Preoperative Peak Oxygen Uptake in Lung Cancer Subjects With Neoadjuvant Chemotherapy: A Cross-Sectional Study

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BACKGROUND: In non-small-cell lung cancer patients, high peak oxygen uptake (peak $\dot{V}_{O_2}$) predicts lower rates of postoperative complications and better long-term survival. Neoadjuvant chemotherapy (NAC) may negatively impact peak $\dot{V}_{O_2}$. METHODS: Cardiopulmonary exercise testing (CPET) was performed in 34 consecutive stage IIIA/IIIB non-small-cell lung cancer subjects scheduled for elective lung surgery. Using multivariate linear regression adjusted for potential confounders, we compared CPET results in subjects receiving or not receiving NAC (NAC+, $n = 19$; NAC−, $n = 15$). RESULTS: Adjusted peak $\dot{V}_{O_2}$ was lower in NAC + compared with NAC− subjects (−5.3 mL/min/kg [95% CI −8.3 to −2.2], $P = .01$). Likewise, oxygen pulse, maximal work load, and ventilatory threshold were also lower in NAC+ subjects, whereas peak heart rate and breathing reserve were similar. NAC+ subjects presented lower values of diffusion capacity for carbon monoxide (D_{LCO}) ($P = .035$) and hemoglobin concentrations ($P < .001$). D_{LCO} was strongly correlated with peak $\dot{V}_{O_2}$ ($r^2 = 0.56$). Adjustment for D_{LCO} reduced the effect of NAC on peak $\dot{V}_{O_2}$ without suppressing it. CONCLUSIONS: NAC was associated with lower preoperative peak $\dot{V}_{O_2}$ in subjects with non-small-cell lung cancer. This lower aerobic fitness may result from NAC-induced reduction in pulmonary gas exchange or heart toxicity. Since lower fitness is linked to poorer outcome, the decision for NAC may have to be balanced with its possible toxicity. *Key words:* chemotherapy, peak oxygen uptake, cardio-pulmonary exercise tests, lung cancer, lung surgery, training, post operative complications. [Respir Care 2016;61(8):1059–1066. © 2016 Daedalus Enterprises]

Introduction

Patients with non-small-cell lung cancer generally have limited exercise capacity.[1] Aerobic exercise capacity is a key variable for the decision to perform tumor resection. This process involves oxygen transport and delivery by the pulmonary and cardiovascular systems and oxygen consumption by the skeletal muscles.[2] Peak oxygen uptake (peak $\dot{V}_{O_2}$), as determined during cardiopulmonary exer-

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cise testing (CPET), is the reference method to evaluate exercise capacity and predicts early postoperative complications as well as long-term outcome.[3-6] Besides aging, comorbidities such as COPD, diabetes mellitus, hypertension, peripheral artery disease, and heart failure are highly prevalent in these patients and may all limit aerobic exercise capacity.[7] Moreover, sedentary behavior and the inflammatory component associated with cancer contribute to muscle wasting and decreased peripheral aerobic metabolic capacity. Finally, there can be deleterious effects of surgery, radiotherapy, and chemotherapy.[1]

Chemotherapeutic agents can affect the cardiovascular system and induce anemia, both impeding cardiovascular oxygen transport.[8] Platinum-based chemotherapy may affect the pulmonary system, worsening pulmonary oxygen uptake.[8] The effects of other classes of chemotherapeutic agents and the effects of chemotherapy in general on other components of oxygen delivery and consumption are still poorly explored.[9] Despite such serious adverse effects, survival is improved with preoperative neoadjuvant chemotherapy (NAC) followed by surgery, compared with surgery alone.[10-12] By reducing the tumor burden and downgrading the tumor stage, NAC facilitates surgical resection and may improve long-term outcome by eradicating micrometastases. But NAC may be a double-edged sword. There is emerging evidence that NAC may decrease physical fitness by affecting oxygen transport system components, although it is still unclear which NAC toxicity-related effects result in lowered aerobic capacity.[13]

To address this point, we compared preoperative CPET-derived parameters in a cohort of non-small-cell lung cancer subjects scheduled for curative lung resection and receiving or not receiving NAC. We hypothesized that subjects receiving NAC would have lower aerobic exercise capacity compared with subjects not treated with NAC.

Methods

Study Design and Setting

This prospective study took place over a period of 49 months, from January 2011 to February 2014, as part of an ongoing randomized controlled trial comparing the effect of short-term preoperative exercise training versus usual care in subjects with operable non-small-cell lung cancer.[14] All subjects were recruited in the pulmonary di-

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QUICK LOOK

Current knowledge

In patients with non-small-cell lung cancer, the postoperative complication rate is associated with low peak oxygen uptake. Neoadjuvant chemotherapy has been shown to be effective in improving survival when compared with surgery alone in selected patients. However, toxicity of chemotherapeutic agents may affect heart and lung function beyond anemia, thus reducing peak oxygen uptake.

What this paper contributes to our knowledge

Neoadjuvant chemotherapy was associated with significantly lower preoperative oxygen uptake in subjects with non-small-cell lung cancer. This lower aerobic fitness may result from chemotherapy-induced reduction in diffusion capacity and heart or skeletal muscle toxicity.

visions of 3 tertiary care centers located in the French-speaking part of Switzerland (University Hospitals of Geneva, University Hospital of Lausanne, and Hôpital du Valais, Sion). A cross-sectional analysis was carried out to assess preoperative exercise capacity (as measured by CPET) in non-small-cell lung cancer subjects with or without NAC scheduled for elective curative lung resection.

Participants

We included all subjects >18 y old with non-small-cell lung cancer IIIA and IIIB, documented by CT scan, positron emission tomography-CT, and pathological confirmation and judged eligible for tumor resection (open thoracotomy or video-assisted thoracoscopy), with or without NAC. The institutional research ethics board approved the study and informed written consent was obtained from each subject. Institutional review board approval (Protocol 09-263) was obtained from the University Hospitals of Geneva on August 10, 2010.

Based on preoperative investigations, subjects were staged according to the guidelines of the American Joint Committee on Cancer.[15] Decisions to offer NAC were made by a multidisciplinary tumor board, based on guidelines, clinical judgment, and subjects' preferences. Exclusion criteria consisted of contraindications to perform CPET (uncontrolled heart disease, severe pulmonary hypertension) or functional limitations related to joint or psychiatric disease that precluded CPET.

Outcomes, Exposure Variables, and Potential Confounders

The main outcome variable was peak $\dot{V}_{O_2}$ obtained from CPET. Secondary outcomes were other CPET results (maximal work load, ventilatory threshold, ventilatory equivalents [$\dot{V}_E/\dot{V}_{O_2}$ and $\dot{V}_E/\dot{V}_{CO_2}$], breathing reserve [estimated], peak heart rate, and oxygen pulse [$\dot{V}_{O_2}$/heart rate]). Data were collected preoperatively after a median of 3.1 ± 0.5 cycles of NAC. In accordance with international guidelines, NAC regimens consisted of platinum-based doublet chemotherapy (supplementary Table 1; see the supplementary materials at http://www.rcjournal.com).[16,17]

Nineteen subjects with stage IIIA and IIIB non-small-cell lung cancer who received NAC as part of a multimodal treatment were considered as exposed (NAC+). Subjects with non-small-cell lung cancer stage IIIA and IIIB who did not receive NAC ($n = 15$) were considered as the control group (NAC−). Subjects with stage I to IIB operable lung cancer who did not receive NAC ($n = 113$) were used as additional controls in a sensitivity analysis. The following potential confounders or precision variables were taken into account in the statistical analysis: age, sex, weight, height, self-reported comorbidities (cardiovascular disease, hypertension), pulmonary function (FEV_1, carbon monoxide diffusion capacity [D_{LCO}]), venous blood hemoglobin concentration, and N-terminal prohormone of brain natriuretic peptide (NT-proBNP).

Pulmonary Function and CPET Procedures

All subjects performed pulmonary function testing according to American Thoracic Society/European Respiratory Society recommendations with measurement of post-bronchodilator FEV_1 and carbon monoxide diffusion capacity (D_{LCO} adjusted for hemoglobin according to the following formula: D_{LCO} predicted for Hb = D_{LCO} predicted $\times$ (1.7 Hb/10.22 + Hb).[18,19] Symptom-limited CPET was performed on a cycle ergometer (Vmax Encore, SensorMedics, San Diego, California) with a maximal incremental work load protocol (10–15-W increments every minute, after a 3-min warm-up at 25 W), recording work load, breath-by-breath gas exchange, electrocardiogram, pulse oximetry, and noninvasive blood pressure. The flow meter was calibrated with a 3-L syringe, and the gas analyzers were calibrated with certified calibration gas mixtures before each test. The subjects exercised until exhaustion or until reaching criteria for exercise termination according to the American Thoracic Society/American College of Chest Physicians statement.[20] CPET was considered objectively maximal if the respiratory quotient was >1.2 or peak heart rate was >80% predicted.[21] It was considered as subjectively maximal if the subject perceived breathlessness of 9–10 on a 0–10 Borg scale. Ventilatory

threshold was determined with the ventilatory equivalent method and the V-slope method.[20] Breathing reserve was estimated with the formula: (measured maximal ventilation [MVV] predicted − MVV)/MVV predicted.[22]

Statistical Analysis

Categorical and continuous variables were compared between the NAC+ and NAC− groups with parametric Student test or chi-square test. Univariate and multivariate linear regressions were performed with CPET parameters as dependent variables and NAC exposure (dichotomous) as the main independent variable. Potential confounders were added hierarchically into the models.

Model 1 was unadjusted. Model 2 was adjusted for anthropometric variables (age, sex, height, and weight). Model 3 controlled for comorbidities (cardiovascular disease, hypertension, and FEV_1 as proxy of chronic obstructive pulmonary disease). Model 4 was further adjusted for hemoglobin, whereas Model 5 was further adjusted for D_{LCO}.

A supplementary analysis including as comparators all NAC− lung cancer subjects (stages I to III instead of stage III only) was performed. Statistical analyses were performed with STATA IC 11 (StataCorp, College Station, Texas).

Results

Between January 2011 and February 2014, we enrolled 34 non-small-cell lung cancer subjects from the University Hospitals of Geneva ($n = 24$) and Lausanne ($n = 5$) and the Valais Hospital ($n = 5$). Subjects' characteristics are shown in Table 1. NAC+ subjects had either stage IIIA non-small-cell lung cancer ($n = 13$) or stage IIIB non-small-cell lung cancer ($n = 6$). Overall, NAC+ subjects tended to be younger and had lower hemoglobin and D_{LCO} but similar percent-of-predicted FEV_1 and NT-proBNP compared with those without NAC.

Chemotherapeutic regimens were platinum-based for all subjects (cisplatin $n = 16$; carboplatin $n = 3$) combined with docetaxel ($n = 16$), paclitaxel ($n = 1$), gemcitabin ($n = 1$), or vinorelbine ($n = 1$). Two subjects received a combined treatment of cisplatin-docetaxel and cetuximab. The median number of cycles was 3 (range 1–4). Mean time between first cycle of NAC and CPET was 76 d (95% CI 62–90).

Table 2 compares the main CPET results between non-small-cell lung cancer IIIA and IIIB subjects with and without NAC. Peak $\dot{V}_{O_2}$, ventilatory threshold, and oxygen pulse at peak were lower in the NAC+ group as compared with control groups. Maximal heart rate reserve at peak (expressed in percent of maximal predicted heart rate) was similar in both groups (12% ± 14% in NAC−; 11% ± 11% in NAC+). Table 3 displays the differences in CPET

Table 1.   Subjects' Baseline Characteristics

Characteristics	NAC+, Stages IIIA/IIIB (n = 19)	NAC−, Stages IIIA/IIIB (n = 15)	P
Age, mean ± SD y	59 ± 12	66 ± 14	.12
Male sex, %	12 (63.2)	9 (60.0)	>.99
Height, mean ± SD cm	172 ± 8	170 ± 7	.31
Weight, mean ± SD kg	75 ± 15	69 (13)	.32
Hemoglobin, mean ± SD g/dL	11.3 ± 1.5	13.5 (1.9)	<.001
Pulmonary function, mean ± SD			
FEV$_1$, mean ± SD % predicted	85 ± 17	89 ± 20	.61
D$_{LCO}$, mean ± SD % predicted	60 ± 19	75 ± 18	.035
NT-proBNP, mean ± SD pg/mL	47 ± 38	66 ± 63	.31
Comorbidities, n (%)			
Cardiovascular disease	4 (21.1)	3 (20.0)	>.99
Hypertension	6 (31.6)	4 (26.7)	>.99
COPD	6 (31.6)	7 (46.7)	.48
Depression	4 (22.2)	3 (21.4)	>.99
Preoperative staging, n (%)			
IIIA	13 (68.4)	14 (93.3)	
IIIB	6 (31.6)	1 (6.7)	

NAC = neoadjuvant chemotherapy
D$_{LCO}$ = carbon monoxide diffusion capacity adjusted for hemoglobin
NT-proBNP = N-terminal prohormone of brain natriuretic peptide

Table 2.   Cardiopulmonary Exercise Test Results

Parameters	NAC+, Stages IIIA/IIIB (n = 19)	NAC−, Stages IIIA/IIIB (n = 15)	P
Peak V̇$_{O_2}$, mL/min	1,174 ± 306	1,446 ± 596	.09
Peak V̇$_{O_2}$, mL/min/kg	16.4 ± 3.6	20.5 ± 6.5	.02
Peak power, W	89.0 ± 27.8	97.3 ± 51.7	.55
Ventilatory threshold, % predicted peak V̇$_{O_2}$ (SD)	39.7 ± 11.1	51.3 ± 14.4	.02
Peak V̇$_E$, L/min	60.3 ± 16.7	63.8 ± 23.5	.65
V̇$_E$/V̇$_{O_2}$ at ventilatory threshold	36.7 ± 5.9	36.8 ± 6.0	.97
V̇$_E$/V̇$_{CO_2}$ at ventilatory threshold	37.21 ± 5.2	37.3 ± 4.9	.95
S$_{pO_2}$, % at peak	96.1 ± 1.0	95.4 ± 1.5	.14
Breathing reserve, % at peak	38.4 ± 20.7	32.5 ± 16.0	.40
Peak heart rate, beats/min	143.6 ± 22.4	135.2 ± 23.1	.29
Heart rate reserve, beats/min at peak	17.5 ± 16.8	18.8 ± 21.2	.85
Oxygen pulse, mL/beat at peak	8.3 ± 2.3	10.6 ± 3.3	.02

Data are means ± SD.
NAC = neoadjuvant chemotherapy
V̇$_{O_2}$ = oxygen consumption
V̇$_E$ = minute ventilation
V̇$_E$/V̇$_{O_2}$ and V̇$_E$/V̇$_{CO_2}$ = ventilatory equivalents at ventilatory threshold

parameters in subjects with versus without NAC as obtained from the multivariate analysis.

Peak V̇$_{O_2}$ was significantly lower in NAC+ subjects in multivariate linear regression models when compared with NAC− subjects. Lower peak V̇$_{O_2}$ associated with NAC was also found in Models 2 and 3 controlling for anthropometric variables and comorbidities, respectively (−5.3 mL/min/kg [95% CI −8.3 to −2.2], P = .001 and

−5.2 mL/min/kg (95% CI −8.2 to −2.3), P = .001). The impact on peak V̇$_{O_2}$ was less pronounced in Models 4 and 5, which were additionally adjusted for hemoglobin and D$_{LCO}$, respectively, suggesting a role for these 2 variables in exercise capacity. Maximal work load was lower in the NAC+ subjects in Models 2 and 3, and ventilatory threshold was lower in Models 1–3.

The relations between peak V̇$_{O_2}$ and D$_{LCO}$, against peak heart rate, are depicted in supplementary Figures 1 and 2. We observed no statistically significant differences between groups for V̇$_E$/V̇$_{O_2}$, V̇$_E$/V̇$_{CO_2}$, breathing reserve, and heart rate. By contrast, the slope of the V̇$_{O_2}$/heart rate relationship was flatter in NAC+ subjects (peak V̇$_{O_2}$ = 9.3 ± 0.5, r² = 0.09, P = .20) compared with the NAC− subjects (peak V̇$_{O_2}$ = −1.1 ± 0.16, r² = 0.31, P = .035) (supplementary Fig. 2). Supplementary Figures 3 and 4 show similar relations between V$_{O_2}$ and D$_{LCO}$ against heart rate, based on the sensitivity analysis, including all cancer subjects as controls. We also noted a lower oxygen pulse at peak exercise in subjects with NAC in all multivariate models (see Table 3).

Discussion

As hypothesized, we found that subjects with non-small-cell lung cancer stage IIIA and IIIB who received NAC had a 25.8% lower preoperative peak V̇$_{O_2}$ (−5.3 mL/min/kg) compared with those not receiving NAC, after adjustment for anthropometric variables, comorbidities, and FEV$_1$. NAC+ subjects also reached a lower maximal work load, had a lower oxygen pulse at peak exercise, and had a decreased ventilatory threshold, whereas breathing reserve, heart rate at peak exercise, and ventilatory equivalents at ventilatory threshold were similar in both groups. FEV$_1$ and NT-proBNP were comparable in NAC+ and NAC− subjects, but D$_{LCO}$ and hemoglobin level were lower in the NAC+ group. D$_{LCO}$ and, to a somewhat lesser extent, hemoglobin were associated with exercise capacity. The finding of a flatter V̇$_{O_2}$/heart rate regression slope and a lower peak oxygen pulse in the NAC+ group compared with the control groups suggests a cardiac component to their lower aerobic capacity (see Table 2 and supplementary Fig. 2).

Three different mechanisms may explain the lower aerobic capacity in the non-small-cell lung cancer subjects receiving NAC. First the reduction in D$_{LCO}$, although nonspecific, suggests impaired gas exchange limiting exercise capacity. Second, reduced blood hemoglobin concentration limits oxygen carrying capacity. Third, the data presented are consistent with a lower cardiac stroke volume and therefore cardiac output, limiting oxygen delivery. We cannot exclude a peripheral component involved in the decrease in peak V̇$_{O_2}$, such as muscle (mitochondrial)

Table 3. Adjusted Differences From Multivariate Analyses in Cardiopulmonary Exercise Test Parameters of Subjects With Stage IIIA/IIIB Non-Small-Cell Lung Cancer Receiving Neoadjuvant Chemotherapy Versus Subjects Not Receiving Neoadjuvant Chemotherapy

Parameters	Model 1		Model 2		Model 3		Model 4		Model 5	
	Median (95% CI)	P	Median (95% CI)	P	Median (95% CI)	P	Median (95% CI)	P	Median (95% CI)	P
Peak $\dot{V}_{O_2}$, mL/min	−272.4 (−557.0 to 12.3)	.061	−436.1 (−654.3 to −217.9)	<.001	−402.0 (−604.3 to −199.7)	<.001	−299.8 (−518.9 to −80.6)	.01	−229.8 (−447.2 to −12.5)	.038
Peak $\dot{V}_{O_2}$, mL/min/kg	−4.2 (−7.7 to −0.6)	.02	−5.3 (−8.3 to −2.2)	.001	−5.2 (−8.2 to −2.3)	.001	−4.5 (−7.7 to −1.3)	.01	−3.3 (−6.6 to −0.2)	.039
Power, W	−8.3 (−32.9, 16.2)	.50	−22.1 (−42.3 to −1.9)	.032	−18.6 (−36.4to −0.8)	.041	−12.3 (−31.8 to 7.3)	.22	−6.0 (−25.3 to 13.3)	.54
Ventilatory threshold, % of predicted maximum $\dot{V}_{O_2}$	−11.6 (−20.2 to −3.0)	.01	−11.9 (−20.2 to −3.6)	.01	−11.6 (−19.7to −3.6)	.01	−5.6 (−14.0 to 2.7)	.18	−4.2 (−12.8 to 4.4)	.34
$\dot{V}_E/\dot{V}_{O_2}$, at ventilatory threshold	−0.01 (−3.8 to 3.6)	.96	0.2 (−3.5 to 3.9)	.90	−.20 (−3.8 to 3.4)	.91	−1.0 (−4.8 to 2.8)	.59	−0.8 (−4.6 to 2.9)	.67
$\dot{V}_E/\dot{V}_{CO_2}$, at ventilatory threshold	−0.1 (−3.8 to 3.5)	.95	0.8 (−2.7 to 4.3)	.65	0.4 (−2.9 to 3.7)	.81	−0.5 (−3.9 to 3.0)	.79	−0.4 (−3.8 to 3.0)	.83
Breathing reserve, %	5.9 (−8.2 to 20.0)	.41	5.1 (−9.1 to 19,30)	.48	4.9 (−9.2 to 18.9)	.50	−0.5 (−15.2 to 14.1)	.94	−1.6 (−16.1 to 13.0)	.83
Heart rate, beats/min	8.4 (−6.3 to 23.2)	.26	1.3 (−12.1 to 14.7)	.90	2.7 (−10.5 to 16.0)	.68	8.1 (−6.3 to 22.5)	.27	10.2 (−4.6 to 25.1)	.18
Oxygen pulse, mL/beat (95% CI)	−2.3 (−4.1 to −0.5)	.01	−2.9 (−4.4 to −1.5)	<.001	−2.8 (−4.2 to −1.4)	.001	−2.4 (−3.9 to −0.9)	.002	−2.0 (−3.6 to −0.5)	.01

n = 19 subjects receiving neoadjuvant chemotherapy; n = 15 subjects not receiving neoadjuvant chemotherapy. Model 1: unadjusted; Model 2: adjusted for age, sex, height, and weight; Model 3: additionally adjusted for comorbidities (ischemic heart disease, stroke, peripheral arteriopathy, conduction blockade, arrhythmia, or hypertension) + FEV₁; Model 4: additionally adjusted for hemoglobin; Model 5: additionally adjusted for D_{LCO}.
NAC = neoadjuvant chemotherapy
$\dot{V}_{O_2}$ = oxygen consumption
$\dot{V}_E$ = minute ventilation
$\dot{V}_E/\dot{V}_{O_2}$ and $\dot{V}_E/\dot{V}_{CO_2}$ = ventilatory equivalents at ventilatory threshold

toxicity of NAC, but we have no data to support this hypothesis.

Diffusion Capacity

In our study, D_{LCO} was 15 points lower in NAC+ compared with NAC− subjects. D_{LCO} is an important determinant of aerobic capacity. For example, in COPD patients, D_{LCO} is a strong predictor of peak $\dot{V}_{O_2}$.[23] A decrease in D_{LCO} is a common finding when performing lung function tests during or after chemotherapy. Lakoski et al[9] reviewed the effects of chemotherapeutic agents on components of oxygen transport and suggested that platinum-based chemotherapy impacts its pulmonary component, presumably by diminishing diffusion capacity. Pulmonary toxicity was also reported for taxanes and gemcitabine. Kreuter et al[24] assessed lung function after 2 different adjuvant chemotherapeutic regimens for early stage non-small-cell lung cancer and found a decline of D_{LCO} after a cisplatin-vinorelbine regimen (−8%) but not after cisplatin-pemetrexed (−0.4%). This is consistent with the results of Rivera et al[25] who found an 8% D_{LCO} decline after 3 courses of gemcitabine plus carboplatin, cisplatin, or paclitaxel for stage I and II non-small-cell lung cancer. Leo et al[26] compared pre- and post-NAC (3 courses of cisplatin-gemcitabine) lung function in 30 subjects with stage IIIA-N2 non-small-cell lung cancer. They found an 11% D_{LCO} reduction after chemotherapy. Takeda et al[27] found a 21% reduction in D_{LCO} after induction therapy (chemotherapy alone or chemo-radiotherapy) for stage IIB (Pancoast), IIIA, and IIIB non-small-cell lung cancer. Importantly, D_{LCO} was an independent predictor of postoperative pulmonary morbidity.[28]

Oxygen Transport

From the Fick principle, we know that a reduction in blood hemoglobin content will result in a reduction of peak $\dot{V}_{O_2}$.[29] Virtually all chemotherapeutic agents may cause anemia through different pathways (deficient production or destruction of red blood cells, excessive blood loss). Anemia during chemotherapy occurs in 30–100% of patients.[30] A correlation between hemoglobin levels and peak $\dot{V}_{O_2}$ reduction was described for women receiving adjuvant chemotherapy for breast cancer.[31] In our study, adjustment for hemoglobin marginally altered the association between NAC and peak $\dot{V}_{O_2}$, suggesting that the effect of NAC on peak $\dot{V}_{O_2}$ in our cohort was mainly mediated by other mechanisms.

Cardiotoxicity

Several chemotherapeutic agents are cardiotoxic. Anthracylines, trastuzumab, and tyrosine kinase inhibitors are frequently associated with left ventricular dysfunction and impairment in cardiovascular autonomic regulation.[32,33] Antimicrotubule agents such as paclitaxel are reported to induce various cardiac problems, including bradyarrhythmias, atrioventricular conduction blocks, bundle branch blocks, and cardiac ischemia. Our observation of a flattening of the peak $\dot{V}_{O_2}$/heart rate relationship and a lower peak oxygen pulse is compatible with a cardio-toxic component of NAC, although simple deconditioning cannot be excluded.

Lung Volumes

In our study, NAC was not associated with lower lung volumes. This is in line with published literature showing similar total lung capacity, FVC, and FEV_1 in subjects exposed to different combinations of chemotherapeutic agents, mainly platinum-based doublet. Kreuter et al[24] and Rivera et al[25] reported no decrease of FEV_1, FVC, or total lung capacity. Two studies even reported an improvement in lung volumes after NAC.[24,26]

Limitations

Several limitations should be taken into account when interpreting our results. First, direct toxicity on pulmonary, circulatory, neural, and muscular components cannot be distinguished from the indirect effects of chemotherapeutic agents such as deconditioning or changes in body weight and composition due to physical inactivity. Second, our study was not designed to determine the relationship between NAC and short- or long-term surgical therapeutic outcome, precluding any conclusions on this specific point. Finally, we did not perform CPET before starting NAC to measure longitudinally its impact on CPET results. Observations were made on the basis of the CPET post-NAC only. Our cross-sectional design thus limits any strong conclusions on causality, although collectively, the literature convincingly suggests such a causal relationship. We find that the potential limitation of peak $\dot{V}_{O_2}$ after NAC should nevertheless be taken into account in the still ongoing debate of choosing preoperative versus postoperative chemotherapy. Research should specifically address the effects of NAC on postoperative complications and the role of CPET as a risk-stratifying tool.

Implications for Clinical Decision and Research

Clinicians in charge of multimodal therapy in non-small-cell lung cancer should carefully weigh the risks against the potential benefits of NAC, since it may contribute to decreasing fitness level and thus impact the short- and long-term outcome of primary tumor resection. Patients should be advised to maintain or even increase their level

of fitness when started on NAC. In this perspective, randomized controlled trials suggests benefits from preoperative high intensity training in subjects with non-small-cell lung cancer bring new therapeutic modalities when addressing surgical risk for lung cancer patients.[34,35] However, exercise training in patients with NAC may represent a significant challenge.

Conclusion

NAC was associated with a reduced exercise capacity in potentially resectable stage IIIA and IIIB non-small-cell lung cancer subjects. Impaired gas exchange (reduced D$_{LCO}$), decreased oxygen transport (anemia), cardiotoxicity, and physical deconditioning are plausible mechanisms involved. Because peak V̇$_{O_2}$ is a major predictive factor for peri- and postoperative complications and of short-term survival, NAC could potentially influence these outcomes. Randomized controlled trials should be conducted to assess whether the reduced exercise capacity related to NAC influences outcome and whether it could be improved by concurrent physical rehabilitation.

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