Targeting dynamic hyperinflation in moderate to severe asthma – a randomised controlled trial

A. N. van der Meer, K. de Jong, A. Hoekstra-Kuik, E. H. Bel, A. ten Brinke

Please cite this article as: van der Meer AN, de Jong K, Hoekstra-Kuik A, et al. Targeting dynamic hyperinflation in moderate to severe asthma – a randomised controlled trial. ERJ Open Res 2021; in press (https://doi.org/10.1183/23120541.00738-2020).

This manuscript has recently been accepted for publication in the ERJ Open Research. It is published here in its accepted form prior to copyediting and typesetting by our production team. After these production processes are complete and the authors have approved the resulting proofs, the article will move to the latest issue of the ERJOR online.
Targeting dynamic hyperinflation in moderate to severe asthma - a randomized controlled trial

A. N. van der Meer¹, K. de Jong¹, A. Hoekstra-Kuik¹, E. H. Bel², A. ten Brinke³

¹Medical Centre Leeuwarden - Leeuwarden (Netherlands), ²Amsterdam University Medical Centres - Amsterdam (Netherlands)

Corresponding author:
A.N. van der Meer
Henri Dunantweg 2
8934 AD Leeuwarden
The Netherlands
Telephone: +31 58 286 6190
Fax: +31 58 286 6112
E-mail: a.n.van.der.meer@mcl.nl

Take home message: Dynamic hyperinflation: a target for treatment in asthma, which can be reduced by systemic anti-inflammatory treatment.
ABSTRACT

**Background:** Dynamic hyperinflation (DH) is highly prevalent in moderate to severe asthma, which may significantly impede activities of daily life. We hypothesized that DH in asthma is due to inflammation of large and small airways and can be reduced by systemic anti-inflammatory treatment. Therefore, we investigated the effect of systemic glucocorticoids on DH in moderate to severe asthma patients and explored the relationships between inflammatory markers and changes in DH.

**Methods:** In this randomized placebo-controlled trial we included 32 asthma patients on inhaled glucocorticoid therapy showing DH, defined by a ≥10% reduction in inspiratory capacity measured by standardized metronome-paced tachypnea test. Patients received either triamcinolone (80mg) or placebo intramuscularly. Before and 2 weeks after treatment, patients completed respiratory health questionnaires, had blood eosinophils and exhaled nitric oxide levels measured and underwent lung function and DH testing.

**Results:** After adjustment for potential confounders, DH was significantly reduced by 28.1% in the triamcinolone group, and increased by 9.4% in the placebo group (p=0.027). In the triamcinolone-treated patients, the reduction in DH was greater in patients with higher blood eosinophils at baseline (r=-0.592, p=0.020) and tended to be associated with a reduction in blood eosinophils (r=0.412, p=0.127) and exhaled nitric oxide (r=0.442, p=0.099).

**Conclusions:** This exploratory study suggests that dynamic hyperinflation in asthma can be reduced by systemic anti-inflammatory treatment, particularly in patients with elevated blood eosinophils. This supports the hypothesis that dynamic hyperinflation in asthma is due to airway inflammation and should be considered an important target for treatment.

**Keywords:** asthma, hyperinflation, airway, inflammation, treatment
INTRODUCTION

Asthma is a heterogeneous airway disease affecting the large and small airways exhibiting a variety in clinical, functional and inflammatory characteristics [1, 2]. Recently, we have shown that dynamic hyperinflation (DH) is highly prevalent in moderate to severe asthma and is associated with poorer overall health and impaired daily life activity [3]. Because of this impact on important patient related outcomes, DH might be a new target for treatment in moderate to severe asthma.

DH is a well-known feature in COPD, but its importance in asthma has only recently been appreciated [4]. In COPD, DH is mainly due to abnormal lung mechanics caused by decreased elastic recoil, loss of alveolar attachments and collaps of small airways [5]. In asthma, however, the mechanisms underlying DH appear to be different. Studies have shown that asthma patients with systemic eosinophilic inflammation were more likely to show air trapping as compared to their non-eosinophilic controls [6], and in patients with severe asthma the degree of air trapping showed to be significantly related to the level of exhaled alveolar nitric oxide [7]. These and other findings suggest that airway inflammation, particularly of the peripheral airways, may be the major contributor to reduced airway caliber, premature airway closure, air trapping and eventually DH in patients with asthma [8–10]. Conceivably, inflammation of the peripheral airways cannot be adequately controlled with inhaled glucocorticoids and therefore systemic anti-inflammatory therapy may be more suitable.

In the present study we hypothesize that in asthma patients DH is mainly caused by peripheral airway inflammation and can be reduced by systemic anti-inflammatory treatment. To that end, we investigated the effect of a single high dose of intramuscular triamcinolone on the degree of DH as measured by metronome-paced tachypnea (MPT) test in moderate to severe asthma patients on GINA step 4-5 treatment [11]. In addition, we explored the relationship between inflammatory markers (blood eosinophils and exhaled nitric oxide) and the change in DH.
METHODS

Study participants

Patients (age ≥18 years) with moderate to severe asthma, using GINA step 4-5 treatment (inhaled corticosteroids/long-acting beta agonists and/or muscarinic antagonists) [11] for at least 6 months, were consecutively recruited from an outpatient clinic of a large teaching hospital in the Netherlands (Medical Centre Leeuwarden) between June 2016 and January 2018. All patients were non-smokers or ex-smokers with ≤ 10 pack years, had a body mass index (BMI) ≤30, had airway obstruction with a FEV₁/FVC ≤ 80% of predicted, and had stable respiratory disease prior to inclusion. A patient was considered to be atopic when showing allergen-specific IgE level of ≥ 0.35 IU/mL to any of the tested common respiratory allergens. Patients with concurrent respiratory disease, major comorbidities and pregnancy were excluded. The study was approved by the local medical ethics committee and all patients gave their written informed consent. The trial is registered at the Netherlands Trail Register under number NTR5873.

Study design

This study is part of a research program on the role of DH in asthma. For the current randomized, double-blind placebo-controlled intervention study, patients were included only if the degree of DH measured by MPT was >10% and confirmed by a cardio pulmonary exercise test [3, 12–15]. At baseline patient characteristics were collected. Patients were then randomized 1:1 to one of the two treatment arms using a randomisation list with a block size of 6, with stratification for level of baseline blood eosinophils (threshold at 0.4*10⁹ cells/L). Two weeks after the administration of the study medication the effect on the degree of DH was measured by MPT test[16]. Before and 2 weeks after the administration of study medication patients completed a set of respiratory health questionnaires, had blood drawn, and underwent lung function tests.

The administered study medication consisted of one single intramuscular injection of either 2 mL (40 mg/mL) triamcinolone acetonide (Kenacort-A® ‘40’, Bristol-Myers Squibb, Utrecht, The Netherlands) or matched placebo (2 mL NaCl 0.9%). Study medication was prepared and blinded at the hospital pharmacy by an independent member of the pharmacy and
administered to the patients by an independent nurse. Therefore participants, care providers and those assessing outcomes remained blinded till the study ended. During the study patients continued their own medication.

**Study measurements**

*MPT-induced dynamic hyperinflation*

The degree of DH was assessed after bronchodilation with 400 mcg inhaled salbutamol [12, 14]. For detailed explanation of the MPT testing procedure, see the online supplementary material. The degree of DH was calculated as the difference between the post-MPT inspiratory capacity and baseline inspiratory capacity at rest.

*Lung function and questionnaires*

Spirometry and body plethysmography testing were performed after inhalation of 400mcg Salbutamol [17, 18]. This was followed by a $\text{FE}_{\text{NO}}$ measurement wherein subjects performed a slow expiratory vital capacity manoeuvre with a constant expiratory flow of 50mL/s. Levels of $\text{FE}_{\text{NO}}$ were expressed as ppb [19]. Symptoms were assessed using specific and general respiratory health questionnaires (Table 2) [3].

**Statistical analysis**

*Sample size*

A sample size of 16 subjects per group was calculated to have 80% power (with $\alpha=0.05$) to detect a difference in change in DH of 50% from pre to post intervention between the two groups [20].

*Analysis*

First, between-group differences at baseline were investigated by independent t-tests, Mann-Whitney U tests or Fishers Exact tests.

Primary outcome: The primary outcome was the change in postbronchodilator MPT-induced DH from baseline to post-treatment measured as the difference between DH 2 weeks after study medication minus DH at baseline as percentage of DH at baseline. The difference in change in DH between the placebo and triamcinolone group, was assessed by independent t-test, followed by linear regression analyses to adjust for potential confounders, i.e.
variables with baseline differences (p<0.1) between the two groups (FE_{NO}, BMI, FEV\textsubscript{1}/FVC and FRC/TLC).

Secondary outcomes: As secondary outcome we evaluated the treatment-induced effects on symptoms, lung function and inflammatory parameters for which we used paired t-tests or Wilcoxon rank tests (within-group differences) and independent t-tests or Mann-Whitney U tests (between-group differences). Finally, the relationship between (change in) DH and (change in) inflammatory markers was assessed by Spearman rank correlation coefficients. All analyses were performed using SPSS software (Armonk, NY), version 24.

**RESULTS**

**Randomisation**

Seventy-seven patients were assessed for eligibility of whom 32 patients met the inclusion criteria and were enrolled in this study (see flowchart Figure 1). 17 patients were randomized to placebo and 15 to triamcinolone treatment. Due to a technical incorrect measurement one patient randomized to placebo was excluded prior to the analyses.

**Baseline characteristics**

There were no significant differences between the two groups in sex, age or smoking history, but BMI tended to be slightly higher in the triamcinolone treated patients compared to placebo (Table 1). We found no difference in blood eosinophil levels, as expected after stratification, however baseline FE\textsubscript{NO} was significantly lower in the triamcinolone group as compared to the placebo group (median (IQR)= 21 (13-26) ppb vs 35 (22-92) ppb, p=0.036). There were no significant between-group differences in baseline lung function parameters, though we observed a trend towards higher FEV\textsubscript{1}/FVC and lower FRC/TLC values in the triamcinolone versus placebo treated patients.
Definitions of abbreviations: BMI = body mass index, OCS = oral corticosteroids, $\text{FE}_{\text{NO}}$ = exhaled fraction of nitric oxide, Pb = post bronchodilator, $\text{FEV}_1$ = forced expiratory volume in one second, FVC= forced vital capacity, FRC= function residual capacity, TLC = total lung capacity, % pred = percentage of predicted value, ACQ = asthma control questionnaire, SD = standard deviation, IQR = interquartile range

**Effects of triamcinolone treatment**

*Effect on dynamic hyperinflation*

At baseline, there was no significant difference in the degree of postbronchodilator MPT-induced DH between the groups (median (IQR) = 600 mL (370-860 mL) vs 520 mL (330-730 mL) for triamcinolone vs placebo group respectively, p=0.527). Two weeks after administration of the study medication, there was a reduction in the degree of DH of 23.2 % (95% CI -46.6 to 0.25) compared to baseline in the triamcinolone group versus an increase of 4.8 % (95% CI -17.9 to 27.5) in the placebo group, (between group difference p=0.087) (Figure 2). After adjustment for differences in baseline $\text{FE}_{\text{NO}}$, one of the potential confounding factors, it appeared that the effect of triamcinolone treatment on DH was even stronger, with a reduction of 28.1% (95% CI -51.1 to -5.1) in DH in the group treated with triamcinolone and an increase of 9.4% (95% CI -12.9 to 31.6) in the placebo group (between group difference p=0.027) (Figure 3). Adjustment for other potential confounders at baseline (BMI, $\text{FEV}_1$/FVC and FRC/TLC) did not change this result (see Figure 1 in the online supplementary material).

*Effect on inflammatory parameters, lung function and questionnaire scores*

Blood eosinophil levels decreased and neutrophil levels increased after triamcinolone treatment, whereas these levels were unaffected by placebo (between group differences for blood eosinophils p=0.011 and neutrophils p=0.006) (Table 2).

With respect to lung function, treatment with triamcinolone significantly improved $\text{FEV}_1$ and FVC (between group differences p≤0.004), but parameters of static hyperinflation and air trapping did not change in both treatment arms (between group differences for FRC/TLC and RV/TLC p≥0.175).
All questionnaires showed an improvement in total scores after triamcinolone as well as placebo treatment (Table 2). There was a significantly larger improvement in the Clinical COPD Questionnaire score in the triamcinolone group as compared to placebo (p=0.030).

**Dynamic hyperinflation and inflammation**

At baseline, in the group as a whole, a higher degree of DH was related to higher baseline levels of blood eosinophils (r=0.446, p=0.012) and to higher FE\textsubscript{NO} (r=0.278, p=0.131). In addition, higher levels of blood eosinophils at baseline were associated with greater reductions in DH following treatment with triamcinolone (r=-0.592, p=0.020). In the triamcinolone-treated patients, the reduction in DH tended to be related to the reduction in blood eosinophils (r=0.412, p=0.127) and reduction in FE\textsubscript{NO} (r=0.442, p=0.099). Furthermore, in these patients the improvement in FE\textsubscript{V1} was shown to be associated with the reduction in DH (r=-0.603, p=0.017).

**DISCUSSION**

This study shows that the degree of dynamic hyperinflation in patients with moderate to severe asthma was significantly reduced by systemic anti-inflammatory treatment such as intramuscular glucocorticoids. This was independent of the degree of airway obstruction. Moreover, the decrease in dynamic hyperinflation was greater in patients with higher baseline blood eosinophils and tended to be related to a decrease in blood eosinophils and FE\textsubscript{NO}. These results support the hypothesis that dynamic hyperinflation is largely caused by airway inflammation and is therefore an important treatable trait, especially in patients with eosinophilic asthma.

Our study expands previous findings on the importance of DH in asthma and provides evidence that this disabling symptom is most prevalent in patients with elevated blood eosinophils, and, unlike in patients with COPD, can be ameliorated by systemic anti-inflammatory treatment. We selected patients with DH and observed a higher age in this group as compared to regular asthma populations. In addition, the majority of our included patients with DH were male patients with an adult onset non-atopic asthma and elevated blood eosinophils, suggesting that DH might be more prominent in the so-called “late onset eosinophilic asthma” phenotype. A few previous studies have investigated therapeutic interventions on DH in asthma. One unblinded study in 10 patients with moderate to severe
allergic asthma, showed that the degree of DH decreased with omalizumab treatment [21] whereas another study showed improvements in hyperinflation indices in a subgroup of severe asthma patients treated with benralizumab [22]. More recently, the degree of MPT-induced DH was found to be related to serum periostin levels in mild to severe asthma patients [23], again suggesting a role for inflammation in the development of DH in asthma. While the mechanisms underlying the development of DH in asthma merit further research, these and our results suggest that systemic anti-inflammatory treatments, including monoclonal antibodies, may have the potential to reduce impairments in daily life activities and improve exercise capacity by decreasing DH, at least in a subset of asthma patients.

The strengths of our study are the prospective randomised controlled design of the study, the selection of patients with exercise-test-confirmed DH, the inclusion of inflammatory parameters and the use of a solid systemic anti-inflammatory intervention. In this way, it was possible to demonstrate a clear relationship between DH and airway inflammation, as well as to provide a potential treatment option.

Our study has limitations as well. First, there appeared to be a suboptimal balance between the groups in asthma severity (lower FE\textsubscript{NO} and better lung function in the triamcinolone-treated group). This might create a risk of underestimation of the effects of triamcinolone and therefore we adjusted for these variables. Second, the current study was not primarily designed to investigate the effect on symptoms or quality of life. Two weeks after trial medication we found a small improvement in favor of triamcinolone treatment for one symptom score (CCQ), whereas the other symptom questionnaires improved equally in both treatment arms. A longer follow-up period will be necessary to evaluate whether reduction of DH indeed leads to an improvement in asthma symptoms and quality of life on the long term.

The mitigating effect of triamcinolone on DH supports a causal role for airway inflammation in the development of this phenomenon in asthma. Since the patients in our study were already treated with inhaled anti-inflammatory drugs, our findings suggest residual inflammation in the bronchial tree, which may occur in the central airways but certainly also in the peripheral airways, especially because the peripheral airways are known to be sub-optimally reached by inhaled medications [24, 25]. Residual inflammation in the peripheral airways causing DH may also explain why many patients with severe eosinophilic asthma require systemic glucocorticoids or steroid-sparing biologics in addition to inhaled
medication to control their disease. This is supported by studies showing that the anti-IL-5 monoclonal antibody mepolizumab improves indices of peripheral airway function [26] and computational modelling studies that confirm the impact of anti-inflammatory type 2 biologics on small airway caliber [27].

Our findings have clinical implications. The current study provides evidence that DH in asthma, a major contributing factor to asthma symptoms and impairment of daily life activities, can be treated with systemic anti-inflammatory treatments in addition to inhaled glucocorticoids and beta-2 agonists. This differs from COPD, where DH is usually difficult to treat because it mostly results from irreversible narrowing and collapsibility of the small airways. Now that we know that in patients with type-2 asthma DH can be reversed with systemic anti-inflammatory treatments, the long-term benefits on asthma control and quality of life have to be confirmed to further support that DH deserves a prominent place on the list of "treatable traits" [28].

In conclusion, this study shows that dynamic hyperinflation, a common and underestimated disability in patients with asthma, improves after treatment with systemic glucocorticoids. This suggests that in asthma, unlike in COPD, dynamic hyperinflation is at least partly caused by steroid-sensitive inflammatory processes in the airways. The improvement in dynamic hyperinflation was found to be most pronounced in patients with elevated blood eosinophils, suggesting that these patients will benefit most from systemic anti-inflammatory therapies like the novel anti-eosinophil biologics.

ACKNOWLEDGEMENTS

None

CONTRIBUTORS

A-N. van der Meer MD: contributed to development of the study design, subject recruitment, collecting study data, performed statistical analysis and wrote the manuscript.
Dr. K. de Jong: contributed in statistical analysis, interpretations and manuscript preparation.
A. Hoekstra-Kuik: performed the pulmonary function tests and MPT measurement. Prof. dr. E.H. Bel MD and dr. A. ten Brinke, MD: contributed to the development of the study design, statistical analysis and manuscript preparation.
COMPETING INTERESTS

Non-declared.

FUNDING

This study was supported by unrestricted grants from Medical Centre Leeuwarden research fund, Stichting Longgeneeskunde Fryslân, GlaxoSmithKline and Teva.
REFERENCES


Definitions of abbreviations: DH = dynamic hyperinflation; reduction in inspiratory capacity (IC) measured as the difference between IC at rest and IC following metronome-paced tachypnea, MPT = metronome paced tachypnea, CPET = cardio pulmonary exercise test.
Figure 2.
Effect of treatment with intramuscular placebo or triamcinolone on dynamic hyperinflation.

Definitions of abbreviations: DH = dynamic hyperinflation; reduction in inspiratory capacity (IC) measured as the difference between IC at rest and IC following metronome-paced tachypnea, L = liter.
Data are presented as median (interquartile ranges).
Figure 3.
Change from baseline in dynamic hyperinflation after triamcinolone or placebo.

The change measured as the difference between DH post-treatment minus DH at baseline as a percentage of DH at baseline and adjusted for differences in baseline exhaled fraction of nitric oxide (FE\textsubscript{NO}).
Data are presented as the adjusted mean and 95% confidence interval estimated from the regression model conditional on the mean value for the level of FE\textsubscript{NO} at baseline.
Table 1. Baseline characteristics

<table>
<thead>
<tr>
<th></th>
<th>Placebo (N= 16)</th>
<th>Triamcinolone (N= 15)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex, male, n (%)</td>
<td>9 (56)</td>
<td>9 (60)</td>
<td>1.000</td>
</tr>
<tr>
<td>Age, yrs†</td>
<td>65 (55-74)</td>
<td>63 (51-67)</td>
<td>0.452</td>
</tr>
<tr>
<td>Adult-onset (&gt;18 yrs) asthma, n (%)</td>
<td>11 (69)</td>
<td>8 (53)</td>
<td>0.473</td>
</tr>
<tr>
<td>Atopic, n (%)</td>
<td>7 (44)</td>
<td>5 (33)</td>
<td>0.716</td>
</tr>
<tr>
<td>BMI, kg/m²*</td>
<td>25.2 ± 2.3</td>
<td>26.8 ± 2.8</td>
<td>0.080</td>
</tr>
<tr>
<td>Pack years†</td>
<td>0 (0-1.5)</td>
<td>0 (0-5)</td>
<td>0.830</td>
</tr>
<tr>
<td>Fluticasone equivalent, mg†</td>
<td>500 (500-1000)</td>
<td>500 (500-1000)</td>
<td>0.578</td>
</tr>
<tr>
<td>OCS dependent, n (%)</td>
<td>3 (19)</td>
<td>2 (13)</td>
<td>1.000</td>
</tr>
<tr>
<td>Exacerbations, preceding yr†</td>
<td>2 (0-3)</td>
<td>2 (1-5)</td>
<td>0.493</td>
</tr>
<tr>
<td>Blood eosinophils, x 10⁹/L†</td>
<td>0.2 (0.1-0.4)</td>
<td>0.2 (0.1-0.3)</td>
<td>0.951</td>
</tr>
<tr>
<td>FE₂NO, ppb†</td>
<td>35 (22-92)</td>
<td>21 (13-26)</td>
<td>0.036</td>
</tr>
<tr>
<td>Pb FEV₁, % pred†</td>
<td>66 ± 16</td>
<td>77 ± 17</td>
<td>0.235</td>
</tr>
<tr>
<td>Pb FEV₁/FVC, % pred†</td>
<td>65 ± 12</td>
<td>72 ± 8</td>
<td>0.060</td>
</tr>
<tr>
<td>FRC/TLC, % pred†</td>
<td>119 ± 14</td>
<td>111 ± 15</td>
<td>0.097</td>
</tr>
<tr>
<td>ACQ, total score†</td>
<td>1.5 (1.0-2.4)</td>
<td>1.3 (0.8-2.8)</td>
<td>0.874</td>
</tr>
</tbody>
</table>

* mean ± SD; † median (IQR)
Table 2. Differences between triamcinolone and placebo treatment

<table>
<thead>
<tr>
<th></th>
<th>Triamcinolone (N=15)</th>
<th>Baseline</th>
<th>Post treatment</th>
<th>Within-group p-value *</th>
<th>Placebo (N=16)</th>
<th>Baseline</th>
<th>Post treatment</th>
<th>Within-group p-value *</th>
<th>Between-group p-value **</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood eosinophils, x 10^9/L</td>
<td>0.2 (0.1-0.3)</td>
<td>0.1 (0.1-0.2)</td>
<td>0.010</td>
<td>0.2 (0.1-0.4)</td>
<td>0.2 (0.1-0.5)</td>
<td>0.392</td>
<td>0.011</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood neutrophils, x 10^9/L</td>
<td>4.9 (3.4-6.1)</td>
<td>6.6 (5.7-8.6)</td>
<td>0.001</td>
<td>4.8 (4.1-6.1)</td>
<td>5.1 (4.5-6.3)</td>
<td>0.133</td>
<td>0.006</td>
<td></td>
<td></td>
</tr>
<tr>
<td>FE\textsubscript{NO}, ppb</td>
<td>21 (13-26)</td>
<td>15 (12-22)</td>
<td>0.090</td>
<td>35 (22-92)</td>
<td>34 (20-70)</td>
<td>0.088</td>
<td>0.470</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood eosinophils, x 10^9/L</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pb FE\textsubscript{V1}, % pred</td>
<td>77 ± 17</td>
<td>87 ± 20</td>
<td>0.001</td>
<td>66 ± 16</td>
<td>69 ± 19</td>
<td>0.333</td>
<td>0.004</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pb FVC, % pred</td>
<td>109 ± 19</td>
<td>116 ± 17</td>
<td>&lt;0.001</td>
<td>106 ± 19</td>
<td>103 ± 17</td>
<td>0.215</td>
<td>&lt;0.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pb FE\textsubscript{V1}/FVC, % pred</td>
<td>72 ± 8</td>
<td>77 ± 11</td>
<td>0.010</td>
<td>65 ± 12</td>
<td>69 ± 14</td>
<td>0.017</td>
<td>0.654</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TLC, % pred</td>
<td>114 ± 17</td>
<td>115 ± 17</td>
<td>0.100</td>
<td>110 ± 13</td>
<td>112 ± 16</td>
<td>0.199</td>
<td>0.379</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RV, % pred</td>
<td>141 ± 41</td>
<td>132 ± 37</td>
<td>0.268</td>
<td>148 ± 32</td>
<td>152 ± 41</td>
<td>0.552</td>
<td>0.078</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RV/TLC, %pred</td>
<td>113 ± 23</td>
<td>105 ± 22</td>
<td>0.233</td>
<td>124 ± 20</td>
<td>125 ± 22</td>
<td>0.796</td>
<td>0.175</td>
<td></td>
<td></td>
</tr>
<tr>
<td>FRC, % pred</td>
<td>138 ± 30</td>
<td>138 ± 28</td>
<td>0.932</td>
<td>142 ± 23</td>
<td>147 ± 32</td>
<td>0.242</td>
<td>0.423</td>
<td></td>
<td></td>
</tr>
<tr>
<td>FRC/TLC, % pred</td>
<td>111 ± 15</td>
<td>114 ± 14</td>
<td>0.730</td>
<td>119 ± 14</td>
<td>120 ± 16</td>
<td>0.609</td>
<td>0.800</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACQ, total score</td>
<td>1.3 (0.8-2.8)</td>
<td>1.2 (0.5-1.8)</td>
<td>0.172</td>
<td>1.5 (1.0-2.4)</td>
<td>1.2 (0.5-2.2)</td>
<td>0.033</td>
<td>0.654</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CCQ, total score</td>
<td>1.5 (0.8-2.0)</td>
<td>0.8 (0.6-1.6)</td>
<td>0.018</td>
<td>2.0 (0.7-2.3)</td>
<td>1.6 (0.6-2.5)</td>
<td>0.876</td>
<td>0.030</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SGRQ, total score</td>
<td>28.9 (10.8-47.4)</td>
<td>19.9 (8.1-51.2)</td>
<td>0.078</td>
<td>38.3 (20.1-53.5)</td>
<td>31.8 (18.9-53.5)</td>
<td>0.918</td>
<td>0.281</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LCADL, total score</td>
<td>16 (15-30)</td>
<td>16 (14-24)</td>
<td>0.207</td>
<td>22 (15-35)</td>
<td>17 (15-28)</td>
<td>0.074</td>
<td>0.654</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SOBDA, total score</td>
<td>1.2 (1.0-3.1)</td>
<td>1.3 (1.0-1.8)</td>
<td>0.657</td>
<td>1.3 (1.1-2.1)</td>
<td>1.3 (1.0-1.6)</td>
<td>0.311</td>
<td>0.626</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* mean ± SD; † median (IQR)

Definitions of abbreviations: FE\textsubscript{NO} = exhaled fraction of nitric oxide, Pb = post bronchodilator, FE\textsubscript{V1} = forced expiratory volume in one second, FVC = forced vital capacity, TLC = total lung capacity, RV = residual volume, FRC= function residual capacity, % pred = percentage of predicted
value, ACQ = Asthma Control Questionnaire, total score, CCQ = Clinical COPD Questionnaire, total score, SGRQ = St. George Respiratory Questionnaire, total score, LCADL = London Chest Activity of Daily Living questionnaire, total score, SOBDA = Shortness of Breath with Daily Activities questionnaire, total score, SD = standard deviation, IQR = interquartile range, * within-group p-value = difference between baseline and post treatment values of symptoms, lung function and inflammatory parameters measured separately for the triamcinolone group and placebo group, ** between-group p-value = difference between the triamcinolone and placebo induced changes in symptoms, lung function and inflammatory parameters.
Supplementary material

Targeting dynamic hyperinflation in moderate to severe asthma - a randomized controlled trial

A. N. van der Meer¹, K. de Jong¹, A. Hoekstra-Kuik¹, E.H. Bel², A. ten Brinke¹

¹Medical Centre Leeuwarden - Leeuwarden (Netherlands), ²Amsterdam University Medical Centres - Amsterdam (Netherlands)

Procedure to assess dynamic hyperinflation

The presence and degree of dynamic hyperinflation (DH) persisting after maximal bronchodilatation was assessed by metronome-paced tachypnea test (1). The test was performed after inhalation of 400 mcg Salbutamol. Performing metronome-paced tachypnea test, subjects were seated, breathing through a mouthpiece connected to the spirometer (MasterScreen-PFT, Jaeger) and were instructed how to perform the inspiratory capacity (IC) manoeuvres. At the start of this test the baseline IC was measured as the mean of three acceptable IC manoeuvres while the patient was at rest. Subjects were then asked to breathe at a metronome-paced frequency of twice the resting breathing rate for 20 seconds and immediately afterwards an IC manoeuvre was performed (2). The procedure was repeated after subjects had returned to their resting breathing level. Subjects were encouraged to maintain a stable tidal volume. DH was calculated as the difference between the IC measured during increased pacing and the IC at rest. A decrease in IC of ≥ 10% was considered as DH (2, 3).

REFERENCES

2. Lahaije AJMC, Willems LM, van Hees HWH, Dekhuijzen PNR, van Helvoort HAC, Heijdra YF. Diagnostic accuracy of metronome-paced tachypnea to detect dynamic


**LEGENDS**

![Diagram](image)

**Figure 1.**

Change from baseline in dynamic hyperinflation after triamcinolone or placebo.

The change measured as the difference between DH post-treatment minus DH at baseline as a percentage of DH at baseline and adjusted for differences in baseline FE\textsubscript{NO}, BMI, FEV\textsubscript{1}/FVC and FRC/TLC.

Data are presented as the adjusted means and 95% confidence intervals estimated from the regression model and conditional on the potential confounders being centered around their mean values.