ERJ Express. **Published on January 20, 2012 as doi: 10.1183/09031936.00169311**

Abstract word count: 199

Body word count: 2500

Title: Increased oxygen pulse after LVRS is associated with reduced dynamic hyperinflation

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Drs. Lammi, Ciccolella, Marchetti, Kohler, and Criner have no actual or potential conflicts of interest related to this work.

Abstract

Stroke volume augmentation during exercise is limited in COPD patients because of decreased preload from dynamic hyperinflation (DH). We hypothesized that O_2 pulse and pulse pressure (PP) improve following LVRS and the magnitude of improvement correlates with reduction in DH.

We compared 16 emphysema patients undergoing LVRS with 6 emphysema patients not undergoing LVRS. O_2 pulse and PP were calculated from maximal cardiopulmonary exercise tests at baseline and six months later. End-expiratory lung volume to total lung capacity (EELV/TLC) represented DH. Comparisons were made between baseline and 6 months at metabolic isotimes (%VCO_2max).

At baseline, the LVRS group was older with higher FEV_1, but had similar hyperinflation to the non-LVRS group. At 6 months, O_2 pulse (50%, 75%, and 100%VCO_2max) and PP (50% and 75%VCO_2max) increased in LVRS, but not in the non-LVRS group. Baseline FRC/TLC inversely correlated with resting O_2 pulse (r=-0.449,p=0.04). Decreased EELV/TLC correlated with increased O_2 pulse at 75% (r=-0.487,p=0.02) and 100%VCO_2max (r=-0.548,p=0.008).

LVRS led to increased O_2 pulse and PP during exercise at metabolic isotimes 6 months following surgery. Reductions in DH correlated with increases in O_2 pulse during exercise. Reduction in lung volume may improve stroke volume response to exercise by decreasing dynamic hyperinflation.

Introduction

Chronic obstructive pulmonary disease (COPD) patients have impaired exercise tolerance which limits their quality of life. While ventilatory limitations, including dynamic hyperinflation, are the main cause of exercise intolerance in this population [1], causes for this impairment are likely multifactorial [2].

Impairment in cardiac mechanics in COPD may be one of the most important contributing factors. Stroke volume is reduced in COPD, especially during exercise [3]. Decreased stroke volume is due to increased intrathoracic pressures and decreased cardiac right-sided filling [4,5,6].

Along with its beneficial effects on mortality [7] and pulmonary function [8], lung volume reduction surgery (LVRS) improves exercise capacity by altering lung mechanics [7,9,10]. LVRS also favorably affects stroke volume, both at rest [8] and during exercise [11]. Increased right ventricular stroke volume has been reported post-LVRS to correlate with decreased resting hyperinflation [11]. The effect of dynamic hyperinflation on cardiac function during exercise in COPD, however, is unknown.

To investigate the effect of dynamic hyperinflation and LVRS on cardiac performance during exercise, we retrospectively analysed data from emphysema patients who had cardiopulmonary exercise tests before and after LVRS and compared their changes with those who did not undergo LVRS. We hypothesized that LVRS would lead to an increase in non-invasive markers of stroke volume (O_2 pulse [12,13,14] and pulse pressure [15,16]) during exercise and that these improvements would correlate with a reduction in dynamic hyperinflation.

Methods and Materials

Study design and patient selection

This was a retrospective, observational analysis. Sixteen patients were consecutively evaluated from our LVRS program (2/2004-11/2005). All patients included in this study underwent bilateral LVRS following Center for Medicare/Medicaid Services (CMS) approval of the procedure in January of 2004 and met standard criteria for LVRS [7]. Patients with a left ventricular ejection fraction less than 45%, pulmonary hypertension, or significant coronary artery disease were excluded from LVRS. Six emphysema patients who did not undergo LVRS (non-LVRS group) due to diffuse disease were consecutively selected from our advanced lung disease clinic. These patients were part of the medical arm of a clinical trial. All patients underwent CPET after pulmonary rehabilitation (baseline) and 6 months later (after surgery in the LVRS group). All patients were maximally treated with bronchodilators, oxygen if indicated, and none were current smokers. Temple University Hospital institutional review board approval was obtained to analyse patient data (protocol #13477).

Data collection

Pulmonary Function Testing

Pulmonary function testing was performed at baseline and again at 6 months. Spirometry was performed according to ATS/ERS guidelines [17] before and after the administration of a bronchodilator. The reference standard used was NHANES III [18]. Post-bronchodilator values for FEV_1, TLC, and RV were used in the subsequent analyses. Lung volumes were measured by body plethysmography [19] and D_LCO [20] measurements were done using standard techniques.

Cardiopulmonary Exercise Testing (CPET)

CPET was performed on a braked cycle ergometer (ViaSprint 150P; ViaSys Healthcare; Hoechberg, Germany) according to ATS/ERS guidelines [21] using the protocol employed in the NETT [9]. Exercise was performed while breathing oxygen through a mouthpiece with a calibrated pneumotachograph. Patients exercised on supplemental oxygen so that hypoxaemia was not a factor in limiting exercise performance, at the same fractional inspired concentration (30%) at baseline and 6 months later. A metabolic cart (VMax Encore; ViaSys Healthcare) was used to measure oxygen uptake (VO_2) and carbon dioxide production (VCO_2), and all data were collected on a breath-by-breath basis and reported as 20 second averages. Baseline data were collected while sitting on the bike at rest for 5 minutes, followed by 3 minutes of unloaded cycling as a warm-up. This was followed by the symptom-limited maximal exercise phase, which consisted of increasing levels of tension on the bike at a rate of 5 or 10 watts per minute until exhaustion. All patients were in normal sinus rhythm during the CPET.

Parameters were measured at metabolic isotimes expressed as %VCO_2max obtained during the baseline CPET. For instance, patient 1 had a VCO_2max on the baseline CPET of 0.941mL/min. In this example, parameters were measured at 100% VCO_2max (0.941 mL/min), 75%VCO_2max (0.706 mL/min), and 50%VCO_2max (0.471 mL/min) during the baseline and 6 month CPETs to match metabolic workloads.

Variables calculated

Pulse pressure

Blood pressure was measured manually using a sphygmomanometer and stethoscope at rest and every 2 minutes during the CPET.

Pulse pressure (mmHg) = systolic BP – diastolic BP

Oxygen pulse

Oxygen pulse, a non-invasive marker of stroke volume [12,13,14], was calculated from VO_2 and heart rate collected breath-by-breath during the CPET as previously described [22].

Oxygen pulse (mL/beat) = VO_2/HR

Measurement of Dynamic Lung Volumes

In order to measure end-expiratory lung volume (EELV) during exercise, the inspiratory capacity (IC) was measured by instructing the patient to inhale deeply from functional residual capacity to TLC as previously reported. Because TLC changes at most minimally during exercise [23], EELV can be calculated by subtracting IC from TLC.

EELV = TLC – IC.

Patients were instructed in the technique of performing the IC maneuver and three IC measurements were taken during the baseline phase of CPET. The baseline IC reported is the mean of these three measurements. The IC was measured every two minutes throughout exercise. The EELV/TLC ratio at peak exercise was the marker of dynamic hyperinflation.

Statistical Analysis

Data are reported as median (interquartile range). Baseline characteristics were compared using the Mann-Whitney U test. Changes in exercise parameters at metabolic

isotimes (%VCO_2max, see "Cardiopulmonary exercise testing" above) were compared within groups using the Wilcoxon signed rank test. Comparisons between groups in changes of pulmonary function and O_2 pulse/pulse pressure were performed using the Mann-Whitney U test. Correlations between changes in O_2 pulse and pulse pressure and changes in lung volumes were performed using Spearman rank order correlations. A p-value of <0.05 was considered statistically significant.

Results

Study participants

Baseline characteristics are displayed in Table 1. Compared to the non-LVRS group, LVRS patients were older, more likely to be male, and had a higher FEV_1. Lung volumes (RV, TLC, EELV/TLC), were similar between groups. The usage of respiratory medicines (bronchodilators, inhaled corticosteroids, and prednisone) was equal between groups. There were no changes in medications over the 6 month period in either group.

Changes in pulmonary function and exercise parameters at 6 months

Changes in pulmonary function, dynamic hyperinflation, and work performed on CPET are shown in Table 2. From baseline to 6 months, the LVRS group had greater increases in FEV_1 and FEV_1/FVC. Compared to the non-LVRS group, RV and TLC tended to be lower following LVRS after 6 months, but this did not reach statistical significance. Dynamic hyperinflation, as measured by the EELV/TLC ratio, had a greater reduction at 6 months in the LVRS compared to the non-LVRS group. Patients in the LVRS group performed more work during the 6 month CPET, but not to the level of statistical significance.

Changes in non-invasive measures of stroke volume from baseline to 6 months later

When assessed at metabolic isotimes (%VCO_2max), there was a statistically significant increase in O_2 pulse in the LVRS group from baseline to 6 months at all measured exercise time points (Table 3A). There was no increase in O_2 pulse in the non-LVRS group when measured at the same time points. For pulse pressure, the LVRS group experienced a significant increase during submaximal exercise (50% and 75%VCO_2max) at 6 months; there was no such change in the non-LVRS group (Table 3B).

Figure 1 displays the change in O_2 pulse and pulse pressure at metabolic isotimes from baseline to 6 months in the LVRS compared to non-LVRS group. Comparing the LVRS to the non-LVRS group (Figure 1A), there were greater increases in O_2 pulse at 50% ($p=0.04$) and 75%VCO_2max ($p=0.04$). There were no statistically significant differences in the change in pulse pressure at 6 months between groups (Figure 1B).

Correlations between changes in non-invasive markers of stroke volume and changes in lung volumes

Throughout both groups at baseline and 6 months, there was a significant negative correlation between EELV/TLC and O_2 pulse (Figure 2). Reductions in hyperinflation correlated with an increase in O_2 pulse. A decrease in static hyperinflation (FRC/TLC) significantly correlated with an increase in resting O_2 pulse at 6 months ($r=-0.449$, $p=0.04$, $n=22$) (Figure 3). A decrease in dynamic hyperinflation (EELV/TLC) correlated with an increase in O_2 pulse at 75%VCO_2max ($r=-0.487$, $p=0.02$, $n=22$) and 100%VCO_2max ($r=-0.548$, $p=0.008$, $n=22$) (Figure 4). When correlations were performed using only the LVRS group, the relationship between change in O_2 pulse and

change in EELV/TLC at 50% and 75%VCO_2max was no longer significant; a statistically significant correlation persisted when EELV/TLC was measured at 100%VCO_2max.

Discussion

The major finding of this study is that LVRS improved non-invasive markers of cardiac stroke volume during exercise. O_2 pulse and pulse pressure were significantly increased 6 months after LVRS, whereas these markers were not changed in emphysema patients with comparable levels of hyperinflation who did not undergo LVRS. Increased lung volumes correlated with lower O_2 pulse, and we are the first to show that reductions in static and dynamic hyperinflation are associated with an improvement in O_2 pulse during exercise.

It has been recognized for decades that hyperinflation in COPD may lead to decreased venous return [6]. Jorgensen *et al* used MRI to show that multiple cardiac parameters were impaired in severe COPD [5]. Decreased intrathoracic blood volume correlated with left ventricular end-diastolic index and stroke volume index; however, no measures of lung volumes were reported. While most studies showing similar findings have been conducted in severe COPD, recent studies have shown that impaired LV filling is related to percent emphysema on CT scan even in cases of mild airflow obstruction [24]. Watz *et al*, extended these findings by demonstrating that hyperinflation correlated with decreased LV end-diastolic diameter across all GOLD stages. Importantly, impaired LV diastolic filling was independently associated with reduced six minute walk distance [25]. Thus, reducing hyperinflation and improving stroke volume, as shown in our study, may lead to improved functional status.

The stroke volume response to exercise is diminished in COPD due to reduced preload, as evidenced by a lack of decrease in right ventricular end-systolic volume [3]. Impaired cardiac filling and increased pulmonary capillary wedge pressure (PCWP) during exercise in COPD appears to relate to gas trapping [4]. However, evidence that decreased filling and stroke volume during exercise is related to dynamic hyperinflation is sparse.

If cardiac performance is impaired by hyperinflation in COPD, then it would be expected that LVRS would improve filling and stroke volume by reducing hyperinflation. By increasing preload, LVRS led to immediate post-operative increases in cardiac index and stroke volume index [5]. In addition to its immediate effects, an increased RV stroke volume induced by LVRS persists until at least 3 months after surgery [8]. LVRS has been shown to lower PCWP without a change in pulmonary artery pressure [26,27,28]. Therefore the lowered wedge pressure may be due to reduced intrathoracic pressures. In one study, LVRS improved the stroke volume response to exercise; this improvement correlated to a reduction in static hyperinflation [11].

Many of the above referenced studies have relied on invasive measures of cardiac performance. O_2 pulse is a non-invasive measure that correlates well to stroke volume during exercise [12,14]. Prior studies investigating the effect of LVRS on O_2 pulse have yielded inconsistent results. O_2 pulse has repeatedly been shown to increase after LVRS at peak exercise [10,29,30]. However, it is possible that the O_2 pulse is proportionally increased due to higher workloads performed after LVRS. The present study avoids this confounding factor by matching metabolic isotimes. O_2 pulse was significantly higher after LVRS when measured at 100% VCO_2max, which is independent of external

workload. Only one prior study [30] demonstrated an improvement in O_2 pulse during submaximal exercise after LVRS. In our study there were increases in O_2 pulse at 50% and 75% VCO_2max, which is clinically important since most activities of daily living are performed at submaximal levels, not peak exercise [31]. The differing results compared to prior studies may be due to the fact that, after an intervention such as LVRS, metabolic isotimes may theoretically be a better comparator as opposed to isowatt exercise.

The present study extends prior work by Vassaux *et al*, who investigated 87 COPD patients and 46 matched healthy controls [32]. They found significant correlation between IC/TLC and O_2 pulse at rest, as well as during exercise. Those with COPD and IC/TLC<25% had a lower peak O_2 pulse than those with a ratio >25%, and in multivariate analysis the IC/TLC was an independent predictor of O_2 pulse. Therefore, the reduced O_2 pulse at rest and during exercise in COPD was related to static and dynamic hyperinflation. We have further strengthened this conclusion by demonstrating for the first time that LVRS, by reducing hyperinflation, leads to an improvement in O_2 pulse. A recent study [33] demonstrated that, in the NETT cohort, a reduction in static hyperinflation after LVRS was associated with an increased isowork O_2 pulse. Due to the fact that we were able to measure inspiratory capacity during exercise, we could directly associate reductions in dynamic hyperinflation to improvements in O_2 pulse, which is a more physiologically relevant relationship than static hyperinflation.

This is the first study to demonstrate an improvement in pulse pressure, another non-invasive measure of stroke volume [15,16], during exercise after LVRS. However, improvements in pulse pressure did not correlate with reductions in lung volumes after LVRS. This may be due to the fact that pulse pressure not only depends on stroke

volume, but also on vascular properties such as endothelial function [34] and aortic compliance [35]. The effects of LVRS on endothelial function and aortic compliance are currently unknown, and thus future studies are needed to address this issue.

The present study has limitations. The overall sample size is small and this is a retrospective analysis, although statistically significant differences were found that are consistent physiologically and supported by prior literature. Also, we used a non-invasive measure of stroke volume (O_2 pulse) which requires the assumption that the arteriovenous oxygen content difference (CaO_2-CvO_2) remains constant during exercise. Prior studies of CaO_2-CvO_2 during exercise in COPD patients have yielded conflicting results, with some suggesting that extraction is stable during exercise [36, 37], whereas others [38] found that oxygen extraction during exercise in COPD is lower than that of normal subjects. Compared to the LVRS group, the non-LVRS group was different in demographics and level of airflow obstruction, but there were no significant differences in baseline static or dynamic lung volumes, which were the physiologic measurements of interest in this study. Additionally, we investigated changes (rather than baseline differences) in exercise parameters, which should be less influenced by differences between groups. All patients exercised on 30% F_iO_2, which could have influenced VO_2 and subsequently O_2 pulse. However, the level of supplemental oxygen was standardized and *changes* in O_2 pulse were analysed; therefore, supplemental oxygen should not have affected our conclusions.

Conclusions

In summary, LVRS improved non-invasive markers of stroke volume (O_2 pulse and pulse pressure) during exercise and the increase in O_2 pulse seen after LVRS

correlated with reductions in static and dynamic hyperinflation. Therefore, the impaired stroke volume response to exercise that is known to occur in COPD appears to correlate with dynamic hyperinflation. More importantly, by reducing lung volumes, LVRS had a favorable effect on stroke volume measured by O_2 pulse. Whether decreasing hyperinflation and increasing cardiac filling and stroke volume leads to an improved functional status should be evaluated in future studies.

Acknowledgements

Author contributions: Dr. Lammi had full access to all of the data in the study and takes responsibility for the integrity of the work as a whole, from inception to published article.

Dr. Lammi performed the data collection, study analysis, and wrote the manuscript

Dr Ciccolella assisted with statistical analysis and reviewing the manuscript

Dr. Marchetti assisted with study design and reviewing the manuscript

Dr. Kohler assisted with study design and reviewing the manuscript

Dr. Criner assisted with study design and reviewing the manuscript

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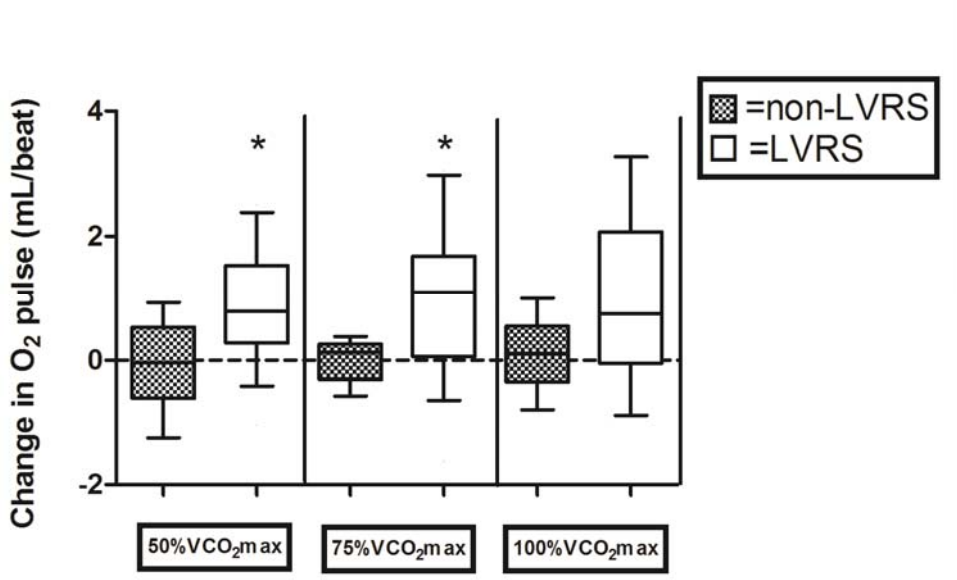
Figure Legends

Figure 1—Change in O_2 pulse (A) and pulse pressure (B) at metabolic isotimes from baseline to 6 months in non-LVRS and LVRS groups. Hyphenated line at 0 is no change. *p=0.04



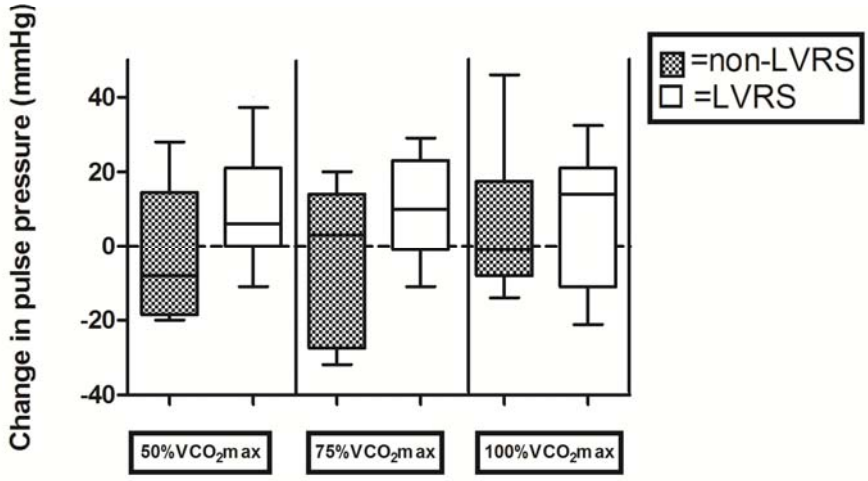


Figure 2—Correlation between dynamic hyperinflation (EELV/TLC) and O_2 pulse at 100%VCO_2max for both groups at baseline (A) and 6 months (B). Significant correlations also existed when O_2 pulse was measured at 50%VCO_2max and 75%VCO_2max (data not shown). Open circles are LVRS patients; closed circles are non-LVRS patients.

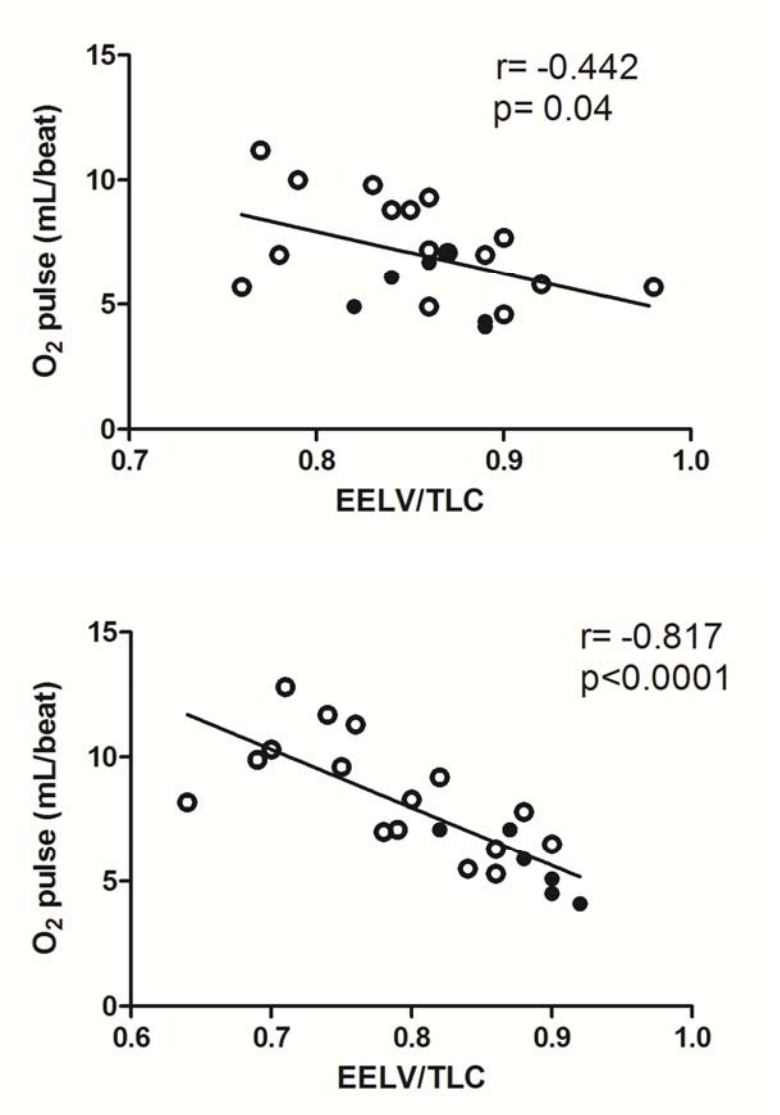


Figure 3—Improvements in static hyperinflation (FRC/TLC) correlated with increases in resting O_2 pulse at 6 months (n=22). Open circles are LVRS patients; closed circles are non-LVRS patients.

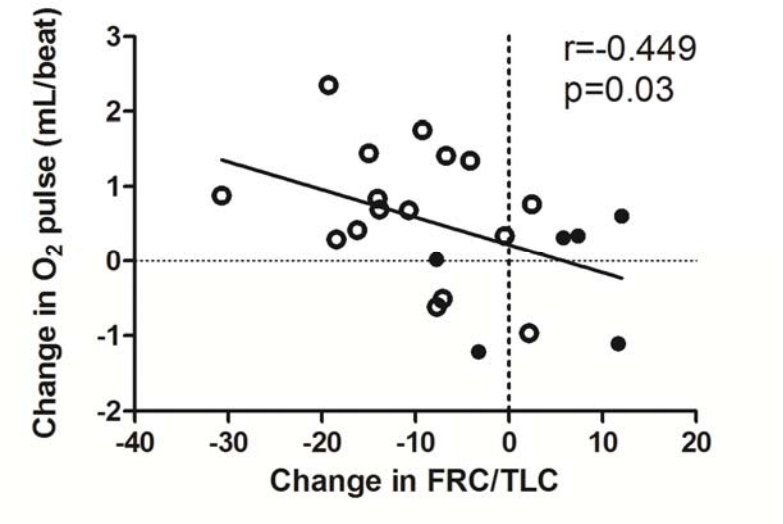
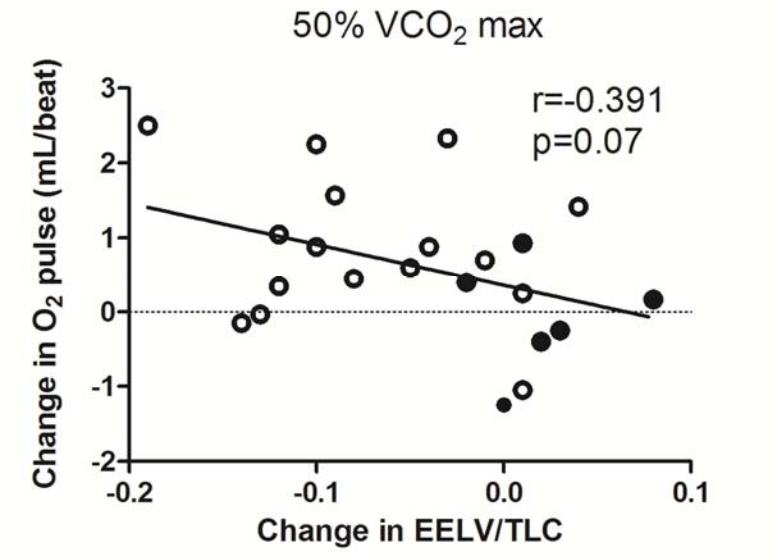
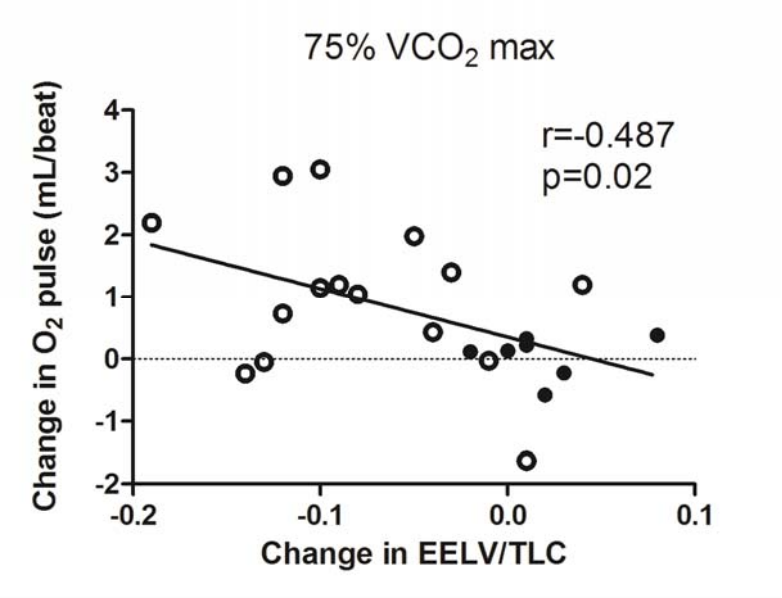


Figure 4—Correlation of change (from baseline to 6 months later, n=22) in EELV/TLC ratio with change in O_2 pulse at (A) 50%VCO_2max, (B) 75%VCO_2max, and (C) 100%VCO_2max. Open circles are LVRS patients; closed circles are non-LVRS patients.




75% VCO2 max
r=-0.487
p=0.02
Change in O2 pulse (mL/beat)
Change in EELV/TLC
4
3
2
1
0
-1
-2
-0.2
-0.1
0.0
0.1

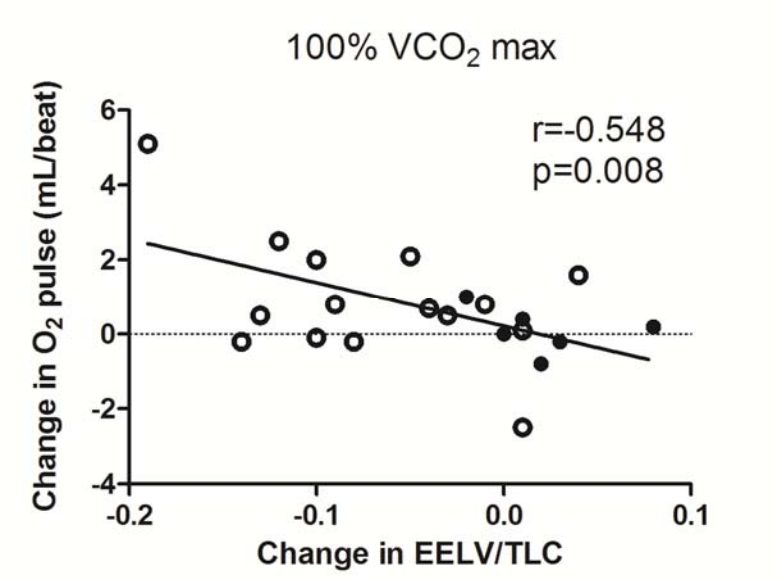

100% VCO2 max
r=-0.548
p=0.008
Change in O2 pulse (mL/beat)
Change in EELV/TLC
6
4
2
0
-2
-4
-0.2
-0.1
0.0
0.1

Table 1--Baseline Patient Characteristics

	LVRS (n=16)	Non-LVRS (n=6)	p value
Age (years)	67.0 (63.8, 72.2)	58.5 (55.3, 60.8)	0.02
Sex (% male)	63%	17%	0.15
FEV1 (L)	0.79 (0.65, 0.95)	0.53 (0.48, 0.68)	0.03
FEV1 (% predicted)	24.5 (22.0, 36.3)	20.5 (17.5, 22.8)	0.03
TLC (% predicted)	125 (108, 133)	134 (128, 144)	0.08
RV (% predicted)	191 (161, 250)	235 (219, 265)	0.22
FRC/TLC (%)	75 (73, 79)	81 (73, 82)	0.08
EELV/TLC at peak exercise	0.86 (0.80, 0.90)	0.87 (0.84, 0.89)	0.82
Peak Watts	40.0 (34, 59)	30.0 (24, 45)	0.13
LVEF (%)	55 (55, 65)	62.5 (45, 65)	0.42
BMI (m/kg^2)	27.0 (24.9, 29.3)	24.5 (20.3, 27.5)	0.20
Smoking history (pack-years)	63.0 (42.3, 85.0)	60.0 (47.0, 63.8)	0.71

FEV1=forced expiratory volume in one second; TLC=total lung capacity; RV=residual volume; EELV=end-expiratory lung volume; LVEF=left ventricular ejection fraction, BMI=body mass index FRC=functional residual capacity. Data are expressed as median (interquartile range)

Table 2--Changes from baseline to 6 months later in pulmonary function, dynamic hyperinflation during exercise, and work performed on CPET

	LVRS (n=16)	Non-LVRS (n=6)	p value
∆ FEV1 (L)	0.48 (0.16,0.68)	-0.05 (-0.07,0.02)	<0.001
∆ FEV1/FVC (%)	5.0 (2.3,6.0)	-2.5 (-3.3,-0.8)	<0.001
∆ TLC % predicted	-7.5 (-18.0,3.3)	-0.5 (-7.0,29.5)	0.12
∆ RV % predicted	-35.0 (-72.8,-4.3)	-6.5 (-22.8, 24.5)	0.1
∆ FRC/TLC (%)	-10.0 (-15.9, -4.8)	4.0 (-4.4, 8.6)	0.01
∆ EELV/TLC	-0.09 (-0.12,-0.02)	0.02 (-0.01,0.04)	0.007
∆ Watts	10.0 (3.3,20.5)	1.5 (-1.0,6.3)	0.054

FEV1=forced expiratory volume in one second; TLC=total lung capacity; RV=residual volume; EELV=end-expiratory lung volume; CPET=cardiopulmonary exercise test; FRC=functional residual capacity; ∆=change. Data are expressed as median (interquartile range)

Table 3--O2 pulse (A) and pulse pressure (B) measured at metabolic isotimes (represented as $\%VCO_2max$) at baseline and 6 months later. Comparisons are made within group (eg. O_2 pulse at $50\%VCO_2max$ for LVRS at baseline vs. 6 months). Data are presented as median (interquartile range).

A)

		LVRS O_2 pulse	p value		Non-LVRS O_2 pulse	p value
$50\%VCO_2$	Baseline	5.7 (4.9, 6.8)	0.006	Baseline	4.1 (3.7, 5.7)	0.84
	6 months	6.3 (5.5, 8.0)		6 months	4.3 (4.0, 4.8)	
$75\%VCO_2$	Baseline	6.6 (5.2, 8.0)	0.01	Baseline	4.7 (4.0, 6.0)	0.84
	6 months	7.0 (6.3, 8.9)		6 months	4.9 (3.9, 5.6)	
$100\%VCO_2$	Baseline	7.2 (5.7, 9.2)	0.02	Baseline	5.5 (4.3, 6.8)	0.81
	6 months	8.3 (6.6, 10.2)		6 months	5.5 (4.4, 7.1)	

B)

		LVRS Pulse pressure	p value		Non-LVRS Pulse pressure	p value
$50\%VCO_2$	Baseline	46.0 (42.0, 65.8)	0.03	Baseline	74.0 (59.5, 80.5)	0.69
	6 months	62.0 (49.0, 79.0)		6 months	57.0 (49.5, 87.0)	
$75\%VCO_2$	Baseline	68.0 (53.0, 77.5)	0.02	Baseline	85.0 (65.0, 105.5)	0.84
	6 months	76.0 (64.0, 89.0)		6 months	78.0 (68.5, 92.5)	
$100\%VCO_2$	Baseline	81.0 (59.5, 106.0)	0.20	Baseline	89.0 (80.5, 115.5)	1.00
	6 months	87.0 (71.0, 115.0)		6 months	99.5 (83.5, 117.5)	