CHAPTER

9

Comparing endobronchial valve size to CT based airway lumen diameters

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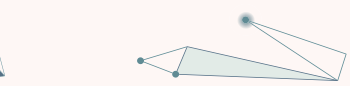

TO THE EDITOR,

Bronchoscopic lung volume reduction using one-way endobronchial valves is an effective treatment option for well-selected patients with advanced emphysema and substantial static hyperinflation [110]. However, over 40% of patients require a revision bronchoscopy following treatment, primarily due to a decline in or complete loss of the initial treatment benefit which, in the majority of cases, is attributed to the formation of granulation tissue causing valve dysfunction and/or dislocation [111]. The primary instigators of this granulation tissue formation after endobronchial valve treatment are currently unknown.

One potential contributory factor might be inaccurate sizing of the valves with respect to the airway lumen, causing mechanical irritation to the airway wall either by excessive pressure or friction [169, 179, 180]. The most often used valve type (Zephyr endobronchial valves (EBV), PulmonX Corporation, USA) is available in two width sizes: 4.0-EBV and 5.5-EBV, and two length sizes: regular and short (LP). The 4.0-EBV is designed for airways with a lumen diameter between 4.0 mm and 7.0 mm, while the 5.5-EBV is intended for airways with a lumen diameter between 5.5 mm and 8.5 mm. The determination of the appropriate valve size currently relies on the width sizing wings and depth markers on the delivery catheter [23]. Nevertheless, this method is not very precise and can be affected by various factors, such as the interpretation and preference of the bronchoscopist, swelling of the airway mucosa during bronchoscopy, and local airway collapsibility. Consequently, this may contribute to the potential use of valves with the incorrect size which in turn might instigate granulation tissue formation. To evaluate this hypothesis, the objective of this study was to evaluate if there is a relation between incorrect valve sizing and the formation of granulation tissue.

We included patients who received one-way endobronchial valves between September 2016 and September 2020 in our hospital and were enrolled in our national registry (BREATHE-NL, ClincalTrials.gov identifier: NCT02815683). The airway lumen diameter was quantified on the pre-treatment CT scan using airway tree segmentation (LungQ, Thirona, Nijmegen, The Netherlands) [181]. This software automatically segments the bronchial tree and measures the inner diameter of each airway. If needed manual adjustments were made by experienced technicians. Patients were excluded if the size or location of at least one valve could not be extracted from the available data or if the software could not determine the airway lumen diameter.

Electronic patient files were evaluated to identify patients who underwent a revision bronchoscopy before 1 July 2023, the indication for this bronchoscopy, and if granulation tissue formation was observed. The CT-derived airway lumen diameter were compared to the size of the implanted valves both per valve and per patient. Patients were, subsequently, categorized into three groups: 1) patients in whom granulation tissue formation was observed, 2) patients who underwent a revision bronchoscopy, but no granulation tissue was observed, and 3) patients who did not undergo a revision bronchoscopy and the number

and percentage of oversized valves were compared. Data are presented as mean ± standard deviation or median [interquartile range], where appropriate. Analysis were performed using R (version 4.3.1).

In the study period, 188 patients received treatment of which 114 patients could be included in our analysis: 75% female, 63 [58, 68] years, forced expiratory volume in 1 second 26±7% predicted, residual volume 250 [219, 283]%predicted, 6-min walk distance of 319±95m, and St. George's respiratory questionnaire total score 57±12 points. Sixty-seven patients (59%) underwent a revision bronchoscopy: loss of initial treatment effect (n=26), no or minimal treatment effect (n=16), haemoptysis (n=10), pneumothorax (n=5), valve expectoration (n=4), recurrent infections/exacerbations (n=3), hypoxemia (n=2), and persistent cough (n=1). Granulation tissue formation was observed in 43 of the patients who underwent a revision bronchoscopy (64%).

A total of 449 one-way valves were implanted of which 235 (52%) were of the 4.0-EBV type and 214 (48%) of the 5.5-EBV type. Figure 1 displays all implanted valves with the corresponding CT-derived airway lumen diameter and the designated airway diameter range for the type of valve. Of the implanted valves, 176 (39%) had the appropriate size according to the CT-derived airway lumen diameter (113 of the 4.0-EBV and 63 of the 5.5-EBV). Most of the implanted valves (n=271, 60%) were oversized (120 of the 4.0-EBV and 151 of the 5.5-EBV), meaning the CT-derived airway lumen diameter was smaller than the lower limit of the airway diameter range for which the selected valve is designed. The median difference between this lower limit and the CT-derived airway lumen was 0.85 mm, ranging from 0.06 to 4.27 mm. Only two endobronchial valves were too small according to the CT-derived airway lumen diameter (both 4.0-EBV).

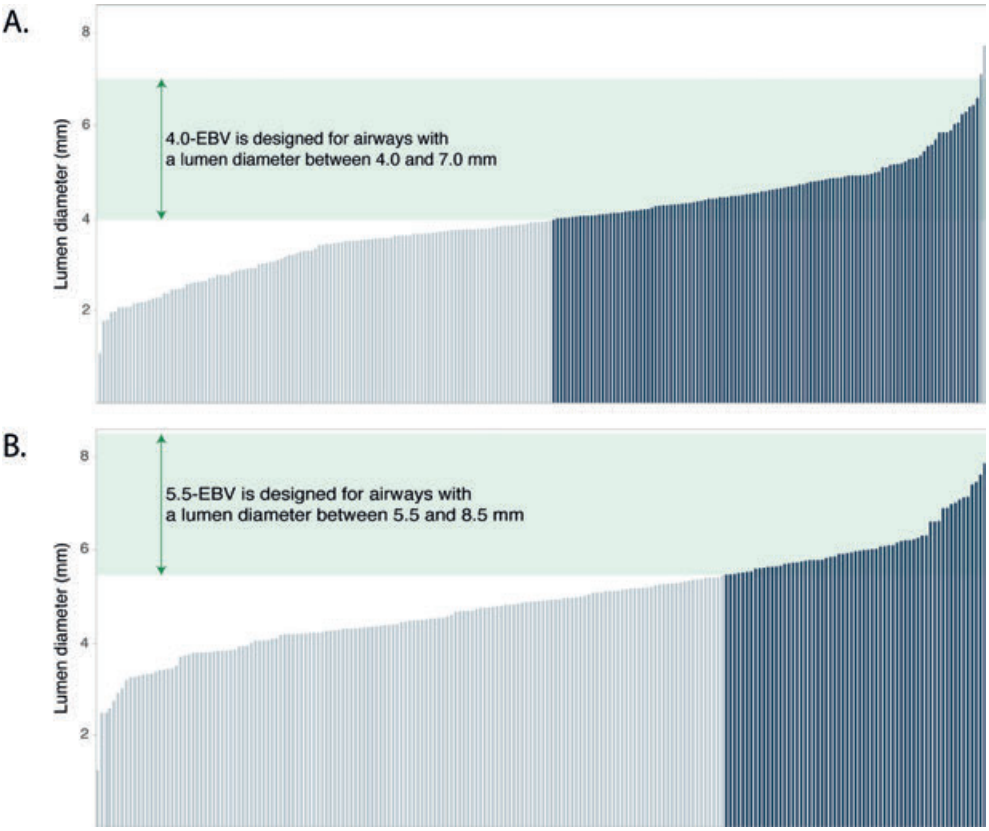

Figure 1. Waterfall plots displaying the CT-derived lumen diameter of the airway in which the endobronchial valve (EBV) was implanted A) 4.0-EBV B) 5.5-EBV. The green area indicates the airway lumen diameter range for which the valves are designed. The dark blue bars indicate the valves that have the appropriate size based on the CT-derived airway lumen diameter.

Between groups, significant differences were observed in the proportion of oversized valves, and the count and proportion of >1mm oversized valves (table 1). Post hoc pairwise comparison using Dunn's test revealed that these outcomes were significantly different between the no granulation and no revision bronchoscopy group. The proportion of oversized valves in general and the count and proportion of valves >1mm oversized was higher in patients in the no revision bronchoscopy group. Taking the no granulation and no revision bronchoscopy groups as one (n = 71) and comparing this to the confirmed granulation tissue group, no significant differences were found.

Table 1. Comparison of endobronchial valve characteristics between groups.

	Granulation (n = 43)	**No granulation (n = 24)**	**No revision bronchoscopy (n = 47)**	***p* value**
Number of EBV	4 [3.5, 5]	4 [3, 5]	4 [3, 4]	.150
Number of 4.0-EBV	2 [1, 3]	2 [0.75, 3.25]	2 [0, 3]	.395
Number of 5.5-EBV	2 [1.5, 2.5]	2 [1, 2.25]	2 [1, 3]	.608
Percentage of 5.5-EBV	5 [33, 75]	53 [23, 85]	50 [25, 100]	.751
Number of regular length EBV	3 [2, 4]	3 [2, 4]	3 [2, 3.5]	.741
Number of short (LP) EBV	1 [0, 2]	0 [0, 1.25]	1 [0, 1]	.502
Percentage regular length EBV	75 [59, 100]	90 [50, 100]	75 [60, 100]	.875
Number of oversized EBV	2 [2, 3]	2 [1, 3]	2 [2, 3]	.388
Percentage of oversized EBV	50 [50, 71]	50 [33, 67]*	75 [50, 92]*	.020
Number of >1mm oversized EBV	1 [0, 2]	0.5 [0, 1]*	1 [0, 2]*	.041
Percentage of >1mm oversized EBV	25 [0, 40]	8 [0, 33]*	33 [0, 63]*	.027

Data are presented as median [interquartile range]. *P* values were calculated using Kruskal Wallis test. The groups were defined as: granulation = patients in whom granulation tissue formation was observed during a revision bronchoscopy, no granulation = patients who underwent a revision bronchoscopy but no granulation tissue formation was observed, and no revision bronchoscopy = patients who did not underwent a revision bronchoscopy. *Dunn's test for multiple comparisons showed significant differences. EBV = endobronchial valve.

Our study showed that many implanted one-way valves are oversized based on the CT-derived airway lumen diameter but that this was not directly associated to granulation tissue formation. This could suggest that slight oversizing of the valve alone is not enough to trigger granulation tissue formation. It is likely that the formation of granulation tissue after one-way valve treatment is triggered by a combination of factors, both patient- and device-related, and that especially an individual's pre-disposition might play a key role [180]. Limitations of our study are the also not very precise nature of CT-derived airway lumen measurements. Furthermore, we did not include the length of the airway in relation to the valve length since this data was not available. To conclude, based on our results inappropriate valve sizing does not seem to be associated with granulation tissue formation.