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Title: Heterogeneity of small airways flow and hyperinflation are markers of a persistent obstruction phenotype in severe non-controlled asthmatics

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Body: Persistent functional impairment in some severe asthmatics, even after maximal treatment, is usually linked to inflammation, which does not explain all asthma limitations and seems to be determined by small airways structural changes too. Objective: Evaluate functional mechanisms related to persistent airflow obstruction (PAO) after an intensive therapeutic regimen in severe asthmatics. Methods: Non-controlled severe asthmatics received high inhaled corticosteroid dose (ICs) plus LABA for 12 weeks and oral corticosteroid (OC) in the first two weeks, after which they were classified into PAO by an FEV₁ after BD < 80% plus FEV₁/FVC ≤ 0.70. Complete airway reversibility were labeled non persistent airflow obstruction (NPAO). Both groups were compared. Ex smokers >10 pack-years were excluded. Results: At baseline, FEF₂₅₋₇₅, RV/TLC and resistance (Raw) were significant different between NPAO and PAO.

	NPAO(n=14)		PAO(n=48)	
	Baseline	After OC	Baseline	After OC
FEF 25-75	39±12	69±28*	24±13†	33±15* †
Raw	208±82	105±38*	330±119†	268±132†
VR/TLC	137±28	117±25*	173±32†	159±33* †
dN2	368±171	125±78*	572±336	338±296* †

All PAO values, including Slope of phase III of the single breath nitrogen washout test (dN2), became different after OC and did not return to normal. ACQ in NPAO decreased to near normal values (1.75±0.94). Conclusion: Persistent obstruction phenotype in severe asthmatics showed a high heterogeneity of airflow measured by dN2 and early airway closure due to high RV/TLC suggesting a fixed impairment in small airways. VEF₁ changes in these patients seem to be influenced by small airway disease. PAO also impairs

improvement in asthma control scores.