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CLINICAL ARTICLE - NEUROSURGICAL TECHNIQUES

The phrenic nerve as a donor for brachial plexus injuries: is it safe and effective? Case series and literature analysis

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Abstract
Background Controversy exists surrounding the use of the phrenic nerve for transfer in severe brachial plexus injuries. The objectives of this study are: (1) to present the experience of the authors using the phrenic nerve in a single institution; and (2) to thoroughly review the existing literature to date.
Methods Adult patients with C5-D1 and C5-C8 lesions and a phrenic nerve transfer were retrospectively included. Patients with follow-up shorter than 18 months were excluded. The MRC muscle strength grading system was used to rate the outcome. Clinical repercussions relating to sectioning of the phrenic nerve were studied. An intense rehabilitation program was started after surgery, and compliance to this program was monitored using a previously described scale. Statistical analysis was performed with the obtained data.
Results Fifty-one patients were included. The mean time between trauma and surgery was 5.7 months. Three-quarters of the patients had C5-D1, with the remainder C5-C8. Mean post-operative follow-up was 32.5 months A MRC of M4 was achieved in 62.7 % patients, M3 21.6 %, M2 in 3.9 %, and M1 in 11.8 %. The only significant differences between the two groups were in graft length (9.8 vs. 15.1 cm, $p=0.01$); and in the rehabilitation compliance score (2.86 vs. 2.00, $p=0.01$).
Conclusions Results of phrenic nerve transfer are predictable and good, especially if the grafts are short and the rehabilitation is adequate. It may adversely affect respiratory function tests, but this rarely correlates clinically. Contraindications to the use of the phrenic nerve exist and should be respected.

Keywords Brachial plexus injury · Phrenic nerve · Extraplexual transfer · Nerve transfer

Introduction

Brachial plexus lesions are devastating, and occur predominantly in young and economically active male individuals. Most of these injuries are related to motorcycle trauma and have become a serious societal problem, especially in big cities [1]. Controversy exists surrounding the use of the phrenic nerve as a source of transferable axons for this type of injury. While some high-volume brachial plexus centers use this strategy frequently, other equally experienced departments never use the phrenic nerve for neurotization. The most commonly cited argument against using the phrenic nerve relates to the unknown deleterious respiratory effects that could develop from diaphragmatic paralysis, both short- and long-term. As one of the most important principles in medicine is "first do not harm", we believe that this argument against using the phrenic nerve as a donor should not be denied superficially. On the other hand, many surgeons, even among those who deny

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using it, accept that the phrenic nerve is a powerful motor nerve that yields predictably good results when transferred to certain nerve targets. Moreover, the literature describes several compensatory mechanisms that appear to limit the negative effects of hemidiaphragmatic paralysis.

The general objectives of the present paper are: (1) to present our experiences over 10 years of clinical practice using the phrenic nerve as an axon donor in surgeries performed at the Peripheral Nerve & Brachial Plexus Program in Buenos Aires, Argentina; and (2) to thoroughly review the existing literature to date to identify all empirical evidence for and against the use of phrenic nerve transfers for brachial plexus injuries. Specific objectives related to the current series were (1) to identify the percentage of patients who experience a good result, as per the British MRC scale, using the phrenic nerve as an axon donor; and (2) to compare those achieving a good result versus those not achieving a good result with respect to baseline demographic and clinical, as well as surgical variables.

Methods

From January 1, 2004 to December 13, 2013, a total of 276 traumatic brachial plexus injuries were treated with surgery at the Peripheral Nerve & Brachial Plexus Surgery Program within the Department of Neurosurgery at the University of Buenos Aires. Only those adults patients with severe brachial plexus palsy (C5-D1 and C5-C8) and an extraplexual phrenic nerve transfer were retrospectively included in the present series. Patients under 14 years old, those with follow-up shorter than 18 months, and those with superior limb amputations were excluded from analysis. Written informed consent was obtained from each patient. Variables like patient age, sex, weight, time from trauma to surgery, and extent of the lesion were recorded.

The preoperative patient evaluation included neurophysiological studies (nerve conduction studies and electromyography), pre-operative respiratory function tests, and myelo-MRI. Nerve transfers were considered when preoperative evaluation and intraoperative findings ruled out the presence of an available root for reconstruction. Cases with a partial root avulsion according to MRI where excluded for phrenic nerve transfer, and the same occurred in partial (upper/middle) trunk palsies, where other options for nerve transfer were available.

The surgical technique included a supraclavicular incision one standard finger-breadth over the clavicular line, which allowed for complete exposure of the proximal brachial plexus and its branches (including the upper and middle trunks with their anterior and posterior divisions, and the suprascapular nerve), the phrenic nerve, and the spinal accessory nerve. Once available roots and other potential extraplexual axon donors were identified, distal targets were selected by (1) using the just-mentioned proximal targets (e.g., the anterior division of the upper trunk to re-establish elbow flexion) or (2) creating a new incision starting at the axilla and following the proximal medial brachial fossa. In the procedure described in (1), a short nerve graft would generally be required, while in (2), a nerve graft longer than 10 cm is needed. Pertinent distal targets (musculocutaneous nerve or its branches to the biceps, the radial nerve, or its branches to the triceps, or the pectoral and axillary nerves) were identified. Once donor and corresponding target nerves, according to availability, were decided upon, direct neurorrhaphy or autologous nerve grafts were employed to bridge the gap. It is important to mention that in all cases of this series, when the phrenic nerve was transferred in an attempt to restore a certain upper limb function, this was the only attempt to recover that function (i.e., if the phrenic was transferred to the anterior division of the upper trunk, no intercostal to musculocutaneous nerve transfer was performed simultaneously). Otherwise, it would be impossible to determine the real result of the phrenic nerve transfer.

Postoperative evaluations were performed on a regular basis every three months for a minimum of 18 months. An intense rehabilitation program was started 3 weeks after surgery, and compliance to this program was monitored using a previously described scale, which rates rehab compliance between 1 (little compliance) and 4 (full compliance), presented in Table 1. [2]. The Medical Research Council (MRC) muscle strength grading system (ranging from 0=no contraction to 5=normal strength) was used to rate the final primary outcome. An overall good result was considered MRC grade 3 strength or better, and a bad result grades 0, 1, or 2. Clinical repercussions relating to sectioning of the phrenic nerve were investigated at every postoperative evaluation, with specific tests indicated if any answer to screening questions was affirmative or if any respiratory symptom had developed. In each postoperative interview, several questions were performed in

Table 1 The rehabilitation quality scale used to quantify adherence to and the quality of a patient's postoperative rehabilitation program

Score description
.1 No rehabilitation therapy at all or less than once a week
.2 Rehabilitation therapy more than once per week, but not at a specialized neuro-rehabilitation center
.3 Good adherence with the entire rehabilitation program, but not at a specialized neuro-rehabilitation center; periodically assessed at a specialized neuro-rehabilitation center
.4 Patient adheres perfectly to the entire rehabilitation program at a specialized neuro-rehabilitation center

Table 2 Questionnaire for patients in postoperative control after phrenic nerve section

.1-Do you feel shortness of breath when you are lying in bed?
.2-Can you wake up from bed, dress yourself, and bathe without dyspnea?
.3-Can you run 300 meters without stopping for dyspnea?
.4-Can you climb 3 flights of stairs without stopping for dyspnea?

order to address this issue (Table 2). If any sign of ventilator compromise was present, respiratory studies were performed sequentially to determine the exact grade of affection and its evolution.

Statistical analysis

Means and standard deviations were calculated for all continuous variables and percentages for all categorical variables. Prior to selecting the appropriate statistical test for inferential testing, for each variable the Kolmogorov–Smirnov test was used to test for normality and Levene's test for equality of variances. To compare patients with good versus poor MRC outcomes, Student's *t* tests were used for comparisons of normally distributed continuous variables—like age, body mass index, and length of time between injury and surgery—and Pearson $\chi 2$ analysis to compare categorical variables like gender, mechanism of injury, and lesion level, with $p<0.05$ set as the threshold for statistical significance and all tests two-tailed. A Pearson correlation coefficient was calculated for the MRC versus the score of each patient for the rehabilitation scale, with an a priori *r* level of 0.40 set as the threshold for moderate correlation, and $r=0.70$ set as the threshold for a strong correlation.

Results

Demographic and baseline characteristics of the sample are presented in Table 3. The sample of 51 patients was overwhelmingly male, and 61 % were between the ages of 20 and 29, though ages ranged from 14 to 56. Roughly 60 % were of normal weight, with the remainder either overweight (n = 19) or obese ($n=2$). The mechanism of injury was a motorcycle accident in all but four cases. The mean time between trauma and surgery was 5.7 months (standard deviation, 3.5), ranging from 1 to 24 months; 40 of the patients (78 %) underwent their reconstruction within 6 months, nine (18 %) between 6 and 12 months after their injury, and two (4 %) after more than 12 months. Three-quarters of the patients had involvement of the C5 through D1 levels, with the remainder from C5 through C8. As stated previously as an inclusion criteria, all patients suffered from complete avulsion of each of the affected roots.

The most commonly performed phrenic nerve graft was to the musculocutaneous nerve ($n=21$, 41 %) followed by grafting phrenic nerve to the anterior division of the upper trunk ($n=11$, 22 %) (Table 4). The majority (69 %) of phrenic nerve grafts were targeted to peripheral nerves, with 25.5 % attached at the division level and only 6 % at the cord level.

Mean post-operative follow-up was 32.5 months, ranging from 18 to 57 months. The process of strength recovery started with subtle muscle movements related to full inspiration. The physiotherapist took advantage of this fact, and after a variable period of 4 to 9 months, a strongest recovery was observed, still related to respiration (breathing arm). Finally, the movement becomes independent from the respiration. A British MRC level strength rating of M4 was achieved in 32 of the 51 patients (62.7 %) by the time of final follow-up, with M3 achieved in 11 (21.6 %), M2 in two (3.9 %), and M1 in six (11.8 %). Using the MRC threshold of≥M3 as a good result, a good outcome was thereby achieved in 43 of the 51 patients (84.3 %). A rehabilitation compliance rating of 4 was achieved in ten patients (19.6 %), of three in 20 patients (39.2 %), and of two and one in 16 (31.4 %) and four (7.8 %) patients, respectively. A moderately strong correlation was noted between the final MRC and the rehabilitation score ($r=0.40$, $p=0.004$). Only two of 51 patients experienced any respiratory symptoms, both were mild and transitory.

Table 3 Demographics and baseline clinical characteristics of the sample

	N	%
Total sample	51	
Males	47	92.2 %
Age at time of surgery		
<20	7	13.7 %
20–29	31	60.8 %
30–39	8	15.7 %
≥40	5	9.8 %
Weight by BMI		
Normal weight	30	58.8 %
Overweight	19	37.3 %
Obese	2	3.9 %
Level of lesion		
C5-D1	39	76.5 %
C5-C8	12	23.5 %
Mechanism of injury		
Motorcycle accident	47	92.2 %
Car accident	3	5.9 %
Other cause	1	2.0 %

Table 4 Surgical procedure and results

	N	%
Total sample	51	
Procedure		
Phrenic nerve to musculocutaneous nerve	21	41.2 %
Phrenic to anterior division, upper trunk	11	21.6 %
Other	19	37.3 %
Target level of graft		
Division	13	25.5 %
Cord	3	5.9 %
Branch	35	68.6 %
Outcomes		
British MRC strength rating		
M1	6	11.8 %
M2	2	3.9 %
M3	11	21.6 %
M4	32	62.7 %
Overall outcome		
Good	43	84.3 %
Poor	8	15.7 %
Rehabilitation scale score		
1	4	7.8 %
2	16	31.4 %
3	20	39.2 %
4	10	19.6 %
Respiratory symptoms	2	3.9 %

Comparing those patients achieving a good versus poor outcome, those in the former group were almost 4½years older, but this difference failed to achieve statistical significance (p=0.18; Table 5). They also underwent surgery an average of roughly 2 months earlier than their less responsive counterparts; but this difference also failed to achieve statistical significance (p=0.16). The only significant differences between the two groups was in graft length, the length of graft in responders being more than 5 cm shorter (9.8 vs. 15.1 cm, p=0.01); and in the mean rehabilitation compliance score (2.86 vs. 2.00, p=0.01).

Two patients answered positively to the questions #3 & 4 of Table 2. The first patient was a 31-year-old man with obesity and a right brachial plexus complete avulsion who developed postoperatively a dyspnea after efforts like running shortly or climbing stairs. A vital capacity reduction of 21 % was observed at 3 months, gradually diminishing to 9 % at 2 years. Positive clinical signs—only after questioning, but not spontaneously—remained present for 1 year. The other patient was a 48-year-old overweight (but not obese) woman who had a right-sided complete brachial plexus palsy: the postoperative respiratory evolution was similar as the former patient. Vital capacity reduced 19 % at 4 months and 10 % at 2 years, and symptoms disappeared 18 months after the surgery.

Discussion

The current series of 51 patients with complete palsy resulting from either a C5-D1 or C5-C8 injury makes a strong case for both the effectiveness and safety of phrenic nerve grafts in reconstruction, given the functional results (M3 or M4) that we observed in 84 % of our patients, and the very low rate of respiratory symptoms (4 %), all of which were not life-threatening. Even both two patients had a right palsy, due this small number; no statistical analysis was possible regarding the differences between right and left sided diaphragmatic consequences of phrenic nerve section. There were just two predictors of a successful outcome. One was graft length, with graft lengths appreciably shorter in those who responded versus

Table 5 Comparing patients with poor versus good MRC outcomes

	Good outcome	Poor outcome	Test statistic	Significance
N	43	8		
Mean age	27.2	22.8	t=1.37	p=0.18
Females (%)	9.3 %	0.0 %	χ2=0.81	p=0.37
Mean height (cm)	168.7	170.4	t=0.46	p=0.65
Mean weight (kg)	69.4	72.3	t=0.68	p=0.50
Mean BMI	24.4	24.7	t=0.28	p=0.78
Overweight (%)	50.0 %	39.5 %	χ2=0.31	p=0.58
Mean time since injury (months)	5.4	7.3	t=1.43	p=0.16
Motorcycle accident (%)	90.7 %	100.0 %	χ2=0.81	p=0.67
C5-D1 (%)	74.4 %	87.5 %	χ2=0.64	p=0.42
Mean graft length (cm)	9.8	15.1	t=2.90	p=**0.01**
Mean follow-up (months)	32.7	31.0	t=0.31	p=0.76
Rehabilitation compliance score	2.86	2.00	t=2.67	p=**0.01**

those with a less satisfactory result. Even though it was previously reported by our group [3] that long grafts would theoretically avoid dispersion of the growing axons and direct them towards a more precisely elected target, this comparative study demonstrates that the shorter the graft, the better the result. The other predictor was in the degree of compliance with post-operative rehabilitation, as measured with the previously reported rehabilitation compliance score; moreover, the British MRC strength rating and the compliance scale rating were moderately correlated, suggesting that compliance with post-operative rehabilitation and, therefore, rehabilitation itself are important components of overall treatment. Though our sample lacked the power to confirm this statistically, there also seemed to be better results in older patients and patients who waited less time to undergo reconstruction following their injury.

One confounder factor regarding the results of our series could be the existence of a prefixed brachial plexus receiving a large contribution from the C4 spinal nerve. These spared nerve fibers might have contributed to some of the observed recovery. The fact that our patients developed "breathing arm" (without any concomitant intercostal nerve transfer performed in the same patient) favors the phrenic nerve as axon source. Also, many nerve transfers were done proximally (i.e., to the anterior division of the upper trunk, which was sectioned completely to receive the donor axons, eliminating the possibility of an eventual reception of a C4 contribution to the biceps), and finally, if we analyze the literature regarding the destination of C4 fibers, the percentage of so-called "pre-fixed plexus" (this means, a large contribution of C4 going to the brachial plexus) is around 20 to 25 % in the normal population [4]. Eighty percent of these prefixed brachial plexuses receive contributions to the musculocutaneous nerve, while 50 % of the axillary receive fibers from C4 in those pre-fixed plexus. Nevertheless, the number of fibers directed to these targets is 5 % of the total number of fibers of that nerve. For example, for the axillary nerve, a mean of 245 fibers come from C4 (for a total of 6700 fibers in that nerve), and for the musculocutaneous, a mean of 298 fibers arise from C4, for a total of 6500 approximately [5]. In conclusion, considering all these numbers, even in the statistically uncommon scenario that some unrecognized and spared nerve fibers might proceed from C4, the number of these fibers are approximately the same as one intercostal nerve [1]. The power of this number of fibers for contributing to some of the observed recovery is undoubtedly low.

Scientific arguments against using the phrenic nerve as a donor for brachial plexus reconstruction

The main concern related to using the phrenic nerve as a donor for brachial plexus reconstruction is the potential for either transient or permanent loss of pulmonary function.

However, in their series, Luedemann et al. [6] identified a statistically significant reduction in vital ventilatory capacity only when the right phrenic nerve was used, and this was not clinically evident. The authors concluded that phrenic nerve use for brachial plexus reinnervation is contraindicated only when preoperative maximum inspiratory pressure is decreased. Accessory phrenic nerve function has been related to the absence of clinical effects after phrenic nerve section [6], which relates to Luedeman et al. study if we consider that most reported origins of the phrenic nerve have been on the right side [7]. Our two patients who had respiratory symptoms after phrenic nerve section had a right-sided palsy, but this number was too small to make any statistical analysis on this topic. Meanwhile, Songcharoen et al. followed 12 patients over 2 years, and none presented with either signs or symptoms of respiratory failure or post-operative respiratory complications. In addition, 25 % had normal diaphragmatic movement on the affected side, all respiratory function tests were normal, and vital capacity was reduced only in 9.4 %, returning to normal after 6–24 months [8].

In a series published by Chuang et al. in which the phrenic nerve was used as a donor in 19 patients with brachial plexus injuries, 42 % reported some post-operative dyspnea, but it disappeared within 6 months of the procedure, though a persistent 8 % decrease in total pulmonary respiratory function was noted [9]. This finding was corroborated by Siqueira et al., in 80 % of their patients with 2 years of follow-up, but no clinical symptoms appeared affecting quality of life [10]. This latter group considers the phrenic nerve as a primary good donor for brachial plexus reconstructive surgery.

Other investigators have documented a greater extent of respiratory compromise, like Zheng et al. [11], who observed a decrease in forced vital capacity, forced respiratory volume, and total pulmonary volume in 26.3, 28.0, and 25.2 % of their patients, respectively, associated with a mean hemidiaphragmatic elevation of 1.0 to 1.5 intercostal spaces in 90.5 % of patients. These data contrast with clinical symptoms in the same series, however; when asked, only 2 % reported mild dyspnea during exercise. Moreover, sacrificing one or two intercostal nerves 2 months after the first procedure was similarly well tolerated [11]. It is also worthy to note that the long-term effects of phrenic nerve versus phrenic plus intercostal nerve transfers were similar in a series with a median follow-up of 10 years [11, 12].

In other series of patients wherein a phrenic nerve lesion was observed as a complication of another procedure (e.g., cardioablation), the percentage with symptomatology profile has been completely different, with 88 % presenting with dyspnea, cough and hiccups, a standard recovery time of 4–5 months, and 16 % still without complete recovery after 3 years [2, 13, 14]. Of course, those series included patients with previous illnesses, who are unlike the generally young and otherwise healthy patient with a brachial plexus injury.

Considering all the aforementioned information, before performing a phrenic nerve transfer, diaphragmatic and pulmonary function should be evaluated; and if it is altered, the phrenic nerve should not be used. In cases of thoracic trauma, multiple costal fractures and/or pulmonary contusions, the nerve transfer should be delayed until final healing of those injuries [3, 15]. For the same reason, simultaneous phrenic and intercostal nerve transfers should be avoided, though no published evidence exists documenting any important respiratory effects if they are used in a two-stage procedure [9, 16]. Some authors believe that there are fewer respiratory effects when intercostal nerves are used instead of the phrenic nerve as a donor [17].

That phrenic nerve transfers are contraindicated in children below 3 years of age has been demonstrated convincingly. Infants born with diaphragmatic paralysis usually have severe respiratory complications [8]; and children under 3 years of age have a higher incidence of respiratory problems, chest deformities, and gut abnormalities when the phrenic nerve is sectioned. Moreover, the younger the child, the more severe the expected complications are. Children older than 3 years of age generally tolerate phrenic nerve use much better [18]. Reasons for the poor tolerability in those younger than three include the later development of accessory respiratory muscles, the paradoxical movements of a paralyzed hemi-diaphragm, mediastinal hyper-motility, their greater volume of respiratory secretions, and the prolongation of REM sleep in infants, among others [19, 20].

The main disadvantage of phrenic nerve transfers, which is shared by all other extraplexual transfers, is that cerebral cortical plasticity plays an important role in the final results [21]. When the recovery of strength is in its initial stages, patients tend to move their arm by taking a deep breath, as mentioned in the results. Even though the vast majority of patients tend to perform this movement independent of the diaphragm, it can take 2–3 years to achieve this, and it needs specific rehabilitation that can be frustrating in patients who lack diaphragmatic power [8, 22].

Physiological arguments that favor using the phrenic nerve as an axon donor for brachial plexus reconstruction

Lurje [23] is known to have been the first to propose using the phrenic nerve as an axon donor for brachial plexus injuries; but it was Gu, in China, who initially started using it, in 1970, publishing his first series in 1989 [24]. The phrenic nerve primarily originates from C4, with variable contributions from C3 and C5, and an accessory phrenic nerve present in 25–38 % of patients [8]. That the phrenic nerve shares a common embryonic origin with the brachial plexus, though posteriorly their trajectories diverge [25], makes it an ideal extraplexual donor. This is further supported by its location in the neck, which facilitates its approach during supraclavicular plexus dissection, and in some cases, allows for coaptation with the target without the need for interposed grafts [6]. Moreover, the nerve generally has 800 to 1750 pure motor myelin-coated fibers [10], much more than an intercostal nerve, which has approximately 200 [1]. Nevertheless, the cervical portion is not long enough for direct coaptation when an infraclavicular or more distal target must be reached, necessitating a graft, and in many cases a long one. Some authors have proposed an intra-thoracic nerve dissection as a way to obtain a longer phrenic nerve and perform direct neurorrhaphy to targets as distal as the medial contribution for the median nerve, without grafts [26].

As mentioned previously, accessory phrenic nerves are present in 20–84 % of patients, originating from a surprisingly diverse constellation of nerves, like the subclavian, sternohyoideus, accessory, and hypoglossal [15]. That it might join the main phrenic nerve at the cervical or, more importantly, thorax level may be one of the explanations for the minimal effect that sectioning of the cervical portion has on vital capacity and other respiratory function tests [5, 15]. Unfortunately, there is currently no way to determine the exact contribution of each phrenic nerve to pulmonary function, or to predict the effects of its sectioning on function tests [6, 27–29]. It has been demonstrated that unilateral diaphragmatic palsy has minimum effects on the respiratory function clinically [30], while bilateral palsy can be catastrophic [31].

What actually explains the minimal respiratory effect observed after phrenic nerve section? Many compensatory mechanisms exist. In order to understand these mechanisms, we must briefly review diaphragmatic innervation. Sensory afferents are the phrenic nerve, the vagus, and the sympathetic chain, while motor afferents are the phrenic and intercostal nerves [13]. Cervical afferents, in a rat model under normal conditions, comprise less than 30 % of the available respiratory motoneurons [5]; to increase diaphragm strength, they must fire those motor neurons more frequently, and recruit other motor units in the diaphragm [25]. Di Rocco also showed in rats that 1 week after phrenic nerve sectioning, a 32 % increase in respiratory frequency maintains normal ventilator volumes; nevertheless, 1 week later, accessory muscle hypertrophy is evident [32]. Bach also reported no differences in the rat model after a unilateral phrenic nerve section, both at rest and during exercise, the only acute change being prolongation of the response to hypoxia, which normalized 1 month later. This was presumed to be due to an increase in a2 receptors, together with a bigger contribution by the hypoglossal nerve [33].

Another compensatory mechanism that plays an important role after a section of the phrenic nerve is the so-called "crossed phrenic phenomenon". This happens because premotor bulbospinal motor neurons (in the ventral respiratory group) have bilateral projections to both phrenic nuclei that remain in latency [34]; due to neuroplasticity, this bilateral

activation appears within 1–4 months (25–73 % within the first 2 months) due to hypercapnia [34–38]. All these mechanisms are mediated both biochemically [39] and genetically [37]. Even though the "crossed nerve phenomenon" is observed after a spine hemisection followed by a contralateral phrenic nerve section—and not in a scenario of a single phrenic nerve section, as occurs when this nerve is used as donor in brachial plexus surgery—it is possible to speculate that a similar compensatory phenomenon could be present after a phrenicotomy. More studies in this field are needed to clarify this point.

In those compensatory mechanisms that take place after a phrenic nerve section, as described above, the accessory phrenic nerves play an important role. Therefore, it is correct to presume that a long intra-thoracic phrenic nerve dissection could directly affect this response by eliminating accessory phrenic nerve connections to the main nerve [40, 41]. This fact is only theoretical and still remains to be proven.

Previous series supporting the use of phrenic nerves as axon donors

In a group of 12 patients described by Songcharoen, phrenic nerve neurotization achieved an MRC score of 3 or more every time when the suprascapular nerve was employed as a target (at 8 months, 70° of abduction and 30° of external rotation), versus 66 % observed elsewhere with the axillary nerve (70° of abduction and anterior flexion) and 60 % with the musculocutaneous nerve (90° flexion), the latter two requiring an interposed graft [8, 30]. In Chuang's series of 37 patients in whom both the suprascapular and axillary nerve were used as targets for the phrenic nerve, 20–40° abduction was achieved with the former, versus less than 20° with the latter [42]. Meanwhile, for Sungpet, ten patients submitted to phrenic to suprascapular nerve transfer experienced 20–60° of abduction of [43], and Gu achieved MRC scores $\geq$3 in 77 % (45 % $\geq$4) of 65 patients who underwent a phrenic to musculocutaneous nerve transfer [24], a result comparable to those of Luedemann et al., with 92 % M3+M4 and 58 % M4 alone [6]; of Xu et al. : 73 and 36 % [44]; of Monreal (20 patients, 70 % M3+M4 and 30 % M4 [1]; and of Siqueira et al., with 70 % M3 and 20 % M4 [10]. Better and worse results have also been published, ranging from 100 % M4 achieved by El-Gammal [45, 46] in four patients and 100 % MRC $\geq$3 by Vekris [47] to just 29 % MRC $\geq$3 by Chalidapong [17].

Other targets have yielded similar results. For example, in 33 patients undergoing phrenic nerve transfer to the anterior division of the upper trunk, an MRC score $\geq$3 was achieved in 85 % and an MRC score$\geq$4 in 64 % [18]. Other studies have shown M3 scores in 75 % and M4 results in 42 % [11, 12]. Finally, performing a phrenic to median nerve transfer in three patients, Xuachieved MRC scores $\geq$3 in all three [48]. For a summary of the above-mentioned studies, see Table 6.

Final remarks

In the literature, it is well appreciated that phrenic nerve sectioning is associated with clear compromise of respiratory function tests [2, 9–11, 13, 14, 16]. However, this effect does not appear to be clinically evident or to adversely affect the quality of life of patients in any way [6–8, 11]. It also is worth noting that, in the vast majority of the above-noted reports, no comparisons against baseline/pre-operative respiratory status were performed, postoperative parameters only being compared against population norms adjusted for age, sex, body mass index, etc. [11]. Other potentially clinically relevant respiratory problems associated with the primary trauma that caused the brachial plexus injury also have not been systematically analyzed [9].

It has been suspected that the lack of any clinically pertinent respiratory effects of phrenic nerve sections are related to the so-called "crossed phrenic phenomenon" [34–39], as well as to the existence of accessory respiratory musculature, accessory phrenic nerves, contralateral phrenic and diaphragmatic hyperactivity, and other factors [13, 25, 35, 36, 38–41]. These mechanisms have been studied only in animal models—especially in rats and dogs—most models related to spinal cord rather than phrenic nerve sections, the results of which do not allow for definitive conclusions regarding their role in the latter.

Having these data in mind, it is important to note certain contraindications against using the phrenic nerve as a donor during brachial plexus reconstruction; for example, severe pre-existing pulmonary pathology, severe thoracic trauma, multiple rib fractures, or pulmonary contusions secondary to trauma [6, 8]. The procedure also is contraindicated in patients younger than 3 years old [8, 18–20].

On the other hand, it has been demonstrated that the phrenic nerve is a reliable and predictable nerve for transfer [1, 6, 8, 10, 12, 16, 17, 24, 42–45, 47, 48, 50, 51] and that, having the above-mentioned precautions and contra-indications in mind, the technique is safe. The main complaint patients have is the time delay for the muscle to be re-innervated, which is related to the growth rate of the regeneration axon and the distance to the muscle target, not to the type of donor nerve [8, 22].

The reluctance of many very experienced brachial plexus surgeons to use the phrenic nerve as axon source contrast with the data presented in the papers cited above and with our personal experience presented in this study. It is presumable that other reasons not analyzed here, i.e., the presence of a predominantly obese population of patients, the consideration of eventual legal problems,

Table 6 Published series on the use of the phrenic nerve for neurotization in brachial plexus injuries

Results of phrenic nerve transfer described in the literature

Authors	No. of patients	Receptor	Result	Respiratory complications
Songcharoen et al. [10]	12	Suprascapular Axillary Musculocutaneous	MRC ≥3: 75 % MRC ≥3: 66 % MRC ≥3: 60 %	Asymptomatic VC reduction 9.4 %
Chuang et al. [42]	37	Suprascapular Axillary	Abduction 20–40° Abduction <20°	NR
Sungpet et al. [49]	10	Suprascapular	Abduction 20–60°	Asymptomatic
Gu et al. [24]	65	Musculocutaneous	MRC ≥3: 77 % MRC ≥4: 45 %	Mild diminution in TV 1 year, recovered 2 years. Five YO child transitory respiratory problems
Luedemann et al. [15]	12	Musculocutaneous	MRC ≥3: 92 % MRC ≥4: 58 %	Compromised TV 14.3 % right side, 3.6 % left side, asymptomatic
Xu et al. [38]	11	Musculocutaneous	MRC ≥3: 73 % MRC ≥4: 36 %	Asymptomatic. Spirometry values similar to pre-op 1Y after surgery except for MIP
Monreal et al. [7]	20	Musculocutaneous	MRC ≥3: 70 % MRC ≥4: 30 %	NR
Siqueira et al. [14]	10	Musculocutaneous	MRC ≥3: 70 % MRC ≥4: 20 %	Asymptomatic. Mild forced vital capacity 2 years after surgery
El-Gammal et al. [46]	4	Musculocutaneous	MRC ≥4: 100 %	NR
Vekris et al. [29]	17	Musculocutaneous	MRC ≥3: 100 %	NR
Chalidapong et al. [17]	17	Musculocutaneous	MRC ≥3: 29 %	Asymptomatic Tidal respiratory volume compromise in spirometry
Liuet al. [36, 44]	33	ADUT	MRC ≥3: 85 % MRC ≥4: 64 %	Asymptomatic
Zheng et al. [41]	12	ADUT	MRC ≥3: 75 % MRC ≥4: 42 %	Symptoms only with heavy efforts. No significant spirometric alterations
Xu et al. [40]	3	Median	MRC ≥3: 100 %	Normal function one year after surgery
Socolovsky et al. (present series)	51	Musculocutaneous, suprascapular, axillary, median, ADUT, PDUT, radial, Gracilis	MRC ≥3 83.5 % M4 60 %	Asymptomatic except two cases, with mild and transitory complains

the absence of long-term effects respiratory function tests results, or even the lack of experience in this nerve transfer, could explain this preference.

Conclusions

The phrenic nerve, due to its pure motor nature, the easy manipulation of its axons, and its convenient location in the surgical field, is a very good axon donor for severe brachial plexus injuries. Results are predictable and generally good, with roughly 80 % of patients achieving a BMRC scale grade of 3 or more. As far as we know, our series presents the largest number of patients undergoing this procedure outside of China.

Using the phrenic nerve may adversely affect respiratory function tests, but this rarely correlates clinically. Many potential explanations exist for this repeatedly observed discrepancy between respiratory tests and symptoms, but research still is warranted to clarify this issue.

It is also clear that contraindications to the use of the phrenic nerve exist and should be respected, such as patients less than 3 years of age, patients with severe thoracic trauma or cardiorespiratory morbidity, and those who are obese, among others.

Both our study and our literature review have limitations. The greatest limitation with the former was that the sample was too small to statistically detect possibly important predictive effects of time from injury to surgery and patient age on outcomes. The greatest limitation with the latter is that negative studies tend not to be published, potentially biasing conclusions. Nonetheless, we feel that the evidence is clear—that with the correct balance of patient selection, appropriate surgical techniques, and well-administered post-operative rehabilitation, good results with phrenic nerve transfers for brachial plexus reconstruction are likely. Nevertheless, further, more-extensive studies on the long-term effects of phrenic

nerve transfers, and comparisons of this technique against others, still wait to be conducted.

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References

1. Monreal R (2007) Restoration of elbow flexion by transfer of the phrenic nerve to the musculocutaneous nerve after brachial plexus injuries. Hand (N Y) 2(4):206–211
2. Andrié R, Schrickel JW, Nickenig G, Lickfett L (2012) Left phrenic nerve injury during cryoballoon ablation of the left superior pulmonary vein. Pacing Clin Electrophysiol 35(11):e334–e336
3. Socolovsky M, Di Masi G, Battaglia D (2011) Use of long autologous nerve grafts in brachial plexus reconstruction: factors that affect the outcome. Acta Neurochir (Wien) 153(11):2231–2240
4. Hur MS, Woo JS, Park SY, Kang BS, Shin C, Kim HJ, Lee KS (2011) Destination of the C4 component of the prefixed brachial plexus. Clin Anat 24(6):717–720
5. Norkus T, Norkus M, Ramanauskas T (2005) Donor, recipient and nerve grafts in brachial plexus reconstruction: anatomical and technical features for facilitating the exposure. Surg Radiol Anat 27(6): 524–530
6. Luedemann W, Hamm M, Blömer U, Samii M, Tatagiba M (2002) Brachial plexus neurotization with donor phrenic nerves and its effect on pulmonary function. J Neurosurg 96(3):523–526
7. Marie J, Lerosey Y, Dehesdin D, Tadié M, Andrieu-Guitrancourt J (1999) Cervical anatomy of phrenic nerve roots in the rabbit. European Group for Research on the Larynx. Ann Otol Rhinol Laryngol 108(5):516–521
8. Songcharoen P (2008) Management of brachial plexus injury in adults. Scand J Surg 97(4):317–323
9. Chuang ML, Chuang DC, Lin IF, Vintch JR, Ker JJ, Tsao TC (2005) Ventilation and exercise performance after phrenic nerve and multiple intercostal nerve transfers for avulsed brachial plexus injury. Chest 128(5):3434–3439
10. Siqueira M, Martins RS (2009) Phrenic nerve transfer in the restoration of elbow flexion in brachial plexus avulsion injuries: how effective and safe is it? Neurosurgery 65(4 Suppl):A125–A131
11. Zheng MX, Qiu YQ, Xu WD, Xu JG (2012) Long-term observation of respiratory function after unilateral phrenic nerve and multiple intercostal nerve transfer for avulsed brachial plexus injury. Neurosurgery 70(4):796–801
12. Zheng MX, Xu WD, Qiu YQ, Xu JG, Gu YD (2010) Phrenic nerve transfer for elbow flexion and intercostal nerve transfer for elbow extension. J Hand Surg [Am] 35(8):1304–1309
13. Chang FY, Lu CL (2012) Hiccup: mystery, nature and treatment. J Neurogastroenterol Motil 18(2):123–130
14. Sacher F, Monahan KH, Thomas SP et al (2006) Phrenic nerve injury after atrial fibrillation catheter ablation: characterization and outcome in a multicenter study. J Am Coll Cardiol 47(12):2498–2503
15. Loukas M, Kinsella CR Jr, Louis RG Jr, Gandhi S, Curry B (2006) Surgical anatomy of the accessory phrenic nerve. Ann Thorac Surg 82(5):1870–1875
16. Zheng MX, Xu WD, Shen YD, Xu JG, Gu YD (2012) Reconstruction of elbow flexion by end-to-side neurorrhaphy in phrenic nerve transfer. Plast Reconstr Surg 129(3):573e–575e
17. Chalidapong P, Sananpanich K, Kraisarin J, Bumroongkit C (2004) Pulmonary and biceps function after intercostal and phrenic nerve transfer for brachial plexus injuries. J Hand Surg (Br) 29(1):8–11
18. Yang Y, Chen L, Gu YD, Hu SN, Zhang H (2006) Long-term impact of transfer of phrenic nerve on respiratory system of children: a clinical study of 34 cases. Zhonghua Yi Xue Za Zhi 86(17): 1179–1182
19. Haller JA Jr, Pickard LR, Tepas JJ, Rogers MC, Robotham JL, Shorter N, Shermeta DW (1979) Management of diaphragmatic paralysis in infants with special emphasis on selection of patients for operative plication. J Pediatr Surg 14(6):779–785
20. Shoemaker R, Palmer G, Brown JW, King H (1982) Aggressive treatment of acquired phrenic nerve paralysis in infants and small children. Ann Thorac Surg 32(3):250–259
21. Bertelli JA, Ghizoni MF (2011) Results and current approach for brachial plexus reconstruction. J Brachial Plex Peripher Nerve Inj 6(1):2
22. Addas BM, Midha R (2009) Nerve transfers for severe nerve injury. Neurosurg Clin N Am 20(1):27–38
23. Lurje A (1948) Concerning surgical treatment of traumatic injury to the upper division of the brachial plexus (Erb's type). Ann Surg 127(2):317–326
24. Gu YD, Ma MK (1996) Use of the phrenic nerve for brachial plexus reconstruction. Clin Orthop Relat Res 323:119–121
25. Greer JJ, Allan DW, Martin-Carballo M, Lemke RP (1999) An overview of phrenic nerve and diaphragm muscle development in the perinatal rat. J Appl Physiol 86(3):779–786
26. Wood MB, Murray PM (2007) Heterotopic nerve transfers: recent trends with expanding indication. J Hand Surg [Am] 32(3):397–408
27. Berkmen YM, Davis SD, Kazam E, Auh YH, Yankelevitz D, Girgis FG (1989) Right phrenic nerve: anatomy, CT appearance, and differentiation from the pulmonary ligament. Radiology 173(1):43–46
28. Fackler CD, Perret GE, Bedell GN (1967) Effect of unilateral phrenic nerve section on lung function. J Appl Physiol 23(6): 923–926
29. Strauss P, Turndorf H (1990) The contribution of the right phrenic nerve to ventilation. J Cardiothorac Anesth 4(1):97–101
30. Songcharoen P (1995) Brachial plexus injury in Thailand: a report of 520 cases. Microsurgery 16(1):35–39
31. De Troyer A, Kelly S (1982) Chest wall mechanics in dogs with acute diaphragmatic paralysis. J Appl Physiol Respir Environ Exerc Physiol 53(2):373–379
32. Rocco PR, Faffe DS, Feijóo M, Menzes SL, Vasconcellos FP, Zin WA (1997) Effects of uni- and bilateral phrenicotomy on active and passive respiratory mechanics in rats. Respir Physiol 110(1):9–18
33. Bach KB, Mitchell GS (2000) Effects of phrenicotomy and exercise on hypoxia-induced changes in phrenic motor output. J Appl Physiol 89(5):1884–1891
34. Golder FJ, Fuller DD, Davenport PW, Johnson RD, Reier PJ, Bolser DC (2003) Respiratory motor recovery after unilateral spinal cord injury: eliminating crossed phrenic activity decreases tidal volume and increases contralateral respiratory motor output. J Neurosci 23(6):2494–2501
35. Golder FJ, Reier PJ, Bolser DC (2001) Altered respiratory motor drive after spinal cord injury: supraspinal and bilateral effects of a unilateral lesion. J Neurosci 21(21):8680–8689
36. Liou WW, Goshgarian HG (1994) Quantitative assessment of the effect of chronic phrenicotomy on the induction of the crossed phrenic phenomenon. Exp Neurol 127(1):145–153
37. Malakhova OE, Davenport PW (2001) c-Fos expression in the central nervous system elicited by phrenic nerve stimulation. J Appl Physiol 90(4):1291–1298
38. Vinit S, Stamegna JC, Boulenguez P, Gauthier P, Kastner A (2007) Restorative respiratory pathways after partial cervical spinal cord

injury: role of ipsilateral phrenic afferents. Eur J Neurosci 25(12): 3551–3560
39. Nantwi KD, Goshgarian HG (2002) Actions of specific adenosine receptor A1 and A2 agonists and antagonists in recovery of phrenic motor output following upper cervical spinal cord injury in adult rats. Clin Exp Pharmacol Physiol 29(10):915–923
40. Xu W, Gu YD, Lu JB, Yu C, Zhang CG, Xu JG (2005) Pulmonary function after complete unilateral phrenic nerve transaction. J Neurosurg 103(3):464–467
41. Zhang CG, Ma JJ, Terenghi G, Mantovani C, Wiberg M (2004) Phrenic nerve transfer in the treatment of brachial plexus avulsion: an experimental study of nerve regeneration and muscle morphology in rats. Microsurgery 24(3):232–240
42. Chuang DC, Lee GW, Hashem F, Wei FC (1995) Restoration of shoulder abduction by nerve transfer in avulsed brachial plexus injury: evaluation of 99 patients with various nerve transfers. Plast Reconstr Surg 96(1):122–128
43. Sungpet A, Suphachatwong C, Kawinwonggowith V (2000) Restoration of shoulder abduction in brachial plexus injury with phrenic nerve transfer. Aust N Z J Surg 70(11):783–785
44. Xu W, Gu YD, Xu JG, Tan LJ (2002) Full-length phrenic nerve transfer by means of video-assisted thoracic surgery in treating brachial plexus avulsion injury. Plast Reconstr Surg 110(1):104–111
45. El-Gammal TA, El-Sayed A, Kotb MM (2003) Surgical treatment of brachial plexus traction injuries in children, excluding obstetric palsy. Microsurgery 23(1):14–17
46. El-Gammal TA, Fathi NA (2002) Outcomes of surgical treatment of brachial plexus injuries using nerve grafting and nerve transfers. J Reconstr Microsurg 18(1):7–15
47. Vekris MD, Beris AE, Johnson EO, Korobilias AV, Pafilas D, Vekris AD, Soucacos PN (2006) Musculocutaneous neurotization to restore elbow flexion in brachial plexus paralysis. Microsurgery 26(4):325–329
48. Xu WD, Lu JZ, Qiu YQ, Jiang S, Xu L, Xu JG, Gu YD (2008) Hand prehension recovery after brachial plexus avulsion injury by performing a full-length phrenic nerve transfer via endoscopic thoracic surgery. J Neurosurg 108(6):1215–1219
49. Stradling JR, Kozar LF, Dark J, Kirby T, Andrey SM, Phillipson EA (1987) Effect of acute diaphragm paralysis on ventilation in awake and sleeping canines. Am Rev Respir Dis 136(3):633–637
50. Liu Y, Lao J, Gao K, Gu Y, Zhao X (2013) Comparative study of phrenic nerve transfers with and without nerve graft for elbow flexion after global brachial plexus injury. Injury 45(1):227–231
51. Liu Y, Lao J, Zhao X (2014) Comparative study of phrenic and intercostal nerve transfers for elbow flexion after global brachial plexus injury. Injury. doi:10.1016/j.injury.2014.11.034

Comments

One of the prime tenets of medicine is “primum non nocere” or “first do no harm.” The desire by the physician to help must always be balanced against the risks of doing harm. This consideration becomes important and most relevant to the peripheral nerve surgeon in the clinical setting of severe brachial plexus injuries where all, or almost all, of the spinal nerve roots supplying the upper extremity have been avulsed from the spinal cord, resulting in very limited repair options involving distal neurotization of a functionally important nerve supplying the biceps muscle with an intact proximal nerve such as the spinal accessory nerve, intercostal nerves, or even the phrenic nerve as discussed in this paper. The reluctance of many peripheral nerve surgeons to use the phrenic nerve as a donor nerve to restore elbow flexion function, as noted by the authors, stems from the belief and fear that doing so either compromises the patient’s pulmonary function significantly or at the very least puts the patient at risk of suffering such a fate in the future. The results of this paper go a long way in reassuring the surgeon that many appropriately selected patients with good preoperative lung function can tolerate sacrificing phrenic nerve innervation of the diaphragm, in an effort to restore biceps function, on one side for a variety of possible reasons mediated by several possible biological mechanisms. This paper is well written and reviews the results of a large experience with severe and extensively injured brachial plexus patients. I think this paper makes an important contribution to the field and phrenic nerve neurotization is a viable repair option to the peripheral nerve surgeon when confronted with a severe brachial plexus injury that leaves him or her with very limited repair options.

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