The Laryngoscope

Cervical Variations of the Phrenic Nerve

Abie H. Mendelsohn, MD; Adam DeConde, MD; H. Wayne Lambert, PhD; Sean C. Dodson, BS; Blake T. Daney, BS; M. Elena Stark, MD, PhD; Gerald S. Berke, MD; Jonathan J. Wisco, PhD

Objectives/Hypothesis: Selective reinnervation of the posterior cricoarytenoid muscle with a single phrenic nerve rootlet has been shown to restore physiologic motion in animal models. However, clinical translation of this work is challenged by the limited knowledge of the cervical anatomy of the phrenic nerve.

Study Design: Prospective collaborative study.

Methods: Dissection of 111 cadaveric necks (88 embalmed and 23 unembalmed) from 56 cadavers.

Results: The mean (standard deviation) lengths of unembalmed cadaver C3, C4, and C5 nerve rootlets were 3.9 (2.4), 3.6 (2.6), and 0.5 (0.8) cm, respectively. Embalmed cadavers had shorter C3 and C4 phrenic nerve rootlet lengths than unembalmed cadavers ($P = .02$ and $P = .03$, respectively). There was no difference in mean nerve rootlet length based on sex, body height or weight, or side of dissection. A total of eight unique phrenic nerve rootlet patterns were identified. The most common pattern consisted of phrenic with single C3 and C4 rootlets with an immeasurable C5 rootlet, which was present in 30 of 111 (26%) of the necks. The classic three branching pattern of single C3, C4, and C5 rootlets was found in 25 of 111 (22%) of the necks. Six of 111 (5%) of the dissections displayed accessory phrenic nerves arising from the C3, C4, or C5 anterior rami. A χ^2 analysis showed no difference between side or sex and frequency of pattern.

Conclusions: The present study demonstrates the wide variability within the cervical anatomy of the phrenic nerve.

Key Words: Anatomy, bilateral vocal cord paralysis, laryngeal reinnervation.

Level of Evidence: 2b.

***Laryngoscope,* 121:1920–1923, 2011**

INTRODUCTION

Restoring dynamic function to vocal folds after bilateral vocal fold paralysis remains a challenging problem. The dynamic and highly coordinated glottic physiology allows for protection from aspiration during deglutition, phonation during speech, and a patent airway during respiration. Although current reinnervation procedures have produced improved muscle tone and bulk to the adductor muscle groups,[1] restoration of active abduction has been elusive. The lack of abduction following reinnervation of the recurrent laryngeal nerve (RLN) can be due to the development of synkinesis[2] and subsequent muscular discoordination. Yet dynamic abduction has been achieved with selective reinnervation of the posterior cricoarytenoid (PCA) muscle in the animal model.[3]

From the Division of Head and Neck Surgery, University of California (A.H.M., A.D., G.S.B.), Los Angeles, California; Department of Neurobiology and Anatomy (H.W.L.), West Virginia University School of Medicine, Morgantown, West Virginia, West Virginia University School of Medicine (S.C.D., B.T.D.), Morgantown, West Virginia; and Department of Pathology and Laboratory Medicine, Division of Integrative Anatomy, University of California (M.E.S., J.J.W.), Los Angeles, California, U.S.A.

Editor's Note: This Manuscript was accepted for publication April 6, 2011.

Presented as an oral presentation at the American Laryngological Association at Combined Otolaryngological Spring Meeting, Chicago, Illinois, U.S.A, April 28, 2011.

The authors have no funding, financial relationships, or conflicts of interest to disclose.

Send correspondence to Jonathan J. Wisco, PhD, David Geffen School of Medicine at UCLA, Room 50-094 CHS, Los Angeles, CA 90095-1732. E-mail: jjwisco@mednet.ucla.edu

DOI: 10.1002/lary.21894

The phrenic nerve has long been suggested as a potential nerve graft to drive PCA activation. The phrenic nerve has been described as arising from C4 with smaller and more variable contributions from C3 and C5 anterior cervical rami.[4] Traveling through the posterior neck into the mediastinum, the phrenic ultimately innervates the pulmonary diaphragm. Although it has been postulated that the phrenic nerve contains some sensory afferents,[4] its main function is diaphragm motor control causing pulmonary expansion and respiratory inhalation. The harmonious timing of both vocal fold abduction and inhalation makes the phrenic nerve an ideal candidate for PCA reinnervation. Although PCA activation occurs 40 to 100 milliseconds prior to diaphragm activation,[5] the ultimate functional difference is negligible.[6] Moreover, both PCA and diaphragm firing rates are increased by hypoxemia and hypercarbia.[7] Both muscle groups are inhibited during coughing and speaking.[8] Based on these similarities, the phrenic nerve is a promising nerve graft for abductor reinnervation.

However, sacrifice of the cervical phrenic nerve trunk will inevitably lead to hemidiaphragmatic paralysis and possible respiratory compromise. Crumley had suggested split phrenic graft to minimize pulmonary morbidity, but it was met with limited clinical success.[6] Alternatively, Baldissera et al.[9] suggested sacrifice of a single contributing phrenic nerve rootlet, thereby harnessing the intrinsic properties of the phrenic and minimizing diaphragm morbidity.[10] The phrenic nerve rootlet reinnervation has successfully restored dynamic abduction in multiple animal models.[3,9,11] Further

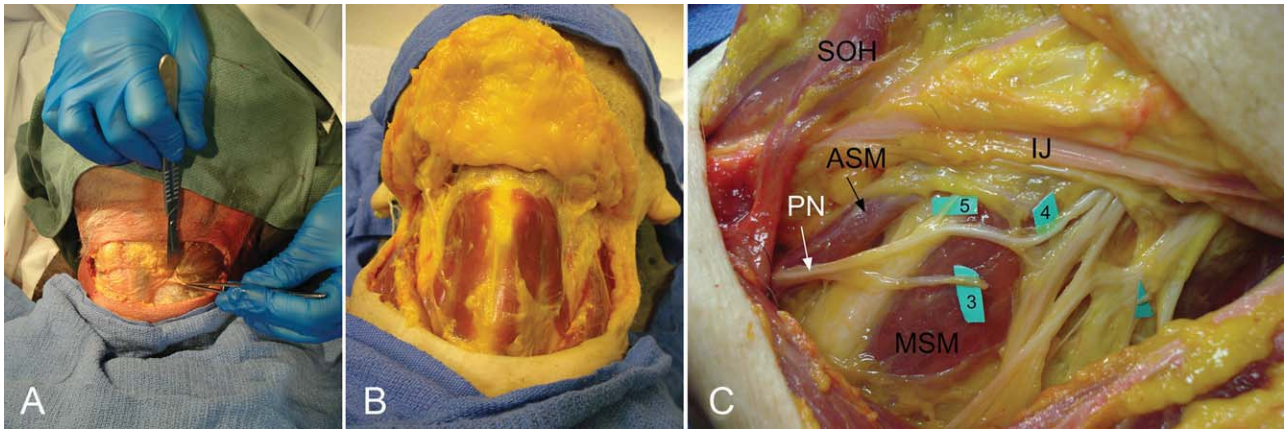

Fig. 1. Exposure of left phrenic nerve in an unembalmed cadaver neck specimen. (A) Following skin and platysma incision, the sternocleidomastoid muscle is exposed. (B) With the sternocleidomastoid and contents of the carotid sheath retracted medially, the anterior scalene muscle is dissected. (C) After transecting the prevertebral fascial layer, the phrenic nerve is exposed. The blue labels are placed for visualization of the nerve as well as labeling of the cervical rootlets (C3, C4, C5). PN = phrenic nerve; 3, cut = C3 rootlet; 4 = C4 rootlet; 5 = C5 rootlet; ASM = anterior scalene muscle; MSM = middle scalene muscle; SOH = superior belly of omohyoid muscle; IJ = internal jugular vein (with common carotid artery).

translational research in this technique is currently hampered by deficient knowledge of human phrenic nerve anatomy. Phrenic nerve anatomic studies to date have concentrated on its thoracic course or toward the presence of accessory phrenic nerves;[12] however, no study in the literature has specifically identified the branching anatomy of the phrenic nerve.

Our study seeks to describe the patterns of the phrenic nerve rootlets and the frequencies of the phrenic nerve rootlet patterns to determine the surgical potential of using these rootlets for PCA reinnervation.

MATERIALS AND METHODS

This study was determined to be exempt from review by the institutional review board.

A total of 23 unembalmed cadaveric phrenic nerve dissections were carried out in 12 specimens. A total of 88 embalmed cervical phrenic nerve dissections were carried out in 44 specimens. One of the unembalmed specimen necks was damaged in the handling process and was therefore unusable.

Exposure of the phrenic nerve on both unembalmed (Fig. 1) and embalmed (Fig. 2) specimens was achieved by the following surgical protocol: The procedure began with a transverse incision at the level of the cricothyroid membrane (Fig. 1A). After elevation of subplatysmal flaps superiorly to the level of the thyroid notch and inferiorly to the sternal notch (Fig. 1B), the fascia overlying the anterior border of the sternocleidomastoid muscle was incised and reflected laterally. The carotid sheath was identified immediately deep to the sternocleidomastoid. The internal jugular vein was then followed inferiorly to the level of the omohyoid muscle. At the crossing of the omohyoid and internal jugular vein, the dissection was directed posteriorly. With medial retraction of the internal jugular vein, the main phrenic nerve trunk was consistently seen overlying the medial aspect of the anterior scalene. At this point, the prevertebral fascia, which encases the phrenic nerve and the scalene musculature, was incised. The main trunk of the phrenic nerve was finely dissected rostrally toward the contributing cervical rootlets (Fig. 1C).

Once adequate phrenic nerve rootlet exposure was achieved, cervical rootlet lengths were measured using a measuring tape and the branching pattern was documented. We measured each rootlet from its point of emergence from the anterior spinal ramus to its joining another rootlet to form the main phrenic trunk. Rootlets that contributed solely to the phrenic nerve were measured as 7.0 cm.

Continuous data were summarized with means and standard deviations. The t test was used to determine differences in nerve rootlet length between embalmed and unembalmed cadavers, male and female cadavers, and laterality. Regression analysis was used to determine if nerve rootlet length was impacted by height, weight, and age. Categoric data were described with frequencies and percentages. Pearson's χ^2 test was used to determine association between sex, laterality, and pattern of phrenic nerve rootlets. A significance level of .05 was assumed for all tests. All statistics were performed using the program SPSS version 18.0.2 (SPSS Inc., Chicago, IL).

RESULTS

The mean lengths of each phrenic nerve rootlet and their standard deviations are given in Table I. The data are stratified by laterality, sex, and cadaveric processing. Cadaveric processing is the only variable that

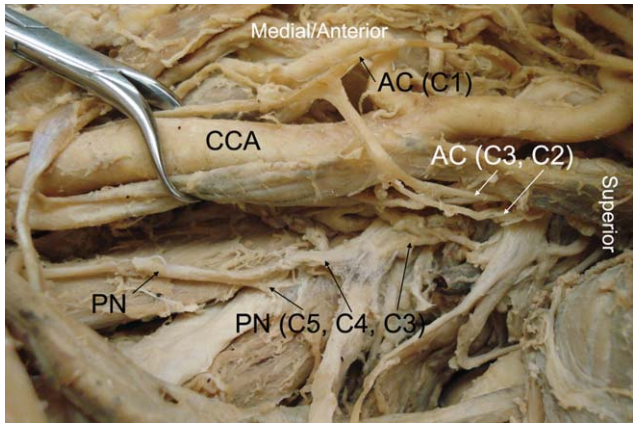

Fig. 2. Dissection of left phrenic nerve in an embalmed cadaver neck specimen. PN = phrenic nerve; AC = ansa cervicalis; CCA = common carotid artery.

TABLE I.
Phrenic Nerve Rootlet Measurements.

	C3	C4	C5
Total (n = 111)	2.70 (1.70)	2.58 (1.78)	0.73 (1.16)
Embalmed cadavers (n = 88)	2.36 (1.29)	2.32 (1.41)	0.76 (1.20)
Unembalmed cadavers (n = 23)	3.91 (2.36)	3.62 (2.56)	0.5 (0.76)
P value	.02	.03	.42
Male (n = 62)	2.42 (1.95)	2.42 (1.51)	0.82 (1.36)
Female (n = 49)	3.05 (1.24)	2.79 (2.05)	0.55 (0.51)
P value	.09	.30	.24
Right neck (n = 56)	2.42 (1.49)	2.46 (1.55)	0.57 (0.99)
Left neck (n = 55)	2.98 (1.87)	2.71 (1.97)	0.89 (1.30)
P value	.17	.46	.25

The length of each rootlet present in all specimens was measured from the point at which it emerged from the ventral ramus to where it combined with another rootlet to contribute to the phrenic nerve when present. Each cervical level phrenic rootlet is stratified by associated variables regardless of specimen preparation. Only cadaveric processing displayed significant differences in mean distances. Values are expressed as mean (SD). Student *t* test was used to determine *P* values.

significantly impacted length of the phrenic nerve rootlets, and the phrenic nerve rootlets at levels C3 and C4 were significantly shortened ($P = .02$, $P = .03$, respectively). The C3 embalmed rootlets were 1.55 cm shorter and C4 nerve rootlets were 1.30 cm shorter than the unembalmed cadaver nerve rootlets. Phrenic nerve rootlet length did not correlate with height or weight by regression analysis for C3 ($P = .80$ and .25 for height and weight, respectively), C4 ($P = .57$ and $P = .38$, respectively) or C5 ($P = .63$ and $P = .61$, respectively).

The eight various branching patterns encountered are diagrammed in Figure 3. There was a wide variability of patterns, the most common being type B, which was encountered in only 26% of the necks. The classic pattern (type A) of contributions from C3, C4, and C5 was seen in 22% of necks. Patterns C and H represent patterns with a phrenic nerve based on a lone cervical nerve rootlet and were represented in 13% of the specimens.

DISCUSSION

There has been extensive study of the innervation of the diaphragm. However, the majority of the studies in the literature have investigated the anatomy of the phrenic nerve within the thorax in the context of cardiothoracic surgery.[12,13] Classic anatomic texts state that the cervical phrenic nerve receives contributions from cervical spinal nerve rootlet levels C3, C4, and C5.[4] The predominate view describes the phrenic main contribution from C4, with branches from C3 and C5 augmenting the main trunk.[4]

Despite this putative anatomy, there remains only a single preliminary report to date describing the actual cervical patterns in three patients who underwent reinnervation of paralyzed larynges with superior phrenic nerve rootlets.[14] Verin et al. described two patients with a classic C3, C4, and C5 innervation and one patient with an absent C5 and a doubled C3 rootlet. Interestingly, in the 111 cadaveric necks we dissected, we did not encounter a double C3 nerve root. This study highlights the distribution of the nerve root patterns: Almost three quarters of the nerve rootlet patterns are composed of one of three patterns (types A, B, and E), and the remaining rootlet patterns fall into a somewhat miscellaneous category (types C, D, F, G, H) that were not highly represented despite 111 dissections. It is therefore not entirely surprising that Verin et al. describes additional branching variability.

Our data do expand the classic description of C3, C4, and C5 cervical nerve rootlet contributions to the phrenic nerve, as this pattern is seen in only 22% of necks. Two of the patterns had a lone contributing cervical nerve rootlet accounting for 12% of the necks examined.

Our work also demonstrates the value of unembalmed cadavers. The length of nerve rootlets was significantly altered by cadaveric processing at the C3 and C4 nerve rootlet levels (2.36 cm and 2.32 cm in embalmed cadavers vs. 3.91 cm and 3.62 cm in unembalmed cadavers, $P = .02$ and $P = .03$, respectively). We recommend future studies with measurements of nerve length be confirmed with unembalmed-cadaver data when feasible.

Future work should look to examine the anatomic feasibility of neurorrhaphy versus a need for a cable graft between nerve rootlets and the main trunk of the RLN with subsequent selective denervation of the adductor branches. In addition, further characterizing the physiologic distribution of phrenic nerve innervation across the cervical nerve rootlets will be important to help better predict donor site morbidity, as Verin et al. have begun to illustrate with their preliminary data. There is also a need to identify patients preoperatively

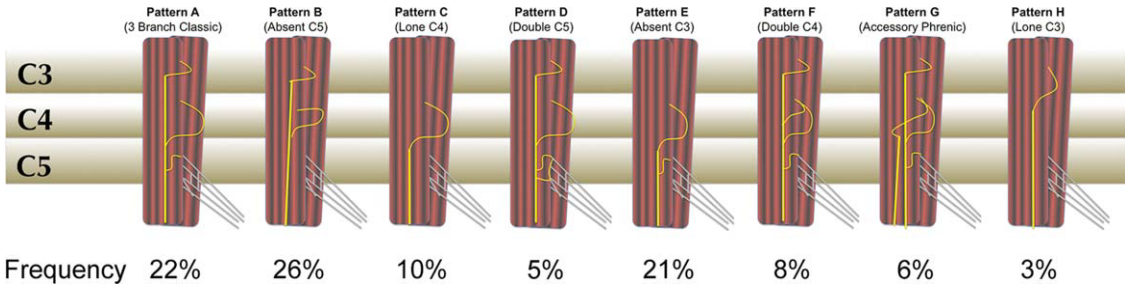

Fig. 3. Descriptive illustrations of phrenic nerve rootlets patterns as they lie on the middle and posterior scalenes. Substantial variability in phrenic branching patterns is seen. The most frequent pattern B (absent C5 contribution) was found in 26% of the specimens (regardless of side). The classically taught branching pattern A was found in only 22% of specimens.

as not viable candidates based on nerve pattern before controlled trials for human translation of this procedure.

CONCLUSION

We have described the cervical nerve rootlet patterns of the phrenic nerve. Our data further challenges the classic understanding of contributions from C3, C4, and C5 (a pattern that is realized in only 22% of the specimens) and describes the frequencies in which the variable patterns were encountered. Twelve percent of the necks demonstrated a lone phrenic nerve rootlet, which raises an issue of the reliability of a phrenic nerve rootlet to RLN innervation procedure in humans. We have also shown that embalmed cadaver data on nerve lengths are different from unembalmed cadaver data. We recommend confirming cadaveric nerve lengths with unembalmed cadaver data when feasible.

BIBLIOGRAPHY

1. Lorenz RR, Esclamado RM, Teker AM, et al. Ansa cervicalis-to-recurrent laryngeal nerve anastomosis for unilateral vocal fold paralysis: experience of a single institution. *Ann Otol Rhinol Laryngol* 2008;117:40–45.
2. Paniello RC. Laryngeal reinnervation. *Otolaryngol Clin North Am* 2004; 37:161–181, vii–viii.
3. van Lith-Bijl JT, Stolk RJ, Tonnaer JA, et al. Selective laryngeal reinnervation with separate phrenic and ansa cervicalis nerve transfers. *Arch Otolaryngol Head Neck Surg* 1997;123:406–411.
4. The peripheral nervous system. In: Clemente CD, ed. *Gray's Anatomy*, 30th ed. Baltimore, MD: Williams & Wilkins; 1985:1085, 1223–1225.
5. Green JG, Neil E. The respiratory function of the laryngeal muscles. *J Physiol* 1955;129:134–141.
6. Crumley RL. Experiments in laryngeal reinnervation. *Laryngoscope* 1982; 92(9 pt 2 Suppl 30):1–27.
7. Suzuki M, Kirchner JA. The posterior cricoarytenoid as an inspiratory muscle. *Ann Oto* 1969;78:849–964.
8. Guth L, Soutter L, Frank K, et al. Diaphragmatic function following anastomosis of recurrent laryngeal and phrenic nerves. *Exp Neurol* 1960;2: 251–260.
9. Baldissera F, Cantarella G, Marini G, Ottaviani F, Tredici G. Recovery of inspiratory abduction of the paralyzed vocal cords after bilateral reinnervation of the cricoarytenoid muscles by one single branch of the phrenic nerve. *Laryngoscope* 1989;99:1286–1292.
10. Marie JP, Tardif C, Lerosey Y, et al. Selective resection of the phrenic nerve roots in rabbits. Part II: Respiratory effects. *Respir Physiol* 1997; 109:139–148.
11. Marie J, Lacoume Y, Laquerriere A, et al. Diaphragmatic effects of selective resection of the upper phrenic nerve root in dogs. *Respir Physiol Neurobiol* 2006;154:419–430.
12. Loukas M, Kinsella CR, Louis RG, Gandhi S, Curry B. Surgical anatomy of the accessory phrenic nerve. *Ann Thorac Surg* 2006;82:1870–1875.
13. Hidayet MA, Wahid HA, Wilson AS. Investigations on the innervation of the human diaphragm. *Anat Rec* 1974;179:507–516.
14. Verin E, Marie J, Similowski T. Cartography of human diaphragmatic innervation: Preliminary data. *Respir Physiol Neurobiol* 2011;176:68–71.