Resting End-tidal Carbon Dioxide Predicts Respiratory Complications in Patients Undergoing Thoracic Surgical Procedures

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Background. **Ventilatory efficiency ($\dot{V}E/\dot{V}CO_2$ slope [minute ventilation to carbon dioxide output slope]) has been shown to predict morbidity and mortality in lung resection candidates. Patients with increased $\dot{V}E/\dot{V}CO_2$ during exercise also exhibit an increased $\dot{V}E/\dot{V}CO_2$ ratio and a decreased end-tidal CO_2 at rest. This study hypothesized that ventilatory values at rest predict respiratory complications and death in patients undergoing thoracic surgical procedures.**

Methods. **Inclusion criteria for this retrospective, multicenter study were thoracotomy and cardiopulmonary exercise testing as part of routine preoperative assessment. Respiratory complications were assessed from the medical records (from the hospital stay or from the first 30 postoperative days). For comparisons, Student's *t* test or the Mann-Whitney *U* test was used. Logistic regression and receiver operating characteristic analyses were performed for evaluation of measurements associated with respiratory complications. Data are summarized as mean ± standard deviation; $p < 0.05$ is considered significant.**

Results. **Seventy-six subjects were studied. Postoperatively, respiratory complications developed in 56 (74%) patients. Patients with postoperative respiratory complications had significantly lower resting tidal volume (0.8 ± 0.3 vs 0.9 ± 0.3L; $p = 0.03$), lower rest end-tidal CO_2 (28.1 ± 4.3vs 31.5 ± 4.2 mm Hg; $p < 0.01$), higher resting $\dot{V}E/\dot{V}CO_2$ ratio (45.1 ± 7.1 vs 41.0 ± 6.4; $p = 0.02$), and higher $\dot{V}E/\dot{V}CO_2$ slope (34.9 ± 6.4 vs 31.2 ± 4.3; $p = 0.01$). Logistic regression (age and sex adjusted) showed resting end-tidal CO_2 to be the best predictor of respiratory complications (odds ratio: 1.21; 95% confidence interval: 1.06 to 1.39; area under the curve: 0.77; $p = 0.01$).**

Conclusions. **Resting end-tidal CO_2 may identify patients at increased risk for postoperative respiratory complications of thoracic surgical procedures.**

(Ann Thorac Surg 2016;■:■–■)

Cardiopulmonary exercise testing (CPET) is recommended for preoperative evaluation and risk stratification of lung resection candidates [1, 2]. One of the most frequently used CPET measurements is peak oxygen consumption ($\dot{V}O_2$) [3]. However, ventilatory efficiency ($\dot{V}E/\dot{V}CO_2$ slope [minute ventilation to carbon dioxide output slope]) has also been demonstrated to predict respiratory complications and death of lung resection candidates and has been shown superior to peak oxygen consumption ($\dot{V}O_2$) [1].

The $\dot{V}E/\dot{V}CO_2$ slope is frequently used in patients with chronic heart failure as a marker of prognosis and functional capacity [4]. However, $\dot{V}E/\dot{V}CO_2$ has also been shown to be related to pulmonary artery pressure, pulmonary vascular resistance and ventilatory drive in patients without heart failure [5]. Underlying mechanisms that alter $\dot{V}E/\dot{V}CO_2$ seem to operate during exercise as well as at rest. Indeed, patients with an increased $\dot{V}E/\dot{V}CO_2$ ratio and a low partial pressure of end-tidal CO_2 ($PETCO_2$) during peak exercise have been shown to have an increased $\dot{V}E/\dot{V}CO_2$ ratio and a low $PETCO_2$ at rest also [6, 7], a finding suggesting that resting ventilatory measurements may have value for risk prediction. Identification of a simple, easy to obtain resting ventilatory measurements that effectively predicts respiratory complications and death after thoracotomy may be useful because many patients are not able or are unwilling to perform CPET [8]. Furthermore, it would allow screening of a greater number of patients.

We hypothesized that resting ventilatory measurements predict respiratory complications and death in

Accepted for publication May 17, 2016.

Presented at the Poster Session of The International Conference of The American Thoracic Society, San Francisco, CA, May 13–18, 2016.

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0003-4975/$36.00
http://dx.doi.org/10.1016/j.athoracsur.2016.05.070

Abbreviations and Acronyms

CPET	=	cardiopulmonary exercise testing
D_{LCO}	=	diffusing lung capacity for carbon monoxide
ERS/ESTS	=	European Respiratory Society and the European Society of Thoracic Surgery
FEV_1	=	forced expiratory volume in 1 second
FVC	=	forced vital capacity
ICU	=	intensive care unit
O_2	=	oxygen
P_{ETCO_2}	=	partial pressure of end-tidal carbon dioxide
$\dot{V}_{CO_2}$	=	carbon dioxide output
$\dot{V}_E$	=	minute ventilation
$\dot{V}_E/\dot{V}_{CO_2}$	=	ventilatory efficiency
$\dot{V}_{O_2}$	=	oxygen consumption
V_T	=	tidal volume

patients undergoing thoracic surgical procedures. Accordingly, the aim of this study was to compare ventilatory measurements at rest and during exercise, hospital and intensive care unit (ICU) length of stay, and mortality rates in patients with and without postoperative respiratory complications after thoracic surgical procedures.

Patients and Methods

Patient Selection

The study subjects were consecutive patients who underwent thoracotomy because of lung infiltration (confirmed or highly suspected lung tumor) and CPET as part of their preoperative assessment. Patients were retrospectively selected from three centers in the Czech Republic from 2011 to 2015. According to the European Respiratory Society and the European Society of Thoracic Surgery (ERS/ESTS) guidelines, CPET was indicated and was performed in all patients with a preoperative forced expiratory volume in 1 second (FEV_1) or a single-breath diffusing capacity for carbon monoxide (D_{LCO}) lower than 80% of predicted values [3]. Video-assisted thoracoscopic surgical procedures were not included. This retrospective study was conducted in accordance with the declaration of Helsinki and approved by the Ethics Committee of the Thomayer Hospital in Prague, Czech Republic (2036/15G-15-10-02); the Ethics Committee of the University Hospital Brno, Czech Republic (EKFNBRNO-14102015/1); and the Ethics Committee of St. Anne's University Hospital, Brno, Czech Republic (66V/2015).

Cardiopulmonary Exercise Testing

All patients performed preoperative symptom-limited CPET until exhaustion on an electronically braked cycle ergometer (Ergoline, Ergometrics 800, Bitz, Germany) with a 12-channel electrocardiography unit (Schiller AG, AT-104, Baar, Switzerland) using a linearly increasing (25 W/min) ramp protocol. Expired gases and volumes were analyzed using the PowerCube-Ergo cardiopulmonary exercise system (Ganshorn Medizin Electronic GmbH, Niederlauer, Germany). Measured variables included peak oxygen consumption ($\dot{V}_{O_2}$), CO_2 output ($\dot{V}_{CO_2}$), P_{ETCO_2}, tidal volume (V_T), and minute ventilation ($\dot{V}_E$). All data were continuously monitored and recorded. Variables were reported as averages obtained over the final 30 seconds of each workload. Derived measurements included ventilatory efficiency slope ($\dot{V}_E/\dot{V}_{CO_2}$ slope), $\dot{V}_E/\dot{V}_{CO_2}$ ratio for rest and peak exercise [9], respiratory exchange ratio (RER), and O_2 pulse defined as a ratio of $\dot{V}_{O_2}$ and heart rate.

Pulmonary Function Tests

Pulmonary function tests were performed before CPET. Pulmonary function measurements included spirometry and D_{LCO}. Measurements chosen for further assessment were forced vital capacity (FVC), FEV_1, FEV_1/FVC, and D_{LCO}. These values are expressed as a percentage of predicted value. All measurements were made in accordance with American Thoracic Society standards [10].

Inoperability Criteria

Inoperability criteria were defined as peak predicted postoperative $\dot{V}_{O_2}$ of less than 10 mL/kg/min or less than 35% predicted, in association with predicted postoperative FEV_1 of less than 30% and D_{LCO} of less than 30%, according to published ERS/ESTS guidelines [3]. The predicted postoperative values were calculated using the ERS/ESTS compliant "split function" calculation (the segment method) [3].

Mortality Rates and Pulmonary Complications

In all subjects, ICU stay, hospital stay, and 30- and 90-day mortality rates were assessed. Respiratory complications were assessed from the medical records by one investigator from each center from the first 30 postoperative days or from the hospital stay.

Respiratory complications were defined similar previous studies [1, 11–13]: pneumonia (chest roentgenogram infiltrates and at least two other markers including fever or leukocytosis or leukopenia or purulent sputum production); atelectasis (chest roentgenogram signs and bronchoscopy with plug removal); respiratory failure requiring mechanical ventilation (noninvasive ventilation or tracheal intubation and invasive pulmonary ventilation); adult respiratory distress syndrome (arterial partial pressure of O_2/fraction of inspired O_2 <300) [14]; pneumothorax present on the third postoperative day, as confirmed by chest roentgenogram (changes or a new air-fluid level in case of pneumonectomy), thoracic ultrasound, or drain leak; tracheostomy. Additionally, long-lasting pleural effusions present on the third postoperative day, as confirmed by chest roentgenogram (rapid filling of the postpneumonectomy cavity with a shift toward the opposite side in case of pneumonectomy), thoracic ultrasound, or drainage of more than 200 mL/day, were also considered respiratory complications.