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ORIGINAL RESEARCH

Pulmonary Rehabilitation Reduces Airway Inflammation in Asthma Patients with High Fe_{NO} Levels

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Purpose: Pulmonary rehabilitation (PR) is a well-established non-pharmacological intervention for patients with asthma. While PR improves asthma control and exercise capacity, its impact on airway inflammation remains unclear. Fractional exhaled nitric oxide (Fe_{NO}) is a biomarker of type 2 airway inflammation, yet its response to PR has not been extensively studied. Therefore, aim of this study was to investigate diurnal variations in Fe_{NO} and how Fe_{NO} develops during PR in asthmatic patients with different levels of Fe_{NO}.

Patients and Methods: This prospective, single-center study investigated Fe_{NO} changes in asthma patients undergoing a comprehensive three-week inpatient PR program. The study observation period covered 15 consecutive days of FeNO measurements. Patients were divided into three subgroups according to their initial Fe_{NO} measurement: low (<25 ppb), intermediate (25–50 ppb) and high (>50 ppb). Fe_{NO} was measured three times a day, along with assessments of asthma control, lung function, blood eosinophils and exercise capacity before and after PR.

Results: Sixty-two patients were included. Only patients in the high Fe_{NO} group (n=22) showed a significant 40% decrease in Fe_{NO} from pre to post PR (93±29 ppb to 56±27 ppb, p<0.001), independent of medication changes. Fe_{NO} levels of patients with low (17±8 ppb to 16±10 ppb) and intermediate levels (39±12 ppb to 30±10 ppb) remained unchanged. Asthma control and exercise capacity improved across all three subgroups, with the greatest gains observed in patients with initially high Fe_{NO}. No significant Fe_{NO} changes occurred in the low and intermediate Fe_{NO} groups.

Conclusion: PR significantly reduced Fe_{NO} levels in asthma patients with high baseline Fe_{NO}, suggesting an anti-inflammatory effect beyond pharmacological treatment. These findings highlight the role of PR as a complementary strategy in asthma management, particularly for patients with persistent airway inflammation despite optimized medication. Further randomized trials are needed to confirm these results and explore long-term effects.

Keywords: fractional exhaled nitric oxide, type 2 inflammation, biomarker, eosinophil, asthma control, diurnal variation

Introduction

Asthma is a chronic inflammatory airway disease characterized by variable airflow obstruction and bronchial hyperresponsiveness.[1] While inhaled corticosteroids (ICS) remain the cornerstone of anti-inflammatory therapy, a subset of patients continues to exhibit elevated markers of airway inflammation, highlighting the need for complementary non-pharmacological interventions.[2]

Pulmonary rehabilitation (PR) is a multidisciplinary intervention comprising structured exercise training, respiratory physiotherapy, patient education, behavioural modifications and others. Many studies have shown that PR improves exercise capacity, quality of life and asthma control.[3] However, there is only limited evidence on the role

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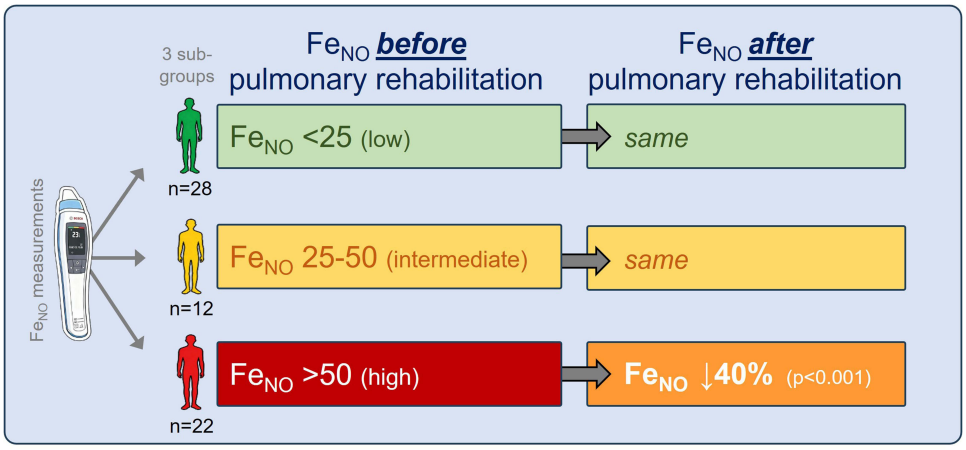
Graphical Abstract



of PR on airway inflammation.[4] One possible mechanism by which PR influences airway inflammation may be related to the beneficial effects of exercise training in improving immune cell function, leading to reduced release of inflammatory mediators.[5,6] In addition, PR may reduce airway inflammation through improved airway clearance, reduced oxidative stress, and modulation of inflammatory signaling pathways independent of medication.[7] To date, there is a lack of biomarkers to monitor the inflammatory response to PR, particularly in asthmatics with high levels of airway inflammation.[4]

Type 2 inflammation, which characterizes the Th2-high asthma endotype, plays a major role in driving airway eosinophilia and response to targeted therapies.[8] Fractional exhaled nitric oxide (Fe_{NO}) is a well-established non-invasive biomarker of type 2 airway inflammation.[9] Elevated Fe_{NO} levels are associated with eosinophilic airway inflammation and corticosteroid responsiveness, making it a valuable tool for assessing disease activity and guiding pharmacological treatment decisions.[10] Furthermore, a recent meta-analysis has shown that Fe_{NO}-guided asthma treatment probably results in fewer exacerbations.[11] Therefore, monitoring FeNO could be a valuable tool for managing asthma, both pharmacologically and non-pharmacologically.

The role of Fe_{NO} in monitoring non-pharmacological interventions like PR remains unclear. Since PR may reduce airway inflammation through mechanisms independent of corticosteroids, Fe_{NO} could help assess these effects. Therefore, the aim of this study was to evaluate Fe_{NO} changes during a PR program in patients with asthma and different levels of airway inflammation.

Materials and Methods

Study Design

This prospective, single-center study investigated changes in Fe_{NO} during PR in patients with asthma between May 2021 and December 2024. This observational study was approved by the responsible ethics committee of the Philipps-University Marburg, Germany and registered at clinicaltrials.gov (NCT06751550). Participants gave informed consent to participate in the study prior to enrolment and our study complies with the Declaration of Helsinki.

Study Participants

Patients with a confirmed diagnosis of bronchial asthma (all severity levels) were eligible for inclusion. Exclusion criteria comprised a primary diagnosis of COPD without an asthmatic component, lack of consent for study participation, and inability to independently use the Fe_{NO} measurement device. All asthma patients admitted to inpatient pulmonary

rehabilitation at the Schön Klinik Berchtesgadener Land in Schönau, Germany, were screened for study eligibility and invited to participate.

Pulmonary Rehabilitation Program

All participants underwent a standardized, multidisciplinary, three-week inpatient PR program, as this is the standard setting in the German healthcare system. The comprehensive program included optimization of drug therapy (in accordance with current *Global Strategy for Asthma Management and Prevention* (GINA) guidelines, if necessary), respiratory physiotherapy, patient education on disease management, nutritional counseling, relaxation skills and exercise training (more details are described elsewhere).[12] The exercise regimen consisted of a combination of endurance and resistance training (45 minutes total per session) on five to six days per week, complemented by group activities such as nordic walking and aqua jogging.

Fe_{NO} Measurements

Fe_{NO} levels were measured using the Vivatmo *me* device (Healthcare Solutions GmbH, Waiblingen, Germany). Each patient was provided with a personal device for self-administered measurements throughout the PR period. Daily Fe_{NO} assessments were performed at fixed time points (9 am, 1 pm, and 5 pm) using a new mouthpiece with every measurement, taking into account potential confounding factors such as recent medication use, dietary habits, and PR activities. Measurements were conducted according to manufacturer guidelines, requiring patients to exhale into the device with a steady flow and pressure for ten seconds (eFigure 1). All valid measurements were digitally saved on the devices.

The minimal clinically important difference (MCID) for Fe_{NO} in asthma is suggested to be a 10 ppb reduction for baseline levels between 25–50 ppb and a 20% reduction for levels above 50 ppb.[9]

Outcomes

Comprehensive clinical assessments were performed at baseline and at the end of the PR program, including asthma control test (ACT), body plethysmography, blood sample parameters (eosinophils, total immune globulin, and C-reactive protein (CRP)) and exercise tests (six-minute walk test,[13] incremental cycle test).

Sample Size and Statistical Analyses

A power analysis based on an average change of 4.5±10.4 ppb in the Fe_{NO} levels, observed during a training program in asthma patients, resulted in a sample size of 62 patients for an α=5% and β=5%.[14]

Baseline data are presented as mean ± SD for continuous variables and as frequencies and percentages for nominal data. Baseline differences between the three subgroups were assessed as follows. A chi-squared test was used to compare categorical variables. One-way ANOVA was used for metric data (if normally distributed). In the case of variance inhomogeneity (Levene's test), Welch's ANOVA was used. Missing data were handled by complete-case analysis, and no imputation methods were applied. Parameters before and after PR were analyzed by paired *t*-test if normally distributed. If normality was violated, a Wilcoxon signed-rank test was used. For variables measured at three or more time points, a repeated measures ANOVA or a mixed-effects model was used as appropriate. For significant results, post-hoc pairwise comparisons were performed with Bonferroni correction. A two-tailed significance level of $\alpha = 0.05$ was used for all statistical tests.

Results

Sixty-two out of 73 eligible patients were included in the study. Eleven patients were excluded due to the following reasons: 9 refused to participate, and 2 were not able to perform the Fe_{NO} manoeuvre.

Baseline Characteristics

Patients were divided into subgroups according to their initial Fe_{NO} measurement on PR admission: low Fe_{NO} <25ppb (n=28), intermediate Fe_{NO} of 25–50ppb (n=12), or high Fe_{NO} >50ppb (n=22) (Table 1). General characteristics, asthma

Table 1 Baseline Characteristics

	All	Subgroup with Baseline Fe_{N0} <25ppb	Subgroup with Baseline Fe_{N0} 25–50ppb	Subgroup with Baseline Fe_{N0} >50ppb	p (Between Subgroups)
General Characteristics					
n	62	28	12	22	
Age, years	55.5 ± 12.5	51.6 ± 12.0	60.3 ± 6.9	57.7 ± 14.4	0.078
Gender, female (%)	37 (60.0%)	11 (39.2%)	6 (50.0%)	8 (36.3%)	0.730
BMI, kg/m^2	27.2 ± 5.4	27.1 ± 5.1	27.0 ± 4.6	27.4 ± 6.2	0.977
Smoking status: never/ex-smoker/current/unknown, n	50/1/8/3	23/1/2/2	9/0/3/0	18/0/3/1	0.290
Co-morbidities, n	1.9 ± 1.6	1.5 ± 1.5	2.6 ± 1.7	2.0 ± 1.7	0.120
Asthma Phenotypes *(according to GINA classification)*					
Allergic asthma	26 (41.9%)	14 (50.0%)	4 (33.3%)	8 (36.4%)	0.50
Non-allergic asthma	23 (37.1%)	8 (28.6%)	6 (50.0%)	9 (40.9%)	0.39
Late-onset asthma	12 (19.4%)	5 (17.9%)	2 (16.7%)	5 (22.7%)	0.88
Obesity-associated asthma	1 (1.6%)	1 (3.6%)	0 (0%)	0 (0%)	0.54
Asthma Control					
Asthma control test, score	15.9 ± 4.8	16.7 ± 4.5	15.8 ± 5.2	15.1 ± 4.9	0.561
Controlled asthma according to ACT, n (%)	15 (24.2%)	6 (21.4%)	3 (25.0%)	6 (27.2%)	0.780
Airway Inflammation					
Fe_{NO}, ppb	47 ± 13	17 ± 8	39 ± 12	96 ± 64	<0.001
Drug Therapy					
ICS, yes	60 (96.8%)	27 (96.4%)	12 (100%)	21 (95.4%)	0.77
OCS, yes	4 (6.5%)	1 (3.6%)	1 (8.3%)	2 (9.0%)	0.70
LABA, yes	54 (87,1%	25 (89.3%)	11 (91.7%)	18 (81.8%)	0.64
LAMA, yes	32 (51.6%)	13 (52.0%)	5 (41.7%)	14 (63.6%)	0.36
Biological therapy, yes	13 (21.0%)	2 (7.1%)	1 (8.3%)	10 (45.4%)	0.002
Lung Function					
FEV_1, %predicted	76.7 ± 23.1	83.3 ± 20.7	67.1 ± 20.7	73.7 ± 25.6	0.094
FEV_1/FVC, %	73.2 ±17.3	75.1 ± 17.8	65.5 ± 17.3	74.9 ± 16.2	0.230
PEF, %predicted	83.5 ± 27.2	90.8 ± 26.9	83.3 ± 29.8	74.3 ± 24.4	0.100
MEF_{25}, %predicted	117.9 ± 72.2	126.5 ± 74.1	83.1 ± 49.4	125.8 ± 77.1	0.180
Rtot, %predicted	148.1 ± 115.3	100.3 ± 47.9	123.4 ± 62.7	123.8 ± 75.3	0.340
Blood Sample Parameters					
Eosinophils, absolute	261 ± 215	216 ± 120	287 ± 156	304 ± 311	0.320
Eosinophils, %	3.9 ± 3.3	3.3 ± 1.9	4.2 ± 2.0	4.6 ± 4.9	0.410
IgE, IU/mL	354 ± 484	322 ± 575	383 ± 342	385 ± 418	0.140
CRP	6.1 ± 10.7	5.6 ± 10.2	3.7 ± 5.6	7.9 ± 13.2	0.530
Exercise Performance					
Peak work rate, W	113 ± 53	116 ±50	89 ±24	121 ± 64	0.350
6-minute walk distance, m	496 ± 106	524 ± 74	499 ± 83	461 ± 139	0.170

Abbreviations: ACT, Asthma Control Test; BMI, Body Mass Index; FEV_1, Forced Expiratory Volume in 1 Second; FVC, Forced vital capacity; GINA, Global Strategy for Asthma Management and Prevention; ICS, Inhaled Corticosteroids; IgE, immune globulin E; LABA, Long-Acting Beta-Agonist; LAMA, Long-Acting Muscarinic Antagonist; MEF_{25}, Maximal Expiratory Flow at 25% of Forced Vital Capacity; OCS, Oral Corticosteroids; PEF, Peak Expiratory Flow; Rtot, Total Airway Resistance.

phenotypes (according to GINA classification),[1] asthma control, lung function, blood parameters, and exercise capacity did not differ significantly between the three subgroups. The only significant difference in our sample was that patients with high Fe_{NO} levels were significantly more likely to be treated with biological therapy. Baseline Fe_{NO} levels correlated significantly with baseline blood eosinophils (eFigure 2).

Diurnal Variation of Fe_{NO} Levels

To assess the influence of diurnal variation of Fe_{NO} levels, all available data from morning, noon, and evening measurements were pooled within the three subgroups (Figure 1). Fe_{NO} levels were fairly stable throughout the day. Only the group with high Fe_{NO} baseline levels showed significantly lower Fe_{NO} levels in the evening (61±22ppb) compared to noon (68±24ppb; p=0.001).This difference of 10.3% is below the suggested MCID of a 20% change.[9]

Changes in Fe_{NO} Over the Course of PR

Although the study included patients over the course of a three-week PR programme, we were only able to collect Fe_{NO} data for 15 consecutive days. This was due to a time lag in the onboarding of the study participants. Patients with low and intermediate Fe_{NO} levels had stable Fe_{NO} levels over 15 days. However, patients with high baseline Fe_{NO} levels had a significant (p<0.001) 40% decrease in mean Fe_{NO} levels by from 93±29 ppb (day 1) to 56±27 ppb (day 15), with the greatest decrease occurring within the first few days of Fe_{NO} measurement (Figure 2). This difference was not

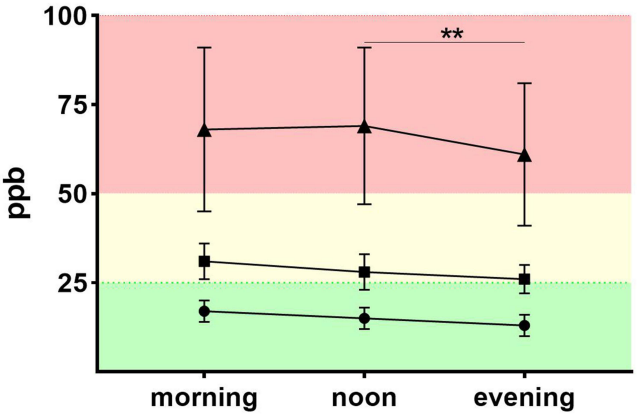


Figure 1 Diurnal variation of Fe_{NO} levels between morning (9am), noon (12pm), and evening (5pm) in patients with asthma. Each point represents mean values (±95% CI) collected over 15 consecutive days during an in-patient pulmonary rehabilitation programme in patients with high (>50ppb, ▲), intermediate (25–50ppb, ■) or low baseline Fe_{NO} levels (<25ppb, ●), **p=0.001.

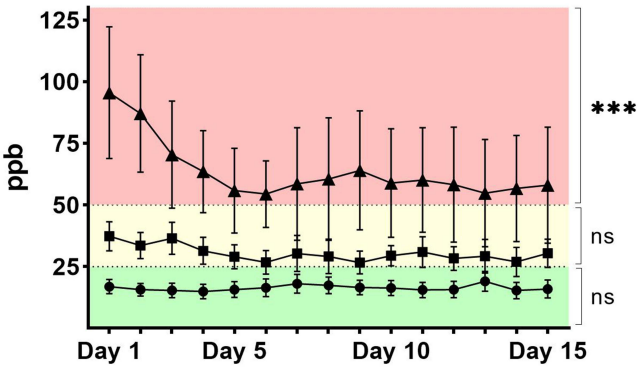


Figure 2 Changes in Fe_{NO} levels over 15 consecutive days during an in-patient pulmonary rehabilitation programme. Fe_{NO} values are the average of all measurements per day (average of morning, noon, and evening data) in patients with high (>50ppb, ▲), intermediate (25–50ppb, ■) or low baseline Fe_{NO} levels (<25ppb, ●). Data are presented as mean values (±95% CI). ***p<0.001, ns = non-significant.

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Table 2 Changes from Admission to Discharge of a 3-week Inpatient Pulmonary Rehabilitation Program in Asthmatic Patients

	Subgroup with Baseline Fe_{N0} <25ppb (n=28)			Subgroup with Baseline Fe_{N0} 25–50ppb (n=12)			Subgroup with Baseline Fe_{N0} >50ppb (n=22)		
	Pre	**Post**	**Delta**	**Pre**	**Post**	**Delta**	**Pre**	**Post**	**Delta**
Airway Inflammation									
Fe_{NO}[a], ppb	17±8	16±10	−1±7	39±12	30±10	**−9±6****	93±29	56±27	**−37±18*****
Asthma Control									
ACT, score	16.7±4.8	18.4±4.0	**1.8±3.1***	15.2±5.5	18.0±4.3	**2.8±3.8***	15.2±5.1	17.9±4.3	**2.7±3.4****
Uncontrolled asthma according to ACT, n (%)	17 (61%)	13 (46%)	−4 (−15%)	9 (75%)	6 (50%)	−3 (−25%)	15 (68%)	10 (45%)	−5 (−23%)
Lung Function									
FEV_1, %predicted	81.4±20.8	83.9±21.7	2.5±8.2	65.5±21.0	69.3±19.2	**3.8±4.9***	73.1±26.0	76.8±24.1	3.7±16.1
FEV_1/FVC, %	77.3±11.5	76.7±10.7	−1.4±6.8	64.7±18.6	65.3±15.9	0.6±5.6	74.6±16.5	76.7±13.6	2.1±7.0
PEF, %predicted	87.8±25.7	92.6±27.2	4.8±13.9	83.2±32.0	86.1±31.6	2.9±10.7	73.6±24.8	84.3±24.7	**10.7±20.2***
MEF_{25}, %predicted	124.3±72.1	125.8±56.9	1.5±42.8	84.0±49.7	85.9±39.8	1.9±16.5	123.0±77.8	132.4±85.1	9.4±42.5
Rtot, %predicted	105.4±48.1	115.3±64.7	9.9±33.8	125.8±68.1	122.3±54.4	−3.4±37.7	126.2±76.3	111.0±56.5	−15.3±90.6
Blood Sample Parameters									
Eosinophils, absolute	229±160	287±156	58±197	246±144	256±174	10±221	304±311	186±167	**−118±250***
Eosinophils, %	3.1±1.4	3.5±2.0	0.4±1.3	4.2±2.1	3.5±2.2	−0.7±1.3	4.6±4.9	3.1±2.7	**−1.5±3.9***
IgE	241±352	207±282	−34±131	457±377	314±239	−143±304	386±432	377±442	−9±42
Exercise Performance									
6MWD, m	521±69	540±79	19±63	487±89	525±66	**38±36***	455±141	515±136	**60±59*****

Notes: [a]Data represent pooled mean values (±SD) of morning, noon and evening Fe_{NO} measurements from 15 consecutive days during pulmonary rehabilitation. *p<0.05, **p<0.01, ***p<0.001 for intra-group pre-post comparisons; bold fonts highlight significant values.

Abbreviations: 6MWD, 6-minute walk distance; ACT, Asthma Control Test; Fe_{NO}, fractional exhaled nitric oxide; FEV_1, Forced Expiratory Volume in 1 Second; FVC, Forced vital capacity; IgE, Immunoglobulin E; MEF_{25}, Maximal Expiratory Flow at 25% of Forced Vital Capacity; PEF, Peak Expiratory Flow; Rtot, Total Airway Resistance.

significantly different whether patients received a change in medication (n=9) or remained on their existing drug therapy (n=13; eFigure 3). Over the course of the PR, 4% of the patients in the low Fe_{NO} group, 42% in the intermediate Fe_{NO} group, and 82% in the high Fe_{NO} group reduced their Fe_{NO} levels more than the MCID.

Changes in Other outcomes Over the Course of PR

Some patients with uncontrolled asthma converted to controlled asthma (according to ACT scores) after PR in all three subgroups (with rates of 24% in the low baseline FeNO group, 33% in the intermediate group and 33% in the high baseline FeNO group, see Table 2). Most lung function parameters did not change significantly with PR. However, exercise capacity as assessed by 6MWD improved most in the group with the highest Fe_{NO} level. In addition to the significant decrease in Fe_{NO} in the group with the highest Fe_{NO} levels, there was also a significant decrease in blood eosinophils.

Discussion

Our study demonstrated that PR significantly reduced Fe_{NO} in asthma patients with high baseline Fe_{NO} levels (>50 ppb), suggesting that PR may have anti-inflammatory effects in eosinophilic asthma. Previous studies on exercise-based PR programs have consistently shown significant and clinically relevant improvements in outcomes such as asthma control, quality of life, and exercise capacity.[3] However, no significant effect of exercise training on markers of airway inflammation has been observed so far, as highlighted by a meta-analysis reporting a standardized mean difference of −0.03 (95% CI: −0.41 to 0.36, p=0.89).[3]

While most studies have not demonstrated Fe_{NO} reduction following PR, some exceptions exist. For instance, Mendes et al reported a significant reduction in Fe_{NO} from 34 ppb to 27 ppb ($p<0.05$) after 12 weeks of aerobic endurance training (2x/week for 30 minutes).[15] However, this change did not exceed the MCID of 10 ppb,[9] limiting its clinical relevance. Similarly, in our study, no meaningful Fe_{NO} reduction was observed in patients with intermediate Fe_{NO} levels. Notably, most previous exercise training studies have focused on asthma patients with intermediate Fe_{NO} levels (19–45 ppb),[3–5,16] potentially underestimating the anti-inflammatory effects of PR in patients with more pronounced eosinophilic inflammation.

To the best of our knowledge, our study is the first to investigate PR-induced Fe_{NO} changes specifically in asthma patients with high baseline Fe_{NO} levels (>50 ppb) and to differentiate the response to PR according to Fe_{NO} baseline levels. This distinction is crucial, as patients with more pronounced eosinophilic inflammation may respond differently to non-pharmacological interventions than those with lower baseline Fe_{NO} levels. Patients with low or intermediate Fe_{NO} levels probably had less airway inflammation initially, which limited the potential for further reduction. It is also notable that patients in the low and intermediate Fe_{NO} level group did not increase their Fe_{NO} levels during the observational PR phase, which is an important safety finding.

Surprisingly, the significant and clinically relevant Fe_{NO} reduction in patients with high baseline Fe_{NO} levels occurred regardless of whether they received medication adjustments (including biological therapy) or remained on their existing treatment (eFigure 3). This suggests that PR itself exerts an anti-inflammatory effect, independent of pharmacological interventions. Several mechanisms may explain this finding. First, patients were already participating in PR for several days before formal study enrolment, meaning that "day 1" in our graphs does not represent the very first day of PR. Acute reductions in Fe_{NO} after a single exercise session have been demonstrated in physically inactive adults with asthma, with even 30 minutes of treadmill walking leading to measurable decreases in airway inflammation.[17] Thus, PR components such as exercise training and respiratory physiotherapy may have initiated anti-inflammatory effects by downregulating pro-inflammatory cytokines[5] such as IL-4, IL-5, and IL-13, and increasing anti-inflammatory mediators, such as IL-10.[7] These changes likely reduced eosinophilic airway inflammation and inhibit remodeling processes. Exercise training may also modulate immune cell function by promoting regulatory T cell activity and decreasing oxidative stress.[18] Additionally, enhancing mucociliary clearance has been shown to improve asthma control and reduce airway inflammation.[19] Learning an optimized inhalation technique may have further contributed to these improvements.[20] Beyond these physiological effects, the inpatient PR setting itself may have played a role. Lower stress levels associated with the structured PR program[21] and the environmental conditions of the PR center - located in a rural area of the German mountains with low allergen and air pollution levels[22] - may have further contributed to Fe_{NO} reductions.

A recent Cochrane review[4] concluded that PR is likely to be associated with clinically meaningful improvements in functional exercise capacity and quality of life in adults with asthma (moderate certainty of evidence). Our study reinforces this by demonstrating improvements in asthma control and exercise capacity. Importantly, our findings suggest that Fe_{NO} may serve as a biomarker to identify patients with high Fe_{NO} levels that most likely benefit from PR in terms of reducing airway inflammation – particularly in cases where medication alone does not achieve sufficient reductions in Fe_{NO} levels.

Clinical Implications

Although PR led to a significant and clinically relevant reduction in Fe_{NO} levels in patients with elevated baseline Fe_{NO}, this reduction did not correlate significantly with improvements in asthma control (as measured by ACT scores). The relationship between Fe_{NO} and asthma control remains controversial, with some studies reporting significant inverse correlations ($r = -0.648$),[23] while others have found no significant association.[24]

These discrepancies may be attributed to differences in study design, patient characteristics, asthma phenotypes, medication use, and methodological approaches. However, despite these inconsistencies, the GINA guidelines recognize Fe_{NO} reduction as an important therapeutic target in asthma management.[1] A prospective study of 304 patients with persistent asthma found that elevated Fe_{NO} levels predicted future uncontrolled asthma at one year.[25] Additionally, Fe_{NO}-guided management strategies have been shown to reduce exacerbation rates in adults with asthma.[26,27] Our study was

among the first to use a home-use device for FeNO self-monitoring. Our study demonstrates the practicality and usability of patient self-monitoring, showing that it can easily be integrated into the daily routines of physicians and patients alike.

While pharmacological therapy remains central to controlling airway inflammation, our findings support the integration of non-pharmacological interventions such as PR to further reduce airway inflammation – particularly in patients with persistently elevated Fe_{NO} levels despite standard treatment. Moreover, digital health interventions have recently demonstrated significant improvements in asthma control without pharmacotherapy.[28] This highlights the potential of combining digital and rehabilitative strategies to optimize both symptom management and underlying inflammation.

Diurnal Variability

The potential influence of diurnal variability on Fe_{NO} measurements is frequently discussed in the literature. While some studies report significantly higher morning Fe_{NO} levels compared to evening levels,[29,30] others find no clinically relevant diurnal variation.[31] In our study, we did also not observe meaningful diurnal fluctuations in Fe_{NO} (Figure 1). To account for potential variability, we used daily mean values from morning, noon, and evening measurements to analyze Fe_{NO} changes throughout the PR program. A sub-analysis confirmed that Fe_{NO} trends remained consistent regardless of whether only morning, noon, or evening values were used (see eFigures 4–6).

However, we observed that 7 out of 22 patients (31%) with high baseline Fe_{NO} levels exhibited diurnal variations exceeding the MCID of 20% (eFigure 7). While this suggests that individual variability exists, the overall Fe_{NO} reduction from baseline to PR discharge was 40%, making it unlikely that natural diurnal fluctuations alone accounted for this change. Instead, this substantial decrease is more plausibly attributed to the PR intervention itself, although the absence of a control group remains a limitation in fully confirming this causal relationship.

Limitations

This study has several limitations. The short duration of Fe_{NO} monitoring (15 days) limits conclusions regarding the long-term effects of PR on airway inflammation. While our findings demonstrate a significant Fe_{NO} reduction, it remains unclear whether these effects persist beyond the PR period. Additionally, the absence of a control group makes it difficult to definitively attribute the observed Fe_{NO} decrease to PR rather than natural variability over time. However, the persistence of significant Fe_{NO} reductions in patients who did not alter their medication suggests that PR played a role in this improvement. Another limitation is the potential influence of medication changes, which cannot be fully excluded as a confounding factor. Nevertheless, our subgroup analysis indicates that the reduction in Fe_{NO} was independent of treatment modifications. Further, Fe_{NO} is a marker of Type 2 inflammation and does not capture other inflammatory pathways, such as neutrophilic inflammation, which may also play a role in asthma pathophysiology.

Future research should explore the long-term sustainability of PR-induced Fe_{NO} reductions and assess additional biomarkers, including sputum eosinophils, IL-5, and markers of systemic inflammation, to clarify the underlying mechanisms. Randomized controlled trials are also needed to establish a causal relationship between PR and airway inflammation reduction.

Conclusion

Our findings align with previous studies demonstrating the beneficial effects of PR on asthma control and exercise performance while providing novel insights into its impact on airway inflammation. To our knowledge, this is the first study to show that PR exerts an anti-inflammatory effect in asthma patients with high baseline Fe_{NO} levels, independent of medication changes. These results highlight the potential role of PR as a complementary strategy in asthma management, particularly for patients with persistent airway inflammation despite optimized pharmacological therapy.

Declaration of Generative AI and AI-Assisted Technologies in the Writing Process

During the preparation of this work the authors used DeepL Write in order to improve language and readability. After using this tool, the authors reviewed and edited the content as needed and takes full responsibility for the content of the publication.

Abbreviations

ACT, Asthma Control Test; ATS, American Thoracic Society; BMI, Body Mass Index; CG, Control Group; COPD, Chronic Obstructive Pulmonary Disease; CRP, C-reactive Protein; FENO, Fractional Exhaled Nitric Oxide; FEV_1, Forced Expiratory Volume in 1 Second; FVC, Forced vital capacity; GINA, Global Initiative for Asthma; ICS, Inhaled Corticosteroids; IgE, immune globulin E; LABA, Long-Acting Beta-Agonist; LAMA, Long-Acting Muscarinic Antagonist; MCID, Minimal Clinically Important Difference; MEF_{25}, Maximal Expiratory Flow at 25% of Forced Vital Capacity; OCS, Oral Corticosteroids; PEF, Peak Expiratory Flow; PR, Pulmonary Rehabilitation; Rtot, Total Airway Resistance; SD, Standard Deviation.

Data Sharing Statement

De-identified individual participant data and a data dictionary defining each field in the set can be made available to others on approval of a written request to the corresponding author. The request will be evaluated by a committee formed by a subset of co-authors to determine the research value. A data-sharing agreement will be needed.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors report no conflicts of interest in this work.

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