Anatomical variations of the phrenic nerve: clinical and surgical implications

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Abstract

Introduction: The phrenic nerve (PN) is a mixed spinal nerve, normally originating from the ventral branches of the C3, C4 and C5 spinal cord segments. It is the only nerve responsible for the motor innervation of the diaphragm muscle, but its sensory fibers reach the central portion of the diaphragm, the mediastinal parietal pleura, the fibrous pericardium and the parietal serous pericardium.Ours was understood as its variant forms of the phrenic nerve (NP) for objective identification in clinical practice.

Material and Methods: This is a systematic review of studies indexed in SciELO; PubMed; Springerlink; Google Scholar; Science Direct and VHL databases, from October to November 2020. Original studies involving anatomical variations of PN in humans were included. For this study, the presence, absence, or variance of PN was considered.

Results: Seven studies were included, characterized as to the sample, method of evaluation of the anatomical structure and main results. The most prevalent anatomical variation was that the PN passing anterior to the subclavian vein (20%). The second most common variation was PN appearing in C4 and C5 segments (11%). In 9.1%, PN arose from C4 segment alone. In 5.4% of the studies, the PN had its normal pattern arising from C3, C4 and C5 and passing posterior to the subclavian vein. In only one study (0.2%) a not-before-reported PN variation was seen entering the fissure in its superior aspect and exiting anterior to the azygos vein inferiorly.

Conclusion: PN anatomical variations are not uncommon findings. Thus, it is necessary to know the normal PN anatomy and its possible variations, to enable early recognition of major complications during surgical procedures.

Keywords — Anatomical Variations; Phrenic Nerve; Unilateral diaphragmatic palsy.

I. INTRODUCTION

The phrenic nerve (PN) is a mixed spinal nerve, normally arising from the ventral branches of C3, C4 and C5 spinal cord segments. It is the only nerve responsible for motor innervation to the diaphragm muscle, but its sensory fibers reach the central portion of the diaphragm, the mediastinal parietal pleura, the fibrous pericardium, and the parietal serous pericardium. Within the cervical region, the superior portion of the lateral border of the scalene anterior muscle arises laterally, and then presents an anterior descending course, covered by prevertebral fascia. It usually reaches the chest, anterior to the subclavian artery and posterior to the subclavian vein [13, 17].

The right PN is shorter and more vertical than the left one and, at the neck root, it is separated from the second part of the right subclavian artery by the anterior scalene muscle. It descends laterally into the right brachiocephalic vein, superior vena cava, and fibrous pericardium that cover the right surface of the right atrium and inferior vena cava and divides slightly above or at the level of the diaphragm. At the neck root, it is generally described that the left PN leaves the medial border of the scalenus anterior muscle and passes anteriorly to the first part of the left subclavian artery and posteriorly to the thoracic duct [5].

However, the right and left phrenic nerves are symmetrical in their cervical course, so that the left PN can cross anteriorly the second part of the left subclavian artery, separated from it by the anterior scalene muscle at the level of the superior opening of the thorax. With this, the left PN crosses anteriorly the left internal thoracic artery, descending through the medial aspect of the left lung apex and its pleura to the first part of the subclavian artery, passing superficially to the left vagus nerve, just above the aortic arch and behind the left brachiocephalic vein [13].

In this context, PN variations have already been reported in the past and have been observed since then [8]. In a study carried out in Japan with 106 cadavers (212 nerves), PN originating in C4 and C5 segments (52% of cases) was observed; the second most common variation was PN arising from the C4 segment alone, corresponding to 43.5% of cases. Of the total, only 1.5% originated in C3, C4 and C5 segments [3].

The location of the main PN branches is important to avoid iatrogenic surgical injuries. Radial incisions in the diaphragm from the costal margin to the esophageal hiatus lead to diaphragmatic paralysis, while thoracoabdominal incisions in a circumferential manner at the periphery of the diaphragm do not involve any significant branches of the phrenic nerves and preserve diaphragmatic function.

Therefore, it is necessary to understand the variant forms of PN in order to identify their implications in clinical practice, including the relationship with unilateral diaphragmatic paralysis, which commonly manifests when there is PN paralysis due to a venous access complication [18]. In this context, this study aimed to evaluate the anatomical variations of PN and its clinical and surgical implications.

II. MATERIAL AND METHODS

This is a systematic review. To carry out this study, the search was on the following: SciELO (Scientific Electronic Library Online); PubMed (National Library of Medicine and National Institute of Health); Springerlink; Google Scholar; Science Direct and VHL (Virtual Health Library). The electronic search was carried out from October to November 2020. Articles were selected without time restriction, in English and Portuguese. For the prospection of the studies, the descriptors were used in combination with Boolean operators (AND). In PubMed, the combination was: “anatomical variation” and “phrenic nerve”. In SciELO, Springerlink, and Google Scholar: "phrenic nerve" and "diaphragmatic paresis". In Science Direct and VHL the combination was "diaphragmatic paresis"

Duplicates were identified and each study was considered only once. From the identified studies, those that met the inclusion criteria were selected, by title and abstract. Original articles involving anatomical variations of the phrenic nerve in humans, prioritizing more relevant studies, were included in this review. Review articles and preclinical studies with animal models were excluded.

The search was performed by two independent reviewers, and the analysis of interobserver agreement was performed using the Kappa test, using the Bioestat V 5.0 software, according to the method of Landis and Koch (1977). The value found was K = 0.78 (Substantial agreement).

The articles were critically analyzed through an interpretation guide, used to assess their individual quality, based on studies by Greenhalgh (1997) and adapted by Macdermid et al. (2009). Items for assessing the quality of studies are expressed by scores in Table 1, where 0 = absent; 1 = incomplete; and 2 = complete.

Table 1: Quality analysis of studies found on phrenic nerve variation.

	Item evaluation criteria												
Studies	1	2	3	4	5	6	7	8	9	10	11	12	Total (%)
Paraskevas, et al. (2011)	2	0	2	NA	2	NA	2	2	2	2	0	2	80%
Codesido e Guerri (2008)	1	0	2	NA	1	NA	1	0	2	1	0	2	50%
Abie H, et al. (2011)	2	0	2	NA	2	NA	2	1	2	2	2	2	85%
Talbot (1978)	2	0	2	NA	2	NA	1	0	2	1	0	2	60%
Banneheka (2008)	2	1	2	NA	2	NA	2	2	2	2	2	2	95%
Prakash, et al. (2007)	1	NA	2	NA	1	NA	2	2	2	2	0	2	77.7%
Bancroft e Stephens (2007)	1	NA	2	NA	1	NA	2	2	2	2	0	2	77.7%

Acronyms: NA, not applicable to paper.

*Assessment criteria: 1. Thorough literature review to define the research question; 2. Specific inclusion/exclusion criteria; 3. Specific hypotheses; 4. Appropriate scope of psychometric properties; 5. Sample size; 6. Follow-up; 7. The authors referenced specific procedures for administration, scoring and interpretation of procedures; 8. Measurement techniques were standardized; 9. Data were presented for each hypothesis; 10. Appropriate statistics-point estimates; 11. Appropriate statistical error estimates; 12. Valid conclusions and clinical recommendations.

III. RESULTS

A flow chart summarizing the selection process is shown in Figure 1. Initially, 29 studies were identified, and 21 were excluded because they were not relevant or because they were duplicates, the remaining 8 were submitted for full-text analysis and verification of inclusion and exclusion criteria. Seven of these adequately met all the inclusion criteria and were included for data extraction and quantitative synthesis.

Figure 1. Search and selection of studies for systematic review

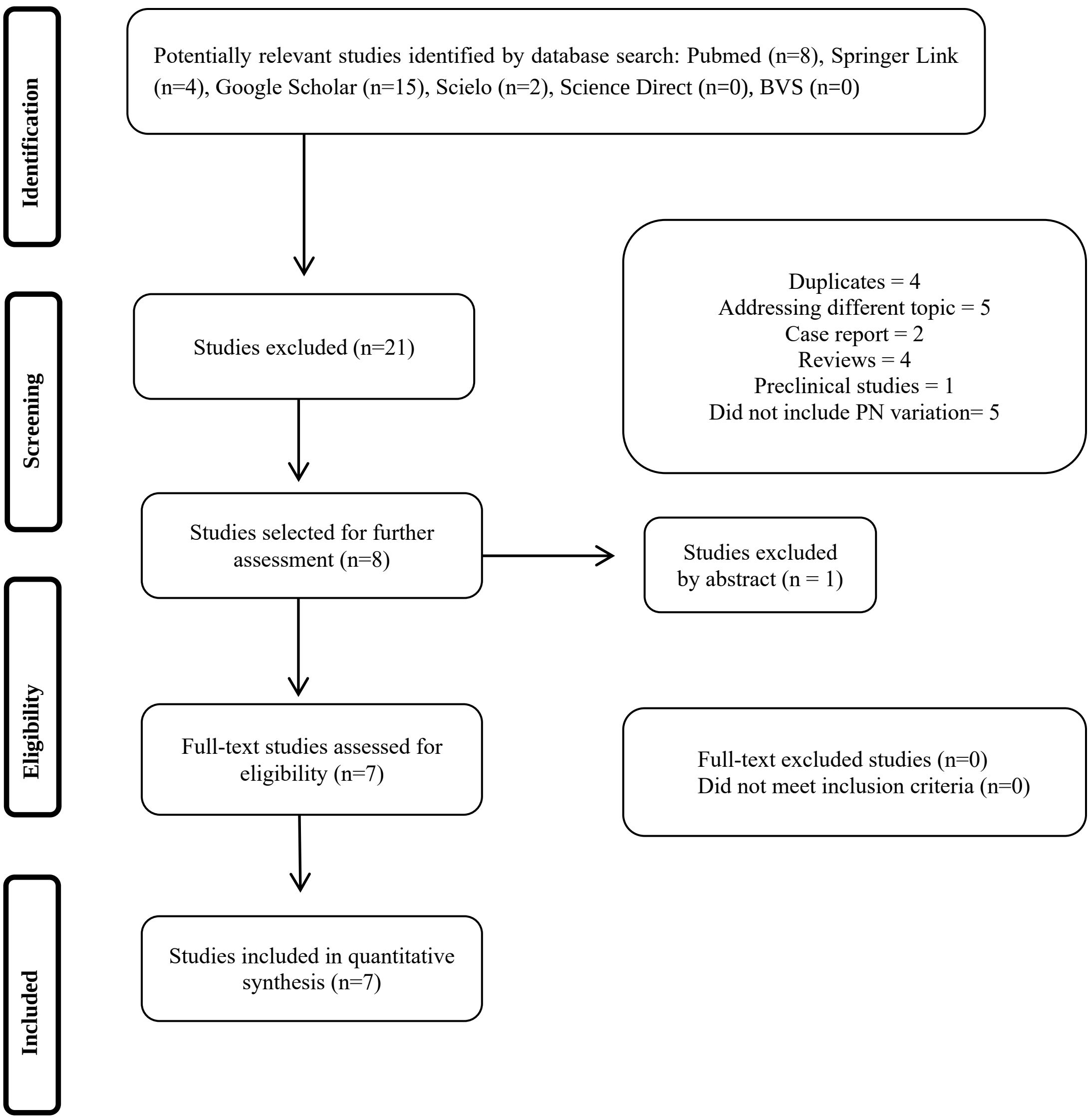

Table 2. Characteristics of studies that evaluated the relationship of phrenic nerve (PN) anatomical variations in humans

Author (year)	Sample	Method	Main results
Paraskevas, et al. (2011)	42 cadavers	Cadaveric dissection	PN was found posterior to the subclavian vein in two cases (2.38%), anterior to the subclavian vein (95%) and in one case (1.19%) crossing through the anterior wall of the subclavian vein.
Codesido & Guerri (2008)	1 cadaver	Cadaveric dissection	The accessory PN passed through a transient division in the subclavian vein before entering the PN, reaching the anterior surface of the subclavian artery, where it went through a ring located 1 cm away within the jugular-subclavian junction. The accessory PN emerged from the posterior surface of the vein to join the PN in the chest.
Talbot (1978)	30 cadavers	Cadaveric dissection	45% of accessory PN passes in front of the subclavian vein. In 66% of the cadavers, none of the PN passed in front of the subclavian. The subclavian vein can cause transient paralysis of the accessory phrenic nerve.
Abie, et al. (2011)	56 cadavers	Cadaveric dissection	PN was formed by C3, C4 and C5 only in 22% of the 56 cadavers. Six of 111 (5%) of the dissections showed accessory PN arising from C3, C4 and C5 in the anterior segment.
Banneheka (2008)	106 cadavers	Cadaveric dissection	In 52% of the cases, the most common origin of PN was in C4 and C5 segments. The second most common origin was the C4 segment alone (43.5%). Only 1.5% of the total originated in C3, C4 and C5 segments.
Prakash, et al. (2007)	1 cadaver	Cadaveric dissection	PN presented a communicating branch to the C5 root of the brachial plexus close to the origin. PN was located in front of the subclavian vein just before entering the thorax. This variation makes PN highly vulnerable to injury during subclavian catheterization for vascular access.
Bancroft & Stephens (2007)	2 cadavers	Cadaveric dissection	In the presence of the azygos lobe in the lung, in a first case, PN was seen between the two pleura layers, entering the fissure in its superior aspect and exiting anterior to the azygos vein inferiorly. In the second case, the azygos fissure did not contain PN.

Five types of variations were observed: Type 1 – PN arising from the ventral branches of C3, C4 and C5 medullary segments and passing posterior to the subclavian vein (normal pattern); Type 2 - PN arising from the segments of C4 and C5 (Variation in its origin); Type 3 – PN arising from the C4 segment alone (Variation in its origin); Type 4 – PN passing anterior to the subclavian vein (Variation in its course); Type 5 – PN entering the fissure in its superior aspect and leaving anterior to the azygos vein inferiorly (Variation in its course).

All studies included in this review used the cadaver dissection method to analyze the anatomical variations of the phrenic nerve [2, 3, 4, 15, 16, 21, 25]. Type 1 variations were observed in 3 of the selected studies, which refers to the normal pattern [3, 15, 25]. Only 1 of the studies showed the variant type 2 and type 3 [3]. Type 4 variations were observed in 3 of the seven included studies [4, 16, 21]. Only 1 study presented type 5 variation [2].

IV. DISCUSSION

The anatomical variations discussed in the literature can be classified as: variations in the nerve roots that originate PN or variations in its course [17].

In this review, 478 PN were identified. Of these, 5.4% of the nerves corresponded to type 1 (PN arising from the ventral branches of spinal cord segments C3, C4 and C5 and passing posterior to the subclavian vein); 11% type 2 nerves (PN appearing in the C4 and C5 segments only); 9.1% to type 3 (PN arising only from the C4 segment alone); 20% to type 4 (PN passing anterior to the subclavian vein); and only 0.2% to type 5 (PN entering superiorly the fissure and leaving anteriorly to the azygos vein inferiorly).

A study with 56 cadavers showed that the phrenic nerve was formed by C3, C4 and C5 only in 22% of the 56 cadavers. Six of 111 nerves (5%) of the dissections showed accessory PN arising from C3, C4 and C5 [25]. In the study by Banneheka [3], PN originated in the segments C3, C4 and C5 only in 1.5% of 106 cadavers. Paraskevas et al. [15], observed that the phrenic nerve was found posterior to the subclavian vein in two cases (2.38%) of the total of 84 nerves. These findings represent type 1 variation, which would be the expected anatomical pattern. In these cases, a possible PN section at the cervical level is responsible for complete paralysis in the corresponding half of the diaphragm, leading to muscle atrophy [5].

Also, in the study by Banneheka [3], with 212 nerves, 52% of the cases the most common origin of PN was from C4 and C5 segments. And the second most common origin was the C4 segment alone (43.5%). This variation in PN origin makes it very close to the brachial plexus in the neck, being in front of the anterior scalene muscle. Thus, in cases of injection of a local anesthetic solution, it can be reached by the dispersion of the anesthetic solution when interscalene and supraclavicular perivascular techniques are used, which results in PN blockade at the level of C4 and C5 [26]. According to Wilson, Brown and Wong [27], this PN blockade leads to paresis or even diaphragmatic paralysis, causing dyspnea and respiratory failure in susceptible patients.

As for the findings found in PN course, the most frequently reported isolated variation is when the nerve, before reaching the thorax, passes anterior to the subclavian vein. This finding was seen in 95% of 84 nerves in the study by Paraskevas, et al. [15]. The PN was in front of the subclavian vein just before entering the thorax, and associated with this variation, the PN presented a communicating branch to the C5 root of the brachial plexus [16]. In 45% of 30 cadavers, the accessory PN passed anterior to the subclavian vein [21]. Some complications are suggested to happen due to this variation. The presence of PN anterior to the subclavian vein (type 4) leaves it in a vulnerable position during puncture and catheterization procedures of this vessel, as described in the studies by Paraskevas, et al. [15]; Prakash et al. [16]; Talbot [21]; and Codesido & Guerri [4]. In these variations, the subclavian vein may cause a transient paralysis of the accessory PN, or it may be the cause of a unilateral diaphragmatic paralysis.

Another finding in its course, observed in the study by Codesido & Guerri [4], is that the accessory PN passed through a transient division of the subclavian vein before entering the PN, reached the anterior surface of the subclavian, where it went through a ring located 1cm away within the jugular-subclavian junction. The accessory PN emerged from the posterior surface of the vein to join the PN in the thorax. The author reports that this is the first time in the literature that this type of variation is reported. According to him, these variations may predispose to complications during subclavian venous catheterization, given that the lumen of the subclavian vein is temporarily divided by the presence of accessory PN.

In addition, Bancroft & Stephens [2] observed during routine dissection the azygos lobe on the right side in 2 cadavers. After dissection of the fissure in one of the cadavers, PN was discovered between the two pleura layers, entering superiorly the fissure, and exiting anterior to the azygos vein inferiorly. This finding may have clinical implications during lobectomy and segmental resection procedures [11]. As well as implications for the thoracentesis procedure, which consists of puncturing the pleural fluid with a fine needle, increasing the risk of injury to the PN when present between the layers of the pleura [22].

There are few reports in the literature about the implications related to PN variations, whether in its origin or course. Several mechanisms have been proposed to explain PN injury during venous catheterization of the subclavian vein. According to Hadeed & Braun [7], a direct injury to the nerve is usually attributed to repeated attempts at nerve puncture. PN hemorrhagic compression by a mediastinal hematoma or even compression of the nerve by the rigid tip of the venous catheter without perforating the subclavian vein can occur, especially in type 4 variation, where the PN passes anterior to the subclavian vein. [20].

According to Steinfeldt, Nimphius, Werner, et al. [19], the size of the needle is a predominant factor for more severe nerve injury in case of needle perforation of the nerve. Transient PN paralysis due to local anesthesia instilled at the beginning of venous catheterization has been reported [14]. Inflammation of the venous wall as a result of catheterization can lead to compression of this nerve, especially when type 2 variation is present, when it originates only from the C4 and C5 segments [1].

In the study by Yang, et al. [23], PN palsy occurred immediately after right subclavian catheterization and resolved completely after catheter removal, the patient did not complain of dyspnea and arterial blood gas data were normal, ultrasound evaluation of both diaphragms demonstrated a decrease in movement of the right diaphragm compared to the left diaphragm. This suggests a reversible paralysis resulting from nerve compression, rather than direct injury to the PN, which can cause irreversible paralysis. Thus, transient unilateral diaphragmatic paralysis after venous catheterization of the subclavian vein may be attributed to PN anatomical variations, with type 2 and 4 variations as the more susceptible ones.

Therefore, knowledge of the normal PN anatomy and its possible variations are essential in order to guarantee safe procedures, especially in cases of venous catheterization of the subclavian vein, nerve punctures, lobectomy and needle perforation of the nerve, in addition to enabling the recognition of major complications, in cases of phrenic nerve block, which predisposes to unilateral diaphragmatic paralysis.

V. CONCLUSION

PN anatomical variations are not uncommon findings, for this reason professionals should always consider their possible occurrence during surgical procedures, such as venous catheterization of the subclavian vein, nerve punctures, lobectomy, and needle perforation of the nerve. Thus, it is necessary to know the normal PN anatomy and its possible variations, in order to enable early recognition of major complications, especially in cases of PN block, which predisposes unilateral diaphragmatic paralysis.

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