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Published in:
Respiratory Medicine

DOI:
10.1016/j.rmed.2021.106604

Publication date:
2021

Respiratory Medicine 188 (2021) 106604

Contents lists available at ScienceDirect

Respiratory Medicine

journal homepage: www.elsevier.com/locate/rmed

Short communication

Rate of lung function decline slows in the 3 years after targeted lung denervation in COPD

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ARTICLE INFO

Keywords:
COPD
Bronchoscopic intervention
Lung function decline

Targeted lung denervation (TLD) is a novel bronchoscopic treatment for COPD GOLD-D patients. The TLD treatment disrupts the peribronchial vagal innervation of the airways by radiofrequency energy, and consequently decreases the release of acetylcholine [1]. TLD has shown to have a positive effect on the occurrence of COPD exacerbations after treatment [1]. Recently, it was shown that 3 years after TLD treatment the lung function was stable compared to before treatment [2]. However, it is not known how this relates to the lung function decline before treatment. Therefore, our aim was to investigate the annual decline in FEV_1 before and up to 3 years after TLD.

We included patients who underwent TLD in the AIRFLOW-1 [3] or AIRFLOW-2 [1] trials in 5 study sites with the highest patient enrolment and who completed the 3 year follow up (FU) visit. Local teams such as referral hospitals and patients' primary care teams were contacted to try to obtain as many pre-treatment spirometry results as possible. To be able to calculate a reliable decline in FEV_1, we only included patients for which we were able to obtain at least 4 pre-treatment spirometry results within at least the preceding 2 years prior to their TLD procedure. At baseline and annually for up to 3 years after treatment, patients visited the study-sites and performed spirometry measurements according to the study protocol. The studies were approved by the ethics committees of all participating hospitals and all patients provided informed consent.

In the selected study sites, 61 patients were treated of whom 23 did not complete the 3 year FU and of 20 patients we were not able to obtain reliable pre-treatment spirometry results. Therefore, 18 patients fulfilled our inclusion criteria for this analysis (50% male, mean age 62 ± 6 years, FEV_1: 38 ± 10% of predicted, FVC: 90 ± 16% of predicted). Table 1 shows the FEV_1 and FVC over time. FEV_1 was not statistically significantly different between the different time points (Repeated measure ANOVA: $F = 2.70$, $p = 0.08$), while FVC was only statistically significantly different between the 1 and 2 year FU time point ($F = 4.99$, $p = 0.014$). The mean annual decline in FEV_1 before treatment was −59 ± 61 mL/year and after treatment −20 ± 51 mL/year, which was statistically significantly different ($p = 0.041$, paired sample *t*-test) (see Fig. 1).

Our results show that the FEV_1 did not significantly decrease compared to baseline at 3 years after treatment. It could be that our findings are an overestimation and positively influenced by the fact that we only included patients who visited the study-sites at 3 year FU and had at least 4 pre-treatment FEV_1 results over a 2 year period. However, our results are comparable with the recently published paper of Pison et al. who also showed that the lung function did not change at 3 years

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https://doi.org/10.1016/j.rmed.2021.106604
Received 10 August 2021; Accepted 3 September 2021
Available online 14 September 2021

Table 1
Lung function outcomes at baseline and up to 3 year follow up after TLD treatment.

	Baseline	1 year follow up	2 year follow up	3 year follow up	F	p-value
FEV_1, liter	1.05 ± 0.32	1.09 ± 0.40	1.05 ± 0.38	0.99 ± 0.35	2.70	0.080
FVC, liter	3.09 ± 0.78	3.22 ± 0.74*	2.97 ± 0.75*	3.00 ± 0.76	4.99	**0.014**

Data are presented as mean ± standard deviation. Repeated-measures ANOVA was used to test for differences between the different timepoints.
FEV_1: Mauchly's test indicated that the assumption of sphericity had been violated ($X^2(5) = 12.82$, $p = 0.025$), therefore Greenhouse-Geisser corrected tests are reported ($\epsilon = 0.69$). *FVC:* Mauchly's test indicated that the assumption of sphericity had been violated ($X^2(5) = 13.33$, $p = 0.021$), therefore Greenhouse-Geisser corrected tests are reported ($\epsilon = 0.64$). FVC was only statistically significantly different between the 1 and 2 year follow up time point.

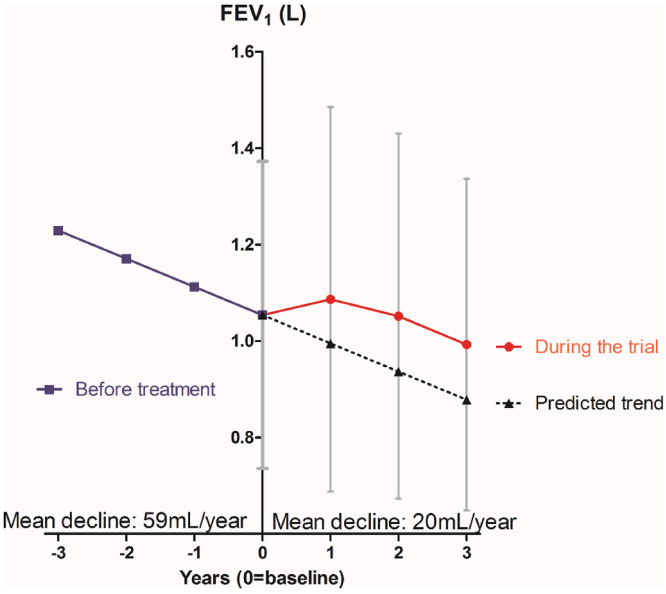

Fig. 1. Decline in Forced Expiratory Volume in 1 s (FEV_1) before and after targeted lung denervation
FEV_1: Forced expiratory volume in 1 s, mL: milliliter.
Baseline and post-treatment FEV_1 are shown as mean (±standard deviation). Redline: change in FEV_1 during trial and after treatment; blue line: mean decline in FEV_1 before treatment, dotted line: predicted trend based on the mean decline before treatment.(For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

after TLD treatment in 74% of the AIRFLOW-1 study patients who completed 3-year study FU [2]. Furthermore, a control group is lacking with information on the actual decline in lung function over time in this specific patient group. Currently a large clinical trial with 5 year follow up is underway (Airflow-3, NCT03639051) [4] which has the potential to confirm our results.

The decline in FEV_1 before treatment in our patients (59 mL/year) was in line with a review that reported an average FEV_1 decline in GOLD stage III patients of 56–59 mL/year [5]. Of course, as COPD progresses and the FEV_1 decreases the decline in FEV_1 will also flatten. However, the FEV_1 decline after treatment in our population (20 mL/year) was 66% lower compared to before treatment, and also lower than the 23 and 34 mL/year found earlier in GOLD stage IV patients [5].

There is previous documentation that frequent COPD exacerbations were associated with a more rapid lung function decline [6]. Therefore, the amelioration of the decline in FEV_1 may be explained by the previously reported decrease in COPD exacerbations after TLD treatment [1].

In contrast, no difference in FEV_1 decline was found in a study that investigated tiotropium versus placebo, while there was a significant reduction in exacerbation frequency in the tiotropium-group compared to the placebo-group [7]. However, this study did not have information on pre-treatment spirometry results. It would have been interesting to have been able to investigate whether the difference between pre-treatment and post-treatment exacerbation rate was associated with the lung function decline following treatment. Unfortunately, the exacerbation rate before treatment was not captured in this study and our sample size is too small for such analysis. Other potential reasons for the amelioration in lung function decline after TLD could be a positive effect of the treatment on bronchial hyperreactivity and/or airway inflammation [8,9]. Recently, a systematic review also showed that pharmacotherapy ameliorated the rate of lung function decline with a 5 mL/yr reduction in favor of active treatment arms [10]. Nonetheless, the evidence of the effect of TLD on both outcomes needs to be investigated further. A further explanation could be due to the patient's having frequent respiratory specialist care as part of the clinical trial for the 3 years following their TLD. However, we perceive this to likely only have a small role, due to the patients selected having already been undergoing lung function monitoring, and thus likely already to be under care of a physician for their COPD.

To conclude, our results show that the lung function remained stable up to 3 years after TLD treatment and that the annual rate of decline in FEV_1 decreased after treatment. The currently executed AIRFLOW-3 trial is currently recruiting and will hopefully confirm our results and explore whether a reduction in COPD exacerbation is the explanation for our findings.

Author's contributions

JEH and DJS designed the analysis, wrote the first draft of the manuscript, and made revisions after feedback from co-authors. All the authors meet the definition of an author as stated by the International Committee of Medical Journal Editors, and all have seen and approved the final manuscript.

Funding statement

The AIRFLOW-1 and AIRFLOW-2 trials were funded by Nuvaira Inc, Minneapolis, MN, USA. The funding source had no involvement in this analysis or in the writing of this manuscript.

Summary statement of competing interests

DJS reports grants, non-financial support and other from Nuvaira, USA, during the conduct of the study. AV reports personal fees from Nuvaira, during the conduct of the study. BD reports personal fees from Nuvaira, during the conduct of the study. FH received personal money for adboard activities and lecture fees from Pulmonx, BTG, Olympus and Uptake. AM, JEH, JT, SWSA, SC and FC have nothing to disclose.

References

[1] D.-J. Slebos, P.L. Shah, F.J. Herth, C. Pison, C. Schumann, R.-H. Hübner, P.I. Bonta, R. Kessler, W. Gesierich, K. Darwiche, B. Lamprecht, T. Perez, D. Skowasch, G. Deslee, A. Marceau, F.C. Sciurba, R. Gosens, J.E. Hartman, K. Srikanthan, M. Duller, A. Valipour, Safety and adverse events after targeted lung denervation for symptomatic moderate to severe COPD (AIRFLOW): a multicenter randomized controlled trial, Am. J. Respir. Crit. Care Med. 200 (2019) 1477–1486, https://doi.org/10.1164/rccm.201903-0624oc.
[2] C. Pison, P. Shah, D.-J. Slebos, V. Ninane, W. Janssens, T. Perez, R. Kessler, J. Garner, J. Hartman, G. Deslee, D. Bruno, A. Mayr, A. Peterson, M. Mayse, A. Valipour, Safety of denervation following targeted lung denervation therapy for COPD: AIRFLOW-1 three-year outcomes, Respir. Res. 22 (1) (2021), https://doi.org/10.1186/s12931-021-01664-5.
[3] A. Valipour, P.L. Shah, C. Pison, V. Ninane, W. Janssens, T. Perez, R. Kessler, G. Deslee, J. Garner, C. Abele, J.E. Hartman, D.J. Slebos, Safety and dose study of

targeted lung denervation in moderate/severe COPD patients, Respiration 98 (2019) 329–339, https://doi.org/10.1159/000500463.
[4] D.J. Slebos, B. Degano, A. Valipour, P.L. Shah, G. Deslée, F.C. Sciurba, Design for a multicenter, randomized, sham-controlled study to evaluate safety and efficacy after treatment with the Nuvaira® lung denervation system in subjects with chronic obstructive pulmonary disease (AIRFLOW-3), BMC Pulm. Med. 20 (2020), https://doi.org/10.1186/s12890-020-1058-5.
[5] C. Tantucci, D. Modina, Lung function decline in COPD, Int. J. COPD. (2012) 95–99, https://doi.org/10.2147/COPD.S27480.
[6] G.C. Donaldson, T.A.R. Seemungal, A. Bhowmik, J.A. Wedzicha, Relationship between exacerbation frequency and lung function decline in chronic obstructive pulmonary disease, Thorax 57 (2002) 847–852, https://doi.org/10.1136/thorax.57.10.847.
[7] D. Tashkin, B. Celli, S. Senn, D. Burkhart, S. Kesten, S. Menjoge, M. Decramer, A 4-year trial of tiotropium in chronic obstructive pulmonary disease, N. Engl. J. Med. 359 (2008) 1543–1554.
[8] B. Rijcken, J.P. Schouten, X. Xu, B. Rosner, S.T. Weiss, Airway hyperresponsiveness to histamine associated with accelerated decline in FEV1, Am. J. Respir. Crit. Care Med. 154 (1995) S246–S249.
[9] L.E. Kistemaker, D.J. Slebos, H. Meurs, H.A. Kerstjens, R. Gosens, Anti-inflammatory effects of targeted lung denervation in patients with COPD, Eur. Respir. J. 46 (2015) 1489–1492, https://doi.org/10.1183/13993003.00413-2015.
[10] B. Celli, A. Julie, N. Cowans, C. Crim, F. Hartley, Benjamin Martinez, A. Morris, H. Quasny, J. Yates, J. Vestbo, P. Calverley, Pharmacotherapy and lung function decline in patients with chronic obstructive pulmonary disease. A Systematic Review, AJRCCM 203 (2021) 689–698.