Pulmonary and Critical Care Medicine

Research Article ISSN: 2398-3108

Gas exchange after bilateral thoracoscopic lung volume reduction surgery

Jürg Hamacher[1,2,3,4,5,*], Peter Ludwig[1,6], Uz Stammberger[1,7], Yalda Hadizamani[2,3] and Walter Weder[7]

[1]Pulmonary Division, Department of Internal Medicine, University Hospital, CH- 8091 Zürich, Switzerland

[2]Lungen-und Atmungsstiftung Bern, 3012 Bern, Switzerland

[3]Pneumology, Clinic for General Internal Medicine, Lindenhofspital Bern, 3012 Bern, Switzerland

[4]Medical Clinic V-Pneumology, Allergology, Intensive Care Medicine and Environmental Medicine, Faculty of Medicine, Saarland University, University Medical Centre of the Saarland, D-66421 Homburg, Germany

[5]Institute for Clinical & Experimental Surgery, Faculty of Medicine, Saarland University, D-66421 Homburg, Germany

[6]Pneumologie/Schlafmedizin, Kantonsspital Graubünden, Chur, Switzerland

[7]Universitätsspital Zürich, Klinik für Thoraxchirurgie, CH 8091 Zürich, Switzerland

Abstract

Background: Lung volume reduction surgery (LVRS) has been shown to improve dyspnoea, pulmonary function, exercise tolerance and quality of life in properly selected patients with pulmonary emphysema. However, the ultimate impact of LVRS on gas exchange is still a matter of debate. The current work tries to provide an insight into this matter.

Methods: Study group of 39 patients undergone to LVRS and reached a follow-up time of 2 years. Pre and postoperative measurements of arterial blood gases (ABG) at rest and the diffusing capacity of the lung (DLCO), 6-min walking distance test and dyspnoea score were recorded at 3, 6, 12, 18 and 24 months after LVRS.

Results: After LVRS, an improvement of preoperative partial pressure of carbon dioxide ($PaCO_2$) (Mean ± SD: 38.5 ± 0.9 mm Hg) of 8% occurred in 3 months and was retained up to 12 months compared to preoperative value. The decrease of $PaCO_2$ correlated weakly with the increase of the forced expiratory volume in one second (FEV1) and vital capacity (VC). Mean preoperative partial pressure of oxygen (PaO_2) (65.2 ± 1.5 mm Hg) in 6 months after LVRS was temporarily improved by 8%. The individual gas exchange parameter alveolar-arterial oxygen gradient ($AaDO_2$), and therefore, PaO_2 were not predictable by assessment of lung mechanics, other biometric parameters, or emphysema morphology. Preoperatively and 6 months after LVRS the same fraction of patients (10 %) fulfilled the ABG criterion PaO_2< 55 mm Hg for long-term oxygen treatment (preop. 10/101 patients; 6 months postop. 8/82 patients).

Conclusion: We observed a slight improvement in PaO_2 for up to 6 months after LVRS, which is secondary to an increase in alveolar ventilation as reflected by a drop in $PaCO_2$. Gas exchange as assessed by $AaDO_2$ and DLCO remained unchanged and a weak correlation between fractional change of FEV1 and VC and change in $PaCO_2$ have been observed. Overall, LVRS temporarily improved alveolar ventilation and resting gas exchange, but on an individual basis, improved or worsened gas exchange and alveolar ventilation at rest.

Introduction

Emphysema is a progressive atypical and permanent dilatation of the airspaces distal to terminal bronchioles by mainly inflammatory processes including proteinases and apoptosis, declining the alveolar and the capillary surface area, i.e. the surface for gas exchange and decreasing lung elasticity [1]. A reduction in lung elastic recoil occurs that predisposes lung hyperinflation and is accompanied by decreased inspiratory capacity. An increase in functional residual capacity occurs which may lead to contractile dysfunction of the inspiratory muscles [1-5]. Abnormal configuration of the diaphragm generated by emphysema may further lead to dyspnoea [2,3,6].

LVRS is an efficient and approved surgical treatment for patients with emphysema and hyperinflation [7]. It represents a bridge and sometimes even substitution for lung transplantation [8] in highly selected patients [8]. LVRS improves lung compliance by better matching the size of the lungs to the size of the thorax [9] and results i) Improvement in lung elastic recoil at analogous thoracic inspiratory volume [10,11], expiratory flow [12] and the mechanical efficiency of healthier parts of the lung; ii) Improvement of FEV1, vital capacity (VC), total lung capacity (TLC) and residual volume (RV) [13]; iii) Reduction in static hyperinflation and dynamic hyperinflation and air trapping causing the improvement of exercise capacity [14-16]; iv) Improving respiratory muscles' function by returning inspiratory muscles including the diaphragm to their optimal length-tension ratio [4,11,16]; v) small increase in DLCO but on average no crucial changes in gas exchange [9]; vi) improvement in quality of life [13] and in part in survival [17].

Correspondence to: Jürg Hamacher, M.D., Lindenhofspital Bern, CH-3012 Bern, Switzerland, Email: hamacher@greenmail.ch, Tel. *41 31 300 35 00, Fax *41 31 300 35 01 and Medizinische Klinik V, Universitätskliniken des Saarlandes, D-66421 Homburg, Germany

Keywords: *Thoracoscopic lung volume reduction surgery, emphysema, gas exchange, chronic obstructive pulmonary disease, pulmonary function, dyspnoea.*

Received: August 24, 2022; **Accepted:** September 12, 2022; **Published:** September 15, 2022

The choice of appropriate candidates, usually by a multidisciplinary approach, can greatly affect the success of LVRS [8]. Accordingly, considering emphysema morphology, target location (s), pulmonary function parameters, cardiac comorbidities, etc. are of high importance [8]. Most centres use comparable LVRS inclusion criteria [8] but in general, patients with heterogeneous/homogeneous emphysema morphology, substantial impaired diffusion capacity, moderate pulmonary arterial hypertension, a history of previous LVRS and alpha 1 -antitrypsin (A1AT) deficiency can be considered as candidates for LVRS [17]. The large multicentre National Emphysema Treatment Trial (NETT) evidenced the improvement of lung function, exercise capacity, dyspnoea and eventually survival rate of patients (n=1218) who underwent LVRS surgery compared to those that received medical therapy predominantly in the subset of subjects with upper lobe dominant emphysema and low baseline exercise capacity [18]. A high-risk subgroup was recognised, which had a baseline % predicted (FEV_1) of ≤20%, harbouring either a homogeneous distribution of pulmonary emphysema or % predicted (DLCO) <20% [18,19].

Exclusion criteria mentioned by Caviezel *et al.* (2018) recommends a daily steroid dose of > 20 mg, CT morphology of significant bronchiectasis, lung function parameters measure of FEV_1 < 20% and DLCO < 20% in the homogeneous emphysema, 6-minute walk distance (6 MWD) > 600m and gas exchange of $PaCO_2$ > 50 mm Hg and PaO_2 < 45 mm Hg in homogeneous emphysema [8]. In patients with A1AT deficiency, more heterogeneous emphysema and less frequent infection exacerbations seem to be associated with successful LVRS [20,21].

In patients with severe COPD different levels of hypoxemia or hypercapnia have been observed [16]. Some studies have suggested exclusion of patients with moderate to severe hypercapnia ($PaCO_2$ > 50 to 55 mm Hg) from LVRS [18,22] due to critical levels of parenchymal lung destruction [22]. However, the changes in post-LVRS $PaCO_2$ exhibit marked intersubjective variability, LVRS is supposed to enable the lung and chest wall to function more efficiently as a pump, and therefore, augment alveolar ventilation and alleviate baseline resting $PaCO_2$ [16]. Accordingly, patients with higher baseline levels of $PaCO_2$ demonstrate the greatest reduction in $PaCO_2$ post-LVRS, [16] One study suggests that the heterogeneity of emphysema in CT scan is more critical than blood gas analysis for assessment of prognosis [23].

One area of concern is the effect of LVRS on gas exchange. We performed a retrospective study, which has been conducted between years 1994 to 1998, we aim to shed the light on the postoperative outcome of LVRS on lung diffusing capacity and resting gas exchange. Hence, in a group of patients who were eligible to participate in such a study, the fundamental parameters related to blood gas and gas exchange as well as lung function parameters, exercise test and dyspnoea score have been measured at defined intervals in a single-centre closed cohort population of 39 patients for two years after bilateral thoracoscopic LVRS. The closed cohort study allowed the best to study physiological changes over time, studied in those 39 patients over two years.

Methods

Patients

In this retrospective study of a single centre study, patient data from every eligible patient for LVRS have been collected from the patients with severe emphysema who undergone bilateral LVRS by video-assisted thoracoscopy (VAT) by one single surgeon (WW) between August 1994 and December 1998. Ethical approval and written patient consent were given. We defined two major groups. From the whole cohort of 101 patients, all 39 patients were the subject of study as they could reach the five postoperative episodes of follow-up in 24 months in order to pathophysiologically best analyze a close cohort. Therefore, we called them study group. 101 consecutive patients (38 women) with severe emphysema underwent bilateral LVRS by video-assisted thoracoscopy (VAT) at our institution between August 1994 and December 1998. Their mean age at operation was 63 years (SE: ± 1 y; range: 38 - 78 years). 13 of them had ZZ homozygous α1-antiprotease deficiency.

Preoperatively, all patients were severely symptomatic with a mean modified Medical Research Council (MRC) dyspnoea score of 3.6 ± 0.1 (mean ± SE). They had severe airflow obstruction with a mean forced expiratory volume in one second (FEV1) of 0.78 ± 0.02 L which was 28 ± 1 % predicted, a mean total lung capacity of 8.27 ± 0.14 L (137 ± 2 % predicted), a mean residual volume of 5.36 ± 0.10 L (241 ± 5 % predicted) and a mean RV/TLC ratio of 0.65 ± 0.01. Mean $PaCO_2$ was normal at 39 ± 1 mm Hg, whereas mean PaO_2 was 66 ± 2 mm Hg. Carbon monoxide (CO) diffusing capacity was decreased to 43 ± 2 % of predicted. Nine deaths occurred in the 2 years follow-up after LVRS, one of them being perioperative, 8 postoperatively, and with no significant difference between preoperatively hypercapnic patients compared to the rest of the cohort. Loss of follow-up - excluding death - occurred during the 2 years postoperatively in four patients, one of them by lung transplantation. (Table 1)

Clinical and functional evaluation

Evaluation has been performed by recording medical history, radiographic, computed tomography (CT) and scintigraphy examinations preoperatively and postoperatively (five evaluation episodes in 3, 6, 12, 18 and 24 months after operation). In addition, clinical evaluations such as pulmonary function tests, arterial blood gas analysis at rest, determination of the 6 MWD, and the assessment of dyspnoea were carried out at each time point. Appraisal condition was upon patients' stable status, otherwise, the examinations were postponed to maximally one month.

Measure of dyspnoea scale: Dyspnoea was rated in accordance with the definition of the American thoracic society's Modified Medical Research Council (MRC) Scale [24]. Hereupon, the degree of dyspnoea

Table 1. Demographic characteristics of patients in both groups at baseline

	Whole cohort	Study group
Number of subjects	101	39
Mean age	63 ± 1	65 ± 1
Gender		
Female	38	13
Male	63	26
Patients with alpha 1-antiprotease deficiency	13	3
Preoperative residual volume (% predicted)	254 ± 9%; p=0.017	228 ± 8%; p=0.017
Pulmonary hyperinflation		
TLC	8.27 ± 0.14 L = 137 ± 2% pred.	
RV/TLC	0.660; p=0.048	0.624; p=0.048
Pulmonary function		
FEV_1	0.77 ± 0.02 L/s = 28 ± 1% pred.	
VC	2.91 ± 0.08; = 81 ± 2% pred.	
Dyspnoea scale (mMRC score)	3.6 ± 0.1	3.5 ± 0.1

is described by grading with an integer from zero to four. Zero indicates breathlessness as a result of strenuous exercise, while four represents the disability of the patient to depart from the house or breathlessness while dressing.

Measure of Pulmonary function: Pulmonary function testing was performed after inhalation of two puffs of salbutamol, adhering to standard criteria [25] with the Sensor Medics Autobox plethysmograph (Yorba Linda, CA, USA).

6-minute walk test: For assessment of 6 MWD, the patients walked uncoached and without oxygen supplementation along the hospital hallway.

Arterial blood gas analysis at rest: Arterial blood gas was determined at rest while breathing room air in an upright sitting position at our institution using an AVL 993 haemoximeter (AVL Medical Instruments Inc., Schaffhausen, Switzerland) after puncture of about 1 ml of blood from the patients' radial artery with a powder pre-heparinized syringe. The sample was analysed within 2 minutes after the puncture.

Measure of alveolar-arterial oxygen gradient ($AaDO_2$): $AaDO_2$ was calculated using the following formula [26]:

$$AaDO_2\ (mm\ Hg) = PAO_2 - PaO_2 = (FIO_2\ (Pb - PH_2O)) - PaCO_2/R - PaO_2$$

PAO_2: alveolar oxygen partial pressurePaO_2: arterial oxygen pressure

F_{IO2}: fraction of inspired O_2. It is assumed to be 0.21

Pb: barometric (atmospheric) pressure = 760 mm Hg at sea level

P_{H2O}: vapor pressure of water, which is 47 mm Hg at body temperature and Pb=760 mm Hg

$PaCO_2$: the CO_2 tension of alveolar gas

R: respiratory coefficient, for people consuming a standard diet = 0.8

$AaDO_2$ was only calculated, as direct measurement might influence resting blood gases, and therefore lead to more exact, but potentially less clinically relevant values.

Surgical technique

LVRS was performed bilaterally by video-assisted thoracoscopy. The most destroyed zones of lung parenchyma, were specified by CT scans and perfusion scintigrams as the target areas for resection and removed using buttressed or non-buttressed endoscopic staplers (Endo-GIA 30 and 60, Auto Suture, United States Surgical Corporation™, Norwalk, CT, USA, or ECL-45, Ethicon Endo-Surgery, Cincinnati, OH, USA) [27]. In cases which with homogeneous emphysema morphology no special target areas could be detected. Thus, the resection was performed mostly in the upper lobes. Approximate volume of 20 to 30% of lung volume on each side was removed, as estimated during operation by the surgeon. Bilateral thoracoscopic LVRS was followed by mean hospital stay of 16 ± 1 day and mean drainage time of 9.7 ± 0.7 days).

Target zones for LVRS were selected using CT scans.

Data analysis

Descriptive statistics, two-tailed tests, and linear regressions were used. Paired or unpaired t-test or analysis of variance followed by Tukey post hoc test, where appropriate, were performed to detect differences in values within the same or between groups. Survival differences between groups were analysed using a stratified Cox regression model and using Kaplan-Meier survival curves. Data were analysed using the SYSTAT for Windows® software package, release 8.03 (SPSS Inc., Chicago IL, USA). Results were expressed as mean values and standard error. A p-value ≤ 0.05 was considered significant.

Literature survey

PubMed Subject Headings (MeSH) database was used to find other studies. The terms implemented in the advanced MeSH search engine were pneumonectomy and pulmonary gas exchange in the form ("pneumonectomy" [mesh]) and ("pulmonary gas exchange" [mesh]). This resulted in 391 articles (July 2022), which were further screened. Studies with animal species as well as studies with insufficient/irrelevant data and those with a follow-up of fewer than 12 months were excluded. In addition, studies authored in some languages such as Russian, Japanese, etc. were excluded due to our limited knowledge

Table 2. Gas exchange, lung functional, exercise test and dyspnoea parameters study group (n=39, Mean Values ± standard error

		Preoperative measurements	Postoperative measurements				
			After 3 Months	After 6 Months	After 12 Months	After 18 Months	After 24 Months
Blood gas and gas exchange parameters	$PaCO_2$ (mm Hg)	38.5 ± 0.9	35.6 ± 0.7*	36.4 ± 0.7*	35.8 ± 0.8*	36.9 ± 1.1	36.9 ± 0.9
	PaO_2 (mm Hg)	65.2 ± 1.5	70.4 ± 1.7*	69.5 ± 1.7*	67.7 ± 1.6	64.7 ± 2.0	65.3 ± 1.7#
	$AaDO_2$ (mm Hg)	28.7 ± 1.7	27.6 ± 2.0	28.0 ± 1.7	30.3 ± 1.9	31.0 ± 2.6	31.1 ± 1.8#
	DLCO (ml/min×mm Hg)	3.83 ± 0.22	4.06 ± 0.19	4.13 ± 0.19	3.89 ± 0.20	3.68 ± 0.24	3.57 ± 0.20#
	DLCO (% pred.)	46 ± 3	48 ± 2	49 ± 2	46 ± 2	44 ± 3	43 ± 2#
Lung function parameters	FEV_1 (L/s)	0.79 ± 0.04	1.26 ± 0.10*	1.21 ± 0.09*	1.14 ± 0.09*	1.10 ± 0.09*	1.02 ± 0.08*#
	FEV_1 (% pred.)	28 ± 1	45 ± 2*	43 ± 2*	40 ± 2*	40 ± 2*	37 ± 2*#
	IVC (L)	2.99 ± 0.14	3.69 ± 0.19*	3.77 ± 0.18*	3.71 ± 0.19*	3.48 ± 0.20*	3.34 ± 0.18*#
	IVC (% pred.)	82 ± 3	100 ± 2*	102 ± 2*	100 ± 3*	96 ± 3*	92 ± 3*#
	RV (L)	5.13 ± 0.16	3.88 ± 0.15*	3.90 ± 0.17*	4.04 ± 0.17*	4.09 ± 0.18*	4.29 ± 0.20*#
	RV (% pred.)	277 ± 8	171 ± 7*	172 ± 8*	177 ± 7*	179 ± 8*	186 ± 9*#
	RV/TLC	0.63 ± 0.01	0.51 ± 0.02*	0.51 ± 0.02*	0.52 ± 0.02*	0.54 ± 0.02*	0.55 ± 0.02*#
Exercise test	6 MWD (m)	266 ± 14	364 ± 12*	370 ± 14*	404 ± 19*	344 ± 18*	338 ± 19*
Dyspnoea scale	mMRC score	3.5 ± 0.1	1.5 ± 0.2*	1.5 ± 0.2*	1.6 ± 0.1*	1.9 ± 0.2*	2.0 ± 0.2*#

*compared to preoperatively: p≤ 0.05; #compared to 3 months postoperatively: p≤ 0.05

6 MWD: 6-minute walk distance; **$AaDO_2$:** alveolar-arterial oxygen gradient; **DLCO:** diffusing capacity for carbon monoxide; **FEV_1:** first second of forced expiration; **IVC:** inspiratory vital capacity; **$PaCO_2$:** partial pressure of carbon dioxide; **PaO_2:** alveolar oxygen partial pressure; **pred.:** predicted; **RV:** Residual volume; **TLC:** Total lung capacity.

Table 3a. Summary of results of clinical trials issuing Lung Volume Reduction Surgery with 12 or 24 months follow up

			Our study		McKenna et al., 1996 [29];		Geddes et al., 2000 [30]	Meyers et al. 2004 [31]	Laghi et al. 2004 [32]	Pompeo et al., 2007 [33]		Tacconi et al. 2008 [34]	Pompeo et al., 2012 [28]		Caviezel et al. 2017 [35]	Criner et al. 2018 [36]
Sample size			39		166		24	20	15	42		17	63		33	128
Age at baseline (years)			65±1		67.8± 0.54		60.7±13	62.7±6.1	63±2	67± 6		66 ±3	67.8± 0.54		64.64± 20.92	64.0±6.85
Unilateral vs bilateral procedure			bilateral		unilateral (n=87)	bilateral (n=79)	bilateral	bilateral	bilateral	bilateral		bilateral	unilateral		bilateral & unilateral	Not mentioned
Follow up period			12	24	12	12	12	12	24	12	24	12	12	24	12	12
Blood gas and gas exchange parameters	$PaCO_2$ (mm Hg)	Preop.	38.5 ± 0.9	38.5 ± 0.9	44.5±0.9	45.2±1.08	37.35±5.51	46.6±6.0	41±1	40±3.07	40±3.07	44.5±2.8	41±5.0	41±5.0	No data	40.1±4.91
		Postop.	35.8 ± 0.8*	36.9 ± 0.9	No data	No data	39.90±4.15	40.3±5.9	40±2	38±3.07	39±2.30	44.5±2.5	39±3.0	41±4.0	No data	No data
	PaO_2 (mm Hg)	Preop.	65.2 ± 1.5	65.2 ± 1.5	60.3±2.4	64±2.4	74±9.45	55.2±7.5	68±4	70± 9.12	70± 9.12	59±2	68±8.0	68±8.0	No data	68.7±11.62
		Postop.	67.7 ± 1.6	65.3 ± 1.7#	No data	No data	75.17±14.12	66.7±11.4	71±3	75±7.67	71± 5.37	61±2	71±9.0	69±9.0	No data	No data
	$AaDO_2$ (mm Hg)	Preop.	28.7 ± 1.7	28.7 ± 1.7	No data	No data	No data	No data	No data	No data	No data	No data	No data	No data	No data	No data
		Postop.	30.3 ± 1.9	31.1 ± 1.8	No data	No data	No data	No data	No data	No data	No data	No data	No data	No data	No data	No data
	DLCO (ml/min×mm Hg)	Preop.	3.83 ± 0.22	3.83 ± 0.22	4.8 ±0.35	5.4±0.32	No data	No data	No data	No data	No data	3.4±1.0	No data	No data	No data	No data
		Postop.	3.89 ± 0.20	3.57 ± 0.20#	No data	No data	No data	No data	No data	No data	No data	3.5±0.9	No data	No data	No data	No data
Lung function parameters	FEV_1(L)	Preop.	0.79 ± 0.04	0.79 ± 0.04	0.69±0.03	0.65±0.03	0.77±0.28	0.46±0.1	0.71±0.06	0.85±0.23	0.85±0.23	0.71±0.1	0.82±0.3	0.82±0.3	0.65±0.19	0.76±0.25
		Postop.	1.14 ± 0.09*	1.02 ± 0.08*#	0.94 No SD	0.94 No SD	0.82±0.24	0.81±0.3	0.76±0.07	1.18±0.28	1.07±0.24	0.89±0.2	1.11±0.2	1.02±0.2	0.76±0.29	0.66±0.32
	FEV_1 (% pred.)	Preop.	28 ± 1	28 ± 1	25.9±1.1	25_±0.92	No data	No data	No data	44±36.08	44±36.08	26 ±3	29±9	29±9	23.36±6.97	28.0±7.45
		Postop.	40 ± 2*	37 ± 2*#	33 No SD	38 No SD	No data	No data	No data	43.19±9.98	38±9.97	30±6	40±9	36±9	32.67±16.75	32.0±10.81
	IVC (L)	Preop.	2.99 ± 0.14	2.99 ± 0.14	No data	No data	No data	No data	No data	No data	No data	No data	No data	No data	No data	2.74±0.9
		Postop.	3.71 ± 0.19*	3.34 ± 0.18*#	No data	No data	No data	No data	No data	No data	No data	No data	No data	No data	No data	No data
	IVC (% pred.)	Preop.	82 ± 3	82 ± 3	No data	No data	No data	No data	No data	No data	No data	No data	No data	No data	No data	No data
		Postop.	100 ± 3*	92 ± 3*#	No data	No data	No data	No data	No data	No data	No data	No data	No data	No data	No data	No data
	RV(L)	Preop.	5.13 ± 0.16	5.13 ± 0.16	4.8±0.13	4.7±0.18	No data	6.33±1.2	6.45±0.35	5.26±0.69	5.26±0.69	4.81± 0.6	5.05±1.0	5.05±1.0	No data	4.71±1.05
		Postop.	4.04 ± 0.17*	4.29 ± 0.20*#	No data	No data	No data	4.26±0.97	6.65±0.43	4.10±0.92	4.4±0.99	4.3± 0.5	4.07±0.9	4.29±0.7	No data	4.22±1.34
	RV (% pred.)	Preop.	277 ± 8	277 ± 8	No data	No data	227.07±43.34	No data	No data	226±46.82	226±46.82	217±15	217±40	217±40	268.10±49.59	224.5±42.45
		Postop.	177 ± 7*	186 ± 9*#	No data	No data	185±58.13	No data	No data	180.13±49.90	192±32.23	186±20	174±34	181±28	260.32±47.07	No data
	TLC	Preop.	8.27 ± 0.14	8.27 ± 0.14	No data	No data	No data	No data	9.62±0.65	7.9±1.46	7.9±1.46	6.7±0.5	8.17±1.5	8.17±1.5	8.12±1.84	7.54±1.59
		Postop.	No data	No data	No data	No data	No data	No data	9.17±0.51	7.18±1.23	7.1±0.15	6.6±0.6	7.40±1.5	7.50±1.5	7.60±1.76	7.22±1.71
	RV/TLC	Preop.	0.63 ± 0.01	0.63 ± 0.01	0.69 ± 0.01	0.69 ± 0.01	No data	No data	No data	0.66±1.19	0.66±1.19	No data	0.62±0.04	0.62±0.04	No data	0.63±0.09
		Postop.	0.52 ± 0.02*	0.55 ± 0.02*#	No data	No data	No data	No data	No data	0.57±0.41	0.62±0.2	No data	0.55±0.17	0.57±0.14	No data	0.58±0.12
Exercise test	6 MWD (m)	Preop.	266 ±14	266 ± 14	No data	No data	No data	No data	865±127	385±53.73	385±53.73	248±60	300±112	300±112	No data	311±81.00
		Postop.	404 ±19*	338 ± 19*	No data	No data	No data	No data	1121±77	478.23±65.24	446.45±38.37	308±68	403±78	391±83	No data	323.98±81.00
Dyspnoea scale	mMRC score	Preop.	3.5 ± 0.1	3.5 ± 0.1	2.89 No SD	2.14 No SD	No data	No data	No data	3.35±0.76	3.35±0.76	3.5±0.5	3.5±0.6	3.5±0.6	No data	2.4 ± 0.97
		Postop.	1.6 ± 0.1*	2.0 ± 0.2*#	2.9 No SD	1.8 No SD	No data	No data	No data	2.00±0.00	2.00±0.00	2.6±0.6	2.00±0.6	2.26±0.8	No data	1.9±1.52

*compared to preoperatively: p≤ 0.05; #compared to 3 months postoperatively: p≤ 0.05;6 MWD: 6-minute walk distance; AaDO2: alveolar-arterial oxygen gradient; DLCO: diffusing capacity for carbon monoxide; FEV1: first second of forced expiration; IVC: inspiratory vital capacity; PaCO2: partial pressure of carbon dioxide; PaO2: alveolar oxygen partial pressure; pred.: predicted; RV: Residual volume; TLC: Total lung capacity.

Table 3b. Summary of results of clinical trials issuing Bronchoscopic Lung Volume Reduction with 12 or 24 months follow up

			Shah *et al.* (2011) [37]	Venuta *et al.* (2012) [38]	Yang *et al.* (2019) [39]
Sample size			208	40	7
Age at baseline (years)			64.1 ± 7.29	60.5 ± 9.8	75.29 ± 2.59
Unilateral vs bilateral procedure			Not mentioned	unilateral	unilateral
Follow up period			12	12	12
Blood gas and gas exchange parameters	**$PaCO_2$ (mm Hg)**	Preop.	No data	41.2 ± 4.5	No data
		Postop.	No data	39.5 ± 3.4	No data
	PaO_2 (mm Hg)	Preop.	No data	72.7 ± 11.3	No data
		Postop.	No data	74.6 ± 6.7	No data
	$AaDO_2$ (mm Hg)	Preop.	No data	No data	No data
		Postop.	No data	No data	No data
	DLCO (ml/min×mm Hg)	Preop.	No data	No data	No data
		Postop.	No data	No data	No data
Lung function parameters	**FEV_1(L)**	Preop.	0.65 ± 0.19	0.88 ± 0.3	0.83 ± 0.09
		Postop.	0.63 ± 0.27	1.09 ± 0.4	0.90 ± 0.07
	FEV_1 (% pred.)	Preop.	23.23 ± 6.08	No data	36.83 ± 3.24
		Postop.	23.08 ± 9.75	No data	No data
	IVC (L)	Preop.	No data	No data	No data
		Postop.	No data	No data	No data
	IVC (% pred.)	Preop.	No data	No data	No data
		Postop.	No data	No data	No data
	RV(L)	Preop.	5.25 ± 1.16	4.4 ± 1.2	4.82 ± 0.77
		Postop.	5.19 ± 0.46	4.4 ± 1.2	4.31 ± 0.52
	RV (% pred.)	Preop.	244.14 ± 52.81	No data	206.93 ± 38.21
		Postop.	238.54 ± 52.81	No data	183.14 ± 25.83
	TLC	Preop.	7.64 ± 1.56	7.45 ± 1.1	No data
		Postop.	No data	7.28 ± 1.0	No data
	RV/TLC	Preop.	0.69 ± 0.06	0.59 ± 0.18	No data
		Postop.	No data	0.60 ± 0.17	No data
Exercise test	**6 MWD (m)**	Preop.	302 ± 88	286 ± 72	200.33 ± 56.54
		Postop.	281 ± 109	349 ± 105	No data
Dyspnoea scale	**mMRC score**	Preop.	2.64 ± 0·62	3.9 ± 0.8	No data
		Postop.	2.23 ± 1.17	2.4 ± 0.6	No data

*compared to preoperatively: p≤ 0.05; #compared to 3 months postoperatively: p≤ 0.05
6 MWD: 6-minute walk distance; $AaDO_2$: alveolar-arterial oxygen gradient; DLCO: diffusing capacity for carbon monoxide; FEV_1: first second of forced expiration; IVC: inspiratory vital capacity; $PaCO_2$: partial pressure of carbon dioxide; PaO_2: alveolar oxygen partial pressure; pred.: predicted; RV: Residual volume; TLC: Total lung capacity.

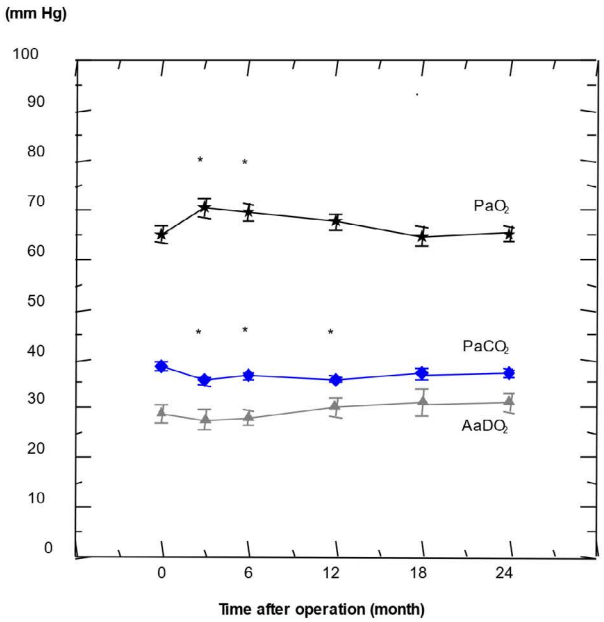

Figure 1. Resting blood gas parameters $PaCO_2$, PaO_2, and the calculated $AaDO_2$ in the study group (n= 39) from preoperative values (set as 0 months) up to 24 months after LVRS; Results are given as mean and standard error ($p < 0.05$ vs. preop.)

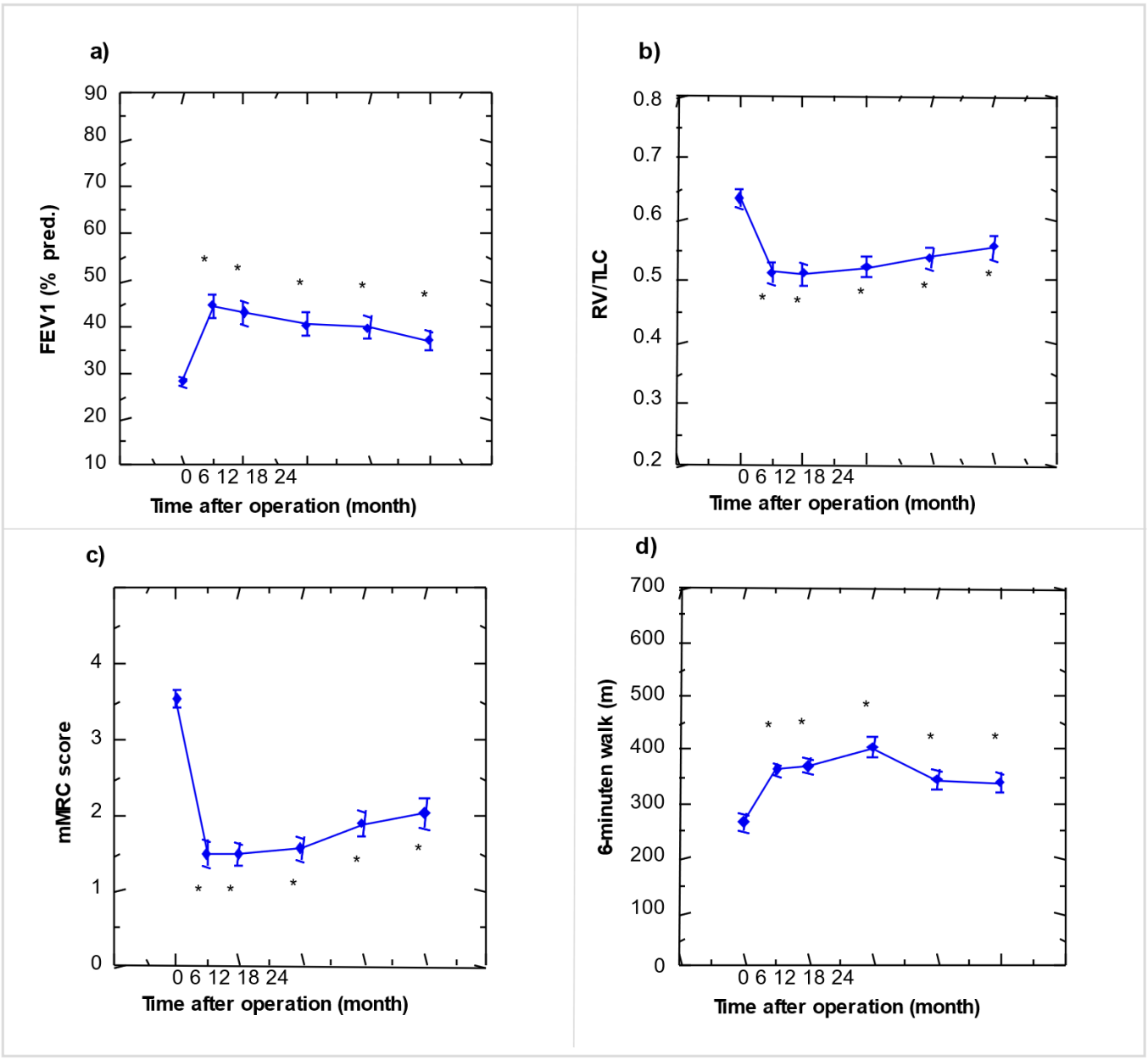

Figure 2. Lung function parameters, exercise test measure and dyspnoea scale, preoperatively up to 24 months after LVRS in the study group (n=39)

a) FEV1; b) RV/TLC quotient; c) 6-minutes walking distance; d) mMRC score. Results are given as mean and standard error. (* $p < 0.05$ compared to preoperative 0: preoperative)

of those languages. However, this method seems not to be sufficient to have all studies. For example, the study by Pompeo, *et al.* (2012) [28] did not include 391 results. Therefore, supplementary searches in PubMed and Google Scholar have been performed to provide better coverage in finding the most relevant studies.

Results

Preoperative and postoperative characteristics in the study group

Preoperative and postoperative measurements including gas exchange, lung function, exercise test and dyspnoea scale in study group of 39 patients upon 24 months follow up have been presented in table 2.

Parameters of alveolar ventilation and gas exchange at rest: $PaCo_2$: Alveolar ventilation in terms of mean $PaCO_2$ slightly decreased between preoperative and 3 months postoperative stages, reflected by a slight drop of mean $PaCO_2$ of 8% or 2.9 mm Hg from 38.5 ± 0.9 mm Hg to 35.6 ± 0.7 mm Hg (table 2, figure 1 and 2), corresponding to an individual $PaCO_2$ decrease of 4.2 ± 1.2%. Compared to preoperative values, this decrease remained significant up to 12 months after the operation, which was no longer the case 24 months after LVRS (data is not shown). The 3 months postoperative $PaCO_2$ was the lowest postoperative value observed.

PaO_2: A significant increase of the mean PaO_2 of 8% or 5.2 mm Hg from 65.2 ± 1.5 to 70.4 ± 1.7 mm Hg was observed 3 months after LVRS if compared to preoperative values (table 2, figure 1 and 2),

whereas the individual PaO_2 increased by 7.2 ± 1.5%. The increase was less pronounced, but still significant 6 months after LVRS, whereas 12 months after LVRS it was no longer different from preoperative value [29-35].

$AaDO_2$: During the whole of the study period the main parameter of pulmonary gas exchange, mean $AaDO_2$, was almost unchanged at rest (table 2, figure 1 and 2). At 6 months after LVRS, the fraction of hypoxemic patients with a PaO_2 of 55 mm Hg or lower remained unchanged at 10% of patients if compared to the preoperative situation. Furthermore, on an individual basis, the 3 months postoperative $AaDO_2$ was erratic when preoperative resting blood gases were known. The correlation of both pre- and postoperative $PaCO_2$ with their corresponding PaO_2 (preop.: r=-0.37; p<0.0001; 3 months postop.: r= -0.28; p=0.01) was weak which suggested a rather high variation in gas exchange, i.e. of $AaDO_2$ before as well as after LVRS. This suggests the rather erratic individual evolution of gas exchange by LVRS (figure 1).

DLCO: There was no significant increase in DLCO after LVRS. However, there was a significant decrease in DLCO 24 months after operation compared to DLCO at three, six, or twelve months postoperatively (table 2).

KCO (DLCO/VA): There was a steady and highly significant decline of 16% of the KCO from preoperatively of 0.92 ± 0.05 ml/min*mm Hg*L to 24 months postoperatively of 0.79 ± 0.04 ml/min*mm Hg*L, but no change by LVRS, i.e., between preoperative and 3 months postoperative KCO.

Overall, between 3 and 24 months postoperatively, mean PaO_2, $AaDO_2$, and DLCO deteriorated slightly, but significantly. Such a slight and significant deterioration was also observed in the lung functional parameters including FEV_1, VC, RV, and RV/TLC, and in MRC dyspnoea score, but not in 6-minute walking distance (table 2, figures 1 and 2).

Static and dynamic lung volumes: FEV_1: Related data in the table 2 and figure 2 show a significant increase of FEV_1 from the preoperative value of 0.79 ± 0.04 (L/s) to 1.26 ± 0.10 three months after surgery. At 6,12,18 and 26 months after LVRS, still FEV_1 shows a greater value than before the operation. However, in 3 months after LVRS FEV_1 reached its maximum value.

IVC (L): IVC reaches its maximum value at 3 (3.69 ± 0.19) and 6 months (3.77 ± 0.18) after LVRS, while before operation it was less and after 6 months also it has a downward trend (table 2).

RV (L): Preoperative value of RV shows 5.13 ± 0.16 (L), while three months post-operation it is significantly reduced to 3.88 ± 0.15 (L). Although 6,12,18, and 24 months postoperative measures shows an increasing trend, it still could not reach its preoperative value (table 2).

RV/TLC: Related values shown in table 2 and figure 2, demonstrate a significant decline of RV/TLC from a preoperative value of 0.63 ± 0.01 to 0.51 ± 0.02 three months after LVRS. In the rest of measuring times, it harbored increasing but nevertheless, it did not reach its preoperative value.

Exercise test: Preoperational 6-min walking distance shows 266 ± 14(m), while postoperative values are between 364 ± 12 in 3 months after LVRS to maximum of 404 ± 19 (m) twelve months after LVRS. Generally, all postoperative values are significantly more than preoperational measures (table 2 and figure 2).

Dyspnoea score: There was a substantial improvement in modified MRC dyspnoea score from 3.5 ± 0.1 preoperatively to 1.5 ± 0.2 three months after LVRS. This result was deteriorated up to 24 months (2.0 ± 0.2; p<0.05 vs. preop.; table 2 and figure 2), however, it is still better than preoperative baseline [36-39].

Blood gas versus lung function relationships

Correlations of preoperative and 3 months postoperative blood gas parameters in study group (n=39): Preoperative $PaCO_2$ and PaO_2 correlated weakly (r= -0.37; p<0.0001). Also, preoperative $PaCO_2$ correlates with $AaDO_2$ (r= -0.35; p=0.001). Three months postoperatively, $PaCO_2$ weakly correlated with PaO_2 (r=-0.28; p=0.01) as well as $PaCO_2$ with $AaDO_2$ (r=-0.29; p=0.007) (figure 2).

A higher negative correlation was found between the difference in preoperative to 3 months postoperative $PaCO_2$ and preoperative $PaCO_2$ (r=-0.59; p<0.0001).

Correlations of preoperative and postoperative blood gas parameters with lung functional, dyspnoea and walking test parameters: Whereas weak correlations of $PaCO_2$ were found with lung volumes, resting arterial PaO_2 did neither correlate with lung functional parameters, nor with MRC dyspnoea score, 6 MWD, or DLCO. The same was true with the gas exchange parameter $AaDO_2$. Also, multiple regression did not reveal relations between 3 months postoperative PaO_2 or ΔPaO_2 and the lung functional parameters including DLCO.

At 3 months after LVRS, VC showed the best correlation with $PaCO_2$ (r=-0.43; p<0.0001), followed by FEV1 (r=-0.37; p=0.001) and RV/TLC (r=0.34; p=0.001).

Are there predictors of blood gas parameters after LVRS (n=39)?

There was a significant decline of mean $PaCO_2$ between preoperative and 3 months postoperative resting ABG. Therefore, the question was addressed whether changes in $PaCO_2$ were related to lung functional parameters. There were significant correlations found between $\Delta PaCO_2$ and the fractional change of FEV_1 compared to preoperative value ($\Delta\%FEV_{1pre\text{-}3mo}$; r=-0.45; p=0.0001) as well as between $PaCO_2$ and the fractional change of VC compared to preoperative VC ($\Delta\%VC_{pre\text{-}3mo}$; r=-0.37; p=0.002), but not with the change in RV/TLC quotient between preoperative and 3 months postoperative value (ΔRV/TLC) (figure 3).

Importantly, there was no correlation between $\Delta PaCO_2$ and ΔPaO_2 (r=0.14; p=0.24; figure 4d3d). Thus, in an individual patient with given preoperative $PaCO_2$ pre and PaO_2 pre and a given $PaCO_2$ 3 months the corresponding individual's PaO_2 3 months is not predictable. Accordingly, as at a given $PaCO_2$ 3 months the PaO_2 3 months is not predictable, the resulting $AaDO_2$ is also not predictable. No correlation between preoperative and 3 months postoperative changes in resting $PaCO_2$ (alveolar ventilation) and the corresponding change in PaO_2 at rest means that in case of an individual preoperative blood gas analysis with given $PaCO_2$ pre and PaO_2 pre and a given postoperative $PaCO_2$ 3 months, the corresponding individual's PaO_2 3 months is not predictable. Consequently, the resulting $AaDO_2$ of an individual patient is also not predictable. In the severely debilitated emphysema patient before LVRS, both RV/TLC (r=0.34; p=0.001) and the related FEV_1 (r=-0.32; p=0.002) correlated with $PaCO_2$. No correlation was found between $\Delta PaCO_2$ and ΔPaO_2 (figure 3).

LVRS- induced changes in $PaCO_2$ between preoperative and 3 months postoperative controls, on the other hand, did not correlate with the changes in RV/TLC attained by LVRS, but with corresponding changes in FEV_1 or VC. Both regression lines passed near zero of both $\Delta PaCO_2$ and the %change of the lung function parameter and illustrate

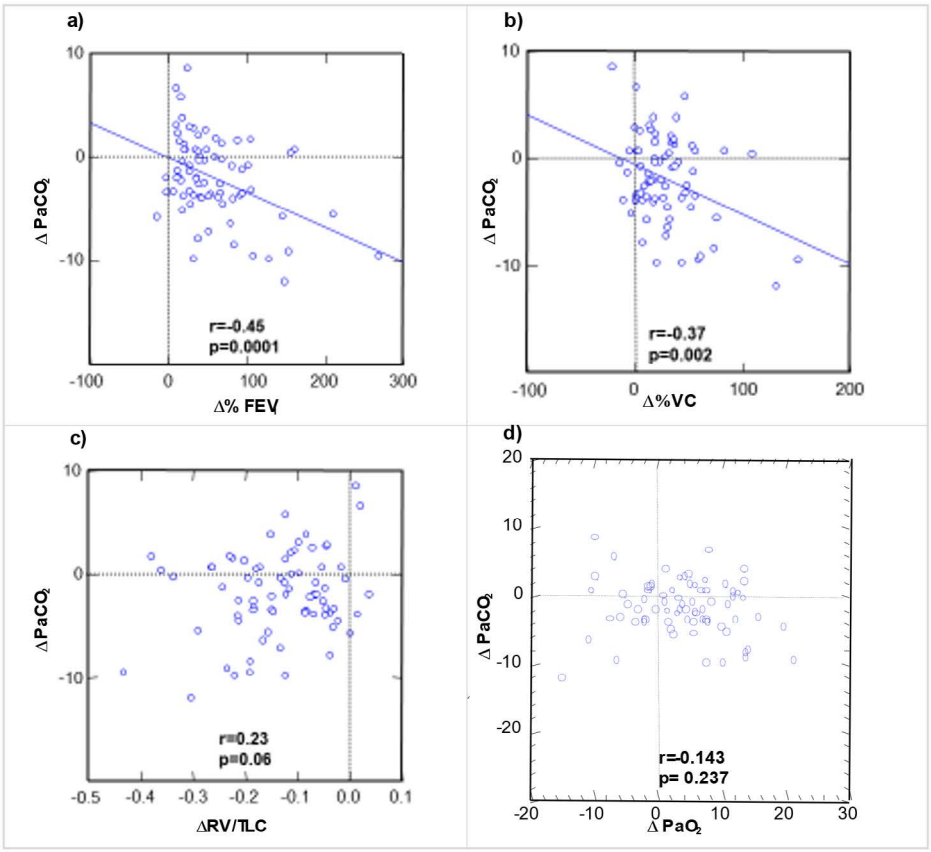

Figure 3. LVRS induced changes in lung function and alveolar ventilation in study group (n=39)

Relationships between preoperative and 3 months postoperative change in $PaCO_2$ (alveolar ventilation) and the fractional changes of FEV1 (a) and VC (b), RV/TLC ratio (c), and $PaCO_2$ (d). The solid lines represent regression lines where significance level was achieved and underline the negative correlations of FEV1 change and VC change with the change in resting $PaCO_2$, and, thus, the importance of lung volumes for the alveolar ventilation at rest.

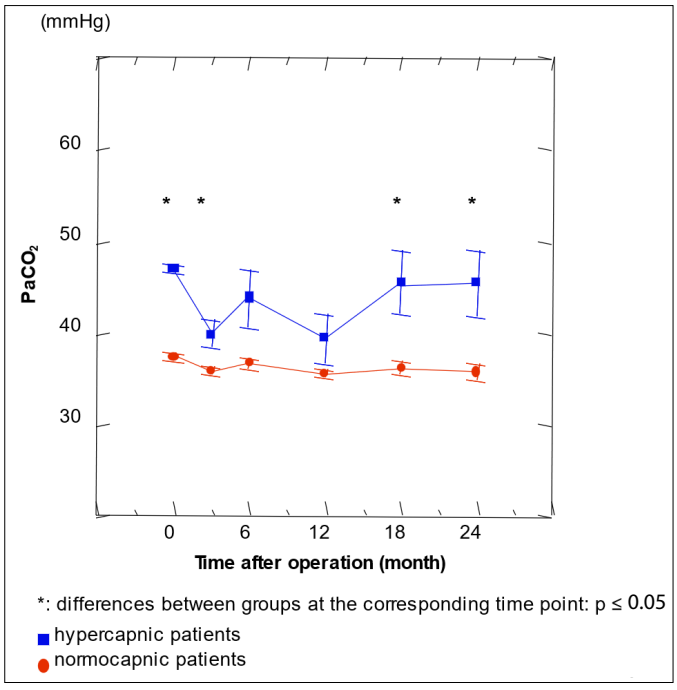

Figure 4. Evolution of preoperatively hypercapnic patients resting $PaCO_2$ (n=12) compared with the rest of the LVRS study group (n=27 normacapnic); N=39 and Results are given as mean and standard error

the weak relationship between corresponding LVRS-mediated differences in $PaCO_2$ and gains in FEV_1 or VC that apparently determined alveolar ventilation in our study population. Thus, in an individual patient with given preoperative $PaCO_{2\ pre}$ and $PaO_{2\ pre}$ and a given $PaCO_{2\ 3\ months}$ the corresponding individual's $PaO_{2\ 3\ months}$ is not predictable. Accordingly, as at a given $PaCO_{2\ 3\ months}$ the $PaO_{2\ 3\ months}$ is not predictable, the resulting $AaDO_2$ is also not predictable. This means that blood gas changes induced by LVRS do not predict resting $AaDO_2$ as the central parameter of resting pulmonary gas exchange.

Evolution of 12 preoperatively hypercapnic patients ($PaCO_2$ > 45 mm Hg)

12 patients (4 women) had preoperatively $PaCO_2$ > 45 mm Hg (mean, 47.0 ± 0.04 mm Hg; range, 45.3 - 48.7 mm Hg). Biometric data like age, sex, body mass index, or number of pack-years smoking history did not differ from the rest of the study population; however, only preoperative, but not postoperative FEV1 (preop.: 23.3 ± 1.7 vs 28.9 ± 0.7 % pred.; p=0.012), VC (preop.: 71.3 ± 5.9% vs. 82.6 ± 1.7%; p=0.039) and inspiratory capacity (24.6 ± 1.7 vs. 30.5 ± 0.8 IC/pred. TLC; p=0.018) were lower in hypercapnic patients. Hypercapnic patients gained significantly more increase in FEV_1 as well as in VC than the rest of the study population (p=0.02 and p=0.006, respectively), and decreased $PaCO_2$ between preoperatively and 3 months postoperatively by - 6.9 ± 1.3 mm Hg in contrast to the remainder of patients where a decrease of - 1.3 ± 0.4 mm Hg was observed (p<0.0001 for both groups). Neither preoperatively, nor postoperatively, RV/TLC, DLCO, or 6-minute walking distance differed significantly. Preoperatively, the hypercapnic patients' $PaCO_2$ was significantly higher (p<0.0001) and $AaDO_2$ (23.6 ± 1.4 vs. 28.1 ± 1.1 mm Hg; p=0.038) was significantly lower than that of the rest of the population. However, PaO_2 was significantly lower (60.1 ± 2.5 vs. 66.3 ± 0.9 mm Hg; p=0.013) than in the remainder of the study population. Figure 4 shows the evolution over time of the $PaCO_2$ values of the preoperatively hypercapnic patients and the rest of the population and demonstrated a new increase of $PaCO_2$ in the evolution with a difference compared to the rest of the study population which was above significance level 18 and 24 months after LVRS.

Patients with a preoperative $PaO_2 \leq 55$ mm Hg

Preoperatively 10 of 101 (10%) patients fulfilled the criterion of $PaO_2 \leq 55$ mm Hg which is main criterion for long-term oxygen supplementation. At 6 months and at 24 postoperatively, 8 patients of 82 (10%) respectively 7 of 39 patients (18%) fulfilled this criterion. 8 of the 10 patients (80%) with a preoperative $PaO_2 \leq 55$ mm Hg fulfilled within the 24 months following LVRS again this criterion at least once. On the other hand, 17 patients of the whole study cohort who did not have preoperative $PaO_2 \leq 55$ mm Hg developed hypoxemia with this criterion within 24 months after LVRS.

Discussion

Some surgical lung volume reduction studies showed no gas exchange improvements [40], some improvements in $PaCO_2$ [16] or in PaO_2 [41], and a number of them in both [42]. The current study can be categorized into the latter group, as it exhibits significant but only temporary improvements of both $PaCO_2$ and PaO_2 at rest. As we showed, both the gas exchange parameters $AaDO_2$ and PaO_2 were uncorrelated to parameters of lung mechanics, which might be an indication of more complex changes by LVRS. These data suggest that after LVRS gas exchange is basically unpredictable and not favorably changed. Therefore, LVRS may have improved or worsened the individual's gas exchange in an unpredictable way.

The arising question is whether the temporary improvement of PaO_2 at 3 and 6 months post-LVRS is explained by the temporary improvement of alveolar ventilation. Both mean $PaCO_2$ and mean PaO_2 improved between preoperatively and 3 months post-LVRS, whereas $AaDO_2$ was unchanged. This finding suggests that the mean gas exchange was unchanged between those two assessments. If we assume $AaDO_2$ to be "constant", i.e., the same for an individual preoperatively as well as 3 months postoperatively, then the equation $\Delta PaO_2 = \Delta PaCO_2$/respiratory quotient (RQ) derived from the simplified alveolar gas equation assumes a linear relationship between the two parameters (RQ has not been measured in our setting and is taken as 0.8).

The comprehensive analyses of literature conducted by van Dijk and co-workers corroborate our prediction [9]. They accentuate that even if there might be a slight improvement in postoperative DLCO, relatively variable effects on an individual level can be achieved, ranging from a negative to a large beneficial effect [9]. However, due to the various methods which have been employed to receive data, it seems not possible to conclude whether this increase remains statistically significant [9].

This assumption is considered to be reasonable, based on observations with patients who suffered from somewhat less severe COPD [43]. In COPD patients $AaDO_2$ chiefly depends on ventilation-perfusion inequality [44]. As there seemed to represent no relation between any of our measured parameters and changes of preoperative and 3 months postoperative $AaDO_2$ in our population, LVRS seemed to influence ventilation-perfusion inequalities and accordingly $AaDO_2$ in a rather erratic way. As bronchodilators decrease PaO_2 in COPD patients in the range of 3 - 4 mm Hg probably by vessel dilation that chiefly results in ventilation-perfusion inequality [45], it seems plausible that LVRS, by increasing elastic recoil and thus improving obstructive lung function generally in a considerably more significant order of magnitude than any bronchodilator, may also similarly exert critical effects on vessels geometry and thus possibly also vessel tone.

Correlations of $PaCO_2$ changes with the lung volumes VC and FEV1 suggest a primary role of lung mechanics for alveolar ventilation (figure 3). The findings suggest that hyperinflation in terms of RV/TLC influenced alveolar ventilation in preoperative severely obstructive patients in about the same magnitude as FEV_1. Accordingly, good correlations between changes in FEV1 respectively VC and VA derived from the DLCO manoeuvre have been found, whereas changes of TLC did not show a relationship with improved VA [42]. Therefore, the increase in VA respectively the changes of $PaCO_2$ seem to be associated with an improvement in spirometry parameters following LVRS but not with changes in hyperinflation [42].

Surprisingly, no correlation was found between $\Delta PaCO_2$ and ΔPaO_2. This means that in an individual preoperative blood gas analysis with given $PaCO_{2\ pre}$ and $PaO_{2\ pre}$ and a given postoperative $PaCO_{2\ 3\ months}$ the corresponding individual's $PaO_{2\ 3\ months}$ seemed erratic. Due to this dissociation of any individual 3 months postoperative $PaCO_2$ from its corresponding PaO_2 the resulting patients $AaDO_2$ was also not predictable despite the assumed preoperative $AaDO_2$ given by preoperative $PaCO_2$, PaO_2 and RQ. This further suggests that in an individual LVRS patient the 3 months postoperative resting $AaDO_2$ could not be deduced from the patient's preoperative value. The alternative explanation that RQ may chiefly account for the striking variation between ΔPaO_2 and $\Delta PaCO_2$ seems not very likely, but cannot be firmly excluded, as it has not been measured.

Surveying the influence of LVRS on $PaCO_2$ indicates that mainly patients with high preoperative $PaCO_2$ (e.g. hypercapnic patients) had 3 months postoperatively lowered $PaCO_2$ values. This is corroborated by the negative correlation ($r=-0.59$; $p<0.0005$) between preoperative $PaCO_2$ and the difference between pre-and three months postoperative $PaCO_2$, which was not found in every patient and makes the finding of several LVRS groups who described no change in mean $PaCO_2$ [16,43] well conceivable. These data suggest that the temporary improvement of PaO_2 by LVRS in our population is not explained by changes in alveolar ventilation but presumably mainly by the unpredictable alterations in ventilation-perfusion heterogeneity. The same was concluded by other studies based on pre- and postoperative blood gas analysis of 46 patients undergoing LVRS [43].

The evolution of preoperative hypercapnic patients shows that when comparing 12 preoperatively hypercapnic patients with a $PaCO_2 > 45$ mm Hg to the rest of the study population (n=27), preoperative FEV_1 (% pred.) and VC (% pred.) were both significantly lower than in the rest of the population, therefore showing their more severe obstructive lung function and/or air trapping. No further biometric differences between both groups were found. Three months postoperatively, there were no more lung functional differences found. Hypercapnic patients had exclusively preoperatively more severe obstructive lung function and profited by LVRS with a more pronounced decline of $PaCO_2$ (figure 4), as previously have been described by some studies [16] but not all LVRS centres [46] and showed more lung functional improvement than the rest of the study population up to two years after LVRS. Therefore, we agree with Shade and O'Brien who proposed not to exclude patients from LVRS solely on the presence of resting hypercapnia [16,46]. However, contrary to the more important lung functional parameters, the effect on $PaCO_2$ was no longer seen at 18 or 24 months after LVRS in our study population. Although patients with severe hypercapnia have been excluded from most LVRS studies, patients with modest hypercapnia had a $PaCO_2$ improvement to the normal or near-normal range [47], as also shown in the studied population here.

The number of patients with important hypoxemia did not change by LVRS in our study group. Long-term oxygen therapy (LTOT) necessity may importantly interfere with or be associated with important consequences on daily life [48], in particular with a positive impact on cognitive performance [49]. As the indication is primarily based on resting PaO_2, the impact of a low resting PaO_2 (e.g., $PaO_2 \leq 55$ mm Hg) is high. Pathophysiologically one would expect that by both an unchanged $AaDO_2$ after LVRS as observed and a postoperative reduction of $PaCO_2$ due to improved lung mechanical properties less patients might be severely hypoxemic, e.g., be below the threshold of indication for LTOT. Our opposed finding that the proportion of patients with a resting $PaO_2 \leq 55$ mm Hg before operation and 6 months after LVRS remained the same underscores that in our population LVRS did not act primarily beneficially on gas exchange.

This finding further emphasizes that the obvious benefits of LVRS, i.e., alleviation of dyspnoea at rest and on exertion and improvement of exercise capacity were chiefly based on lung and respiratory mechanical properties [50,51], and primarily not on blood gases. The pattern of emphysema determined by CT scan inspection is associated with a change in breathing pattern and consequently gas exchange upon maximum exercise after LVRS [52]. Another study has shown that the proportions of patients reporting use of supplemental oxygen at rest and with exercise fall significantly 6 months after LVRS (53 to 15% for use at rest and 95 of 46% for use on exercise) [53]. To assess the proportion of patients requiring oxygen supplementation before and 6 months after LVRS with an objective parameter, they used $PaO_2 \leq 59$ mm Hg instead of $PaO_2 \leq 55$ mm Hg. Therefore, their results are not directly comparable with ours and the proportion fulfilling the indication for LTOT before and after LVRS in their population remains unclear.

The presented data show a profit to the patients that are at two years follow-up at still clearly improved FEV_1 (that is at 24 months still 230 ml or 29% better than preoperatively, considered above the range of the minimal clinical importance), residual volume RV (that was at 24 months still 840 ml or 19.5% less than preoperatively) and 6-minute walk (that was at 24 months still by 72 m or 27% improved, considered above the range of the minimal clinical importance). We have also to keep in mind that all studied intervention groups are highly specifically selected patient groups [54-56]. Pathophysiologically one may speculate that surgical intervention versus endoscopic intervention may have similar effects on vessels and airways and may not be of a huge difference in terms of ventilation-perfusion pattern change or concerning the reduction of the alveolar gas exchange surface. Whether a real difference to endoscopic procedures exists remains therefore open, as to our knowledge no study has so far been published with similar follow-up with endoscopic procedures and gas exchange parameters. The tables 3a and 3b give evidence on all other published studies found including bronchoscopic lung volume reduction patient studies.

There are a number of limitations to this research. One important constraint is that the data were obtained and analyzed about two and a half decades ago. However, besides the still underestimated role of rehabilitation and maintenance or increase of daily physical activity, only a few pharmacological and non-pharmacological treatment options have changed, and also the surgical techniques have only moderately changed. Another limitation is the retrospective nature of this study. Patients were assessed in a clinically circumscribed and for clinicians usually well perceivable, but not clearly definable "stable condition". For ethical reasons repeated arterial blood gas measurements at each time point could not be performed, leaving open how much variation might have occurred due to factors including pain in a blood gas study. $AaDO_2$ was only calculated, as direct measurement may influence resting blood gases, and therefore lead to more exact, but less clinically relevant values. Bronchodilators and their timing may have influenced the results. The fact that virtually all patients regularly used bronchodilators may have lessened their influence on the blood gas results.

Conclusions

In conclusion, in the retrospective single LVRS centre study of a closed cohort of 39 patients who completed 2 years follow-up we observed a slight improvement in resting PaO_2 for up to 6 months after LVRS. This temporary improvement coincided with a significant drop in $PaCO_2$ up to 12 months after LVRS. Mean gas exchange as assessed by $AaDO_2$ remained unchanged during the study period if compared to the preoperative value. The weak correlations between LVRS-mediated changes of FEV_1 and VC with those temporary changes of $PaCO_2$ corroborated a role of the lung volumes for the $PaCO_2$ improvement 3 months after LVRS. On the other hand for any individual patient, LVRS could unpredictably improve or worsen gas exchange, and the fraction of patients meeting oxygen supplementation criteria at rest remained unaltered after LVRS. The results underscore that at two or more years sustained beneficial effects of LVRS are, contrary to blood gas parameters, based on lung mechanics, with important

outcomes such as 6-minute walk or FEV_1 improvement being still above the minimal clinical importance [16]. As both gas exchange improvement and worsening might ensue after LVRS, this specific uncertainty on gas exchange alterations including the potential need of further oxygen supplementation should be taken into account when patients are given advice before LVRS Whether similar gas exchange results are obtained in bronchoscopic lung volume procedures may be conceivable, but to our knowledge has not been shown so far. Therefore, the results of the presented study and further published LVRS studies hint to the superior improvement of lung functional parameters after LVRS compared to bronchoscopic lung volume reduction. Whereas it may be pathophysiologically probable that similar gas exchange influences occur by bronchoscopic lung volume reduction, to our knowledge this has not been published so far.

Author contribution statements

WW was the surgeon performing operative procedures and he also implicated the study designs. JH, PL and US performed data analysis and wrote the whole manuscript. Y.H. corrected the manuscript, rewrote parts of the manuscript and carried out the submission procedure.

Statement of ethics

The authors have no ethical conflicts to disclose.

Patients consent

Written informed consent was obtained from the patient to be enrolled in a prospective study on the outcome after LVRS for publication of this study, which was approved by the hospital's ethical committee.

Funding

Supported by Grant No. 3200-043358;95.1 from the Swiss National Science Fund and by a grant from the Zürich Lung League. In addition, the work of YH and JH was supported by the Lungen-und Atmungsstifung Bern.

Acknowledgement

The authors thank Mrs. Sabine Wyss Kohl and Ms. Rahel Naef, study nurses, and the pulmonary laboratory staff of the Pulmonary Division for technical assistance.

Conflict of interest

None.

References

1. Gold Report. http://goldcopd.org/2022-gold-reports-2/:2022; V. 2022

2. Rochester DF (1984) The respiratory muscles in COPD State of the art. *Chest* 1984, 85: 47s-50s. [Crossref]

3. Cassart M, Hamacher J, Verbandt Y, Wildermuth S, Ritscher D, et al. (2001) Effects of lung volume reduction surgery for emphysema on diaphragm dimensions and configuration. *Am J respir crit care med* 163: 1171-1175. [Crossref]

4. Criner RN, Yu D, Jacobs MR, Criner GJ (2018) Effect of lung volume reduction surgery on respiratory muscle strength in advanced emphysema. *Chronic Obstr Pulm Dis* (Miami, Fla.) 6: 40-50. [Crossref]

5. Pahal, P.; Avula, A.; Sharma, S. Emphysema; https://www.ncbi.nlm.nih.gov/books/NBK482217/

6. Agrawal S, Gupta N, Gonuguntla HK (2021) Evidence-based review of bronchoscopic lung volume reduction. *Adv Respir Med* 89: 43-48. [Crossref]

7. Weder W, Ceulemans LJ, Opitz I, Schneiter D, Caviezel C (2021) Lung volume reduction surgery in patients with homogeneous emphysema. *Thorac Surg Clin* 31: 203-209. [Crossref]

8. Caviezel C, Franzen D, Weder W (2018) lung volume reduction surgery. Pneumologie (Stuttgart, Germany) 72: 64-78.

9. van Dijk M, Klooster K, Ten Hacken NHT, Sciurba F, Kerstjens HAM. Et al. (2020) The effects of lung volume reduction treatment on diffusing capacity and gas exchange. *Eur Respir Rev* 29: 190171. [Crossref]

10. Gelb AF, McKenna RJ Jr, Brenner M, Epstein JD, Zamel N (2001) Lung function 5 yr after lung volume reduction surgery for emphysema. *Am J Respir Crit Care Med* 163: 1562-1566. [Crossref]

11. Russi EW, Stammberger U, Weder W (1997) Lung volume reduction surgery for emphysema. *Eur Respir J* 10: 208-218.

12. Sharafkhaneh A, Goodnight-White S, Officer TM, Rodarte JR, Boriek AM (2005) Altered thoracic gas compression contributes to improvement in spirometry with lung volume reduction surgery. *Thorax* 60: 288-292. [Crossref]

13. Hamacher J, Büchi S, Georgescu CL, Stammberger U, Thurnheer R, et al. (2002) Improved quality of life after lung volume reduction surgery. *Eur Respir J* 19: 54-60. [Crossref]

14. Lammi MR, Marchetti N, Criner GJ (2014) Reduced dynamic hyperinflation after lvrs is associated with improved exercise tolerance. *Respir Med* 108: 1491-1497. [Crossref]

15. Fessler HE, Scharf SM, Ingenito EP, McKenna RJ Jr, Sharafkhaneh A (2008) Physiologic basis for improved pulmonary function after lung volume reduction. *Proc Am Thoracic Soc* 5, 416-420. [Crossref]

16. Shade D Jr, Cordova F, Lando Y, Travaline JM, Furukawa S, et al. (1999) Relationship between resting hypercapnia and physiologic parameters before and after lung volume reduction surgery in severe chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 159: 1405-1411. [Crossref]

17. Caviezel C, Schneiter D, Opitz I, Weder W (2018) Lung volume reduction surgery beyond the nett selection criteria. *J Thoracic Dis* 10: S2748-S2753. [Crossref]

18. Fishman A, Martinez F, Naunheim K, Piantadosi S, Wise R, et al. (2003) A randomized trial comparing lung-volume-reduction surgery with medical therapy for severe emphysema. *Engl J Med* 2003 348: 2059-2073. [Crossref]

19. Fishman A, Fessler H, Martinez F, McKenna RJ Jr, Naunheim K, et al. (2001) Patients at high risk of death after lung-volume-reduction surgery. *Engl J Med* 345: 1075-1083. [Crossref]

20. Cassina PC, Teschler H, Konietzko N, Theegarten D, Stamatis G (1998) Two-year results after lung volume reduction surgery in alpha1-antitrypsin deficiency versus smoker's emphysema. *Eur Respir J* 12: 1028-1032. [Crossref]

21. Tutic M, Bloch KE, Lardinois D, Brack T, Russi EW, et al. (2004) Long-term results after lung volume reduction surgery in patients with alpha1-antitrypsin deficiency. *J Thorac Cardiovasc Surg* 128: 408-413. [Crossref]

22. Gaissert HA, Trulock EP, Cooper JD, Sundaresan RS, Patterson GA (1996) Comparison of early functional results after volume reduction or lung transplantation for chronic obstructive pulmonary disease. *J Thorac Cardiovasc Surg* 111: 296-306. [Crossref]

23. You B, Zhao Y, Hou S, Hu B, Li H (2018) Lung volume reduction surgery in hypercapnic patients: A single-center experience from china. *J Thoracic Dis* 10: S2698-S2703. [Crossref]

24. Surveillance for respiratory hazards in the occupational setting [american thoracic society] (1982) The American review of respiratory disease 126: 952-956.

25. Quanjer PH, Tammeling GJ, Cotes JE, Pedersen OF, Peslin R, et al. (1993) Lung volumes and forced ventilatory flows. Report working party standardization of lung function tests, european community for steel and coal. Official statement of the european respiratory society. *Eur Respir J* 16: 5-40. [Crossref]

26. Curran-Everett D (2006) A classic learning opportunity from fenn, rahn, and otis (1946): The alveolar gas equation. *Adv Physiol Educ* 30: 58-62. [Crossref]

27. Stammberger U, Klepetko W, Stamatis G, Hamacher J, Schmid RA, et al. (2000) Buttressing the staple line in lung volume reduction surgery: A randomized three-center study. *Annals Thoracic Surg* 70: 1820-1825. [Crossref]

28. Pompeo E, Rogliani P, Tacconi F, Dauri M, Saltini C, et al. (2012) Randomized comparison of awake nonresectional versus nonawake resectional lung volume reduction surgery. *J Thorac Cardiovasc Surg* 143: 47-54. [Crossref]

29. McKenna RJ Jr, Brenner M, Fischel RJ, Gelb AF (1996) Should lung volume reduction for emphysema be unilateral or bilateral? *J Thorac Cardiovasc Surg* 112: 1331-1338. [Crossref]

30. Geddes D, Davies M, Koyama H, Hansell D, Pastorino U, et al. (2000) Effect of lung-volume-reduction surgery in patients with severe emphysema. *Engl J Med* 343: 239-245. [Crossref]

31. Meyers BF, Yusen RD, Guthrie TJ, Patterson GA, Lefrak SS, et al. (2004) Results of lung volume reduction surgery in patients meeting a national emphysema treatment trial high-risk criterion. *J Thorac Cardiovasc Surg* 127: 829-835. [Crossref]

32. Laghi F, Jubran A, Topeli A, Fahey PJ, Garrity ER Jr, et al. (2004) Effect of lung volume reduction surgery on diaphragmatic neuromechanical coupling at 2 years. *Chest* 125: 2188-2195. [Crossref]

33. Pompeo E, Mineo TC (2007) Two-year improvement in multidimensional body mass index, airflow obstruction, dyspnea, and exercise capacity index after non-resectional lung volume reduction surgery in awake patients. *Annals Thoracic Surg* 84: 1862-1869. [Crossref]

34. Tacconi F, Pompeo E, Forcella D, Marino M, Varvaras D, et al. (2008) Lung volume reduction reoperations. *Annals Thoracic Surg* 85: 1171-1177. [Crossref]

35. Caviezel C, Schaffter N, Schneiter D, Franzen D, Inci I, et al. (2017) Outcome after lung volume reduction surgery in patients with severely impaired diffusion capacity. *Annals Thoracic Surg* 105:379-385. [Crossref]

36. Criner GJ, Sue R, Wright S, Dransfield M, Rivas-Perez H, et al. (2018) A multicenter randomized controlled trial of zephyr endobronchial valve treatment in heterogeneous emphysema (liberate). *Am J Respir Crit Care Med* 198: 1151-1164. [Crossref]

37. Shah PL, Slebos DJ, Cardoso PF, Cetti E, Voelker K, et al. (2011) Bronchoscopic lung-volume reduction with exhale airway stents for emphysema (ease trial): Randomised, sham-controlled, multicentre trial. *Lancet (London, England)* 378: 997-1005. [Crossref]

38. Venuta F, Anile M, Diso D, Carillo C, De Giacomo T, et al. (2012) Long-term follow-up after bronchoscopic lung volume reduction in patients with emphysema. Eur Respir J 39: 1084. [Crossref]

39. Yang L, Hsu K, Williamson JP, Peters MJ, Ho-Shon K, et al. (2019) Changes in ventilation and perfusion following lower lobe endoscopic lung volume reduction (elvr) with endobronchial valves in severe copd. *Clin Respir J* 13: 453-459. [Crossref]

40. Leyenson V, Furukawa S, Kuzma AM, Cordova F, Travaline J, et al. (2000) Correlation of changes in quality of life after lung volume reduction surgery with changes in lung function, exercise, and gas exchange. *Chest* 118, 728-735. [Crossref]

41. Snyder ML, Goss CH, Neradilek B, Polissar NL, Mosenifar Z, et al. (2008) Changes in arterial oxygenation and self-reported oxygen use after lung volume reduction surgery. *Am J Respir Crit Care Med* 178: 339-345. [Crossref]

42. Homan S, Porter S, Peacock M, Saccoia N, Southcott AM, et al. (2001) Increased effective lung volume following lung volume reduction surgery in emphysema. *Chest* 120: 1157-1162. [Crossref]

43. Albert RK, Benditt JO, Hildebrandt J, Wood DE, Hlastala MP (1998) Lung volume reduction surgery has variable effects on blood gases in patients with emphysema. *Am J Respir Crit Care Med* 158: 71-76. [Crossref]

44. Wagner PD, Dantzker DR, Dueck R, Clausen JL, West JB (1977) Ventilation-perfusion inequality in chronic obstructive pulmonary disease. *J Clin Invest* 59: 203-216. [Crossref]

45. Khoukaz G, Gross NJ (1999) Effects of salmeterol on arterial blood gases in patients with stable chronic obstructive pulmonary disease. Comparison with albuterol and ipratropium. *Am J Respir Crit Care Med* 160: 1028-1030. [Crossref]

46. O'Brien GM, Furukawa S, Kuzma AM, Cordova F, Criner GJ (1999) Improvements in lung function, exercise, and quality of life in hypercapnic copd patients after lung volume reduction surgery. *Chest* 115: 75-84. [Crossref]

47. Yusen RD, Trulock EP, Pohl MS, Biggar DG (1996) Results of lung volume reduction surgery in patients with emphysema. The washington university emphysema surgery group. *Semin Thoracic Cardiovasc Surg* 8: 99-109. [Crossref]

48. Frey JG, Rochat T, Pichard C, Dousse N, Janssens JP, et al. (1998) Chronic obstructive pulmonary disease patients undergoing home oxygen therapy: A study of clinical parameters, nutritional status and ambulatory capacity. *Revue des maladies respiratoires* 15: 69-78. [Crossref]

49. Kozora E, Emery CF, Ellison MC, Wamboldt FS, Diaz PT, et al. (2005) Improved neurobehavioral functioning in emphysema patients following lung volume reduction surgery compared with medical therapy. Chest 128: 2653-2663. [Crossref]

50. Stammberger U, Bloch KE, Thurnheer R, Bingisser R, Weder W, et al. (1998) Exercise performance and gas exchange after bilateral video-assisted thoracoscopic lung volume reduction for severe emphysema. Eur Respir J 12: 785-792. [Crossref]

51. Hamacher J, Bloch KE, Stammberger U, Schmid RA, Laube I, et al. (1999) Two years' outcome of lung volume reduction surgery in different morphologic emphysema types. Annals Thoracic Surg 68: 1792-1798. [Crossref]

52. Criner GJ, Belt P, Sternberg AL, Mosenifar Z, Make BJ, et al. (2009) Effects of lung volume reduction surgery on gas exchange and breathing pattern during maximum exercise. *Chest* 135: 1268-1279. [Crossref]

53. Yusen RD, Lefrak SS, Gierada DS, Davis GE, Meyers BF, et al. (2003) A prospective evaluation of lung volume reduction surgery in 200 consecutive patients. *Chest* 123: 1026-1037. [Crossref]

54. Klooster K, ten Hacken NH, Hartman JE, Kerstjens HA, van Rikxoort EM, et al. (2015) Endobronchial valves for emphysema without interlobar collateral ventilation. *Engl J Med* 373: 2325-2335. [Crossref]

55. Herth FJ, Noppen M, Valipour A, Leroy S, Vergnon JM (2012) Efficacy predictors of lung volume reduction with zephyr valves in a european cohort. *Eur Respir J* 39: 1334-1342. [Crossref]

56. Posthuma R, Vanfleteren L (2020) The stelvio trial, a game changer for bronchoscopic lung volume reduction in patients with severe emphysema. *Breathe* 16: 200004. [Crossref]