Prevalence and Time-Course of Diaphragmatic Dysfunction Following Lung Resection: A Repeated Ultrasonic Assessment

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Research Article

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Abstract

BACKGROUND: There is little information regarding diaphragmatic dysfunction (DD) following thoracic surgery. Ultrasound allows for non-invasive repeated assessments of diaphragmatic excursion (DE) and thickening fraction (DTF) at the bedside, reflecting DD. We aimed at determining the prevalence of DD and the time-course of DE and DTF following elective thoracic surgery. Secondary endpoints included the association between DD and postoperative complications.

METHODS: We led a prospective, single center, observational study in consecutive patients undergoing thoracic surgery. DE and DTF were measured by two observers blinded to each other at 3 different time-points: prior to surgery (D-1), immediately after extubation (D0) and on postoperative day 3 (D3). The changes in excursion and thickening fraction of both hemi-diaphragms over time were compared according to the side (operated or non-operated) using a two-way ANOVA. The association with postoperative complications was assessed using logistic regression.

RESULTS: Fifty patients, 60% males, aged 60±15 years were included. Surgical procedures included lobectomy (n=30), wedge-resection (n=17) or pneumonectomy (n=3). DD was highly prevalent after thoracic surgery and was observed on the operated side (or both sides) in, at least, 68% of patients immediately after surgery (D0). Among those patients, 46% still had this DD on the operated side on D3. On the operated side, we observed a decrease in DE and DTF at D0 (-0.71±0.12mm, $P<0.05$; -44±30%, $P<0.05$) and D3 (-0.82±0.19mm, $P<0.05$; -39±19%, $P<0.05$) with respect to values at D-1. On the non-operated side, mean values for DE and DTF did not change significantly over the study period. Persistent DD on the operated side, defined by a DD present at the two postoperative time-points, was associated with an increased risk of lung infection ($P=0.001$), ICU-admission ($P=0.04$) according to univariate analysis and a prolonged length in hospital (OR:1.3, 95% CI [1.1-1.7], $P=0.016$) according to multivariate analysis.

CONCLUSIONS: Diaphragmatic Dysfunction (DD) was very common after thoracic surgery, mainly concerned the operated side and was associated with an increase in the diaphragmatic excursion on the non-operated side. When this dysfunction failed to regress within 72 hours, it was associated with a significant increase in the length of hospital stay.

Background

Diaphragmatic dysfunction (DD) can be defined as an imbalance between the diaphragm's ability to provide enough negative pressure to mobilize vital capacity and the workload imposed upon it. DD is increasingly viewed as an organ dysfunction per se, but its assessment remains a matter of debate. Indeed, the monitoring of trans-diaphragmatic pressures (Pdi) combined with electromyographic recordings under supramaximal electrical (or magnetic) phrenic nerve stimulations [1, 2] remains the gold standard. However, this method is burdened with a specific complexity and invasiveness, making it poorly accessible on a routine and rather falls within the physiological research field in specialized centers. This explains the growing interest in the evaluation of the diaphragm using ultrasound techniques. From a functional point of view, DD can result in an impairment of diaphragmatic motion no matter the underlying cause and irrespective of ventilatory consequences. Ultrasound (US) represents an interesting and emerging alternative tool for assessing diaphragmatic function with the advantage of being strictly noninvasive and available at the bedside [3, 4]. Parameters suggested to reflect diaphragmatic function include diaphragmatic excursion (DE) and thickening fraction (DTF). Shear wave elastography (SWE) allows a direct quantification of the mechanical properties of the tissues (stiffness) and enables to obtain the shear modulus [5], correlated with the Pdi [6], but is difficult to acquire with the polypneic patient [7]. Recently, the use of tissue Doppler measuring the velocity of diaphragmatic movements has also shown to provide interesting insights predicting extubation successes after a T-tube trial [8]. It has been demonstrated that DTF correlates with trans-diaphragmatic pressures [14, 15] but the measurement of DE is easier to acquire and more reproducible on spontaneously breathing patients during the postoperative period [16, 17].

Diaphragmatic dysfunction (DD) and diaphragmatic palsy have been described in patients in intensive care settings as well as in the perioperative period. The observed prevalence of this disorder in adult ICU patients ranges from 25 to 40% [18]. DD has also been described after cardiac surgery, especially when pericardial icing was used for myocardial protection [19]. A reflex DD is also well described after upper abdominal surgery, as a consequence of the stimulation of peritoneal afferent nerves [20–22]. In contrast, there is little information concerning the prevalence of DD following thoracic surgery and in particular lung resections. To our knowledge, only two studies have investigated diaphragmatic function after thoracic surgery using bedside ultrasound, one after bilateral lung transplantation [23] and one after lung resection [24]. In the latter study, the time-course of DD has not been explored beyond 24 hours [24].

We aimed at determining the prevalence and time-course of diaphragmatic dysfunction after elective lung resection using serial ultrasound bedside assessments, using DE as the primary endpoint, up to postoperative day 3, and concomitant DTF as a comparison. We analyzed the risk factors for developing diaphragmatic dysfunction and the relation between diaphragmatic dysfunction and respiratory or cardiac postoperative complications during hospital stay. We also compared the inter-observer reproducibility of DE and DTF measurements.

Methods

This study was approved by an independent institutional review board (CPP Ouest 2 Angers #02018/28, registration number: 2018-A00071-54). All patients provided written informed consent before enrolment.

This was a prospective, single center, observational study. We included all consecutive patients, aged 18 years or more, admitted for elective lung resection to the department of thoracic surgery between January 8th and March 11th of 2018. Patients were studied when breathing spontaneously and in the absence of respiratory distress or discomfort. Exclusion criteria were represented by preexisting DD, neuromuscular disorders, pregnancy, mental illness or impossibility for the subject to have a good comprehension of the study, and lack of health insurance coverage. The flow of patients included in the study is presented in Fig. 1.

Diaphragmatic excursions (DE) and diaphragmatic thicknesses (DT) were measured sequentially for each hemi-diaphragm on spontaneously breathing patients, in semi-recumbent position (back at 30°), during quiet and regular breathing. Ultrasound examinations were performed at three different time-points during the hospital stay: prior to surgery (D-1), immediately after extubation (D0), and at postoperative day 3 (D3) as described on the timeline of the study (Fig. 2). All analyzed patients were extubated on the day of the surgery, and the first postoperative ultrasound assessment was done within one hour following extubation. We performed all the measurements using the same commercially available ultrasound platform (CX50 CompactXtreme®, Philips) connected to a 1–5 MHz phased array transducer for the measurements of DE, and to a 5–12 MHz linear transducer for the measurements of DT. A slow scrolling speed of display was used in order to see at least three consecutive respiratory cycles on the same screen with a regular amplitude and frequency (Fig. 3, panels A and B). Each value was calculated as the average of three consecutive cycles for each hemi-diaphragm. The thickening fraction of the diaphragm (DTF) was calculated as:

$$\mathrm{DTF}(\%) = \frac{(\mathrm{endinspiratorythickness} - \mathrm{endexpiratorythickness})}{\mathrm{endexpiratorythickness}} \times 100$$

The measurements were performed twice, by two observers (an expert and a trainee) blinded to each other, to quantify inter-observer variability. The expert always performed the measurements first and marked the best acoustic window on the patient's chest to facilitate the trainee's task, as previously described [16]. We used standard acoustic windows to measure DE and DTF [10, 25]. When DE measurement proved difficult through the subcostal window, we used a more lateral approach from the mid-axillary line, combined with an angle correction, if necessary, using the anatomical motion mode (AMM) as described by Pasero *et al.* [16].

Since the primary endpoint was defined by the measurement of the DE, the patient was recognized as having a DD if the diaphragmatic excursion was 1 cm or less for men and 0.9 cm or less for women during quiet regular breathing, according to the normal ranges defined by Boussuges *et al.* [26]. Diaphragmatic palsy was defined by a paradoxical displacement or an absence of motion (DE $\leq$ 0 cm) visualized using two-dimensional B mode [25].

The primary outcome was the prevalence of diaphragmatic dysfunction or palsy observed at any of the two postoperative time-points (D0 and/or D3). We compared the values and time-course of the two indices of diaphragmatic function (excursion and thickening fraction) between operated and non-operated sides.

The secondary end points of this study included: 1) the evaluation of the reproducibility of DE and DTF measurements, 2) the detection of risk factors associated with postoperative diaphragmatic dysfunction and 3) the association between diaphragmatic dysfunction and postoperative pulmonary or cardiac adverse events. COPD exacerbation and pneumonia were defined according to standard criteria [27, 28].

Data collection

We recorded demographic parameters: age, gender, weight and height, ASA (American Society of Anesthesiology) class, as well as the indication for surgical lung resection and the type of surgery. We also collected informations regarding the type of surgical wound and the use of muscle relaxants. Other events recorded included the occurrence of lung infection, COPD exacerbation, wound infection, pneumothorax, rhythm disturbances and in particular atrial fibrillation (AF), pulmonary edema, renal failure, need for ICU admission, the need for invasive (IV) or noninvasive ventilation (NIV) and its duration, the time before chest tube removal, time to hospital discharge and in-hospital mortality.

Statistical analysis

This was a descriptive exploratory study and estimating a sample size to provide adequate power to our analysis was not appropriate. Categorical data are presented as numbers and percentages, and values are expressed as mean ± SD, or as median and Interquartile Ranges [IQR]. A two-way ANOVA was performed to assess the time-course of DE and DTF with respect to the side (operated or non-operated). In case of significant interaction, we performed multiple comparisons using a Student-Newman-Keuls test. Inter-observer reproducibility was described using Bland & Altman representation of the agreement between experts and trainees regarding the measurement of DE and DTF [29]. The concordance between these 2 measures was assessed using an intra-class concordance coefficient (ICC). The association between postoperative DD and clinically meaningful variables including: age, American Society of Anesthesiologists (ASA) class, gender, body-mass index, smoking history, Chronic heart failure (CHF i.e LVEF < 30%), diabetes, surgical approach (mini-invasive approach or thoracotomy), history of chronic obstructive pulmonary disease (COPD), and duration of surgery was modeled using binary logistic regression analysis and was reported as the estimated crude odds ratio (OR) and relative 95% CI. A logistic regression analysis was applied to investigate the possible risk factors for the occurrence of at least one postoperative respiratory complication or atrial fibrillation. Univariate analysis identified factors for inclusion in multivariate analysis using a p-value < 0.20 as a threshold for inclusion. A step AIC (Akaike Information Criterion) procedure was performed to select a reduced number of predictor variables for building the best performing multiple logistic regression model. Type-I error was fixed at 0.05. All statistical analyses were performed using the R® 4.0.0 software (http://www.R-project.org, the R Foundation for Statistical Computing, Vienna, Austria).

Results

Over the three-month study period, 89 patients underwent thoracic surgery, among which 52 were eligible for an elective lung resection. All candidates for lung resection were enrolled into the study (Fig. 1). Two patients were excluded from the final analysis: one withdrew consent and the other died of a massive hemorrhage precluding the possibility of ultrasound assessment. All 50 remaining patients underwent the complete sequence of data acquisition (at D-1, D0, and D3). Patients' characteristics and types of surgeries are presented in Table 1. The surgery was part of the treatment of a suspected or confirmed neoplasia in 78% (70% for non small-cell lung cancer, and 8% for metastasis), of a carcinoid tumor in 2%, of an infection (tuberculosis, hydatidosis or aspergillosis) in 8%, or of nonspecific inflammatory processes in 12% of the patients. Seventy-eight percent of the surgeries were conducted via a postero-lateral (PLT) or antero-lateral thoracotomy (ALT) while 22% of the patients underwent less invasive approaches (mini-thoracotomy: 14%, and video-assisted thoracoscopy: 8%).

We observed a significant decrease in excursion (Fig. 4, panel A) of the hemi-diaphragm on the operated side at day 0 and day 3 in comparison to the non-operated side and with respect to pre-operative excursion of the same side. The diaphragmatic thickening fraction followed a similar time-course (Fig. 4, panel B). Sixty-eight percent of the patients presented a diaphragmatic dysfunction at Day 0 on the operated side. The kinetics of diaphragmatic dysfunction over the postoperative period according to the side are presented in Fig. 5.

According to univariate analysis, two factors were associated with the risk of postoperative DD on the operated side: the presence of chronic heart failure (36% of patients, odds ratio (OR): 7.4, 95% CI: 1–42, *P* = .02,), and an invasive surgical approach, i.e., PLT or ALT (78% of patients, OR: 5.0, 95% CI: 1–24, *P* = .03). Chronic obstructive pulmonary disease was associated with the presence of a bilateral DD on day 3 for 24% of patients (OR: 12.0, 95% CI: 1–259, *P* = .04). Demographic variables, body mass index, tobacco consumption, diabetes, concomitant treatment or type of surgery had no significant impact on post-operative DD. Likewise, duration of surgery, and cumulative dose of muscle relaxant had no significant impact on the occurrence of DD.

Twenty-three patients presented a DD on the operated side at D0 that persisted at D3. The association between persistent DD on the operated side and postoperative complications is presented in Table 2. The association between surgical approach (invasive versus non invasive) and postoperative complications is presented in Table 3.

We found that median DE values were 1.2 cm (IQR: 0.8–1.7 cm) for the expert and 1.2 cm (0.9–1.7 cm) for the trainee. The intra-class concordance coefficient between these 2 measures was 0.72 (95% CI: 0.66–0.77). The mean bias for DE measurement was 0.0 cm, with limits of agreement (LOA) of ± 1.1 cm (Fig. 6, panel A).

Median DTF values were 39 % (IQR: 18–61 %) for the expert and 25 % (IQR: 10–48 %) for the trainee. The intraclass concordance coefficient between these 2 measures was 0.62 (95% CI: 0.55–0.69). The mean bias for DTF measurements was 11%, with LOA of ± 68% (Fig. 6, panel B).

Discussion

In this prospective cohort study of consecutive patients undergoing lung resection, we observed a high prevalence (68%) of postoperative diaphragmatic dysfunction on the operated side. When still present at day 3 following the surgery, DD was associated with an increase in respiratory infections (pneumonia and COPD exacerbations), need for ICU admission, and hospital length of stay. However, the length in hospital stay is the only one remaining significantly associated with DD according to multivariate analysis. In addition, we noted that DE and DTF followed the same time-course when diaphragmatic function was altered, but DE was easier to assess and more reproducible than DTF.

Most of the data available on postoperative DD has been obtained with patients following cardiac surgery and only a few studies have addressed this issue after thoracic surgery. To our knowledge, only two studies have used bedside ultrasound to characterize DD after lung resection [24] or after bilateral lung transplantation [23]. Spadaro *et al.* reported an incidence of 68% for DD on the operated side on the first postoperative day [24], the exact same figure that was observed in our cohort. We observed that 46% of patients with a DD on the operated side (or both sides) immediately after surgery still had it on day 3. A possible explanation for this persistence is that most patients had chest tubes that might prevent the restoration of a normal diaphragmatic function. Whether this dysfunction disappears after chest tubes removal remains to be established. Spadaro *et al.* highlighted that thoracotomy was the main risk factor of postoperative DD [24], a finding that is confirmed with our results. Unlike these authors, we didn't find any relation between active smoking and DD, but we noticed an association between LVEF < 30% and DD on the operated side. Mild diaphragmatic alterations have been described in patients with heart failure, a condition that might predispose to more frequent DD following thoracic surgery [30]. Nine patients (18%) developed delayed DD (7 on the operated side, 1 on the non-operated side and 1 bilateral) appearing at postoperative day 3. This secondary dysfunction might be explained, in part, by various combinations of reflex mechanisms related to pain, pleural effusion or the persistence of chest tubes [3]. We also noted a trend in increase in DE measurements on the non-operated side at the two postoperative time-points. This could be related to a compensatory mechanism for the contralateral postoperative DD as suggested by several authors, including a study using MRI to assess diaphragmatic function on patients undergoing lung resection surgery [4, 31]. In our cohort, 6 (12%) patients were presented with suspected phrenic nerve injury. This rather high prevalence can be explained by the large proportion of pulmonary resection for neoplasms (n = 39, 78%), usually accompanied by extensive lymph node resection (n = 36, 72%) favoring phrenic nerve damage [32].

Most studies that have looked at diaphragmatic function have analyzed its relation with difficulties in weaning the patient from mechanical ventilation [13, 33, 34]. However, it is not well known whether DD affects outcome beyond extubation and if other complications may occur as a consequence of an impaired diaphragmatic motion. Spadaro *et al.* reported an increase in a composite of various respiratory complications in patients with DD, probably facilitated because the main respiratory muscle was not functioning properly [24]. Even if most patients with unilateral DD or diaphragmatic palsy are asymptomatic [35], they are potentially prone to more frequent respiratory tract infection as a result of altered cough efficiency. In our cohort, DD of the operated side was associated, when still present at day 3 following the surgery, with an increase in respiratory infections (pneumonia and COPD exacerbations), need for ICU admission, and hospital length of stay. Although these findings are to be considered exploratory, it seems relevant to further investigate the relation between DD and postoperative complications after extubation. Longitudinal studies with a thorough follow-up may be helpful to answer this question.

Even if ultrasound techniques are now widely recognized as a promising tool for diaphragmatic evaluation in critically ill or surgical patients at the bedside, the debate remains on the best index to reflect the complex function of this organ. Thickening fraction at the level of the apposition zone has long been shown to correlate with the work of breathing [36]. It remains meaningful even if the patient receives positive pressure ventilation. However, it is sometimes difficult to obtain and small errors in thickness measurements can translate into large differences in DTF. This is probably why inter-observer reproducibility of this measurement is usually not as good as the reproducibility of diaphragmatic excursion. We have previously shown in a population of cardiac surgical patients that the changes and time-course of DTF and DE were similar, suggesting that DE should be preferred on spontaneously breathing patients [17]. The present findings corroborate this previous observation. Recently, Soilemezi *et al.* have demonstrated that the pattern of diaphragmatic displacement velocity measured using tissue Doppler was highly predictable in weaning failure on patients undergoing T-tube breathing challenges prior to extubation [8]. We have not evaluated this parameter on our subjects, but it is certainly worth exploring the value of this measurement in comparison to diaphragmatic excursion in future trials.

To our knowledge, this is only the third study to provide specific information on diaphragmatic function on patients after thoracic surgery, and the second to look at patients undergoing elective lung resection. Although this was a single center study involving a small cohort of patients, all of them were enrolled consecutively and studied serially with no loss to follow-up and almost no missing data (only one patient could not be evaluated on the 3rd postoperative day). Our overall measurement failure rate was only at 0.7%, attesting the effectiveness of modern ultrasound techniques, when this figure was as high as 27% ten years ago [37]. One of the limits of our work relates to the limited duration of the follow-up, i.e. 72 hours after the surgery, at a time when many patients still had chest tubes. It is possible that diaphragmatic function improved afterwards, when pain and reflex inhibitory mechanisms were less important. The ultrasound assessment was always performed by the expert observer first in order to mark the best ultrasound window for the trainee, as described in a previous studies [16, 17]. As a consequence, the inter-observer variability of both DE and DTF might be underestimated in comparison to a setting in which observers are randomized. However, this does not compromise the finding that measurements of DE are more reproducible than those of DTF.

Conclusions

Diaphragmatic dysfunction was very common after elective lung resection, especially on the operated side. When this dysfunction failed to regress within 72 hours, it was associated with an increase in the length of hospital stay. Bedside ultrasound provides simple and reproducible measurements of diaphragmatic excursion that can easily be used to detect diaphragmatic dysfunction. Larger studies are required to confirm the association between persisting reduced DE and adverse outcome. A longer follow-up would be interesting to verify the potential recovery of diaphragmatic function beyond the third postoperative day.

Abbreviations

AF Atrial Fibrillation

ALT Antero-Lateral Thoracotomy

AMM Anatomical Motion Mode

CHF Chronic Heart Failure

COPD Chronic Obstructive Pulmonary Disease

DD Diaphragmatic Dysfunction

DE Diaphragmatic Excursion

DT Diaphragmatic thickness

DTF Diaphragmatic Thickening fraction

ICC Intraclass Concordance Coefficient

ICU Intensive Care Unit

IV Invasive ventilation

LVEF Left Ventricular Ejection Fraction

MT MiniThoracotomy

NIV Non Invasive Ventilation

PLT Postero-Lateral Thoracotomy

VATS Video-Assisted Thoracoscopy

Declarations

Ethics approval and consent to participate: this study was approved by an independent institutional review board (CPP Ouest 2 Angers #02018/28, registration number: 2018-A00071-54). All patients provided written informed consent before enrolment.

Consent for publication: all ultrasound images are taken from anonymized data from patients who provided their prior consent. The CNIL (Commission Nationale de l'Informatique et des Libertés) has also given its agreement for the use of data within the framework of this study.

Availability of data and material: the datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests: the authors declare that they have no competing interests.

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Author's contributions: MD: conceptualization, data acquisition, quality assessment, investigation, data interpretation, statistical and formal analysis, and manuscript drafting. EL: statistical analysis and quality assessment. TMH: study design. JM, MB, KG, DZ, LG, OC, PD, AF: data acquisition, FLPB: thoracic surgery. BC: supervision, study design, methodology, data interpretation and manuscript drafting. All authors provided critical reviews of the manuscript and approved the final version. MD is the guarantor of the content of this manuscript.

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Author's information: BC and MD are intensivist physicians specialized in the study of diaphragmatic function in intensive care patients, in particular using ultrasound.

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Tables

Due to technical limitations, table 1 to 3 is only available as a download in the Supplemental Files section.

Figures

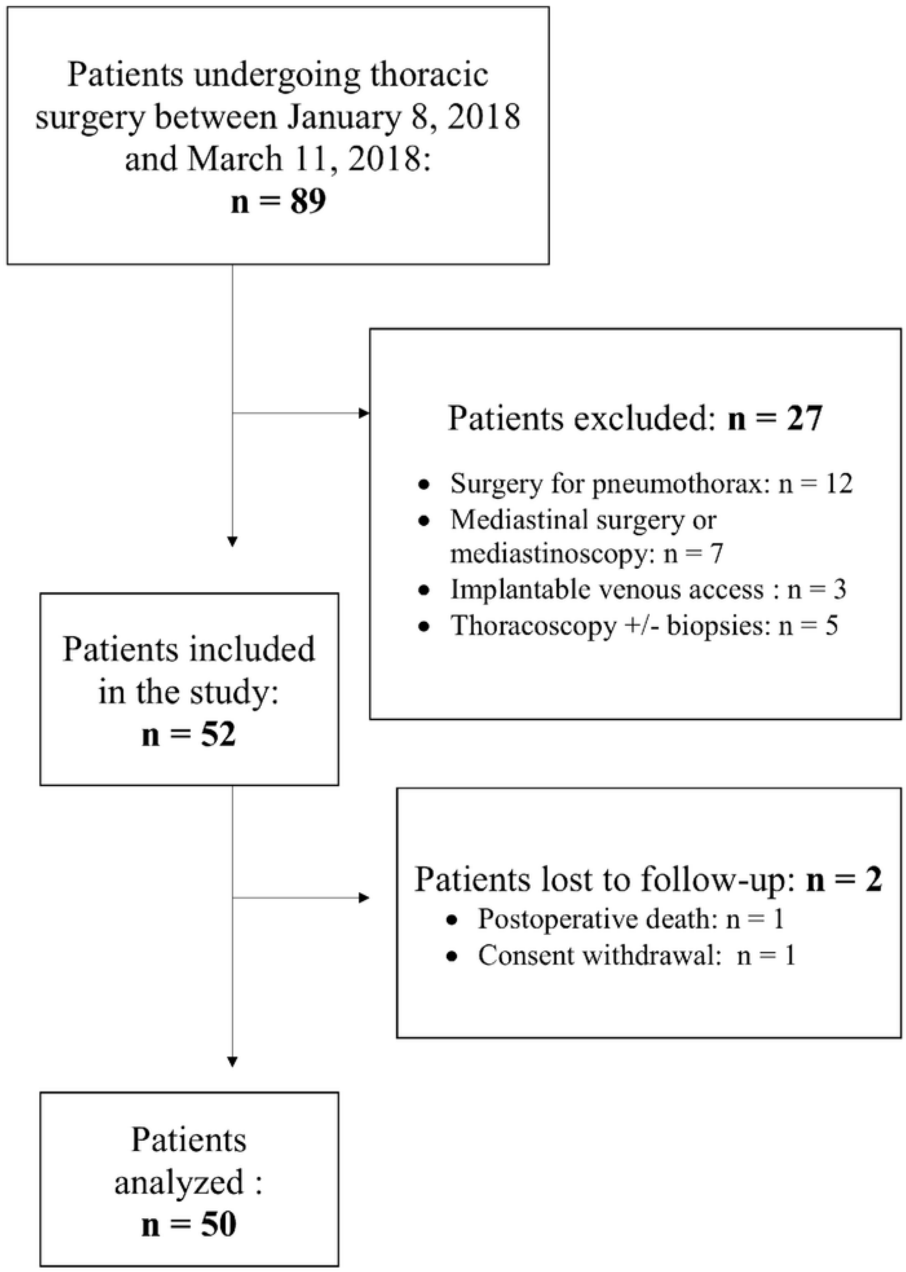

Figure 1

Flow of participants through the study.

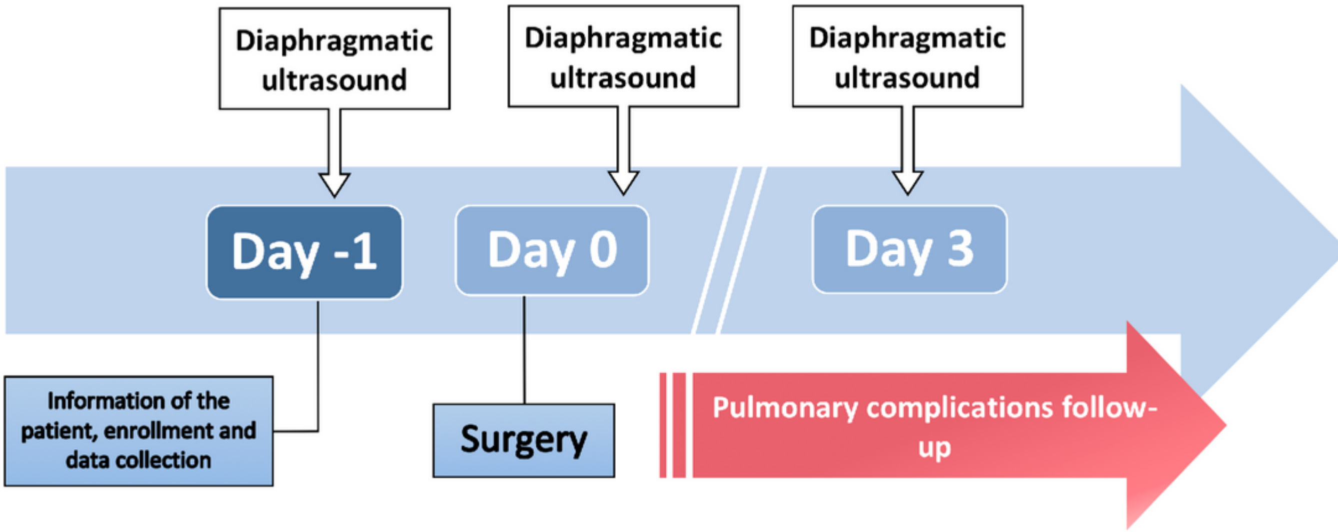

Figure 2

Timeline of the study.

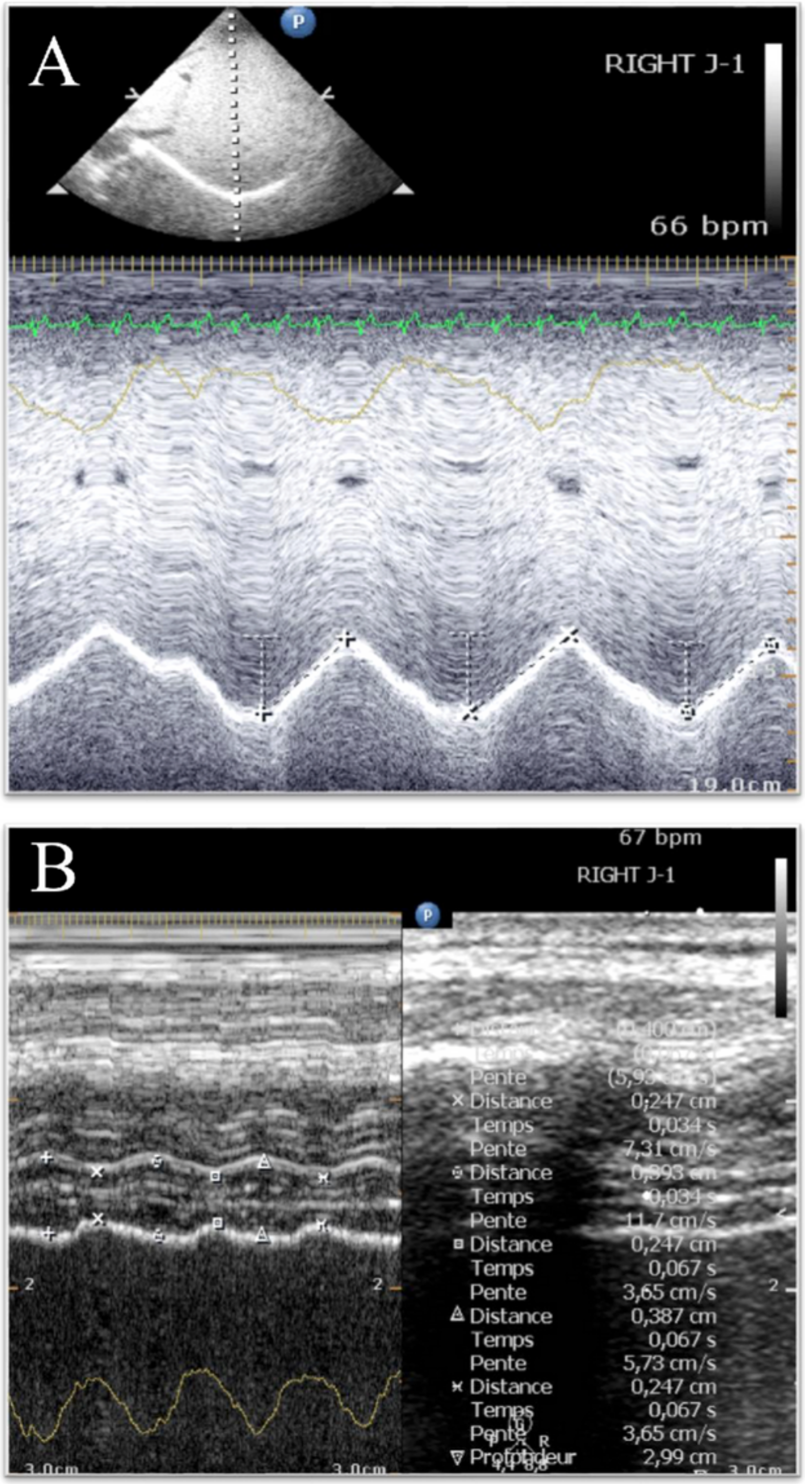

Figure 3

Representative examples of the data acquired in one patient for the measurement of diaphragmatic excursion (panel A) and thickening (panel B) of the right hemi-diaphragm. Measurements were performed using motion-mode (MM). Values were calculated as the average of three consecutive respiratory cycles under conditions of quiet spontaneous breathing.

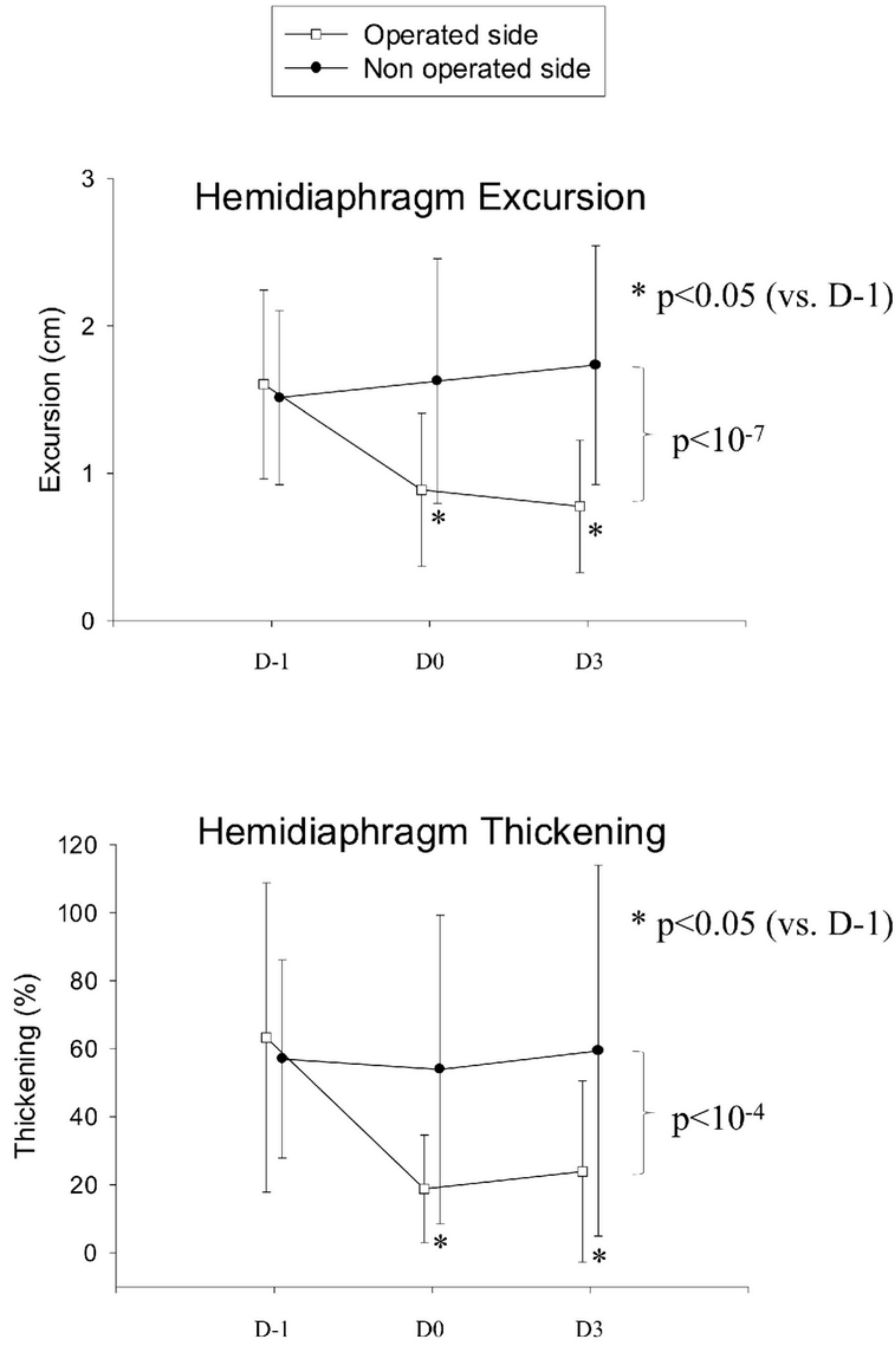

Figure 4

Time-course of hemi-diaphragm excursion (panel A) and thickening (panel B) over the perioperative period: day before surgery (D-1), just after postoperative extubation (D0), and postoperative day 3 (D3).

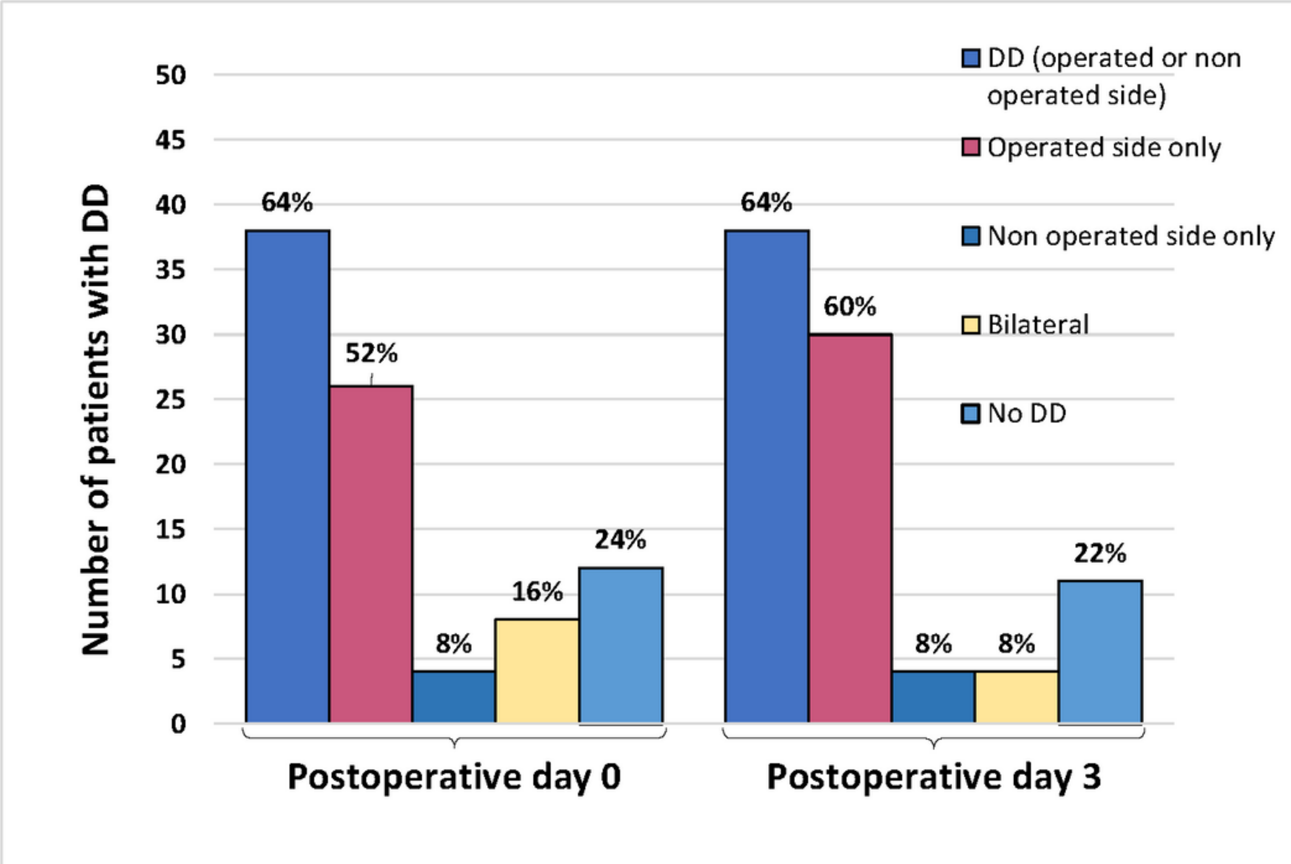

Figure 5

Kinetics of diaphragmatic dysfunction (defined by diaphragmatic excursion below threshold) over the first 3 postoperative days. Numbers and percentages are presented according to the side (operated side, non-operated side, or bilateral) and persistence or appearance of the dysfunction at day 0 and day 3.

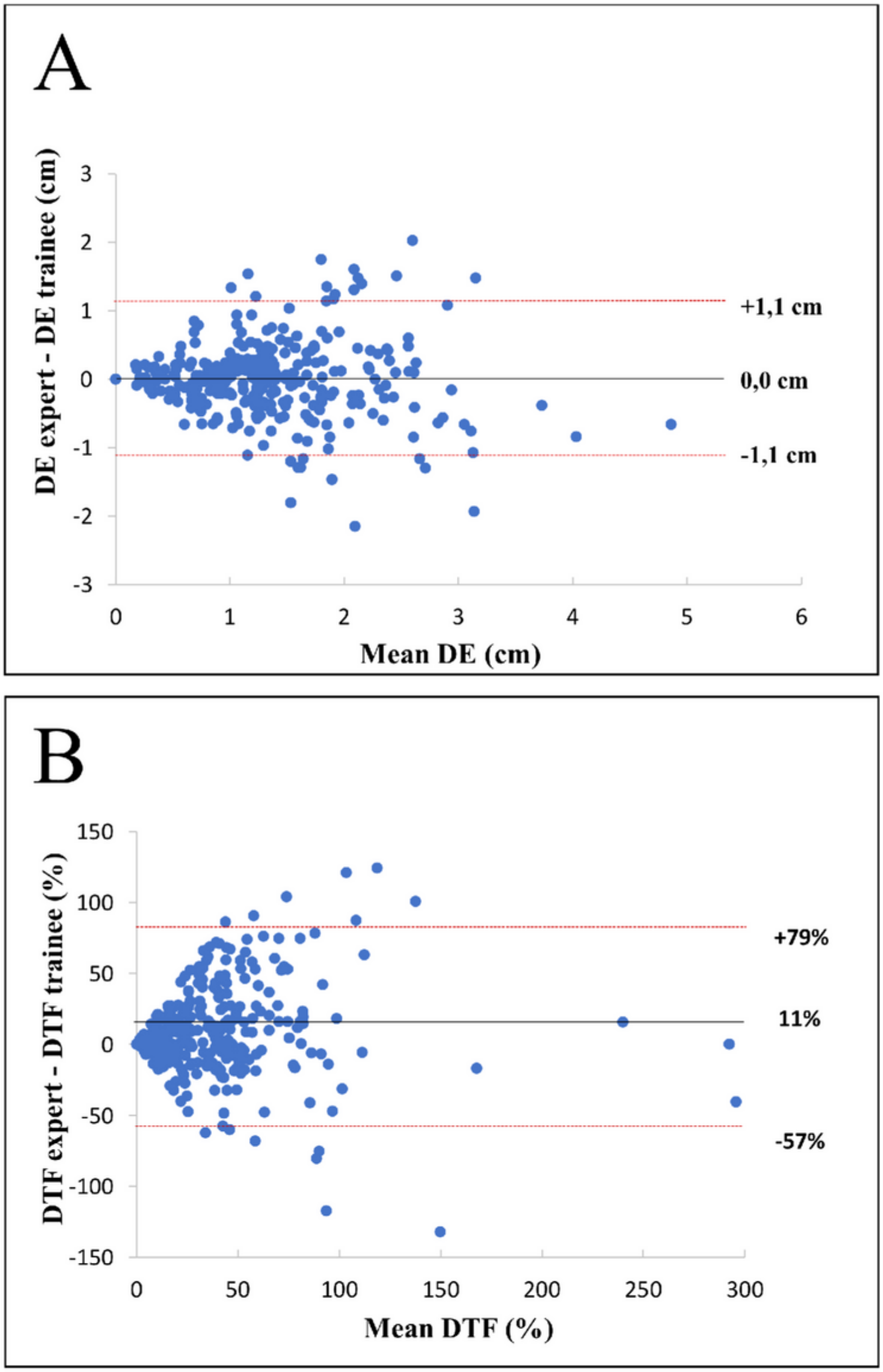

Figure 6

Bland & Altman representations of the agreement between expert and trainee for the measurements of diaphragmatic excursion (DE, panel A) and thickening fraction (DTF, panel B).

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- VisualabstractCC.pdf
- Table1.pdf
- Table2.pdf
- Table3.pdf