ORIGINAL ARTICLE

Bronchodilator Reversibility in the GAN Severe Asthma Cohort

Milger K[1,2], Skowasch D[3], Hamelmann E[4], Mümmler C[1,2], Idzko M[5], Gappa M[6], Jandl M[7], Körner-Rettberg C[8], Ehmann R[9], Schmidt O[10], Taube C[11], Holtdirk A[12], Timmermann H[13], Buhl R[14], Korn S[15,16]

[1]Department of Medicine V, University Hospital, LMU Munich, Munich, Germany
[2]Comprehensive Pneumology Center Munich (CPC-M), Member of the German Center for Lung Research, Munich, Germany
[3]Department of Internal Medicine II - Pneumology/Cardiology, University Hospital Bonn, Bonn, Germany
[4]University Hospital for Pediatrics and Adolescent Medicine, Children's Center Bethel, University of Bielefeld, Bielefeld, Germany
[5]Department of Pulmonary Medicine, Medical University of Vienna, Vienna, Austria
[6]Evangelisches Krankenhaus Düsseldorf, Düsseldorf, Germany
[7]Hamburger Institut für Therapieforschung, Hamburg, Germany
[8]Marienhospital Wesel, Wesel, Germany
[9]Ambulante Pneumologie Stuttgart, Stuttgart, Germany
[10]Pneumologische Gemeinschaftspraxis Koblenz, Koblenz, Germany
[11]Department of Pulmonary Medicine, University Hospital - Ruhrlandklinik, Essen, Germany
[12]CRO Kottmann, Hamm, Germany
[13]Allergopraxis Hamburg, Hamburg, Germany
[14]Pulmonary Department, Mainz University Hospital, Mainz, Germany
[15]IKF Pneumologie Mainz, Mainz, Germany
[16]Thoraxklinik Heidelberg, Heidelberg, Germany

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Abstract

Background: Positive bronchodilator reversibility (BDR) is a diagnostic criterion for asthma. However, patients with asthma may exhibit a negative BDR response.
Aim: To describe the frequency of positive and negative BDR response in patients with severe asthma and study associations with phenotypic characteristics.
Methods: A positive BDR response was defined as an increase in FEV_1 >200 mL and >12% upon testing with a short-acting ß-agonist.
Results: BDR data were available for 793 of the 2013 patients included in the German Asthma Net (GAN) severe asthma registry. Of these, 250 (31.5%) had a positive BDR response and 543 (68.5%) a negative BDR response. Comorbidities significantly associated with a negative response were gastroesophageal reflux disease (GERD) (28.0% vs 40.0%, *P*<.01) and eosinophilic granulomatosis with polyangiitis (0.4% vs 3.0%; *P*<.05), while smoking history (active: 2.8% vs 2.2%; ex: 40.0% vs 41.7%) and comorbid chronic obstructive pulmonary disease (COPD) (5.2% vs 7.2%) were similar in both groups. Patients with a positive BDR response had worse asthma control (median Asthma Control Questionnaire 5 score, 3.4 vs 3.0, *P*<.05), more frequently reported dyspnea at rest (26.8% vs 16.4%, *P*<.001) and chest tightness (36.4% vs 26.2%, *P*<.001), and had more severe airway obstruction at baseline (FEV_1% predicted, 56 vs 64, *P*<.001) and higher fractional exhaled nitric oxide (FeNO) levels (41 vs 33 ppb, *P*<0.05). There were no differences in diffusion capacity of the lung for carbon monoxide, single breath (% pred, 70% vs 71%). Multivariate linear regression analysis identified an association between positive BDR response and lower baseline FEV_1% (*P*<.001) and chest tightness (*P*<.05) and a negative association between BDR and GERD (*P*<.05).
Conclusion: In this real-life setting, most patients with severe asthma had a negative BDR response. Interestingly, this was not associated with smoking history or COPD, but with lower FeNO and presence of GERD.

Key words: Bronchodilator responsiveness. Severe asthma. Real-life cohort. GERD. FeNO.

Resumen

Antecedentes: La reversibilidad broncodilatadora (RB) positiva es un criterio diagnóstico para el asma. Sin embargo, los pacientes con asma pueden presentar una prueba RB negativa.
Objetivos: Describir la frecuencia de RB positivas y negativas en pacientes con asma grave y sus asociaciones con características fenotípicas.
Métodos: La RB positiva se definió como un aumento del FEV_1 > 200 ml y > 12% tras la inhalación de un agonista beta de acción corta (SABA).
Resultados: De 2013 pacientes incluidos en el registro de asma grave del German Asthma Net (GAN), 793 tenían datos sobre RB. De estos, 250 (31,5%) tuvieron una prueba RB positiva y 543 (68,5%) negativa. Las comorbilidades significativamente asociadas con RB

negativa fueron el reflujo gastroesofágico (ERGE) (28,0% frente a 40,0%, p<0,01) y EGPA (0,4% frente a 3,0%; p<0,05), mientras que el antecedente de tabaquismo (activo: 2,8% frente a 2,2%; exfumador: 40,0% vs. 41,7%) y la comorbilidad de la EPOC (5,2% vs. 7,2%) fueron similares en ambos grupos. Los pacientes con RB positiva tenían peor control del asma (mediana ACQ-5 3,4 vs. 3,0, p<0,05), más disnea en reposo (26,8% vs. 16,4%, p<0,001) y mayor opresión torácica (36,4% vs. 26,2%, p<0,001), además presentaban una obstrucción de las vías respiratorias más grave al inicio del estudio (FEV_1% pred: 56 frente a 64, p<0,001) y niveles más altos de FeNO (41 frente a 33 ppb, p<0,05), mientras que la capacidad de difusión fue similar (DLCO-SB% pred. 70% vs. 71%). El análisis de regresión lineal multivariable identificó una asociación de FEV_1% basal inferior (p<0,001) y opresión torácica (p<0,05) con RB positiva y ERGE (p<0,05) con RB negativa.
Conclusión: En este entorno en vida real, la mayoría de los pacientes con asma grave tuvieron una RB negativa. Curiosamente, esto no se asoció con antecedentes de tabaquismo o EPOC, sino con FeNO más bajo y presencia de ERGE.

Palabras clave: Respuesta a broncodilatadores. Asma grave. Cohorte de vida real. ERGE. FeNO.

Summary box

- **What do we know about this topic?**
  Positive bronchodilator response is used as a diagnostic criterion for asthma, even though it may be negative in patients with asthma.
- **How does this study impact our current understanding and/or clinical management of this topic?**
  In our real-life registry, two-thirds of patients with severe asthma did not have a positive bronchodilator response, and a negative response was associated with the comorbidities GERD and EGPA, but not with COPD.

Introduction

Severe asthma is prevalent in around 5%-10% of asthma patients and leads to high morbidity, health care resource use, and cost [1,2]. It is defined as asthma requiring high-dose inhaled corticosteroids (ICS) plus a second controller drug and/or systemic corticosteroids to prevent the disease from becoming uncontrolled or when it remains uncontrolled despite this therapy [1]. The Severe Asthma Registry of the German Asthma Net (GAN) is a large multicenter registry in Germany and Austria with >2000 patients included as of January 1, 2021. It records baseline and long-term follow-up of patients with severe asthma in order to describe disease presentation, clinical course, and care situation [3].

Bronchodilator reversibility (BDR) testing is recommended in the diagnostic workup of asthma by national guidelines [4,5] and international guidelines [6]. After stopping inhaled and other interfering treatments, spirometry is performed before and following inhalation of short-acting ß-agonists (SABAs). A positive BDR response is currently defined as an increase in FEV_1 of >12% and >200 mL. A positive BDR response is regarded as a characteristic of asthma, whereas a negative BDR response points to a diagnosis of chronic obstructive pulmonary disease (COPD) [6]. However, BDR response may also prove negative in patients with asthma for various reasons, including ß2-receptor down-regulation, owing to high-frequency SABA use [7] or airway remodeling in long-standing disease [6,8]. Such characteristics are frequently found in patients with severe uncontrolled asthma. Still, a positive BDR response has generally been used as an inclusion criterion for asthma trials and in recent randomized controlled trials in severe asthma [9-11]. Furthermore, so called irreversible airway obstruction may lead to a premature diagnosis of COPD and, in turn, to suboptimal treatment if severe asthma is indeed the underlying disease.

The aims of the present analyses, therefore, were to describe the frequency of positive and negative BDR response in a large real-life cohort of patients with severe asthma and to study associations with other disease parameters and symptoms.

Methods

The GAN Severe Asthma Registry prospectively collects routine clinical parameters from patients with severe asthma at baseline and annual follow-up data [3,12]. All patients fulfill the criteria for severe asthma as per assessment by a specialized pulmonologist based on the definition of the European Respiratory Society/American Thoracic Society [1]. The parameters include demographics, comorbidities, medications, pulmonary function test findings, and symptoms. All patients provided their written informed consent prior to participation in the registry, which was approved by the Ethics Committee of the University of Mainz, as well as the local institutional review boards. The study was performed in accordance with the principles of the Declaration of Helsinki. Like all other registry data, the BDR test was performed in the participating centers as part of clinical routine. According to recommendations, patients were advised to withhold inhaled and other interfering treatments before testing [12,13]. A positive BDR test response was defined as an increase in FEV_1 of > 12% and 200 mL after inhalation of 200-400 µg of SABAs; otherwise, results were classed as negative.

The present analyses include the baseline visits of all registry patients as of January 1, 2021. Firstly, we selected patients with available BDR test results. Then, patients were stratified as having a positive or negative BDR response. Fraction of exhaled nitric oxide (FeNO) was measured using any available device [14]. Values of <5 ppb were classed as 0.

Statistical Analysis

Statistical analyses were performed using SAS 9.4 (TS1M6) for Microsoft Windows. To compare the frequency of parameters between positive and negative BDR groups, we used the χ^2 test and Mann-Whitney test for dichotomous and continuous variables, respectively. All statistical tests were 2-tailed, with a significance level (α) of .05. Statistical significance was set at $P<.05$.

Next, in the case of significant differences in parameters between BDR-positive and BDR-negative groups, we performed further analyses on reversibility of FEV_1 (%). For dichotomous parameters, we performed a *t* test to determine whether there was a significant difference in FEV_1 reversibility (%) when stratifying for the dichotomous parameter. For the continuous parameters, we performed univariate linear regression analysis with FEV_1 reversibility (%) as the dependent variable and the continuous parameter as the independent variable. Then, we performed multiple linear regression analysis with the target variable FEV_1 reversibility (%) and the significant parameter of the univariate linear regression analysis or *t* test. Owing to missing information, 83 out of 793 (10.5%) cases were excluded from the multiple regression analysis, which was carried out with 710 patients.

Results

Baseline Characteristics

Data on BDR were available for 793 of the 2013 patients with severe asthma included in the GAN registry. Of these, 250 (31.5%) had a positive BDR response, while 543

Table 1. Clinical Characteristics of Patients With Severe Asthma and Positive or Negative Bronchodilator Reversibility (BDR) Test.

			BDR response		
		Total N=793	Positive n=250	Negative n=543	*P* Value positive vs negative
Female sex	No. (%)	432 (54.5%)	129 (51.6%)	303 (55.8%)	.27
Age, y	Mean (SD)	49.9 (16.3)	49.6 (15.6)	50.0 (16.5)	.64
Children	No. (%)	49 (6.2%)	15 (6.0%)	34 (6.3%)	.88
BMI, kg/m²	Mean (SD)	27.4 (6.3)	27.2 (6.2)	27.5 (6.4)	.68
Duration of asthma, y	Median	18.0 (0-80)	18.0 (0-72)	18.0 (0-80)	
Age at onset, y	Median	31.0	32.5 (0-69)	30.0 (0-84)	.52
Age group at onset	Early (<12 y)	224 (28.4%)	62 (24.8%)	162 (30.0%)	.13
	Late (>12 y)	566 (71.6%)	188 (75.2%)	378 (70.0%)	
Asthma phenotype, ICD10	Predominantly allergic asthma	336 (42.4%)	104 (41.6%)	232 (42.7%)	.95
	Nonallergic asthma	249 (31.4%)	80 (32.0%)	169 (31.1%)	
	Mixed forms of asthma	208 (26.2%)	66 (26.4%)	142 (26.2%)	
Smoking habits	Never-smoker	447 (56.4%)	143 (57.2%)	304 (56.1%)	.81
	Active smoker	19 (2.4%)	7 (2.8%)	12 (2.2%)	
	Former smoker	326 (41.2%)	100 (40.0%)	226 (41.7%)	
Former smoker: pack-years	No.	322	96	226	
	Median (range)	10.00 (0.5-80)	9.00 (0.5-75)	10.00 (0.5-80)	
Active smoker: pack-years	No.	18	7	11	
	Median (range)	7.35	6.50 (0.5; 30)	12.00 (0;56)	
COPD	No.	791	250	541	
	Yes	52 (6.6%)	13 (5.2%)	39 (7.2%)	.29
Incapacity for work	No	437 (55.2%)	131 (52.4%)	306 (56.5%)	.61
	Yes	235 (29.7%)	82 (32.8%)	153 (28.2%)	
	Unknown	50 (6.3%)	16 (6.4%)	34 (6.3%)	
	Not applicable	70 (8.8%)	21 (8.4%)	49 (9.0%)	

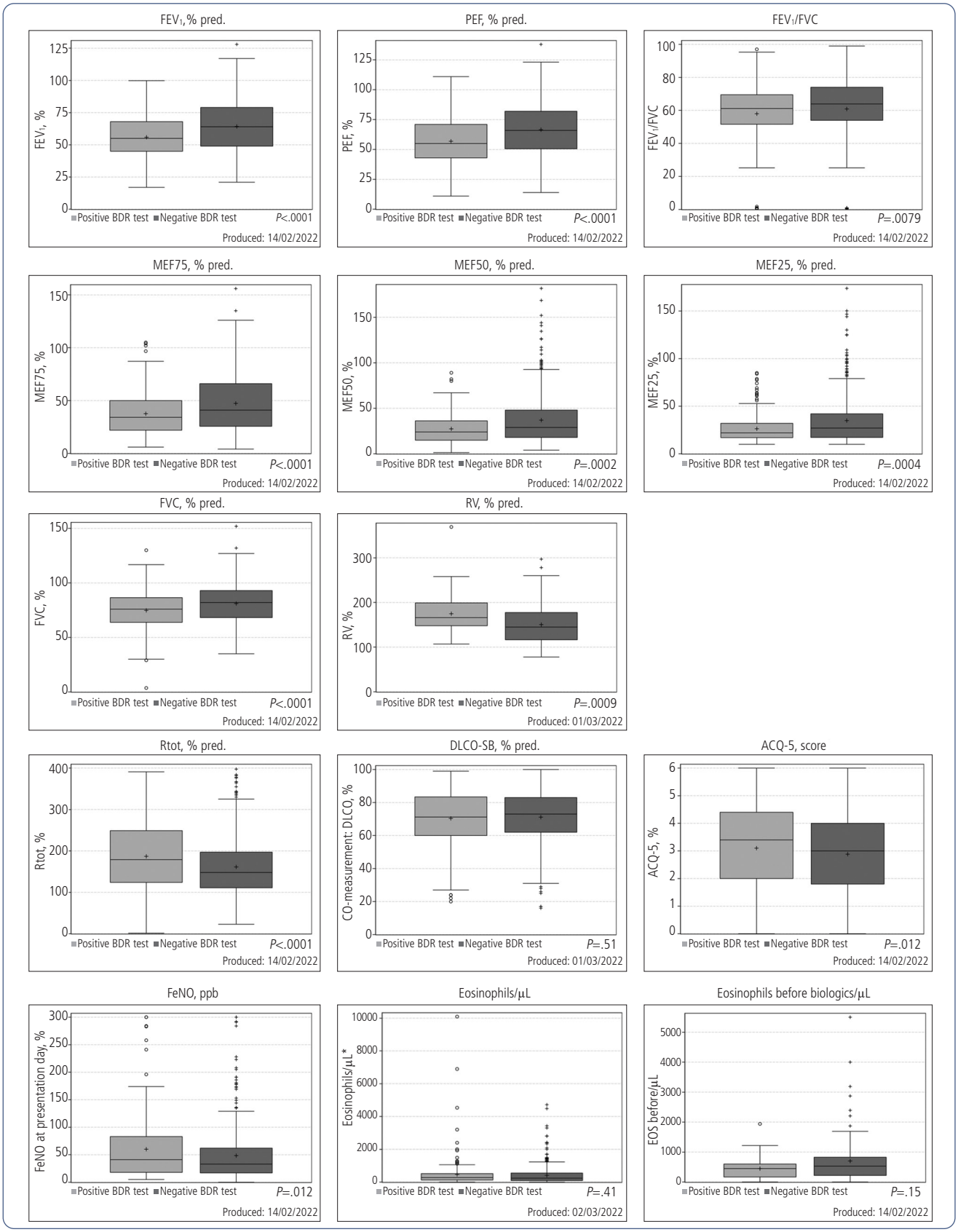

Figure. Comparison of selected parametric variables in patients with a positive vs negative BDR test result including pre-bronchodilator pulmonary function tests, ACQ-5, FeNO, and blood eosinophil count. *P* Values, Mann-Whitney test. All N=793 except for eosinophils before biologics n=134. Figures extracted from German Asthma Net - Annual Report 2020; *Differential blood count: Eosinophils abs. (calc.)

(68.5%) were classified as negative. The mean (SD) age of the patients was 49.9 (16.3) years, and 6.2% were children (Table 1). The asthma phenotype classified according to the current International Classification of Disease, Tenth Revision was predominantly allergic in 42.4% of patients, nonallergic in 31.4%, and mixed in 26.2%. Former smokers accounted for 41.2% of the patients (median, 10 pack-years), and 6.6% had a diagnosis of comorbid COPD. Regarding the baseline characteristics, there were no significant differences between patients with positive and negative BDR responses. Grouped comparisons for all parameters assessed in the registry can be found in Supplementary Table S1.

Pulmonary Function Testing

Pulmonary function testing (PFT) showed more severe airway obstruction in patients with a positive BDR response, namely, lower FEV_1%, FVC%, FEV_1/FVC, peak expiratory flow, maximal expiratory flow 75 (MEF_{75}), MEF_{50}, MEF_{25}, and higher residual volume and resistance (Figure, $P<.01$ for all parameters). In contrast, diffusion capacity of the lung for carbon monoxide (DLCO) was similar (70% vs 71% pred; $P=.51$ [Figure]).

Median FeNO was higher in patients with positive BDR response (41 ppb vs 33 ppb, $P=.012$, [Table 2]), while in the total population, blood eosinophil counts (BECs) did not differ significantly between groups (median BEC, 276.5/µL vs 243.3/µL [Figure]). In the subgroup of patients who subsequently initiated biologics for eosinophilic asthma (mepolizumab, benralizumab, reslizumab, dupilumab [n=135]) in whom BEC values were available before initiation of the biologic, these were higher than in the total population but similar when patients with positive and negative BDR results were compared (median BEC, 450 vs 530/µL; $P=.15$).

Next, we analyzed asthma control and quality of life using the Asthma Control Test (ACT), Asthma Control Questionnaire 5 (ACQ-5), and the Asthma Quality of Life Questionnaire (AQLQ). Patients with positive BDR results had higher a median ACQ-5 score (3.4 vs 3.0, $P<.01$, Figure), more frequently reporting dyspnea at rest (26.8% vs 16.4%, $P=.0006$) and chest tightness (36.4% vs 26.2%, $P=.0034$ [Table 2]), whereas differences were not significant for the ACT or AQLQ (Supplementary table S1).

Regarding systemic treatments, patients with a positive BDR response were more often currently treated with OCS, but not biologics, than those with a negative BDR response (32.8% vs 25.6%), while patients with a negative BDR response received biologics without OCS more frequently (14.0% vs 23.4%, $P=.0130$ [Table 2]).

Comorbidities significantly associated with negative BDR response included gastroesophageal reflux disease (GERD) and eosinophilic granulomatosis with polyangiitis (EGPA) ($P<.05$ [Table 2]), while findings were similar for history of

Table 2. Comparison of Selected Dichotomous Parameters in Positive vs Negative BDR Results.

		Bronchodilator reversibility			
Item		**Total**	**Positive**	**Negative**	***P* Value**
Resting dyspnea	N	792	250	542	
	Yes	156 (19.7%)	67 (26.8%)	89 (16.4%)	.0006[a]
Chest tightness/chest pain	N	792	250	542	
	Yes	233 (29.4%)	91 (36.4%)	142 (26.2%)	.0034[a]
Gastroesophageal reflux	N	790	250	540	
	Yes	286 (36.2%)	70 (28.0%)	216 (40.0%)	.0011[a]
Chronic sinusitis	N	791	250	541	
	Yes	364 (46.0%)	105 (42.0%)	259 (47.9%)	.1233[a]
Nasal polyps	N	118	273	391	
	Yes	41 (34.7%)	99 (36.3%)	140 (35.8%)	.77[a]
EGPA	N	791	250	541	
	Yes	17 (2.1%)	1 (0.4%)	16 (3.0%)	.0211[a]
Systemic therapies OCS - biologics	N	793	250	542	
	Without OCS and without biologics	321 (40.5%)	105 (42.0%)	216 (39.9%)	.0130[a]
	With OCS and without biologics	221 (27.9%)	82 (32.8%)	139 (25.6%)	
	Without OCS and with biologics	162 (20.5%)	35 (14.0%)	127 (23.4%)	
	With OCS and with biologics	88 (11.1%)	28 (11.2%)	60 (11.1%)	

Abbreviations: EGPA, eosinophilic granulomatosis and polyangiitis; OCS, oral corticosteroids.
[a]*P* value by χ^2 test.

chronic sinusitis (42% vs 47.9%) and nasal polyps (34.7 vs 36.3%) (Table 2).

We performed further analyses for parameters with significant differences in frequency between patients with positive and negative BDR responses. For dichotomous parameters, we compared FEV_1 reversibility (%) between the 2 groups of the dichotomous parameter. Here, we found significant differences in FEV_1 reversibility (%) when stratifying patients for presence of resting dyspnea, chest pain, GERD, and EGPA, as well as current use of OCS

Table 3. FEV_1 Reversibility (%) for Dichotomous Parameters.[a]

				95% CI		*t* Test	
Item	**N**	**Mean**	**SE**	**Lower**	**Upper**	***t* value**	***P* value**
Resting dyspnea							
No	636	10.53	0.72	9.12	11.94		
Yes	156	17.54	2.65	12.30	22.77		
Difference		–7.01	2.75	–12.43	–1.59	–2.55	.0115
Chest tightness/chest pain							
No	559	10.15	0.65	8.88	11.41		
Yes	233	16.13	2.15	11.91	20.36		
Difference		–5.99	2.24	–10.40	–1.58	–2.67	.0080
Current use of OCS							
No	483	10.51	0.78	8.97	12.05		
Yes	309	14.09	1.59	10.97	17.21		
Difference		–3.58	1.77	–7.05	–0.10	–2.02	.0438
Current use of biologics							
No	542	12.97	0.98	11.04	14.91		
Yes	250	9.59	1.26	7.11	12.08		
Difference		3.38	1.60	0.24	6.52	2.11	.0351
EGPA							
No/unknown	774	12.08	0.80	10.51	13.65		
Yes	17	4.73	1.42	1.72	7.73		
Difference		7.35	1.63	4.01	10.69	4.52	.0001
GERD							
No/unknown	504	13.12	1.09	10.99	15.26		
Yes	286	9.81	1.01	7.81	11.80		
Difference		3.32	1.49	0.40	6.23	2.23	.0259

Abbreviations: EGPA, eosinophilic granulomatosis with polyangiitis; GERD, gastroesophageal reflux disease; OCS, oral corticosteroids; SE, standard error.
[a]A *t* test was performed to determine whether there was a significant difference in FEV_1 reversibility (%) between the 2 groups of the dichotomous parameter (Table 3).

Table 4. Univariate Linear Regression Analysis for Continuous Parameters.[a]

						95% CI	
Item	**Estimate**	**SE**	***t* value**	***P* value**	**Standard estimate**	**Lower limit**	**Upper limit**
ACQ-5	1.56707	0.46850	3.34	0.0009	0.12455	0.64725	2.48689
FEV_1, %	–0.33624	0.03820	–8.80	<0.0001	–0.29938	–0.41123	–0.26126
FeNO at baseline, ppb	0.02301	0.01519	1.51	0.1304	0.06331	–0.00683	0.05285

Abbreviations: ACQ-5, Asthma Control Questionnaire 5; FeNO, fractional exhaled nitric oxide; FEV_1, forced expiratory volume in 1 second; SE, standard error.
[a]For the continuous parameters, a univariate linear regression analysis was performed with the target variable FEV_1 reversibility (%) and the continuous variable as the independent parameter.

Table 5. Multivariate Linear Regression Analysis.[a]

Item	Estimate	SE	*t* value	*P* value	Standard estimate	95% CI	
						Lower limit	Upper limit
ACQ-5	–0.00360	0.52822	–0.01	.9946	–0.00029	–1.04067	1.03348
FEV_1, %	–0.26397	0.03533	–7.47	<.0001	–0.28060	–0.33332	–0.19461
Resting dyspnea	2.67390	1.82865	1.46	.1441	0.05570	–0.91638	6.26418
Chest tightness/chest pain	3.10083	1.54392	2.01	.0450	0.07592	0.06957	6.13209
Systemic corticosteroids	–0.52893	1.41514	–0.37	.7087	–0.01391	–3.30735	2.24948
Biologics	–1.56801	1.45484	–1.08	.2815	–0.03932	–4.42437	1.28835
EGPA	–5.24051	4.54253	–1.15	.2490	–0.04202	–14.15910	3.67808
GERD	–3.03815	1.36898	–2.22	.0268	–0.07957	–5.72595	–0.35036
Backward elimination *P*<.150							
FEV_1, %	–0.26522	0.03389	–7.83	<.0001	–0.28194	–0.33177	–0.19868
Resting dyspnea	2.90417	1.74826	1.66	.0971	0.06050	–0.52824	6.33658
Chest tightness/chest pain	3.15516	1.48983	2.12	.0345	0.07725	0.23013	6.08019
GERD	3.08614	1.36311	–2.26	.0239	0.08082	0.40989	5.76238

Abbreviations: ACQ-5, Asthma Control Questionnaire 5; EGPA, eosinophilic granulomatosis with polyangiitis; OCS, oral corticosteroids FeNO, fractional exhaled nitric oxide; FEV_1, forced expiratory volume in 1 second; GERD, gastroesophageal reflux disease; SE, standard error.
[a]Multiple linear regression analysis with the target variable FEV_1 reversibility (%) and the significant parameter of the univariate linear regression analysis or *t* test.
Owing to missing information, 83 out of 793 (10.5 %) cases were excluded from the analysis. Thus, the analysis was carried out with 710 patients.

and biologics (Table 3). For the continuous parameters, we performed a univariate linear regression analysis with the target variable FEV_1 reversibility (%) and the continuous variable as the independent parameter (Table 4). Here, higher ACQ-5 and lower FEV_1% at baseline were significantly associated with FEV_1 reversibility (%). Furthermore, using multiple regression analysis, we found a positive association between chest tightness and lower FEV_1 % at baseline and a negative association between GERD and FEV_1 reversibility (%) (Table 5).

Discussion

In the present large real-life severe asthma cohort, most patients had a negative BDR response, suggesting that this parameter is of limited value for diagnosis and differentiation from COPD in patients with severe uncontrolled disease. The prevalence of comorbid COPD in our cohort was low, and even though 41.2% of patients reported having smoked in the past, the median exposure of 10 pack-years was only moderate. Furthermore, mean DLCO was only mildly reduced (DLCO-SB, 70% predicted) and did not differ between patients with positive and negative BDR responses. In summary, these characteristics suggest that smoking history and consequent COPD do not explain negative BDR findings in most patients with severe asthma.

However, we found other comorbidities to be significantly associated with BDR. GERD was more frequent in patients with a negative BDR response, and the multivariate analysis revealed significant associations. The association between asthma and GERD is well-known and represents a bidirectional epidemiological relationship, as recently reconfirmed in a large Korean cohort study [15]. Pathophysiologically, bidirectional associations are also assumed with acid reflux causing cough, vagal stimulation, and airway inflammation, whereas hyperinflation induced by severe asthma may predispose to GERD [16]. Specifically, GERD can lead to small airway inflammation, mucus plugging, and fibrosis [16]. Our results support the hypothesis that co-occurrence of asthma with GERD may be associated with a specific asthma phenotype characterized by negative BDR. Recently, Enríquez-Matas et al [17] found that GERD negatively affected quality of life, especially in elderly patients with asthma, and that the more generally increased comorbidities are associated with exacerbations [18].

EGPA was also significantly associated with a negative BDR response, although the prevalence of this comorbidity (2.1%) was low in our cohort. Patients with EGPA may have lung manifestations beyond asthma that play a role in the mechanisms underlying BDR. Similarly, in their study of 89 patients with EGPA, Berti et al [19] found that PFT results did not improve in the long term, regardless of therapy with ICS or OCS.

FeNO reflects the level of local type 2 inflammation in the airways and predicts the response to inhaled and systemic corticosteroids [20,21]. Here, we found an association between higher FeNO levels and positive BDR response. Similarly, Janson et al [22] found that higher FeNO levels correlated with a more pronounced BDR in patients with

asthma in large population-based studies. Additionally, Nerpin et al [23] reported that this was not only true for patients with asthma but that it even held in nonasthmatic individuals. We previously showed that FeNO was associated with disease burden in severe asthma [24], as supported by the findings presented here. Interestingly, in contrast to FeNO, BEC did not differ between patients with positive and negative BDR responses in the present analysis, either for the total cohort or for patients later treated with biologics. Along these lines, Caminati et al [25] found that increased FeNO, but not BEC, was associated with markers of disease severity. Still, these findings might be influenced by treatments, as BEC is lowered by both systemic and, to a lesser degree, inhaled corticosteroids [26,27].

We found interesting associations for systemic treatments, namely, that patients with a positive BDR response more frequently received OCS without biologics, whereas patients with a negative BDR response more frequently received biologics without OCS. However, given the observational, cross-sectional design of the study, it is not possible to elucidate whether there is a causal relationship with the drugs or whether differences in treatment reflect different patient characteristics. It is possible that patients in the positive BDR group were more frequently treated with OCS owing to the severity of their disease, which is characterized by poorer lung function. On the other hand, an improvement in lung function in response to OCS can also be used as a diagnostic test when the BDR response is negative in suspected asthma [4] and when OCS treatment improves lung function in asthma, irrespective of initial BDR [28].

Anti–IL-5R and anti–IL-4R biologics also improve lung function, although it is not known whether this impacts on BDR. Of note, patients with a negative BDR response were excluded from licensing trials of biologics; therefore, the reported increases in FEV_1 of around 100-160 mL following anti–IL-5/R and anti–IL-4R treatment reflect patients with positive BDR only [9-11]. Interestingly, it was recently shown that the new anti-TSLP biologic tezepelumab reduces airway hyperresponsiveness provoked by mannitol inhalation [29], suggesting that the degree of variability in airway obstruction might be influenced by targeting specific components of type 2 inflammation.

Moreover, we found asthma control measured by ACQ-5 to be worse in patients with a positive BDR response, and the specific symptoms of resting dyspnea and chest tightness were significantly associated with a positive BDR response. This higher symptom load might be explained in part by more severe PFT impairments at baseline in this group. However, the multivariate regression analysis showed that, in addition to FEV_1%, chest tightness was independently associated with BDR, suggesting that this could be a symptom with a certain specificity for pronounced variability in airway obstruction.

In patients with severe uncontrolled asthma, several factors may render obstruction nonreversible upon application of bronchodilators. Firstly, frequent use of SABAs may lead to ß receptor down-regulation and, therefore, reduce the effect of SABAs [7]. Secondly, airway remodeling with muscular hypertrophy and subepithelial fibrosis can occur, especially in long-standing disease [30,31]. We also found that in patients with a positive BDR response, PFT parameters revealed more severe obstructive defects at baseline.

Heffler et al [32] showed that a positive BDR response is a marker of poor asthma control even when BDR testing was performed without pausing asthma medications except for long-acting ß agonists.

Our findings are in line with results of the Severe Asthma Research Program, which found the highest reversibility in the cluster with worst baseline lung function. This cluster also had the highest FeNO levels and symptom load [33]. When high reversibility was compared with low reversibility in patients with nonsevere asthma, similar observations were made, namely, worse pulmonary function and less well-controlled disease in the high reversibility group [34]. This may be due in part to the current definition of BDR, which includes an increase in FEV_1 of >12%. This value can be reached more easily when baseline values are low. Thus, the current FEV_1%-related definition has become a matter of debate in recent years. Even in the general population and in asthma patients with disease of varying severity, Janson et al [22] found that only 17% of asthma patients fulfilled the current criteria for positive BDR response. Our data further corroborate this notion for severe asthma, with two-thirds of patients in this large real-life cohort being BDR-negative. Interestingly, Janson et al suggested that instead of a flow-related definition of FEV_1, a volume-related assessment of BDR by measurement of FVC might be more relevant. This is supported by data from Quanjer et al [35] for severe obstruction. Indeed, evidence is growing that small airway dysfunction may be more relevant for symptoms in asthma than FEV_1 and small airway dysfunction, and that response to bronchodilators might be better captured using oscillometry combined with mean expiratory flow values [36,37] or plethysmographic measures of air trapping, such as residual volume [38]. Moreover, using the improvement in z-scores could circumvent some of the limitations associated with the FEV_1%-based definition of BDR [39]. Here, for BDR, the only available parameter was the standard (FEV_1% and FEV_1 in mL). However, in the future, the GAN registry will collect more comprehensive pulmonary function data during BDR testing for a more detailed exploration.

Additionally, similar to other pulmonary function parameters, BDR may vary over time, and while some patients may continuously exhibit a positive BDR response, a larger proportion have a positive BDR response only intermittently [40,41]. Thus, while a longitudinal observation may provide additional insights, such longitudinal data on BDR were not available here.

The limitations of the study include the real-life setting for data acquisition and BDR. Thus, less than half of the patients included in the registry had data on BDR available at baseline. Furthermore, even though patients were advised to withhold inhaled and other interfering treatments prior to BDR testing as requested by guidelines, this might be difficult for patients with uncontrolled severe asthma. Additionally, the 2019 update on the American Thoracic Society/ European Respiratory Society guidelines on standardization of spirometry [12] recommends longer bronchodilator

withholding times than the previous version [13]. However, reflection of the real-life setting is also a strength of our study and highlights the issue faced in clinical practice, namely, that the BDR response is often negative in severe asthma. Without a thorough evaluation in a specialist setting, this finding might be misinterpreted as COPD. Moreover, the use of the current FEV_1-based definition of positive BDR as an inclusion criterion for RCTs in severe asthma should be revisited, as it excludes most patients seen in real-life.

In summary, a negative BDR response was highly prevalent in a real-life cohort of patients with severe asthma not associated with smoking history and COPD. This finding leads us to question the relevance of BDR for diagnosis of asthma or differentiation between asthma and COPD. The parameters independently associated with a positive BDR response were lower FEV_1% at baseline and chest tightness, while comorbid GERD was associated with a negative BDR response.

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Conflicts of Interest

KM reports personal fees from AstraZeneca, GSK, Norvartis, and Sanofi, all outside the submitted work.

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The remaining authors declare that they have no conflicts of interest.

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Katrin Milger

https://orcid.org/0000-0003-2914-8773
Department of Medicine V
University Hospital, LMU Munich
Marchioninistr.15
81377 Munich
E-mail: Katrin.Milger@med.uni-muenchen.de