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### ► To cite this version:

Kinan El Husseini, Jean-Marc Baste, Anne-Charlotte Bouyeure-Petit, Elodie Lhuillier, Antoine Cuvelier, et al.. Respiratory muscle metabolic activity on PET / CT correlates with obstructive ventilatory defect severity and prognosis in patients undergoing lung cancer surgery. *Respirology*, 2023, 28 (6), pp.551-560. 10.1111/resp.14475 . hal-04175525

**HAL Id: hal-04175525**

**<https://hal.science/hal-04175525v1>**

Submitted on 30 May 2024



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# Respiratory muscle metabolic activity on PET/CT correlates with obstructive ventilatory defect severity and prognosis in patients undergoing lung cancer surgery

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Associate Editor: David Barnes;

Senior Editor: Phan Nguyen

## Abstract

**Background and Objective:** Respiratory muscle activity is increased in patients with chronic respiratory disease. <sup>18</sup>F-FDG-PET/CT can assess respiratory muscle activity. We hypothesized that respiratory muscles metabolism was correlated to lung function impairment and was associated to prognosis in patients undergoing lung cancer surgery based on the research question whether respiratory muscle metabolism quantitatively correlates with the severity of lung function impairment in patients? Does respiratory muscle hypermetabolism have prognostic value?

**Methods:** Patients undergoing <sup>18</sup>F-FDG-PET/CT and pulmonary function tests prior to lung cancer surgery were identified. Maximum Standardized Uptake Value (SUVm) were measured in each respiratory muscle group (sternocleidomastoid, scalene, intercostal, diaphragm), normalized against deltoid SUVm. Respiratory muscle hypermetabolism was defined as SUVm >90th centile in any respiratory muscle group. Clinical outcomes were collected from a prospective cohort.

**Results:** One hundred fifty-six patients were included, mostly male [110 (71%)], 53 (34%) with previous diagnosis of COPD. Respiratory muscle SUVm were: scalene: 1.84 [1.51–2.25], sternocleidomastoid 1.64 [1.34–1.95], intercostal 1.01 [0.84–1.16], diaphragm 1.79 [1.41–2.27]. Tracer uptake was inversely correlated to FEV1 for the scalene ( $r = -0.29$ ,  $p < 0.001$ ) and SCM ( $r = -0.17$ ,  $p = 0.03$ ) respiratory muscle groups and positively correlated to TLC for the scalene ( $r = 0.17$ ,  $p = 0.04$ ). Respiratory muscle hypermetabolism was found in 45 patients (28.8%), who had a lower  $\dot{V}O_2$  max (15.4 [14.2–17.5] vs. 17.2 mL/kg/min [15.2–21.1],  $p = 0.07$ ) and poorer overall survival when adjusting to FEV1% ( $p < 0.01$ ).

**Conclusion:** Our findings show respiratory muscle hypermetabolism is associated with lung function impairment and has prognostic significance. <sup>18</sup>F-FDG/PET-CT should be considered as a tool for assessing respiratory muscle activity and to identify high-risk patients.

## KEYWORDS

lung cancer surgery, lung physiology, metabolic imaging, PET/CT, Positron emission tomography/computed tomography, respiratory drive, respiratory muscles

This study was previously presented at the Annual Congress of the American Thoracic Society (ATS) Congress 2020 and the 'Congrès de Pneumologie en Langue Française' (CPLF) 2021.

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## INTRODUCTION

Chronic respiratory diseases are generally associated with an increased neural drive to breathe (or neural respiratory drive), aiming to overcome the heightened impedance of the respiratory system, which translates to an increase in respiratory muscle activity.<sup>1-3</sup> This increase has been associated with various clinical outcomes, such as the severity of dyspnoea, the risk of readmission or mortality following a COPD exacerbation.<sup>4-6</sup> Respiratory muscle activity evaluation, using surface or invasive sensors, has also demonstrated its usefulness in critically ill patients, for guiding ventilator parameter adjustments or detecting asynchronies.<sup>7,8</sup>

Consequently, the efficient assessment of respiratory mechanics and muscle function, through neurophysiology or imaging techniques, is now considered critical for clinical and research purposes in a variety of conditions, from respiratory diseases to neuromuscular diseases, critically ill patients and sports medicine.<sup>9</sup> Yet, this evaluation is currently made difficult by the complexity of the respiratory muscle system,<sup>10</sup> and is often fragmented, focusing on a single muscle group at a time (i.e., the diaphragm, scalene muscles, intercostal muscles, etc.), or global with all muscles assessed simultaneously. Moreover, advanced techniques of respiratory muscle function evaluation are usually only available in expert centres. Thus, translation of data acquired in research protocols into actual clinical care is rare.<sup>9</sup> Currently, no reliable and accessible approach has been evaluated to assess the contribution of each respiratory muscle group.

Positron emission tomography/computed tomography (PET/CT) could be a useful and available tool to capture this type of data. At rest, locomotor muscles normally accumulate 2-deoxy-2-[<sup>18</sup>F]-fluorodeoxyglucose (<sup>18</sup>F-FDG) in a mild and homogeneous manner, resulting in low enhancement on <sup>18</sup>F-FDG-PET/CT. However, vigorous exercise or the administration of insulin before a PET/CT can cause intense tracer uptake in skeletal muscles.<sup>11</sup> This well-known pitfall justifies that <sup>18</sup>F-FDG PET/CT imaging guidelines require exercise avoidance within 24 h before <sup>18</sup>F-FDG administration. However, respiratory muscle activity can by nature not be avoided. While permanent baseline activity does not usually result in noticeable hypermetabolism on <sup>18</sup>F-FDG PET/CTs in healthy individuals, increases in tracer uptake have been described in the diaphragm, intercostal muscles and scalene muscles of patients with stable chronic obstructive pulmonary disease (COPD),<sup>12,13</sup> a clinical condition known to be associated with increased respiratory muscle activity. Although studies using electrodes and balloon catheters housing pressure probes to measure neural respiratory drive have demonstrated that increased neck and intercostal muscle activity is a staple of respiratory diseases and a physiological response to experimental respiratory challenges,<sup>14-16</sup> the metabolic activity of these muscles has never been quantitatively correlated to lung function before.

For this research, we hypothesized that respiratory muscle metabolism measured on <sup>18</sup>F-FDG PET/CT would

## SUMMARY AT A GLANCE

Respiratory muscle activity quantitatively correlated to FEV1 and TLC in patients undergoing lung cancer surgery. Hypermetabolism was associated with poorer survival and may indicate respiratory fragility. Beyond cancer staging, <sup>18</sup>F-FDG/PET-CT may improve risk stratification of patients by providing valuable information on respiratory muscle metabolism and appears worthy of further investigation.

quantitatively correlate with the severity of lung function impairment in patients. Would it be the case, we also hypothesized that respiratory muscle hypermetabolism (RMH) would have value as prognostic biomarker. To test these hypotheses, we analysed <sup>18</sup>F-FDG respiratory muscle uptake in a cohort of patients undergoing surgery for lung cancer after PET/CT staging and assessed the relation between muscle tracer uptake and respiratory parameters. We also compared the clinical characteristics and outcomes of patients with RMH to those without.

## METHODS

### Study population

We included all consecutive patients over the age of 18 years who had undergone a pre-operative pulmonary function test (PFT), a PET/CT as well as lung resection for lung cancer between March 2013 and March 2018. To identify patients who had undergone <sup>18</sup>F-FDG PET/CT as well as pulmonary function testing (PFT), we cross-referenced a prospective clinical database maintained by our Thoracic Surgery Department of patients receiving lung resection surgery, and a database of patients who underwent PET/CT with a cancer staging indication, during the same period. Patients with indications for lung surgery other than local-stage lung cancer were excluded, for the sake of homogeneity. Two patients with a prior diagnosis of unilateral diaphragm paralysis were secondarily excluded, to avoid false positives resulting from an overloading of the neck muscles.

### <sup>18</sup>F-FDG PET/CTs image acquisition and analysis

All <sup>18</sup>F-FDG PET/CTs were performed in the Nuclear Medicine department of Centre Henri Becquerel. Patients were asked to fast for at least 6 h before the time of <sup>18</sup>F-FDG administration to ensure that the serum glucose and serum insulin levels were low. Preparation protocols

and procedures followed EANM procedure guidelines.<sup>17</sup> Pre-operative <sup>18</sup>F-FDG PET/CTs images were analysed as follows: using uncorrected PET reconstructions, maximum Standardized Uptake Values (SUV<sub>m</sub>) for all respiratory muscles were recorded, bilaterally in the case of the sternocleidomastoid, scalene, and intercostal muscles, choosing the maximum value, or as a single measure in the case of the diaphragm. To normalize respiratory muscle SUV<sub>m</sub>, deltoid muscle was used as a reference peripheral skeletal muscle, not involved in respiration processes nor locomotion. Deltoid muscles also show little morphological alteration in COPD patients compared with control individuals, allowing for a straightforward measurement of tracer uptake.<sup>18</sup> In each respiratory muscle group, hypermetabolism was defined as a corrected tracer uptake above the 90th centile of recorded values in all patients in this muscle group. Patients with respiratory muscle hypermetabolism (RMH) were defined as having hypermetabolism in at least one respiratory muscle group.

## Data collection

Clinical data were extracted from the institutional electronic health record systems, including included demographic variables, anthropometry (height, weight), co-morbid conditions, pulmonary function tests (PFT) and pre-operative cardiopulmonary exercise testing (CPET). Using the surgical prospective database,<sup>19</sup> we collected surgical intervention details, patient characteristics including Charlson Comorbidity Score (CCS, measuring burden of disease and predictive of 1-year mortality risk),<sup>20</sup> peri-operative outcomes, hospital stay durations and follow-up data.

## Statistical analysis

Quantitative variables are presented as median [interquartile range], and qualitative variables as absolute and relative frequencies. Comparisons of quantitative and qualitative variables were made using Mann–Whitney test and Chi-square or Fisher exact test, respectively. Patients with RMH were compared to patients without RMH regarding clinical characteristics and peri-operative outcomes. Correlations between quantitative variables across all patients included were performed using Spearman non-parametric ranked test. All tests were two-sided, with  $p = 0.05$  indicating statistical significance. Adjustment for multiple comparisons was performed using the Benjamini-Hochberg procedure, with an acceptable false discovery rate threshold set at 20% on account of the exploratory nature of the analysis. Cox proportional hazard models were used for survival analysis. Predictor variables were chosen according to clinical relevance while taking into account variable homogeneity across groups. Adjusted Kaplan–Meier survival curves were constructed based on results from the Cox models and compared using Log-rank test. All statistical

analyses were performed using the R environment (R v4.2.0).

## RESULTS

### Demographic characteristics

One-hundred-and-fifty-six patients fulfilled criteria for inclusion (Figure S1 in the Supporting Information). Median age was 64 years [58–71], and 110 (70.9%) patients were male, with a pre-existing diagnosis of respiratory disease in 72 (46.2%) cases. As per study design, all patients underwent pre-operative <sup>18</sup>F-FDG-PET/CT and PFT, with a FEV1 (forced expiratory volume in one second) of 84.0% of predicted value (% pred.) [67.8–97.0] and KCO (carbon monoxide transfer coefficient) of 74.1% pred. [61.0–87.0]. Exercise testing was performed in 53 (34.0%) patients, with a VO<sub>2</sub> max of 16.3 mL/kg/min [14.6–19.7] (Table 1).

### Surgical management

All 156 patients underwent surgery, mainly using minimally invasive surgical approaches [116 (74%)], with mostly lobar resections [119 (76%)] followed by pneumonectomies [13 (8%)]. Neoplasm histology was adenocarcinoma in 98 (63%) patients and squamous cell carcinoma in 48 (31%) cases. Seventy-seven (49%) patients experienced grade  $\geq 1$  complications following surgery, with respiratory complications in 52 (34%) patients (Table S1 in the Supporting Information).

### Respiratory muscle hypermetabolism

Median respiratory muscle SUV<sub>m</sub>, normalized against deltoid tracer uptake, were: 1.84 [1.51–2.25] for the scalene muscle group, 1.64 [1.34–1.95] for the sternocleidomastoid muscle group, 1.01 [0.84–1.16] in the intercostal muscles and 1.79 [1.41–2.27] for the diaphragm. A density plot of the distribution of normalized SUV<sub>m</sub> for all muscle groups is presented in Figure 1. A total of 45 patients (29%) had pre-operative RMH.

### Comparison of patient characteristics

Patients with RMH were more comorbid (CCS of 6 [4–7] versus 5 [4–6],  $p = 0.028$ ), with a higher prevalence of arterial hypertension as well as obliterating arteriopathy of the lower limbs. VO<sub>2</sub> max was lower in patients with RMH compared to those without: 15.1 [14.1–17.5] versus 17.2 [15.2–21.1] mL/kg/min, respectively,  $p = 0.074$  (among 53 patients who underwent CPET, 19/53 [36%] and 34/53 [64%] were in the RMH and non-RMH groups, respectively). Comparison of population characteristics according

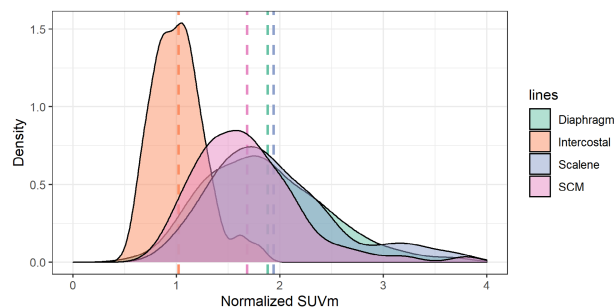
**TABLE 1** Study population characteristics.

| Variable   | Total population (n = 156) |
|--|----------------------------|
| Age at surgery, years                                | 64 [58–71]                 |
| BMI, kg/m <sup>2</sup>                               | 24.9 [22.3–29.6]           |
| Gender, n (%)  |                            |
| Male   | 110 (71)                   |
| Female   | 46 (29)                    |
| Smoking status                                       |                            |
| Non-smoker, n (%)                                    | 9 (6)                      |
| Active smoker, n (%)                                 | 76 (48)                    |
| Previous smoker, n (%)                               | 73 (46)                    |
| Tobacco exposure, pack-year                          | 40 [25–50]                 |
| Pre-existing diagnosis of respiratory disease, n (%) |                            |
| COPD   | 53 (34)                    |
| Obstructive sleep apnoea                             | 15 (10)                    |
| Other comorbid conditions, n (%)                     |                            |
| Arterial hypertension                                | 85 (53)                    |
| Diabetes   | 29 (19)                    |
| Obliterating arteriopathy of the lower limbs         | 25 (16)                    |
| Hyperlipemia   | 58 (37)                    |
| Myocardial infarction                                | 23 (15)                    |
| Past malignancy history                              | 30 (19)                    |
| Charlson comorbidity index, n (%)                    |                            |
| 1–3  | 68 (44)                    |
| 4–6  | 71 (46)                    |
| > 6  | 17 (10)                    |
| Performance status, n (%)                            |                            |
| 0  | 79 (51)                    |
| 1  | 64 (41)                    |
| 2–3  | 13 (8)                     |
| Pulmonary function tests                             |                            |
| FEV1, L  | 2.2 [1.8–2.7]              |
| FEV1, % predicted                                    | 84.0 [67.8–97.0]           |
| FVC, L   | 3.2 [2.7–3.9]              |
| FVC, % predicted                                     | 95.0 [81.2–108.5]          |
| TLC, % predicted                                     | 110.0 [97.6–121.2]         |
| FEV1/FVC <0.7, n (%)                                 | 67 (48.0)                  |
| KCO, % predicted (n = 138/158, 87.3%)                | 74.1 [61.0–87.0]           |
| Exercise testing (n = 53/156, 34.0%)                 |                            |
| Pre-operative VO <sub>2</sub> max, mL/kg/min         | 16.3 [14.6–20.1]           |

Note: Previous smoker: smoked more than 100 cigarettes in their life with smoking cessation >1 year.

Abbreviations: BMI, body mass index; COPD, chronic obstructive pulmonary disease; FEV1, forced expiratory volume in one second; FVC, forced vital capacity; TLC, total lung capacity; KCO, carbon monoxide diffusion coefficient; VO<sub>2</sub> max, maximal oxygen uptake.

to RMH status are presented in Table 2. Information on cancer histology, staging (pT, pN) and surgical treatment strategy are presented in Table S1 in the Supporting



**FIGURE 1** Density plot showing the smoothed distributions of SUVm measurement for each respiratory muscle group, normalized on deltoid SUVm. Vertical dashed lines represent mean SUVm for each group. SCM, sternocleidomastoid muscles; SUVm, maximum Standard Uptake Value. Vertical axis: probability density function. The probability of a value being between two points on the horizontal axis is the total shaded area of the curve between these two points.

Information. There was no significant difference between RMH and non-RMH patients, aside for surgical intervention duration (Non-RMH: 155 min [120–180] versus RMH 180 min [150–200],  $p = 0.013$ ).

### Correlation of respiratory muscle tracer uptake to functional variables

FEV1 (L) was inversely correlated to normalized SUVm in the scalene ( $R = -0.29 [-0.43; -0.14]$ ,  $p < 0.001$ ) and sternocleidomastoid ( $R = -0.17 [-0.33; -0.01]$ ,  $p = 0.029$ ) muscle groups, whereas TLC (L) was only positively correlated to scalene normalized SUVm ( $R = 0.17 [0.00; 0.34]$ ,  $p = 0.04$ ), but not to other muscle groups SUVm (Figure 2). Intercostal muscle normalized SUVm did not correlate to any respiratory variables. An additional post-hoc analysis limited to patients with a pre-established diagnosis of COPD found an even stronger correlation between FEV1 and scalene normalized SUVm ( $R = -0.45 [-0.65; -0.20]$ ,  $p < 0.001$ ; Figure S2 in the Supporting Information). There was no significant correlation in patients with OSA (Figure S3 in the Supporting Information).

### Follow-up and survival

Median follow-up was 20.7 months in the study population. One-year mortality was 15.5% in the RMH group compared to 8.1% in the non-RMH group, comparison of survival curves found a hazard ratio of 1.35 [0.66–2.75] for death in the RMH group ( $p = 0.42$ ). (Figure S4 in the Supporting Information). To test whether RMH presence could be a prognostic factor for patients, nested Cox proportional hazards models were constructed to identify predictors of postoperative survival. Predictor variables selected were: pre-operative Charlson Comorbidity Score (CCS), RMH (absence selected as baseline) and baseline FEV1%

**TABLE 2** Comparison of patients with and without respiratory muscle hypermetabolism.

| Variable                                     | RMH ( <i>n</i> = 45) | No RMH ( <i>n</i> = 111) | <i>p</i> -value  | ( <i>i/m</i> )Q |
|--|----------------------|--------------------------|------------------|-----------------|
| Age at surgery, years                        | 64 [57;70]           | 67 [60;71]               | 0.286            | 0.114           |
| BMI, kg/m <sup>2</sup>                       | 24.9 [22.1;30.2]     | 24.2 [22.8;27.8]         | 0.848            | 0.175           |
| Female gender, <i>n</i> (%)                  | 10 (22)              | 35 (32)                  | 0.205            | 0.078           |
| Tobacco exposure, pack-year                  | 40 [30;50]           | 40 [20;50]               | 0.241            | 0.105           |
| Underlying respiratory disease, <i>n</i> (%) |                      |                          |                  |                 |
| COPD   | 17 (38)              | 36 (32)                  | 0.523            | 0.149           |
| Obstructive sleep apnoea                     | 5 (11)               | 10 (9)                   | 0.686            | 0.158           |
| Any respiratory disease                      | 21 (47)              | 44 (40)                  | 0.420            | 0.123           |
| Other comorbid conditions, <i>n</i> (%)      |                      |                          |                  |                 |
| Arterial hypertension                        | 30 (67)              | 53 (48)                  | <b>0.031</b>     | 0.035           |
| Diabetes                                     | 10 (22)              | 19 (17)                  | 0.458            | 0.132           |
| Obliterating arteriopathy of the lower limbs | 15 (33)              | 10 (9)                   | <b>&lt;0.001</b> | 0.018           |
| Myocardial infarction                        | 9 (20)               | 14 (13)                  | 0.238            | 0.096           |
| Charlson comorbidity index                   | 6 [4;7]              | 5 [4;6]                  | <b>0.028</b>     | 0.029           |
| Total hospital stay, days                    | 8 [6;13]             | 7 [5;10]                 | 0.103            | 0.053           |
| Pulmonary function tests                     |                      |                          |                  |                 |
| FEV1, % predicted                            | 80.0 [61.0;98.0]     | 84.0 [70.5;96.0]         | 0.213            | 0.088           |
| FVC, % predicted                             | 95.0 [77.0;109.2]    | 95.0 [85.5;108.5]        | 0.767            | 0.184           |
| TLC, % predicted                             | 110.5 [102;121.2]    | 110.0 [102.0;120.9]      | 0.517            | 0.140           |
| FEV1/FVC <0.7, <i>n</i> (%)                  | 22 (49)              | 45 (41)                  | 0.133            | 0.061           |
| KCO, % predicted                             | 76.0 [62.8;87.3]     | 73.0 [61.0;86.0]         | 0.700            | 0.167           |
| Exercise testing, <i>n</i> (%)               | 19 (42)              | 34 (31)                  | 0.166            | 0.070           |
| VO <sub>2</sub> max, mL/kg/min               | 15.4 [14.2;17.5]     | 17.2 [15.2;21.1]         | 0.074            | 0.342           |

Abbreviations: BMI, body mass index; COPD, chronic obstructive pulmonary disease; FEV1, forced expiratory volume in one second; FVC, forced vital capacity; (*i/m*)Q, Benjamini–Hochberg critical value, with a chosen false discovery rate of 20%; IQR, inter-quartile range; KCO, carbon monoxide diffusion coefficient; RMH, respiratory muscle hypermetabolism; TLC, total lung capacity; VO<sub>2</sub> max, maximal oxygen uptake. Bolded *p*-values indicate statistical significance after Benjamini–Hochberg correction.

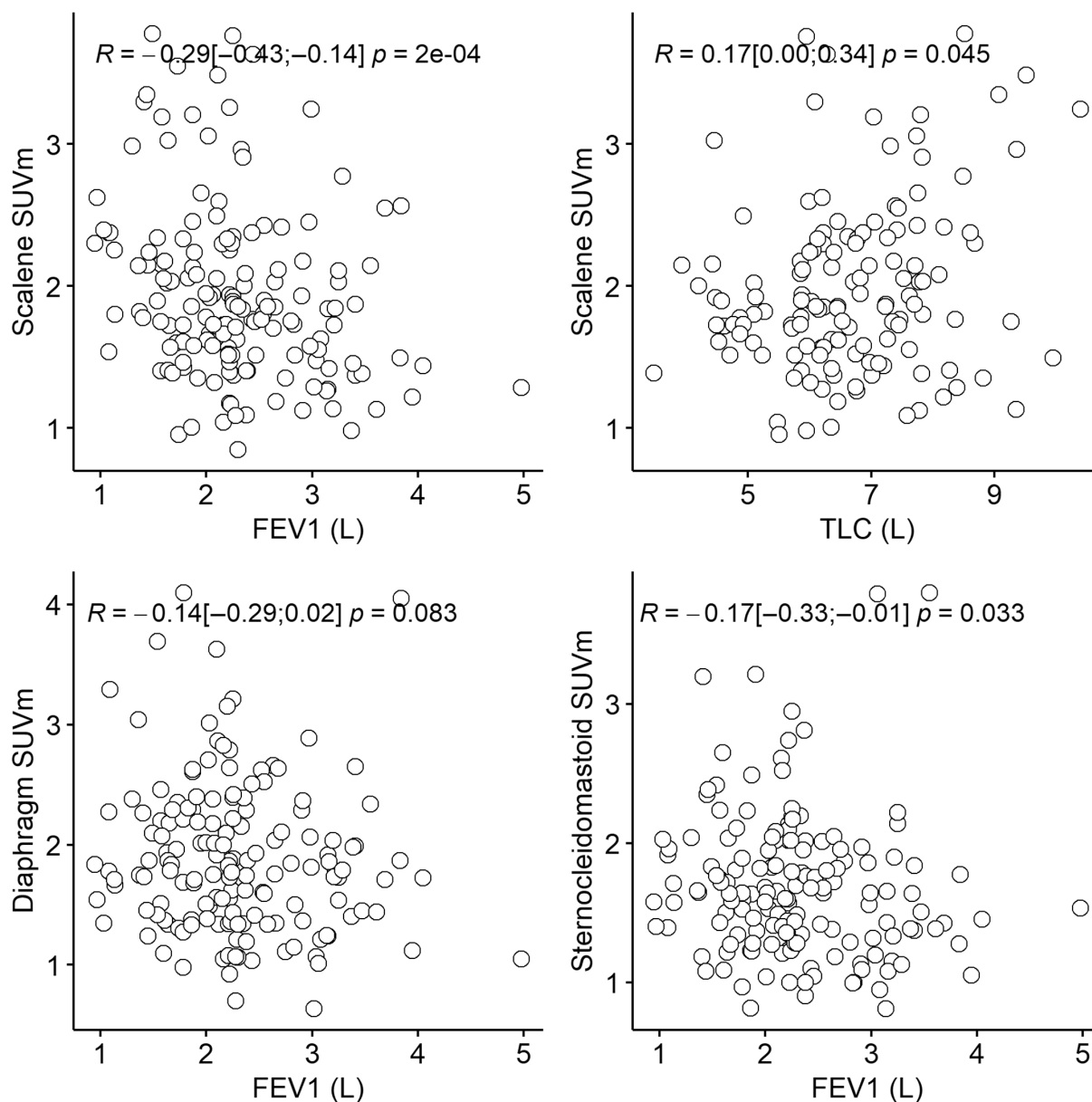
(% predicted); considering the correlation between FEV1 and respiratory muscle metabolic activity, the interaction between RMH and FEV1(%) as covariates was also taken into account. Cancer-related variables were not selected considering their homogeneity across groups (Table S1 in the Supporting Information). Table 3 describes the three nested Cox PH models constructed and reports their comparison. CCS contributed significantly to survival in all models, but the model including the RMH and FEV1% covariates as predictors was found to be more efficient compared to a model based on CCS alone (*p* = 0.006). Illustratively, Figure 3 presents the Kaplan–Meier curves for four groups according to FEV1 (normal/abnormal) and RMH (absent/present). Proportional hazards assumption was assessed graphically by testing the correlation of scaled Schoenfeld residuals with time (Figure S5 in the Supporting Information).

## DISCUSSION

To our knowledge, this is the first study to quantitatively assess respiratory muscle metabolic activity on <sup>18</sup>F-FDG-PET/CT, its correlation to lung function variables and its putative contribution as a prognostic biomarker. In this

study, higher respiratory muscle SUV<sub>m</sub> weakly but significantly correlated to decreased FEV1 and increased TLC in different muscle groups, while patients with RMH had significantly poorer prognosis when taking into account FEV1 (%) values.

As a tracer, <sup>18</sup>F-FDG displays the same whole-body distribution as glucose, entering cells via the GLUT transporters.<sup>21</sup> This wide biodistribution grants high sensitivity to <sup>18</sup>F-FDG-PET/CT for the detection of malignancies as cancer cells display increased glucose metabolism,<sup>22</sup> somewhat offset by a low specificity, as infectious, inflammatory processes or even laboring muscles—tissues with high glucose consumption—appear as <sup>18</sup>F-FDG-avid on PET/CT. Respiratory muscle hypermetabolism in particular is now recognized as a common incidental finding on <sup>18</sup>F-FDG-PET/CT. In 1164 patients undergoing <sup>18</sup>F-FDG-PET/CT for cancer staging, Jackson et al. demonstrated that 12.5% of patients had unusual tracer uptake by respiratory muscles, mostly affecting the scalene and sternocleidomastoid muscle groups.<sup>23</sup> In another cohort of 96 patients undergoing <sup>18</sup>F-FDG-PET/CT, Jacene et al. demonstrated a higher semi-quantitative respiratory muscle tracer uptake score in 50% of smokers compared to 9% of non-smokers.<sup>24</sup> Another retrospective study of 411 all-comers undergoing <sup>18</sup>F-FDG-PET/CT also showed



**FIGURE 2** Scatter-plots of normalized respiratory muscle tracer uptake against respiratory variables in different muscle groups, across the whole study population. (A) Scalene SUVm against FEV1. (B) Scalene SUVm against TLC. (C) Diaphragm SUVm against FEV1. (D) Sternocleidomastoid SUVm against FEV1. All SUVm values were normalized against deltoid tracer uptake. FEV1 was selected for its value in grading the severity of obstructive respiratory disease; TLC was selected for its value in assessing lung hyperinflation. FEV1, forced expiratory volume in one second;  $p$ ,  $p$ -value;  $R$ , Spearman Rho statistic; SUVm, maximum standard uptake value; TLC, total lung capacity.

that increased scalene muscle tracer uptake (compared to neighbouring adipose tissue) was present in 36% of patients, with mostly bilateral, symmetrical and linear signals.<sup>25</sup> According to previous reports,<sup>12,25</sup> approximately one third of cancer patients referred for oncologic  $^{18}\text{F}$ -FDG-PET/CT are found to have RMH, similar to the 29.7% in our study.

Other studies have specifically utilized  $^{18}\text{F}$ -FDG-PET/CT to assess respiratory muscle use in the context of COPD, a common, progressive, obstructive respiratory disease.<sup>26</sup> The usual respiratory mechanics alterations of this condition lead to an increase in respiratory muscle use in these patients.<sup>27–29</sup> Aydin et al. demonstrated a higher prevalence

of thoracic and abdominal muscle  $^{18}\text{F}$ -FDG uptake,<sup>30</sup> while Osman et al. reciprocated these results, showing that abnormal RMH significantly correlated with COPD severity.<sup>13</sup> Similarly, Basu et al. described intercostal tracer uptake in patients with COPD, asthma, interstitial lung disease and pulmonary embolism.<sup>31</sup> Finally, in a recent retrospective study on 33 patients with COPD, Kothekar et al. demonstrated a correlation of qualitative respiratory muscle metabolic activity with GOLD disease severity grade (dependent on FEV1).<sup>12</sup> Our study therefore coheres with the published literature. It complements current knowledge by providing a quantitative aspect that has not been examined before.

**TABLE 3** Description and comparison of nested Cox proportional hazards models predicting patient survival.

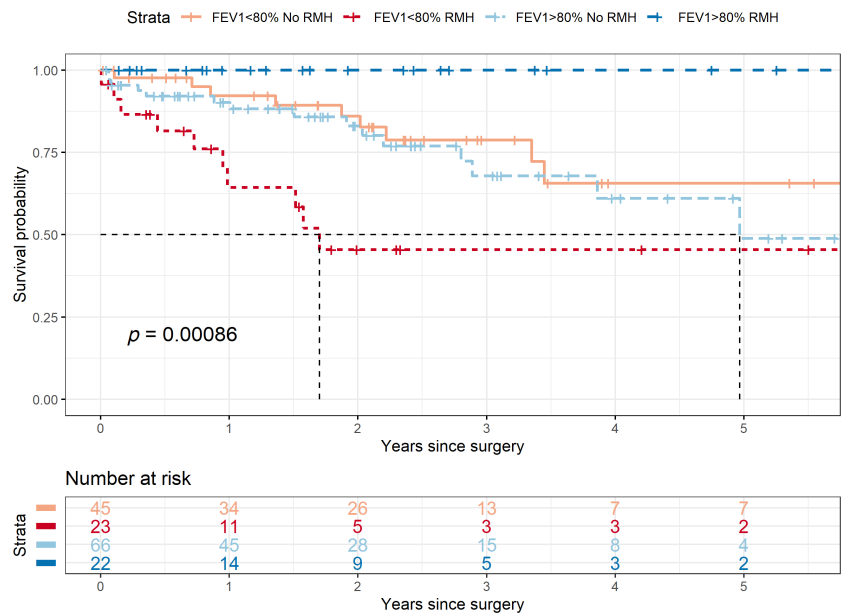
| Characteristic | Model A<br><i>Survival ~ CCS</i> |            |                  | Model B<br><i>Survival ~ CCS + FEV1%</i> |             |                  | Model C<br><i>Survival ~ CCS + FEV1%*RMH</i> |              |                  |
|----------------|----------------------------------|------------|------------------|--|-------------|------------------|--|--------------|------------------|
|                | log(HR)                          | 95% CI     | <i>p</i> -value  | log(HR)                                  | 95% CI      | <i>p</i> -value  | log(HR)                                      | 95% CI       | <i>p</i> -value  |
| CCS            | 0.30                             | 0.16, 0.45 | <b>&lt;0.001</b> | 0.29                                     | 0.15, 0.44  | <b>&lt;0.001</b> | 0.32   | 0.18, 0.47   | <b>&lt;0.001</b> |
| FEV1% (%pred)  |                                  |            |                  | -0.01                                    | -0.02, 0.01 | 0.2              | 0.01   | -0.01, 0.02  | 0.6              |
| RMH+ (present) |                                  |            |                  |  |             |                  | 4.4  | 1.5, 7.2     | <b>0.006</b>     |
| FEV1%*RMH+     |                                  |            |                  |  |             |                  | -0.06  | -0.10, -0.02 | <b>0.006</b>     |

| ANOVA                      | Model A | Model B | Model C      |
|----------------------------|---------|---------|--------------|
| LLR                        | -144.01 | -143.40 | -138.41      |
| Chi <sup>2</sup> statistic | -       | 1.2240  | 9.9776       |
| Df                         | -       | 1       | 2            |
| <i>p</i> -value            | -       | 0.270   | <b>0.006</b> |

Abbreviations: CCS, Charlson Comorbidity Score; CI, confidence interval; Df, degrees of freedom; HR, hazard ratio; LLR, log-likelihood ratio; *p*-value; FEV1%, forced expiratory volume in one second, relative value; RMH, respiratory muscle hypermetabolism. Bolded *p*-values indicate statistical significance.

**FIGURE 3** Kaplan–Meier survival curves from the time of surgery according to FEV1% value (normal or abnormal) and RMH (presence or absence). FEV1%, forced expiratory volume in one second, percent of predicted value; RMH, respiratory muscle hypermetabolism. Surgical procedures were lung resections for local-stage non-small-cell lung cancer, with similar oncological prognosis across the study population.



Of notice, beyond a link between the intensity of respiratory muscle <sup>18</sup>F-FDG uptake and FEV1, we evidenced a link between respiratory muscle metabolism and TLC, a measure of hyperinflation,<sup>32</sup> a phenomenon known to be a major determinant of respiratory muscle function in COPD.<sup>33</sup> Finally, in our study, 55 patients (34.8%) underwent cardio-pulmonary exercise testing (CPET), with lower VO<sub>2</sub> max values in those with RMH. CPET has now been integrated to pretreatment risk assessment algorithms<sup>34</sup> and helps guide respiratory rehabilitation programs worldwide.<sup>35</sup> However, this test still suffers from a lack of accessibility in some centres due to resource limitations,<sup>9,36</sup> and poses the risk of over-estimating risks in up to 30% of patients who cannot provide the necessary maximum effort to ensure validity of VO<sub>2</sub> measurements.<sup>37</sup> Additional tools to identify patients with respiratory fragility who could potentially

benefit from rehabilitation programs are therefore needed.<sup>38,39</sup> <sup>18</sup>F-FDG-PET/CT is in a unique position in this regard, owing to its growing ubiquity in the tumour staging workups of patients with lung cancer.

Overall, our observations lend support to the idea that <sup>18</sup>F-FDG-PET/CT may be worth investigating as a means to evaluate respiratory muscle activity globally and quantitatively. As a technique already in use for assessing skeletal muscles in other applications,<sup>40,41</sup> <sup>18</sup>F-FDG-PET/CT could give access to new information, currently inaccessible in the clinical setting, namely a description of the recruitment of the various respiratory muscle groups and of the relative intensities of their recruitment. This could be of particular interest to assess the efficacy of therapeutic interventions aiming at reducing respiratory muscle activity, including noninvasive ventilatory support, an often-difficult clinical



challenge.  $^{18}\text{F}$ -FDG PET/CT could also be used to revisit the contribution of respiratory muscles to bodily energy expenditure in chronic respiratory diseases, the excess of which can theoretically be involved in the wasting process observed in these diseases,<sup>42</sup> and the reduction of which can be a non-respiratory benefit of ventilatory support.<sup>43</sup>

An interesting aspect of our results was the preponderant importance of scalene hypermetabolism in patients with lung function impairment compared to other respiratory muscle groups. This coheres with previous studies which demonstrated increased scalene activity in the neck of patients with COPD or in healthy subjects undergoing respiratory challenge, even while sternocleidomastoid muscles remained silent.<sup>14</sup> In addition, numerous other studies have since shown that neck muscle activation is correlated to clinical outcomes, such as dyspnoea severity or sleep quality.<sup>16</sup> This supports the validity of our findings regarding the importance of this respiratory muscle group.

The main limitations of our study are its retrospective and single-centre nature and the absence of consensual baseline values for respiratory muscle SUV<sub>m</sub> on  $^{18}\text{F}$ -FDG-PET, which prevented us from defining RMH according to the general population. Also, reproducibility of measurements could not be assessed, as images were reviewed by a single investigator. Although respiratory muscle SUV<sub>m</sub> significantly correlated with PFT values in physiologically coherent directions, coefficients were weak at best. This highlights the fact that baseline respiratory function (generally measured weeks if not months before PET/CT in our study) does not fully explain the variance of respiratory muscle SUV<sub>m</sub>. This could be further explored with same-day tests in another study protocol. Finally, intercostal muscles stood out against other respiratory muscles, with lower metabolic activity, not correlating to respiratory function. This could be due to the relative difficulty of measuring single intercostal SUV<sub>m</sub> values compared to the other muscle groups, owing to their small axial surface area relative to the spatial resolution of  $^{18}\text{F}$ -FDG-PET/CT, which led to the capture of both inspiratory and expiratory intercostal muscle activity.

In conclusion, our study indicates that  $^{18}\text{F}$ -FDG-PET/CT can be used as a respiratory muscle evaluation tool pending further investigation. Our findings suggest a pathophysiological link between respiratory muscle metabolic activity on  $^{18}\text{F}$ -FDG-PET/CT and pulmonary function but also its potential as a stratification tool for patient undergoing lung cancer surgery. Future prospective studies should be conducted focusing on patients with respiratory diseases to establish specific respiratory muscle metabolic activity patterns and to confirm its prognostic value.

#### HUMAN ETHICS APPROVAL DECLARATION

The study protocol was approved by an institutional review board at Centre Henri Becquerel and validated by an ad-hoc ethics committee at Rouen University Hospital. Epithor is a nationwide prospectively cohort, operating since 2003, and registered with the National Commission for Data Protection (CNIL N°809833). All patients gave consent to be

included in the Epithor cohort. All recorded data were anonymized.

#### AUTHOR CONTRIBUTION

**Kinan El Hussein:** Conceptualization (equal); data curation (lead); formal analysis (lead); investigation (lead); visualization (lead); writing – original draft (lead); writing – review and editing (equal). **Jean-Marc Baste:** Conceptualization (supporting); methodology (equal); resources (equal); writing – review and editing (equal). **Anne-Charlotte Boueyre-Petit:** Conceptualization (supporting); methodology (equal); resources (equal); writing – review and editing (equal). **Elodie Lhuillier:** Conceptualization (supporting); methodology (equal); resources (equal); writing – review and editing (equal). **Antoine Cuvelier:** Conceptualization (supporting); methodology (equal); project administration (equal); resources (equal); writing – review and editing (equal). **Pierre Decazes:** Conceptualization (supporting); methodology (equal); resources (equal); writing – review and editing (equal). **Pierre Vera:** Conceptualization (supporting); methodology (equal); resources (equal); writing – review and editing (equal). **Thomas Similowski:** Formal analysis (equal); supervision (supporting); writing – review and editing (equal). **Maxime Patout:** Conceptualization (equal); formal analysis (equal); methodology (lead); project administration (equal); supervision (lead); writing – review and editing (equal).

#### ACKNOWLEDGEMENTS

This research received no specific funding from any entity in the public, private or not-for-profit sectors.

#### CONFLICTS OF INTEREST STATEMENT

Thomas Similowski reports personal fees for consulting and teaching activities from ADEP Assistance, AstraZeneca France, Chiesi France, KPL consulting, Lungpacer Inc., OSO-AI, TEVA France and Vitalaire. Maxime Patout reports grants or contracts from Fisher & Paykel & Resmed, consulting fees from Philips Respironics, Resmed & GSK, honoraria for presentations for Philips Respironics, Resmed, Fisher & Paykel, SOS Oxygène, Asten Santé, Air Liquide Médical, Antadir, board participation for Resmed & Philips Respironics, stock options for Kernel Biomedical, receipt of services from Philips Respironics, Resmed and Fisher & Paykel. Maxime Patout and Elodie Lhuillier report support for attending meetings from SOS Oxygène & ASTEN Santé. Kinan El Hussein, Jean-Marc Baste, Anne-Charlotte Boueyre-Petit, Antoine Cuvelier, Pierre Decazes and Pierre Vera report no conflict of interest, perceived or otherwise.

#### DATA AVAILABILITY STATEMENT

Data used to perform this study is available upon request to the corresponding author.

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## SUPPORTING INFORMATION

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**How to cite this article:** El Husseini K, Baste J-M, Bouyeure-Petit A-C, Lhuillier E, Cuvelier A, Decazes P, et al. Respiratory muscle metabolic activity on PET/CT correlates with obstructive ventilatory defect severity and prognosis in patients undergoing lung cancer surgery. *Respirology*. 2023;28(6):551–60. <https://doi.org/10.1111/resp.14475>