Lung deflation and oxygen pulse in COPD: Results from the NETT randomized trial

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Summary
Background: In COPD patients, hyperinflation impairs cardiac function. We examined whether lung deflation improves oxygen pulse, a surrogate marker of stroke volume.
Methods: In 129 NETT patients with cardiopulmonary exercise testing (CPET) and arterial blood gases (ABG substudy), hyperinflation was assessed with residual volume to total lung capacity ratio (RV/TLC), and cardiac function with oxygen pulse (O₂ pulse = VO₂/HR) at baseline and 6 months. Medical and surgical patients were divided into “deflators” and “non-deflators” based on change in RV/TLC from baseline (ΔRV/TLC). We defined deflation as the ΔRV/TLC

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Introduction

There is increasing recognition of an association between expiratory airflow limitation, hyperinflation, and cardiac dysfunction in patients with chronic obstructive pulmonary disease (COPD).1–3 This interaction may be mediated by several factors including the association between COPD and cardiovascular disease6,7 as well as lung-cardiac interdependence with pulmonary hyperinflation in a closed thoracic cage. In a large population-based study of normals and subjects with mild COPD, Barr et al.8 demonstrated that the extent of emphysema, as measured by computed tomography (CT), and the severity of spirometrically assessed airflow obstruction were significantly associated with reduced left ventricular end diastolic volume, stroke volume, and cardiac output. These findings were thought to be due to a hyperinflated lung extrinsically compressing the left ventricle (LV) or to an underappreciated degree of vascular remodeling in subjects with emphysema. Recently, in a study of 138 patients with mild-to-severe COPD, Watz and colleagues9 showed that hyperinflation was significantly associated with impaired LV filling and right ventricular dysfunction, and that impaired LV filling was independently associated with decreased exercise tolerance. The extent to which impaired cardiac function can be improved by reducing hyperinflation may have implications in patient management.

Several prior investigations in limited numbers of patients have studied this question with mixed results3,9–13; however, the general consensus is that reducing the degree of hyperinflation may improve cardiac function. We postulated that data from the patients enrolled in the National Emphysema Treatment Trial (NETT),14 provided the best available source of information to answer this question, because patients had lung volumes and cardiopulmonary exercise testing measured over time and were randomized to lung volume reduction surgery (LVRS) or medical therapy. We therefore used this cohort to determine whether reduction of hyperinflation (assessed by the change in ratio of residual volume to total lung capacity, ΔRV/TLC) with LVRS improves left ventricular function as measured by oxygen pulse (O₂ pulse), a non-invasive correlate of stroke volume.15

Materials and methods

NETT compared the effects of LVRS vs. medical therapy on survival and exercise capacity in COPD patients without significant left ventricular dysfunction or pulmonary vascular disease.12,14,16 All patients underwent cardiopulmonary exercise (CPET) and pulmonary function testing (PFT) at baseline (after completion of pulmonary rehabilitation) and post-randomization.17 A subset of patients simultaneously participated in an exercise substudy with blood gases (ABG substudy). Only patients who completed all tests at baseline and at 6 months were included in this analysis. The original NETT study was approved by the institutional review board at each participating center, and all patients provided written informed consent. Data analysis for the current study was approved by the Brigham and Women's Hospital IRB (2008P00157).

Exercise testing

CPET was performed while breathing 30% oxygen (CPET protocol has previously been published in detail).17 In the ABG substudy, oxygen uptake (VO₂), carbon dioxide production (VCO₂), heart rate (HR), and workload were measured every minute during exercise. Patients with a respiratory exchange ratio (RER = VCO₂/VO₂) at peak VO₂ of <0.7 or >1.3 were excluded as values outside this range suggest poor quality data.13,16,19 For the remaining (non-ABG substudy) patients (validation cohort), VO₂ was not recorded and VCO₂ was used to calculate VO₂ using an RER of 0.8.15 In this cohort, HR and VCO₂ were measured at rest, during unloaded pedaling, and at peak exercise. Patients with different exercise protocols at baseline and 6 months were excluded from this analysis.

Oxygen pulse

In COPD, the O₂ pulse (VO₂/HR) is used as a simple marker of stroke volume (SV).1,9,10,13,20,21 Assuming a relationship between cardiac output and VO₂, changes in the O₂ pulse approximate changes in SV. This study’s primary outcome was the percent change in peak O₂ pulse from baseline (ΔO₂
pulse). In the ABG substudy, peak O2 pulse was calculated using peak VO₂ and HR at peak VO₂. Baseline and follow-up O2 pulse were compared at iso-work (5, 10, 15, and 20 W) in a subset of patients who exercised for at least 3 min and reached at least 25 W (further details regarding this analysis are available in the online data supplement, Figure 1S). In the validation cohort, ΔO₂ pulse was examined at rest, during unloaded pedaling, and at peak exercise.

**Pulmonary function tests and other clinical data**

We chose RV/TLC to represent the degree of hyperinflation. Additional analysis using inspiratory capacity presented in the online data supplement (Figure 2S) provided similar findings. ΔRV/TLC was expressed as percent change from baseline. Anthropometric data, medications, and resting room air blood gases were obtained at baseline and at 6 months. The baseline CT scan distribution of emphysema was classified as upper or non-upper lobe predominant.

**Statistical analysis**

We used the intention-to-treat principle. Medical and surgical arms were subdivided into lung "deflators" and "non-deflators." Deflators were those patients who experienced a decrease in the value of RV/TLC (ΔRV/TLC) that was more negative than −4.43%. This threshold was chosen based on the minimal improvement seen in 75% of patients in the ABG substudy surgical cohort. Baseline characteristics, ΔRV/TLC, and ΔO₂ pulse between groups were compared with parametric and non-parametric tests as appropriate. Within group values at baseline and 6 months were compared using paired t-tests. To determine whether deflation is associated with improvement in O₂ pulse (ΔO₂ pulse > 0), a logistic regression model was created with improved O₂ pulse (yes/no) at submaximal exercise as the outcome and deflation (yes/no) as the primary predictor. Covariates (all measured at baseline) were selected on the basis of their biological plausibility to confound the relationship between deflation and improvement in O₂ pulse. Finally, we tested for effect modification of treatment assignment on the relationship between deflation and improvement in O₂ pulse by adding an interaction term to the model. A p-value < 0.05 was considered significant. Data was analyzed using SAS 9.1 (NC, USA).

**Results**

Of the 1218 patients enrolled in NETT, 847 completed baseline and 6 month follow-up CPETs and PFTs (Fig. 1). In addition 238 of the 1218 patients participated in the ABG substudy. One hundred and nine of these patients were excluded because of missing data (99 patients) or because their calculated RER fell outside of the pre-specified range (10 patients). The remaining 129 patients overlapped completely with the above 847 patients. Therefore, the two groups were treated as separate cohorts: ABG substudy (N = 129), validation cohort (N = 718).

**Figure 1**  Consort diagram of the study cohorts. 1218 patients were enrolled in NETT. Of those, 847 completed baseline and 6 month follow-up non-invasive cardiopulmonary exercise tests (CPET) and had pulmonary function tests. Of the original 1218 patients, 238 were simultaneously enrolled in the ABG substudy. Of these, 129 had baseline and follow-up CPET data and had normal respiratory exchange ratios (RER). These 129 overlapped completely with the 847 patients. Therefore, the two groups were treated as separate cohorts (*): ABG substudy (N = 129), validation cohort (N = 847 − 129 = 718). 67 patients from the ABG substudy cohort met criteria for inclusion in the iso-work analysis.

**ABG substudy**

Of the 129 patients from the ABG substudy, 67 had been randomized to continued medical treatment and 62 to LVR. Baseline characteristics of these patients dichotomized by deflator/non-deflator are presented in Table 1. Forty-eight percent of the cohort deflated; of these deflators, 76% were in the surgical arm and 24% were in the medical arm. Deflators were more likely to have upper lobe predominant emphysema (p = 0.02). There was a significant inverse correlation between ΔO₂ pulse and ΔRV/TLC (Spearman correlation coefficient −0.50, p-value < 0.0001). Surgical deflators had a greater improvement in hyperinflation than medical deflators (median −18.0% vs. −9.3%, p = 0.0003; Fig. 2A). Median absolute changes in RV and TLC in surgical deflators were −1.36 L (−1.85 to −1.06) and −1.09 L (−1.59 to −0.70) and in medical deflators −0.6 L (−0.97 to −0.32) and −0.27 L (−0.47 to 0.17), respectively. Surgical and medical non-deflators experienced worsening hyperinflation (RV/TLC ratios increased by a median of 1.9% and 4.4%, respectively). Compared with medical and surgical non-deflators, surgical deflators had a significant improvement in ΔO₂ pulse at peak exercise. Surgical deflators also had a higher ΔO₂ pulse at peak exercise than medical deflators,
Table 1  Baseline characteristics of ABG substudy cohort dichotomized by deflator/non-deflator.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Deflators, N = 62</th>
<th>Non-deflators, N = 67</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surgical patients — no. (%)</td>
<td>47 (76%)</td>
<td>15 (22%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Age yrs</td>
<td>68 (64–71)</td>
<td>67 (63–72)</td>
<td>0.75</td>
</tr>
<tr>
<td>Female sex — no. (%)</td>
<td>19 (31%)</td>
<td>14 (21%)</td>
<td>0.23</td>
</tr>
<tr>
<td>White race — no. (%)</td>
<td>57 (92%)</td>
<td>58 (87%)</td>
<td>0.40</td>
</tr>
<tr>
<td>BMI – kg/m²</td>
<td>24.9 (22.5–27.9)</td>
<td>25.6 (22.5–28.1)</td>
<td>0.79</td>
</tr>
<tr>
<td>Pack years</td>
<td>62 (46–86)</td>
<td>60 (40–77)</td>
<td>0.22</td>
</tr>
<tr>
<td>Upper lobe predominant distribution of emphysema on CT — no. (%)a</td>
<td>43 (69%)</td>
<td>32 (48%)</td>
<td>0.02</td>
</tr>
<tr>
<td>FEV₁ % predictedb</td>
<td>28 (22–31)</td>
<td>28 (22–31)</td>
<td>0.82</td>
</tr>
<tr>
<td>TLC % predictedb</td>
<td>131 (116–135)</td>
<td>126 (115–137)</td>
<td>0.36</td>
</tr>
<tr>
<td>RV % predictedd</td>
<td>215 (184–250)</td>
<td>215 (179–249)</td>
<td>0.34</td>
</tr>
<tr>
<td>DLCO % predictedc</td>
<td>29 (22–36)</td>
<td>29 (24–35)</td>
<td>0.97</td>
</tr>
<tr>
<td>RV/TLC</td>
<td>0.63 (0.59–0.68)</td>
<td>0.60 (0.55–0.66)</td>
<td>0.07</td>
</tr>
<tr>
<td>Room air PaO₂ — mmHgd</td>
<td>64 (55–72)</td>
<td>63 (55–70)</td>
<td>0.44</td>
</tr>
<tr>
<td>Room air PaCO₂ — mmHgd</td>
<td>41 (38–44)</td>
<td>41 (37–45)</td>
<td>0.90</td>
</tr>
<tr>
<td>6 min walk distance — m</td>
<td>398 (330–457)</td>
<td>396 (342–444)</td>
<td>0.72</td>
</tr>
<tr>
<td>Maximal workload — W</td>
<td>39 (29–60)</td>
<td>39 (25–50)</td>
<td>0.52</td>
</tr>
<tr>
<td>O₂ pulse — mL/beat</td>
<td>6.8 (5.92–8.72)</td>
<td>7.43 (5.9–9.07)</td>
<td>0.55</td>
</tr>
</tbody>
</table>

Medications

<table>
<thead>
<tr>
<th>Medication</th>
<th>Deflators, no. (%)</th>
<th>Non-deflators, no. (%)</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beta blocker — no. (%)</td>
<td>1 (2%)</td>
<td>0 (0%)</td>
<td>0.48</td>
</tr>
<tr>
<td>Digoxin — no. (%)</td>
<td>6 (10%)</td>
<td>2 (3%)</td>
<td>0.15</td>
</tr>
<tr>
<td>Anti-hypertensive — no. (%)</td>
<td>11 (18%)</td>
<td>14 (21%)</td>
<td>0.66</td>
</tr>
<tr>
<td>Anti-arrhythmic — no. (%)</td>
<td>4 (6%)</td>
<td>4 (6%)</td>
<td>1.00</td>
</tr>
<tr>
<td>Long acting beta agonist — no. (%)</td>
<td>35 (56%)</td>
<td>35 (52%)</td>
<td>0.72</td>
</tr>
<tr>
<td>Short acting beta agonist — no. (%)</td>
<td>51 (82%)</td>
<td>62 (93%)</td>
<td>0.11</td>
</tr>
<tr>
<td>Anticholinergic — no. (%)</td>
<td>53 (85%)</td>
<td>62 (93%)</td>
<td>0.26</td>
</tr>
<tr>
<td>Oral bronchodilator — no. (%)</td>
<td>1 (2%)</td>
<td>1 (1%)</td>
<td>1.00</td>
</tr>
<tr>
<td>Inhaled corticosteroid — no. (%)</td>
<td>50 (81%)</td>
<td>44 (66%)</td>
<td>0.07</td>
</tr>
</tbody>
</table>

Definition of abbreviations: BMI = body mass index, FEV₁ = forced expiratory volume in one second, TLC = total lung capacity, RV = residual volume, DLCO = diffusing capacity of carbon monoxide.

Data presented as medians and interquartile ranges unless otherwise specified.

a Non-deflators missing data for one patient.
b Measurement obtained post-bronchodilator.
c Baseline DLCO was obtained prior to pulmonary rehabilitation; all other baseline pulmonary function measures were completed after pulmonary rehabilitation.
d Deflators missing data for one patient.

though this was not statistically significant (median 13.6% vs. 1.8%, p = 0.12; Fig. 2B).

To determine whether improved O₂ pulse in deflators was due to an improvement in the ventilatory limitation to exercise rather than to an improvement in cardiovascular function, absolute change in O₂ pulse (6 month follow-up minus baseline) was studied at submaximal (iso-work) exercise: 5 W, 10 W, 15 W, and 20 W. Sixty-seven of the 129 patients, who met our predefined criteria outlined in the Methods section and the online data supplement, were considered in this iso-work analysis. This group was comprised of 34 medical patients (11 deflators, 23 non-deflators) and 33 surgical patients (24 deflators, 9 non-deflators). Baseline characteristics of the surgical patients, dichotomized by deflator/non-deflator, are presented in Table 2. Surgical deflators were significantly more likely to have upper lobe predominant emphysema and more hyperinflation at baseline than surgical non-deflators. There was no difference between the groups in medication use at any time. In surgical deflators, the difference between baseline and follow-up O₂ pulse widened at each load, becoming significant at 20 W (Fig. 3A). This improvement in O₂ pulse corresponded with a significant decrease in HR without a significant change in VO₂ (Fig. 3C, B). These findings were not replicated in the other three groups (surgical non-deflators, medical deflators, and medical non-deflators).

Validation cohort

Of the 718 patients in this analysis, 335 were medical (263 non-deflators, 72 deflators) and 383 were surgical (80 non-deflators, 303 deflators). Baseline characteristics of this cohort dichotomized by deflator/non-deflator were similar to those of the ABG substudy cohort (online data supplement, Table 1S). Medication use did not differ between deflators and non-deflators at any time. Surgical deflators experienced a larger decrease in their mean RV/TLC than medical deflators (−18.2% vs. −10.0%, p < 0.0001). As in the substudy, medical and surgical non-deflators had an increase in their mean RV/TLC (4.6% and 3.6% respectively).
with worsening of their $O_2$ pulse (mean $-3.2\%$ and $-4.5\%$ respectively). At six months, there was a greater improvement in $O_2$ pulse at peak exercise in surgical deflators than medical deflators (mean $18.9\%$ vs. $1.1\%, p < 0.0001$).

In surgical deflators, improvement in $O_2$ pulse from baseline to six month follow-up was significant at rest $(0.32 \text{ mL/beat}, p < 0.0001)$, during unloaded pedaling $(0.47 \text{ mL/beat}, p < 0.0001)$ and at peak exercise $(1.16 \text{ mL/beat}, p < 0.0001)$. The improvements at iso-work were associated with reductions in HR and improvements in VO$_2$ (Fig. 4). Similar trends were observed in the medical deflators at peak exercise and during unloaded pedaling. $O_2$ pulse worsened in surgical and medical non-deflators at both unloaded pedaling and peak exercise. In surgical deflators, mean hemoglobin decreased from baseline to follow-up $(0.42 \text{ g/dL}, p < 0.0001)$, but mean oxygen saturation increased minimally at rest $(0.60\%, p < 0.0001)$, during unloaded pedaling $(0.89\%, p < 0.0001)$, and at peak exercise $(0.59\%, p = 0.0006)$.

### Relationship between deflation and improvement in $O_2$ pulse

In the validation cohort, 386 of the 718 patients had an improvement in $O_2$ pulse at submaximal exercise. On univariate analysis the odds of having an improved $O_2$ pulse for deflators was $2.23$ times that of non-deflators (CI $1.70-3.09$, $p < 0.0001$). This relationship was attenuated though still highly significant after adjusting for treatment assignment, age, sex, body mass index, distribution of emphysema, FEV$_1$ percent predicted, and DLCO percent predicted (OR $1.88$, CI $1.30-2.72$, $p = 0.0008$). There was no evidence of effect modification by treatment assignment (interaction $p > 0.05$).

### Discussion

In this study of 847 patients from NETT, a decrease in hyperinflation as measured by the RV/TLC after LVRS, and in some patients after medical therapy, was associated with improved $O_2$ pulse 6 months following randomization. The improvement in $O_2$ pulse was significant at rest, at peak exercise, and at submaximal levels of exercise. The improvement was associated with a decrease in HR and an increase in oxygen uptake at iso-work. The effect was independent of the means by which a patient was deflated, and the magnitude of improvement was directly related to the degree of deflation. These findings suggest that decreased hyperinflation through effective lung volume reduction is associated, at least in part, with improved cardiac function.

Prior investigations have shown an association between hyperinflation and impaired cardiac function. Two studies demonstrated an improvement in $O_2$ pulse following LVRS in limited numbers of patients. In a study of 21 patients, Benditt and colleagues found significant increases in maximal work, oxygen uptake, heart rate, $O_2$ pulse, and minute ventilation at peak exercise three months after LVRS. The improvement was thought to be secondary to increases in ventilatory reserve. At iso-work there was a non-significant increase in $O_2$ pulse that the authors suggested could be due to improved right or left ventricular performance. In a single center case series of 25 patients with severe COPD, Cordova et al. found a significant decrease in RV/TLC ratio and a significant increase in maximal $O_2$ pulse three months after LVRS. In 20 of these patients, the authors demonstrated a significant improvement in $O_2$ pulse at iso-time (though only a single time point); as in our study, the iso-time improvement in $O_2$ pulse was associated with a significant decrease in heart rate from baseline. Non-significant improvements in $O_2$ pulse at max work and at iso-time persisted at 6 months and 12 months. The lack of significance was likely due to the
small number of patients (n = 10). Our findings extend these observations in a much larger cohort, thus facilitating multivariate modeling to determine whether deflation is independently associated with improvement in O₂ pulse. Additionally, comparison with a control group (patients randomized to the medical arm), allowed demonstration that improvements in hyperinflation were associated with improvements in O₂ pulse regardless of treatment mode. In our study, medical deflators also experienced a non-significant improvement in O₂ pulse at 6 month follow-up. The deflation in medical patients was smaller in magnitude which could account for the non-significant improvement in O₂ pulse in the medical deflators. These findings are consistent with the effects seen in a smaller randomized controlled trial of bronchodilator therapy.

Criner et al. suggested that improved exercise capacity following LVRS could be due to improvements in ventilatory mechanics with an improvement in ventilatory reserve. Thus, an improvement in O₂ pulse at peak exercise could merely reflect a lifting of the ventilatory limit to exercise and subsequently a longer duration of exercise. This was true for lung "deflators" in this study who exercised longer and reached a higher peak exercise heart rate. However, the improvements in O₂ pulse that we observed at iso-time and submaximal exercise were not due to a longer duration of exercise. We believe that at iso-work an improvement in ventilatory mechanics results in improved cardiac function manifested as a decrease in heart rate with improved O₂ pulse. Likewise, the minimal changes seen in hemoglobin and oxygen saturation from baseline to follow-up suggest a change in oxygen content is not responsible for our findings at iso-time or at peak exercise.

This study was not designed to determine the mechanism by which heart function improved after LVRS though the literature suggests several potential mechanisms. The swings in intrathoracic pressure decrease at rest and more so during exercise after LVRS. Decreases in the swing of intrathoracic pressures may alter cardiac preload and/or afterload thereby affecting cardiac function. Mineo et al. determined resting and exercise pulmonary hemodynamics in 12 patients before and 6 months after LVRS. Changes in rest vs. exercise right ventricular systolic volume and right ventricular ejection fraction correlated well with reduction in RV/TLC ratio (r = −0.68, p = 0.01; r = −0.65, p = 0.02, respectively) suggesting that a reduction in hyperinflation was a major determinant of the overall improvement in right ventricular performance. Montes de Oca and coworkers described a significant direct relationship between inspiratory intrathoracic pressures and maximal O₂ pulse in 25 patients with very severe COPD, suggesting that a reduction in left ventricular afterload may be the most important mechanism in improving SV after LVRS. Another potential mechanism, a decrease in pulmonary vascular resistance, has not been observed. Finally, LVRS may have anti-inflammatory effects affecting intrinsic cardiac function, as described by Mineo and colleagues who demonstrated an association between reduction in lung hyperinflation after LVRS and reduction in levels of circulating inflammatory mediators. Whatever the mechanism, improvement in central hemodynamics after LVRS may improve peripheral muscle oxygen delivery or utilization as suggested by Berton and colleagues.

We acknowledge limitations in this study. First, this was a post hoc analysis with obvious survivor bias. Second, we
used a non-invasive surrogate for cardiac function. Most investigators but not all, suggest that O₂ pulse is a good surrogate marker of SV in COPD. However, in this study, each patient served as his/her own control, and oxygen extraction was likely stable before and after LVRS. We believe this is reasonable, because an improvement in oxygen extraction after LVRS would bias our results against our findings. Third, in this study, exercise testing was done with all patients breathing 30% oxygen rather than room air. While the increase in fractional inspired oxygen (FiO₂) might affect measurements of VO₂, this would likely have resulted in a systematic bias. Additionally, this issue was addressed by using VCO₂, which should not be appreciably affected by an increased FiO₂, to calculate VO₂. Furthermore, using VCO₂ and an RER value of 0.8 to calculate VO₂ provided estimates of O₂ pulse at maximal exercise that correlated very well with estimates obtained when VO₂ was directly measured in the ABG substudy (Spearman correlation coefficient 0.81, p < 0.0001). While the RER value may increase as high as 0.95 during moderate exercise, our
findings of improved $O_2$ pulse at maximal exercise were replicated during unloaded pedaling and at rest. Additionally, when the analyses were done with assumed RER values of 0.9 and 1.0, similar results were obtained (analyses not shown). Notably during the baseline CPET in the ABG sub-study cohort, median RER values at one minute and peak exercise were 0.80 (0.76–0.87) and 0.86 (0.80–0.92), respectively. Finally, the NETT cohort was fairly homogeneous, comprised of patients with severe COPD, so it is unclear whether these results are generalizable to patients with less hyperinflation.

In conclusion, our findings suggest that decreased hyperinflation through effective lung volume reduction is associated with improved left ventricular function as measured by $O_2$ pulse. Further studies are needed to understand the clinical implications of these findings.

Conflicts of interest

None of the authors have any conflicts of interest to disclose.

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References


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