ANESTHESIOLOGY

Point of Care Ultrasound to Identify Diaphragmatic Dysfunction after Thoracic Surgery

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EDITOR'S PERSPECTIVE

What We Already Know about This Topic

- Patients undergoing thoracic surgery are at high risk for postoperative pulmonary complications
- The feasibility of using point of care ultrasound to diagnose diaphragmatic dysfunction is unclear

What This Article Tells Us That Is New

- Point of care ultrasound can be used to detect diaphragmatic dysfunction after thoracic surgery
- Diaphragmatic dysfunction may be associated with postoperative pulmonary complications

ABSTRACT

Background: Postoperative diaphragmatic dysfunction after thoracic surgery is underestimated due to the lack of reproducible bedside diagnostic methods. We used point of care ultrasound to assess diaphragmatic function bedside in patients undergoing video-assisted thoracoscopic or thoracotomic lung resection. Our main hypothesis was that the thoracoscopic approach may be associated with lower incidence of postoperative diaphragm dysfunction as compared to thoracotomy. Furthermore, we assessed the association between postoperative diaphragmatic dysfunction and postoperative pulmonary complications.

Methods: This was a prospective observational cohort study. Two cohorts of patients were evaluated: those undergoing video-assisted thoracoscopic surgery *versus* those undergoing thoracotomy. Diaphragmatic dysfunction was defined as a diaphragmatic excursion less than 10 mm. The ultrasound evaluations were carried out before (preoperative) and after (*i.e.*, 2 h and 24 h postoperatively) surgery. The occurrence of postoperative pulmonary complications was assessed up to 7 days after surgery.

Results: Among the 75 patients enrolled, the incidence of postoperative diaphragmatic dysfunction at 24 h was higher in the thoracotomy group as compared to video-assisted thoracoscopic surgery group (29 of 35, 83% *vs.* 22 of 40, 55%, respectively; odds ratio = 3.95 [95% CI, 1.5 to 10.3]; $P = 0.005$). Patients with diaphragmatic dysfunction on the first day after surgery had higher percentage of postoperative pulmonary complications (odds ratio = 5.5 [95% CI, 1.9 to 16.3]; $P = 0.001$). Radiologically assessed atelectasis was 46% (16 of 35) in the thoracotomy group *versus* 13% (5 of 40) in the video-assisted thoracoscopic surgery group ($P = 0.040$). Univariate logistic regression analysis indicated postoperative diaphragmatic dysfunction as a risk factor for postoperative pulmonary complications (odds ratio = 5.5 [95% CI, 1.9 to 16.3]; $P = 0.002$).

Conclusions: Point of care ultrasound can be used to evaluate postoperative diaphragmatic function. On the first postoperative day, diaphragmatic dysfunction was less common after video-assisted than after the thoracotomic surgery and is associated with postoperative pulmonary complications.

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Lung cancer resection surgery carries a substantial risk of postoperative pulmonary complications. Postoperative pulmonary complications are associated with mortality,[1,2] intensive care admission, longer hospital length of stay,[3] and increased costs.[4,5] Video-assisted thoracoscopic surgery has recently gained wide popularity for cancer resection. Indeed, as compared to the standard thoracotomic approach, video-assisted thoracoscopic surgery decreases surgical complications, postoperative pain, and the overall incidence of postoperative pulmonary complications.[6–8]

Postoperative diaphragmatic dysfunction has been documented after thoracic surgery with the thoracotomic approach within the first postoperative day.[9] Surgical injury of the diaphragm or of the phrenic nerve and diaphragmatic fatigue due to postoperative respiratory mechanics impairment play an important role in its pathogenesis.[10] However, postoperative diaphragmatic dysfunction is largely underestimated as a contributing factor for postoperative pulmonary complications[11] due to the lack of reproducible diagnostic methods. Furthermore, little is known on the impact of video-assisted thoracoscopic surgery, as compared

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to the standard thoracotomic technique, on postoperative diaphragmatic dysfunction and postoperative pulmonary complications.

The reference methods to evaluate diaphragmatic function are phrenic nerve stimulation[12] and transdiaphragmatic pressure assessment.[13] Both of these techniques are invasive, require considerable expertise, and are often unavailable at the bedside. Furthermore, they do not allow one to distinguish between bilateral and unilateral diaphragmatic dysfunction. Recently, the ultrasound technique has emerged as a noninvasive point of care tool to assess diaphragmatic function.[14,15] A decreased inspiratory diaphragmatic dome excursion has been recently validated as an index of diaphragmatic dysfunction both in critically ill[16] and in surgical patients.[17–19]

In this study, we assessed the postoperative diaphragmatic function through the ultrasound technique after cancer resection surgery. Our main hypothesis was that the video-assisted thoracoscopic surgery technique, as compared to the thoracotomic approach, could decrease the postoperative diaphragm dysfunction. Our secondary endpoint was to assess the clinical variables associated with postoperative diaphragmatic dysfunction and the impact of postoperative diaphragmatic dysfunction on postoperative pulmonary complications within the first 7 postoperative days.

Materials and Methods

Patients

The study was performed at the Sant'Anna University Hospital of Ferrara, Italy. All patients receiving elective lung resection surgery for pulmonary neoplasm between February 2016 and November 2016 were included. The study was approved by the ethics committee of our institution (February 23, 2016) and was recorded retrospectively on clinicaltrial.gov (NCT03347578). Written informed consent was obtained from each patient during the preoperative visit.

We enrolled patients 18 yr or older, with an American Society of Anesthesiologists physical status classification score of II to III, scheduled for thoracotomy or video-assisted thoracoscopic surgery lung resection surgery for cancer. The surgical approach was nonrandomly assigned and decided upon technical and/or oncologic reasons by the surgeon. A standard posterolateral thoracotomy with muscle-sparing technique was adopted in the open technique; for the video-assisted thoracoscopic surgery approach, two small incisions (at the eighth intercostal space in midaxillary and posterior axillary line) and a 5-cm utility incision at the level of the fifth intercostal space (for lung tissue removal) were performed.

The exclusion criteria were body mass index greater than 35 kg/m^2, contraindications for epidural catheter positioning, history of neuromuscular disease, previous thoracic surgery, and phrenic nerve palsy. Patients were further excluded from the final analysis if correct diaphragm visualization was not achievable (such as in case of postoperative subcutaneous emphysema).

All patients admitted to the study underwent a preoperative physiologic assessment including cardiovascular evaluation (electrocardiogram and echocardiography), pulmonary function tests, and arterial blood gas analysis according to clinical practice guidelines.[20] Pulmonary function tests consisted of spirometry performed according to the American Thoracic Society recommendations[21] using a SpiroPro spirometer (SpiroPro, Jaeger, Germany).

On the first postoperative day, pulmonary function tests were repeated in the semirecumbent position (with the head of the bed elevated at an angle of 45°). Pulmonary function tests were performed by a technician and validated by a pulmonologist. Spirometric measurements on the first postoperative day included forced vital capacity, forced expiratory volume in 1 s and tidal volume (V_T) was performed through a portable spirometer (MicroLoop Spirometer; CareFusion Corp., USA) that meets the American Thoracic Society standards. For both the preoperative and postoperative pulmonary function test assessments, the highest value of three spirometric measurements was recorded.

Anesthesia

Before general anesthesia induction, a thoracic epidural catheter (Tuohy; Braun Laboratories, Melsungen AG, Germany) was placed at T3 to T6 for postoperative pain control under local anesthesia. The position of the catheter tip was verified by a test dose of 4 ml of 1% lidocaine.

Propofol (1.5 to 2 $mg \cdot kg^{-1}$) and fentanyl (3 $\mu g \cdot kg^{-1}$) were used to induce anesthesia. Muscle paralysis was obtained with rocuronium bromide (0.6 $mg \cdot kg^{-1}$) to facilitate tracheal intubation. The trachea was intubated with an appropriately sized and side double lumen tube (Broncho-part; Rush, Germany). The correct position of the tube was checked by a fiberoptic bronchoscope in supine position after intubation and in lateral decubitus. Anesthesia was maintained with a continuous infusion of propofol (70 to 100 $\mu g \cdot kg^{-1} \cdot min^{-1}$), remifentanil (0.1 to 0.2 $\mu g \cdot kg^{-1} \cdot min^{-1}$), and rocuronium bromide (7 $\mu g \cdot kg^{-1} \cdot min^{-1}$). The Bispectral Index (BIS) was used to monitor the depth of anesthesia. The BIS was calculated and displayed continuously using an Aspect A2000 electroencephalogram analyzer (Aspect Medical System, USA) with the anesthetics titrated to maintain a BIS index between 40 and 60.

The lungs were ventilated through a Dräger Primus ventilator (Drägerwerk AG & Co. KGaA, Germany) with a square flow waveform with a V_T of 6 to 8 $ml \cdot kg^{-1}$ ideal body weight in two-lungs ventilation and a protective one-lung ventilation with a V_T of 4 to 5 $ml \cdot kg^{-1}$.[22] Intraoperative positive end-expiratory pressure was selected by the treating physician. Patients in one-lung ventilation were ventilated using oxygen and air with a fraction of inspired oxygen (F_{IO_2}) set to maintain the oxygen saturation measured by

pulse oximetry (Spo_2) 92% or greater. Intraoperative respiratory rates, positive end-expiratory pressure, and Fio_2 were manually recorded, and the mean of all measurements for each phase was finally reported. As usual care in our department, recruitment maneuvers were used as a rescue therapy in case of intraoperative hypoxemia (defined as Spo_2 less than 90%).[22,23] Balanced crystalloid solutions were administered at a rate of $3\,ml \cdot kg^{-1} \cdot h^{-1}$. Patients were monitored by electrocardiogram, pulse oximetry, end-tidal carbon dioxide, and invasive arterial pressure using a Datex Ohmeda S/5 monitor (Datex-Ohmeda Division, Instrumentarium Corp., Finland).

At the end of surgery, train-of-four (TOF-Watch acceleromyographs; Organon-Teknika, France) stimulations were used to assess the presence of a residual neuromuscular block, with a train-of-four ratio 0.9 or greater considered suitable for extubation. If a train-of-four ratio less than 0.9 was present, neuromuscular block was reversed with sugammadex 4 mg/kg, and patients were extubated in the operating room. The standard extubation criteria were as follows: (1) cooperative and alert patient; (2) smooth spontaneous ventilation; (3) train-of-four 0.9 or greater at the adductor pollicis; (4) Spo_2 greater than 96% on Fio_2 of 0.4 or less and end-tidal carbon dioxide less than 45 mmHg; (5) stable hemodynamic; (6) core temperature 36.5°C or greater; and (7) no evidence of early surgical complications.

Ultrasonography

Ultrasonographic assessments were performed by a single well-trained anesthesiologist with 3 yr of certified experience (R.R.) by using an ultrasonography machine (M-Turbo; SonoSite, Inc., USA). All measurements were performed in spontaneously and resting tidal breathing patients lying in the semirecumbent position.

The liver and spleen were regarded as echographic windows for the right and left hemidiaphragm, respectively. Diaphragmatic excursion was evaluated using a 3.5- to 5-MHz convex ultrasound probe. The subcostal acoustic window described by Boussuges *et al.*[24] for diaphragm examination was used. For the visualization of right hemidiaphragm, the probe was placed between the midclavicular and anterior axillary lines, while for the left hemidiaphragm, a subcostal or low intercostal probe position was chosen between the anterior and midaxillary lines. This approach was chosen due to medications and chest tubes. The two-dimensional mode (B-mode) was used to select the hemidiaphragm exploration line. With the probe fixed on the chest wall, the ultrasound probe was medially, cephalad, and dorsally directed so that the ultrasound beam reached the posterior part of the hemidiaphragmatic dome at an angle as close to 90° as possible.[25,26] The ultrasonography machine was then switched to the motion mode (M-mode). During inspiration, the normal diaphragm contracts and moves caudally toward the transducer; this is recorded as an upward motion of the motion mode tracing and regarded as the diaphragmatic excursion during inspiration, which was measured on the vertical axis from the baseline to the point of maximum height of inspiration, on a frozen image (fig. 1).

Diaphragmatic excursion was recorded using a sweep speed set in order to detect at least three consecutive respiratory cycles on the same screenshot. Recordings measurements were considered suitable only if the diaphragmatic excursion pattern was regular in amplitude and frequency. To reduce the measurement error, the diaphragmatic excursion estimation was averaged over three consecutive respiratory cycles.

Analgesia and Postoperative Pain Assessment

Postoperative analgesia was administered through the epidural catheter. An epidural analgesia solution of 300 ml, consisting of 0.2% levobupivacaine, was delivered at rate of 5 to 7 ml/h. Intravenous nonsteroidal anti-inflammatory drugs were added to the aforementioned analgesic protocol upon the treating physician's decision.

Postoperative pain was assessed by the same two physicians throughout the study period using an 11-point numerical rating scale (0 = no pain; 10 = worst possible pain) at rest. Additional IV morphine 2 mg was administered when numerical rating scale was 3 or greater at rest.

Outcome Measures

The primary outcome of the study was the occurrence of postoperative diaphragmatic dysfunction through point of care ultrasound, defined as a diaphragmatic excursion less than 10 mm or negative. This cutoff value has been validated in different patients (*i.e.*, after abdominal surgery, in critically ill patients or in healthy volunteers).[17,24,27] The diaphragmatic excursion is negative in case of unilateral or bilateral diaphragmatic palsy.[28]

Postoperative pulmonary complications were recorded from the first to the seventh postoperative day by the attending physicians who were blinded to the diaphragmatic ultrasonographic parameters. We considered the following as postoperative pulmonary complications: hypoxemia, bronchospasm, atelectasis, new pulmonary infiltrates, suspected pulmonary infection, and pleural effusion. The postoperative pulmonary complications definitions details are reported in the Appendix.

Study Protocol

The timeline of the protocol is summarized in figure 2. Diaphragmatic ultrasound was performed by the same anesthesiologist (R.R.) the day before operation (preoperative) and 2 and 24 h postoperatively. Pulmonary function tests were conducted on the same day of the preoperative evaluation and at 24 h postoperatively. The postoperative pain intensity was assessed at 2 h postoperatively and 24 h postoperatively. The occurrence and type of pulmonary

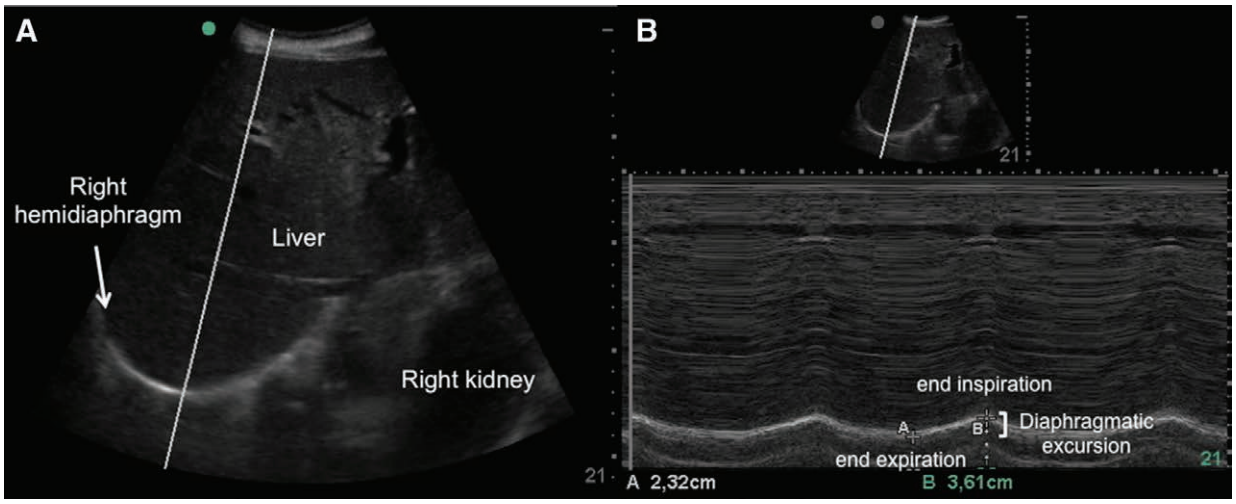

Fig. 1. Ultrasound images of the right hemidiaphragm. (*A*) A two-dimensional mode diaphragm picture: the *bright curved line* depicts the diaphragm; motion mode selected beam was directed as perpendicular as possible to the posterior part of the diaphragm. (*B*) A motion mode image of diaphragmatic excursion: caliper *A* indicates the end of expiration, and caliper *B* the end of inspiration. The distance between the two points, measured as the difference between the two caliper lines linked to the *bottom* of the image, shows an excursion of 12.9 mm.

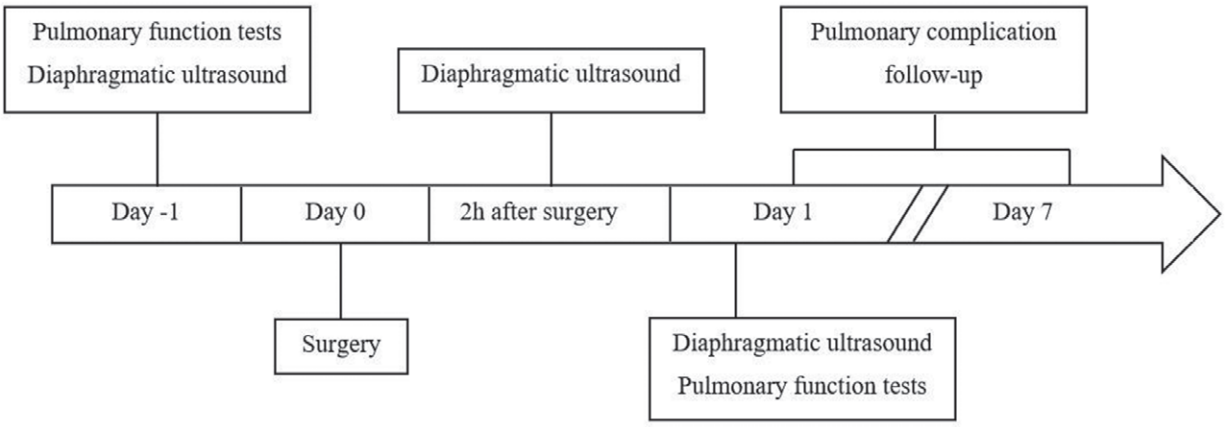

Fig. 2. Study protocol timeline.

complications were evaluated daily from the first to the seventh postoperative day.

Statistical Analysis

This is the primary analysis of these data, and all the analyses reported are preplanned. Normal distribution of data was tested by the Shapiro–Wilk Normality Test. Data are reported as mean ± SD or median [interquartile range], as appropriate. Unpaired Student's *t* tests or Mann–Whitney U tests were used to test the differences between groups (*i.e.*, thoracotomy *vs.* video-assisted thoracoscopic surgery) for data with normal or not normal distribution, respectively. Pearson's chi-square test or the Fisher exact test was used to compare categorical data. Differences between diaphragmatic excursion at different times in the same subject were assessed through the Friedman rank analysis or the Wilcoxon signed-rank test for matched data as appropriate. When multiple comparisons were made, *P* values were adjusted by the Bonferroni *post hoc* procedure.

The association between diaphragmatic dysfunction as expressed by a diaphragmatic excursion less than 10 mm in at least one measurement and clinically meaningful perioperative variables, including surgical access, chronic obstructive pulmonary disease history, length of surgery, age, American Society of Anesthesiologists physical status

score, sex, body mass index, and smoking history, was modeled using binary logistic regression analysis and was reported as the estimated crude odds ratio and relative 95% CI. In the same fashion, logistic regression analysis was applied to investigate the possible risk factors for the occurrence of at least one postoperative pulmonary complication. Furthermore, the significance of the interaction between surgery type and diaphragmatic dysfunction was tested using the likelihood-ratio test.

A two-tailed *P* value less than 0.05 was considered statistically significant. The *P* values of the comparison between diaphragmatic excursion in the two groups during the study were adjusted by the Bonferroni *post hoc* procedure.

Statistical analysis was performed with using SPSS Statistics for Windows, Version 25.0 (IBM, USA).

The sample size was calculated according to the primary endpoint, *i.e.*, the occurrence of diaphragmatic dysfunction after lung resection surgery. To detect a mean difference of 4.8 mm in diaphragmatic excursion after 24 h from operation (assuming a SD of 5 mm for preoperative values and 3 mm for postoperative values) using paired sample *t* tests with an α of 0.05 and 99% power, a minimum of 28 patients were required for each group. This was the observed difference in diaphragmatic excursion found in a previous study on the effect of upper abdominal surgery on diaphragmatic movements.[17] Taking into account a loss to follow up of 20%, we decided to enroll at least 35 patients for each group. The sample size analysis was performed using MedCalc software (9.3.6.0; Mariakerke, Belgium).

Results

Patient Population

During the study period, 101 patients were screened for eligibility. Of these, 79 met the inclusion criteria. Four were subsequently excluded due to a not achievable diaphragmatic ultrasonographic visualization. We did not have any further missing or lost data. Accordingly, 75 patients (35 in the thoracotomy group and 40 in the video-assisted thoracoscopic surgery group) completed the study (fig. 3). Clinical and demographic characteristics of the patients are described in table 1. Two patients in thoracotomy group and one patient in video-assisted thoracoscopic surgery group received an intraoperative recruitment maneuver. Neuromuscular block was reversed through sugammadex in 14 patients (6 in the thoracotomy and 8 in the video-assisted thoracoscopic surgery group; $P = 0.776$). All patients met the standard extubation criteria at the end of the surgery. Preoperative and intraoperative variables did not differ significantly between groups (table 1 and Supplemental Digital Content 1, http://links.lww.com/ALN/B952).

Perioperative Trend in Diaphragmatic Excursion and Pulmonary Function Tests

Fifty-one of 75 patients (68%) experienced diaphragm dysfunction in the operated side 24 h postoperatively. Diaphragm dysfunction was diagnosed in 22 of 40 patients (55%) in the video-assisted thoracoscopic surgery group and in 29 of 35 patients (83%) in the thoracotomy group ($P = 0.019$). Diaphragmatic excursion decreased in the operated side by 56% [36 to 72%] in the thoracotomy group and by 43% [23 to 58%] in the video-assisted thoracoscopic surgery group ($P = 0.033$ for comparison between groups) 24 h postoperatively, as compared to preoperatively (fig. 4). None of the enrolled patients had a negative diaphragmatic excursion. In the nonoperated side, the diaphragmatic excursion remained unchanged, regardless of the surgical technique (fig. 4).

Diaphragm dysfunction 2 h postoperatively was detected in 17 of 40 patients (42%) in the video-assisted thoracoscopic surgery group and 25 of 35 (71%) in the thoracotomy group ($P = 0.019$). Decline in diaphragmatic excursion 2 h postoperatively in the operated side was 44% (18 to 69%) in the thoracotomy group and 32% (8 to 57%) in the video-assisted thoracoscopic surgery group ($P = 0.202$ for comparison between groups). Table 2 reports the perioperative values of diaphragmatic excursions in the operated side, V_T, and pulmonary function tests.

In the thoracotomy group, going from preoperatively to 24 h postoperatively, tidal volume (V_T) decreased by 38% [25 to 49%], whereas in the video-assisted thoracoscopic surgery group, it decreased by 27% [12 to 40%] (both $P < 0.001$ compared to baseline). The V_T decline was more pronounced in the thoracotomy group ($P = 0.044$ *vs.* video-assisted thoracoscopic surgery group). Regardless of the surgical approach, V_T at 24 h postoperatively decreased more in the 51 patients with diaphragmatic dysfunction (*i.e.*, 39% [20 to 49%]), than in the 24 patients without diaphragmatic dysfunction (*i.e.*, 26% [12 to 43%]; $P = 0.034$).

The postoperative decline of forced expiratory volume in 1 s (FEV_1) did not differ between the thoracotomy (–60% [–67 to –51%]) and the video-assisted thoracoscopic surgery group (–59% [–72 to –50%]; $P = 0.941$ for comparison between groups). Patients with diaphragmatic dysfunction experienced a more enhanced FEV_1 reduction as compared to those without diaphragmatic dysfunction (–50% *vs.* –61%, respectively; $P = 0.002$).

As compared to preoperative values, the forced vital capacity decreased by 62% in the thoracotomy group and by 52% in the video-assisted thoracoscopic surgery group ($P = 0.026$ between groups at 24 h postoperatively). A higher impairment in forced vital capacity was found in patients with diaphragmatic dysfunction where the forced vital capacity decreased by 58% compared to 42% in patients without diaphragmatic dysfunction ($P < 0.001$).

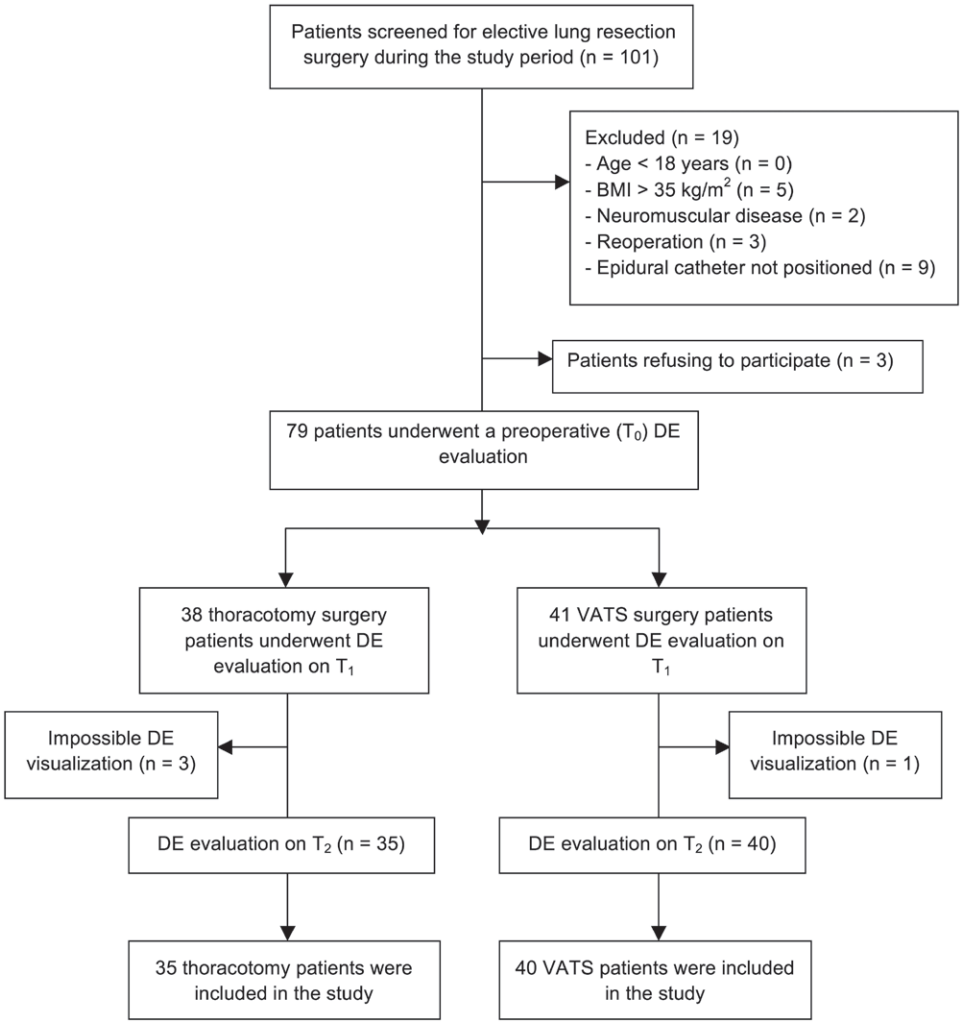

Fig. 3. Flowchart of the study. BMI, body mass index; DE, diaphragmatic excursion; T, time; VATS, video-assisted thoracoscopy.

Factors Associated with Postoperative Diaphragm Dysfunction at 24 h

Table 3 shows that, according to the univariate analysis, patients receiving thoracotomy and being active smokers at the time of the operation were at higher risk of developing diaphragmatic dysfunction 24 h postoperatively. Among them, the thoracotomic approach was the risk factor associated with the highest odds ratio (odds ratio = 3.95 [95% CI, 1.5 to 10.3]) for postoperative diaphragmatic dysfunction.

Impact of Diaphragm Dysfunction on Postoperative Pulmonary Complications

The postoperative pulmonary complications are summarized in Supplemental Digital Content 2 (http://links.lww.com/ALN/B953). Overall, 39 of 75 (52%) patients developed at least one postoperative pulmonary complication. The occurrence of postoperative pulmonary complications was 69% in the patients who had thoracotomy (24 of 35 patients) and 38% in the patients who had video-assisted thoracoscopic surgery (15 of 40 patients; $P = 0.007$; odds ratio = 3.63 [95% CI, 1.4 to 9.5]; table 4 and Supplemental Digital Content 2, http://links.lww.com/ALN/B953). Patients with diaphragmatic dysfunction at 24 h postoperatively had a higher percentage of postoperative pulmonary complications compared with patients without diaphragmatic dysfunction (33 of 51 patients [65%] *vs.* 6 of 24 patients [25%]; $P = 0.001$; odds ratio = 5.5 [95% CI, 1.9 to 16.3]; table 4 and Supplemental Digital Content 3, http://links.lww.com/ALN/B954). Patients with diaphragmatic dysfunction at 24 h postoperatively experienced more postoperative pulmonary complications (2 [0 to 3] *vs.* 0 [0 to 1.5]; $P = 0.012$).

Table 1. Perioperative Characteristics of Patients Enrolled

Variables	Total	Thoracotomy	VATS	*P* Value
No. of patients	75	35	40	
Age, yr	67 ± 11	66 ± 11	68 ± 10	0.323
BMI, kg · m^{-2}	26.1 ± 4.2	26.0 ± 3.5	26.1 ± 4.7	0.953
Male	46 (61)	18 (51)	28 (70)	0.099
Smoking history	62 (83)	30 (86)	32 (80)	0.622
Current smokers	24 (32)	13 (37)	11 (28)	
Pack-yr	40 [25–52]	40 [37–56]	36 [21–53]	0.202
Comorbidities				
Chronic heart disease	49 (65)	19 (54)	30 (75)	0.060
COPD	23 (31)	10 (29)	13 (33)	0.713
Metabolic pathology	43 (57)	23 (66)	20 (50)	0.170
Chronic liver disease	7 (9)	3 (9)	4 (10)	0.832
NYHA classification				
2	26 (35)	10 (29)	16 (40)	0.339
3	3 (4)	1 (3)	2 (5)	0.999
ASA physical status				
II	24 (32)	15 (43)	9 (23)	0.101
III	51 (68)	20 (57)	31 (78)	0.101
Surgical site				
Right	40 (54)	14 (41)	26 (65)	0.069
Surgical procedures				
Lobectomy	46 (61)	30 (86)	16 (40)	< 0.001
Wedge resection	25 (33)	2 (6)	23 (58)	< 0.001
Bilobectomy	4 (5)	3 (6)	1 (3)	0.339
Intraoperative mechanical ventilation				
Tidal volume, TLV, ml/kg	6.5 ± 0.9	6.7 ± 0.9	6.3 ± 0.9	0.102
Tidal volume, OLV, ml/kg	4.9 ± 0.5	5.0 ± 0.8	4.9 ± 0.5	0.814
Respiratory rate	15 ± 2	14 ± 2	16 ± 2	0.081
PEEP (cm H_2O)	5 ± 2	5 ± 2	6 ± 2	0.182
FIO_2	0.39 ± 0.09	0.40 ± 0.07	0.38 ± 0.12	0.265
Duration of operation, min	133 [100–201]	130 [100–190]	135 [95–210]	0.787

Normally distributed variables are reported as mean ± SD and nonnormally distributed variables as median [interquartile range]; percentage data are shown as No. (%).

ASA, American Society of Anesthesiologists; BMI, body mass index; COPD, chronic obstructive pulmonary disease; FIO_2, fraction of inspired oxygen; NYHA, New York Heart Association; OLV, one-lung ventilation; PEEP, positive end-expiratory pressure; TLV, two-lungs ventilation; VATS, video-assisted thoracoscopy.

The surgical approach did not have any significant effect on the association between diaphragmatic dysfunction and postoperative pulmonary complication development (likelihood-ratio test for interaction term: $P = 0.515$). The analysis of standardized differences between groups is shown in Supplemental Digital Content 4 (http://links.lww.com/ALN/B955).

Postoperative pain did not differ between the two groups, both at 2 h postoperatively (numerical rating scale thoracotomy 3 [1 to 3] *vs.* numerical rating scale video-assisted thoracoscopic surgery 2 [0 to 3], $P = 0.171$) and at 24 h postoperatively (numerical rating scale thoracotomy 3 [1 to 4] *vs.* numerical rating scale video-assisted thoracoscopic surgery 3 [2 to 3], $P = 0.634$). Rescue IV opioids were given in 37% of the patients in the thoracotomy group and in 28% of the patients in the video-assisted thoracoscopic surgery group at 2 h postoperatively (13 of 35 patients *vs.* 11 of 40 patients, $P = 0.518$), while at 24 h postoperatively, patients receiving opioids were 43% in thoracotomy group and 28% in video-assisted thoracoscopic surgery group (15 of 35 patients *vs.* 11 of 40 patients; $P = 0.249$). None of patients received more than two rescue boluses per day.

Discussion

The main result of the current study is that elective lung cancer resection frequently induces postoperative diaphragmatic dysfunction on the operated side (68%). We found that, as compared with the standard thoracotomic technique, video-assisted thoracoscopic surgery had a less detrimental impact on diaphragmatic excursion. Diaphragmatic dysfunction 24 h postoperatively was associated with postoperative pulmonary complications occurring within the first 7 postoperative days.

Thoracic surgery[29] as well as general anesthesia and mechanical ventilation, *per se,* may decrease diaphragmatic performance.[30–32] Welvaart *et al.*[29] showed a marked and selective diaphragm muscle fiber dysfunction occurring as early as 2 h after thoracic surgery. In our patients, the diaphragmatic excursion in the nonoperated side remained unchanged throughout the study, and the diaphragmatic dysfunction was more common after thoracotomy rather than after video-assisted thoracoscopic surgery (83% *vs.* 55%, $P = 0.010$). Our data seem to confirm and expand previous data obtained in patients undergoing lung biopsy,

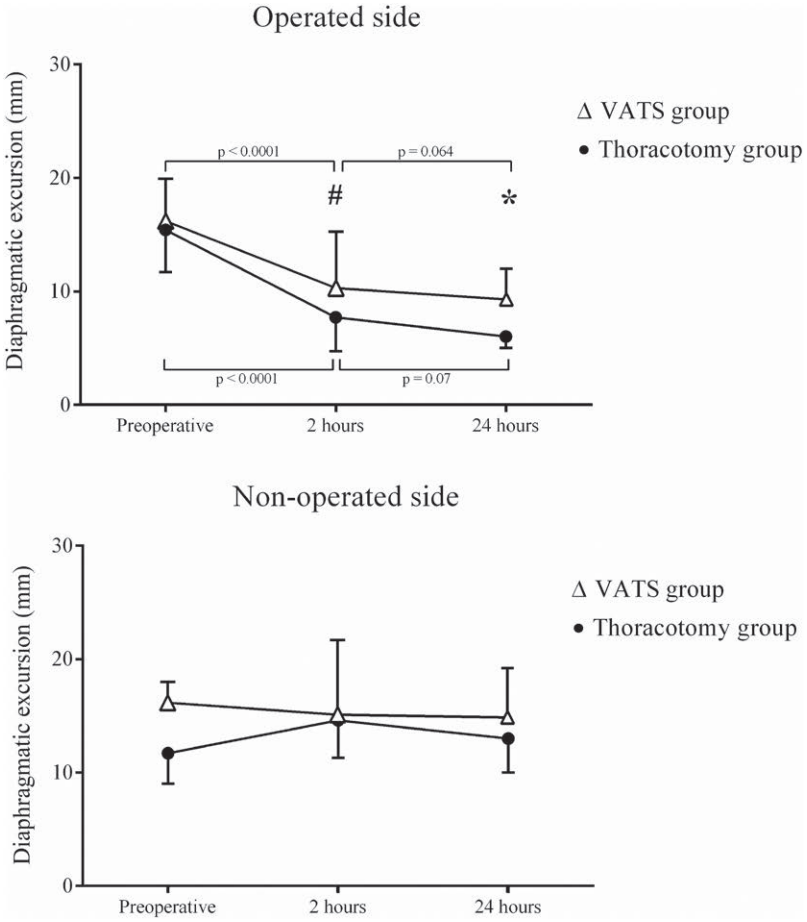

Fig. 4. Diaphragmatic excursion data are shown as median and first and third quartiles (*error bars*). Preoperative, 2 h and 24 h after operation diaphragmatic excursion in the video assisted thoracoscophy (VATS) and in the thoracothomy group. #$P = 0.007$ between groups after 2 h; *$P < 0.0001$ between groups after 24 h. Pairwise comparisons were adjusted using Bonferroni correction.

Table 2. Perioperative Diaphragmatic Excursion of the Operated Side, Tidal Volume, and Pulmonary Function Tests in Patients with or without Diaphragmatic Dysfunction 24 h Postoperatively

	Diaphragmatic Dysfunction (n = 51)		Nondiaphragmatic Dysfunction (n = 24)	
Variables	**Preoperative**	**24 h Postoperatively**	**Preoperative**	**24 h Postoperatively**
Diaphragmatic excursion, operated side, mm	16 [12.0–18]	6 [5–8]*†	17 [12–21]	12 [11–14]*
Diaphragmatic excursion, nonoperated side, mm	15 [11–19]	13 [10–20]	16 [12–18]	16 [13–21]
Tidal volume, ml	650 [480–650]	400 [250–450]*†	620 [510–675]	450 [352–510]*
FEV_1/FVC	75.2 [69.9–82.0]	76 [64.5–86.0]	73.5 [68.0–73.5]	70.5 [65–79.2]
FEV_1, l	2.4 ± 0.7	0.9 ± 0.3*†	2.3 ± 0.6	1.1 ± 0.2*
FVC, l	3.2 [2.5–3.6]	1.2 [0.9–1.6]*†	3.1 [2.7–3.5]	1.6 [1.1–1.7]*

Data are expressed as median [interquartile range] or mean ± SD. Diaphragmatic dysfunction was defined as a diaphragmatic excursion less than 10 mm or negative on the operated side.

*$P < 0.05$ *versus* preoperative. †$P < 0.05$ *versus* nondiaphragmatic dysfunction patients.

FVC, forced vital capacity; FEV_1, forced expiratory volume in the first second.

Table 3. Association between Diaphragmatic Dysfunction 24 h Postoperatively and Perioperative Variables According to Logistic Regression Analysis

	Univariate Analysis		
	Crude Odds Ratio	95% CI	*P* Value
Surgical access (ref: VATS)			
Thoracotomy	3.95	1.5–10.3	0.005
COPD/asthma (ref: absence)			
Presence	0.89	0.4–2.4	0.847
Length of surgery (ref: < 130 min)			
≥ 130 min	1.41	0.8–3.8	0.105
Age (ref: < 65 yr)			
≥ 65 hr	1.06	0.4–2.7	0.952
ASA (ref: < III)			
III	1.03	0.4–2.5	0.905
Sex (ref: male)			
Female	1.49	0.6–3.8	0.378
BMI (ref: < 24.9)			
≥ 25.0	1.98	0.8–5.1	0.159
Smoking history (ref: nonsmoker)			
Actual smoker	2.78	1.0–7.6	0.044

Diaphragmatic dysfunction was defined as a diaphragmatic excursion less than 10 mm or negative on the operated side.

ASA, American Society of Anesthesiologists physical status classification; BMI, body mass index; COPD, chronic obstructive pulmonary disease; ref, reference; VATS, video-assisted thoracoscopy.

Table 4. Association between Perioperative Variables and Development of at Least One Postoperative Pulmonary Complication According to Logistic Regression Analysis

	Univariate Analysis		
Variable	Crude Odds Ratio	95% CI	*P* Value
Diaphragmatic dysfunction 24 h postoperatively	5.5	1.9–16.3	0.002
Diaphragmatic dysfunction 2 h postoperatively	1.60	0.6–4.0	0.316
Thoracotomy surgical access (ref: VATS)	3.63	1.4–9.5	0.008
History of COPD/asthma (ref: absence)	2.88	1.0–8.2	0.047
Length of surgery ≥ 130 min (ref: < 130 min)	2.37	0.8–6.4	0.011
Age ≥ 65 yr (ref: < 65 yr)	1.12	0.4–3.0	0.812
ASA = III (ref: < III)	0.69	0.3–1.8	0.452
METs	1.25	0.9–1.8	0.204
MRC	0.95	0.4–2.2	0.904
NYHA classification ≥ 2	1.04	0.4–2.5	0.970
FEV_1, %	1.00	1.0–1.0	0.453
FEV_1/FVC, %	1.01	1.0–1.0	0.825
Sex female (ref: male)	0.98	0.4–2.5	0.970
BMI ≥ 25.0 (ref: < 24.9)	1.58	0.6–4.0	0.335
Smoking history (ref: nonsmoker)			
Actual smoker	3.22	0.8–13.0	0.104
Past smoker	1.44	0.4–5.2	0.578
Preoperative Spo_2 ≤ 96% (ref: Spo_2 > 96%)	1.31	0.5–3.5	0.592

Diaphragmatic dysfunction was defined as a diaphragmatic excursion less than 10 mm or negative on the operated side.

ASA, American Society of Anesthesiologists physical status classification; BMI, body mass index; COPD, chronic obstructive pulmonary disease; FEV_1, forced expiratory volume in the first second; FVC, forced vital capacity; MET, metabolic equivalent; MRC, Medical Research Council scale for dyspnea; NYHA, New York Heart Association; Spo_2, oxygen saturation measured by pulse oximetry; VATS, video-assisted thoracoscopy.

showing that, as compared to thoracotomy, video-assisted thoracoscopic surgery is associated with better recovery of respiratory muscle function.[33] Overall, it is tempting to speculate that, in our patients, postoperative diaphragmatic dysfunction was caused more by surgery-induced variations in chest wall conformation and resting diaphragm length[9] rather than by phrenic nerve inhibition due to the postoperative pain or postoperative respiratory drive impairment. Indeed, we maintained an adequate postoperative pain control (numerical rating scale values between 2 and 3) by positioning a thoracic epidural catheter, a technique with minimal impact on the respiratory drive as compared to intravenous opioids.[34]

Diaphragmatic dysfunction affects both the lung and chest wall mechanics and favors the development of atelectasis.[9,35,36] Interestingly, we found radiologic evidence of atelectasis in 18 patients among the 51 patients with diaphragmatic dysfunction at 24 h postoperatively (35%) and only in 3 patients among the 24 without diaphragmatic dysfunction (13%, $P = 0.040$; Supplemental Digital Content 3, http://links.lww.com/ALN/B954). The relationship between diaphragmatic disfunction and atelectasis can be explained by the decrease in transdiaphragmatic pressure.[35] The diaphragmatic contraction provides a differential pressure between the abdomen and chest. When the diaphragm is dysfunctional, it is less effective in maintaining distinct pressures in the two cavities. Furthermore, confirming previous studies,[14,15,37] we found that the diaphragmatic dysfunction decreased the ability to generate V_T, another mechanism to explain the development of atelectasis.[38]

Maeda *et al.*[39] showed a significant decrease in maximal transdiaphragmatic pressure after thoracotomy, whereas Fratacci *et al.*[9] observed a marked reduction in diaphragmatic contractility after pulmonary resection using electromyography. Takazakura *et al.*[40] reported a decrease of 36% in the diaphragmatic excursion on the operated side after thoracotomy, assessed by dynamic magnetic resonance. Most of these techniques are difficult to apply at the bedside. Conversely, we reported the incidence of diaphragm dysfunction after thoracic surgery with a reliable, noninvasive, and widely available ultrasonographical examination. Given the increasing popularity of diaphragmatic ultrasound in several postoperative contexts,[41] our research might represent a starting reference for further studies. Since we found a significant association between diaphragmatic dysfunction and postoperative pulmonary complications (table 4), the ultrasound assessment of diaphragm motion could be a useful tool to identify patients at greater risk of postoperative pulmonary complications that should be managed more cautiously, for example, with continuous positive airway pressure,[36] noninvasive ventilation, or incentive ventilation and physiotherapy.

Several study limitations must be acknowledged. First, we did not exclude a direct phrenic nerve injury in our patients by measuring the phrenic nerve conduction time. However, a surgical trauma of the phrenic nerve is at least improbable during lung cancer resection. Second, we did not randomize the surgical procedures; however, we reasoned that a strict randomization to a more invasive surgical procedure such as thoracotomy would have probably been unethical. In our study, the surgical approach was decided upon technical and/or oncologic reasons by the surgeon. We should acknowledge that it was impossible to blind the ultrasonographer due to the easily discernible differences between the video-assisted thoracoscopic surgery and the thoracotomy incisions. However, the physician performing the ultrasound evaluation was not involved in the patient's postoperative care and did not communicate the results to the treating physicians. Thus, we can exclude that the postoperative care was influenced by the result of diaphragmatic ultrasonography. Third, we only took into account the diaphragmatic excursion to assess the diaphragmatic dysfunction; other techniques, such as the measurement of the diaphragmatic thickness, could have provided more information to our study. Nevertheless, the evaluation of the diaphragmatic thickness *versus* diaphragmatic excursion seems to be appropriate more in mechanically ventilated than in spontaneously breathing patients, as it was in our study.[27] Fourth, the relatively small sample size did not allow an alternative statistical model, which would clarify the independent effect of each covariate in the outcomes investigated; this limitation is reflected by wide CIs for the observed relationship. Finally, even if we analyzed the occurrence of postoperative pulmonary complications for the first 7 postoperative days, we evaluated the diaphragmatic excursion only after 2 and 24 h after surgery and, thus, we do not know what was the diaphragmatic excursion on the day of postoperative pulmonary complication diagnosis. However, the aim of our study was to investigate whether the ultrasound evaluation of the diaphragm could screen patients at high risk of postoperative pulmonary complications; for this purpose, an early risk assessment seems appropriate.

In conclusion, point of care ultrasound, a noninvasive, bedside-available tool, can be used to detect diaphragmatic dysfunction after thoracic surgery. Confirming our main hypothesis, we found that the thoracotomic technique carries a higher risk of diaphragmatic dysfunction as compared to video-assisted thoracoscopic surgery. Also, postoperative pulmonary complications were more frequent in patients with diaphragmatic dysfunction at 24 h. Given the increasing popularity of diaphragmatic ultrasound in several postoperative contexts, our study might represent a starting reference for further studies designed to clarify whether ultrasonography assessment of diaphragm function could carry significant clinical advantages.

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Competing Interests

The authors declare no competing interests.

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Appendix. Definitions of Pulmonary Postoperative Complications

Postoperatively, a physician not aware of the patient study group and not involved in the patient's ongoing care collected data on the occurrence of a symptomatic and clinically significant postoperative pulmonary complications during the hospital length of stay or within the first 7 postoperative days through review of clinical records, laboratory, and radiology data.

1. Hypoxemia

Pa_{O_2} less than 60 mmHg or oxygen saturation measured by pulse oximetry less than 90% in room air but responding to supplemental oxygen (excluding hypoventilation)

2. Severe hypoxemia

Need for noninvasive or invasive mechanical ventilation or a Pa_{O_2} less than 60 mmHg or oxygen saturation measured by pulse oximetry less than 90% despite supplemental oxygen (excluding hypoventilation)

3. Bronchospasm

Defined as newly detected expiratory wheezing treated with bronchodilators

4. Suspected pulmonary infection

Defined as new or progressive radiographic infiltrate plus at least two of the following: antibiotic treatment, tympanic temperature greater than 38°C, leukocytosis or leucopenia (leukocyte count less than 4,000 cells/mm^3 or greater than 12,000 cells/mm^3), and/or purulent secretions

5. New pulmonary infiltrates

Chest radiograph demonstrating new monolateral or bilateral infiltrate without other clinical signs

6. Atelectasis

Chest radiograph demonstrating lung opacification with shift of the mediastinum, hilum, or hemidiaphragm toward the affected area, and compensatory overinflation in the adjacent nonatelectatic lung

7. Pleural effusion

Chest radiograph demonstrating blunting of the costophrenic angle, loss of the sharp silhouette of the ipsilateral hemidiaphragm in upright position, evidence of displacement of adjacent anatomical structures, or (in the supine position) a hazy opacity in one hemithorax with preserved vascular shadows

Source: PROVE Network Investigators for the Clinical Trial Network of the European Society of Anesthesiology, Hemmes SN, Gama de Abreu M, Pelosi P, Schultz MJ. High *versus* low positive end-expiratory pressure during general anesthesia for open abdominal surgery (PROVHILO trial): A multicentre randomised controlled trial. Lancet 2014; 384:495–503