

Nasal Nitric Oxide Measurement and a Modified PICADAR Score for the Screening of Primary Ciliary Dyskinesia in Adults with Bronchiectasis

Messung des nasalen Stickstoffmonoxids und ein modifizierter PICADAR-Score als Screening für primär ciliäre Dyskinesie in Erwachsenen mit Bronchiektasen

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ABSTRACT

Background Determining the underlying diagnosis is essential for the targeted and specific treatment of bronchiectasis. Primary ciliary dyskinesia (PCD) is a rare genetic disease, which is characterized by abnormalities in ciliary structure and/or function and which may result in bronchiectasis. The disease is probably underestimated among adults with bronchiectasis due to the fact that extensive diagnostic testing is required and that the recognition of PCD is low.

Objective To evaluate a feasible screening algorithm for PCD among adults with bronchiectasis.

Methods Data from all patients who presented to our bronchiectasis outpatient clinic from June 2010 until July 2016 were retrospectively analysed from our database. Nasal NO (nNO) and a modified PICADAR score (Primary

Ciliary Dyskinesia Rule) were measured and compared in the two groups of PCD-bronchiectasis and non-PCD-bronchiectasis.

Results 185 of 365 patients (75 males, 110 females) had a sufficient measurement of nNO concentration and complete clinical data and were eligible for analysis. The mean (SD) nNO concentration in nL/ml was significantly lower in the PCD group compared to the non-PCD group (25 [31] and 227 [112] nL/min, respectively; $p < 0.001$). A nNO level of 77 nL/min had the best discriminative value to differentiate between the two groups. Patients with PCD had a significant higher modified PICADAR score than patients without PCD (5 [2] and 1 [1], respectively [$p < 0.001$]). Using ROC curve analysis, the modified PICADAR score of 2 had the best discriminative value with a sensitivity of 1.00 and a specificity of 0.89.

Conclusions Low nNO concentration and the modified PICADAR score are suitable and cheap screening tests for PCD in adults with bronchiectasis.

ZUSAMMENFASSUNG

Hintergrund Um Patienten mit Bronchiektasen gezielt und effektiv therapieren zu können, ist es notwendig die zugrunde liegende Ätiologie zu kennen. Die primär ciliäre Dyskinesie (PCD) ist eine seltene genetische Erkrankung mit Veränderungen in der Zilienstruktur und/oder -funktion, welche zu Bronchiektasen führen kann. Da die Diagnostik aufwendig, nur selten verfügbar und teuer ist, wird die PCD als Ätiologie für Bronchiektasen zum Teil erst spät erkannt und ist wahrscheinlich unterdiagnostiziert.

Zielsetzung Evaluierung eines einfachen Screeningverfahrens für PCD in Patienten mit Bronchiektasen.

Methoden Es wurden retrospektiv die Daten aller Patienten mit Bronchiektasen in der Spezialambulanz der Medizinischen Hochschule Hannover von Juni 2010 bis Juli 2016 analysiert. Das nasale NO (nNO) und der modifizierte PICADAR-Score (Primary Ciliary Dyskinesia Rule) wurden gemessen und in den zwei Gruppen PCD-Bronchiektasen und Nicht-PCD-Bronchiektasen verglichen.

Ergebnisse 185 von 365 Patienten (75 Männer, 110 Frauen) hatten eine suffiziente nNO-Messung sowie vollständige klinische Daten und konnten in die Analyse eingeschlossen werden. Der Mittelwert (SD) der nNO-Konzentration in nL/ml war signifikant niedriger in der PCD-Gruppe im Vergleich zu Nicht-PCD-Patienten (25 [31] und 227 [112] nL/min; $p < 0,001$). Ein nNO von 77 nL/min ist der beste diskriminative Wert um zwischen diesen beiden Gruppen zu unterscheiden. Patienten mit PCD zeigten einen signifikant

höheren PICADAR score als Patienten ohne PCD (5 [2] und 1 [1], ($p < 0,001$)). Der beste diskriminative Wert des modifizierten PICADAR-Scores lag bei 2 mit einer Sensitivität von 1,00 und einer Spezifität von 0,89.

Schlussfolgerung Die Kombination aus niedrigem nNO und ein hoher modifizierter PICADAR-Score ist ein einfacher und kostengünstiger Screeningtest auf PCD bei Patienten mit Bronchiektasen.

Introduction

Bronchiectasis is a potentially progressive chronic condition related to permanent and abnormal widening of the airways. It may cause chronic cough and copious sputum production, haemoptysis and shortness of breath [1]. There are various aetiologies, which may result in bronchiectasis, including postinfective, chronic obstructive pulmonary disease, connective tissue disease, immunodeficiency, and inherited disorders such as primary ciliary dyskinesia (PCD) [2]. Recently, it has been shown that the burden of bronchiectasis is continuously increasing in UK and German healthcare systems [3–5].

PCD is an autosomal recessive inherited disease with structural and/or functional abnormalities of respiratory cilia leading to abnormal or absent beating of the cilia, impairment of mucociliary clearance and subsequent damage of the upper and lower airways due to chronic infection and inflammation [6]. When accompanied by situs inversus and chronic sinusitis, this disease is known as Kartagener syndrome. Among subjects with bronchiectasis 1–18% have an underlying diagnosis of congenital condition including PCD. It is suspected that this disease is underrecognized [7–9]. Knowledge of PCD as the aetiological diagnosis underlying bronchiectasis is of particular importance due to possible upcoming targeted therapies such as inhaled inhibitors of the epithelial sodium channel (ENaC), the emphasis of physiotherapy, rehabilitation and consequent treatment of upper airway complications. To know the diagnosis of PCD is also important for the necessity for genetic counselling and the risk of infertility in male patients.

Nitric oxide (NO) is a highly reactive gaseous molecule with numerous signalling roles within the airways [10]. Nasal concentration of NO (nNO) is markedly reduced in PCD patients and is now widely used as a screening test for PCD [6, 11]. Exhaled NO (FeNO) from the lower airway is also low in PCD but is less specific at differentiating between PCD and healthy controls [12, 13]. The majority of studies indicate that more than 95% of PCD patients have very low nNO, confirming its suitability as a screening test [14].

Early diagnosis and treatment of PCD may reduce long-term pulmonary morbidity and prevent the development of severe bronchiectasis [8, 15]. The most important clinical features are neonatal respiratory distress, early onset rhinosinusitis, persistent serous otitis media, chronic wet cough, male infertility and abnormal organ situs like situs inversus and heterotaxy syndrome [8, 16]. It is important to be aware of this red-flag symp-

toms that warrant testing for PCD. PICADAR (Primary Ciliary Dyskinesia Rule) is a recently published and validated predictive diagnostic tool for determining the likelihood of an individual daily wet cough that started in early childhood having a diagnosis of PCD [17]. PICADAR includes a number of predictors based in early life, which are difficult to recall in adulthood.

So far, there are limited data for PCD screening tests among adults with bronchiectasis. In our opinion, every symptomatic adult with bronchiectasis requires a comprehensive diagnostic work-up including screening for PCD in order to identify treatable traits as well as associated conditions and/or complication that impact disease management. However, around the globe there are only a few specialist diagnostic centres for PCD.

Thus, we collected nNO levels in 185 patients from our dedicated Adult Bronchiectasis Clinic at Hannover Medical School (MHH) and used a modified PICADAR score in these patients to look whether a combination of these easily performed tests could serve as a useful predictive diagnostic tool for PCD.

Methods

Study design and population

All patients who presented to our bronchiectasis outpatient clinic from June 2010 to July 2016 were analysed. All patients were clinically stable at the time of measurement and none had any evidence of an acute pulmonary exacerbation such as new-onset chest pain, increased shortness of breath or changing of sputum volume. Nasal NO and the modified PICADAR score (Situs inversus, neonatal respiratory distress, congenital cardiac defect, chronic rhinosinusitis, chronic ear and hearing symptoms) [17] were extracted from our database and compared in the two groups of probable or definite PCD bronchiectasis and non-PCD bronchiectasis. Bronchiectasis was confirmed by computed tomography scan of the chest according to established criteria [18]. All patients had undergone an extensive work-up in accordance of the BTS guidelines to determine the cause of their bronchiectasis including HRCT scan of the chest, spirometry, blood test (full blood count, CRP, Serum immunoglobulins (G, A, M) and serum electrophoresis, serum IgE, IgE to *Aspergillus fumigatus* or skin prick testing to *Aspergillus*), test for cystic fibrosis if indicated, sputum [19]. Individuals were classified as having a definite, probable, and possible or no PCD diagnosis, similar as previously described [20]. Patients who fulfilled the following diagnostic criteria had a diagnosis of definite PCD: 1) clinical presentation consis-

tent with PCD and 2) consistent findings specific for PCD by at least two methods (high-frequency video microscopy analysis (HVMA), transmission electronic microscopy (TEM), immunofluorescence microscopy (IF), nNO (<200 ppb or 77 nL/min) or biallelic disease-causing mutations by genotyping. All individuals with typical clinical symptoms and one abnormal diagnostic test were considered to have probable PCD, while all individuals with typical clinical symptoms (bronchiectasis), but no clearly abnormal test were considered to have no PCD (non-PCD group).

Nasal nitric oxide measurements

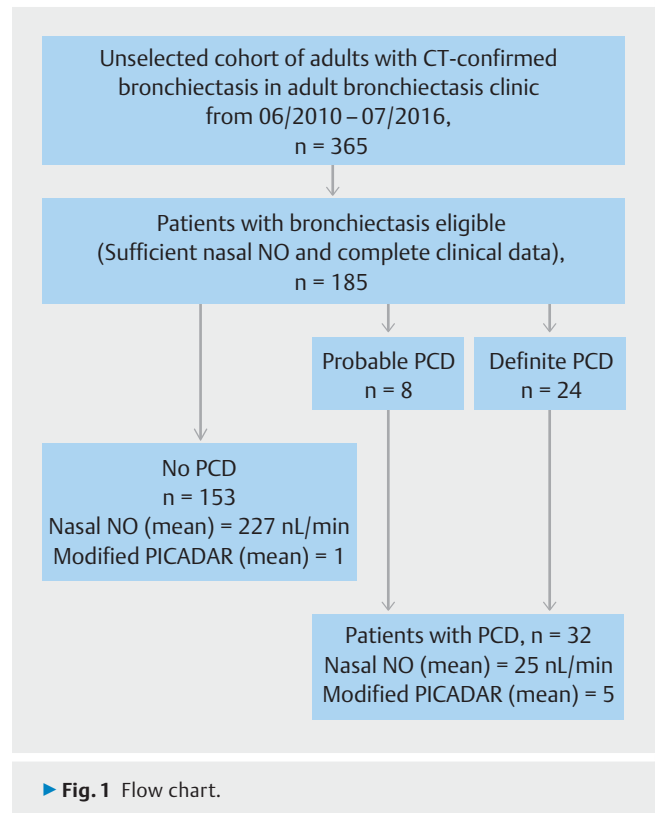
The method of nNO measurement was based on the 2005 American Thoracic Society, European respiratory society ATS/ERS recommendations [21]. Nasal NO was measured by a chemiluminescence analysis detecting NO at concentrations from 1 to 5000 parts per billion (ppb) by volume, adapted for on-line recording of NO-concentration (ECO Medics CLD88sp). Nasal NO was measured in subjects sitting with a Teflon tube inserted inside the nostril ensuring a tight seal. The subject was then asked to take a deep breath out and close their mouth. Patients were encouraged to hold each breath for approximately 20 s until the analyser recorded a plateau in nNO concentrated from the aspirated gas. Two measurements were obtained from each patient using the same nostril and the mean nNO reading was recorded.

Modified PICADAR

Data from all patients were retrospectively analysed from our database. We modified the original PICADAR score [17] because it includes predictors based in early life which are particularly difficult to recall in adulthood. Therefore, we modified the score and skipped “gestational age” and combined “admittance to a neonatal unit” and “neonatal chest symptoms” to any “neonatal respiratory distress”. Neonatal respiratory distress included any history of respiratory abnormalities during the neonatal period. Persistent perennial rhinitis and chronic sinusitis were summarised as chronic rhinosinusitis. According to the original publication situs inversus counts for 4 points. Neonatal respiratory distress and congenital cardiac defect count for 2 points, each. Chronic rhinosinusitis and chronic ear and hearing symptoms count for 1 point, each. The range of the modified PICADAR score was from 0 to 10 points.

Data analysis

The IBM SPSS Statistics (version 24.0, IBM Corp., Armonk, New York) and STATA (version 13.0, StataCorp, College Station, Texas) statistical software programs were used to analyse the data. Comparison of nNO levels between both groups was performed using non-parametric tests. A two sided p value of <0.05 was considered statistically significant. Receiver operator characteristics (ROC) curve using the modified PICADAR score and for the discrimination of the nNO was calculated using SPSS.



Results

Demographics

From June 2010 to July 2016 365 patients with CT-confirmed bronchiectasis were presented to our adult bronchiectasis clinic. Of these, 185 patients (75 males, 110 females) had a sufficient nasal NO level and complete clinical data and were eligible for analysis (► Fig. 1). Sufficient nasal NO means that the test is performed correctly. Patient demographics are shown in ► Table 1. Situs inversus was seen in 10 of 32 patients with PCD (Kartagener syndrome). The performed PCD investigations included HVMA in 29 patients, TEM in 16 patients, IF in 6 patients and genetic analysis in three patients. In summary, 24 patients had a definite diagnosis of PCD and 8 patients had a probable diagnosis of PCD, while 153 subjects were considered to have no PCD.

Nasal NO

The mean (SD) in nNO levels was significantly lower in the PCD group with 25 [31] and 227 [112] nL/min in the non-PCD group, respectively ($p < 0.001$). Using ROC curve analysis a nNO level of 77 nL/min had the best discriminative value (data not shown). Two patients with definite PCD had a nNO concentration >77 nL/min and 5 patients without PCD had nNO levels <77 nL/min. Of those, three had undergone prior sinus surgery.

► **Table 1** Characteristics of the patient cohort (n = 185).

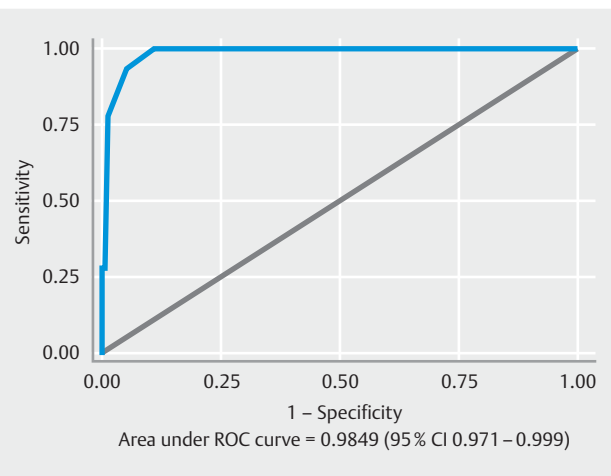
	non-PCD	PCD
Number, n (%)	153 (83)	32 (17)
Age, mean (SD)	55 (16)	32 (12)
Sex, n (%)		
Male	62 (41)	13 (41)
Female	91 (59)	19 (59)
Underlying etiology, n (%)		
Primary ciliary dyskinesia		32 (17)
Idiopathic	69 (37)	
Asthma/ABPA	25 (13)	
Immunodeficiency	9 (5)	
Post-infectious	15 (8)	
Connective tissue disease	8 (4)	
COPD/emphysema	16 (9)	
CFTR-related disorder	6 (3)	
Other (including Swyer James syndrome, Hyper-IgE syndrome, Young's syndrome, aspiration, Crohn's disease)	5 (3)	
FEV1 % predicted, mean (SD)	69 (30)	66 (24)
FVC % predicted, mean (SD)	92 (25)	84 (20)
Body mass index, mean (SD)	24 (5)	23 (3)
MRC dyspnea scale, mean (SD)	2 (1)	1 (1)
Smoking behavior, n (%)		
Active-smoker	5 (3)	0 (0)
Ex-smoker	48 (32)	5 (16)
Never smoked	100 (65)	27 (84)
Exacerbations, median (range)	1 (0–12)	2 (0–9)
Hospitalizations, median (range)	0 (0–10)	0 (0–4)
Bronchiectasis Severity Index		
Mild (0–4), n (%)	41 (27)	11 (34)
Moderate (5–8), n (%)	43 (28)	9 (28)
Severe (≥9), n (%)	69 (45)	12 (35)
Chronic airway infection with PA, n (%)	34 (22)	8 (25)

PICADAR

The modified PICADAR score is shown in ► **Table 2**. The mean (SD) of modified PICADAR was significantly higher in the PCD group with 5 [2] compared to 1 [1] in the non-PCD group, respectively. The receiver operator characteristic (ROC) curve using the modified PICADAR symptom score as a diagnostic tool in PCD is shown in ► **Fig. 2**. Using ROC curve analysis, a

► **Table 2** The PICADAR (Primary Ciliary Dyskinesia Rule) (maximum 14 points) and the modified PICADAR score for adults (maximum 10 points).

	PICADAR	Modified PICADAR
Situs abnormality	4 points	4 points
Full term born	2 points	
Chest symptoms in the neonatal period	2 points	
Admitted to a neonatal unit	2 points	
Any neonatal respiratory distress		2 points
Congenital cardiac defect	2 points	2 points
Chronic rhinosinusitis	1 point	1 point
Chronic ear and hearing symptoms	1 point	1 point

► **Fig. 2** Receiver operated characteristics (ROC) curve analysis showing the diagnostic performance of the modified PICADAR in distinguishing PCD from other underlying conditions of bronchiectasis.

symptom score of 2 had the best discriminative value with a sensitivity of 1.00 and a specificity of 0.89. The distribution of points in the PCD and non-PCD group is shown in ► **Table 3**.

Discussion

Bronchiectasis is a heterogeneous disease with many different underlying and/or associated conditions. It is essential for targeted and specific treatment to determine the underlying diagnosis of bronchiectasis. Only after a comprehensive work-up of all differential diagnoses it is acceptable to label the disease idiopathic. We found that nNO and a clinical score of typical PCD characteristics is a suitable and cheap screening test for PCD among adults with bronchiectasis.

► **Table 3** Modified PICADAR in PCD bronchiectasis compared to Non-PCD bronchiectasis.

Score	PCD bronchiectasis, n (%)	Non-PCD bronchiectasis, n (%)
0	0	81
1	0	55
2	2	9
3	4	6
4	16	1
5	1	1
6	2	0
7	3	0
8	4	0
9	0	0
10	0	0

Nasal NO as a screening test has been described as useful before [22]. Wodehouse and colleagues found that nNO concentrations were significantly lower in PCD than in healthy controls, CF, sinusitis, Young's syndrome and bronchiectasis [6]. Mean nNO concentrations (SD) in parts per billion (ppb) were comparable to our results with 64 [36] in the PCD group and 734 [164] in the idiopathic bronchiectasis group. Overall the sample size of this study was lower, the bronchiectasis patients were younger and only idiopathic bronchiectasis were included. Narang et al. evaluated nNO in children and found a comparable sensitivity and specificity of 97%, and 90%, respectively [13]. Shoemark et al. compared bronchial and peripheral airway contribution to nNO and exhaled NO in patients with PCD, non-PCD bronchiectasis and healthy controls. Patients with PCD had significantly lower exhaled NO concentrations. However, there was an overlap with normal controls which was not observed with nNO [23]. It remains unclear and is discussed controversially whether the additional measurement of exhaled bronchial NO is helpful or not. Horvath suggested that nNO and exhaled NO in combination improve the specificity of NO as a screening test from 93% to 98% [24]. There are two other studies with conflicting results. Mahut and colleagues described that the impairment of NO output is less pronounced in the lower than in the upper respiratory tract in PCD [25]. In our study we decided to evaluate nNO because of better screening test results in earlier investigations. The results of all earlier studies are comparable to our results with regard to nNO [6,23,24], but all earlier studies focused on PCD compared with other conditions. We focused on an unselected cohort of bronchiectasis patients and differentiated between subjects with bronchiectasis due to PCD and subjects with bronchiectasis but without PCD.

Establishing the diagnosis of PCD is demanding [26] and diagnostics are not available at every institution where bronchiectasis patients are managed. The full diagnostic work-up,

including nNO, HVMA, TEM, IF and genotyping requires a specific technical set-up available only in one paediatric center in Germany. In contrast, bronchiectasis in adults is a diagnosis which is mainly managed in outpatient care by chest physicians in practice in Germany [5]. Therefore, we modified and evaluated the recently published PICADAR and compared the results between the PCD and non-PCD group. Patients with PCD have characteristic signs and symptoms [8]. Horvath et al. described clinical characteristics of patients with PCD with neonatal respiratory symptoms (43%), chronic wet cough (86%), chronic rhinosinusitis (93%), recurrent otitis media (79%), situs inversus (43%) and infertility (79%) [24]. Several other authors reported similar results [8,27]. PICADAR included children and adults, but the median age of the derivation group was 9 and 3 in the validation group [17]. It comprises seven predictive variables including full-term gestational age, admittance to a neonatal unit, neonatal chest symptoms, situs abnormalities, congenital cardiac defect, persistent perennial rhinitis, chronic ear and hearing symptoms. A large proportion of the adult population does not know their gestational age and what exactly happened at and after their birth, respectively. Therefore we modified the PICADAR score and skipped the "gestational age" and combined "admittance to a neonatal unit" and "neonatal chest symptoms" to any "neonatal respiratory distress". The modified PICADAR score was significantly higher in patients with PCD ($p < 0.001$). We have no earlier studies to compare our results with. The original PICADAR score had a sensitivity and specificity of 0.90 and 0.75 for a cut-off score of 5 points which is higher than the cut-off score of 2 in our study [17]. But the highest value was 14 in compare to 10 in our modified version for adults. In our opinion the additional use of characteristic signs and symptoms of PCD does not replace the diagnostic work-ups, but may help to identify patients with the suspected diagnosis of PCD who should be send to specialized centers for further evaluation and confirmation of the diagnosis.

The limitations of our study are its retrospective design. The sensitivity and specificity may be overestimated because chest physicians may ask more often for characteristic symptoms in patients with PCD and thus may miss those in patients without PCD. Second, evaluation of nNO as a screening tool for PCD was difficult in our study, because it is used as a diagnostic criteria for PCD as well. Third, we have a misbalance of the two groups, what might lead to random error.

In conclusion, a clinical scoring system of characteristic symptoms of PCD and low nNO production rates/concentrations are useful screening tests for PCD in adults with bronchiectasis. Clinicians without the access to the measurement of nNO should perform the modified PICADAR score in their adult bronchiectasis patients and refer patients for further investigation in case of a score ≥ 2 . PCD is probably underdiagnosed and diagnosed too late particularly in countries with low healthcare expenditure [9]. Further validation of the modified PICADAR score in the adult bronchiectasis population is warranted. With our findings we hope to contribute to the recognition of PCD as a relevant and easy to screen potential fatal inheritable disease.

KEY MESSAGES

- PCD is probably underestimated among adults with bronchiectasis
- There are only a few specialist diagnostic centres for PCD worldwide
- Nasal NO is a useful screening test
- A clinical scoring system of characteristic symptoms can help to screen patients for further investigations
- Further information on <http://www.kartagener-syndrom.org>

ABBREVIATIONS

ENaC	Epithelial sodium channel
FeNO	Exhaled nitric oxide
HVMA	High-frequency video microscopy analysis
nNO	nasal nitric oxide
PCD	Primary ciliary dyskinesia
PICADAR	Primary Ciliary Dyskinesia Rule
TEM	Transmission electronic microscopy
IF	Immunofluorescence microscopy

Competing interests

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References

- [1] Barker AF. Bronchiectasis. *N Engl J Med* 2002; 346: 1383–1393
- [2] Lonni S, Chalmers JD, Goeminne PC et al. Etiology of Non-Cystic Fibrosis Bronchiectasis in Adults and Its Correlation to Disease Severity. *Ann Am Thorac Soc* 2015; 12: 1764–1770
- [3] Quint JK, Millett ER, Joshi M et al. Changes in the incidence, prevalence and mortality of bronchiectasis in the UK from 2004 to 2013: a population-based cohort study. *Eur Respir J* 2016; 47: 186–193
- [4] Ringshausen FC, de Roux A, Pletz MW et al. Bronchiectasis-associated hospitalizations in Germany, 2005–2011: a population-based study of disease burden and trends. *PLoS One* 2013; 8: e71109
- [5] Ringshausen FC, de Roux A, Diel R et al. Bronchiectasis in Germany: a population-based estimation of disease prevalence. *Eur Respir J* 2015; 46: 1805–1807
- [6] Wodehouse T, Kharitonov SA, Mackay IS et al. Nasal nitric oxide measurements for the screening of primary ciliary dyskinesia. *Eur Respir J* 2003; 21: 43–47
- [7] Altenburg J, Wortel K, van der Werf TS et al. Non-cystic fibrosis bronchiectasis: clinical presentation, diagnosis and treatment, illustrated by data from a Dutch Teaching Hospital. *Neth J Med* 2015; 73: 147–154
- [8] Coren ME, Meeks M, Morrison I et al. Primary ciliary dyskinesia: age at diagnosis and symptom history. *Acta Paediatr* 2002; 91: 667–669
- [9] Kuehni CE, Frischer T, Strippoli MP et al. ERS Task Force on Primary Ciliary Dyskinesia in Children. Factors influencing age at diagnosis of primary ciliary dyskinesia in European children. *Eur Respir J* 2010; 36: 1248–1258
- [10] Lundberg JO, Weitzberg E, Nordvall SL et al. Primarily nasal origin of exhaled nitric oxide and absence in Kartagener's syndrome. *Eur Respir J* 1994; 7: 1501–1504
- [11] Bush A, Chodhari R, Collins N et al. Primary ciliary dyskinesia: current state of the art. *Arch Dis Child* 2007; 92: 1136–1140
- [12] Karadag B, James AJ, Gültekin E et al. Nasal and lower airway level of nitric oxide in children with primary ciliary dyskinesia. *Eur Respir J* 1999; 13: 1402–1405
- [13] Narang I, Ersu R, Wilson NM et al. Nitric oxide in chronic airway inflammation in children: diagnostic use and pathophysiological significance. *Thorax* 2002; 57: 586–589
- [14] Walker WT, Jackson CL, Lackie PM et al. Nitric oxide primary ciliary dyskinesia. *Eur Respir J* 2012; 40: 1024–1032
- [15] Shah A, Shoemark A, MacNeill SJ et al. A longitudinal study characterising a large adult primary ciliary dyskinesia population. *Eur Respir J* 2016; 48: 441–450
- [16] Noone PG, Leigh MW, Sannuti A et al. Primary ciliary dyskinesia: diagnostic and phenotypic features. *Am J Respir Crit Care Med* 2004; 169: 459–467
- [17] Behan L, Dimitrov BD, Kuehni CE et al. PICADAR: a diagnostic predictive tool for primary ciliary dyskinesia. *Eur Respir J* 2016; 47: 1103–1112
- [18] McShane PJ, Naureckas ET, Tino G et al. Non-cystic fibrosis bronchiectasis. *Am J Respir Crit Care Med* 2013; 188: 647–656
- [19] Pasteur MC, Bilton D, Hill AT. British Thoracic Society Bronchiectasis non-CF Guideline Group. British Thoracic Society guideline for non-CF bronchiectasis. *Thorax* 2010; 65: 577
- [20] Werner C, Lablans M, Ataian M et al. An international registry for primary ciliary dyskinesia. *Eur Respir J* 2016; 47: 849–859
- [21] American Thoracic Society, European Respiratory Society. ATS/ERS recommendations for standardized procedures for the online and offline measurement of exhaled lower respiratory nitric oxide and nasal nitric oxide. *Am J Respir Crit Care Med* 2005; 171: 912–930
- [22] Collins SA, Gove K, Walker W et al. Nasal nitric oxide screening for primary ciliary dyskinesia: systematic review and meta-analysis. *Eur Respir J* 2014; 44: 1589–1599
- [23] Shoemark A, Wilson R. Bronchial and peripheral airway nitric oxide in primary ciliary dyskinesia and bronchiectasis. *Respir Med* 2009; 103: 700–706
- [24] Horváth I, Loukides S, Wodehouse T et al. Comparison of exhaled and nasal nitric oxide and exhaled carbon monoxide levels in bronchiectatic patients with and without primary ciliary dyskinesia. *Thorax* 2003; 58: 68–72
- [25] Mahut B, Escudier E, de Blic J et al. Impairment of nitric oxide output of conducting airways in primary ciliary dyskinesia. *Pediatr Pulmonol* 2006; 41: 158–163
- [26] Jackson CL, Behan L, Collins SA et al. Accuracy of diagnostic testing in primary ciliary dyskinesia. *Eur Respir J* 2016; 47: 837–848
- [27] Nüsslein T, Brinkmann F, Ahrens P et al. Diagnostik der primären ziliären Dykinesie. *Monatsschr Kinderheilkd* 2013; 161: 406–416