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Effective Bronchoscopic Lung Volume Reduction Accelerates Exercise Oxygen Uptake Kinetics in Emphysema

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BACKGROUND: The impact of bronchoscopic lung volume reduction (BLVR) on physiologic responses to exercise in patients with advanced emphysema remains incompletely understood. We hypothesized that effective BLVR (e-BLVR), defined as a reduction in residual volume > 350 mL, would improve cardiovascular responses to exercise and accelerate oxygen uptake ($\dot{V}O_2$) kinetics.

METHODS: Thirty-one patients (FEV_1, 36% ± 9% predicted; residual volume, 219% ± 57% predicted) underwent a constant intensity exercise test at 70% peak work rate to the limit of tolerance before and after treatment bronchoscopy (n = 24) or sham bronchoscopy (n = 7). Physiologic responses in patients who had e-BLVR (n = 16) were compared with control subjects (ineffective BLVR or sham bronchoscopy; n = 15).

RESULTS: e-BLVR reduced residual volume (−1.1 ± 0.5 L, $P = .001$), improved lung diffusing capacity by 12% ± 13% ($P = .001$), and increased exercise tolerance by 181 ± 214 s ($P = .004$). $\dot{V}O_2$ kinetics were accelerated in the e-BLVR group but remained unchanged in control subjects (Δ mean response time, −20% ± 29% vs 1% ± 25%, $P = .04$). Acceleration of $\dot{V}O_2$ kinetics was associated with reductions in heart rate and oxygen pulse response half-times by 8% (84 ± 14 to 76 ± 15 s, $P = .04$) and 20% (49 ± 16 to 34 ± 16 s, $P = .01$), respectively. There were also increases in heart rate and oxygen pulse amplitudes during the cardiodynamic phase post e-BLVR. Faster $\dot{V}O_2$ kinetics in the e-BLVR group were significantly correlated with reductions in residual volume ($r = 0.66$, $P = .005$) and improvements in inspiratory reserve volume ($r = 0.56$, $P = .024$) and exercise tolerance ($r = 0.63$, $P = .008$).

CONCLUSIONS: Lung deflation induced by e-BLVR accelerated exercise $\dot{V}O_2$ kinetics in patients with emphysema. This beneficial effect appears to be related mechanistically to an enhanced cardiovascular response to exercise, which may contribute to improved functional capacity.

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KEY WORDS: chronic obstructive pulmonary disease; exercise pulmonary; exercise testing

ABBREVIATIONS: 6MWD = 6-min walk distance; BLVR = bronchoscopic lung volume reduction; CWR = constant work rate; D_{LCO} = diffusing capacity of the lung for carbon monoxide; HR = heart rate; HRCT = high-resolution CT; IC = inspiratory capacity; IRV = inspiratory reserve volume; LVRS = lung volume reduction surgery; mMRC = Modified Medical Research Council; MRT = mean response time; MVC = maximum ventilatory capacity; O_2 = oxygen; PFT = pulmonary function test; RV = residual volume; SGRQ = St. George's Respiratory Questionnaire; τ = time constant; t_{50} = half-time; TD = time delay; TLC = total lung capacity; Tlim = time to the limit of tolerance; $\dot{V}CO_2$ = CO_2 output; $\dot{V}E$ = minute ventilation; $\dot{V}O_2$ = oxygen uptake; WR = work rate

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Improved exercise capacity is a key objective of therapeutic interventions in patients with COPD. Exercise intolerance in COPD is multifactorial,[1,2] and understanding the physiologic mechanisms that underlie exercise limitation may provide a rationale for designing novel treatment and rehabilitative strategies.[3] Lung hyperinflation during exercise, with associated reduction in dynamic compliance and reduced respiratory muscle efficiency, results in an increased work of breathing in COPD.[2] Increased intrathoracic pressures may also impair the central hemodynamic responses to exercise with negative consequences on oxygen (O_2) delivery to the exercising muscles.[4] Impaired O_2 uptake ($\dot{V}O_2$) kinetics during the rest-to-exercise transition are characteristically related to higher operating lung volumes in COPD[5,6]; however, therapeutic interventions able to functionally deflate the lungs (either pharmacologic or nonpharmacologic) have been associated with improved O_2 delivery, faster $\dot{V}O_2$ kinetics, and increased exercise tolerance in patients with moderate to severe COPD.[5-7]

In advanced COPD, lung volume reduction surgery (LVRS) has been found to improve ventilatory neuromechanical coupling,[8] right and left ventricular preload,[9-11] and oxyhemoglobin saturation,[12] which may enhance O_2 delivery to the exercising muscles and contribute to increased exercise capacity.[13] Interestingly, lung deflation induced by bronchoscopic lung volume reduction (BLVR) has also shown beneficial effects on the central hemodynamic responses at rest and during exercise.[14,15] The postprocedure recovery period is typically substantially shorter with BLVR than LVRS, with few systemic catabolic processes associated with surgery and minimal muscle deconditioning due to prolonged convalescence.[16,17]

Swift changes in lung volumes occurring after effective BLVR (e-BLVR) should allow examination of the specific impact of mitigating lung hyperinflation on $\dot{V}O_2$ kinetics, without the confounding effects of surgery. We, therefore, tested the primary hypothesis that lung deflation induced by e-BLVR would accelerate $\dot{V}O_2$ kinetics in patients with emphysema. We also postulated that these beneficial findings would be associated with improved cardiovascular adjustments to exercise and greater exercise tolerance.

Materials and Methods

Subjects

Thirty-one patients (25 men) with severe to very severe COPD were included in this study from a total of 114 enrolled into previous BLVR treatment trials (endobronchial valves,[14,18] lung volume reduction coils,[19] or endobronchial autologous blood instillation[20]) performed between 2003 and 2013 at Royal Brompton and Harefield NHS Foundation Trust (#11/LO/1608, 09/H0708/51, and 08/H0708/100). All patients had a heterogeneous pattern of disease with a target area identified by thoracic high-resolution CT (HRCT) scan. Patients in whom BLVR effectively deflated the lungs comprised the "e-BLVR" group (n = 16). We chose a reduction in residual volume (RV) > 350 mL as the threshold for defining e-BLVR based on the accepted minimal clinically important difference for RV reduction in similar patient populations following BLVR.[21] The control group (n = 15) included patients who had either noneffective BLVR (RV reduction < 350 mL) or a bronchoscopy with sham treatment.[18] Subjects were excluded if they were unable to perform a constant work rate (CWR) test on a cycle ergometer for at least 4 min at a minimum of 5 W, thereby precluding kinetics characterization.[22,23] Other exclusion criteria included severe cardiovascular comorbidity and long-term O_2 therapy (> 15 h/d to treat persistent hypoxia). None of the patients participated in rehabilitation programs between the procedure and follow-up testing.

Study Design

In this retrospective study, after written informed consent, most patients (10 of 16 in e-BLVR and 12 of 15 in control subjects) completed the four study visits within approximately 3 months of the planned procedure (e-BLVR: mean [range], 90 [31-223] days; control subjects: 102 [83-239] days). Visit 1 (within 2 weeks prior to the planned bronchoscopic procedure) included demographics, medical history, St. George's Respiratory Questionnaire (SGRQ),[24] modified Medical Research Council (mMRC) dyspnea scale,[25] prebronchodilator and postbronchodilator pulmonary function tests (PFTs), resting arterialized capillary blood gas analyses,[26] an HRCT scan of the thorax,[27] a 6-min walking distance (6MWD) test,[28] and an incremental cardiopulmonary exercise test.[29] Visit 2 (within 1 week from visit 1) included CWR at 70% of the previously determined peak work rate (WR) (e-BLVR = 41 [22-70] W; control subjects: 26 [7-70] W) to the limit of tolerance (Tlim). Visit 3 involved the planned bronchoscopic procedure (endobronchial valve treatment, endobronchial coil placement, endobronchial blood instillation, or a sham bronchoscopy).[14,18-20] Visit 4 included SGRQ, mMRC dyspnea scale, resting PFTs, resting arterialized capillary blood gas analyses, 6MWD, chest HRCT scan, and CWR at the same WR in visit 2.

Procedures

Spirometry,[30,31] diffusing capacity of the lung for carbon monoxide (D_{LCO}),[26] and body plethysmography[32] were measured using a CompactLab system (Erich Jaeger GmbH). Blood gas tensions were analyzed in arterialized earlobe capillary samples. Breath-by-breath cardiopulmonary variables were obtained using a metabolic cart (Oxycon Pro; Erich Jaeger GmbH). Peak $\dot{V}O_2$ and WR were expressed as % predicted normal values.[33] Minute ventilation ($\dot{V}_E$) was

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