



HAL
open science

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

Kinan El Husseini, Jean-Marc Baste, Anne-Charlotte Bouyeure-Petit, Elodie Lhuillier, Antoine Cuvelier, Pierre Decazes, Pierre Vera, Thomas Similowski, Maxime Patout

► 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-04175525>

Submitted on 30 May 2024



HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.



Distributed under a Creative Commons Attribution 4.0 International License

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

Kinan El Hussein^{1,2,3}  | Jean-Marc Baste⁴ | Anne-Charlotte Bouyeure-Petit⁵ |
 Elodie Lhuillier⁶ | Antoine Cuvelier^{1,7} | Pierre Decazes⁵ | Pierre Vera⁵ |
 Thomas Similowski^{8,9} | Maxime Patout^{9,10} 

¹Service de Pneumologie, Oncologie Thoracique et Soins Intensifs Respiratoires, CHU Rouen, Rouen, France

²Inserm UMRS1152 Physiopathologie et épidémiologie des maladies respiratoires, Université Paris-Cité, Paris, France

³Service de Pneumologie A, Hôpital Bichat, FHU APOLLO, AP-HP, Paris, France

⁴Service de Chirurgie Thoracique, CHU Rouen, Rouen, France

⁵Service de Médecine Nucléaire, Centre Henri Becquerel, Rouen, France

⁶Unité de recherche clinique, Centre Henri Becquerel, Rouen, France

⁷EA3830-GRHV, Institute for Research and Innovation in Biomedicine (IRIB), Normandie Université, UNIRouen, Rouen, France

⁸Département R3S (Respiration, Réanimation, Réhabilitation respiratoire, Sommeil), AP-HP, Groupe Hospitalier Universitaire APHP-Sorbonne Université, site Pitié-Salpêtrière, Paris, France

⁹Inserm UMRS1158 Neurophysiologie Respiratoire Expérimentale et Clinique, Sorbonne Université, Paris, France

¹⁰AP-HP, Groupe Hospitalier Universitaire APHP-Sorbonne Université, site Pitié-Salpêtrière, Service des Pathologies du Sommeil (Département R3S), Paris, France

Correspondence

Kinan El Hussein
 Email: kinan.elhousseini@aphp.fr

Associate Editor: David Barnes;

Senior Editor: Phan Nguyen

Abstract

Background and Objective: Respiratory muscle activity is increased in patients with chronic respiratory disease. ¹⁸F-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 ¹⁸F-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. ¹⁸F-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.

This is an open access article under the terms of the [Creative Commons Attribution](https://creativecommons.org/licenses/by/4.0/) License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited.

© 2023 The Authors. *Respirology* published by John Wiley & Sons Australia, Ltd on behalf of Asian Pacific Society of Respirology.

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.¹⁻³ 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.⁴⁻⁶ 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.^{7,8}

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.⁹ Yet, this evaluation is currently made difficult by the complexity of the respiratory muscle system,¹⁰ 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.⁹ 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-[¹⁸F]-fluorodeoxyglucose (¹⁸F-FDG) in a mild and homogeneous manner, resulting in low enhancement on ¹⁸F-FDG-PET/CT. However, vigorous exercise or the administration of insulin before a PET/CT can cause intense tracer uptake in skeletal muscles.¹¹ This well-known pitfall justifies that ¹⁸F-FDG PET/CT imaging guidelines require exercise avoidance within 24 h before ¹⁸F-FDG administration. However, respiratory muscle activity can by nature not be avoided. While permanent baseline activity does not usually result in noticeable hypermetabolism on ¹⁸F-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),^{12,13} 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,¹⁴⁻¹⁶ 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 ¹⁸F-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, ¹⁸F-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 ¹⁸F-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 ¹⁸F-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.

¹⁸F-FDG PET/CTs image acquisition and analysis

All ¹⁸F-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 ¹⁸F-FDG administration to ensure that the serum glucose and serum insulin levels were low. Preparation protocols

and procedures followed EANM procedure guidelines.¹⁷ Pre-operative ¹⁸F-FDG PET/CTs images were analysed as follows: using uncorrected PET reconstructions, maximum Standardized Uptake Values (SUV_m) 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_m, 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.¹⁸ 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,¹⁹ we collected surgical intervention details, patient characteristics including Charlson Comorbidity Score (CCS, measuring burden of disease and predictive of 1-year mortality risk),²⁰ 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 ¹⁸F-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 VO₂ 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 ≥ 1 complications following surgery, with respiratory complications in 52 (34%) patients (Table S1 in the Supporting Information).

Respiratory muscle hypermetabolism

Median respiratory muscle SUV_m, 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_m 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. VO₂ 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 ²	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 ₂ 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; VO₂ 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

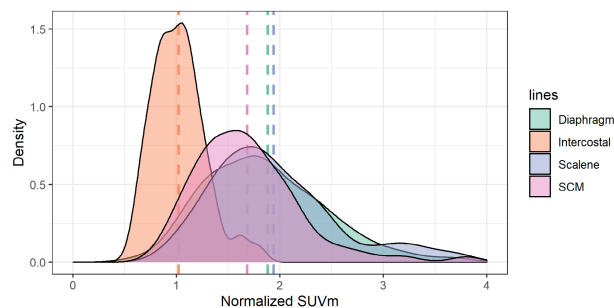


FIGURE 1 Density plot showing the smoothed distributions of SUVm measurement for each respiratory muscle group, normalized on deltoid SUVm. Vertical dashed lines represent mean SUVm for each group. SCM, sternocleidomastoid muscles; SUVm, maximum Standard Uptake Value. Vertical axis: probability density 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 ²	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)	0.031	0.035
Diabetes	10 (22)	19 (17)	0.458	0.132
Obliterating arteriopathy of the lower limbs	15 (33)	10 (9)	<0.001	0.018
Myocardial infarction	9 (20)	14 (13)	0.238	0.096
Charlson comorbidity index	6 [4;7]	5 [4;6]	0.028	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 ₂ 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; VO₂ 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 ¹⁸F-FDG-PET/CT, its correlation to lung function variables and its putative contribution as a prognostic biomarker. In this

study, higher respiratory muscle SUV_m 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, ¹⁸F-FDG displays the same whole-body distribution as glucose, entering cells via the GLUT transporters.²¹ This wide biodistribution grants high sensitivity to ¹⁸F-FDG-PET/CT for the detection of malignancies as cancer cells display increased glucose metabolism,²² somewhat offset by a low specificity, as infectious, inflammatory processes or even laboring muscles—tissues with high glucose consumption—appear as ¹⁸F-FDG-avid on PET/CT. Respiratory muscle hypermetabolism in particular is now recognized as a common incidental finding on ¹⁸F-FDG-PET/CT. In 1164 patients undergoing ¹⁸F-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.²³ In another cohort of 96 patients undergoing ¹⁸F-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.²⁴ Another retrospective study of 411 all-comers undergoing ¹⁸F-FDG-PET/CT also showed

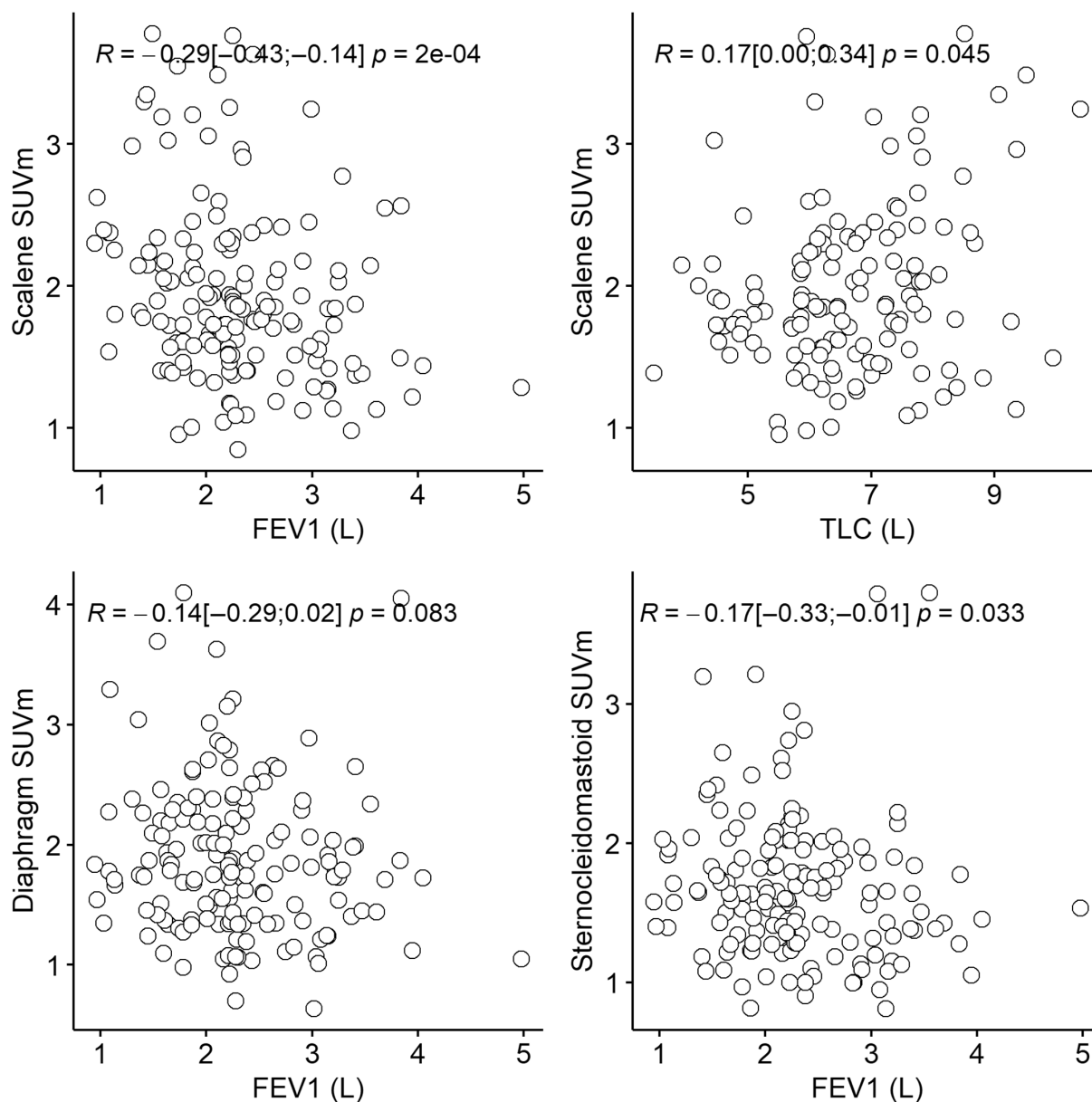


FIGURE 2 Scatter-plots of normalized respiratory muscle tracer uptake against respiratory variables in different muscle groups, across the whole study population. (A) Scalene SUVm against FEV1. (B) Scalene SUVm against TLC. (C) Diaphragm SUVm against FEV1. (D) Sternocleidomastoid SUVm against FEV1. All 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.²⁵ According to previous reports,^{12,25} approximately one third of cancer patients referred for oncologic ¹⁸F-FDG-PET/CT are found to have RMH, similar to the 29.7% in our study.

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

of thoracic and abdominal muscle ¹⁸F-FDG uptake,³⁰ while Osman et al. reciprocated these results, showing that abnormal RMH significantly correlated with COPD severity.¹³ Similarly, Basu et al. described intercostal tracer uptake in patients with COPD, asthma, interstitial lung disease and pulmonary embolism.³¹ 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).¹² Our study therefore coheres with the published literature. It complements current knowledge by providing a quantitative aspect that has not been examined before.

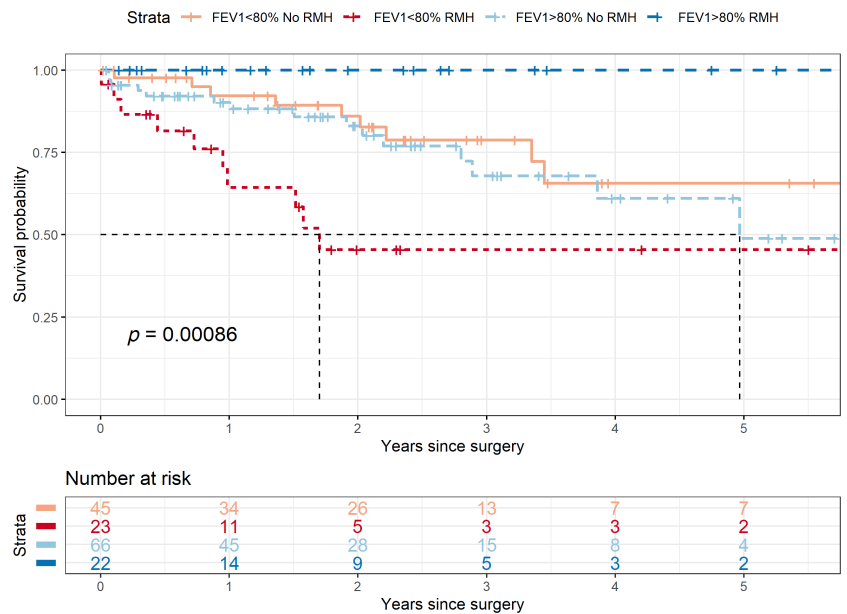
TABLE 3 Description and comparison of nested Cox proportional hazards models predicting patient survival.

Characteristic	Model A <i>Survival ~ CCS</i>			Model B <i>Survival ~ CCS + FEV1%</i>			Model C <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	<0.001	0.29	0.15, 0.44	<0.001	0.32	0.18, 0.47	<0.001
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	0.006
FEV1%*RMH+							-0.06	-0.10, -0.02	0.006

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

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 ¹⁸F-FDG uptake and FEV1, we evidenced a link between respiratory muscle metabolism and TLC, a measure of hyperinflation,³² a phenomenon known to be a major determinant of respiratory muscle function in COPD.³³ Finally, in our study, 55 patients (34.8%) underwent cardio-pulmonary exercise testing (CPET), with lower VO₂ max values in those with RMH. CPET has now been integrated to pretreatment risk assessment algorithms³⁴ and helps guide respiratory rehabilitation programs worldwide.³⁵ However, this test still suffers from a lack of accessibility in some centres due to resource limitations,^{9,36} 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 VO₂ measurements.³⁷ Additional tools to identify patients with respiratory fragility who could potentially

benefit from rehabilitation programs are therefore needed.^{38,39} ¹⁸F-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 ¹⁸F-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,^{40,41} ¹⁸F-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}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,⁴² and the reduction of which can be a non-respiratory benefit of ventilatory support.⁴³

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.¹⁴ In addition, numerous other studies have since shown that neck muscle activation is correlated to clinical outcomes, such as dyspnoea severity or sleep quality.¹⁶ 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 SUVm on ^{18}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 SUVm 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 SUVm. 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 SUVm values compared to the other muscle groups, owing to their small axial surface area relative to the spatial resolution of ^{18}F -FDG-PET/CT, which led to the capture of both inspiratory and expiratory intercostal muscle activity.

In conclusion, our study indicates that ^{18}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}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.

ORCID

Kinan El Hussein  <https://orcid.org/0000-0001-9188-833X>
Maxime Patout  <https://orcid.org/0000-0002-1366-8726>

REFERENCES

- Schaeffer MR, Ryerson CJ, Ramsook AH, Molgat-Seon Y, Wilkie SS, Dhillon SS, et al. Neurophysiological mechanisms of exertional dyspnoea in fibrotic interstitial lung disease. *Eur Respir J*. 2018;51:1701726. <https://doi.org/10.1183/13993003.01726-2017>
- Reilly CC, Ward K, Jolley CJ, Lunt AC, Steier J, Elston C, et al. Neural respiratory drive, pulmonary mechanics and breathlessness in patients with cystic fibrosis. *Thorax*. 2011;66:240–6. <https://doi.org/10.1136/thx.2010.142646>
- Jolley CJ, Luo Y-M, Steier J, Reilly C, Seymour J, Lunt A, et al. Neural respiratory drive in healthy subjects and in COPD. *Eur Respir J*. 2009;33:289–97. <https://doi.org/10.1183/09031936.00093408>
- Suh E-S, Mandal S, Harding R, Ramsay M, Kamalanathan M, Henderson K, et al. Neural respiratory drive predicts clinical deterioration and safe discharge in exacerbations of COPD. *Thorax*. 2015;70:1123–30. <https://doi.org/10.1136/thoraxjnl-2015-207188>
- Georges M, Morawiec E, Raux M, Gonzalez-Bermejo J, Pradat PF, Similowski T, et al. Cortical drive to breathe in amyotrophic lateral sclerosis: a dyspnoea-worsening defence? *Eur Respir J*. 2016;47:1818–28. <https://doi.org/10.1183/13993003.01686-2015>
- Patout M, Meira L, D'Cruz R, Lhuillier E, Kaltsakas G, Arbane G, et al. Neural respiratory drive predicts long-term outcome following admission for exacerbation of COPD: a post hoc analysis. *Thorax*. 2019;74:910–3. <https://doi.org/10.1136/thoraxjnl-2018-212074>
- Vaporidi K, Akoumianaki E, Telias I, Goligher EC, Brochard L, Georgopoulos D. Respiratory drive in critically ill patients. Pathophysiology and clinical implications. *Am J Respir Crit Care Med*. 2020;201:20–32. <https://doi.org/10.1164/rccm.201903-0596SO>
- Mirabella L, Cinnella G, Costa R, Cortegiani A, Tullo L, Rauseo M, et al. Patient-ventilator asynchronies: clinical implications and practical solutions. *Respir Care*. 2020;65:1751–66. <https://doi.org/10.4187/respcare.07284>
- Laveneziana P, Albuquerque A, Aliverti A, Babb T, Barreiro E, Dres M, et al. ERS statement on respiratory muscle testing at rest and during exercise. *Eur Respir J*. 2019;53:1801214. <https://doi.org/10.1183/13993003.01214-2018>
- De Troyer A, Boriek AM. Mechanics of the respiratory muscles. *Compr Physiol*. 2011;1:1273–300. <https://doi.org/10.1002/cphy.c100009>
- Abouzi MM, Crawford ES, Nabi HA. 18F-FDG imaging: pitfalls and artifacts. *J Nucl Med Technol*. 2005;33:145–55. quiz 162–3.
- Kothekar E, Borja AJ, Gerke O, Werner TJ, Alavi A, Revheim ME. Assessing respiratory muscle activity with 18F-FDG-PET/CT in patients with COPD. *Am J Nucl Med Mol Imaging*. 2019;9:309–15.
- Osman MM, Tran IT, Muzaffar R, Parkar N, Sachdeva A, Ruppel GL. Does 18F-FDG uptake by respiratory muscles on PET/CT correlate with chronic obstructive pulmonary disease? *J Nucl Med Technol*. 2011;39:252–7. <https://doi.org/10.2967/jnmt.111.089961>
- De Troyer A, Peche R, Yernault JC, Estenne M. Neck muscle activity in patients with severe chronic obstructive pulmonary disease. *Am J Respir Crit Care Med*. 1994;150:41–7. <https://doi.org/10.1164/ajrccm.150.1.8025770>
- Gandevia SC, Leeper JB, McKenzie DK, De Troyer A. Discharge frequencies of parasternal intercostal and scalene motor units during breathing in normal and COPD subjects. *Am J Respir Crit Care Med*. 1996;153:622–8. <https://doi.org/10.1164/ajrccm.153.2.8564108>
- Schmidt M, Kindler F, Gottfried SB, Raux M, Hug F, Similowski T, et al. Dyspnea and surface inspiratory electromyograms in mechanically ventilated patients. *Intensive Care Med*. 2013;39:1368–76. <https://doi.org/10.1007/s00134-013-2910-3>
- Boellaard R, Delgado-Bolton R, Oyen WJG, Giammarile F, Tatsch K, Eschner W, et al. FDG PET/CT: EANM procedure guidelines for tumour imaging: version 2.0. *Eur J Nucl Med Mol Imaging*. 2015;42:328–54. <https://doi.org/10.1007/s00259-014-2961-x>
- Hernández N, Orozco-Levi M, Belalcázar V, Pastó M, Minguela J, Broquetas JM, et al. Dual morphometrical changes of the deltoid muscle in patients with COPD. *Respir Physiol Neurobiol*. 2003;134:219–29. [https://doi.org/10.1016/s1569-9048\(03\)00015-6](https://doi.org/10.1016/s1569-9048(03)00015-6)
- Die Loucou J, Pagès P-B, Falcoz P-E, Thomas P-A, Rivera C, Brouchet L, et al. Validation and update of the thoracic surgery scoring system (Thoracoscore) risk model. *Eur J Cardio-Thorac Surg*. 2020;58:350–6. <https://doi.org/10.1093/ejcts/ezaa056>
- Roffman CE, Buchanan J, Allison GT. Charlson comorbidities index. *J Physiother*. 2016;62:171. <https://doi.org/10.1016/j.jphys.2016.05.008>
- Ahmad SS. Physiological uptake in FDG PET simulating disease. *Biomed Imaging Interv J*. 2006;2:2. <https://doi.org/10.2349/biij.2.4.e59>
- Hawkins RA, Hoh C, Dahlbom M, Choi Y, Glaspy J, Tse N, et al. PET cancer evaluations with FDG. *J Nucl Med*. 1991;32:1555–8.
- Jackson RS, Schlarman TC, Hubble WL, Osman MM. Prevalence and patterns of physiologic muscle uptake detected with whole-body 18F-FDG PET. *J Nucl Med Technol*. 2006;34:29–33.
- Jacene HA, Patel PP, Chin BB. 2-Deoxy-2-[18F] fluoro-D-glucose uptake in intercostal respiratory muscles on positron emission tomography/computed tomography: smokers versus nonsmokers. *Mol Imaging Biol*. 2004;6:405–10. <https://doi.org/10.1016/j.mibio.2004.08.002>
- Jacene HA, Goudarzi B, Wahl RL. Scalene muscle uptake: a potential pitfall in head and neck PET/CT. *Eur J Nucl Med Mol Imaging*. 2008;35:89–94. <https://doi.org/10.1007/s00259-007-0548-5>
- GOLD Science Committee. Global Strategy for Diagnosis, Management and Prevention of COPD. 2020 Update 2020 [accessed 5 Jun 2020]. Available from: https://goldcopd.org/wp-content/uploads/2019/12/GOLD-2020-FINAL-ver1.2-03Dec19_WMV.pdf
- Martinez FJ, de Oca MM, Whyte RI, Stetz J, Gay SE, Celli BR. Lung-volume reduction improves dyspnea, dynamic hyperinflation, and respiratory muscle function. *Am J Respir Crit Care Med*. 1997;155:1984–90. <https://doi.org/10.1164/ajrccm.155.6.9196106>
- Sanchez J, Brunet A, Medrano G, Debesse B, Derenne JP. Metabolic enzymatic activities in the intercostal and serratus muscles and in the latissimus dorsi of middle-aged normal men and patients with moderate obstructive pulmonary disease. *Eur Respir J*. 1988;1:376–83.
- Duiverman ML, de Boer EWJ, van Eykern LA, de Greef MHG, Jansen DF, Wempe JB, et al. Respiratory muscle activity and dyspnea during exercise in chronic obstructive pulmonary disease. *Respir Physiol Neurobiol*. 2009;167:195–200. <https://doi.org/10.1016/j.resp.2009.04.018>
- Aydin A, Hickeson M, Yu JQ, Zhuang H, Alavi A. Demonstration of excessive metabolic activity of thoracic and abdominal muscles on FDG-PET in patients with chronic obstructive pulmonary disease. *Clin Nucl Med*. 2005;30:159–64. <https://doi.org/10.1097/00003072-200503000-00003>
- Basu S, Alzeair S, Li G, Dadparvar S, Alavi A. Etiopathologies associated with intercostal muscle hypermetabolism and prominent right ventricle visualization on 2-Deoxy-2-[F-18]fluoro-d-glucose-positron emission tomography: significance of an incidental finding and in the setting of a known pulmonary disease. *Mol Imaging Biol*. 2007;9:333–9. <https://doi.org/10.1007/s11307-007-0102-7>
- D'Ascanio M, Viccaro F, Calabrò N, Guerrieri G, Salvucci C, Pizzirusso D, et al. Assessing static lung hyperinflation by whole-body plethysmography, helium dilution, and impulse oscillometry system (IOS) in patients with COPD. *Int J Chron Obstruct Pulmon Dis*. 2020;15:2583–9. <https://doi.org/10.2147/COPD.S264261>
- Casanova C, Cote C, de Torres JP, Aguirre-Jaime A, Marin JM, Pinto-Plata V, et al. Inspiratory-to-total lung capacity ratio predicts mortality in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med*. 2005;171:591–7. <https://doi.org/10.1164/rccm.200407-867OC>
- Postmus PE, Kerr KM, Oudkerk M, Senan S, Waller DA, Vansteenkiste J, et al. Early and locally advanced non-small-cell lung cancer (NSCLC): ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol*. 2017;28:iv1–iv21. <https://doi.org/10.1093/annonc/mdx222>
- Salhi B, Troosters T, Behaegel M, Joos G, Derom E. Effects of pulmonary rehabilitation in patients with restrictive lung diseases. *Chest*. 2010;137:273–9. <https://doi.org/10.1378/chest.09-0241>

36. Azzi M, Debeaumont D, Bonnevie T, Aguilaniu B, Cerasuolo D, Boujibar F, et al. Evaluation of the 3-minute chair rise test as part of preoperative evaluation for patients with non-small cell lung cancer. *Thorac Cancer*. 2020;11:2431–9. <https://doi.org/10.1111/1759-7714.13548>
37. Gravier F-E, Bonnevie T, Boujibar F, Médriinal C, Prieur G, Combret Y, et al. Cardiopulmonary exercise testing in patients with non-small cell lung cancer: trust the V̇ O₂ peak? *J Thorac Dis*. 2020;12:5313–23. <https://doi.org/10.21037/jtd-20-1528>
38. Boujibar F, Gillibert A, Gravier FE, Gillot T, Bonnevie T, Cuvelier A, et al. Performance at stair-climbing test is associated with postoperative complications after lung resection: a systematic review and meta-analysis. *Thorax*. 2020;75:791–7. <https://doi.org/10.1136/thoraxjnl-2019-214019>
39. Gravier F-E, Smondack P, Prieur G, Medriinal C, Combret Y, Muir JF, et al. Effects of exercise training in people with non-small cell lung cancer before lung resection: a systematic review and meta-analysis. *Thorax*. 2022;77:486–96. <https://doi.org/10.1136/thoraxjnl-2021-217242>
40. Palestro CJ. FDG-PET in musculoskeletal infections. *Semin Nucl Med*. 2013;43:367–76. <https://doi.org/10.1053/j.semnuclmed.2013.04.006>
41. Kothekar E, Raynor WY, Al-Zaghal A, Jonnakuti VS, Werner TJ, Alavi A. Evolving role of PET/CT-MRI in assessing muscle disorders. *PET Clin*. 2019;14:71–9. <https://doi.org/10.1016/j.cpet.2018.08.010>
42. Mason SE, Moreta-Martinez R, Labaki WW, Strand MJ, Regan EA, Bon J, et al. Longitudinal association between muscle loss and mortality in ever smokers. *Chest*. 2022;161:960–70. <https://doi.org/10.1016/j.chest.2021.10.047>
43. Georges M, Morélot-Panzini C, Similowski T, Gonzalez-Bermejo J. Noninvasive ventilation reduces energy expenditure in amyotrophic lateral sclerosis. *BMC Pulm Med*. 2014;14:17. <https://doi.org/10.1186/1471-2466-14-17>

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: El Hussein 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>