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Respiratory Medicine 206 (2023) 107059

Contents lists available at ScienceDirect

Respiratory Medicine

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

Short communication

Computed tomographic airway morphology after targeted lung denervation treatment in COPD

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A B S T R A C T

This post-hoc analysis of the AIRFLOW-2 trial investigated the changes in airway CT-parameters after targeted lung denervation (TLD) and whether these changes are associated with treatment response. In the treatment group (n = 32), an improvement in air trapping was significantly associated with an improvement in residual volume (RV). Furthermore, improvements in Pi10 and airway lumen were significantly associated with an improvement in both RV and FEV_1. Our results could suggest that when improving airway characteristics like decreasing airway wall thickness and increasing the airway lumen, this leads to less air trapping and an improvement in clinical outcomes.

The bronchoscopic targeted lung denervation (TLD) treatment is a potential new therapy for COPD patients with frequent exacerbations [1]. So far, positive outcomes of the treatment were reported on the frequency of COPD exacerbations and stabilization of lung function and deterioration of lung function decline in the longer term [2–5]. By use of radiofrequency the TLD treatment aims to disrupt the peribronchial vagal innervation of the airways and consequently decrease the release of acetylcholine. Potentially, the treatment could also improve airway characteristics like airway wall thickness and consequently air trapping in the lung. However, this has not been investigated so far. Therefore, the aim of this post-hoc analysis of the AIRFLOW-2 trial (NCT20258459) [4] was to investigate the changes in airway CT-parameters after the TLD treatment and furthermore whether these changes are associated with treatment response.

The AIRFLOW-2 trial investigated the safety and impact of the TLD treatment by comparing the treatment with sham-controlled placebo [4]. Ethics committees of participating hospitals approved the trial and all 82 patients provided informed consent. As part of the trial, computed tomography (CT) scans were performed at baseline and after 1 year follow-up. Furthermore, patients performed spirometry, body plethysmography and filled out the St. George's respiratory questionnaire (SGRQ) at the same timepoints. For this post-hoc analysis, a quantitative CT-scan analysis (QCT) was performed using LungQ-software (Thirona, The Netherlands). Outcomes of the quantitative analysis were lung volumes, quantification of emphysema and air trapping and airway measurements (Pi10, airway wall thickness and lumen diameter).

In total 66 patients had QCT analysable scans at both baseline and 1 year follow-up and were included (mean age 64 ± 7, FEV_1 0.94 ± 0.28 L, SGRQ total score 55 ± 16; see Table S1, Online supplement). Baseline characteristics did not differ between the patients with QCT analysable or non-analysable scans (Table S2, Online supplement). In the treatment group, 32 patients had analysable inspiratory scans (of which 24 had both in- and expiratory scans) and 34 in the sham-control group (24 with in- and expiratory scans).

No significant differences (p-value<0.05) were found between the treatment and sham-control group for changes in CT-parameters. Furthermore, in the treatment group we only found a significant increase in air trapping due to emphysema, and in the control group only a

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https://doi.org/10.1016/j.rmed.2022.107059
Received 16 August 2022; Received in revised form 11 November 2022; Accepted 22 November 2022
Available online 26 November 2022

Table 1
Changes in CT characteristics between baseline and 12 month follow up.

	Treatment group	n	*Within group p-value*	Sham-control group	n	*Within group p-value*	Between group	
							Difference	**p-value**
Δ Lung volume inspiratory, mL	−77.9 ± 505.6	32	0.39	−87.2 ± 262.6	34	0.061	9.36 ± 98.3	0.92
Δ VERA normal, %	−1.04 ± 3.5	23	0.17	−1.08 ± 6.5	24	0.42	0.04 ± 1.53	0.98
Δ VERA emphysema, %	0.10 ± 5.0	23	0.35*	0.1 ± 2.7	24	0.81*	0.005 ± 1.16	0.55**
Δ VERA air trapping general, %	−0.34 ± 4.4	23	0.72	0.60 ± 7.1	24	0.68	−0.94 1.73	0.59
Δ VERA air trapping emphysema, %	1.28 ± 2.2	23	**0.011**	0.38 ± 2.0	24	0.35	0.90 ± 0.61	0.15
Δ Pi10, mm	0.004 ± 0.19	32	0.91	0.066 ± 0.28	33	0.19	−0.06 ± 0.06	0.31
Δ Airway wall thickness (segmental), mm	0.00 ± 0.20	32	0.25*	0.014 ± 0.11	33	0.43*	−0.01 ± 0.04	0.16**
Δ Airway lumen (segmental), mm	−0.013 ± 0.32	32	0.82	−0.146 ± 0.38	33	**0.033**	0.13 ± 0.09	0.13

Within group differences between baseline and 12 month follow up were tested with a paired *t*-test or * Wilcoxon signed-rank test. Between group differences were tested with an independent sample *t*-test or **Mann-Whitney *U* test. Significant values ($p < 0.05$) are depicted in bold.
N: valid number, Δ: change between baseline and 12 month follow up, mL: milliliter, mm: millimeter, VERA: Ventilation estimation from registered analysis (*an AI registration-based method that identifies regions in the lung that empty more slowly than expected during expiration. Based on inspiration-expiration image registration, this analysis extracts local differences in how lung regions empty during expiration. By estimating which regions empty abnormally slow, quantitative information can be deducted on air that remains trapped after expiration (air trapping)*), Pi10: the square root of wall area at airways with a perimeter of 10 mm.

significant decrease in airway lumen at segmental level (Table 1). However, these changes were small and not clinically relevant. No differences were found between patients who were treated in all 8 quadrants versus 7 or 6 quadrants (8 quadrants is a complete treatment). We also investigated whether there were significant associations between change in residual volume (RV), forced expiratory volume in 1 s (FEV_1) or SGRQ and change in CT-parameters. In the treatment group, an improvement in general air trapping was significantly associated with an improvement in RV. Furthermore, improvements in Pi10 (the square root of wall area at airways with a perimeter of 10 mm) and airway lumen were significantly associated with an improvement in both RV and FEV_1(Table 2).

We performed a cluster analysis in the treatment group using Viscovery-SOMine v7.2 (Viscovery-Software-GmbH, Austria) which is based on the Kohonen algorithm [6,7]. The following variables were entered in the software: age, gender, BMI, change in lung lumen diameter segmental, change in Pi10, change in air trapping (non--emphysema), change in RV, change in FEV_1, change in SGRQ and number of quadrants treated (entered with equal weight). The cluster analysis, using the SOM-Ward algorithm, generated 4 clusters of which one could be defined as a 'responder' cluster. This cluster, including 11 patients, had significant changes in lumen diameter, Pi10, air trapping, RV, FEV_1 and SGRQ compared to the total population (Fig. 1-cluster 3'Yellow').

We investigated whether there were differences at baseline between the 'responder' group and the other patients. The responder group had a larger difference between with and without using pulmonary medication in FEV_1 ($p = 0.029$) and borderline significant difference between with and without using pulmonary medication in CAT score ($p = 0.080$). No other differences between groups were found (Table S3, online supplement).

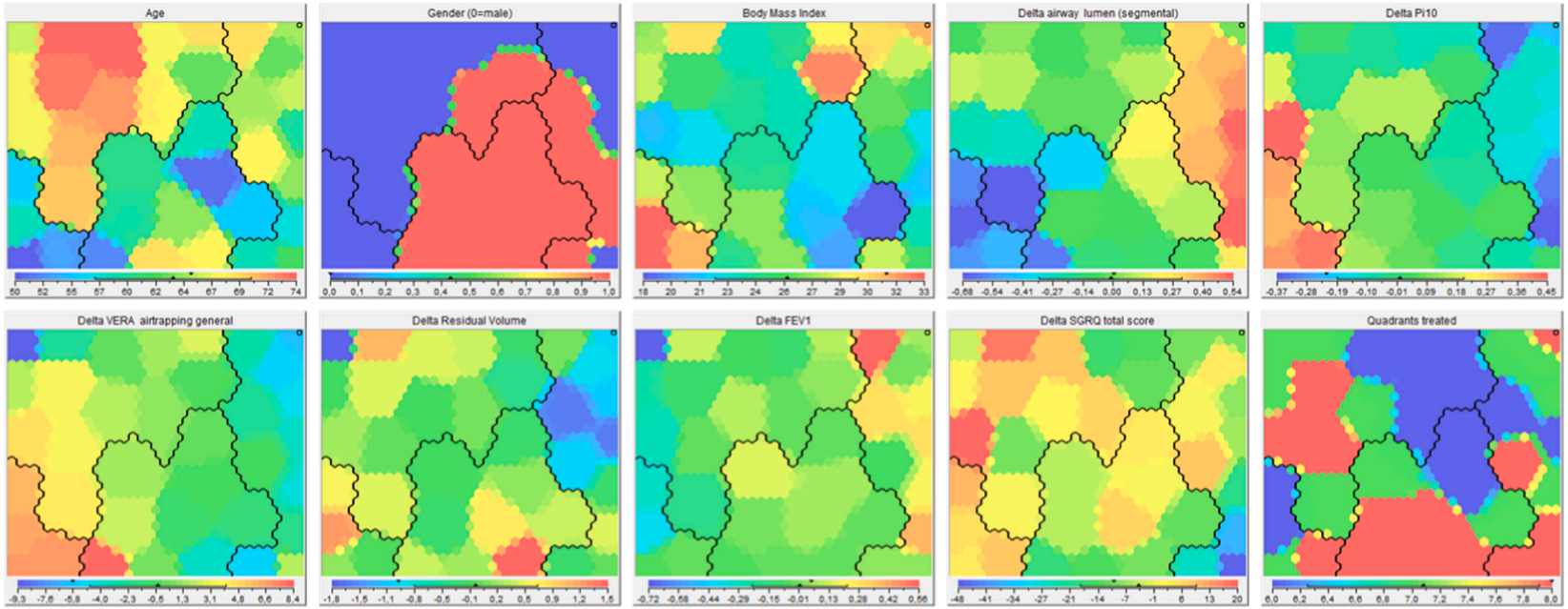
To summarize, we did not find a clinically relevant change in airway parameters measured on CT scan after TLD treatment between the treatment and control group. We did find that an improvement in airway parameters and air trapping was associated with an improvement in lung function and quality of life and a group of responders was identified through a cluster analysis.

Our results could suggest that when improving airway characteristics like decreasing airway wall thickness and increasing the airway lumen, this leads to less air trapping and an improvement in clinical outcomes. Pharmacological treatment with anticholinergic drugs like tiotropium has a comparable mechanism of action to the TLD treatment, as both block the acetylcholine release in airway smooth muscle. Two previous studies have shown that the inhalation of anticholinergic agents led to an increase in luminal area and this increase in luminal area was significantly associated with an improvement in pulmonary function

Table 2
Associations between change in CT characteristics and change in clinical outcomes.

TREATMENT GROUP	Δ RV		Δ FEV_1		Δ SGRQ total score	
	cc	p-value	cc	p-value	cc	p-value
Δ Lung volume inspiratory	−0.299	0.097	0.023	0.90	**−0.364**	**0.040**
Δ VERA normal	−0.210	0.34	0.124	0.57	0.125	0.57
Δ VERA emphysema	−0.228*	0.30	0.154*	0.48	−0.142*	0.52
Δ VERA air trapping general	**0.524**	**0.010**	−0.146	0.51	0.112	0.61
Δ VERA air trapping emphysema	−0.026	0.91	−0.016	0.94	0.247	0.26
Δ Pi10	**0.359***	**0.044**	**−0.482***	**0.005**	0.347*	0.052
Δ Airway wall thickness (segmental)	−0.001*	0.997	−0.081*	0.66	0.245*	0.18
Δ Airway lumen (segmental)	**−0.358***	**0.044**	**0.444***	**0.011**	−0.119*	0.52
CONTROL GROUP	**Δ RV**		**Δ FEV_1**		**Δ SGRQ total score**	
	cc	p-value	cc	p-value	cc	p-value
Δ Lung volume inspiratory	**0.457**	**0.007**	−0.111	0.53	−0.016	0.93
Δ VERA normal	−0.301	0.15	0.349	0.062	0.031	0.89
Δ VERA emphysema	0.237*	0.27	**−0.634***	**0.001**	−0.084*	0.70
Δ VERA air trapping general	0.143	0.51	−0.023	0.91	−0.081	0.71
Δ VERA air trapping emphysema	0.332	0.11	−0.314	0.14	0.039	0.86
Δ Pi10	0.216*	0.23	**−0.359***	**0.040**	−0.124*	0.49
Δ Airway wall thickness (segmental)	0.203*	0.26	−0.072*	0.69	−0.069*	0.70
Δ Airway lumen (segmental)	0.024*	0.90	0.063*	0.73	**0.355***	**0.043**

Data are presented as Pearson correlation coefficient or * Spearman's rho. Significant values ($p < 0.05$) are depicted in bold.
Cc: Correlation coefficient, Δ: change between baseline and 12 month follow up, mL: milliliter, mm: millimeter, VERA: Ventilation estimation from registered analysis (see Table 1 for further explanation), Pi10: the square root of wall area at airways with a perimeter of 10 mm, RV: residual volume, FEV_1: Forced expiratory volume in 1 s, SGRQ: St. George's respiratory questionnaire.



Cluster characteristics

Cluster	N	Age	Gender	BMI	Δlumen diameter-segmental	ΔPI10	ΔAirtrapping general	ΔRV	ΔFEV_1	ΔSGRQ	Quadrants treated
1. Blue	13	69*	0.15*	25.8	-0.09	0.06	0.68	0.029	-0.112*	0.96	6.8
2: Red	9	60*	1.00*	22.8*	-0.10	0.03	0.99	0.316	0.012	-5.37	7.3
3: Yellow	11	63	0.46	25.8	0.31*	-0.19*	-3.20*	-0.644*	0.177*	-13.6*	7.3
4: Green	4	54*	0.00	31.3*	-0.58	0.38*	6.5	0.445	-0.198	7.07	6.8

*values were significantly different ($p<0.05$) from the total population (n=37), performed with a t-test.
Gender 0=male. Δ= change between baseline and 12 month follow up.

Fig. 1. Cluster analysis in the treatment group (n = 37).
Legend: Figure created with Viscovery software (Viscovery-Software-GmbH, Austria). The cluster analysis placed patients on the map based on their multidimensional response profile and created 4 clusters. The more subjects are similar the closer they are on the map and the more they differ the further away they are form each other. The colours represent the size of the attribute. A red colour indicates the highest value or response and the blue colour the lowest value or response.

(both FEV_1 and RV) [8,9]. These findings are in line with our results.

The cluster analysis identified a responder group and we were interested whether we could find baseline predictors that identify these patients. We found that these patients had a significantly larger positive difference in FEV_1 and borderline in CAT between after washout of their inhaler therapy and with the regular use of inhaler therapy. During washout period, patients were not allowed to use LAMA drugs for at least 7 days (all washout requirements are shown in Table S4 in the online supplement). These results could indicate that better responders to LAMA or other pulmonary medication also better respond to TLD treatment.

To conclude, our results suggest that when the TLD treatment leads to an improvement in airway parameters, like airway wall thickness and lumen area, that this is associated with a favourable treatment response. Patients with a greater response to bronchodilators are the best responders.

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-2 trial was funded by Nuvaira Inc, Minneapolis, MN, USA. The funding source had no involvement in this analysis or in the writing of this manuscript.

Declaration of competing interest

DJS is a PI for Nuvaira, USA and reports consultancy fees from Nuvaira paid to the institution. AV reports speaker fees from Nuvaira in the past. PS reports clinical trial expenses reimbursed to the host institutions in the past 36 months. CP reports payments for lectures and to CHUGA to conduct phase 3 trials from Nuvaira (AIRFLOW 2 and 3 trials), GSK, AZ, Boehringer Ingelheim, Novartis and Chiesi. JH and FH have nothing to disclose.

Acknowledgements

We would like to thank the Dutch Foundation for Asthma Prevention (Noorderlijke CARA stichting) for the grant we received which allowed us to purchase the software used for this analysis.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.rmed.2022.107059.

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