and we delineate the course of the second branch of intercostal nerve, the lateral cutaneous nerve. We hypothesize that a better understanding of the forgotten branch (collateral branch) and the lateral cutaneous branch anatomy will increase the cryoablation effectiveness for Nuss procedure.

Methods

The design of this study is as follows. Perform human cadaveric dissections to define the intercostal nerve anatomy. Based on the new findings, cryoablation technique was modified. We then reviewed the series of Nuss procedures with the new cryoablation technique specifically looking at postoperative pain levels. We compared the pain score results to the results that we previously reported.

Cadaveric Specimen Dissections: Eleven adult cadavers were procured from the University of New England College of Osteopathic Medicine Donor Program and dissected from January 2021 until June 2021. Each cadaver was chosen from those without a history or gross appearance of thoracic pathology. The skin, subcutaneous tissue, pectoralis major and minor muscles were dissected off from the anterior and lateral thoracic walls. Both clavicles were cut at the midclavicular line using an oscillating saw. Starting at rib 1 and continuing to rib 12, the ribs were cut following the midclavicular line using a saw or bone cutters. The sternopericardial ligaments were cut from the posterior surface of the sternum and the anterior chest wall was then elevated and reflected inferiorly as an intact unit. The contents of the thoracic cavity were removed to fully visualize the posterior and lateral thoracic walls. The costal pleura and

endothoracic fascia were removed from the intercostal musculature and rib surfaces. The innermost layer of intercostal muscles and subcostalis muscles were carefully dissected away to reveal the path of the intercostal nerves of ribs 4, 5, 6, and 7. For each intercostal space, the main intercostal nerve, the collateral branch of the intercostal nerve, the lateral cutaneous nerve, and any communicating branches between these nerves were revealed. Dissection of the lateral cutaneous branches of the intercostal nerves were also performed on the external aspects of the anterior chest wall. To determine the exact location of the midaxillary line, the distance from the spinous process to the center of the sternum was measured. The midaxillary line was calculated by dividing this measurement in half. Measurements were made on the external surface of the thoracic wall to determine the location where the lateral cutaneous nerve pierces the internal and external intercostal muscles to reach the external thoracic wall. Measurements were taken from the spinous processes of T4-T7 to the location where lateral cutaneous nerve crosses from the interior thoracic cavity to the exterior thoracic wall. The location of this nerve passage was determined to be anterior to the midaxillary line, at the midaxillary line, or posterior to the midaxillary line where anterior is defined as more distal to the spine, and posterior is defined as more proximal to the spine.

Cryoablation of Intercostal Nerve: Consecutive twenty two male patients underwent Nuss procedure with cryoanalgesia during the year 2022 at the University of California San Francisco Benioff Children's Hospitals. Steps of cryoablation technique for Nuss procedure are detailed in our previous reports [5,6] and illustrated in Figure 1. The main difference compared to the previously reported technique is the additional cryoablation of the collateral branch. To summarize, cryoanalgesia was performed prior to Nuss bar placement using thoracoscopic visualization and a cryoprobe (cryoICE: AtriCure, Inc., West Chester, Ohio, USA). After

bilateral thoracoscopic port placements, the patient's anterior sunken chest wall was elevated using the T-fastener suture technique [9]. The retrosternal space was dissected under direct camera visualization from the left chest toward the right chest to create a communicating channel between the two sides. A rigid 30° thoracoscope was passed across the anterior mediastinum to gain access to the contralateral chest wall. Under thoracoscopic view, cryoprobe was passed either via transthoracic route or through the ipsilateral chest incision and angled posteriorly. A 5 mm segment of the main branch of intercostal nerve and the accompanying lateral cutaneous nerve were cryoablated at -60°C for 2 minutes. The probe contact location is about 2-3 cm posterior to the midaxillary line at the inferior surface of the corresponding rib. The collateral branch at the same level is targeted at the location immediately superior to the next inferior rib (Fig.2). Cryoablation is utilized at 16 locations in total to target the main branch, lateral cutaneous branch and the collateral branch of the intercostal nerves 4th-7th. After the freeze cycle, the probe was thawed and allowed to fall off the pleural lining without traction.

Patients were admitted to the postanalgesia care unit after the operation, then to a regular hospital room. Patients were allowed to have intravenous morphine and oral narcotic (acetaminophen/hydrocodone) as needed (the same pain management protocol as reported in our first series in 2017 [6]). Numerical Pain Rating Scale (0-10) was used to record the patient's pain level, which was obtained by the attending surgeon on postoperative day 1. After hospital discharge, patients presented for postoperative clinic visits 2 weeks after surgery, then 6 months after surgery.

All data were recorded using Microsoft Excel for Mac 2011 (Microsoft Corporation, Redmond, WA). Median and interquartile range (IQR) were analyzed using GraphPad Prism 7 (GraphPad Software, La Jolla, CA).

Institutional review board approvals were obtained for the study (UCSF IRB #18-24898) and cadaver dissections.

Results

Eleven adult cadavers (7 female, 4 male) with an average age of 87.8 were dissected to study the passages of the intercostal nerve and its branches. Figure 3A illustrates a representative specimen of a hemisected cadaver with the internal thoracic cavity exposed, intercostal arteries and veins removed, and the intercostal nerve 4-7 and its branches preserved. Collateral branches are noted to traverse near the superior edge of the inferior rib. There are multiple communicating collateral branches that connect the collateral branch to the inferior level main intercostal nerve.

Total of 92 lateral cutaneous branches of the intercostal nerve were dissected and measured as they pierced the intercostal muscle. Table 1 shows the branching patterns of the bilateral intercostal nerves. In summary, the lateral cutaneous branch of the intercostal nerve tended to pierce the intercostal muscle anterior to the midaxillary line 78% of time (mean 3.0 cm anterior, standard deviation 1.8). The percentage of lateral cutaneous branches piercing the intercostal muscle posterior to the midaxillary line was 19% (mean 1.6 cm posterior, standard deviation 0.9), and those on the midaxillary line was 3%. On average for the right chest, lateral cutaneous branches of intercostal nerves 3, 4, 5, 6, and 7 pierced the intercostal muscle 5.1 cm,

3.2 cm, 3.5 cm, 2.6 cm, and 2.6 cm posterior to the midaxillary line, respectively. The remaining lateral cutaneous branches of intercostal nerves 4, 5, 6, and 7 pierced the intercostal muscle 2.3 cm, 2.0 cm, 1.6 cm, and 1.6 cm anterior to the midaxillary line, respectively. On average for the left chest, lateral cutaneous branches of intercostal nerves 3, 4, 5, 6, 7, and 8 pierced the intercostal muscle 3.4 cm, 3.2 cm, 3.4 cm, 2.4 cm, 1.8 cm, and 0.5 cm posterior to the midaxillary line, respectively. The remaining lateral cutaneous branches of intercostal nerves 3, 4, 5, 6, 7, and 8 pierced the intercostal muscle 0.3 cm, 1.0 cm, 1.0 cm, 1.3 cm, 2.9 cm, and 2.0 cm anterior to the midaxillary line.

Consecutive twenty two male patients underwent Nuss procedure with cryoanalgesia. No female patients presented during the study period. The median age (IQR:interquartile range) was 15(2) years. The median Haller Index (IQR) was 3.73(0.85). The length of hospital stay was 1 day for all patients compared to our previously reported median length of stay of 2.0(1.5) days [6]. Using a verbal pain scale of 0-10, median pain score (IQR) on postoperative day one was 1(1.75). These results can be compared to our previously reported control group whose collateral branch was not cryoablated: median pain score of 3.7(3.5), median age was 15.5(5), and the median Haller Index was 4.2(1.2) [6]. Nine (40%) of the 22 patients reported a pain score of zero. None of the patients developed symptoms of neuralgia. Sensation returned gradually in all patients, progressing from lateral to medial within three months. All patients expressed anterior chest pressure sensation, which typically resolved within two weeks.

Discussion

Davies et al published their intercostal nerve dissection results in 1932 [8]. In their paper, they stated that intercostal nerves and vessels lie deep to the internal intercostal muscles,

that their manner of branching was not correctly described in the past and postulated the correct description of the intercostal nerves. Prior to reaching the angle of the rib, the trunk of the intercostal nerve sends a branch to the external intercostal muscle. Thereafter, the trunk divides into three main branches: (1) upper anterior cutaneous branch (main nerve) which lie in the subcostal groove, (2) lower branch, which they named collateral branch that travels along the upper border of the rib below, (3) the intermediate branch, which is named the lateral cutaneous branch. They also noted that there are fine communicating branches that connect the neighboring intercostal nerves. We confirmed these observations from our cadaver dissections. In particular, we noted that communicating branches that connect the neighboring intercostal nerves arise from the collateral branch, which travels over the undersurface of the inferior rib and joins the anterior cutaneous branch (the main branch) corresponding to the rib below. The communicating branch is hitherto unnamed, which we will name as communicating collateral branch. The significance of the communicating collateral branch is related to the cryoablation applied to the lowest intercostal nerve that is treated, which in our case is nerve level 7. Sensory pain picked up in regions covered by intercostal nerve 8 can be referred to level 7 via the communicating collateral branch. The communicating collateral nerve is similar in function as the nerve of Kuntz, which directly connects the first intercostal nerve to the 2nd intercostal nerve and is relevant during thoracoscopic sympathectomy procedure for palmar hyperhidrosis. In order to obtain complete anterior chest regional block, it is essential to cryoablate all three branches of intercostal nerve since cryoablation of the primary trunk located posterior to the angle of rib is difficult to achieve due to poor exposure. To properly cryoablate the lateral cutaneous branch, we need to know the location where the nerve pierces the intercostal muscle since it becomes inaccessible thereafter to intrathoracic cryoablation.

Our dissections showed intercostal location where the lateral cutaneous nerve penetrates the intercostal muscle is not uniform. Most of the nerves penetrated the muscle anterior to the midaxillary line. Since the nerve is not visible within the chest, we need to approximate the point where the nerve penetrates the intercostal muscle relative to the midaxillary line to apply the cryoprobe. Our cadaver dissection revealed that lateral cutaneous nerves corresponding to the upper ribs (i.e., rib 4 and 5) tended to penetrate the intercostal muscle further anterior to the midaxillary line compared to the lower ribs (rib 6 and 7). On average, if the cryoprobe is applied about 2 cm posterior to the midaxillary line, most lateral cutaneous branches will be cryoablated. If the lateral cutaneous branch pierces the muscle further posterior than 2 cm, then the nerve may not be captured by the cryoprobe, and the pain sensations will be felt by the patient. If the cryoablation is done on the intercostal nerve trunk proximal to the takeoff of the collateral branch (collateral branch comes off first followed by the lateral cutaneous branch), only one point cryoablation per rib level will be needed. However, the location of the collateral branch takeoff is close to the spine and is difficult to reach with the patient in a supine position, which is the position that we utilize for Nuss procedure. If the patient is in the lateral decubitus position, however, cryoablation can be done more easily. Both sides of the chest would need to be cryoablated in decubitus position followed by final supine position for the Nuss procedure. We intend to report another study in the future looking at the collateral branch takeoff anatomy and performing the operation as described above.

Use of cryoanalgesia to lessen pain is one of the oldest forms of analgesia, dating back to ancient Egypt and Hippocrates (460-377 BC), who described the use of snow packs for relieving surgical pain [10]. In present time, the term cryoanalgesia refers to localized freezing of peripheral nerves. Treatment occurs through application of a cryoprobe, which achieves freezing

temperature by the Joule-Thomson effect of rapidly expanding gasses that are contained within the chambers of the probe [11]. Common gasses used for medical applications are nitrous oxide or carbon dioxide. When the nerve axon is frozen, the transmission of electrical signals along the axon is prevented, providing analgesia. Thereafter, Wallerian degeneration of axons occurs, starting at the point of thermal injury and moving toward the nerve endings [12]. Since fibrous neural structures including the perineurium and epineurium remain intact, these structures facilitate axonal regeneration. The rate of this axonal regeneration is approximately 1-3 mm/day.

Cryoanalgesia has been used in adult patients for acute pain control following thoracotomy, as well as for treatment of chronic thoracic pain due to surgery or post-herpetic neuralgia since the 1970s [1]. For this report, we applied thoracoscopic cryoanalgesia during Nuss procedure and cryoablated all three branches of intercostal nerve. Unlike our previous 2017 case series [6] where we concentrated on anterior cutaneous branch (main branch) and lateral cutaneous branch cryoablation, we cryoablated all three branches and reduced the verbal pain score from 3.7 to 1 out of 10. Close to half of the patients expressed zero pain. The maximal discomfort felt by the patient occurred on postoperative day 0. The discomfort slowly improved over time. It did not get worse a few days or weeks later. All patients expressed anterior pressure sensation from the metal bar preventing the chest from sinking toward the spine. The pressure sensation cannot be alleviated with pain medications but needs passage of time to resolve. For a typical patient, two weeks were sufficient time for the pressure sensation to fade. One limitation of the current study is that we compared the results of the cryoablation to results we published in 2017; in other words, this is not a single blinded prospective study. Despite the limitation, we can say that in the 2017 report no patient expressed zero pain score.

When applying the cryoablation technique to an open thoracotomy procedure, cryoablation of the collateral branch will be relevant in order to attain complete regional block.

We acknowledge that if the present study was done as a randomized single blinded study that the pain score results would be more meaningful. We chose to proceed with nonblinded treatment, because it became obvious that the pain control was better, not slightly better, after performing the first few cases. We also acknowledge that patients will tend to report what the attending surgeons want to hear. However, many of the patients reported the same score to the surgical and nursing staff taking care of them. One caveat to the pain score scale, unlike the pain score recording, is that pressure sensation patients feel immediately after the operation is difficult to gauge and can be difficult to differentiate from pain sensation. All the patients expressed a sense of chest pressure due to the bar preventing the chest from sinking. They liken the sensation to someone sitting on their chest. The pressure sensation is distinct from a typical pain sensation. This pressure can be articulated as a pain sensation by patients who have a very stiff chest.

Conclusion

To achieve complete anterior chest regional block using cryoablation, the main intercostal nerve and its two branches need to be targeted. We recommend these three steps: 1) identify the mid-axillary line, 2) target the intercostal space about 2 cm proximal to the mid-axillary line, and 3) if the intercostal space is narrow, cryoprobe will freeze all three branches; however, if the space is wide, both inferior rib space and superior aspect of the lower rib should be cryoablated.

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Figure and Table Legends:

Fig. 1: Chest is elevated using a T-fastener suture technique. Anterior mediastinal tunnel is created to allow a thoracoscope to pass across the mediastinum. Cryoprobe is used to cryoablate the intercostal nerve ipsilateral or from the contralateral side.

Fig. 2: Upper panel shows cryoablation being done on the 5th main and lateral cutaneous branch. The 4th collateral branch is already treated. Lower panel shows cryoablation being done on the 5th collateral branch.

Fig. 3: (A) Intercostal nerves 4 through 7 are illustrated. Collateral branch travels above the rib inferior. Most lateral cutaneous branch crosses the midaxillary line before it pierces the intercostal muscle. (B) A cadaver dissection picture illustrates the relative location of the lateral cutaneous branch separation (indicated by the arrow marked by BF), exit of lateral cutaneous branch from the chest (marked by yellow pins) and mid-axillary line (marked by the green pins). (C) A cadaver dissection picture illustrates the course of the main intercostal nerve, collateral branch and communicating collateral branch.

Table 1: Distribution of lateral cutaneous branch of the intercostal nerve relative to the midaxillary line

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	Anterior to Midaxillary Line	*On Midaxillary Line*	*Posterior to Midaxillary Line*
	N = 72	N = 3	N = 17
Frequency	78.3%	3.3%	18.5%
Mean ± SE (cm)	3.01 ± 1.81	0	1.64 ± 0.93

	Mean Distance (cm) relative to Midaxillary Line			
	Left		Right	
Rib	*Anterior to Midaxillary Line*	*Posterior to Midaxillary Line*	*Anterior to Midaxillary Line*	*Posterior to Midaxillary Line*
3	3.39	0.25	5.10	-
4	3.16	1.00	3.21	2.30
5	3.40	1.04	3.54	2.00
6	2.38	1.29	2.58	1.60
7	1.78	2.88	2.55	1.56
8	0.50	2.00	-	-