Interventional Pulmonology

Respiration

Respiration 2020;99:62–72
DOI: 10.1159/000504183

Received: September 2, 2019
Accepted after revision: October 16, 2019
Published online: November 22, 2019

Efficacy of the Spiration Valve System in Patients with Severe Heterogeneous Emphysema: A Systematic Review and Meta-Analysis

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Keywords

Spiration Valve System · Intrabronchial valve · Endobronchial valves · Bronchoscopic lung volume reduction · Severe emphysema · Bronchoscopy · Chronic obstructive pulmonary disease

Abstract

Background: Spiration Valve System (SVS) is an alternative for patients with severe heterogeneous emphysema; however, data about efficacy from randomized controlled trials (RCT) are unclear. ***Objectives:*** To explore both efficacy and safety of SVS in patients with severe emphysema and hyperinflation. ***Methods:*** We included PubMed, EMBASE, Cochrane database. All searches were performed until August 2019. Only RCTs were included for analysis. Risk of bias was assessed using Cochrane risk of bias tool. A meta-analysis evaluated change in forced expiratory volume in 1 s (FEV_1), 6-min walking test (6MWT), residual volume, modified medical research council (mMRC) and Saint George respiratory questionnaire (SGRQ), all-cause mortality, risk of pneumothorax, and risk of acute exacerbation of chronic obstructive pulmonary disease (AECOPD). Quality of the evidence was rated using GRADE approach. ***Results:*** Four RCTs including 629 subjects were included. SVS showed an overall change of 0.03 L (–0.07 to 0.13, $I^2 = 90\%$) in the in FEV_1 (L) and a 2.03% (–2.50 to 6.57, $I^2 = 96\%$) in the predicted FEV_1 (%) compared to baseline; however, studies without collateral ventilation (CV) showed an improvement of 0.12 L (95% CI 0.09–0.015, $I^2 = 0\%$), This subgroup also reported better results in SGRQ –12.27 points (95% CI –15.84 to –8.70, $I^2 = 0\%$) and mMRC –0.54 (95% CI –0.74 to –0.33, $I^2 = 0\%$). We found no benefit in 6MWT mean difference = 4.56 m (95% CI –21.88 to 31.00, $I^2 = 73\%$). Relative risk of mortality was 2.54 (95% CI 0.81–7.96, $I^2 = 0\%$), for pneumothorax 3.3 (95% CI 0.61–18.12, $I^2 = 0\%$) and AECOPD 1.68 (95% CI 1.04–2.70, $I^2 = 0\%$). ***Conclusion:*** In patients with severe heterogeneous emphysema and hyperinflation without CV, SVS is an alternative that showed an improvement in pulmonary function, quality of life, and dyspnea score with an acceptable risk profile.

Study register: PROSPERO CRD42016040001.

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Introduction

Chronic obstructive pulmonary disease (COPD) is currently the fourth leading cause of death worldwide [1]. Emphysema affects an estimated 1.8% of the world population, and the pathophysiological effects are loss of lung elastic recoil, air trapping, and lung hyperinflation [2].

Current therapeutic options for patients with COPD include lifestyle modification, pharmacotherapy, pulmonary rehabilitation, and long-term oxygen therapy [3–5]; however, subjects with severe emphysema remain significantly disabled despite optimal medical management. Unfortunately, these therapies have limited ability to either reverse or decrease lung hyperinflation caused by alveolar destruction [1].

For the subset of patients with advanced emphysema and hyperinflation, the National Emphysema Treatment Trial showed that lung volume reduction surgery led to an improvement in pulmonary function, respiratory symptoms, quality of life, exercise capacity, and survival; however, it was associated with significant 90-day morbidity and mortality [6]. Currently, 2 types of endobronchial valves are available and approved by the FDA in the United States [7]: Zephyr® endobronchial valve (PulmonX) and Spiration Valve System (SVS)® (Formerly known as Intrabronchial valve, Olympus Respiratory America) that can achieve lung volume reduction in a minimally invasive method [8]. They consist of a one-way valve that blocks inspired airflow to the target lobe while allowing air and mucus out, thus leading to atelectasis of the emphysematous lung distal to the valve [9]. Compared to the Zephyr® valve, evidence about the efficacy of SVS® valve is unclear. The aim of this systematic review and meta-analysis is to explore the efficacy of the SVS®, including current randomized controlled trials (RCT) available in the literature.

Methods

We conducted a systematic review of intervention following the current recommendations of PRISMA statement and Cochrane handbook of systematic reviews of interventional studies [10, 11]. The protocol was previously registered in PROSPERO database (CRD42016040001).

Literature Search

A review author (C.P.) performed the literature search without language restriction in August 2019. We identified studies from the following sources: MEDLINE, Lilacs, Trip Database, Directory of open access journal, Cochrane database, and Epistemonikos. We also searched the proceedings of major respiratory conferences from 2014 to 2018 of the European Respiratory Society, American Thoracic Society and The American College of Chest Physicians. Details of the strategies are reported in online supplementary Appendix S1 (for all online suppl. material, see www.karger.com/doi/10.1159/000504183). Finally, we searched the reference lists of all primary studies.

Inclusion Criteria

We included adult patients with COPD according to current guidelines with severe heterogenous emphysema and hyperinflation as evidenced by high-resolution chest CT (HRCT) (≥40% emphysema destruction in the target lobe and a ≥10% difference with the ipsilateral lobe) and pulmonary function test (forced expiratory volume in 1 s [FEV_1] <45%, TLC >100% and residual volume [RV] >150%) [1]. We defined the use of SVS® for the intervention and the usual standard of care as the comparator. Data collected include: changes in pulmonary function (FEV_1, measured in liters and % predicted volume), quality of life using the Saint George respiratory questionnaire ([SGRQ] measured in points), changes in RV (measured in liters), changes in dyspnea score using modified medical research council ([mMRC] measured in points), and changes in the 6-min walking test ([6MWT] measured in meters). For the safety analysis, we included the following outcomes: All-cause mortality, risk pneumothorax after the intervention, for this outcome we used the prevalence of pneumothorax in emphysema patients previously published [12] and the risk of an acute exacerbation of COPD (AECOPD). Finally, we limited our inclusion criteria only to RCTs. We excluded studies with others BLVR techniques (endobronchial valves, thermal vapor ablation, and coils).

Selection of Studies

Two reviewers (G.L. and J.P.U.) evaluated the abstracts obtained after the literature search and independently selected the studies based the established criteria. A third reviewer (S.F.-B. and A.M.) was involved resolving any discrepancies.

Data extraction was performed by 2 authors (G.L. and J.P.U.) independently obtaining outcomes data from eligible studies, and one of those authors (G.L.) transferred the data to the Review Manager software version 5.3.

Assessment of Risk of Bias in Included Studies

Two of the authors (G.L. and J.P.U.) assessed risk of bias independently for each study, using the criteria outlined in the Cochrane handbook of systematic review of intervention tool for randomized studies [11]. Any disagreement was resolved by discussion including the main authors.

Data Management

We used participants as the unit of analysis and the data of participant allocated to SVS® or placebo was pooled in a meta-analysis using the DerSimonian Laird method. Dichotomous data and pooled data were expressed as risk ratios (RRs) and 95% CI for each analysis. Pooled data of continuous variables were presented as the mean difference (MD) with (CI). Every meta-analysis was conducted following an intention to treat principle and a randomized analysis model. Heterogeneity was evaluated using the I^2 statistic to measure heterogeneity among the studies in each analysis. We defined I^2 >50% as substantial heterogeneity. In situations of substantial heterogeneity, we explored possible causes by prespecified

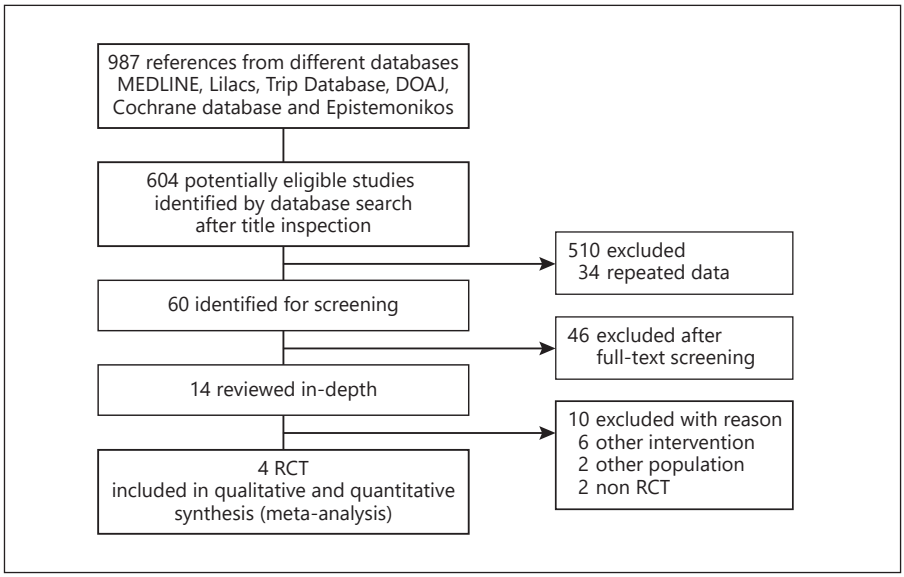

Fig. 1. Prisma flowchart and included studies. DOAJ, Directory of open access journal; RCT, randomized controlled trial.

subgroup analysis according to (1) risk of bias of included studies; (2) collateral ventilation (CV; absence/presence) measure by Chartis (PulmonX) or HRCT [13]; and(3) follow-up (3, 6 and 12 months) after valve placement [14].

Publication bias was evaluated through a visual inspection of a funnel plot. Finally, we reported the main results using a summary of findings table and rated the quality of evidence according to GRADE criteria [15].

Results

Study Characteristics

From a total of 987 references, 14 studies were potentially included after our literature search and 10 were excluded based on the preestablished criteria [16–25]. Finally, 4 multicenter RCT's including a total of 629 subjects (364 in the SVS® arm and 265 for control) were included for qualitative and quantitative analysis [17, 26–28]. A summary of the literature search following PRISMA statement is presented in Figure 1. All studies were parallel RCTs, and the comparator was standard of care (optimized medical management). Baseline characteristics of the subjects included in an average age ranging from 61- to 66 years old, a predominance of males, FEV_1 at baseline ranged from 27.3 to 35% of predicted volume, predicted % RV ranged from 216.0 to 261.4, 6MWT (m) ranged from 303.5 to 338.7, and the SGRQ ranged from 54.79 to 61.0 points. Two trials included only patients with no CV evidenced by >90% fissure completeness with no segmental vessels crossing between adjacent lobes on HRCT using the VIDA (Apollo® software) system [17, 28]. None of the studies included used the Chartis system to evaluate the presence of CV (Table 1).

Quality Assessment

The included studies reported a low index of bias in most domains; however, we found high or unclear (performance) bias in all the studies [17, 26–28]. One study reported unclear risk of selection bias [26]. A full report of the risk of bias assessment is presented in Figure 2.

Efficacy Analysis

Changes in FEV_1

Changes in the predicted FEV_1 (%) after SVS placement were evaluated in 3 of the studies [17, 27, 28]. The analysis showed a MD 2.03% (95% CI –2.50 to 6.57, I^2 = 96%) in the predicted FEV_1 (GRADE: LOW). However, A subgroup analysis based on the preprocedural assessment for CV showed a MD 4.16% (95% CI 2.90–5.42, I^2 = 0%) in patients without CV [17, 28] and a MD –2.15% (95% CI –3.47 to –0.83, I^2 = not applicable) in patients with CV [27], For this analysis, the intergroup heterogeneity was statistically significant I^2 = 96% (p value <0.00001).

On the other hand, changes in FEV_1 in litters were evaluated in all the studies [17, 26–28]. Pooled data showed FEV_1 improvement with a MD 0.03 L (95% CI –0.07 to 0.13, I^2 = 90%) compared to baseline (GRADE: LOW; Fig. 3).

Subgroup analysis was performed to explore the effect of FEV_1 improvement following SVS® placement by CV.

Table 1. Characteristic of included trials

Variable	EMPROVE (n = 113)	REACH (n = 66)	IBV Trial (n = 142)	Ninane et al. (n = 37)
Total valves placed, n	476	Not reported	931	Not reported
EBV, mean ± SD	Not reported	5.2±1.1	6.6	7.3±2
Age, years, mean ± SD	66.7±6.6	63.5±6.7	64.67±6.25	61±7
Male %	47.8	100	Not reported	23 (62)
FEV1, % predicted, mean ± SD	30.8±8.1	27.3±6.7	29.79±7.48	35±10
TLC, % predicted, mean ± SD	126.5±14.5	136.0±23.6	128.06±15.98	130±19
RV, %, mean ± SD	4.573±1.253	261.4±74.4	216.01±50.10	238±74
mMRC, mean ± SD	2.7±0.7	2.7±0.6	2.68±0.66	2.8±0.7
SGRQ (total score), mean ± SD	57.2±14.8	56.4±14.3	54.79±15.47	61±11
6MWT, m, mean ± SD	303.5±84.5	338.7±94.5	314.12±88.60	337±106
Fissure Completeness assessment with HRCT (>90%)	Yes	Yes	No	No
Chartis system	No	No	No	No

IBV, intrabronchial valve; FEV_1, forced expiratory volume in 1 s; TLC, total lung capacity; RV, residual volume; mMRC, modified medical research council; 6MWT, 6-min walking test; HRCT, high-resolution chest computed tomography.

A full summary of subgroup analysis on major outcomes is reported in Table 2. In the subgroup without CV, SVS® showed an improvement in FEV_1 (L) of 0.12 L (95% CI 0.09–0.015, I^2 = 0%). Meanwhile subgroup with CV shows a MD of –0.07 (95% CI –0.11 to –0.03, I^2 = 0%). For this analysis, the intergroup heterogeneity was statistically significant I^2 = 95% (p < 0.00001; Fig. 4).

Regarding the follow-up time, a subgroup analysis following randomization evidenced at 3 months a change in FEV_1 (L) MD 0.04L (95% CI –0.09 to 0.17, I^2 = 39%); for 6 months of follow-up the MD was 0.05 L (95% CI –0.08 to 0.18, I^2 = 97%). Finally, for 12months of follow-up, MD 0.10 L (95% CI 0.05–0.15; online suppl. Fig. 1).

Changes in Quality of Life (SGRQ)

Four trials reported the change in the total score of the questionnaire after SVS® placement with a decrease of the MD –6.50 points (95% CI –16.05 to 3.04, I^2 = 94%; Fig. 5a). For this outcome, intergroup heterogeneity was statistically significant I^2 = 94% (p < 0.001), subgroup analysis by CV showed a MD –12.27 points (95% CI –15.84 to –8.70, I^2 = 0%) in subjects without CV by HRCT. Patients without evaluation for CV on HRCT showed a MD of 0.85 points (95% CI –5.9 to 7.63, I^2 = 65%), intergroup heterogeneity I^2 = 93% (p < 0.0001; online suppl. Fig. 2). We rate this evidence as MODERATE due to publication bias and indirectness.

In the subgroup by follow-up including patients with and without CV, at 3 months we found a MD –6.98 (95% CI –13.99 to 0.04, I^2 = 78%); at 6 months, the reported

Fig. 2. Risk of bias summary: review authors' judgments about each risk of bias item for each included study.

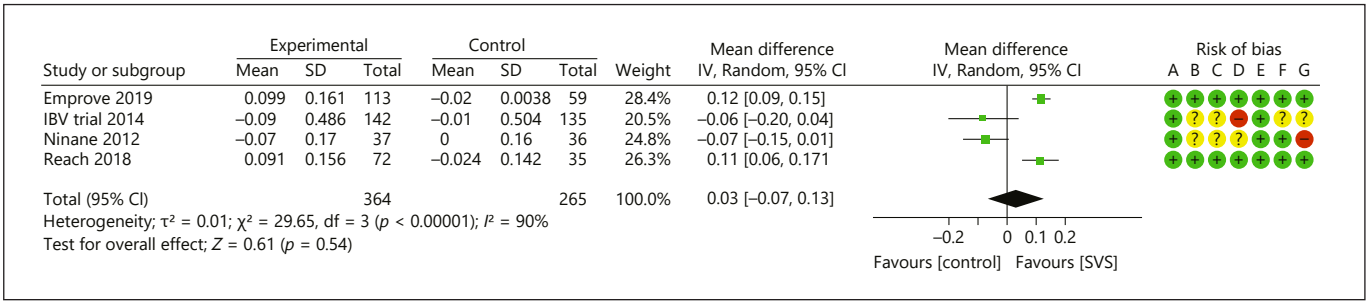

Fig. 3. Forest plot. Changes in FEV_1. SVS, Spiration Valve System.

Table 2. Subgroup analysis according to both emphysema distribution and follow-up

Outcome	HRCT assessment for collateral ventilation (pre-procedural)			Follow-up			
	yes	no	residual I^2, %	3 months	6 months	12 months	residual I^2, %
FEV_1	0.12 (0.09 to 0.015)	−0.07 (−0.11 to −0.03)	98.40	0.04 (−0.09 to 0.17)	0.05 (−0.08 to 0.18)	0.10 (0.05 to 0.15)	0
I^2	0%	0%		39%	97%	NA	
SGRQ	−12.27 (−15.84 to −8.75)	0.85 (−5.93 to 7.63)	93	−6.98 (13.99 to 0.04)	−6.47 (−18.33 to 5.40)	−9.50 (−13.66 to −5.34)	0
I^2	0%	65%		78%	95%	NA	
6MWT	19.02 (−9.43 to 47.47)	−19.64 (−36.52 to 47.47)	80.90	4.28 (−15.79 to 24.36)	5.30 (−24.31 to 34.91)	NA	0
I^2	60%	0%		36%	82%	NA	
RV	−0.36 (−0.56 to −0.16)	0.38 (0.13 to 0.64)	94.90	0.02 (−0.64 to0.67)	0.06 (−0.67 to 0.78)	NA	0
I^2	0%	0		44%	79%	NA	
Pneumothorax	4.64 (0.82 to 28.16)	0.61 (0.15 to 2.47)		NA	3.33 (0.61 to 18.2)	NA	NA
I^2	71%	0%		NA	0%	NA	

FEV_1, forced expiratory volume at 1 s; SGRQ, Saint George respiratory questionnaire; 6MWT, 6-min walking test; RV, residual volume; I^2, heterogeneity.

MD −6.47 (95% CI −18.33 to 5.40, I^2 = 95%). Finally, at 12 months, MD −9.50 (95% CI −15.09 to 3.56). Intergroup heterogeneity I^2 = 93% (p < 0.001; online suppl. Fig. 3).

Changes in mMRC

Four trials after SVS® placement showed a decrease of the MD was −0.33 points (95% CI −0.61 to −0.05, I^2 = 65%) in the mMRC (GRADE: LOW; Fig. 5b).

Subgroup analysis by CV showed a MD of −0.54 points (95% CI −0.74 to −0.33, I^2 = 0%) in subjects without CV. On the other hand, in patients without assessment of CV on HRCT (with CV), the MD was −0.11 points (95% CI −0.33 to 0.10, I^2 = 0%). Intergroup heterogeneity I^2 = 65% (p = 0.03).

Subgroup analysis by follow-up at 3 months showed a MD of −0.45 points (95% CI −0.69 to −0.22, I^2 = 30%); at 6 months, the MD was −0.36 (95% CI −0.69 to −0.02, I^2 = 76%). At 12 months, the MD was −0.80 (95% CI −1.05 to −0.55, I^2 = not applicable). Intergroup heterogeneity was I^2 = 70% (p = 0.003; online suppl. Fig. 4).

Changes in 6MWT

A total of 358 participants reported a change of the MD of 4.56 m (95% CI −21.88 to 31.00, I^2 = 73%) (GRADE: VERY LOW; Fig. 5c). in the 6MWT after the procedure.

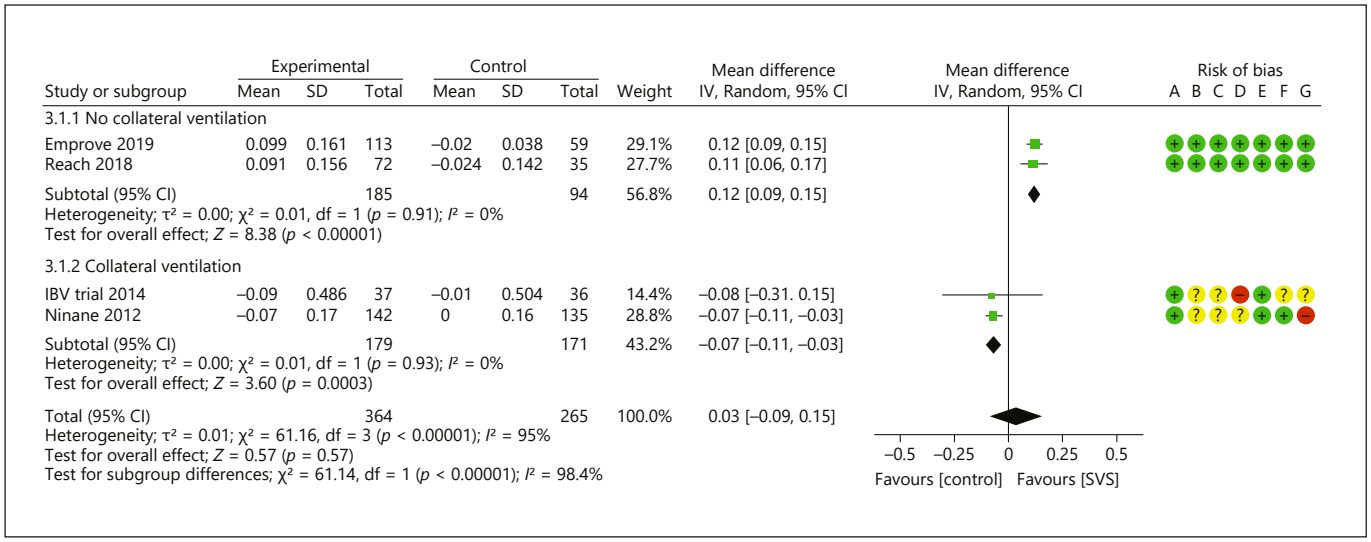

Fig. 4. Forest plot. Subgroup change in FEV_1 according to CV. SVS, Spiration Valve System.

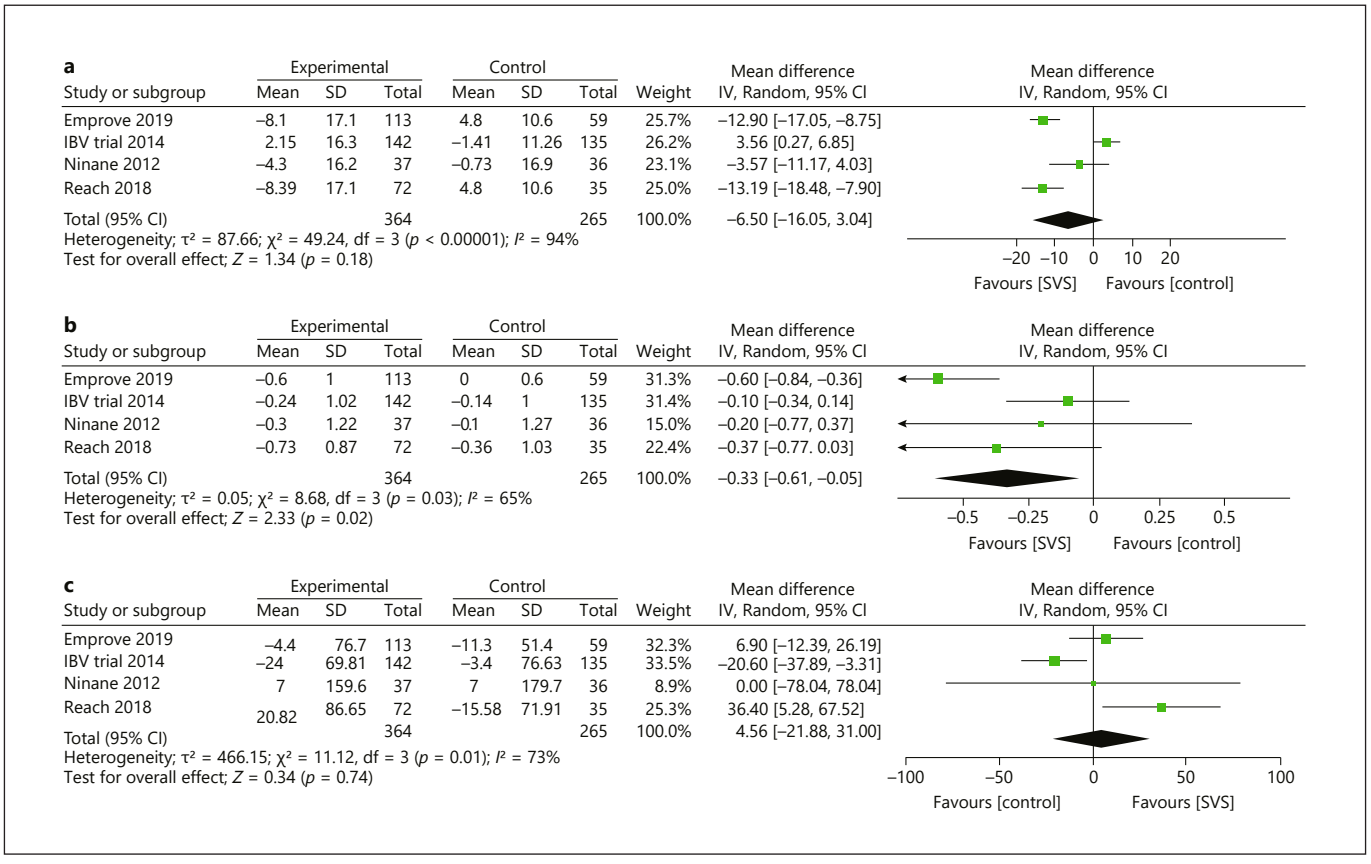

Fig. 5. Forest plot. **a** Change in SGRQ. **b** Change in mMRC dyspnea score. **c** Change in 6MWT. SVS, Spiration Valve System.

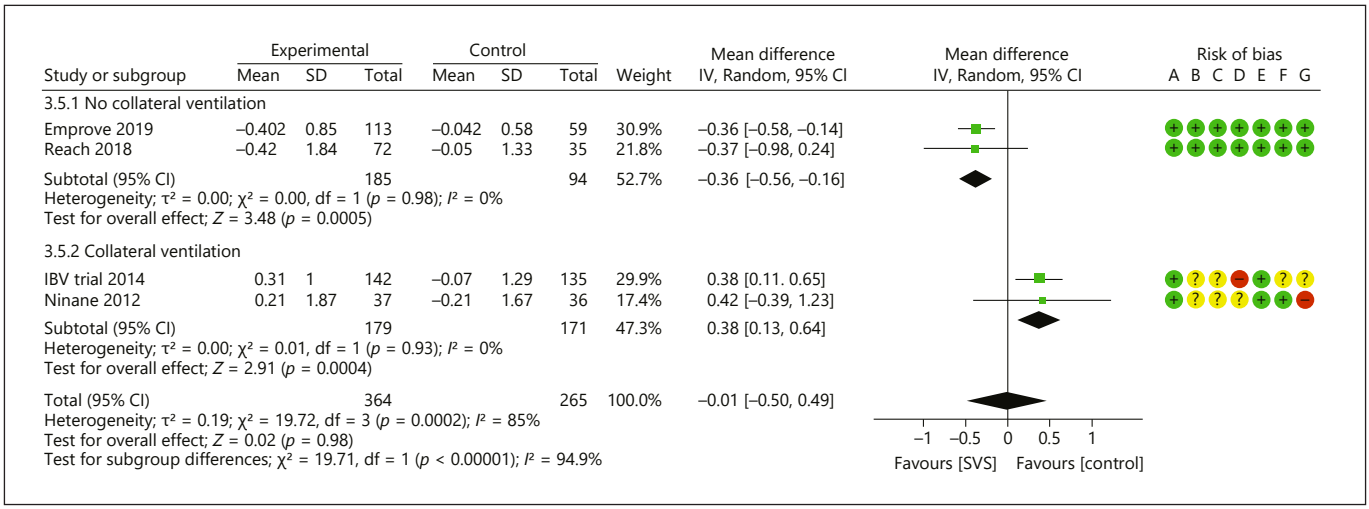

Fig. 6. Forest plot. Change in RV. SVS, Spiration Valve System.

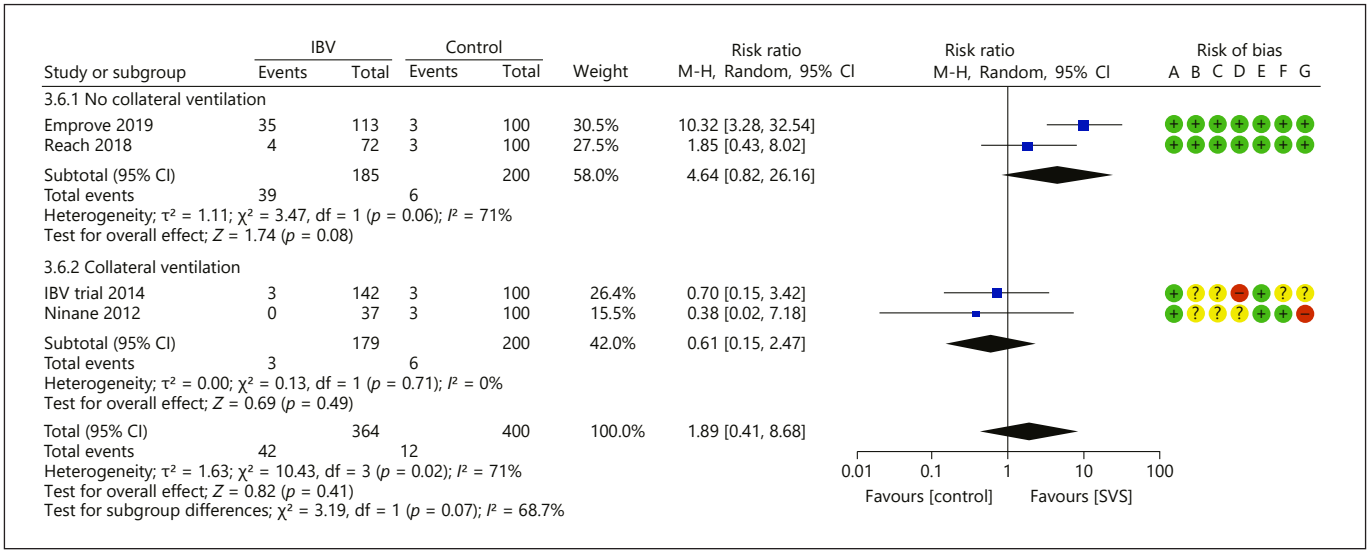

Fig. 7. Forest plot. Risk of pneumothorax. SVS, Spiration Valve System.

Subgroup analysis by the presence of CV showed a MD of 19.02 m (95% CI –9.43 to 47.47, $I^2 = 60\%$) in subjects without CV. On the other hand, in patients without evaluation for the presence of CV on HRCT, the MD was –19.64 m (95% CI –36.52 to –2.76, $I^2 = 0\%$). Intergroup heterogeneity $I^2 = 73\%$ ($p = 0.01$; online suppl. Fig. 5).

Subgroup analysis by follow-up at 3 months including patients with and without CV showed a MD of 4.28 m (95% CI –15.79 to 24.36, $I^2 = 36\%$); and at 6 months, the MD was 5.30 m (95% CI –24.31 to 34.91, $I^2 = 82\%$). Intergroup heterogeneity $I^2 = 65\%$ ($p = 0.01$; online suppl. Fig. 6).

Changes in RV (L)

Four trials reported changes in RV. MD of change was –0.01 L (95% CI –0.50 to 0.49, $I^2 = 85\%$; GRADE: LOW; Fig. 6). The subgroup analysis without CV showed a MD of –0.36 L (95% CI –0.56 to –0.16, $I^2 = 0\%$). On the other hand, in patients with CV shows a MD of 0.38 L (95% CI 0.13–0.64, $I^2 = 0\%$). Intergroup heterogeneity $I^2 = 94\%$ ($p < 0.001$).

The subgroup analysis by follow-up including patients with and without CV showed at 3 months shows a MD of 0.02 L (95% CI –0.64 to 0.67, $I^2 = 44\%$). At

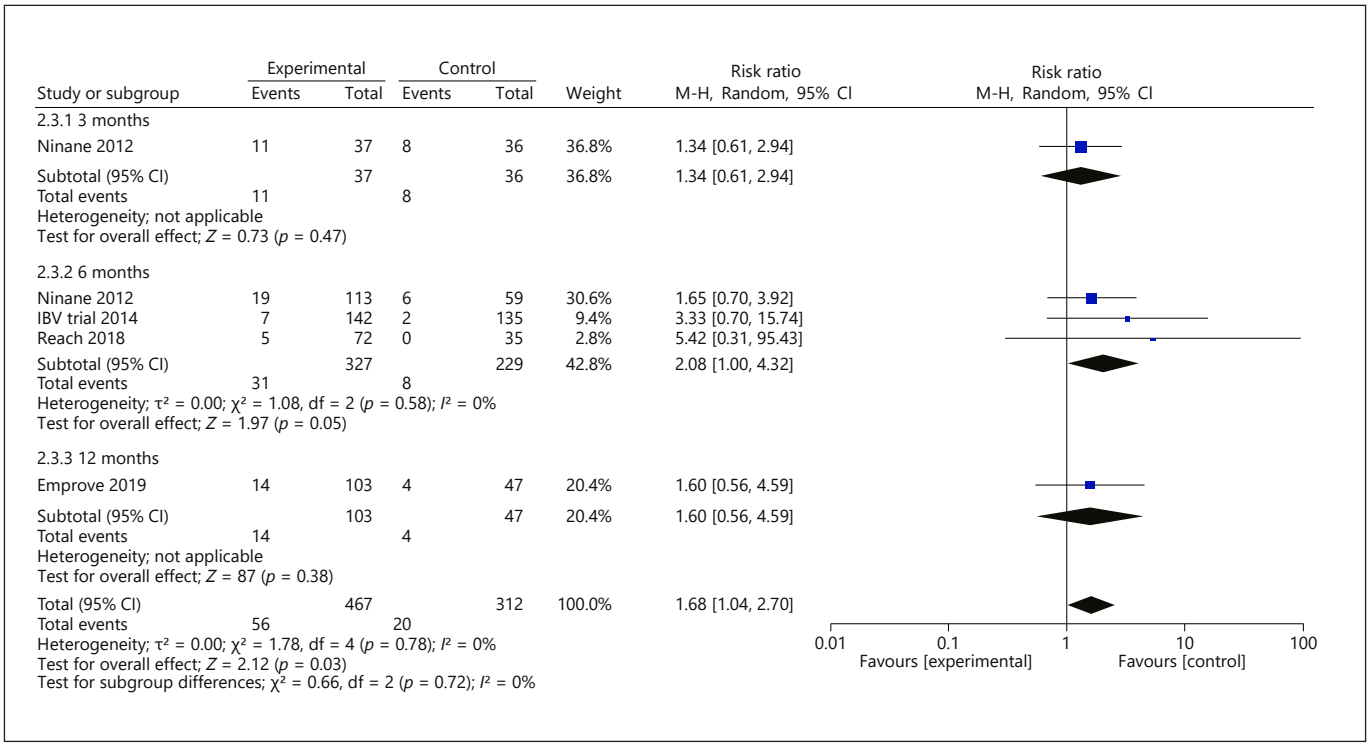

Fig. 8. Forest plot. Risk of COPD exacerbation. SVS, Spiration Valve System.

6 months of follow-up, the MD was 0.06 L (95% CI –0.67 to 0.7, I^2 = 79%). Intergroup heterogeneity I^2 = 61% (p = 0.05).

Safety Analysis

For the SVS® group, the RR of mortality was 2.54 (95% CI 0.81–7.96, I^2 = 0%) (GRADE: LOW); at the first trimester was 2.92 (95% CI 0.12–69.43, I^2 = not applicable). At 6 months, RR of 1.99 (95% CI 0.33–12.24, I^2 = 42%), and at 12 months, RR 3.23 (95% CI 0.17–61,32, I^2 = not applicable). Intergroup heterogeneity I^2 = 0% (p = 0.48; online suppl. Fig. 7).

The risk of pneumothorax was evaluated at 6 months in 3 trials [17, 27, 28], showing an increased risk in all of them, Ninane et al. [26] reports no pneumothorax during the trial period in both groups. The overall RR of developing pneumothorax during was 1.89 (95% CI 0.41–8.68, I^2 = 71%; Fig. 7; GRADE: LOW). Regarding pneumothorax severity, most patients required conventional management with chest tube insertion.

A subgroup analysis based on the preprocedural assessment of CV showed that in patients without CV, the RR was 4.64 (95% CI 0.82–26.16, I^2 = 71%); meanwhile, in patients with CV, the RR was 0.61 (95% CI 0.15–2.47, I^2 = 0%). For this outcome, intergroup heterogeneity was statistically significant (p = 0.02), and I^2 was 71%.

With regard to AECOPD, overall RR was 1.68 (95% CI 1.04–2.70), I^2 = 0% (GRADE: MODERATE). At 3 months, Ninane et al. [26] reported a RR of 1.34 (95% CI 0.61–2.94, I^2 = not applicable). At 6 months, RR 2.08 (95% CI 1.00–4.32, I^2 = 0%), and at 12 months, the RR was 1.60 (95% CI 0.56–4.59, I^2 = not applicable). For this outcome, intergroup heterogeneity was not statistically significant I^2 = 0% (p = 0.78; Fig. 8).

Finally, a summary of funnel plots is showed in online suppl. Fig. 8–12, and summary of evidence table using GRADE approach is shown in Table 3.

Discussion

The results of the current systematic review and meta-analysis showed a clinically significant improvement in lung function and health-related quality of life following SVS®, placement in patients with severe heterogeneous emphysema, and hyperinflation. However, pooled data from randomized control trials reported high heterogeneity, specially associated with the evaluation of CV. Only the

Table 3. Summary of findings and confidence of evidence using GRADE

Outcomes	Anticipated absolute effects (95% CI)		Relative effect (95% CI)	Participants, *n* (studies)	Certainty of the evidence (GRADE)
	risk with medical therapy	risk with endobronchial valve			
Change in FEV_1 (L) predicted (FEV_1) assessed with: % Scale from: –100 to 100 follow-up: range 3 to 12 months	The mean change in FEV_1 (ml) predicted was 0.03 L	The mean change in FEV_1 (%) predicted in the intervention group was 0.03 L higher (–0.07 higher to 0.13 higher)	–	629 (4 RCTs)	⊕⊕⊕◯ Low[a, c]
Change in SGRQ assessed with points (total score) Scale from: –10 to 10 follow-up: range 3 to 12 months	The mean change in St. George Respiratory Questionnaire was 6.56 points	The mean change in St. George Respiratory Questionnaire in the intervention group was 6.56 points lower (16.05 lower to 3.04 higher)	–	629 (4 RCTs)	⊕⊕⊕◯ Low[a, b]
Change in 6MWT assessed with: meters follow up: range 3 to 12 months	The mean change in 6MWT was 4.56 m	The mean change in 6MWT in the intervention group was 4.56 m higher (22 lower to 31 higher)	–	629 (4 RCTs)	⊕⊕◯◯ Very low[a–d]
All-cause mortality (mortality) assessed with: risk follow-up: range 3 months to 12 months	1 per 100	3 per 100 (0 to 3)	RR 2.92 (0.12 to 69.43)	629 (4 RCTs)	⊕◯◯◯ Very low[b, c]
Risk of Pneumothorax (PneumoTx) assessed with: risk follow-up: range 3 to 12 months	0 per 100	3 per 100 (0 to 0)	RR 3.33 (0.31 to 12.12)	629 (4 RCTs)	⊕⊕⊕◯ Very low[b, d]

[a] Risk of bias between studies. [b] Nonprincipal outcome (indirectness). [c] Publication bias. [d] Wide confidence interval (imprecision). SGRQ, Saint George Respiratory Questionnaire; 6MWT, 6-min walking test.

EMPROVE and REACH Trials included patients without CV based on a preprocedural HRCT evidencing >90% integrity of interlobar fissure without segmental vessels crossing between adjacent lobes. Additionally, none of the studies included a physiological assessment of CV with Chartis; thus, the results may provide a false impression about the lower efficacy as well as a lower rate of pneumothorax after the intervention compared to the standard of care. The potential benefits of the SVS® are more pronounced in carefully selected patients as evidenced by a subgroup analysis including just the RCTs without CV [17, 28]. This analysis showed an overall improvement in the predicted FEV_1 of 30 mL; however, subgroup analysis by both risk of bias and CV showed an improvement of 120 mL, similar to the results obtained on our previous meta-analysis evaluating the Zephyr® endobronchial valves [29].

In a previous systematic review and meta-analysis, we evaluated the efficacy and safety of Zephyr® endobronchial valves in the treatment of severe emphysema in patients without CV [29], like our subgroup analysis. We found that BLVR with endobronchial valves provides significant and clinically meaningful short-term improvements in both patients with severe heterogeneous, homogeneous emphysema and hyperinflation without CV, but with an increase in adverse events such as pneumothorax, AECOPD, or pneumonia [2]. In another recently published systematic review and meta-analysis including the vast majority of available techniques to reduce lung volume, they showed that the greatest improvements were in the predicted % FEV_1 (21.77%) and the 6MWT (increase of 49 m) after endobronchial valves placement compared with other procedures such as lung volume reduction surgery, sclerosing agents, and coils. They did not include the SVS® in the analysis, but our results are comparable for the change in the predicted % FEV_1 [30]; however, we did not find an improvement on the 6MWT, possibly due to high inconsistency between the studies, lack of assessment for the presence of CV in half of the trials included in the analysis [26, 27], and inconsistent use of pulmonary rehabilitation in the postoperative period. This contrasts with the Zephyr® valves, which showed a significant improvement in the 6MWT after the procedure where pulmonary rehabilitation was required.

RV was also improved after SVS® in patients without CV, change after therapy, mean change was according to minimally important difference previously published by Hartman et al. [31]. Regarding the quality of life, our analysis showed an improvement on the overall SGRQ, and a

subgroup analysis showed that this change persisted over a period of at least 12 months of follow-up. In contrast, Zephyr® showed a slightly greater improvement in the score (–8.42 points) [29].

According to our analysis, we found an overall increase in the risk of pneumothorax; however, a subgroup analysis showed a significant increase of pneumothorax in patients with confirmed fissure integrity (RR 4.64). The risk of pneumothorax was lower compared with Zephyr® valves, which showed a relative risk for pneumothorax of 6.32 [29].

Additionally, we found an increased risk of AECOPD as expected after these procedures, especially during the first 6 months after the procedure patients reports 2 times higher risk than controls. However, these complications are not associated to an increased risk of mortality.

The current evidence from RCTs included in our review highlighted the importance of patient selection prior to the use of SVS placement for the treatment of advanced emphysema. Studies published before 2015 showed negative results in several outcomes as compared with those published since then which have shown positive findings. This may be explained by study methodology including the preprocedural assessment of the integrity of interlobar fissures to determine the presence of CV. This was evidenced by the positive results obtained by the EMPROVE and REACH trials in the predicted (%) FEV_1 and SGRQ. However, these studies did not show a significant improvement in the 6MWT likely due to the inconsistent use of pulmonary rehabilitation although further studies are needed to confirm this hypothesis. Our findings suggest that, in selected patients with severe heterogeneous emphysema, hyperinflation without CV, SVS® should be a therapeutic alternative with improvement sustained up to 12 months after valve placement. The results of this meta-analysis should not be used as a direct comparison with previous studies and meta-analysis using the Zephyr valve since the patient population and selection criteria have significant differences. Furthermore, studies focused on the direct comparison are needed in order to improve the body of evidence.

Major limitation of this review is (1) the limited number of RCTs included after our literature search and publication bias encountered after our visual inspection, (2) most of the outcomes were rated as LOW or VERY LOW using grade approach, and (3) main results were principally drawn by 2 RCTs due to the lack of assessment of CV in the remaining studies. Additionally, the assessment of CV was based solely on HRCT measurement, and none of the studies used the Chartis System.

Conclusion

In carefully selected patients with severe heterogeneous emphysema, hyperinflation and absence of CV, the SVS is a safe alternative that showed an improvement in pulmonary function, health-related quality of life, and dyspnea score with an acceptable risk profile.

Disclosure Statement

No conflict of interest regarding this manuscript.

Funding Sources

No funding for this manuscript.

Author Contributions

A.M. and G.L.: manuscript conception, data extraction, data analysis, risk of bias assessment, manuscript redaction, and final approval. Guarantor for the entire manuscript. J.P.U.: data extraction, data analysis, risk of bias assessment, manuscript redaction, and final approval. C.P.: literature search, study inclusion, critical analysis, and final approval. E.F. and N.M.P.: manuscript conception, data extraction, data analysis, risk of bias assessment, manuscript redaction and final approval. F.K., A.M., and H.J.M.: data analysis, Risk of Bias assessment, manuscript redaction, critical analysis, and final approval. F.J.F.H. manuscript conception, manuscript redaction, critical analysis, and final approval. S.F.-B.: manuscript conception, data analysis, manuscript redaction, critical analysis, and final approval.

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