Extrapulmonary effects of lung volume reduction in severe emphysema: a systematic review

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Surgical and bronchoscopic lung volume reduction have, besides a significant impact on pulmonary function, exercise performance and quality of life, multiple beneficial extrapulmonary effects in patients with severe emphysema, further supporting its use. https://bit.ly/4gttv7q

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Abstract

Background Lung volume reduction, either surgical or bronchoscopic, is an effective therapeutic strategy that improves pulmonary function, quality of life and exercise capacity in patients with advanced emphysema. The aim of this review was to evaluate the extrapulmonary effects of this treatment.

Methods PubMed, Embase and Web of Science were searched until 19 August 2024. The extrapulmonary effects were classified into nine distinct domains. Studies that reported outcomes related to one of the predefined extrapulmonary domains with a follow-up duration of at least 1 month were eligible for inclusion. A descriptive summary of the effects from all studies was compiled.

Results A total of 85 articles were included. The majority of studies were conducted in patients who underwent lung volume reduction surgery (74%). The greatest improvements were found in respiratory muscle strength, ventilatory drive, diaphragm morphology and body mass index. While the effects were less pronounced, beneficial outcomes were also observed for body composition, inflammation, oxidative stress, anxiety, depression and bone mineral density. The overall treatment effect of lung volume reduction on cardiac function and pulmonary arterial pressure was inconclusive; however, there is no evidence to suggest any significant deterioration. For the extrapulmonary domains of cognition, sleep and peripheral muscle function, evidence is currently insufficient to determine whether lung volume reduction has any impact.

Conclusion Lung volume reduction treatment has multiple beneficial extrapulmonary effects in patients with severe emphysema and lung hyperinflation. These findings support the use of lung volume reduction as a treatment for this patient population.

Introduction

COPD is a major cause of chronic morbidity and mortality worldwide [1]. The emphysema phenotype of COPD is characterised by air trapping and hyperinflation, driven by the loss of elastic recoil and the subsequent increase in airflow resistance, resulting from the destruction of lung parenchyma [2]. In addition to significant impairment in pulmonary function, these patients often present with multiple extrapulmonary comorbidities, such as cardiovascular diseases, altered body composition, osteoporosis and neuropsychiatric disorders [3]. Some of these comorbid conditions have been adversely associated with survival and quality of life in this patient population [4].

Lung volume reduction strategies have emerged as a potential treatment option for selected patients with advanced emphysema who continue to have substantial disease burden despite receiving optimal medical therapy. Lung volume reduction surgery (LVRS) was the first option introduced [5]. Subsequently, less invasive endoscopic approaches were developed, with the most commonly performed bronchoscopic lung volume reduction (BLVR) treatment being the insertion of endobronchial valves (EBVs) [6]. Other types of BLVR include the use of intrabronchial valves (IBVs), endobronchial coils, vapour ablation or AeriSeal [7–10].

A systematic review and meta-analysis by VAN GEFFEN *et al.* [11] reported that lung volume reduction treatment, either surgical or bronchoscopic, is an effective therapeutic strategy that improves pulmonary function, quality of life and exercise capacity. Numerous studies have investigated whether reducing hyperinflation in patients with advanced emphysema can also provide benefits beyond the pulmonary system, as hyperinflation has been physiologically linked to several extrapulmonary manifestations, including respiratory muscle dysfunction, impaired cardiovascular function and, to some extent, peripheral muscle impairment [12].

To date, no concise overview has been provided of these potential extrapulmonary effects associated with lung volume reduction treatment. Therefore, the primary aim of this systematic review was to evaluate the extrapulmonary effects of lung volume reduction treatment and to identify knowledge gaps.

Methods

Protocol and registration

This systematic review was conducted according to the updated guideline for reporting systematic reviews, namely the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) 2020 statement [13]. The study protocol was prospectively registered in the International Prospective Register of Systematic Reviews (PROSPERO) on 30 December 2023 (registration ID: CRD42023495135).

Search strategy and eligibility criteria

A systematic literature search was conducted to identify all studies investigating the extrapulmonary effects of lung volume reduction treatment. The following types of lung volume reduction treatment were included in this search: LVRS and BLVR using EBVs (BLVR-EBV), IBVs (BLVR-IBV), coils (BLVR-coil, AeriSeal (BLVR-AeriSeal) or vapour ablation (BLVR-vapour). The extrapulmonary effects were classified into nine distinct domains, including 1) respiratory muscle function and central ventilatory drive, 2) cardiac function and pulmonary arterial hypertension, 3) body composition and metabolism, 4) inflammation, endothelial function and oxidative stress, 5) anxiety and depression, 6) cognition, 7) sleep, 8) peripheral muscle function, and 9) bone mineral density (BMD). PubMed, Embase and Web of Science were searched using free-text words and a database-specific vocabulary, including Medical Subject Headings (MeSH) and Emtree terms. The full search strategy for each database is provided in supplementary methods S1.1–S1.3. No language or date restrictions were applied. The last search update was performed on 19 August 2024. The following eligibility criteria were used at the study level: 1) all prospective and retrospective observational studies, that 2) reported outcomes related to one or more of the specified extrapulmonary domains with 3) a follow-up duration of at least 1 month. Case reports and reviews were excluded, along with studies concerning lung volume reduction treatment performed for indications other than emphysema.

Study selection

Duplicate records were initially removed according to the deduplication method described by BRAMER *et al.* [14]. Afterwards, two reviewers (E.A.M.D. ter Haar and J.E. Hartman) independently screened all records in a two-step process. First, the titles and abstracts were screened, followed by a full-text evaluation of the remaining records. Any conflicts were resolved through discussion. The percentage of inter-observer agreement was calculated at each step to assess the level of concordance between the two reviewers.

Data extraction and synthesis

For each eligible study, the following information was systematically collected by one reviewer (E.A.M.D. ter Haar): type of lung volume reduction treatment, domain of extrapulmonary effect, study design, sample size, follow-up duration, study measurements, evaluated variables, reported outcomes and the article's conclusion. In cases of duplicate study populations, data were extracted from the most recent publication. Studies were categorised based on the specified extrapulmonary domains and the type of lung volume reduction employed. For all documented outcome variables, the direction of change and its statistical significance were recorded and tabulated. No meta-analysis was conducted because of the heterogeneity in the measurement methods of the studied variables and variations in follow-up duration. An estimation of the overall treatment effect, by calculating the weighted mean difference adjusted for sample size, was performed only for the outcomes maximal inspiratory pressure (P_{Imax}) and body mass index (BMI), as sufficient samples were available for these measures.

Quality assessment

Risk of bias was assessed for each study individually (E.A.M.D. ter Haar). For randomised controlled trials (RCTs), the revised Cochrane Risk of Bias tool (RoB2) was applied, while the Risk of Bias in Non-Randomized Studies of Interventions (ROBINS-I) tool was used to evaluate the risk of bias in single-arm observational studies [15, 16].

Results

Selection of eligible studies

The study selection process is illustrated in figure 1. In total, 4403 records were identified through the initial search, from which 1114 duplicates were removed. Screening of titles and abstracts resulted in the exclusion of 3025 irrelevant studies with a 99% inter-observer agreement. Following full-text review, 80 articles were considered eligible for inclusion in the systematic review with a 97% inter-observer agreement. The reasons for exclusion are summarised in figure 1 and are detailed for each excluded record in table S1. The search update on 19 August 2024 retrieved an additional five publications, resulting in a total of 85 articles included in this review.

Quality assessment

The risk of bias for the RCTs varied from some concerns to high risk. For the single-arm observational studies, risk of bias ranged from moderate to critical risk. A summary of the risk of bias assessment is

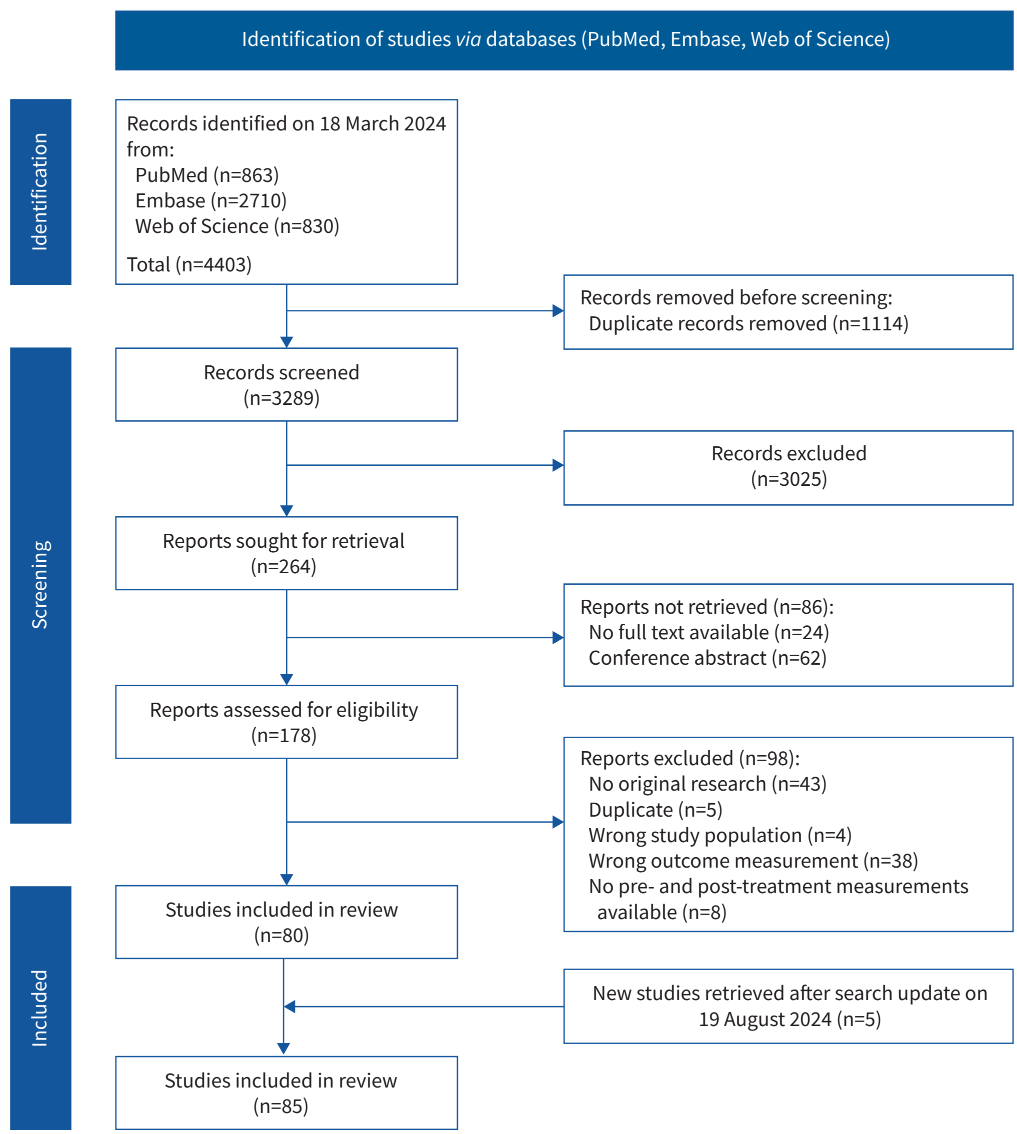

FIGURE 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram.

depicted in figure 2. Detailed assessment of each included study can be found in supplemental figures S1 and S2.

Study characteristics

The majority of publications included in this review were prospective in nature (63%). Retrospective studies made up 21% of publications, while RCTs accounted for 11% and 5% was unclear (figure 3a). Three quarters of the studies involved LVRS. The remaining quarter comprised BLVR treatments, with EBV and coils most commonly used (figure 3b). The extrapulmonary domains that have been most extensively investigated were 1) respiratory muscle function and central ventilatory drive, 2) cardiac function and pulmonary arterial hypertension, and 3) body composition and metabolism. For all the other domains only a limited number of publications was found (figure 3c).

Extrapulmonary effects of lung volume reduction

An overview of all included articles, detailing the sample size, follow-up period, study measurements and their respective outcomes, can be found in supplemental tables S2–S10. A summary of the most frequently examined variables within each extrapulmonary domain is presented in table 1 and will be discussed by topic below.

Respiratory muscle function and central ventilatory drive

Within this extrapulmonary domain, respiratory muscle strength has been most thoroughly investigated. 11 [17–27] out of 13 [28, 29] studies observed a significant increase in P_{Imax}, indicating an improvement in the strength of inspiratory muscles after lung volume reduction treatment. The overall treatment effect, calculated by the weighted mean difference adjusted for sample size, showed an increase of 16.6 cmH_2O at 1–6 months follow-up [17–24, 26–29]. This positive effect persisted for up to 60 months following treatment [25]. On the other hand, maximal expiratory pressure, which evaluates the strength of the expiratory muscles, was only investigated over a follow-up period of 3–6 months. This showed varying responses, resulting in an inconclusive overall effect [17–19, 21, 23, 24, 26, 28, 29]. The only RCT

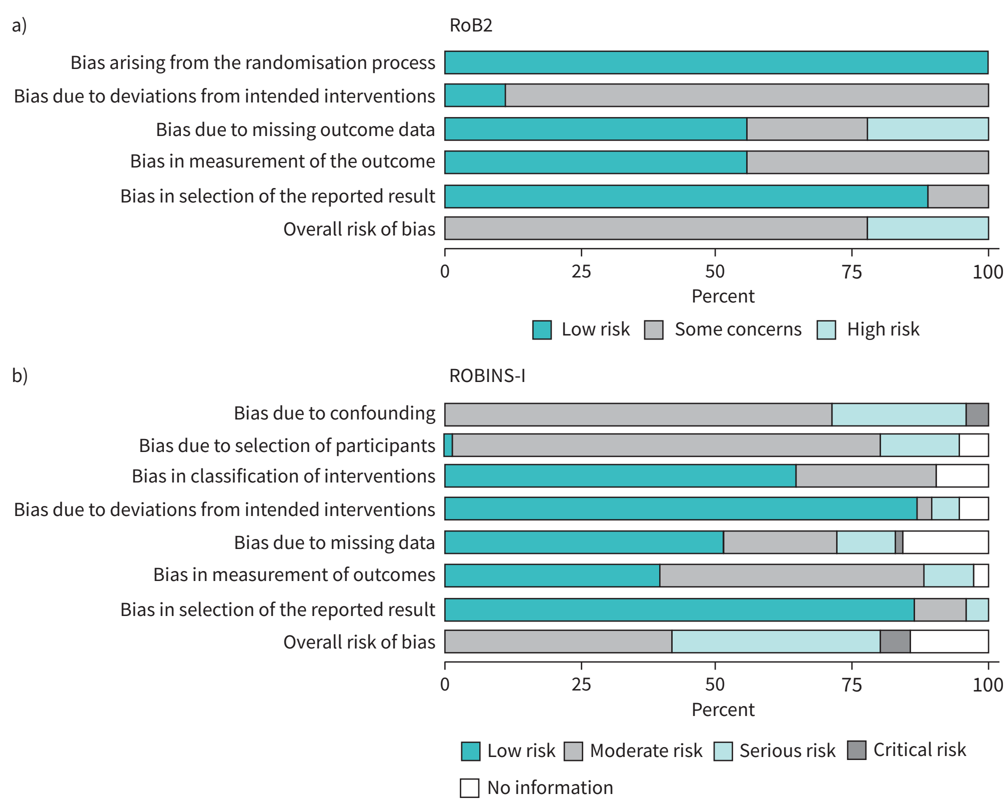

FIGURE 2 Summary of risk of bias assessments using a) the revised Cochrane Risk of Bias tool (RoB2) for randomised trials and b) the Risk Of Bias In Non-randomised Studies of Interventions tool (ROBINS-I). Judgments regarding each risk of bias item are presented as percentages across all included studies.

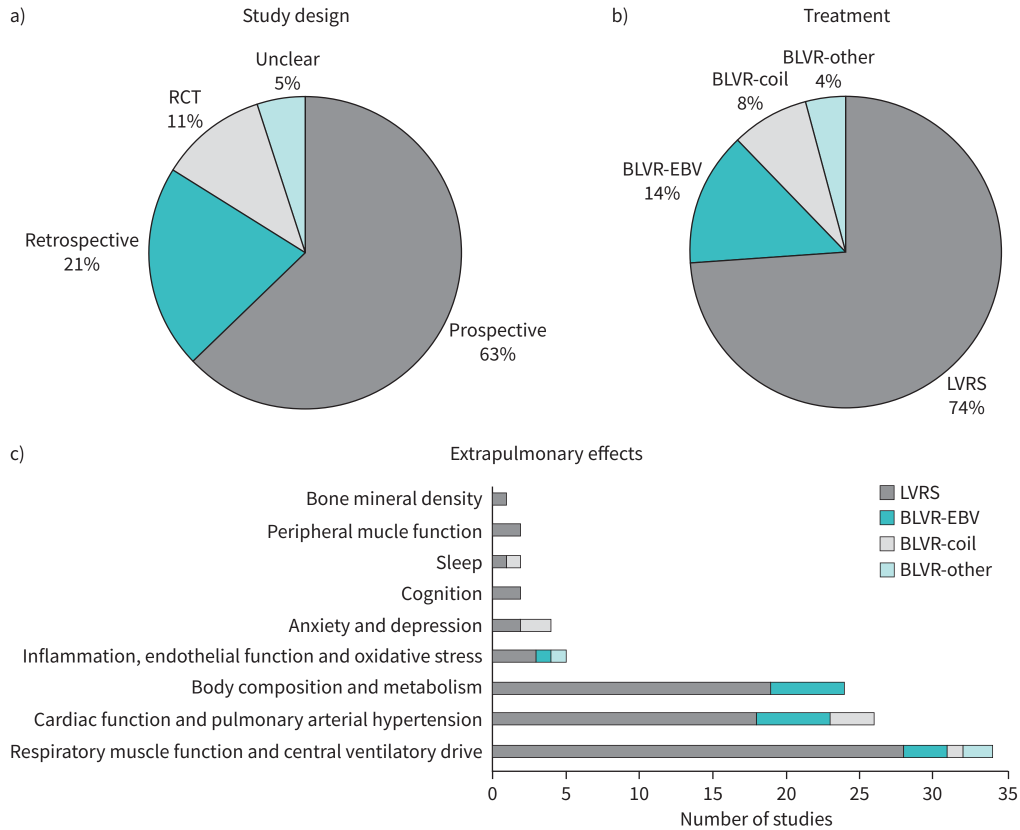

FIGURE 3 Distribution of publications reviewed by a) study design, b) treatment type and c) domains of extrapulmonary effects. BLVR: bronchoscopic lung volume reduction; EBV: endobronchial valve; LVRS: lung volume reduction surgery; RCT: randomised controlled trial.

conducted in this domain found similar results for both outcomes, consistent with those reported in other studies [26]. Diaphragm strength has also been investigated more specifically using gastric and oesophageal balloon catheters, as this method isolates diaphragm function by excluding the involvement of the accessory muscles. All nine studies measuring transdiaphragmatic pressures demonstrated a significant increase following treatment [19, 23, 27, 30–35]. Additionally, the study performed by Benditt *et al.* [36] showed that the improvement in diaphragm function led to reduced recruitment of the accessory muscles after LVRS. Although more extensively studied in LVRS, the effect of lung volume reduction on respiratory muscle strength appeared comparable in patients who underwent either surgery or a bronchoscopic treatment.

Not only has the output of the respiratory muscles been investigated, but also the drive towards these muscles to initiate muscle contraction. Electromyography and measurement of the airway occlusion pressure were the two methods used to assess ventilatory drive, which was only performed in patients undergoing LVRS. All five studies observed a significant decrease in the ventilatory drive following surgery [18, 27, 33, 37, 38]. Furthermore, two studies have examined the oxygen cost of breathing, which is the percentage of total oxygen consumption used by the respiratory muscles. These studies demonstrated that patients with advanced emphysema had an abnormally elevated baseline oxygen cost of breathing, which significantly decreased following LVRS [29, 39].

Morphology of the diaphragm has also been studied by assessing diaphragm length or area using chest radiographs and computed tomography (CT) scans. All eight studies showed a significant increase in diaphragm length and area following lung volume reduction [30, 34, 35, 38, 40–43]. A few studies have also examined the curvature of the diaphragm. Taton *et al.* [35] observed a significant increase in the curvature on chest CT scan after BLVR using EBVs, which was associated with an increase in diaphragm strength. In contrast, Takasugi *et al.* [44] did not demonstrate any change in the diaphragmatic arc on chest radiograph after LVRS. A single study investigated the morphology of the intercostal muscles in patients

TABLE 1 Overview of extrapulmonary effects of lung volume reduction treatment

Variable	Studies (n) (% LVRS)	Patients (total)	Description of outcomes	Overall effect
Respiratory muscle function				
P_{Imax}	13 (85)	743	Follow-up period ranged from 1 to 60 months 11 studies observed a significant improvement [17–27] Two studies observed a slight, but nonsignificant, increase [28, 29]	Positive
P_{Emax}	9 (78)	168	Follow-up period ranged from 3 to 6 months Two studies observed a significant improvement [17, 21] Two studies observed a slight, but nonsignificant, increase [19, 29] Three studies observed no change [23, 24, 26] Two studies observed a slight, but nonsignificant, decrease [18, 28]	Inconclusive
P_{di} (max/sniff/twitch)	9 (89)	139	Follow-up period ranged from 1 to 12 months All studies observed a significant increase [19, 23, 27, 30–35]	Positive
Ventilatory drive	5 (100)	59	Follow-up period ranged from 1 to 14 months All studies observed a significant decrease [18, 27, 33, 37, 38]	Positive
Diaphragm length/area	8 (88)	128	Follow-up period ranged from 6 weeks to 14 months All studies observed a significant increase [30, 34, 35, 38, 40–43]	Positive
Cardiac function and pulmonary arterial hypertension				
Cardiac output	7 (86)	107	Follow-up period ranged from 8 weeks to 12 months Two studies observed a significant increase [50, 61] Two studies showed a slight, but nonsignificant, increase [51, 53] One study observed no change [49] Two studies observed a slight, but nonsignificant, decrease [18, 48]	Inconclusive
RVEF	5 (60)	124	Follow-up period ranged from 8 weeks to 6 months One study observed a significant increase [57] One study observed a slight, but nonsignificant, increase [61] One study observed no change [50] Two studies observed a slight, but nonsignificant, decrease [48, 62]	Inconclusive
LVEF	6 (50)	153	Follow-up period ranged from 8 weeks to 6 months Two studies observed a significant increase [57, 61] Two studies observed a slight, but nonsignificant, increase [53, 62] Two studies observed a slight, but nonsignificant, decrease [48, 60]	Inconclusive
PAP	15 (60)	341	Follow-up period ranged from 1 month to 12 months One study observed a significant increase [53] Four studies observed a slight, but nonsignificant, increase [51, 52, 56, 60] Five studies observed no change [48–50, 58, 61] One study observed a slight, but nonsignificant, decrease [18] Four studies observed a significant decrease [54, 55, 57, 59]	Inconclusive
HR_{max}	4 (100)	113	Follow-up period ranged from 3 to 7 months Three studies observed a significant increase [63–65] One study observed a slight, but nonsignificant, increase [66]	Positive
Body composition and metabolism				
Body weight	6 (50)	183	Follow-up period ranged from 3 to 12 months Four studies observed a significant increase [70, 74, 78, 79] Two studies observed a slight, but nonsignificant, increase [69, 77]	Positive
BMI	14 (86)	832	Follow-up period ranged from 6 weeks to 60 months 10 studies observed a significant increase [25, 29, 68, 70–76] Three studies showed a slight, but nonsignificant, increase [24, 69, 77] One study observed no change [41]	Positive
FM	5 (80)	155	Follow-up period ranged from 3 to 60 months Two studies observed a significant increase [25, 73] Two studies observed a slight, but nonsignificant, increase [69, 78] One study observed a slight, but nonsignificant, decrease [74]	Positive
FFM	6 (67)	165	Follow-up period ranged from 3 to 60 months Five studies observed a significant increase [25, 69, 73, 74, 78] One study observed a slight, but nonsignificant, increase [77]	Positive
REE	3 (100)	63	Follow-up period ranged from 3 to 12 months One study observed no change [29] Two studies observed a significant decrease [24, 39]	Positive

Continued

TABLE 1 Continued

Variable	Studies (n) (% LVRS)	Patients (total)	Description of outcomes	Overall effect
Inflammation and oxidative stress				
CRP	3 (67)	52	Follow-up period ranged from 3 to 12 months Two studies observed a slight, but nonsignificant, decrease [77, 81] One study observed a significant decrease [80]	Positive
WBCs	1 (100)	28	Follow-up period of 12 months One study observed a significant decrease [80]	Positive
MDA	2 (100)	72	Follow-up period ranged from 3 to 6 months One study observed a slight, but nonsignificant, decrease [81] One study observed a significant decrease [82]	Positive
Anxiety and depression				
Anxiety	3 (67)	79	Follow-up period ranged from 3 to 12 months One study observed no change [85] One study observed a slight, but nonsignificant, decrease [84] One study observed a significant decrease [83]	Positive
Depression	3 (67)	79	Follow-up period ranged from 3 to 12 months One study observed no change [85] One study observed a slight, but nonsignificant, decrease [84] One study observed a significant decrease [83]	Positive
Cognition				
Visuomotor speed (TMT A)	2 (100)	363	Follow-up period ranged from 6 to 24 months One study observed a slight, but nonsignificant, decrease [86] One study observed a significant decrease [84]	Inconclusive
Cognitive flexibility (TMT B)	2 (100)	363	Follow-up period ranged from 6 to 24 months Two studies observed a slight, but nonsignificant, decrease [84, 86]	Inconclusive
Sleep				
Sleep efficiency	2 (50)	24	Follow-up period ranged from 6 to 12 months One study observed a significant increase [87] One study observed a slight, but nonsignificant, decrease [88]	Inconclusive
Arousal index	2 (50)	24	Follow-up period ranged from 6 to 12 months One study observed a slight, but nonsignificant, increase [88] One study observed a significant decrease [87]	Inconclusive
Peripheral muscle function				
Quadriceps strength	1 (100)	9	Follow-up period of 3 months One study observed a slight, but nonsignificant, decrease [31]	Inconclusive
Sit-to-stand test	1 (100)	19	Follow-up period ranged from 2 to 22 months One study observed a slight, but nonsignificant, increase [89]	Inconclusive
Handgrip strength	1 (100)	19	Follow-up period ranged from 2 to 22 months One study observed a slight, but nonsignificant, increase [89]	Inconclusive
Bone mineral density				
Bone mineral density	1 (100)	40	Follow-up period of 12 months One study observed a significant increase [90]	Positive

BMI: body mass index; CRP: C-reactive protein; FFM: fat-free mass; FM: fat mass; HR_{max}: maximal heart rate; LVEF: left ventricular ejection fraction; LVRS: lung volume reduction surgery; MDA: malondialdehyde; PAP: pulmonary arterial pressure; P_{di}: transdiaphragmatic pressure; P_{Emax}: maximal expiratory pressure; P_{Imax}: maximal inspiratory pressure; REE: resting energy expenditure; RVEF: right ventricular ejection fraction; TMT: trail making test; WBC: white blood cell.

undergoing BLVR with EBVs. While no significant changes were observed in parasternal intercostal muscle echogenicity or thickness, they found that reduction in hyperinflation was associated with an increase in parasternal muscle thickness in the treated hemithorax [45].

Finally, three studies have been conducted to assess diaphragm mobility during breathing. All three studies demonstrated a significant increase in maximum amplitude, measured either by dynamic magnetic resonance imaging (MRI) or ultrasound [43, 46, 47].

Cardiac function and pulmonary arterial hypertension

The primary focus in this extrapulmonary domain was on changes in pulmonary arterial pressure (PAP). Resting PAP was measured either invasively with right heart catheterisation or noninvasively with cardiac ultrasound or MRI in a total of 341 patients up to 12 months following treatment [18, 48–61]. Only one study observed a significant deterioration in PAP [53], whereas four studies demonstrated a significant reduction in PAP after lung volume reduction [54, 55, 57, 59]. The other 10 studies investigating PAP did not report any significant changes [18, 48–52, 56, 58, 60, 61]. One study specifically assessed changes in PAP in patients with elevated baseline values (mean PAP ⩾25 mmHg) and found that PAP significantly decreased [57]. There were no differences in PAP responses following LVRS or BLVR. Additionally, no differences were observed between the single RCT conducted and the other studies. The overall treatment effect of lung volume reduction on resting PAP remains inconclusive; however, there is no evidence to suggest a substantial risk of deterioration.

Cardiac function at rest was mainly investigated by measuring cardiac output and assessing right and left ventricular ejection fraction (RVEF and LVEF). Out of the seven studies evaluating cardiac output, one study was performed in patients undergoing BLVR, which reported a significant increase [61]. Additionally, another study conducted in patients who underwent LVRS also showed a significant increase in cardiac output [50]. The other five studies did not identify any significant differences after LVRS, including one RCT [18, 48, 49, 51, 53]. On the other hand, RVEF and LVEF were equally studied in patients undergoing LVRS or BLVR, yielding similar results to those observed for cardiac output [48, 50, 53, 57, 60–62]. Three [50, 57, 61] out of four [62] studies that evaluated right ventricular end-diastolic volume as a measure of cardiac preload demonstrated a significant improvement. The overall impact of lung volume reduction on cardiac function at rest remains inconclusive; however, there is evidence of a modest positive effect and, at least, it does not lead to any significant deterioration.

Changes in heart rate have been exclusively investigated in patients undergoing LVRS. Resting heart rate significantly decreased in one study [63], showed a slight but nonsignificant decrease in another [64] and remained unchanged in a third study [65]. Maximal heart rate during cardiopulmonary exercise testing significantly increased [63–66], whereas heart rate at iso-workload significantly decreased, suggesting an improvement in stroke volumes [50, 63, 65]. Two studies also evaluated the percentage of predicted heart rate reserve (%HRR) as a measure of chronotropic incompetence, defined as the heart's inability to increase its rate in response to exercise. The findings revealed a significant increase in %HRR, which could be indicative of improvement in chronotropic incompetence following LVRS [63, 64]. An RCT found no changes in cardiac repolarisation following LVRS [67]. Overall, lung volume reduction has a beneficial effect on heart rate and enhances the ability to respond to exercise.

Body composition and metabolism

BMI has been extensively studied in 832 patients up to 60 months after treatment [24, 25, 29, 41, 68–77]. The majority of studies reported a significant increase in BMI, with a baseline value of 22.2 and 23.9 $kg \cdot m^{-2}$ and a weighted mean difference of 0.53 and 1.19 $kg \cdot m^{-2}$ at 6 [41, 68, 74, 77] and 12 [68, 70, 71, 73] months, respectively, after the procedure. The increase in BMI was observed up to 60 months following treatment [25]. In contrast, the two studies involving 33 BLVR patients did not show a significant increase in BMI [69, 77]. Studies investigating body weight showed similar results [69, 70, 74, 77–79]. No differences were observed between the RCTs and the other studies. Overall, lung volume reduction has a positive impact on BMI and body weight.

Fat-free mass (FFM) and fat mass (FM) has been evaluated using bioelectric impedance analysis, deuterium dilution or dual energy X-ray absorptiometry (DEXA). Five [25, 69, 73, 74, 78] out of six [77] studies demonstrated a significant increase in FFM. Of the five studies assessing FM, two reported a significant increase [25, 73], while two, including one RCT, observed a slight but nonsignificant increase [69, 78] and one noted a slight but nonsignificant decrease [74]. Overall, these findings suggest that both FFM and FM tend to increase following lung volume reduction, contributing to an improvement in body composition.

Several studies have examined the body's energy consumption. Of the three studies investigating resting energy expenditure (REE), two reported a significant decrease following LVRS [24, 29, 39]. While REE has not been studied in BLVR, basal metabolic rate (BMR) has been measured in patients undergoing BLVR. Both studies on BMR found no significant changes following treatment [69, 77]. Two studies investigated caloric intake after LVRS, of which one study reported a significant increase [74], while an RCT observed a slight, nonsignificant increase [78]. Overall, evidence suggests that LVRS reduces resting energy expenditure, whether this also affects caloric intake remains unclear.

Inflammation, endothelial function and oxidative stress

C-reactive protein (CRP) was the most commonly investigated marker of inflammation. Of the three studies measuring CRP, one study observed a significant decrease 12 months after LVRS [80], whereas the other two studies, including one RCT, found a slight but nonsignificant decrease [77, 81]. Only one study evaluated white blood cell count and reported a significant reduction following LVRS [80]. These findings suggest that lung volume reduction may have a beneficial effect on inflammation.

Two studies have measured malondialdehyde (MDA) as a marker of oxidative stress in patients undergoing LVRS. One study reported a significant decrease in MDA levels [82], while the other study, an RCT, observed a slight but nonsignificant decrease [81]. Additionally, the RCT also assessed endothelial function, using flow-mediated dilatation of the brachial artery and found a significant improvement [81]. This may imply that lung volume reduction could potentially reduce oxidative stress and endothelial dysfunction.

Anxiety and depression

Three studies have investigated anxiety and depression using varying validated questionnaires in patients undergoing LVRS and BLVR with coils. One prospective study reported a significant decrease in both anxiety and depression [83]. An RCT observed a slight but nonsignificant reduction in anxiety and depression among LVRS patients; however, compared to the control group, depression was significantly reduced [84]. A third study found no change following LVRS, while progressive deterioration was observed in the control group [85]. Overall, lung volume reduction treatment appears to have a modest positive effect on anxiety and depression.

Cognition

Cognitive function has been evaluated in only two studies involving LVRS patients, using the trail making test (TMT) parts A and B, assessing visuomotor speed and cognitive flexibility, respectively. One smaller RCT assessed the short-term effects of LVRS [84], while the other study was a large RCT involving 347 patients that investigated the long-term effects at 24 months after LVRS [86]. There was a significant short-term improvement in visuomotor speed (TMT A) [84], which did not persist in the long term [86]. In contrast, the control group showed a significant improvement on TMT A [86]. There were no significant changes in cognitive flexibility (TMT B) [84, 86]. Currently, there is insufficient evidence to conclude whether lung volume reduction affects cognition.

Sleep

Sleep has been investigated in two studies using polysomnography. An RCT demonstrated that LVRS resulted in a significant improvement in sleep quality and nocturnal oxygenation, while there was no change in the control group [87]. In contrast, BLVR with coils led to a nonsignificant deterioration in sleep quality [88]. The overall impact of lung volume reduction on sleep remains inconclusive.

Peripheral muscle function

Peripheral muscle function was only assessed in patients undergoing LVRS. Quadriceps strength was investigated in two studies by either measuring voluntary maximal isometric contractions or by performing the sit-to-stand test. Both studies did not objectify a significant change in quadriceps strength [31, 89]. Handgrip strength was evaluated in one study, which did not significantly change either [89]. Although with little evidence, lung volume reduction appears not to effect peripheral muscle function.

BMD

Only one study examined changes in BMD and reported a significant improvement in BMD, as measured by DEXA, following LVRS. This improvement was seen despite patients continuing to receive oral steroids. Additionally, LVRS appeared to enhance bone metabolism, mineral content and various nutritional and bone-related parameters [90].

A schematic overview of the aforementioned extrapulmonary effects of lung volume reduction treatment described in literature is illustrated in figure 4.

Discussion

This systematic review demonstrates that lung volume reduction, either surgical or bronchoscopic, has an impact that extend beyond the lungs in patients with severe emphysema and lung hyperinflation. Three quarters of the identified studies were conducted in patients who underwent LVRS, making this the primary source of information. The most robust evidence was found in the extrapulmonary domains of 1) respiratory muscle function and ventilatory drive, 2) cardiac function and pulmonary arterial hypertension, and 3) body composition and metabolism. The greatest improvements were found in inspiratory muscle function, ventilatory drive, diaphragm morphology and body composition. While the

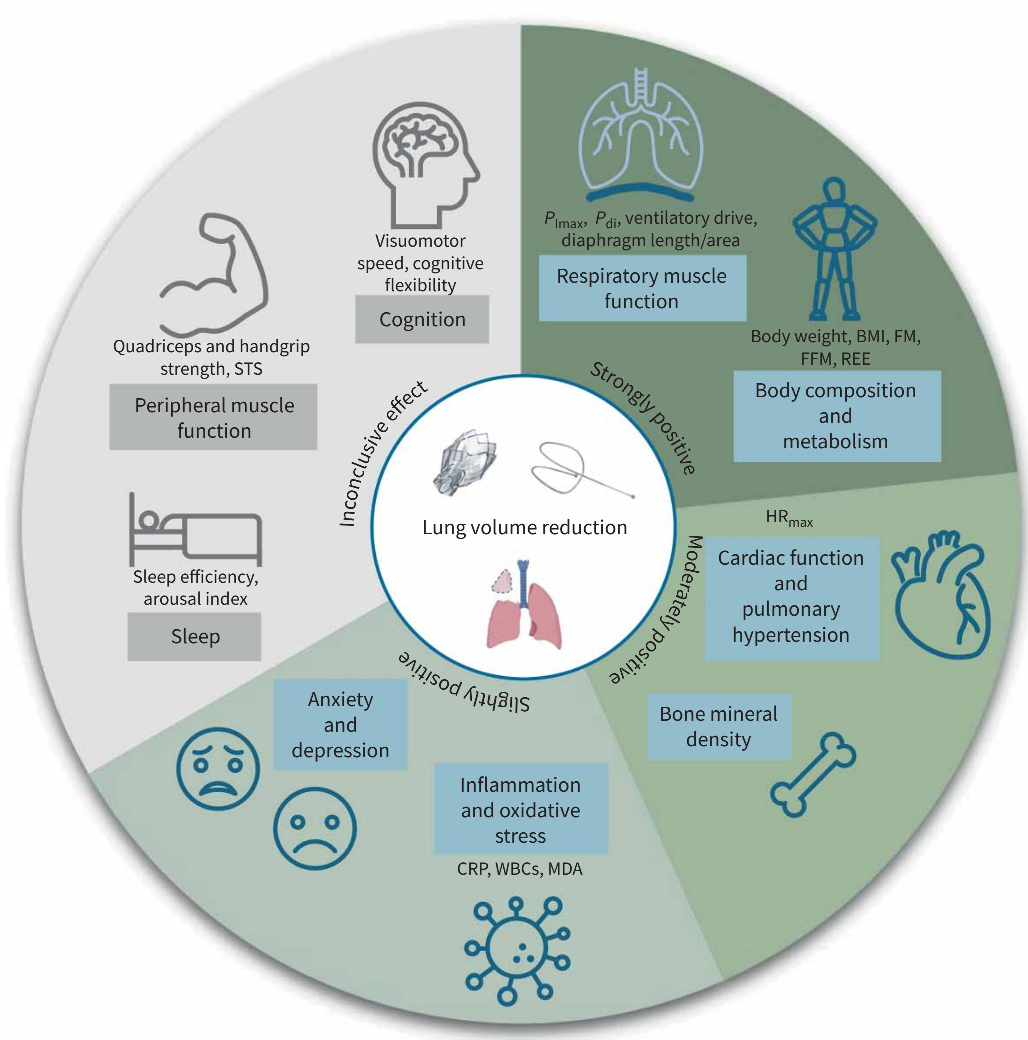

FIGURE 4 Schematic overview of extrapulmonary effects of lung volume reduction treatment. The domains represented in the green section of the circle indicate a positive overall effect, ranging from strongly to moderately to slightly positive, while the domains depicted in grey reflect an inconclusive overall effect. BMI: body mass index; CRP: C-reactive protein; FM: fat mass; FFM: fat-free mass; HR_{max}: maximal heart rate; MDA: malondialdehyde; P_{di}: transdiaphragmatic pressure; P_{Imax}: maximal inspiratory pressure; REE: resting energy expenditure; STS: sit-to-stand test; WBC: white blood cell.

effects were less pronounced, beneficial outcomes were also noted in relation to inflammation and oxidative stress, as well as anxiety, depression and BMD. However, this is based on limited evidence and further research is needed to validate these findings. The overall treatment effect of lung volume reduction on cardiac function and PAP was inconclusive, nevertheless, there is no evidence to suggest any significant deterioration after treatment. For the extrapulmonary domains of cognition, sleep and peripheral muscle function, evidence is currently insufficient to determine whether lung volume reduction has any impact.

This review showed that lung volume reduction led to increases in diaphragm length, area and curvature [30, 34, 35, 38, 40–43]. Lung hyperinflation reduces the diaphragm's ability to generate transdiaphragmatic pressures through several mechanisms, including deterioration of the length–tension relationship, a reduction in the zone of apposition and a decrease in the diaphragm's curvature [91]. Therefore, the restoration of diaphragm configuration after lung volume reduction may result in more efficient muscle contractions, which could explain the significant increase in diaphragm strength observed [19, 23, 27, 30–35]. P_{Imax} increased by a weighted mean difference of 16.6 cmH_2O, approaching the minimal clinically important difference (MCID) established in individuals with persistent post-COVID-19 symptoms following a respiratory muscle training programme [92]. Consequently, this improvement in strength may account for the reduced ventilatory drive observed, as less respiratory effort by the patient is required to generate similar breathing forces [18, 27, 33, 37, 38]. This might be one of the mechanisms contributing to reduced dyspnoea severity following lung volume reduction treatment, as an elevated neural respiratory drive has been closely related to breathlessness in patients with COPD [93].

One study reported that the improvement in diaphragm function led to reduced recruitment of the accessory muscles after LVRS [36]. Remarkably, only two studies did specifically investigate the accessory muscles. One study evaluated the morphology of the intercostal muscles and found that reducing hyperinflation was associated with an increase in parasternal muscle thickness [45]. Another study observed that the activity of the scalene muscles decreased following LVRS [38]. Hypothetically, it is reasonable to assume that a decrease in muscle activity after lung volume reduction could lead to a reduction in muscle thickness, as lower muscle activity levels would likely limit hypertrophy. However, further research is needed to clarify the relationship between reduction in hyperinflation and the function and morphology of the accessory muscles.

PAP was a major focus of interest, as pulmonary arterial hypertension has been considered as a relative contraindication for lung volume reduction treatment due to the higher risk of complications in these patients [5, 94]. Moreover, reducing the pulmonary vascular bed is thought to further impair pulmonary haemodynamics [95]. On the other hand, lung hyperinflation increases pulmonary vascular resistance due to elevated end-inspiratory lung volume, which contributes to the development of higher pulmonary pressures [96]. Additionally, lung hyperinflation impairs cardiac function by reducing right ventricular preload and increasing left ventricular afterload, driven by high intrathoracic pressure swings required to overcome decreased elastic recoil, and consecutively increased airflow resistance [2, 97, 98]. Therefore, alleviating lung hyperinflation may improve cardiovascular function. Although the overall treatment effect of lung volume reduction on PAP and cardiac function was inconclusive, there is no evidence to suggest a substantial risk of deterioration. Therefore, the presence of elevated pulmonary pressures and diminished cardiac function should not necessarily exclude the possibility of lung volume reduction, potentially allowing more patients to benefit from this treatment.

The majority of patients experienced a significant increase in BMI following lung volume reduction treatment. The reported baseline values were 22.2 and 23.9 $kg \cdot m^{-2}$, with a weighted mean increase of 0.53 and 1.19 $kg \cdot m^{-2}$ at 6 and 12 months, respectively, after the procedure. This may indicate that some patients reach a BMI above 25 $kg \cdot m^{-2}$ following lung volume reduction, indicating mild overweight. Therefore, an increase in BMI may not always be beneficial. However, two studies categorised patients into subgroups based on their baseline BMI. These findings suggest that patients with a lower baseline BMI significantly gained weight, whereas those with a higher baseline BMI experienced significant weight loss [99, 100]. Furthermore, the weighted mean increases in BMI may cause some patients to transition from a BMI of $\leqslant$21 to >21 $kg \cdot m^{-2}$, which is associated with a reduction in the BODE (BMI, airflow obstruction, dyspnoea severity and exercise capacity) index score and an improved prognosis for survival [101]. In conclusion, lung volume reduction positively impacts BMI, regardless of baseline values, and may offer a survival benefit.

The observed increases in BMI could be attributed to significant gains in both FM and FFM [25, 69, 73, 74, 78]. The increase in FM may, in turn, result from reversing the hypermetabolic-catabolic state by a lower resting energy expenditure due to reduced oxygen cost of breathing, along with an increased appetite and caloric intake due to less dyspnoea [24, 39, 74, 102]. This could also be one of the underlying mechanisms behind the observed increase in BMD [90]. The increase in FFM could be attributed to improved exercise capacity, enhanced physical activity levels and increased oxygen availability in skeletal muscles [11, 103]. However, one of the studies demonstrated that the significant improvement in FFM was most likely a result of a significant increase in intracellular and extracellular water rather than increase in muscle cell mass itself [69]. None of the other studies looked into the origin of the changes in FM and FFM. Alternatively, the cross-sectional area of skeletal muscle, as measured by CT scan at the first lumbar level, showed a significant increase following BLVR, which was associated with improvements in exercise performance [79]. Therefore, an improvement in body composition, alongside the observed positive changes in BMI, is likely to occur.

Emphysema is characterised by a low-grade systemic inflammatory state, with lung hyperinflation contributing to parenchymal inflammation [104]. Elimination of inflammatory emphysematous tissue through LVRS may lead to a reduction in inflammation and oxidative stress, as observed in a study on patients undergoing this procedure [80]. In contrast, BLVR does not remove emphysematous tissue and, in one study investigating inflammation, no changes in CRP were observed [77]. This suggests that removing destructed lung parenchyma is necessary to achieve positive effects on inflammation and oxidative stress. However, since CRP is not a highly sensitive marker of inflammation, the possibility that other inflammatory markers may change after BLVR cannot be excluded. Contrarily, BLVR involves the use of implantable devices, which occasionally induces the formation of granulation tissue, an inflammatory process [105, 106]. Consequently, it is reasonable to hypothesise that BLVR might exacerbate the inflammatory state; however, no supporting evidence for this hypothesis has been reported thus far. Further research is needed to validate the above hypotheses.

The modest positive impact on anxiety and depression that has been reported is more likely attributable to indirect mechanisms rather than a direct effect of reducing lung hyperinflation. It can be speculated that improvements in pulmonary function, exercise capacity and dyspnoea severity following lung volume reduction enhance participation in daily activities, thereby alleviating the sociopsychological burden of emphysema. Furthermore, anxiety has been independently associated with poorer survival outcomes in patients with severe lung hyperinflation [4]. Therefore, lung volume reduction has the potential not only to improve health-related quality of life, but also to provide a survival benefit.

Currently, there is insufficient evidence to determine whether lung volume reduction affects the extrapulmonary domains of peripheral muscle function, sleep and cognition. However, there are reasons to hypothesise that it may have a beneficial effect on these domains. Regarding muscle function, in a systematic review by van Geffen *et al.* [11], it was shown that lung volume reduction led to a significant increase in exercise capacity. This improvement may result from enhanced pulmonary function; however, increased peripheral muscle function could also contribute to the improved exercise capacity. Sleep quality is frequently compromised in patients with COPD [107]. Although the exact causes are not entirely clear, it is believed that increased inspiratory loads resulting from hyperinflation elevate the work of breathing, potentially eliciting arousals through the stimulation of mechanoreceptors in the chest wall and lower airways [108]. Therefore, reducing hyperinflation could potentially enhance sleep quality in patients with COPD. Cognitive performance is often impaired in patients with severe COPD [109]. One of the key mechanisms of this decline is neuronal damage mediated through hypoxia. Inflammatory mediators have also been linked to cognitive dysfunction [110]. Since lung volume reduction can improve oxygenation and has been associated with a reduction in inflammatory markers, it may also lead to improvements in cognitive function. Validating this hypothesis across these three domains in future research would be valuable.

The major strength of this systematic review lies within its extensive scope, covering nine predefined extrapulmonary domains including LVRS, as well as various endoscopic approaches, all aiming to reduce the emphysematous lung hyperinflation. This broad strategy allowed us to provide a comprehensive overview of all extrapulmonary effects of lung volume reduction treatment supported by the current evidence. However, we also encountered certain limitations. Firstly, there was substantial heterogeneity among the included studies in terms of study measurements, outcome variables and follow-up duration. This variability limited the ability to pool evidence, allowing primarily a descriptive summary of effects. Consequently, comparing the outcomes with MCIDs was not feasible, although this could have provided valuable additional insights. Secondly, only 11% of the included studies were RCTs, while the remaining studies were either prospective or retrospective observational cohort studies. These types of studies carry a greater risk of confounding, as indicated by the risk of bias assessment. Therefore, the observed effects may not solely be attributable to lung volume reduction but could also result from other interventions implemented simultaneously, such as rehabilitation, nutritional support or pharmacotherapy with anxiolytics or antidepressants. The scarcity of RCTs also underscores their tendency to focus on a limited number of efficacy outcome measures, such as pulmonary function, exercise capacity and quality of life. Most RCTs, however, have not considered extrapulmonary effects. Lastly, since most studies were conducted in patients undergoing LVRS, some of the outcomes may not be generalisable to patients receiving a bronchoscopic type of lung volume reduction, highlighting a need for more research in this area.

In conclusion, this systematic review shows that lung volume reduction, both surgical and bronchoscopic, has multiple direct and indirect beneficial extrapulmonary effects in patients with severe emphysema and lung hyperinflation. This underscores the physiological interaction between hyperinflation and various extrapulmonary manifestations, suggesting that reducing hyperinflation may partially reverse its detrimental effects in this patient population.

Points for clinical practice

- Lung volume reduction has multiple beneficial extrapulmonary effects in patients with severe emphysema and lung hyperinflation.
- Lung volume reduction can restore diaphragm morphology and function.
- Lung volume reduction does not adversely affect PAP or cardiovascular performance; therefore, it should not be regarded as a strict contraindication.
- Lung volume reduction has a positive impact on BMI and body composition.
- Lung volume reduction can potentially reduce anxiety, depression, inflammation and oxidative stress.

Questions for future research

- Does BLVR provide extrapulmonary benefits comparable to those of LVRS?
- Does lung volume reduction affect the morphology and function of the accessory respiratory muscles?
- Can future research validate the positive effects of lung volume reduction on inflammation, oxidative stress, anxiety, depression and BMD?
- Can lung volume reduction improve cognition, sleep quality and peripheral muscle function?

Provenance: Submitted article, peer reviewed.

Data availability: The data that support the findings of this study are available from the corresponding author upon reasonable request.

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