

Additional file 1:

Table S1. Baseline characteristics

	Total	Smokers	Ex-smokers
	n=43	n=22	n=21
Male, n (%)	18 (42)	9 (41)	9 (43)
Age, years	44.98 (12.64)	39.55 (12.01)	50.67 (10.84)
Presence of atopy, n (%)	27 (64)	14 (67)	13 (62)
Number of packyears*	16.80 (11.00; 24.00)	20.00 (11.75; 29.44)	14.00 (10.00; 23.00)
BMI, kg m ⁻²	26.54 (5.62)	25.83 (6.14)	27.27 (5.08)
Waist/hip ratio	0.91 (0.10)	0.88 (0.08)	0.93 (0.12)
Blood neutrophils (10 ⁹ /L)	4.50 (1.73)	5.25 (1.71)	3.62 (1.32)
Blood eosinophils (10 ⁹ /L)	0.29 (0.20)	0.35 (0.22)	0.24 (0.18)
Total IgE, kIU/L*	107 (23.97; 483.75)	138 (20.60; 548.50)	89 (22.95; 321.0)
PD ₂₀ adenosine, mg	2.69 (3.41)	2.38 (3.25)	3.07 (3.66)
FEV ₁ , % predicted	83 (14.47)	83 (11.98)	84 (16.99)
FEV ₁ /FVC, %	67 (10.24)	70 (10.84)	65 (9.31)
FEF ₂₅₋₇₅ , % predicted	49 (22.56)	52 (22.22)	45 (22.87)
TLC, % predicted	105 (12.22)	103 (13.58)	107 (10.53)
RV, % predicted	115 (27.57)	113 (28.81)	117 (26.81)
RV/TLC, % predicted	102 (18.96)	103 (17.79)	102 (20.55)
R ₅ -R ₂₀ , kPa sL ⁻¹	0.13 (0.13)	0.11 (0.13)	0.15 (0.13)
X ₅ , kPa sL ^{-1*}	-0.14 (-0.21; -0.09)	-0.14 (-0.21; -0.08)	-0.13 (-0.22; -0.10)
F _{res} , Hz	17.19 (6.35)	16.49 (6.68)	17.91 (6.05)
AX, Hz kPa sL ^{-1*}	0.75 (0.24; 1.82)	0.59 (0.19; 1.51)	0.94(0.29; 2.07)
LCI at 2.5%	10.21 (2.06)	9.74 (1.72)	10.63 (2.28)
S _{cond} , L ⁻¹	0.04 (0.03)	0.04 (0.02)	0.04 (0.03)
S _{acin} , L ⁻¹	0.17 (0.09)	0.14 (0.06)	0.20 (0.11)

Data are presented as mean with standard deviation (SD), unless stated otherwise:

*median with interquartile ranges (IQR); BMI: body mass index; PD₂₀ adenosine:

provocative dose of small particle adenosine causing a 20% drop in FEV₁; FEV₁:

forced expiratory volume in 1 second; FVC: forced vital capacity; FEF₂₅₋₇₅: forced

expiratory flow between 25% and 75% of FVC; TLC: total lung capacity; RV: residual

volume; RV/TLC: the ratio of residual volume to total lung capacity; R₅-R₂₀: the

difference between resistance at 5 Hz and 20 Hz; X₅: the reactance at 5 Hz; F_{res}:

resonance frequency; AX: the area under curve of reactance; LCI: lung clearance

index; S_{cond}: ventilation heterogeneity of the conductive airways; and S_{acin}: ventilation

heterogeneity of the acinar structures.

Table S2. Baseline values of measurements of small airways dysfunction

	Patients with SAD n=18	Patients without SAD n=25
FEF ₂₅₋₇₅ , % predicted	37 (13.20)	58 (23.95)
RV/TLC, % predicted	113 (20.89)	95 (13.71)
R ₅ -R ₂₀ , kPa sL ⁻¹	0.22 (0.14)	0.06 (0.07)
S _{acin} , L ⁻¹ *	0.20 (0.07)	0.14 (0.09)
S _{cond} , L ⁻¹ *	0.06 (0.03)	0.03 (0.01)

Data are presented as mean with standard deviation (SD); SAD: small airways dysfunction; FEF₂₅₋₇₅: forced expiratory flow between 25% and 75% of forced vital capacity (FVC); RV/TLC: the ratio of residual volume to total lung capacity; R₅-R₂₀: the difference between resistance at 5 Hz and 20 Hz; S_{acin}: ventilation heterogeneity of the acinar structures; and S_{cond}: ventilation heterogeneity of the conductive airways.

Table S3. Difference in ΔPD_{20} adenosine in patients with and without small airways dysfunction after treatment with QVAR, Clenil and Flixotide

ΔPD_{20} adenosine	Patients with SAD		Patients without SAD		<i>p</i> -value
	n (%)	Median (IQR)	n (%)	Median (IQR)	
QVAR (n=41)	17 (41)	0.69 (-0.02; 2.07)	24 (59)	0.82 (0.06; 1.86)	0.653 [‡]
Clenil (n=41)	18 (44)	1.73 (0.80; 2.14)	23 (56)	-0.00 (-0.75; 1.47)	0.306 [‡]
Flixotide (n=38)	17 (45)	0.96 (0.03; 2.58)	21 (55)	0.27 (-0.59; 1.86)	0.756 [‡]
QVAR vs Clenil	<i>p</i> =0.157 [£]		<i>p</i> =0.305 [£]		
QVAR vs Flixotide	<i>p</i> =0.357 [£]		<i>p</i> =0.232 [£]		

Data are presented as number with percentages (%) and median with interquartile ranges (IQR); *p*-values are obtained from [‡]student t-test/ Mann-Whitney test and [£]paired t-test/ Wilcoxon test; ΔPD_{20} : the change from baseline to post-treatment in the provocative dose of small particle adenosine causing a 20% drop in forced expiratory volume in 1 second; SAD: small airways dysfunction.

Table S4: Univariate linear regression analysis of baseline variables and change in airway hyperresponsiveness (ΔPD_{20}) in patients treated with QVAR, Clenil and Flixotide.

	ΔPD_{20} QVAR (n=41)		ΔPD_{20} Clenil (n=41)		ΔPD_{20} Flixotide (n=38)	
	B	95% CI	B	95% CI	B	95% CI
Age, years	0.01	-0.04; 0.05	-0.03	-0.08; 0.02	-0.02	-0.07; 0.03
Sex, male/ female	0.45	-0.69; 1.59	1.17 [#]	-0.14; 2.49	0.58	-0.70; 1.87
Current smoking, yes/no	-0.88	-1.99; 0.22	-1.10 [#]	-2.41; 0.21	-0.79	-2.06; 0.48
Presence of atopy, yes/no	-0.19	-1.38; 0.99	0.17	-1.28; 1.63	-0.05	-1.43; 1.32
Number of packyears	-0.03	-0.07; 0.02	-0.06 [*]	-0.11; -0.01	-0.03	-0.08; 0.01
BMI, kg/m ²	-0.08	-0.18; 0.02	-0.04	-0.16; 0.08	-0.12 [*]	-0.23; -0.01
Waist/hip ratio	-1.67	-7.02; 3.68	-4.93	-11.14; 1.28	-4.07	-9.80; 1.66
Blood neutrophils, 10 ⁹ /L	-0.48 ^{**}	-0.78; -0.17	-0.37 [#]	-0.77; 0.03	-0.55 ^{**}	-0.89; -0.22
Blood eosinophils, 10 ⁹ /L	1.00	-1.77; 3.77	2.73	-0.68; 6.13	2.32	-0.89; 5.52
Total IgE, kIU/L	0.00	-0.002; 0.001	0.001	-0.001; 0.002	0.00	-0.002; 0.001
FEV ₁ , % predicted	0.06 ^{**}	0.02; 0.09	0.06 [*]	0.01; 0.10	0.05 ^{**}	0.01; 0.10
FEV ₁ /FVC, %	0.03	-0.02; 0.08	0.04	-0.02; 0.11	0.03	-0.03; 0.09
FEF ₂₅₋₇₅ , % predicted	0.03 ^{**}	0.01; 0.06	0.04 [*]	0.01; 0.06	0.03 [*]	0.01; 0.06
TLC, % predicted	0.03	-0.01; 0.08	0.04	-0.02; 0.09	0.01	-0.04; 0.07
RV, % predicted	-0.01	-0.03; 0.01	-0.002	-0.03; 0.02	-0.02	-0.04; 0.01
RV/TLC, % predicted	-0.03 [*]	-0.06; -0.001	-0.01	-0.05; 0.02	-0.04 [*]	-0.07; -0.01
R ₅ -R ₂₀ , kPa sL ⁻¹	-2.67	-7.00; 1.66	-1.86	-6.98; 3.27	-3.50	-8.27; 1.28
X ₅ , kPa sL ⁻¹	1.78	-1.73; 5.29	0.78	-3.43; 5.00	2.43	-1.43; 6.29
F _{res} , Hz	-0.06	-0.15; 0.03	-0.04	-0.14; 0.07	-0.05	-0.16; 0.04
AX, Hz kPa sL ⁻¹	-0.15	-0.48; 0.18	-0.11	-0.50; 0.28	-0.20	-0.56; 0.16
LCI at 2.5%	-0.43 [*]	-0.75; -0.11	-0.19	-0.59; 0.21	-0.46 [*]	-0.81; -0.10
S _{cond} , L ⁻¹	-17.75	-44.25; 8.74	15.28	-16.77; 47.34	-7.08	-37.71; 23.54
S _{acin} , L ⁻¹	-5.36	-12.82; 2.10	-5.67	-14.44; 3.10	-6.13	-14.20; 1.94

Data are presented as regression coefficients (B) and 95% confidence intervals (CI); ** $p < 0.01$; * $p < 0.05$; # $p < 0.1$; ΔPD_{20} : the change from baseline to post-treatment in the provocative dose of small particle adenosine causing a 20% drop in FEV₁; BMI: body mass index; FEV₁: forced expiratory volume in 1 second; FVC: forced vital capacity; FEF₂₅₋₇₅: forced expiratory flow between 25% and 75% of FVC; TLC: total lung capacity; RV: residual volume; RV/TLC: the ratio of residual volume to total lung capacity; R₅-R₂₀: the difference between resistance at 5 Hz and 20 Hz; X₅: the reactance at 5 Hz; F_{res}: resonance frequency; AX: the area under curve of reactance; LCI: lung clearance index; S_{cond}: ventilation heterogeneity of the conductive airways; and S_{acin}: ventilation heterogeneity of the acinar structures.

Figure legend

Figure S1. Scatterplots of significant correlations between baseline variables and ΔPD_{20} adenosine. ΔPD_{20} : the change from baseline to post-treatment in the provocative dose of small particle adenosine causing a 20% drop in forced expiratory volume in 1 second (FEV1). Figure S1:A shows the correlation between age and ΔPD_{20} after treatment with Clenil; Figures S1:B-D show the correlation between blood neutrophils and ΔPD_{20} after treatment with QVAR, Clenil and Flixotide, respectively; Figures S1:E show the correlation of blood eosinophils and ΔPD_{20} after treatment with Flixotide

