Mechanisms of gas exchange response to lung volume reduction surgery in severe emphysema

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Lung volume reduction surgery (LVRS) improves lung function, respiratory symptoms, and exercise tolerance in selected patients with chronic obstructive pulmonary disease, who have heterogeneous emphysema. However, the reported effects of LVRS on gas exchange are variable, even when lung function is improved. To clarify how LVRS affects gas exchange in chronic obstructive pulmonary disease, 23 patients were studied before LVRS, 14 of whom were again studied afterwards. We performed measurements of lung mechanics, pulmonary hemodynamics, and ventilation-perfusion (VA/Q) inequality using the multiple inert-gas elimination technique. LVRS improved arterial PO2 (Pao2) by a mean of 6 Torr (P = 0.04), with no significant effect on arterial PCO2 (Paco2), but with great variability in both. Lung mechanical properties improved considerably more than did gas exchange. Post-LVRS Pao2 depended mostly on its pre-LVRS value, whereas improvement in Paco2 was explained mostly by improved Va/Q inequality, with lesser contributions from both increased ventilation and higher mixed venous Po2. However, no index of lung mechanical properties correlated with Pao2. Conversely, post-LVRS Paco2 bore no relationship to its pre-LVRS value, whereas changes in Paco2 were tightly related (r2 = 0.96) to variables, reflecting decrease in static lung hyperinflation (intrinsic positive end-expiratory pressure and residual volume/total lung capacity) and increase in airflow potential (tidal volume and maximal inspiratory pressure), but not to Va/Q distribution changes. Individual gas exchange responses to LVRS vary greatly, but can be explained by changes in combinations of determining variables that are different for oxygen and carbon dioxide.

chronic obstructive lung disease; multiple inert elimination technique

LVRS improves lung function, respiratory symptoms, and exercise tolerance in selected patients with chronic obstructive pulmonary disease (COPD) who have heterogeneous emphysema (16). The underlying mechanisms of improvement have not been fully elucidated, although increased elastic recoil (30), reduction in dynamic hyperinflation (20), and augmented force exerted by the diaphragm (10, 32) have been suggested to explain the improvement in forced expiratory volume in 1 s (FEV1).

The reported effects of LVRS on gas exchange are variable. Initial small observational trials have reported improvement (31), no change (22), or a deterioration in gas exchange (1). Randomized studies were similarly variable in outcome, reporting either no change (11, 17, 21) or small improvements after surgery (18). Furthermore, in most studies, great variability in the individual responses has been observed (34). The large National Emphysema Treatment Trial (NETT) with over 1,000 individuals confirmed a slight improvement after surgery (33). This powerful study demonstrated the importance of less severe disease and the predominance of upper lobe emphysema in improved gas exchange after LVRS. None of these studies, however, was designed to determine the specific and detailed mechanisms of change in gas exchange following surgery.

Structure-function correlation studies conducted in patients with moderate COPD have shown that emphysema results in ventilation-perfusion (Va/Q) mismatching, with a wide spectrum of Va/Q heterogeneity, including areas of low Va/Q ratio, probably due to reduced ventilation because of airway narrowing and distortion (6). There is a steady progression of Va/Q imbalance from mild to very severe COPD stages (6, 28, 35). LVRS could lead to improved pulmonary gas exchange in several possible ways. First, if before surgery, excised tissue exhibited very abnormal Va/Q relationships, its removal could per se leave the remaining lung more homogeneous. Second, changes in lung mechanical properties caused by LVRS could alter the distribution of ventilation, perfusion, or both in such a way as to improve gas exchange. Third, if LVRS enables greater alveolar ventilation, arterial Po2 (PaO2) could improve, even if the Va/Q distributions are per se unaffected. Fourth, if LVRS results in an increase in mixed venous Po2 (PvO2), due to either increases in cardiac output (Qt), or decreased oxygen consumption (Vo2), or both, this alone would contribute to an increase in PaO2, with other factors unchanged. Most of these mechanisms can be individually assessed by combining the multiple inert-gas elimination technique (MIGET) (27) with respiratory blood-gas analysis using arterial and mixed venous sampling and at the same time assessing changes in lung mechanics. Accordingly, we undertook the present study to (1) assess the mechanisms of pulmonary gas exchange impairment in patients with upper lobe, predominant heterogeneous emphysema eligible for LVRS and well characterized by lung function, imaging, and pathology; 2) investigate the effects of...
LVRS on gas exchange by using the MIGET; and 3) analyze whether changes in gas exchange after LVRS can be related to altered $\dot{V}A/Q$ distribution, alveolar ventilation, and/or $V_O2$ and/or $Q_T$. We also asked whether lung mechanical changes produced by LVRS could account for the gas exchange alterations.

**METHODS**

**Subjects**

Twenty-three patients undergoing evaluation for LVRS in S. Maugeri Foundation, Veruno, Italy ($n = 12$), and Hospital Clinic, Barcelona, Spain ($n = 11$), consented to the study approved by the Ethical Committees of both institutions. Candidate selection followed the National Heart, Lung, and Blood Institute (36) and the NETT guidelines (3). Indications for surgery were disabling dyspnea, severe airway obstruction with lung hyperinflation, despite maximal medical therapy, and predominantly upper-lobe involvement. Assessment for suitability involved clinical history and physical examination, lung function testing, 6-min walk test, high-resolution computed tomography scan, echocardiography, and $V_A/Q$ scans. On acceptance for surgery, patients underwent lung mechanics, right heart catheterization, and gas exchange studies. LVRS was performed 7–10 days after assessment. The type of procedure was decided by the surgeons purely on clinical grounds, but, in all cases, involved surgical reduction of the upper lobe. Thoracic computed tomography and perfusion scans were used to decide the site and extent of tissue to be removed.

**Pulmonary Function Testing**

Lung function testing was performed on all patients and included spirometry, body plethysmography, and single-breath gas transfer for carbon monoxide (MasterScreen, E. Jaeger, Wuerzburg, Germany; and Vmax 2200D, Sensor Medics, Yorba Linda CA). European Respiratory Society reference values were used (9, 24, 26).

**Assessment of Pulmonary Mechanics**

Pulmonary mechanics were assessed in seated patients during stable breathing in ambient air measuring simultaneous flow and esophageal and gastric pressures (23, 29). Dynamic pulmonary compliance ($C_{dyn}$), inspiratory airway resistance ($R_{aw}$) and dynamic intrinsic positive end-expiratory pressure (PEEPi) corrected for expiratory muscle activity were measured from the signals reported above with standard methods previously published (4). Only eight patients consented to the necessary balloon catheters, of whom six were also studied postsurgery. Minute ventilation ($V_e$), breathing frequency, respiratory cycle duration ($T_{iT}$), tidal volume ($V_t$), inspiratory ($T_i$) and expiratory times ($T_e$), and flows ($V_{T/T_i}$ and $V_{T/T_e}$, respectively) were calculated from the flow and pressure records.

**Hemodynamic Measurements**

Intravascular pressures were continuously recorded (M1166A, Hewlett-Packard, Boeblingen, Germany) by means of balloon-tipped 7F Swan-Ganz pulmonary artery (Edwards Laboratories, Santa Ana, CA; and Arrow International) and radial artery catheters (Seldicath 3F, Plastimed; and Arterial Line Kit, Arrow). Measurements of pulmonary vascular pressures were taken at the end of expiration. $Q_T$ was determined by thermodilution (M1012A, Hewlett-Packard) as the mean of three measurements. Pulmonary (PVR) and systemic vascular resistances were calculated using standard formulas.

**Gas Exchange Assessment**

The MIGET technique was used to assess $V_A/Q$ distribution (27). Patients were studied in a semirecumbent position while breathing ambient air. $V_O2$ and $CO2$ production were calculated from mixed expired air (CPX System, Medical Graphics, St. Paul, MN). $PAO_2$, $PACO_2$, $PA_CO_2$, and pH were analyzed in duplicate using standard electrodes (860 Gas Analyzer, CIBA-Corning; Medfield, MA; and ABL300, Radiometer, Copenhagen, Denmark); the alveolar-arterial $PO_2$ gradient [(A-a)$PO_2$] was calculated according to the standard formula measuring the respiratory gas exchange ratio.

**Statistical Analysis**

Data are expressed as means ± SD. Comparisons between patients or pre- and post-LVRS were performed using Student’s t-test or Wilcoxon signed-rank test, as appropriate. Correlation between changes in $PAO_2$ and $PA_CO_2$ and other variables was investigated by simple regression. Stepwise multiple linear regression (MLR) identified the most parsimonious model using adjusted $R^2$ values and controlling for collinearity. The contribution of each variable to the model was assessed by standardized $\beta$-coefficients. Reported $P$ values are for two-tailed tests, considered significant when $P < 0.05$.

**RESULTS**

**Preoperative Findings (23 Patients)**

Patients had severe emphysema with marked airflow obstruction ($FEV_1 = 0.84$ liter; $33\%$ predicted), static lung hyperinflation, pronounced air trapping, and substantial reduction in transfer factor for carbon monoxide ($DLCO$) (Table 1). The only significant differences between patients studied in Veruno and in Barcelona, in terms of general characteristics, consisted of a 5% lower $FEV_1$-to-forced vital capacity (FVC) ratio (attributable to a slightly larger FVC) and a 15% lower $Q_T$ in the Barcelona group. There were small differences in specific gas exchange parameters derived from MIGET, but, taken altogether, these differences were insufficient to cause group differences in $PAO_2$, $PA_CO_2$, or (A-a)$PO_2$. On average, patients showed moderate hypoxemia, normocapnia, and increased (A-a)$PO_2$. While all patients exhibited severe airflow obstruction, there was wide variation in arterial blood-gas values: $PAO_2$ ranged between 48 and 91 Torr, $PA_CO_2$ between 31 and 60 Torr, and (A-a)$PO_2$ between 19 and 60 Torr.

In agreement with these findings, there was also wide variation in the degree of $V_A/Q$ inequality. All patients but one had increased $V_A/Q$ mismatching, as shown by an abnormal value of the dispersion of retention minus excretion of inert gases corrected for dead space (DISP R-E*), which ranged between 2.0 (one patient) and 33.0. Characteristics of $V_A/Q$ distributions were comparable to other series involving patients with severe COPD (14, 35), with all but one patient showing abnormal log $SDV_1$ (the second moment of the ventilation distribution; >0.65) (8). The distribution of ventilation was broad and unimodal in 11 patients and bimodal in 12. Inert dead space varied widely, from 16 to 55% of $V_e$. Most patients also showed areas with high $V_A/Q$ ratio, which ranged between 0.4 and 13.1% of alveolar ventilation. The log $SDQ_2$ (the second moment blood flow distribution) was abnormal (>0.6) (8) in 17 patients, with a broad and unimodal distribution in 11 patients and bimodal in 6. Seven patients showed a shunt of >5.0% of $Q_T$, although, on average, shunt was discrete and similar to that in other reported series of COPD patients (Table 1). Perfusion to lung units with low $V_A/Q$ ratios (between 0.1 and 0.005) was minimal (<1% $Q_T$) in all patients.

Mean baseline $DL_CO$ (27% of normal) was in the range of overt diffusion limitation. MIGET allows for an indirect assessment of diffusion limitation at any inspired fraction of $O_2$. 


by means of the comparison between PaO₂ predicted by MIGET (i.e., ignoring diffusion limitation) against observed PaO₂. The implication is that, if predicted PaO₂ is systematically higher than the observed values, diffusion limitation should be present. Overall predicted-observed PaO₂ was −0.5 ± 4.6 Torr, with 6 out of 23 subjects showing positive differences (range 1.2–13 Torr). Similarly, mean observed-predicted (A-a)PaO₂ was 2.6 ± 10.3 Torr, which was not significantly different from zero (P = 0.4), indicating that, even accounting for changes in alveolar ventilation, diffusion limitation was not significant at rest while breathing ambient air. No correlation was observed between mean observed-predicted (A-a)PaO₂ and DLco (R² = 0.02).

Pulmonary hemodynamics were normal or only mildly impaired in the majority of patients (15). Only six patients showed a mean pulmonary artery pressure > 20 Torr, with the highest value being 27 Torr, similar to that found in the NETT study (13). The cardiac index was >2.1 min⁻¹·m⁻² in all but one patient. PVR ranged between 119 and 353 dyn·s·cm⁻⁵.

From a lung mechanical viewpoint, Cdyn, Raw, and PEEPi were moderately increased, whereas inspiratory-to-total cycle ratio (T/Ttot) and maximal inspiratory pressure (MIP) were reduced.

Regression analysis showed that PaO₂ correlated only with inspiratory capacity (r = 0.48, P = 0.031) and DISP · R-E* (r = −0.45, P = 0.03), with both variables together accounting for, and contributing equally to, ~50% of the total variance in PaO₂ (r² = 0.49, P = 0.001).

**Changes After LVRS (14 Patients)**

**Surgical procedure.** LVRS was performed by video-assisted thoracoscopy (Veruno, n = 8; Barcelona, n = 1), median sternotomy (Veruno, n = 3; Barcelona, n = 8), or thoracotomy (Veruno, n = 1; Barcelona, n = 2). The procedure was bilateral in 17 cases (Veruno, n = 9; Barcelona, n = 8) and unilateral in 6 cases (Veruno, n = 3; Barcelona, n = 3). Of the original 23 patients, 14 (Veruno, n = 9; Barcelona, n = 5) were re-assessed in stable clinical conditions and lung function at around 6 mo after surgery. In the remaining 6 patients in Spain and 3 in Italy, postoperative studies were not conducted because of death (n = 2), substantial postoperative pleural changes impacting on lung function (n = 3), or loss to follow-up (n = 4). While it was not possible to quantify the amount of tissue removed, there was no correlation between type of procedure (surgical approach and uni- or bilateral resection) and change in functional variables.

Key variables are compared before and after surgery in Table 2. LVRS led to a significant (P < 0.004) and relatively substantial increase in FEV₁ of 0.50 ± 0.54 liter (that is, by a mean of 55%). FVC also increased significantly after surgery, such that the FEV₁-to-FVC ratio did not change significantly (Table 2). Total lung capacity (TLC) decreased by 1.27 ± 0.02 liter (i.e., −14% from 127 ± 17 to 107 ± 18% predicted, P = 0.04) and residual volume (RV) by 1.68 ± 0.06 liter (i.e., −28%, RV from 237 ± 53 to 168 ± 75%, P = 0.001) after LVRS, accompanied by a fall in RV/TLC (11%, P = 0.01) and an increase in inspiratory capacity (by 0.65 ± 0.75 liter, +24%, P = 0.02). There were, in addition, significant reductions in Cdyn (14 ± 13 ml/cmH₂O, −25%, P = 0.04), Raw (2.5 ± 2.7 cmH₂O·l⁻¹·s⁻¹, −25%, P = 0.04), and PEEPi (1.9 ± 1.6 cmH₂O, −54%, P = 0.02), and increases in Ti/Ttot (0.05 ± 0.04, +16%, P = 0.02) and MIP (16 ± 19 cmH₂O, +63%, P = 0.03).

On average, PaO₂ increased significantly, but only modestly, by 6 ± 10 Torr (P = 0.04) (Table 2), but with remarkable individual variations; the median change was similar (5 Torr, a 9% increase). The change in PACO₂ after LVRS was also very variable. On average, the value of PACO₂ was 3.5 ± 7.7 Torr lower after surgery, but this apparent fall was not significant.
Values are means ± SD. N, no. of subjects. VT, tidal volume; Ti, inspiratory time; Te, expiratory time; Ti/Ttot, inspiratory duty cycle; BF, breathing frequency; PEEPi, intrinsic positive end-expiratory pressure; MIP, maximal inspiratory pressure; MEP, maximal expiratory pressure; Cdyn, dynamic pulmonary compliance; Raw, airway resistance; PTPdi, pressure-time product for the diaphragm; TTdi, tension-time index for the diaphragm; P0.1, inspiratory occlusion pressure; P50, PEEPi, intrinsic positive end-expiratory pressure; MIP, maximal inspiratory pressure; MEP, maximal expiratory pressure; Cdyn, dynamic pulmonary compliance; Raw, airway resistance; PTPdi, pressure-time product for the diaphragm; TTdi, tension-time index for the diaphragm; P0.1, inspiratory occlusion pressure; P50, PEEPi, intrinsic positive end-expiratory pressure; MIP, maximal inspiratory pressure; MEP, maximal expiratory pressure; Cdyn, dynamic pulmonary compliance; Raw, airway resistance; PTPdi, pressure-time product for the diaphragm; TTdi, tension-time index for the diaphragm; 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Mechanical determinants of \( P_{A\text{O}_2} \) and \( P_{A\text{CO}_2} \) after surgery. Table 2 shows that several indexes of lung mechanical properties were improved after LVRS when the group mean data were analyzed. These included indexes of lung hyperinflation, airflow, and pressure generation. The question that arises is identity, and its offset by 6 Torr represents the average effect of LVRS on \( P_{A\text{O}_2} \), which is independent of pre-LVRS values. In the case of \( P_{A\text{CO}_2} \), post-LVRS \( P_{A\text{CO}_2} \) had no relationship to pre-LVRS \( P_{A\text{CO}_2} \) values, with \( r^2 = 0.17 \). As for \( (A-a)P_{O_2} \), only 28% of the post-LVRS value could be explained by the value before surgery; in addition, LVRS had no significant effect on \( (A-a)P_{O_2} \).
whether the changes in gas exchange can be related to any of the changes in lung mechanical properties.

For PaO₂, MLR analysis revealed that no combination of mechanical property changes was significantly related to PaO₂ changes after LVRS. However, changes in indexes of Vₐ/Q distribution were mainly related to changes in indexes related to hyperinflation. Regression analysis showed that 80% (P < 0.001) of the variance in change in log SDQ before and after LVRS was explained by changes in FEV₁ (47%), TLC (27%), and PVR (26%); 76% (P < 0.001) of the variance in change in shunt was explained by changes in FEV₁ (66%) and RV/TLC.
and 64% ($P = 0.014$) of the changes in DISP-RE* was explained by changes in FEV1 (34%), RV/TLC (49%), and PVR (17%). For PaCO2, the outcome was very different. MLR showed that 96% of the variance in changes in PaCO2 from pre- to post-LVRS could be accounted for ($P < 0.001$) by a model that included four non-covariant mechanical property variables: PEEPi (accounting for 36% of the PaCO2 change), RV-to-TLC ratio (29%), VT (22%), and MIP (14%). This is shown in Fig. 5.

**DISCUSSION**

This study confirms that, in patients with severe emphysema, LVRS results in relatively substantial and uniform improvements in respiratory mechanical properties, but in only modest improvements in gas exchange. A major finding was considerable individual variability in the gas exchange response, reducing the interpretability of group mean data. Another was that changes in PaO2 appear to depend on different sets of determining factors than those affecting PaCO2. What this study adds that is novel is a better understanding of the several possible and simultaneous contributions to altered gas exchange following LVRS.

**Pulmonary Function and Gas Exchange Before LVRS**

At baseline, there was wide variation in gas exchange status despite the fairly strict inclusion criteria deriving from the NETT study, which were used to select the candidates (2). In agreement with the variability in PaO2, there was also wide variation in the degree of V/Q inequality. The dispersion of blood flow and/or ventilation distributions was abnormal in almost all patients, reflecting a wide range of V/Q inequality with high log SDV and log SDQ in agreement with other MIGET studies in COPD patients (5).

Previous V/Q studies in patients with COPD-emphysema have not dealt with patients so fully characterized by imaging, pathology, and lung function. Recently, our laboratory (28) documented a steady progression of V/Q mismatching from Global Obstructive Lung Disease (GOLD) initiative stages 1–4 (25). Compared with these findings, the patients in the present study showed similar degrees of overall V/Q dispersion to those in GOLD stages 3 and 4, consistent with their clinical severity. Increased overall V/Q dispersion was due mainly to increases in log SDV, which was similar to that in GOLD stage 4. In contrast, the distribution of perfusion was dissimilar from that of patients with comparable spirometry with log SDQ values closer to those seen in stages 1 and 2. That said, shunt was twofold higher than in those reported by Rodríguez-Roisin et al. (28). This pattern of modest abnormalities in log SDQ with slightly greater shunt and a wide scatter in log SDV probably reflects the markedly heterogeneous distribution of emphysema in our LVRS candidates, who, by selection, have lung regions that are relatively well preserved, along with others showing severe emphysema. As noted previously (28), the progression of V/Q imbalance with increasing airflow limitation is modest, suggesting that areas with advanced emphysema may contribute little to gas exchange, possibly because they receive not only little blood flow, but also little ventilation. This may be analogous to what occurs in noncommunicating bullous spaces that are apparently neither perfused nor ventilated (19). Nevertheless, even in these severe and highly selected subset of patients, PaO2 was closely dependent on V/Q dispersion, confirming V/Q mismatch as a major cause of arterial hypoxemia in COPD.

**Changes in Lung Mechanical Properties After LVRS**

LVRS resulted in substantially improved airflow rates and reduction in hyperinflation, consistent with previous findings (7). The similar improvements in FVC, FEV1, RV, and RV/TLC, as well as the strong correlation between Raw and RV/TLC (0.96, $P = 0.01$) support suggestions that the im-

![Fig. 5. Plot of measured vs. predicted LVRS-induced changes in PaCO2 obtained from a multiple linear regression model using variables dependent on lung hyperinflation [intrinsic positive end-expiratory pressure (PEEPi), ratio of residual volume to total lung capacity (RV/TLC)], tidal volume (VT), and inspiratory muscle strength (MIP). Essentially all of the post-LVRS change in PaCO2 can be explained by lung mechanical property changes reflecting these key mechanical properties.](http://jap.physiology.org/10.1152/jappl.00567.2009)
improvement in airflow rates resulted from a decrease in static hyperinflation and an increase in elastic recoil, resulting in greater radial traction on peripheral airways. Thus LVRS appears to convey benefit to mechanical lung function in several ways.

Changes in \( V_{A}/Q \) Ratio Distribution After LVRS

In contrast to the large changes in lung mechanical properties, changes in \( V_{A}/Q \) distribution and shunt were less impressive. The modest average changes are consistent with the correspondingly small improvements in mean \( P_{aO_2} \) and lack of significant mean reduction in \( P_{aCO_2} \).

There are several possible mechanisms of improvement in the \( V_{A}/Q \) distribution. First, lung regions compressed by hyperinflated emphysematous areas before LVRS may have been less compressed after removal of emphysematous tissue, therefore improving \( V_{A}/Q \) matching. Second, improvement in airflow rates associated with increased radial traction could lead to better ventilation after LVRS, especially in those patients previously subject to the greatest dynamic compression. Third, reduced hyperinflation and PEEPi might lead to lower PVR and improved blood flow distribution. A fourth possibility is that, by removing the most abnormal lung (in terms of \( V_{A}/Q \) inequality), what is left is, by implication, less abnormal. The results of the present study suggest that improvement in \( V_{A}/Q \) distribution is mainly related to the decrease in hyperinflation, as estimated by improvement in FEV1 and a decrease in RV/TLC and PVR. Not formally assessed, almost all of the patients indicated a reduction of dyspnea independently of the changes in gas exchange parameters. The uniform improvement observed in spirometry and plethysmography would indicate that dyspnea was more affected by the decrease in hyperinflation than by improvement in \( P_{aO_2} \) or \( P_{aCO_2} \).

Determinants of Post-LVRS \( P_{aO_2} \) and \( P_{aCO_2} \)

The small average increase in \( P_{aO_2} \) was similar to that reported in NETT (33). Both \( P_{aCO_2} \) and \((A-a)P_{O_2}\) decreased by 

\(~7\%) to account for this, and, while neither change reached statistical significance individually, \((A-a)P_{O_2}\) correlated well with the increase in \( P_{aO_2} \). Essentially the same observations were made by Albert et al. (1), but others found no significant change in \( P_{aO_2} \) and \((A-a)P_{O_2}\) at rest or on exercise (22), although with wide individual scatter. The NETT study showed that patients with upper lobe predominant emphysema and milder disease (as assessed by lower TLC and as well as by higher baseline \( P_{aO_2} \) and \( D_{lCO_2} \) levels) had a greater chance of improving their \( P_{aO_2} \) after LVRS. However, as the study included only routine lung function testing, no inference could be made regarding the mechanisms underlying the change in \( P_{aO_2} \). In a randomized controlled study, Criner et al. (11) could not show an improvement in \( P_{aO_2} \), but reported a significant amelioration in \( V_{O_2} \) at 3 mo post-LVRS, mainly due to an improvement in \( V_{E} \).

In the present study, in accordance to the results of the NETT study (33), \( P_{aO_2} \) after LVRS was primarily (60%) a function of pre-LVRS values, and was only secondarily (40%) affected by LVRS itself. Considering that the subjects for this study were chosen using the fairly strict NETT criteria, the similarities of our results with those of the NETT study are perhaps unsurprising.

The relatively small (6 Torr) mean increase in \( P_{aO_2} \) after LVRS was accounted for by a combination of the factors that together are known to determine \( P_{aO_2} \), in nonhomogenous lungs (Fig. 6): the level of ventilation; the amount of intrapulmonary gas exchange inefficiency caused by \( V_{A}/Q \) mismatching, intrapulmonary shunt, when present, diffusion limitation; and the value of \( P_{V_{O_2}} \) (reflecting the balance between \( Q_T \) and metabolic rate). Also, diffusion/perfusion inequality would contribute to diffusion limitation, even if total diffusion were normal. It is important to note that, while likely linked physiologically (see below), these factors were not linked mathematically in the present study, demonstrating essentially no colinearity, and thus making possible the assessment of their independent contributions to changes in \( P_{aO_2} \). The quantitative aspect of this partitioning, described as roughly 50% from improved \( V_{A}/Q \) relationships, and the rest roughly equally split between effects of ventilation and of extrapulmonary factors affecting \( P_{V_{O_2}} \) should be interpreted with some caution because of the low number of subjects who provided data, both before and after LVRS for all variables required for the analysis. However, it does seem reasonable to conclude that the changes in \( P_{aO_2} \) (both positive and negative) are multifactorial, with identifiable contributions from all three sources.

The multivariate analysis described in Fig. 4 partitions the importance of these factors, but does not address reasons why each contributed in any mechanistic sense. It is likely that improved mechanical function of the respiratory system would have contributed to all three sources of improved \( P_{aO_2} \). Thus reduced hyperinflation allowing greater \( V_T \) and reduced airways resistance together could enhance ventilation. Reduction in lung hyperinflation and in PEEPi could enhance venous return and \( Q_T \), while decreasing work of breathing, would tend to reduce \( V_{O_2} \). While changes in \( Q_T \) and \( V_{O_2} \) were not evident by group statistics, their combined effects on \( P_{V_{O_2}} \) led to its significant contribution to improved \( P_{aO_2} \) when multiple linear correlation analysis was performed. \( V_{A}/Q \) inequality could

**FACTORS AFFECTING ARTERIAL \( P_{O_2} \)**

![Diagram showing how \( P_{aO_2} \) depends on the integrated effects of extrapulmonary factors (ventilation, blood flow, \( P_{V_{O_2}} \)) and intrapulmonary factors [\( V_{A}/Q \) inequality (which includes shunting) and diffusion limitation]. For each factor, the sign indicates the direction in which \( P_{aO_2} \) will move as the indicated factor increases in value (i.e., the positive or negative effect on \( P_{aO_2} \) of an increase in the factor). Actual \( P_{aO_2} \) thus represents the integrated effects of the individual factors. An increase in blood flow raises \( P_{aO_2} \) by increasing \( P_{V_{O_2}} \), but may at the same time act to lower it by 1) shortening red cell transit time in the lung, worsening diffusion limitation, and 2) causing more \( V_{A}/Q \) inequality.**

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**Fig. 6.** Diagram showing how \( P_{aO_2} \) depends on the integrated effects of extrapulmonary factors (ventilation, blood flow, \( P_{V_{O_2}} \)) and intrapulmonary factors [\( V_{A}/Q \) inequality (which includes shunting) and diffusion limitation]. For each factor, the sign indicates the direction in which \( P_{aO_2} \) will move as the indicated factor increases in value (i.e., the positive or negative effect on \( P_{aO_2} \) of an increase in the factor). Actual \( P_{aO_2} \) thus represents the integrated effects of the individual factors. An increase in blood flow raises \( P_{aO_2} \) by increasing \( P_{V_{O_2}} \), but may at the same time act to lower it by 1) shortening red cell transit time in the lung, worsening diffusion limitation, and 2) causing more \( V_{A}/Q \) inequality.
have improved by several mechanisms. MLR analysis of the relationship between changes in PaO₂ and changes in the several indexes of mechanical function (listed in Table 2) revealed no combination of indexes capable of accounting for the effects of LVRS on PaO₂.

Thus we suggest that, while individual change in PaO₂ can be understood physiologically on the basis of separate contributions from ventilation, V̇A/Q̇ inequality, shunt, and extrapulmonary factors, the mechanistic basis of how these three factors are affected by LVRS remains speculative. While reduced hyperinflation following LVRS does not appear to directly affect PaO₂, it has a major impact on the improvement in V̇A/Q̇ distribution, itself one of the main determinants of PaO₂. The relatively small number of subjects studied may have been a major limitation to the study. On the other hand, this study clearly demonstrated homogenous baseline functional and morphological characteristics of the patients and a uniform pattern of change in lung mechanics. This uniformity was belied by the peculiar and variable distribution of baseline V̇A/Q̇ distribution, as well as it is inconsistent behavior after LVRS that explains, at least in part, the variability of the changes in PaO₂. It is possible that other distributions of emphysema (e.g., homogenous) could have a different pattern of V̇A/Q̇ mismatch and may well have responded differently to LVRS.

As described, there was no effect of LVRS on average group PaCO₂, but there was great variability among patients in their response, with some patients reducing PaCO₂ substantially, some increasing PaCO₂ by a few Torr, and others essentially not changing. In contrast to the findings for PaO₂, no combination of the gas exchange variables in Table 2 accounted for changes in PaCO₂, but a group of mechanical properties was identified that explained almost all (96%) of the variance in post-LVRS PaCO₂ changes. These variables, also shown not to have significant colinearity, included markers of lung hyperinflation (PEEPi, RV-to-TLC ratio), VT, and chest wall muscle function (MIP). Altogether PEEPi and RV/TLC jointly accounted for about two-thirds of the changes in PaCO₂, while VT and MIP jointly contributed roughly one-third (Fig. 5). Although this relationship must be interpreted with caution because it comes from only six patients, it is so tight (r² = 0.96) that it would appear to have some validity. It also makes physiological sense in that PaCO₂ is widely known to be very sensitive to ventilation, and, in turn, the changes in mechanical properties would all directly affect the ability to breathe. In 33 moderately hypercapnic subjects studied before and 3–6 mo after LVRS, Shade et al. (31) also reported a significant correlation between improvement in FEV₁, MIP, and RV-to-TLC ratio, and decrease in PaCO₂, albeit with a large intersubject variability. They also observed that those patients with higher baseline values of PaCO₂ had the greatest reduction in PaCO₂ post-LVRS. Thus the present study suggests that individual changes in PaCO₂ can be predicted and understood on the basis of individual changes in these mechanical properties and not to changes in V̇A/Q̇ distribution. We do acknowledge that, while it is tempting to speculate that mitigation of hyperinflation is the major cause of the improved ventilatory ability, linear regression at best finds associations between variables and cannot identify cause-and-effect relationships.

Conclusions

This study has made a number of novel observations. First, patients all having very severe COPD, satisfying the strict selection criteria for LVRS, show a very wide range of physiological abnormality in terms of pulmonary gas exchange. Second, post-LVRS PaO₂ was found to reflect mostly its pre-LVRS value, with changes after surgery explained mostly by V̇A/Q̇ distribution improvement, with lesser contributions from changes in ventilation and in FV̇O₂, and no direct contribution from changes in lung mechanical properties. Third, improvement in V̇A/Q̇ distribution is mainly due to a reduction in hyperinflation after LVRS. Fourth, the changes in PaCO₂ were closely related to changes in lung mechanical properties and not to the factors that affected PaO₂.

While improvement in gas exchange has never been the main outcome in LVRS, long-term oxygen therapy is burdensome to the patient and expensive. Attempting to optimize the effects of LVRS on arterial oxygenation is important and certainly impacts on the acceptance of the procedure by both patients and health service providers. With the recent advent of bronchoscopic lung volume reduction, where mechanical improvement appears to be more modest (12), gas exchange analysis may prove useful in evaluating clinical outcomes.

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DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the author(s).

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