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A Propensity Matched Assessment of Factors Predicting Improvement in Dyspnea inAdults Following Diaphragm Plication

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Abstract

Objectives: A significant percentage of patients with lifestyle-limiting dyspnea attributable to unilateral diaphragm paralysis experience an improvement in their symptoms and spirometry following diaphragm plication. However, not all patients improve following surgery. The purpose of this investigation was to identify criteria which could differentiate patients who would benefit from plication from those that may not.

Methods: Adult patients undergoing plication of the hemi diaphragm for lifestyle-limiting dyspnea and unilateral diaphragm paralysis were identified. Patients who realized improvement using the Medical Research Council dyspnea score, pulmonary spirometry and activities of daily living questionnaire were propensity matched and then compared to patients who did not improve following plication.

Results: From 117 patients, 23 whose dyspnea and pulmonary spirometry did not improve following diaphragm plication were identified and propensity matched to patients whose symptoms did improve. Multiple logistic regression analysis identified four factors that predicted an improvement following plication; BMI < 35 kg/m^2, FEV_1< 75% predicted, paradoxical diaphragm motion and < 6 years of diaphragm paralysis.

Conclusion: Plication of the hemi-diaphragm produces significant improvements in dyspnea and pulmonary spirometry in the majority of patients with unilateral diaphragm paralysis. The four factors identified in this review can be used to identify patients that are more likely not to realize a significant improvement in their symptoms following plication surgery.

Introduction

Plication of the hemi-diaphragm following unilateral diaphragm paralysis has been shown to result in symptomatic and physiologic improvements in selected adult patients with lifestyle limiting dyspnea [1]. However, not all patients undergoing surgery realize improvement. Furthermore, among the patients who do realize improvement, the benefit can vary significantly. The purpose of this investigation was to identify factors to allow the prediction of the degree of improvement adult patients experience following plication of the hemi-diaphragm.

Methods

The study institution's Institutional Review Board approved this protocol and waived individual patient consent for this investigation with the condition of patient anonymity outside the initial data gathering phase of the study. Patients eighteen years old or older undergoing unilateral plication of the hemi-diaphragm for diaphragm paralysis during the calendar years 2004 through 2013were identified with the institution's prospectively collected general thoracic surgery database. Patient demographics, length of hospital stay, readmission, operative morbidities and mortality as well as Charlson Comorbidity scores for each patient were abstracted.

All patients received a standardized evaluation before consideration for surgery which included a history and physical examination, a chest radiograph, a fluoroscopic "sniff" test, pulmonary spirometry, administration of the Medical Research Council (MRC) dyspnea score (Table 1) and the Manchester Respiratory Activities of Daily Living questionnaire[2, 3]. Patients without a clear etiology for their unilateral diaphragm paralysis also underwent a neurologic consultation and computed tomographic imaging or magnetic residence imaging study of the chest and brain. All patients undergoing diaphragm plication were also required to participate in a pulmonary rehabilitation program under the supervision of a pulmonary medicine physician beginning before surgery.

Table 1: The Medical Research Council Dyspnea Scale

"I only get breathless with strenuousexercise"	Grade 1
"I get short of breath when hurrying on thelevel or up a slight hill"	Grade 2
"I walk slower than peopleof the same age on the level because of breathlessness or haveto stop for breath when walking at my own pace on the level"	Grade 3
"I stop for breath after walking 100 yards or after afew minutes on the level"	Grade 4
"I am too breathless to leavethe house".	Grade 5

Excluded from participation in this investigation were patients with an upper motor neuron or malignant etiology for their diaphragm paralysis, patients with bilateral diaphragm paralysis, patients with acute respiratory failure/mechanically ventilated patients, patients who had undergone prior non-cardiac thoracic surgery including a pulmonary resection or lung transplant or had significant underlying lung disease such as interstitial lung disease or chronic obstructive pulmonary disease.

Patients with lifestyle-limiting dyspnea (MRC dyspnea score ≥ 3) from unilateral diaphragm paralysis present for at least 6 months were offered diaphragm plication. When possible, this was performed utilizing video-assisted thoracoscopic techniques as we have previously described [4]. When using thoracoscopy, three 10-mm ports were utilized in the midclavicular and midaxillary lines of the eighth intercostal space as well as midway between the spine and the medial border of the scapula in the sixth intercostal space. Whether performing thoracoscopy or a thoracotomy, the uncut hemi diaphragm was plicated with a series of six to eight parallel U sutures using contralateral single-lung ventilation. After transecting the inferior pulmonary ligament, sutures were placed beginning laterally on the diaphragm progressing medially until the hemi-diaphragm was nearly flat and taut. If performing the procedure thoracoscopically, the Endostitch (Ethicon Endo-Surgery, Cincinnati, OH) was used for intracorporeal suture placement. After surgery, the pleural space was drained with a chest tube. Patients were discharged home the day after their chest tube was removed when adequate analgesic could be maintained with oral medications and a diet tolerated.

All patients were evaluated 6 months after diaphragm plication and then annually using the MRC dyspnea score, pulmonary spirometry, the activities of daily living questionnaire, a chest radiograph, review of any interim hospitalizations, and assessment of their ability to work. Patients with at least 24 months of follow-up were eligible to be included in this analysis.

Patients were considered to have significantly improved following plication if they realized improvements in at least two of their pulmonary metrics; pulmonary spirometry, MDC score and MRADL score (Table2).Based on these criteria, the propensityscore method was used to populate two patient cohorts from the patients identified; those who did not improve following plication and those that did improve [5,6]. Propensityscores were computed after multivariable regression analysis assessing a set of preoperative risk factors which included etiology of diaphragm paralysis, age, gender, body mass index, preoperative pulmonary function testing, fluoroscopic "sniff" test results, Charlson comorbidity score and time from recognitionof paralysis to plication.Patients who did not improve were matched nearest neighbor in a 1:1 fashion to those who did realize improvement on the basis of the propensityscore so that only patientswith similar scores were compared [7, 8].

Table 2: Failure Criteria for Diaphragm plication

Pulmonary Function Metric	Criteria for Improvement
Pulmonary Spirometry – FEV_1	Increase compared to predicted by 20%
MRC	< 3
MRADL Score	Improvement in score by 3

Bivariate analysis of data was performed using Graph Pad Prism software 4.02 (San Diego, California) for Windows (Microsoft, Redmond WA). Differences between categorical variables were evaluated by the Fisher's exact test. Differences between continuous variables were measured by the two-tailed Student t test or the Mann-Whitney test for non-normally distributed data. Multivariate analysis and propensity matching was performed using Stata version 11 (StataCorp, College Station, Texas, USA). A value of $p < 0.05$was considered significant.

Results

During the ten year study period,117 adult patients underwent plication of the hemi-diaphragm for diaphragm paralysis at the study institution. From those, 23 patients were identified who met the criteria as not improving following diaphragm plication and were propensity matched to 23 of the remaining 94 patients who did realize improvement during the same time period. Table 3 compares the two group's demographic data which implies they are comparable based on the results of the matching process. Also compared is the operative approach used in each group.

Table 3: A comparison of the treatment cohorts before and after propensity matching

	Imp	Imp(pre)	No Imp	p
N	23	94	23	
Age (mean yrs)	56±13	53±16	57±19	0.8
Female	13 (57%)	43 (46%)	12 (52%)	1
Charlson Comorbidity (mean score)	4.6 ± 0.5	5.1 ± 1.1	4.9 ± 0.9	0.2
Etiology of paralysis				
Trauma	8	31	7	
Unrelated surgery	6	19	5	
Idiopathic	9	44	11	

Table 4 displays the outcomes reviewed for the cohort analysis. Significant differences in length of stay and postoperative morbidity were not appreciated between the two groups. No operative mortality occurred in either group. Multiple logistic regression analysis identified four factors that predicted a lack of improvement following plication; a body mass index (BMI) greater than 35 kg/m^2, a preoperative forced vital capacity in one second (FEV_1) more than 75% predicted, lack of paradoxical diaphragm motion demonstrated on fluoroscopy before surgery and a history of more than 6 years of diaphragm paralysis prior to surgery.

Table 4: Outcomes of Cohort Analysis

	Imp	No Imp	p
N	23	23	
Operative approach			
VATs	15 (65%)	13 (57%)	0.8
Thoracotomy	8	10	
Length of stay (mean days)			
VATs	4 ± 0.7	5± 0.8	0.002
Thoracotomy	5 ± 1.2	5± 1.4	1
Morbidity	3 (13%)	4 (17%)	0.2
Mortality	0	0	
Follow up (means months)	39 ± 13	37± 11	0.6

Table 5: Predictive Indicators of Lack of Improvement of Dyspnea Following Diaphragm Plication

	Odds	95% CI	p
BMI > 35 kg/m^2	0.27	0.19 – 0.37	0.0008
FEV_1> 75% predicted	0.33	0.25 – 0.41	0.0007
Lack of paradoxical diaphragm motion	0.39	0.32 – 0.51	0.0009
> 6 years of diaphragm paralysis	0.41	0.36 – 0.49	0.04

Comment

The dome-shaped diaphragm is the principle muscle of inspiration and the most powerful of the respiratory muscles [9-11]. The left and right sides of the diaphragm are innervated by the ipsilateral phrenic nerves which derive from cervical nerve roots three, four, and five [12]. Each nerve divides into four trunks that innervate the anterolateral, posterolateral, sternal, and crural portions of the diaphragm. Interruption or injury to one of the phrenic nerves results in unilateral diaphragmatic paralysis.

The most frequent attribution of paralysis if the hemi-diaphragm, as in this series, remains idiopathic. However other, more specific,causes are recognized. The more commonly reported causes of paralysis of a hemi-diaphragm include phrenic nerve injury due to stretching or cooling during cardiac surgery, Herpes Zoster, poliomyelitis, and other viral infections. Less frequently reported causes include cervical spondylosis, cervical compressive tumors, blunt neck trauma, injury during neck or chest neck surgery, pneumonia, and iatrogenic embolization [13, 14]. Rare causes include neuralgic amyotrophy, an inflammatory disorder of the brachial plexus, and hereditary brachial plexopathy.

Depending upon the degree of diaphragmatic compromise, the contralateral hemi-diaphragm or the accessory muscles of respiration may assume some or all the work of breathing in a patient with unilateral diaphragm paralysis. The normal contralateral hemi-diaphragm is often able to generate enough negative pleural pressure to promote inspiration. The negative intrapleural pressure draws air in through the trachea, but also draws some air across the chest from the side of the paralyzed hemi-diaphragm. During inspiration, the paralyzed hemi-diaphragm may be pliable and mobile enough to move paradoxically during inspiration. The movement of air from one lung to the other increases the work of breathing without improving gas exchange which may cause dyspnea, especially with exertion, and orthopnea.

Most patients with unilateral diaphragmatic paralysis are asymptomatic and require no treatment. The prognosis is good in these patientsand the paralysis can be clinicallyirrelevant in the absence of new or underlying pulmonary disease [15].

However some patients with unilateral diaphragmatic paralysis complain of severe dyspnea and/or orthopnea. This is most likely to occur with the increased ventilatory demands of intense physical activity or the presence of superimposed pulmonary disease.

Surgical plication of the affected hemi-diaphragm has provided excellent results in carefully selected patients [16]. This procedure can be performed via a thoracotomy, celiotomy, thoracoscopic or laparoscopic approach or, most recently, using robotic techniques in the chest or abdomen. Plication may result in improvement in lung function, exercise endurance, and dyspnea [17, 18]. The likely mechanism for the improvement in dyspnea is that the paradoxical movement of the paralyzed hemi-diaphragm is minimized and now resists being pulled up into the thorax when contraction of the functioning hemi-diaphragm generates negative pleural pressure. As a result, the abdominal contents are not pulled upwards during respiration and the adjacent lung segments expand. This improves ventilation to the well-perfused lung and improves gas exchange. Furthermore, the healthy hemi-diaphragm now performs less work, rendering it less susceptible to fatigue and decreasing the need to recruit accessory muscles of ventilation. So, in addition to improving static lung mechanics, plication has the potential to enhance exercise performance, blood gas exchange, and respiratory muscle function.

However, not all adult patient undergoing plication of the hemi-diaphragm realize such benefits following surgery. In modern series, the lack of improvement ranges from 3 to 18%. It is obvious that some of the patients who fail to improve following surgery were not systematically evaluated before or after surgery with object metrics such as a dyspnea score or respiratory focused daily activity score. Nor is it possible, in some series, to document a standardized method by which patients are offered plication surgery.

This investigation was designed to review of population of patients with unilateral paralysis if the hemi-diaphragm who were evaluated in a standardize manner using objective and reproducible subjective measures before and after surgery and underwent a standardized transthoracic diaphragm plication. The principle aim of the study was to assess whether factors could be identified that would allow patients who would not improve following plication surgery to be predicted. Such an ability to predict a lack of improvement in patients would provide clinicians guidance in navigating the options of pulmonary rehabilitation, plication surgery and simple observation.

The analysis of propensity matched cohorts in this investigation identified four patient characteristics that independently predicted improvement following plication of the hemi-diaphragm for diaphragm paralysis. Each characteristic results from an objective metric. While the sample size of these cohorts prevent a legitimate estimation of any cumulative effect of the factors exists, the presence of more than one factor could be additive.

The lack of paradoxical diaphragm motion in patients who failed to improve is not surprising. This is the principle structural manipulation plication effects and minimizes, reversing the physiologic effects of diaphragm paralysis previously outlined. The absence of paradoxical motion minimizes the potential for such improvement.

The length of diaphragm paralysis as a factor predicting success is not as intuitive but is plausible. It is known that the pliability and mobility of a paralyzed hemi-diaphragm is greatest within the first six to twelve months following the onset of denervation paralysis. Both decrease in many patients over time. This is seen clinically in patients whose dyspnea and/or orthopnea improve without treatment and why many do not offer plication to patients within six months of an acute paralysis.

A forced vital capacity at one second greater than 75% predicted implies one of two explanations.Either the patient is well compensated and so the benefit of plicationmay not be significant or the patient's symptoms are derived from another etiology that will not be improved by plication. While this investigation reviewed all of the pulmonary spirometry measured, no other predictive measures were identified.

The finding that morbidly obese patients more often fail to improve following diaphragm plication is not surprising. However the causes are likely not as straight forward as might be assumed. Certainly there is a mechanical disadvantage of respiration in these patients with greater chest wall motion resistance and increased intra-abdominal pressure. There is also evidence that morbid obesity impairs normal diaphragmaticexcursion potentially affecting the non-paralyzed hemi-diaphragm.

Also potentially contributing to many of these patients' dyspnea is a condition known asobesity associated hypoventilation. This condition can also be multifactorial but is most often associated with some degree of obstructive sleep apnea. Physiologically, these patients fail to breath at a proper rate or intensity without elevated levels of carbon dioxide.

While the findings of this investigation offer new information regarding who may and who may not benefit from diaphragm plication, this study has limitations. It represents a single center's experience and methodology for treating patients with unilateral diaphragm paralysis. The absolute numbers within each cohort are also small for what is a relatively rare procedure. Lastly, although attempts were made to use objective measures or reproducible subjective measures to assess improvement in these patients, some patient bias may exist despite the opportunity for trending based on a relatively long period of follow up.

Conclusion

In conclusion, physicians treating patients with unilateral diaphragm paralysis should realize that the majority of patients are relatively asymptomatic. A substantial percentage will have some symptoms acutely that dissipate over three to six months, especially if pulmonary rehabilitation is utilized. Therefore it is the minority of patients that experience sustained, lifestyle limiting dyspnea. The thoracic surgeon is then faced with the dilemma of whether plication of the hemi-diaphragm is warranted and what improvement, if any, can be expected. This investigation identified four factors that, if absent, predict diaphragm plication will improve patients with lifestyle limiting dyspnea or orthopnea.

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