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Treatment of chronic respiratory failure: lung volume reduction surgery *versus* rehabilitation

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Treatment of chronic respiratory failure: lung volume reduction surgery versus *rehabilitation. M. Decramer. ©ERS Journals Ltd 2003.*

ABSTRACT: Several treatment options are available for end-stage chronic obstructive pulmonary disease (COPD). Respiratory rehabilitation and lung volume reduction surgery are reviewed here. Respiratory rehabilitation can now be considered a prime treatment for COPD. Indeed, it has been clearly shown to improve exercise capacity and health status in these patients. Improvements in the former fell just below the minimal clinically important difference, whereas those in the latter exceeded it. In addition, after a respiratory rehabilitation programme, a reduction in the number of hospital admissions and duration of each admission was demonstrated.

It remains, however, difficult to predict accurately which patients will improve after rehabilitation and which will not. Factors that may contribute to this prediction are: baseline peak exercise ventilation/maximal voluntary ventilation, maximal inspiratory pressure, peripheral muscle force, and 6-min walking distance. Several studies have clearly shown that training effects are as pronounced in patients with severe as in those with moderate airflow obstruction. This is the most significant insight in this area of the 1990s.

Lung volume reduction surgery may also be of benefit in patients with end-stage COPD. It is clear that lung function, exercise capacity and health status improve after this procedure, although the results of only six randomised studies are currently available.

It remains difficult to accurately predict which patients will benefit from the procedure. From a model analysis, the most important action mechanism appears to be resizing of the lungs. Only in patients with an increased residual volume/total lung capacity ratio are beneficial effects expected. The model analysis, however, did not fit the experimental data very well in a recent publication. Emphysema heterogeneity is also likely to be related to the response. The question remains as to whether or not lung volume reduction surgery accelerates the decline in forced expiratory volume in one second in the long run. The technique is undergoing considerable progress as numerous new surgical and endoscopic procedures are currently being developed. The results of these procedures have not yet been systematically evaluated.

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Chronic obstructive pulmonary disease (COPD) is without question the most common cause of respiratory failure. Ideally, it should be detected and treated in the early stages before respiratory failure occurs [1]. The only treatment modality that may reduce the progression of COPD is smoking cessation [2]. Nevertheless, many other treatments, such as bronchodilators [3–5], inhaled corticosteroids [6–10], lung transplantation and lung volume reduction surgery (LVRS) [11, 12], may improve lung function. The effect of all these treatments combined, as usually performed in practice, has never systematically been studied. Most patients do not follow appropriate treatments for their disease because they underestimate it and consider it self-inflicted [13, 14].

Several treatment options are currently available for end-stage COPD. These include: pharmacological treatment, rehabilitation, oxygen therapy, LVRS, and lung transplantation. These treatments are increasingly successful, which has resulted in a clear improvement in survival in patients receiving long-term oxygen treatment since the 1980s [15]. Most of these treatment modalities are discussed in the present supplement, with lung transplantation being discussed by LAU and PATTERSON [16]. The present contribution reviews two treatment modalities that are complementary in the treatment of COPD patients: rehabilitation and LVRS. The first of these primarily improves exercise capacity and health status but does not alleviate airflow obstruction. The second has at least the potential of improving pulmonary function substantially in some patients.

For each of the treatment modalities, the potential benefits, selection of candidates, practical organisation and potential future developments are discussed in order.

Respiratory rehabilitation

Potential benefits

The benefits of pulmonary rehabilitation programmes have been well demonstrated since the early 1990s [17–25]. Several randomised controlled trials have been conducted. Table 1

Table 1. – Effects of rehabilitation on quality of life (QoL) and timed walking distance in several large studies

First author [Ref.]	Patients n	Programme duration	QoL		6MWD[#]
			Questionnaire	QoL[#]	
RIES [18]	119	8 weeks	QWB	NS	+9 min[¶]
GOLDSTEIN [17]	89	6 months	CRQ	1.04	0.74
GRIFFITHS [23, 26]	200	6 weeks	CRQ	0.77	0.73[+]
			SGRQ	1.88	
WEDZICHA [20, 27]	66[§]	8 weeks	CRQ	0.89	2.17[+]
			SGRQ	1.35	
	60[f]		CRQ	0.02	-0.08[+]
			SGRQ	0.23	
TROOSTERS [24, 28, 29]	100	6 months	CRQ	1.4	0.96

Selected randomised controlled trials on pulmonary rehabilitation. Effects were expressed in natural units or minimal clinically important difference units. The minimal clinically important difference is the minimal difference perceived by the patient [21, 22]. 6MWD: 6-min walking distance. QWB: Quality of Well-being Scale; CRQ: Chronic Respiratory Disease Questionnaire; SGRQ: St George's Respiratory Questionnaire; NS: nonsignificant. [#]: expressed as a fraction of the minimal clinically important difference; [¶]: treadmill endurance; [+]: shuttle walk test; [§]: moderately dyspnoeic; [f]: severely dyspnoeic.

provides an overview of the effects obtained in the most significant trials. As can be seen, all trials but one demonstrated an improvement in health-related quality of life. The negative trial used the quality of well-being questionnaire to examine the effect [18]. This is a generic instrument that is clearly less sensitive than the disease-specific instruments (Chronic Respiratory Disease Questionnaire and St George's Respiratory Questionnaire) used in the other trials. The effect exceeded the minimal clinically important difference in most trials. Similarly a clear increase in 6-min walking distance (6MWD) or shuttle walking distance was observed. This increase fell just below the minimal clinically important difference (table 1). In one trial, effects were only obtained in the moderately dyspnoeic patients and not in the severely dyspnoeic patients [20]. In this study, however, the severely dyspnoeic patients followed a home exercise programme with less supervision than the moderately dyspnoeic patients, who exercised in the hospital. This may relate to the smaller effects observed in the latter patients.

Besides these improvements in health-related quality of life and functional exercise capacity, a clear reduction in the utilisation of healthcare resources was demonstrated. GRIFFITHS *et al.* [23] demonstrated a reduction in the number of hospitalisations (1.9 *versus* 1.4) and the duration of hospitalisation (18.1 *versus* 9.4 days) in the year following a 6-week lasting rehabilitation programme. Interestingly, the number of visits to the pulmonologist decreased, whereas the number of visits to the general practitioner increased. This signals that COPD patients, after a rehabilitation programme, may use healthcare resources better than before. TROOSTERS *et al.* [24] also found a reduction in the duration of hospitalisation after a rehabilitation programme.

At present, there has been no clear demonstration of improved survival after a pulmonary rehabilitation programme. There are, however, three indications that survival might improve after pulmonary rehabilitation. First, RIES *et al.* [18] found greater survival after a rehabilitation programme during a 6-yr follow-up, but the difference did not reach significance. The power, however, of the study to detect a difference in survival was too low. Secondly, GRIFFITHS *et al.* [23] found a similar tendency, but the number of patients was too low for it to reach significance. Thirdly, TROOSTERS *et al.* [28] found a tendency for greater survival in patients who were admitted to a training programme after hospitalisation for an acute exacerbation of COPD. These three indications, however, are insufficient to fully demonstrate improved survival after pulmonary rehabilitation. Moreover, it will be difficult to design a large-scale trial examining this in the future as randomisation to a control group would no longer be ethically acceptable since the benefits of pulmonary rehabilitation have been clearly demonstrated.

Finally, it was unequivocally demonstrated that the benefits achieved after pulmonary rehabilitation are relatively inexpensive, particularly when the reduction in healthcare resource utilisation caused by rehabilitation is taken into account. Indeed, GRIFFITHS *et al.* [26] demonstrated that the cost of the programme was outweighed by the reduction in healthcare resource utilisation such that the incremental cost of adding rehabilitation to standard care was negative. The treatment is thus clearly cost-effective.

Selection of candidates

In general, it is very difficult to appropriately select candidates for a pulmonary rehabilitation programme on a scientific basis. The relation between functional variables before rehabilitation and response to training is weak and does not allow prediction of the response to rehabilitation. Nevertheless, some variables are, albeit weakly, related to response and may be used as a guideline on which to base clinical decisions.

Some prerequisites are necessary before starting a rehabilitation programme. Medical therapy should be optimised before starting the programme [30]. Optimal medical therapy for COPD is now based on international consensus guidelines [1]. In addition, most programmes require that the patient stops smoking before the programme or that they are at least enrolled in a smoking cessation programme. However, no data at present show that the effects of rehabilitation would be smaller in smokers as compared to nonsmokers [31].

ZUWALLACK *et al.* [32] examined the determinants of improvement in 12-min walking distance (12MWD) in a 6-week programme in 50 COPD patients. They found that the initial 12MWD, breathing reserve, initial maximal oxygen consumption and oxygen pulse were related to the improvement in 12MWD. On multiple regression analysis, the significant contributors to the improvement in 12MWD were forced expiratory volume in one second (FEV1) and initial 12MWD. Several later studies, however, demonstrated that FEV1 was not well related to the effect. MALTAIS *et al.* [33] showed that the training effects were similar in a group of COPD patients with an FEV1 of > or <40% of the predicted value in a 12-week programme. CASABURI *et al.* [34] showed clear training effects in an 8-week lasting rehabilitation

programme in COPD patients with an FEV1 of <1 L and who were barely able to raise their lactate levels during exercise (peak lactate 2.2 mM). These patients showed clear increases in maximal oxygen consumption, reductions in ventilation and cardiac frequency at a given work rate and changes in oxygen uptake kinetics indicative of a training effect. Similarly, TROOSTERS *et al.* [29] found that a measure of ventilatory limitation (peak exercise ventilation/maximal voluntary ventilation), initial maximal inspiratory pressure ($P_{I,max}$) and peripheral muscle force were related to the response in 58 patients who followed a 6-month outpatient training programme. In these patients, FEV1 or other pulmonary function measures were not related to the training response. The factors related to response are summarised in table 2.

The fact that FEV1 is not related to the training response is in contrast with common belief in the early 1980s [35] and as such is of great conceptual interest. Indeed, the immediate consequence is that patients with severe airflow obstruction, such as candidates for LVRS or lung transplantation, are also good candidates for a rehabilitation programme. In the Respiratory Division of the Catholic University of Leuven (Leuven, Belgium), it is now common practice not to consider COPD patients for these procedures unless they have successfully completed a comprehensive rehabilitation programme. A recent study confirmed that COPD patients in Global Initiative for Chronic Obstructive Lung Disease stages I–III benefit from pulmonary rehabilitation [36].

There is some evidence that psychosocial factors may be related to adherence to the programme and also to its effects [37]. Better social support improved adherence to the programme.

In general, candidates for a pulmonary rehabilitation programme are patients who, after smoking cessation, are well motivated to attend the programme and have severely impaired health status and functional status. Contraindications are either diseases that interfere with the rehabilitation process itself, *e.g.* rheumatoid arthritis, or put a patient at excessive risk during training, *e.g.* ischaemic heart disease. The latter contraindication is only relative since cardiologists admit such patients into rehabilitation programmes. The key concept is that any level of airflow obstruction is eligible for pulmonary rehabilitation. In other words, a patient with severe deconditioning and muscle weakness and an FEV1 of 30% pred or the same patient with an FEV1 of 60% pred are equally good candidates for a pulmonary rehabilitation programme [30].

Table 2. – Factors demonstrated to correlate significantly with the training response

Related factors	Unrelated factors
Baseline 6MWD	Age
Ventilatory limitation (V'_E/MVV or BR)	FEV1
Baseline $V'_{O_2,max}$	$T_{L,CO}$
$P_{I,max}$	BMI
Peripheral muscle force	Health status
	P_{a,O_2}
	P_{a,CO_2}
	Exercise saturation

6MWD: 6-min walking distance; V'_E: peak exercise ventilation; MVV: maximal voluntary ventilation; BR: breathing reserve; FEV1: forced expiratory volume in one second; $V'_{O_2,max}$: maximal oxygen consumption; $T_{L,CO}$: transfer factor of the lung for carbon monoxide; $P_{I,max}$: maximal inspiratory pressure; BMI: body mass index; P_{a,O_2}: arterial oxygen tension; P_{a,CO_2}: arterial carbon dioxide tension.

Practical organisation

The programme may be administered on an outpatient or inpatient basis. In terms of cost-effectiveness, outpatient programmes are better, as they do not incur the cost of hospital admission. There is also some evidence on home programmes, which produce smaller effects than clinical programmes [38].

The programme administered is a multidisciplinary programme that consists of education, exercise training, peripheral muscle training, ventilatory muscle training, occupational therapy, dietary advice and psychosocial support. Exercise training and psychosocial support are the most effective components of the programme [39]. The modality of exercise training is usually endurance training, although interval-type training may also be effective [40]. Endurance training in COPD patients at a load of 60% of maximum for 20 min is possible, even in patients with severe airflow obstruction, although it may take several weeks before the appropriate training load and duration can be achieved [33]. Exercises usually include walking on a treadmill, cycling, arm ergometry, stepping and peripheral muscle training.

Peripheral muscle resistance training has also been shown to be useful in the rehabilitation of COPD patients. Indeed, several studies showed that it clearly improved muscle force and health status in COPD patients [41–44]. A recent study demonstrated that endurance training and peripheral muscle resistance training were equally effective in improving exercise capacity, muscle force and health status in patients with COPD and muscle weakness [44]. Peripheral muscle stimulation also appears effective in COPD patients [45, 46]. It is clear that these treatment modalities will play an increasingly important role in COPD rehabilitation in the future. The role of ventilatory muscle training is not yet clearly defined [47, 48], and more research is required in this area.

As ventilatory limitation is usually related to the response to training, it may be worthwhile to attempt to reduce the impact of ventilatory limitation. This could be attempted in three different ways. First, administration of oxygen is expected to reduce the ventilatory requirements during exercise. An improvement of the effects of pulmonary rehabilitation with oxygen has been suggested, but not unequivocally demonstrated [49–51]. Secondly, heliox, a gas mixture in which oxygen and helium replace nitrogen, has also been tried. The lower density of helium reduces the work of breathing and improves ventilatory capacity. However, no significant effect on the training effect was found, although a trend was present [52]. Finally, HAWKINS *et al.* [53] demonstrated that noninvasive ventilation during exercise training enhanced the training effects. This is due to unloading of the ventilatory system such that greater training loads can be obtained. The procedure, however, is tedious in the sense that it is difficult to adjust ventilation to the increased ventilatory demands during exercise such that, at present, it is unclear what its place is in clinical routine.

The role of dietary intervention in COPD patients is clearly beyond the scope of the present article and is not discussed here. There is a need for education since COPD patients underestimate their disease and do not usually follow the proper treatments for their disease [12]. General education programmes, however, on the whole do not appear effective [18]. More targeted education programmes may be more effective.

Although the average programme has an occupational therapy component, its role has never clearly been established in this context. More specifically, it has not been clearly demonstrated whether rehabilitation improves the activities of daily living in a randomised controlled design, nor whether

potential improvement is related to occupational therapy, exercise training or both. Whether programmes should be directed at those specific activities of daily living that pose problems in particular patients is also unclear.

After a rehabilitation programme, some maintenance is likely to be required to maintain the effects achieved during the rehabilitation period, although no randomised trials on this are currently available. Several modalities may be followed. Home exercise with or without supervision by a physiotherapist may be of help. COPD exercise or sports clubs may help as well. At present, it is not clear whether a rehabilitation programme automatically leads to a greater activity level after the programme, although the persistent improvement is usually attributed to increased activity.

Future developments

The question as to whether the effects of rehabilitation may be enhanced by pharmacological therapy remains an interesting one. Several treatments have been studied in this respect. A study on growth hormone therapy in 16 COPD patients demonstrated that, with 3 weeks of this therapy combined with rehabilitation, lean body mass increased, but outcome variables such as $P_{I,max}$, handgrip strength and subjective wellbeing were not affected [54]. The 6MWD even decreased significantly with this therapy. A large study with anabolic steroids was also conducted in 217 COPD patients. Treatment with nutritional intervention and nandrolone decanoate combined with rehabilitation was shown to increase $P_{I,max}$ more than rehabilitation alone [55] but not more than rehabilitation combined with nutritional intervention. The gain in fat-free mass was also greater with the combined treatment. Again, there was no difference between nutritional intervention and anabolic steroids and nutritional intervention alone. Testosterone therapy was shown to have an additional effect on muscle strength in COPD patients with low testosterone levels in combination with resistance training [56].

There is clear evidence that muscle weakness in COPD patients may be related to increased circulating levels of tumour necrosis factor-α or interleukin-6 or -8 [27, 57, 58]. Levels of these cytokines are elevated in stable patients with recent weight loss [58] or during exacerbations of COPD [27, 59]. Recent evidence demonstrates that muscle weakness in the latter patients correlates with serum interleukin-8 levels [59]. As a consequence, treatment with antitumour necrosis factor-α and anti-interleukin-6 and -8 may be considered in the future, not only to affect the progression of the disease but also to reduce muscle weakness. The response to a rehabilitation programme can be influenced by expression of these cytokines. Also, serum levels of insulin-like growth factor-I correlate with muscle weakness in COPD patients [59].

Lung volume reduction surgery

Potential benefits

Following the original observations of COOPER and coworkers [11, 12], many studies have been performed on the effects of LVRS in patients with end-stage emphysema. The original study of COOPER *et al.* [12] showed that, after bilateral LVRS, FEV1 increased by 51%, total lung capacity (TLC) was reduced by 14% and residual volume (RV) by 28%, arterial oxygen tension increased by 1.1 kPa (8 mmHg) and arterial carbon dioxide tension decreased by 0.53 kPa (4 mmHg). Of the patients who had previously required continuous supplemental oxygen, 70% no longer showed this requirement. This improvement in pulmonary function was paralleled by improvement in dyspnoea and quality of life. Subsequent studies found similar improvements. Improvements were generally greater after bilateral than after unilateral procedures [60]. The results of these studies have been recently reviewed [60–63]. On average, the above-mentioned results, as originally reported by COOPER and coworkers [11, 12], were obtained. No improvement in blood gas levels or diffusing capacity was found. These studies are, for the major part, open uncontrolled studies on relatively small numbers of patients except for a few studies involving more than 100 patients [12, 64, 65].

Surprisingly, few randomised studies have been performed. The National Emphysema Treatment Trial (NETT), which is still running, aims to compare the effects of LVRS to those of continued rehabilitation, and was intended to be the definitive randomised controlled study on survival and exercise capacity after LVRS [66]. The study has a duration of 5 yrs with a fixed end-point and a variable follow-up period. The original recruitment target of 4,500 patients was reduced to 2,300 patients and, in June 2001, 1,033 patients were randomised. The results of this trial will be available soon. The results of six randomised studies are already available [67–72]. They are summarised in table 3. Full results have been published for only three of these trials. They showed that LVRS reduced hyperinflation (RV and TLC) and improved FEV1 and forced vital capacity (FVC) compared to control. In addition, the 6MWD or shuttle walk test increased significantly and quality of life improved. The effects on the latter variables were substantial. In general, inspiratory muscle function ($P_{I,max}$ and maximal transdiaphragmatic pressure) also improved, confirming the results of more-targeted studies [74–76]. The

Table 3. – Effects of lung volume reduction surgery (LVRS) on outcome variables in the randomised studies

First author [Ref.]	Patients n		Surgery	Surgical mortality %		Improvement in outcome variable				
	Surg.	Med.		Surg.	Med.	FVC	FEV1 mL	Exercise# m	QoL	$P_{I,max}$
GEDDES [67]	24	24	Bilat VATS or MS	21	12	S	150 (S)	70 (S)	S	S
CRINER [68, 73]	19	18	Bilat MS	9	3	S	200 (S)	33 (NS)	S	–
POMPEO [69]	30	30	17 Bilat VATS, 13 unilat VATS	3	3	S	460 (S)	62 (S)	S	S
LÖFDAHL [72]	29	31	–	–	–	–	270 (S)	101 (S)	S	–
NETT [66, 70]	69	70	Bilat VATS 47, MS 22	16	0	–	– (S)	– (S)	NS	–
GOODNIGHT-WHITE [71]	27	24	MS	3	–	–	260 (S)	177 (S)	S	–

Overview of randomised controlled trials on LVRS. Surg.: surgical group; Med.: medical group; FVC: forced vital capacity; FEV1: forced expiratory volume in one second; QoL: quality of life; $P_{I,max}$: maximal inspiratory pressure; NETT: National Emphysema Treatment Trial; bilat: bilateral; VATS: video-assisted thoracoscopic surgery; MS: median sternotomy; unilat: unilateral; S: significant; NS: nonsignificant; #: 6-min walking distance or shuttle walk.

improvements in inspiratory muscle function are probably due to geometric factors rather than intrinsic improvements in inspiratory muscle function [77, 78]. LVRS is unique in the sense that it is the only procedure that causes substantial improvements in lung function in end-stage emphysema, besides lung transplantation. Rehabilitation improves exercise capacity and health status as well, but does not affect pulmonary function (see above).

The mortality of the procedure is currently <5%, although some recent randomised studies have clearly had higher mortality rates [67, 70]. The data published on the high-risk group clearly demonstrate that, in patients with an FEV1 of <20% pred and homogeneous disease or a transfer factor of the lung for carbon monoxide (TL,CO) of <20% pred, mortality increases after LVRS. This indicates that, in some patients, the procedure may have detrimental effects. Selection of candidates is thus of the utmost importance, but a scientific basis for this is largely lacking (see below).

Several hypotheses have been formulated to explain the beneficial effects observed after the procedure. A comprehensive discussion is clearly beyond the scope of the present publication, and has already been published [79]. The hypotheses explaining the improvement include: improved lung mechanics, increased lung elastic recoil [80, 81], reduced intrinsic positive inspiratory pressure [82], reduced hyperinflation, increased respiratory muscle strength due to geometric factors [74–78], improved ventilation/perfusion matching, and reduced pulmonary vascular resistance. There is evidence that the major mode of action is resizing of the lungs [83–86]. This means that, in emphysema, lung mechanics deteriorate because the lung is disproportionately expanded compared to the chest wall. The intervention restores the balance between lung size and chest wall size and hence lung mechanics improve. The intervention thus primarily increases vital capacity by reducing RV more than TLC. The increase in vital capacity is the prime determinant of the increase in FEV1. Together with increased elastic recoil, this improved lung mechanics reduces the work of breathing. This action mechanism is derived from several model analyses and experimental data. As a consequence, it is expected that postoperative improvement in FEV1 is largely determined by the improvement in vital capacity and is related to the preoperative RV/TLC ratio. Prospective testing of this model, however, has yielded relatively disappointing results. Indeed, FESSLER *et al.* [87] demonstrated that the RV/TLC ratio was related to the postoperative change in FVC in a group of 13 patients, but, in a larger group of 78 patients, this relationship was not present. It thus remains difficult to predict the improvement on the basis of preoperative functional variables. Recently, INGENITO *et al.* [88] demonstrated that patients who respond tend to show a postoperative reduction in RV, whereas those who do not tend not to show this reduction. Their results are depicted schematically in figure 1. This proved to be a better predictor of the effect than the increase in lung elastic recoil, confirming the reasoning developed above and the theoretical model of FESSLER and PERMUTT [83]. This model was also confirmed in a recent animal model [86].

Although it is clear that, in the average patient, LVRS produces beneficial effects on lung mechanics, it remains unclear how long these effects last. Few long-term studies are available. Recently GELB *et al.* [89] published the results of a 5-yr follow-up study in 26 patients. This study demonstrates that the effects are gradually lost over this period. Indeed, at 1 yr, 73% had an FEV1 of >200 mL or FVC of >400 mL above baseline, whereas this proportion was reduced to 8% after 5 yrs. Similarly, the proportion of patients with at least a one unit change in dyspnoea score was reduced from 88 to 15% and the elimination of oxygen dependence was reduced from 78 to 0% over this time period. It thus appears that the

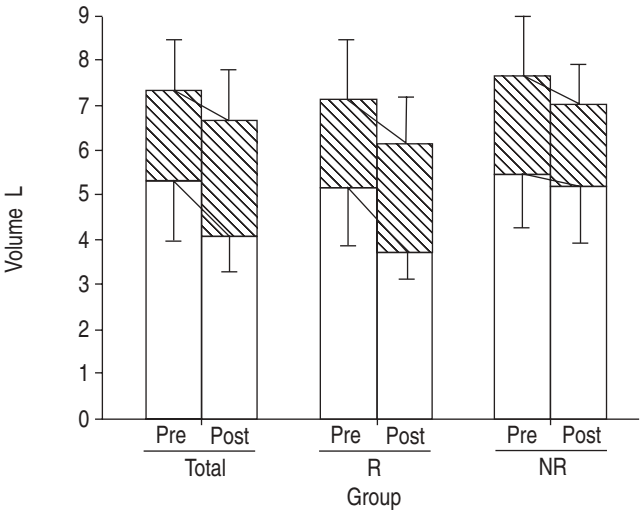

Fig. 1. – Effects of lung volume reduction surgery on the subdivisions (□: residual volume (RV); ▨: vital capacity) of total lung capacity (TLC) in the whole group of patients (total), responders (R) and nonresponders (NR). Data are presented as mean±SD. TLC decreases in all groups, and responders exhibit a decrease in RV, whereas this is not the case for nonresponders. (Modified from INGENITO *et al.* [88]).

effects gradually disappear, although, even with lung function at the baseline level after 5 yrs, improvement compared to a control group may still be present, since FEV1 in COPD patients normally exhibits an annual decline of 60–80 mL. Over 5 yrs, the expected decline in FEV1 would thus be expected to amount to 300–400 mL, such that the effect after 5 yrs may still be substantial. This further underlines the need for an appropriate control group to estimate effects correctly. A similar decline in the effect on FEV1 was found by FUJIMOTO *et al.* [90] over 3 yrs.

Another fundamental question is to what extent LVRS may affect the rate of decline in FEV1. As, in general, a relationship between the rate of decline and the progression of emphysema is expected, this is an important question. Although some indications for accelerated decline after LVRS are present in the sense that, in many studies, the decline observed after LVRS appeared to exceed the expected decline in COPD patients [91], this has never clearly been substantiated directly. KESTEN *et al.* [92] found accelerated decline over 1–2 yrs in six of 17 patients for whom they had follow-up spirometric data available. GELB *et al.* [89] found similar rates of decline as before in five patients in whom they had follow-up spirometric data over a mean of 3.8 yrs before and after the operation. The decline in FEV1 was 116 mL·yr^{-1} before the operation and 78 mL·yr^{-1} afterwards. This observation thus refutes the accelerated decline after LVRS, but is based on a very small number of patients.

Selection of candidates

As clarity regarding the action mechanism is still absent to a large extent and since the size mismatch between the lungs and chest wall is not easy to measure noninvasively, it remains difficult to accurately predict the postoperative response from preoperative functional data. Indeed, although several factors were shown to be significantly related to response, the models, in general, only explain a relatively limited fraction of the variance such that they do not allow proper prediction of the response in an individual patient. Indeed, BRENNER *et al.* [93] analysed the variables related to response in a study comparing buttressed stapled resections with laser coagulation.

Buttressed stapled resections were clearly more effective than laser coagulation. Smoking history and $T_{L,CO}$ were the only significant predictors of outcome. FEV1 and blood gas levels did not add to the predictive power, nor did computed tomography (CT) scores. The model explained a total of only 45% of the variance observed. Similarly, the model of THURNHEER *et al.* [94], based on RV/TLC ratio and CT visual analogue score, explained only ~40% of the variance in postoperative response. This, in general, means that accurate prediction of the response is not possible on a scientific basis.

Several studies have examined the relationship of preoperative functional variables to the response to surgery using univariate analysis. In general, clinical, physiological and imaging factors were examined. Several of these factors were related to the response. They are summarised in table 4. For the clinical criteria, age >75–80 yrs is usually associated with poor outcome [64, 93], although this has been debated in other studies [95]. Severe comorbidity is usually considered to be an exclusion criterion. Particular attention has been paid to the coexistence of nonsmall cell lung cancer [96] and coronary artery disease [97]. This is a very specific problem and is not addressed further in the present article. The presence of severe pulmonary hypertension with a mean pulmonary artery pressure of >35 mmHg is usually considered to be a contraindication [98], although the procedure may significantly improve right ventricular function [99]. Patients with α_1-antitrypsin deficiency seem to respond less favourably in the long run [12, 100–102].

The relationship between physiological criteria and the subsequent response to LVRS has been studied repeatedly. It is now accepted that an FEV1 of <20% pred, $T_{L,CO}$ of <20% pred and homogeneous disease are exclusion criteria, particularly if combined [70]. The ideal candidate appears to be a patient with heterogeneous emphysema with severe hyperinflation, in whom airflow obstruction is due to loss of elastic recoil and not intrinsic airway disease. This was confirmed by INGENITO *et al.* [103], who demonstrated, in 29 patients undergoing bilateral thoracoscopic LVRS, that response was clearly related to inspiratory resistance. Indeed, inspiratory resistance was the only factor related to FEV1 response on both univariate and multivariate analysis. The variance explained by inspiratory resistance was only 40%. Patients with a response also showed higher lung compliance and lower elastic recoil at TLC, confirming that patients with pure emphysema were better candidates. This is without question an interesting concept, but, unfortunately, these results have not been subsequently reproduced by other groups and the predictive value of inspiratory resistance is still too low to allow accurate prediction.

Table 4. – Indications and contraindications for lung volume reduction surgery

Indications	Relative contraindications
Clinical	
Age <75 yrs	Age >75 yrs
Disability despite maximal medical treatment including pulmonary rehabilitation	Comorbid illness with 5-yr mortality >50%
Exsmoker (>3 months)	Severe obesity or cachexia
	Surgical constraint
	α_1-Antitrypsin deficiency
Physiological	
FEV1 <35% pred	FEV1 >40% pred
RV/TLC >60%	RV <150% pred
$T_{L,CO}$ <20–40% pred	TLC <100% pred
6MWD >300 m	Increased inspiratory resistance
	$T_{L,CO}$ <20% pred
	P_{a,CO_2} >55 mmHg
	6MWD <300 m
	MPAP >35 mmHg
Imaging	
Severe heterogeneous emphysema on CT with upper lobe predominance	Minimal emphysema
	Severe homogeneous emphysema

FEV1: forced expiratory volume in one second; RV: residual volume; TLC: total lung capacity; $T_{L,CO}$: transfer factor of the lung for carbon monoxide; 6MWD: 6-min walking distance; P_{a,CO_2}: arterial carbon dioxide tension; MPAP: mean pulmonary artery pressure; CT: computed tomography; pred: percentage of the predicted value; (1 mmHg=0.133 kPa).

Besides these variables, identification of candidates has primarily focused on measures of hyperinflation. TLC [98], RV and RV/TLC [87, 94] ratio have been correlated to response. According to the model of FESSLER and PERMUTT [83], the latter ratio is expected to be the best predictor of postoperative increase in FVC and FEV1. Although several studies show a relationship between RV/TLC ratio and outcome, in general these relationships have been relatively disappointing. An arterial carbon dioxide tension of >6.7–7.3 kPa (>50–55 mmHg) has also been related to poor outcome [12, 104, 105], although this is still debated by other groups [73, 106–108]. Finally, a low preoperative exercise capacity (6MWD <200 m) has been related to poor outcome [105].

Findings with imaging have been related to the response to LVRS as well. Generally, heterogeneous emphysema with upper lobe predominance is the best indication for LVRS. MCKENNA *et al.* [64] analysed the results of 138 patients undergoing bilateral LVRS. Upper lobe-predominant emphysema was found in 106 (77%) patients, lower lobe-predominant emphysema in 10 (7%) and diffusely homogeneous emphysema in 22 (16%). The greatest improvement in FEV1 (73%) was noted in patients with upper lobe emphysema, whereas it was smallest in patients with diffuse emphysema. In the latter patients, however, a 38% improvement in FEV1 was still observed. Similar results were obtained by WEDER *et al.* [109]. They used a qualitative emphysema CT scoring system and demonstrated that, 3 months after a bilateral thoracoscopic procedure, FEV1 improved by 81% in the group with markedly heterogeneous emphysema, 44% in the group with intermediately heterogeneous emphysema and 31% in the group with homogeneous emphysema. Improvement in dyspnoea, however, was similar in the three groups. The same group also published follow-up results after 2 yrs [110]. This confirmed the greater initial improvement in the heterogeneous group, but also demonstrated faster decline in this group. Dyspnoea worsened in all three groups, but it remained improved at 24 months compared to baseline. Survival was greatest in the heterogeneous group, but the functional data at onset were best in this group as well. These results were confirmed by WISSER *et al.* [111].

THURNHEER *et al.* [94] compared the qualitative assessment of emphysema heterogeneity on high-resolution CT (HRCT) with that on lung perfusion scintigraphy in the prediction of response in 70 patients undergoing bilateral video-assisted LVRS. Patients with homogeneous perfusion experienced less short-term improvement in FEV1 (23%) compared with those with intermediately heterogeneous perfusion (38%) or markedly heterogeneous perfusion (57%). However, on multivariate analysis, preoperative RV/TLC ratio (partial r=0.24) and heterogeneity on HRCT (partial r=0.28) were clearly more powerful predictors than heterogeneity on perfusion scintigraphy (partial r=0.01). The contribution of scintigraphy was not significant on multiple regression analysis. INGENITO

et al. [112] further confirmed the superiority of physiological criteria over upper/lower perfusion ratio on scintigraphy in predicting the response of FEV1 in a cohort of 50 patients undergoing bilateral LVRS. Finally, quantitative CT data have also been used recently to predict FEV1 and exercise response to bilateral LVRS in 21 patients. The presence of emphysema in the rind area of the lung was shown to be a better predictor of response than its presence in the core of the lung [113]. This is probably due to the fact that emphysematous rind zones are more accessible to surgery than the core zones. This is, however, unlikely to lead to a fundamentally better prediction of postoperative response than in the past as the best r^2 obtained in this study was still ~0.40, similar to previously published predictions based on physiological variables (see above).

Although several of the above-mentioned studies substantiate a better response in patients with heterogeneous emphysema, a number of caveats should be added to that conclusion. First, patients with homogeneous emphysema, in general, improve as well but less than those with heterogeneous emphysema. Secondly, the difference in response also appears to depend upon the variable studied. WEDER *et al.* [109] found greater FEV1 response in heterogeneous emphysema, but no greater response in dyspnoea. Finally, the best conceptual model for explaining the improvement in lung mechanics after LVRS also allows for improvement in patients with homogeneous emphysema [83].

Taken together, it is not possible to properly select candidates for LVRS on a scientific basis. As the most plausible mechanism of action appears to be resizing of the lungs, better ways of assessing the mismatch between chest wall size and lung size might contribute to a better selection of candidates. Some variables may be used as a clinical guideline, but they do not allow fine discrimination between responders and nonresponders. The most significant variables appear to be RV/TLC ratio and emphysema heterogeneity on imaging studies.

Practical organisation

An exhaustive description of the surgical procedure is beyond the scope of the present article, and several excellent reviews have recently been published on this topic [114–117]. The surgical approach has varied and has included: median sternotomy, standard thoracotomy, and unilateral or bilateral video-assisted thoracoscopic surgery. Some authors also promote laser ablation, but comparative trials have shown this technique to be inferior [93, 118]. In general, bilateral procedures produce better effects than unilateral ones [60]. Several studies demonstrated benefits of the video-assisted thoracoscopic surgical procedures over median sternotomy, although similar improvements in lung function were obtained.

The short-term surgical mortality ranges 0–15%. With proper patient selection and surgical procedure, current mortality is likely to be <5%. Postoperative complications are: postoperative air leaks, subcutaneous emphysema, pneumonia, pneumothorax, and prolonged mechanical ventilation. As postoperative air leak is a frequent complication, some groups have developed no-cut plication procedures to reduce the incidence of air leaks [119].

Future developments

Although LVRS definitely improves the condition of some patients, the controversy continues. This is exemplified by a statement made by the editor of the *The New England Journal of Medicine* in a recent editorial commenting on the results of the high-risk group of the NETT trial, "…in my opinion, it does not make sense for anyone to undergo LVRS outside a controlled trial…" [120]. Conversely, LVRS has without question offered at least temporary palliation to patients for whom little other treatment was available.

Future developments will be directed primarily at developing application modalities that do not exhibit the relatively high postoperative mortality of the present surgical procedures. Technological developments that simplify surgical procedures are one example [119, 121] and bronchoscopic procedures another [122]. The former include no-cut plication procedures [119, 121] and the latter procedures in which bronchoscopic collapse is obtained which is consolidated with tissue glue [123] or the implantation of valves [122]. These technological developments have been shown to be feasible in animals. Recent evidence shows that they may also be applicable to patients with emphysema [122]. At present, however, no randomised studies are available and so the effects still need to be better demonstrated. In addition, the long-term results of such procedures are largely unknown. These need to be available before their use in the treatment of emphysema can be recommended.

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References

1. Pauwels R, Buist A, Calverley P, Jenkins R, Hurd S, on behalf of the GOLD Scientific Committee. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2001; 163: 1256–1276.
2. Anthonisen NR, Connett JE, Kiley JP, *et al.* Effects of smoking intervention and the use of an inhaled anticholinergic bronchodilator on the rate of decline of FEV1. The Lung Health Study. *JAMA* 1994; 272: 1497–1505.
3. Boyd G, Morice AH, Pounsford JC, Siebert M, Peslis N, Crawford C. An evaluation of salmeterol in the treatment of chronic obstructive pulmonary disease (COPD). *Eur Respir J* 1997; 10: 815–821.
4. Vincken W, van Noord JA, Greefhorst APM, *et al.* Improved health outcomes in patients with COPD during 1 year's treatment with tiotropium. *Eur Respir J* 2002; 19: 209–216.
5. Dahl R, Greefhorst L, Nowak D, *et al.*, on behalf of the Formoterol in Chronic Obstructive Pulmonary Disease I (FICOPD I) Study Group. Inhaled formoterol dry powder *versus* ipratropium bromide in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2001; 164: 778–784.
6. Pauwels RA, Lofdahl CG, Laitinen LA, *et al.* Long–term treatment with inhaled budesonide in persons with mild chronic obstructive pulmonary disease who continue smoking. *New Engl J Med* 1999; 340: 1948–1953.
7. Vestbo J, Sørensen T, Lange P, Brix A, Torre P, Viskum K. Long-term effect of inhaled budesonide in mild and moderate chronic obstructive pulmonary disease: a randomised controlled trial. *Lancet* 1999; 353: 1819–1823.
8. Burge PS, Calverley PMA, Jones PW, Spencer S, Anderson JA, Maslen TK, on behalf of the ISOLDE study investigators. Randomised, double blind, placebo controlled study of fluticasone propionate in patients with moderate to severe

chronic obstructive pulmonary disease: the ISOLDE trial. *BMJ* 2000; 320: 1297–1303.
9. The Lung Health Study Research Group. Effect of inhaled triamcinolone on the decline in pulmonary function in chronic obstructive pulmonary disease. *N Engl J Med* 2000; 343: 1902–1909.
10. Sin DD, Tu JV. Inhaled corticosteroids and the risk of mortality and readmission in elderly patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2001; 164: 580–584.
11. Cooper JD, Trulock EP, Triantafillou AN, *et al.* Bilateral pneumectomy (volume reduction) for chronic obstructive pulmonary disease. *J Thorac Cardiovasc Surg* 1995; 109: 106–119.
12. Cooper JD, Patterson GA, Sundaresan RS, *et al.* Results of 150 consecutive bilateral lung volume reduction procedures in patients with severe emphysema. *J Thorac Cardiovasc Surg* 1996; 112: 1319–1329.
13. Rennard S, Decramer M, Calverley PMA, *et al.* Impact of COPD in North America and Europe in 2000: subjects′ perspective of Confronting COPD International Survey. *Eur Respir J* 2002; 20: 799–805.
14. Garcia-Aymerich J, Barreiro E, Farrero E, Marrades RM, Morera J, Antó JM, and the EFRAM investigators. Patients hospitalized for COPD have a high prevalence of modifiable risk factors for exacerbation (EFRAM study). *Eur Respir J* 2000; 16: 1037–1042.
15. Rennard S, Carrera M, Agustí AGN. Management of chronic obstructive pulmonary disease: are we going anywhere? *Eur Respir J* 2000; 16: 1035–1036.
16. Lau CL, Patterson GA. Current status of lung transplantation. *Eur Respir J* 2003; 22: Suppl. 47, 57s–64s.
17. Goldstein RS, Gort EH, Stubbing D, Avendano MA, Guyatt CH. Randomized controlled trial of respiratory rehabilitation. *Lancet* 1994; 344: 1394–1397.
18. Ries AL, Kaplan RM, Limberg TMK, Prewitt LM. Effects of pulmonary rehabilitation on physiological and psychosocial outcomes in patients with chronic obstructive pulmonary disease. *Ann Intern Med* 1995; 122: 823–832.
19. Lacasse Y, Wong E, Guyatt GH, King D, Cook DJ, Goldstein RS. Meta-analysis of respiratory rehabilitation in chronic obstructive pulmonary disease. *Lancet* 1996; 348: 1115–1119.
20. Wedzicha JA, Bestall JC, Garrod R, Garnham R, Paul EA, Jones PW. Randomized controlled trial of pulmonary rehabilitation in severe chronic obstructive pulmonary disease patients, stratified with the MRC dyspnoea scale. *Eur Respir J* 1998; 12: 363–369.
21. Redelmeier DA, Bayoumi AM, Goldstein RS, Guyatt GH. Interpreting a small difference in functional status: the six-minute walking test in chronic lung disease patients. *Am J Respir Crit Care Med* 1997; 155: 1278–1282.
22. Jones PW. Interpreting thresholds for a clinically significant change in health status in asthma and COPD. *Eur Respir J* 2002; 19: 390–391.
23. Griffiths TL, Burr ML, Campbell IA, *et al.* Results at 1 year of outpatient multidisciplinary pulmonary rehabilitation: a randomised controlled trial. *Lancet* 2000; 355: 362–368.
24. Troosters T, Gosselink R, Decramer M. Short- and long-term effects of outpatient rehabilitation in patients with chronic obstructive pulmonary disease: a randomised trial. *Am J Med* 2000; 109: 207–212.
25. Lacasse Y, Brosseau L, Milne S, *et al.* Pulmonary rehabilitation for chronic obstructive pulmonary disease. *Cochrane Database Syst Rev* 2002; CD003793.
26. Griffiths TL, Phillips CJ, Davies S, Burr ML, Campbell IA. Cost effectiveness of an outpatient multidisciplinary pulmonary rehabilitation programme. *Thorax* 2001; 56: 779–784.
27. Wedzicha JA, Seemungal TA, MacCallum PK, Paul EA, Jones PW. Acute exacerbations of chronic obstructive pulmonary disease are accompanied by elevations of plasma fibrinogen and serum IL-6 levels. *Thromb Haemost* 2000; 84: 210–215.
28. Troosters T, Gosselink R, De Paepe K, Decramer M. Pulmonary rehabilitation improves survival in COPD patients with a recent severe acute exacerbation. *Am J Respir Crit Care Med* 2002; 165: A16.
29. Troosters T, Gosselink R, Decramer M. Exercise training in COPD: how to distinguish responders from nonresponders. *J Cardiopulm Rehabil* 2001; 21: 10–17.
30. ZuWallack RL. Selection criteria and outcome assessment in pulmonary rehabilitation. *Monaldi Arch Chest Dis* 1998; 53: 429–437.
31. Morgan MDL. The prediction of benefit from pulmonary rehabilitation: setting, training intensity and the effect of selection by disability. *Thorax* 1999; 54: Suppl. 2, S3–S7.
32. ZuWallack RL, Patel K, Reardon JZ, Clarck BA, Normandin EA. Predictors of improvement in the 12-minute walking distance following a six-week outpatient pulmonary rehabilitation program. *Chest* 1991; 99: 805–808.
33. Maltais F, LeBlanc P, Jobin J, *et al.* Intensity of training and physiologic adaptation in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 1997; 155: 555–561.
34. Casaburi R, Porszasz J, Burns MR, Carithers ER, Chang RS, Cooper CB. Physiologic benefits of exercise training in rehabilitation of patients with severe chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 1997; 155: 1541–1551.
35. Belman MJ, Kendregan BA. Exercise training fails to increase skeletal muscle enzymes in patients with chronic obstructive pulmonary disease. *Am Rev Respir Dis* 1981; 123: 256–261.
36. Berry MJ, Rejeski WJ, Adair NE, Zaccaro D. Exercise rehabilitation and chronic obstructive pulmonary disease stage. *Am J Respir Crit Care Med* 1999; 160: 1248–1253.
37. Young P, Dewse M, Fergusson W, Kolbe J. Respiratory rehabilitation in chronic obstructive pulmonary disease: predictors of nonadherence. *Eur Respir J* 1999; 13: 855–859.
38. Wijkstra PJ, van der Mark TW, Kraan J, van Altena R, Koeter GH, Postma DS. Long-term effects of home rehabilitation on physical performance in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 1996; 153: 1234–1241.
39. Lacasse Y, Guyatt GH, Goldstein RS. The components of a respiratory rehabilitation program: a systematic overview. *Chest* 1997; 111: 1077–1088.
40. Vogiatzis I, Nanas S, Roussos C. Interval training as an alternative modality to continuous exercise in patients with COPD. *Eur Respir J* 2002; 20: 12–19.
41. Simpson K, Killian K, McCartney N, Stubbing DG, Jones NL. Randomised controlled trial of weightlifting exercise in patients with chronic airflow limitation. *Thorax* 1992; 47: 70–75.
42. Bernard S, Whittom F, Leblanc P, *et al.* Aerobic and strength training in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 1999; 159: 896–901.
43. Ortega F, Toral J, Cejudo P, *et al.* Comparison of effects of strength and endurance training in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2002; 166: 669–674.
44. Spruit MA, Gosselink R, Troosters T, De Paepe C, Decramer M. Resistance *versus* endurance training in patients with COPD and peripheral muscle weakness. *Eur Respir J* 2002; 19: 1072–1078.
45. Neder JA, Sword D, Ward SA, Mackay E, Cochrane LM, Clarck CJ. Home based neuromuscular electrical stimulation as a new rehabilitative strategy for severely disabled patients with chronic obstructive pulmonary disease (COPD). *Thorax* 2002; 57: 333–337.
46. Bourjeily-Habr G, Rochester CL, Palermo F, Snyder P,

Mohensin V. Randomised controlled trial of transcutaneous electrical muscle stimulation of the lower extremities in patients with chronic obstructive pulmonary disease. *Thorax* 2002; 57: 1045–1049.
47. Smith K, Cook D, Guyatt GH, Madhavan J, Oxman AD. Respiratory muscle training in chronic airflow limitation: a meta-analysis. *Am Rev Respir Dis* 1992; 145: 533–539.
48. Wanke T, Formanek D, Lahrmann H, *et al.* Effects of combined inspiratory muscle and cycle ergometer training on exercise performance in patients with COPD. *Eur Respir J* 1994; 7: 2205–2211.
49. Rooyackers JM, Dekhuijzen PN, Van Herwaarden CL, Folgering HT. Training with supplemental oxygen in patients with COPD and hypoxaemia at peak exercise. *Eur Respir J* 1997; 10: 1278–1284.
50. Garrod R, Paul EA, Wedzicha JA. Supplemental oxygen during pulmonary rehabilitation in patients with COPD with exercise hypoxaemia. *Thorax* 2000; 55: 539–543.
51. Wadell K, Henriksson-Larsen K, Lundgren R. Physical training with and without oxygen in patients with chronic obstructive pulmonary disease and exercise-induced hypoxaemia. *J Rehabil Med* 2001; 33: 200–205.
52. Johnson JE, Gavin DJ, Adams-Dramiga S. Effects of training with heliox and noninvasive positive pressure ventilation on exercise ability in patients with severe COPD. *Chest* 2002; 122: 464–472.
53. Hawkins P, Johnson LC, Nikoletou D, *et al.* Proportional assist ventilation as an aid to exercise training in severe chronic obstructive pulmonary disease. *Thorax* 2002; 57: 853–859.
54. Burdet L, de Muralt B, Schutz Y, Pichard C, Fitting JW. Administration of growth hormone to underweight patients with chronic obstructive pulmonary disease. A prospective, randomized, controlled study. *Am J Respir Crit Care Med* 1997; 156: 1800–1806.
55. Schols AM, Soeters PB, Mostert R, Pluymers J, Wouters EF. Physiologic effects of nutritional support and anabolic steroids in patients with chronic obstructive pulmonary disease. A placebo-controlled randomized trial. *Am J Respir Crit Care Med* 1995; 152: 1268–1274.
56. Casaburi R, Cosentino G, Bhasin S, *et al.* A randomized trial of strength training and testosterone supplementation in men with chronic obstructive pulmonary disease. *Eur Respir J* 2001; 18: Suppl. 33, A173.
57. Schols AM, Buurman WA, Staal van den Brekel AJ, Dentener MA, Wouters EF. Evidence for a relation between metabolic derangements and increased levels of inflammatory mediators in a subgroup of patients with chronic obstructive pulmonary disease. *Thorax* 1996; 51: 819–824.
58. Di Francia M, Barbier D, Mege JL, Orehek J. Tumor necrosis factor- α levels and weight loss in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 1994; 150: 1453–1455.
59. Spruit MA, Gosselink R, Troosters T, *et al.* Effects of an acute exacerbation requiring hospitalisation (AE) on lung function, muscle force and serum IGF-I levels in male patients with chronic obstructive pulmonary disease (COPD). *Eur Respir J* 2002; 20: Suppl. 38, 564S (abstract).
60. Flaherty KR, Martinez FJ. Lung volume reduction surgery for emphysema. *Clin Chest Med* 2000; 21: 819–848.
61. Stirling GR, Babidge WJ, Peacock MJ, *et al.* Lung volume reduction surgery in emphysema: a systematic review. *Ann Thorac Surg* 2001; 72: 641–648.
62. Berger RL, Celli BR, Meneghetti AL, *et al.* Limitations of randomized clinical trials for evaluating emerging operations: the case of lung volume reduction surgery. *Ann Thorac Surg* 2001; 72: 649–657.
63. McKenna RJ, Gelb A, Brenner M. Lung volume reduction surgery for chronic obstructive pulmonary disease: where do we stand? *World J Surg* 2001; 25: 231–237.
64. McKenna RJ, Brenner M, Fischel RJ, Gelb AF. Should lung volume reduction for emphysema be unilateral or bilateral? *J Thorac Cardiovasc Surg* 1996; 112: 1331–1338.
65. Hazelrigg SR, Boley TM, Naunheim KS, *et al.* Effect of bovine pericardial strips on air leak after stapled pulmonary resection. *Ann Thorac Surg* 1997; 63: 1573–1575.
66. The National Emphysema Treatment Trial Research Group. Rationale and design of the national emphysema treatment trial. *J Cardiopulm Rehabil* 2000; 20: 24–36.
67. Geddes D, Davies M, Koyama H, *et al.* Effect of lung-volume-reduction surgery in patients with severe emphysema. *N Engl J Med* 2000; 343: 239–245.
68. Criner GJ, Cordova FC, Furukawa S, *et al.* Prospective randomized trial comparing bilateral lung volume reduction surgery to pulmonary rehabilitation in severe chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 1999; 160: 2018–2027.
69. Pompeo E, Marino M, Nofroni I, Matteucci G, Mineo TC. Reduction pneumoplasty *versus* respiratory rehabilitation in severe emphysema: a randomized study. *Ann Thorac Surg* 2000; 70: 948–954.
70. National Emphysema Treatment Trial Research Group. Patients at high risk of death after lung-volume-reduction surgery. *N Engl J Med* 2001; 345: 1075–1083.
71. Goodnight-White S, Jones JW, Baaklini WA. Prospective, randomised, controlled trial comparing bilateral lung volume reduction surgery (LVRS) to medical therapy alone in patients with severe emphysema. *Chest* 2000; 118: Suppl. 4, 102S (abstract).
72. Löfdahl CG, Hillerdal G, Ström K. Randomized controlled trial of volume reduction surgery – preliminary results up to 12 months. *Am J Respir Crit Care Med* 2000; 161: A585.
73. Criner GJ, O′Brien G, Furukawa S, *et al.* Lung volume reduction surgery in ventilator-dependent COPD patients. *Chest* 1996; 110: 877–884.
74. Teschler H, Stamatis G, el-Raouf Farhat AA, Meyer FJ, Costabel U, Konietzko N. Effect of surgical lung volume reduction on respiratory muscle function in pulmonary emphysema. *Eur Respir J* 1996; 9: 1779–1784.
75. Martinez FJ, de Oca MM, Whyte RI, Stetz J, Gay E, Celli BR. Lung-volume reduction improves dyspnea, dynamic hyperinflation, and respiratory muscle function. *Am J Respir Crit Care Med* 1997; 155: 1984–1990.
76. Bellemare F, Cordeau MP, Couture J, Lafontaine E, Leblanc P, Passerini L. Effects of emphysema and lung volume reduction surgery on transdiaphragmatic pressure and diaphragm length. *Chest* 2002; 121: 1898–1910.
77. Marchand E, De Leyn P, Gayan-Ramirez G, *et al.* Lung volume reduction surgery does not improve diaphragmatic contractile properties or atrophy in hamsters with elastase-induced emphysema. *Am J Respir Crit Care Med* 2000; 162: 1052–1057.
78. Cassart M, Hamacher J, Verbandt Y, *et al.* Effects of lung volume reduction surgery for emphysema on diaphragm dimensions and configuration. *Am J Respir Crit Care Med* 2001; 163: 1171–1175.
79. Marchand E, Gayan-Ramirez G, De Leyn P, Decramer M. Physiological basis of improvement after lung volume reduction surgery for severe emphysema: where are we? *Eur Respir J* 1999; 13: 686–696.
80. Sciurba FC, Rogers RM, Keenan RJ, *et al.* Improvement in pulmonary function and elastic recoil after lung-reduction surgery for diffuse emphysema. *N Engl J Med* 1996; 334: 1095–1099.
81. Gelb AF, Zamel N, McKenna RJ Jr, Brenner M. Mechanism of short-term improvement in lung function after emphysema resection. *Am J Respir Crit Care Med* 1996; 154: 945–951.
82. Tschernko EM, Wisser W, Wanke T, *et al.* Changes in ventilatory mechanics and diaphragmatic function after lung volume reduction surgery in patients with COPD. *Thorax* 1997; 52: 545–550.
83. Fessler HE, Permutt S. Lung volume reduction surgery and airflow limitation. *Am J Respir Crit Care Med* 1998; 157: 715–722.

84. Loring SH, Leith DE, Connolly MJ, Ingenito EP, Mentzer SJ, Reilly JJ Jr. Model of functional restriction in chronic obstructive pulmonary disease, transplantation, and lung reduction surgery. *Am J Respir Crit Care Med* 1999; 160: 821–828.
85. Ingenito EP, Loring SH, Moy ML, Mentzer SJ, Swanson SJ, Reilly JJ. Interpreting improvement in expiratory flows after lung volume reduction surgery in terms of flow limitation theory. *Am J Respir Crit Care Med* 2001; 163: 1074–1080.
86. Marchand E, De Leyn P, Gayan-Ramirez G, Palecek F, Verbeken E, Decramer M. Effects of lung volume reduction surgery in hamsters with elastase-induced emphysema. *Eur Respir J* 2002; 19: 422–428.
87. Fessler HE, Scharf SM, Permutt S. Improvement in spirometry following lung volume reduction surgery: application of a physiologic model. *Am J Respir Crit Care Med* 2002; 165: 34–40.
88. Ingenito EP, Loring SH, Moy ML, Mentzer SJ, Swanson SJ, Reilly RR. Physiological charcterization of variability in response to lung volume reduction surgery. *J Appl Physiol* 2003; 94: 20–30.
89. Gelb AF, McKenna RJ Jr, Brenner M, Epstein JD, Zamel N. Lung function 5 yr after lung volume reduction surgery for emphysema. *Am J Respir Crit Care Med* 2001; 163: 1562–1566.
90. Fujimoto T, Teschler H, Hillejan L, Zaboura G, Stamatis G. Long-term results of lung volume reduction surgery. *Eur J Cardiothorac Surg* 2002; 21: 483–488.
91. Fessler HE, Wise RA. Lung volume reduction surgery: is less really more? *Am J Respir Crit Care Med* 1999; 159: 1031–1035.
92. Kesten S, Elpern E, Warren W, Szidon P. Loss of pulmonary function gains after lung volume reduction surgery. *J Heart Lung Transplant* 1999; 18: 266–268.
93. Brenner M, McKenna R Jr, Gelb A, *et al.* Objective predictors of response for staple *versus* laser emphysematous lung reduction. *Am J Respir Crit Care Med* 1997; 155: 1295–1301.
94. Thurnheer R, Engel H, Weder W, *et al.* Role of lung perfusion scintigraphy in relation to chest computed tomography and pulmonary function in the evaluation of candidates for lung volume reduction surgery. *Am J Respir Crit Care Med* 1999; 159: 301–310.
95. McKenna RJ Jr, Brenner M, Fischel RJ, *et al.* Patient selection criteria for lung volume reduction surgery. *J Thorac Cardiovasc Surg* 1997; 114: 957–967.
96. McKenna RJ Jr, Fischel RJ, Brenner M, Gelb AF. Combined operations for lung volume reduction surgery and lung cancer. *Chest* 1996; 110: 885–888.
97. Schmid RA, Stammberger U, Hillinger S, *et al.* Lung volume reduction surgery combined with cardiac interventions. *Eur J Cardiothorac Surg* 1999; 15: 585–591.
98. Lefrak SS, Yusen RD, Trulock EP, Pohl MS, Patterson A, Cooper JD. Recent advances in surgery for emphysema. *Annu Rev Med* 1997; 48: 387–398.
99. Mineo TC, Pompeo E, Rogliani P, *et al.* Effect of lung volume reduction surgery for severe emphysema on right ventricular function. *Am J Respir Crit Care Med* 2002; 165: 489–494.
100. Cassina PC, Teschler H, Konietzko N, Theegarten D, Stamatis G. Two-year results after lung volume reduction surgery in α_1-antitrypsin deficiency *versus* smoker's emphysema. *Eur Respir J* 1998; 12: 1028–1032.
101. Teschler H, Thompson AB, Stamatis G. Short- and long-term functional results after lung volume reduction surgery for severe emphysema. *Eur Respir J* 1999; 13: 1170–1176.
102. Gelb AF, McKenna RJ, Brenner M, Fischel R, Zamel N. Lung function after bilateral lower lobe lung volume reduction surgery for α_1-antitrypsin emphysema. *Eur Respir J* 1999; 14: 928–933.
103. Ingenito EP, Evans RB, Loring SH, *et al.* Relation between preoperative inspiratory lung resistance and the outcome of lung-volume-reduction surgery for emphysema. *N Engl J Med* 1998; 338: 1181–1185.
104. Ferguson GT, Fernandez E, Zamora MR, Pomerantz M, Buchholz J, Make BJ. Improved exercise performance following lung volume reduction surgery for emphysema. *Am J Respir Crit Care Med* 1998; 157: 1195–1203.
105. Szekely LA, Oelberg DA, Wright C, *et al.* Preoperative predictors of operative morbidity and mortality in COPD patients undergoing bilateral lung volume reduction surgery. *Chest* 1997; 111: 550–558.
106. Argenziano M, Moazami N, Thomashow B, *et al.* Extended indications for lung volume reduction surgery in advanced emphysema. *Ann Thorac Surg* 1996; 62: 1588–1597.
107. O'Brien G, Furukawa S, Kuzma AM, Cordova F, Criner GJ. Improvements in lung function, exercise, and quality of life in hypercapnic COPD patients after lung volume reduction surgery. *Chest* 1999; 115: 75–84.
108. Wisser W, Klepetko W, Senbaklavaci O, *et al.* Chronic hypercapnia should not exclude patients from lung volume reduction surgery. *Eur J Cardiothorac Surg* 1998; 14: 107–112.
109. Weder W, Thurnheer R, Stammberger U, Burge M, Russi EW, Bloch KE. Radiologic emphysema morphology is associated with outcome after surgical lung volume reduction. *Ann Thorac Surg* 1997; 64: 313–320.
110. Hamacher J, Bloch KE, Stammberger U, *et al.* Two years' outcome of lung volume reduction surgery in different morphologic emphysema types. *Ann Thorac Surg* 1999; 68: 1792–1798.
111. Wisser W, Klepetko W, Kontrus M, *et al.* Morphologic grading of the emphysematous lung and its relation to improvement after lung volume reduction surgery. *Ann Thorac Surg* 1998; 65: 793–799.
112. Ingenito EP, Loring SH, Moy ML, *et al.* Comparison of physiological and radiological screening for lung volume reduction surgery. *Am J Respir Crit Care Med* 2001; 163: 1068–1073.
113. Nakano Y, Coxson HO, Bosan S, *et al.* Core to rind distribution of severe emphysema predicts outcome of lung volume reduction surgery. *Am J Respir Crit Care Med* 2001; 164: 2195–2199.
114. Cooper JD, Patterson GA. Lung volume reduction surgery for severe emphysema. *Semin Thorac Cardiovasc Surg* 1996; 8: 52–60.
115. Dartevelle P, Macchiarini P, Chapelier A. Operative technique of bullectomy. *Chest Surg Clin North Am* 1995; 5: 735–749.
116. Klepetko W. Surgical aspects and techniques of lung volume reduction surgery for severe emphysema. *Eur Respir J* 1999; 13: 919–925.
117. Krucylak PE, Keller CA, Naunheim KS. Current status of thoracoscopic lung volume reduction. *World J Surg* 1999; 23: 1148–1155.
118. McKenna RJ Jr, Brenner M, Gelb AF, *et al.* A randomized, prospective trial of stapled lung reduction *versus* laser bullectomy for diffuse emphysema. *J Thorac Cardiovasc Surg* 1996; 111: 317–322.
119. Swanson SJ, Mentzer SJ, DeCamp MM Jr, *et al.* No-cut thoracoscopic lung plication: a new technique for lung volume reduction surgery. *J Am Coll Surg* 1997; 185: 25–32.
120. Drazen JM. Surgery for emphysema – not for everyone. *N Engl J Med* 2001; 345: 1126–1128.
121. Brenner M, Gonzalez X, Jones B, *et al.* Effects of a novel implantable elastomer device for lung volume reduction surgery in a rabbit model of elastase-induced emphysema. *Chest* 2002; 121: 201–209.
122. Toma TP, Hopkinson NS, Hillier J, *et al.* Bronchoscopic volume reduction with valve implants in patients with severe emphysema. *Lancet* 2003; 361: 931–933.
123. Ingenito EP, Reilly JJ, Mentzer SJ, *et al.* Bronchoscopic volume reduction: a safe and effective alternative to surgical therapy for emphysema. *Am J Respir Crit Care Med* 2001; 164: 295–301.