Observational Study

Atypical Chest Pain: Evidence of Intercostobrachial Nerve Sensitization in Complex Regional Pain Syndrome

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Background: Atypical chest pain is a common complaint among Complex Regional Pain Syndrome (CRPS) patients with brachial plexus involvement. Anatomically, the intercostobrachial nerve (ICBN) is connected to the brachial plexus and innervates the axilla, medial arm and anterior chest wall. By connecting to the brachial plexus, the ICBN could become sensitized by CRPS spread and become a source of atypical chest pain.

Objective: To evaluate the sensitivity of chest areas in CRPS patients and normal controls.

Design: Prospective investigation of pressure algometry in chest areas to determine chest wall sensitivity.

Methods: CRPS patients and normal controls volunteered to participate in our study. Each individual was examined to meet inclusion criteria. Patients' report of chest pain history was collected from every participant. Pressure algometry was used to measure pressure sensitivity in the axilla, anterior axillary line second intercostal space, mid-clavicular third rib, mid-clavicular tenth rib, and midsternal. Each of these measurements were compared to an intra-participant abdominal measure to control for an individuals generalized sensitivity.

The ratios of chest wall sensitivities were compared between CRPS patients and normal controls.

Results: A history of chest pain was reported by a majority (94%) of CRPS patients and a minority (19%) of normal controls. CRPS patients reported lifting their arm as a major initiating factor for chest pain. To pressure algometry, the ratios of CRPS patients were significantly greater than control subjects ($p < 0.02$ throughout), indicating increased chest wall sensitivity.

Limitations: This study is limited by the relatively small number of patients (n=35) and controls (n=21) used.

Conclusion: The results of this study support the idea that chest pain is greater in CRPS patients than normal controls. The ICBN could be the source of this sensitization by CRPS spread from the brachial plexus.

Key words: Intercostobrachial nerve (ICBN), complex regional pain syndrome (CRPS), atypical chest pain, algometry, reflex sympathetic dystrophy (RSD), brachial plexus

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Atypical chest pain is a common clinical problem faced by internists, emergency room physicians and cardiologists. Atypical chest pain most commonly presents in young women. They are less likely to have coronary artery disease (CAD), but if present, have 7% greater risk of death than aged matched men (1). Noninvasive screening tools for atypical chest pain, such as the stress EKG, are less specific in the female population (2). This leads to an increased number of referrals for coronary

angiography in these patients to determine a definitive diagnosis. Approximately 25% of performed coronary angioplasties are normal (3).

Complex regional pain syndrome (CRPS) occurs primarily in young women (age range 36–42 years; 4:1) (4). It is defined as a chronic pain disproportionate to the inciting event with associated sensory (hyperalgesia, mechanical and thermal allodynia, hyperpathia), abnormalities, autonomic dysregulation, motor symptoms, and atrophy and dystrophy (5-7). CRPS typically begins in one peripheral area then spreads proximally, in a mirror distribution, and may generalize. It frequently sensitizes nerves with the affected area (9). Although the pathophysiology isn't completely known, central sensitization and glial activation of the spinal cord appear to be prominent features (8).

The purpose of this paper is to describe a common cause of atypical chest pain more frequent in women that may arise from irritation and sensitization of the intercostobrachial nerve (ICBN), (Fig. 1). The authors had noted that many CRPS patients complained of chest pain which the patients themselves did not think was related to their chronic pain condition. Most of these patients had sought out and received extensive cardiac workups, usually ending with negative angiograms. We hypothesized that patients with CRPS from a brachial plexus injury might have chest sensitivity that could result in atypical chest pain secondary to sensitization of the ICBN from its brachial plexus origin.

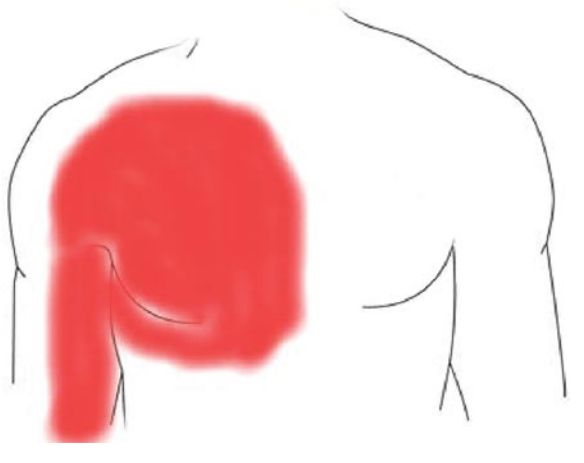

Fig. 1. *Skin distribution of the right ICBN in red.*

Methods

Ethics

All study procedures and recruitment were approved by the Drexel University College of Medicine Institutional Review Board under protocol #17526. All patients signed informed consent.

Inclusion Criteria

Forty patients referred to our pain clinic at Drexel University College of Medicine for evaluation or follow up of CRPS volunteered to enroll in this study. All CRPS patients met all criteria for CRPS of the International Association for the Study of Pain (5). The criteria include:

1. Continuing pain disproportionate to the inciting event
2. Report of at least one symptom in each category:
    a. sensory
    b. vasomotor
    c. sudomotor/edema
    d. motor/trophic
3. Display at least one sign in 2 or more categories
    a. sensory
    b. vasomotor
    c. sudomotor/edema
    d. motor/trophic

The CRPS patients were receiving individualized treatments that generally included pharmacological mono or combined therapy with nonsteroidal antiinflammatory drugs, tricyclic antidepressants, anticonvulsants, and if necessary low or high potency opioids.

Exclusion Criteria

Patients were excluded if: 1) they had undergone IV ketamine or lidocaine infusion within 3 months; 2) had a prior mastectomy, major surgery, or severe chronic illness within 3 months; or 3) were pregnant or lactating. Four CRPS patients were excluded: 3 because of IV ketamine or lidocaine treatment within 3 months of study and one because of a surgical history of bilateral modified radical mastectomy. Eight CRPS subjects did not complete the study secondary to pain or time constraints. Subjects were only included in the analysis of the study portions completed.

Control Subjects

Twenty-one control participants voluntarily enrolled in our study. Control participants were recruited from flyers posted at DUCOM. Exclusion criteria were

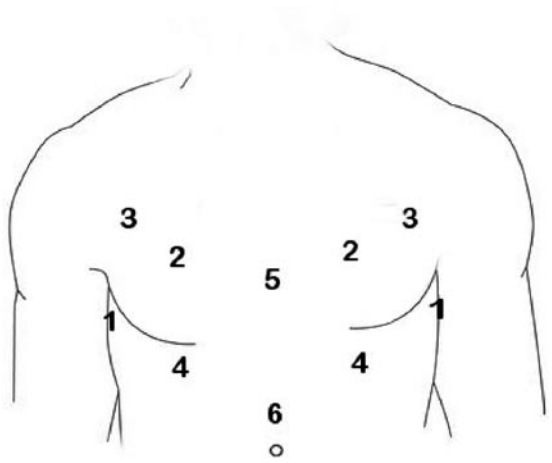

Fig. 2. *Pressure algometry sites: (1) midaxillary third intercostal space; (2)anterior axillary line second intercostal space; (3) mid-clavicular third rib; (4) mid-clavicular tenth rib; (5) middle of sternum; (6) abdomen, 2 inches above the umbilicus.*

any history of a chronic pain disorder, spine surgery, use of narcotic pain medicine one month prior to study, major surgery or medical illness, and females who were pregnant or lactating.

Past History of Chest Pain

All subjects were asked: 1) if they presently or ever has suffered chest pain; 2) its location, quality, and radiations; 3) duration; 4) if they had ever been examined by a physician for chest pain; 5) the diagnostic tests they had attained; 6) and the final diagnosis.

Pressure Algometry

Quantitative mechano-sensitivity was measured at multiple chest sites and the abdomen (Fig. 2). To control for individual differences in overall pressure sensitivity, we divided each chest result by the abdomen result. The following sites were used: 1) midaxillary third intercostal space bilaterally; 2) anterior axillary line, second intercostal space bilaterally; 3) mid-clavicular third rib bilaterally; 4) mid-clavicular tenth rib bilaterally; 5) middle of the sternum; 6) abdomen, 2 inches above the umbilicus (Fig. 2). Thresholds were determined using a handheld pressure algometer (Model FPK Algometer, Wagner Instruments, Greenich, CT) which has a 1 cm^2 flat circular rubber tip and a range of 1 to 10 kg. The rubber tip was placed over the appropriate site and continuous pressure of 1kg/second was applied until the subject reported discomfort or a pressure of 4kg/cm^2 was reached. If no discomfort was expressed at a maximum of 4kg/cm^2, a value of 4.1kg/cm^2 was assigned. Similarly, if a patient could not tolerate pressure for a measurement of 1kg/cm^2 (the minimum value detected by our instrument) a value of 0.9kg/cm^2 was assigned.

Sensory Radiation

Sensory radiations were measured during the pressure algometry. Subjects were asked to report sensations of pain or tingling distant from the pressure algometry testing sites. The descriptions of the radiations were grouped according to the most distant radiation along a standard neurological distribution (8).

Statistics

Clinical features between controls and CRPS patients were compared by use of T-tests and chi-square tests. Pain measures between control and patients were evaluated by the Mann-Whitney tests. Algometry data are presented as pressure threshold on each tested chest region (ICBN territory) divided by the pressure threshold on the abdomen (non-ICBN territory) for each control and CRPS patient. Therefore, a value of 1.0 indicates equal sensitivity of the abdomen and chest region. Values below 1.0 indicate higher sensitivity at the chest region compared to the abdomen.

Table 1. *Baseline demographs for control and CRPS patients.*

Characteristic	Control (n=21)	CRPS (n=35)	*P*-value
Gender (% female)	62%	77%	0.22
Age (Mean (SD))	36.1 (11.6)	45.9 (12.9)	0.006
Years of Symptoms (Mean (SD))	------	10.4 (11.9)	
Narcotic Use (% yes)	0	63%	<0.001

Results

Demographics

The baseline demographics for control and CRPS patients are shown in Table 1. There is no statistically significant difference between genders in each group. There is a statistical difference between control and CRPS ages (36.1 years vs. 45.9 years, P =0.006). Multivariate analysis indicates age does not correlate with our outcome results. None of the control subjects were using narcotic pain medications.

Clinical Characteristics

Chest pain characteristics for each group are summarized in Table 2. The majority (94%) of CRPS patients reported a history of chest pain, while only 19% of control subjects reported ever having chest pain. The majority of chest pain reported by CRPS patients was bilateral (66%), above the breast (79%), and deep in nature (60%), radiating to their jaw/head/neck (51.8%) and shoulder/arm (46%). The major initiating factor for chest pain in 65% of CRPS patients was lifting their arm.

The number of patients seeking care from either the emergency room (ER) or their primary care physician (PCP) and the type of care they received is summarized in Table 3. The majority of CRPS patients seeking care for chest pain presented to their PCP (40%), received an EKG (79%), or were diagnosed with unknown chest pain origin (26%), costochondriatis (21%), or psychosomatic (21%).

Table 2. *Reported demographics.*

Chest Pain Distribution	Control (N=21)	CRPS (N=35)
None	81%	6%
Right	0%	14%
Left	5%	14%
Bilateral	14%	66%
Above Breast	5%	79%
Within Breast	19%	41%
Below Breast	5%	56%
Chest Pain Quality		
Sharp	5%	34%
Deep	0%	60%
Aching	14%	29%
Burning	0%	46%
Radiation		
Jaw/Neck/Head	0%	52%
Shoulder/Arm	0%	46%
Sternum	0%	3%
Back/Deep	0%	12%
Nipple	0%	6%
Multiple Radiations	0%	66%
Lifting Arm Elicits Pain	0%	65%

Pressure Algometry

The statistical analysis of CRPS patients (N=33) versus control (N=21) for relative ratio pressure thresholds of each chest site compared to abdomen are in Table 4. CRPS patients were significantly more sensitive in all chest sites compared to their abdomen than control subjects (P<0.02 throughout).

Sensory Radiation

Forty percent of CRPS patients reported sensory radiation upon pressure testing compared to 5% of controls. No radiations were reported when testing the abdomen. The majority of radiations occurred after testing the second intercostal space (42% of patients reported), with the tenth rib and sternum receiving the fewest reported radiations (30% of patients).

Discussion

The ICBN is rarely mentioned in standard anatomy texts, and only recently have a series of cadaver studies defined its course. The ICBN arises from the second intercostal nerve (T2) with a highly variable contribu-

Table 3. *Chest pain workups.*

	Controls (N=21)	CRPS (N=35)
ER Visit	0%	26%
PCP Visit	14%	40%
Procedures	(N=3)	(N=19)
Chest X-Ray	0%	42%
EKG	33%	79%
Stress Echo	33%	11%
Echo	33%	26%
Mammogram	0%	16%
Diagnosis	(N=3)	(N=19)
Costochondriatis	33%	21%
Hormonal	33%	11%
Psychosomatic	33%	21%
GERD	0%	5%
Cardiac	0%	16%
Unknown	0%	26%

Table 4. *Algometry ratio, site threshold/abdomen threshold.*

Site	Control (n=20)	CRPS (n=33)	*P*–value
Right Axilla	0.67 (0.3–1.0)	0.50 (0.3–1.1)	0.02
Right 2nd Intercostal Space	1.0 (0.5–1.0)	0.66 (0.2–1.6)	<0.001
Right 3rd Rib	0.95 (0.5–1.1)	0.64 (0.2–1.0)	<0.001
Right 10th Rib	1.0 (0.6–1.1)	0.66 (0.3–1.4)	0.001
Sternum	1.0 (0.6–1.0)	0.73 (0.3–1.0)	0.001
Left Axilla	0.74 (0.3–1.0)	0.48 (0.3–1.3)	0.005
Left 2nd Intercostal Space	0.89 (0.4–1.0)	0.48 (0.2–1.0)	<0.001
Left 3rd Rib	0.88 (0.5–1.0)	0.52 (0.3–1.0)	<0.001
Left 10th Rib	1.0 (0.4–1.0)	0.69 (0.3–1.3)	0.004

tion of T3 and T4 nerve roots (9,10). Upon exiting from the second intercostal space, the ICBN innervates the axilla and the medial and anterior arm. In addition, the ICBN contributes to the innervation of the posterior forearm via connections with the posterior antebrachial cutaneous nerve and contributions to the upper anterior chest wall secondary to connections with the long thoracic nerve (9,10). Occasionally, it has reported connections to the pectoralis minor and major muscle (11). Thirty percent of the time, the ICBN is directly connected to the brachial plexus, primarily via the medial cord (9). Recently, it has been demonstrated that T2 has a connection to the brachial plexus 100% of the time, 80% via the ICBN and 20% from direct intrathoracic connections. Since T2 is the primary root of the ICBN, it can be assumed that the ICBN has connections to the brachial plexus (12).

A syndrome of ICBN entrapment has been described after post modified radical mastectomy. Symptoms include pain in the arm on the side of ICBN damage within hours or days. It is described as dull, aching, or burning with intermittent flashes of bright, stabbing pain. This pain is always present, but becomes more severe with movement and radiates to the medial and posterior arm. Pain sensation can include the shoulder and chest. This pain can be intensified with pressure placed on the second intercostal space along the anterior axillary line (13). This pain is severe and persistent enough to be considered a major side effect of modified radical mastectomies and has led to recommendations for ICBN preservation whenever possible (14-16).

Three case reports to date have noted CRPS in the chest wall after breast surgery. After mammoplasty, the first patient had erythema, edema, hyperpathia, and allodynia bilaterally over the chest wall, primarily the inferior breast area. This patient improved with a sympathetic block (17). Another occurred after breast reduction, with pain along the right lateral inferior breast (18). A patient undergoing post modified radical mastectomy experienced pain with the associated signs and symptoms of CRPS in the medial arm in the territory of the ICBN.

The chest pain described by CRPS patients typically occurs above the breast and radiates to the jaw, face, shoulder, and arm. These pain radiations are similar to those described in cardiac chest pain. These radiations are within the territory of the ICBN through its connections to the brachial plexus. We suspect that this pattern of pain radiation could occur with any cause of ICBN sensitization including CRPS. A series of case reports describe presenting symptoms of pancoast tumors as chest pain and sensitivity along the arm, shoulder, and chest secondary to metastatic invasion of the ICBN (19).

This study demonstrated that 94% of CRPS patients reported a history of chest pain versus only 19% of the controls. Half of the CRPS patients that reported chest pain were concerned enough to seek medical care specifically for the chest pain that included a cardiac workup. The majority (84%) of these cardiac workups were negative. CRPS patients did not relate their chest pain to their pain condition.

Sensitization in the territory of specific nerves is a complicated process. It is initiated by nerve injury and consequent increased excitability of pain transmission neurons throughout the CNS due to synaptic plasticity. There is concomitant glial activation both at the segmental level, in a mirror distribution, and at levels above and below the level of injury (20,21). It is a dynamic process that often spreads from the site of the original injury (22). The chest pain described by these CRPS patients is possibly caused by sensitization of spinal cord dorsal horn neurons that subserve the ICBN

and it has similar qualities to coronary artery disease pain. Only 40% of our patients described their chest pain as burning (typical for neuropathic pain) while 60% described it as deep. This may be one reason that most CRPS patients did not relate their chest pain to their typical CRPS burning pain.

An interesting observation in this study was that 65% of the CRPS subjects reported being able to elicit chest pain by raising their arms. This suggests that stretching the brachial plexus might place traction on the ICBN and induce the constellation of chest pain symptoms. It has been shown in experimental animals with nerve injury that somatic mechanical afferents may take on the expression of pain fiber markers and activate dorsal horn pain transmission neurons.

The algometry results indicated that all subjects were more sensitive to pressure in the chest areas than in the abdomen. This would be expected since there is more sensory innervation to the chest wall than the abdomen. However, CRPS subjects were significantly more sensitive in all tested chest areas than control subjects, demonstrating increased pressure sensitivity in the territory of the ICBN.

Conclusion

Sensitization of dorsal horn spinal neurons in the territory of the ICBN can cause severe and clinically relevant chest pain. The pattern is similar to atypical chest pain frequently thought to be of cardiac origin. Future studies are needed to evaluate whether cardiac chest pain produces the same chest wall sensitivity to pressure as seen in our CRPS atypical chest pain population. This would further clarify the role of muscular and subcutaneous innervation by the ICBN in the anterior chest wall and could possibly reveal whether algometry could be used to help rule out non-cardiac chest pain. Our results indicate that sensitization of the afferent dorsal horn input from the ICBN should be included in the differential diagnosis of atypical chest pain. It could prevent unnecessary extensive, and possibly invasive, cardiac work-ups. A major clinical clue is chest pain induced by raising the arm.

References

1. Holper E, Faxon D. Percutaneous Coronary intervention in women. *Journal of the American Medical Womens Association*. 2003; 58:264-271.
2. DeCara JM. Noninvasive cardiac testing in women. *Journal of the American Medical Womens Association* 2003; 58:254-263.
3. Pontone G, Andreini D, Ballerini G, Nobili E, Pepi M. Diagnostic work-up of unselected patients with suspected coronary artery disease: Complementary role of multidetector computed tomography, symptoms and electrocardiogram stress test. *Coronary Artery Disease* 2007; 18:265-274.
4. Stanton-Hicks M. Complex regional pain syndrome: Manifestations and the role of neurostimulation in its management. *J Pain Sympt Manag* 2006; 31(4S):S20-S24.
5. Harden RN, Bruehl SP. Diagnosis of Complex regional pain syndrome: signs, symptoms, and new empirically derived diagnostic criteria. *Clinical Journal of Pain* 2006; 22:415-419.
6. Harden RN. Complex regional pain syndrome. *British Journal of Anaesthesia* 2001; 87:99-106.
7. Schwartzman RJ. Reflex sympathetic dystrophy. *Current Opinion in Neurology & Neurosurgery* 1993; 6:531-536.
8. Borene S, Edwards J, Boezaart A. At the cords, the pinkie towards: Interpreting infraclvicular motor responses to neurostimulation. *Reg Anesth Pain Med* 2004; 29:125-129.
9. Loukas M, Hullett J, Louis RG, Jr., Holdman S, Holdman D. The gross anatomy of the extrathoracic course of the intercostobrachial nerve. *Clinical Anatomy* 2006; 19:106-111.
10. O'Rourke MG, Tang TS, Allison SI, Wood W. The anatomy of the extrathoracic intercostobrachial nerve. *Australian & New Zealand Journal of Surgery* 1999; 69:860-864.
11. Loukas M, Louis RG, Jr., Fogg QA, Hallner B, Gupta AA. An unusual innervation of pectoralis minor and major muscles from a branch of the intercostobrachial nerve. *Clinical Anatomy* 2006; 19:347-349.
12. Loukas M, Louis RG, Jr., Wartmann CT. T2 contributions to the brachial plexus. *Neurosurgery* 2007; 60(2 Suppl 1): ONS13-18; discussion ONS18.
13. Wood KM. Intercostobrachial nerve entrapment syndrome. *Southern Medical Journal* 1978; 71:662-663.
14. Paredes JP, Puente JL, Potel J. Variations in sensitivity after sectioning the intercostobrachial nerve. *American Journal of Surgery* Nov 1990; 160:525-528.
15. Salmon RJ, Ansquer Y, Asselain B. Preservation versus section of intercostalbrachial nerve (IBN) in axillary dissection for breast cancer —a prospective randomized trial. *European Journal of Surgical Oncology* 1998; 24:158-161.
16. Taylor KO. Morbidity associated with axillary surgery for breast cancer. *ANZ Journal of Surgery* 2004; 74:314-317.
17. Steinberg RB, Stueber K. Sympathetically mediated pain after reduction mammoplasty: An unusual complication. *J Clin Anesth* May 1998; 10:246-248.
18. Papay FA, Verghese A, Stanton-Hicks M, Zins J. Complex regional pain syndrome of the breast in a patient after breast reduction. *Annals of Plastic Surgery* 1997; 39:347-352.
19. Marangoni C, Lacerenza M, Formaglio F, Smirne S, Marchettini P. Sensory disorder of the chest as presenting symptom of lung cancer. *Journal of Neurology, Neurosurgery & Psychiatry* 1993; 56:1033-1034.
20. Tsuda M, Inoue K, Salter M. Neuropathic pain and spinal microglial: A big problem from molecules in 'small' glia. *Trends in Neuroscience* 2005; 28:101-107.
21. Schwartzman RJ, Alexander GM, Grothusen J. Pathophysiology of complex regional pain syndrome. *Expert Review of Neurotherapeutics* 2006; 6:669-681.
22. Maleki J, LeBel AA, Bennett GJ, Schwartzman RJ. Patterns of spread in complex regional pain syndrome, type I (reflex sympathetic dystrophy). *Pain* 2000; 88:259-266.