Advances in Clinical Medicine 临床医学进展, 2023, 13(3), 4129-4135
Published Online March 2023 in Hans. https://www.hanspub.org/journal/acm
https://doi.org/10.12677/acm.2023.133593

Hans汉斯

小气道功能障碍与哮喘控制

易良琴[1,2,3,4]，罗征秀[1,2,3,4*]

[1]重庆医科大学附属儿童医院呼吸科，重庆
[2]国家儿童健康与疾病临床医学研究中心，重庆
[3]儿童发育疾病研究教育部重点实验室，重庆
[4]儿科学重庆市重点实验室，重庆

收稿日期：2023年2月17日；录用日期：2023年3月14日；发布日期：2023年3月21日

摘　要

哮喘是常见的慢性气道炎症性疾病，炎症可累及整个气管－支气管树，近年来，小气道被认为是炎症累及和气流阻塞的主要部位，小气道功能障碍是持续性哮喘的特征，与疾病恶化和控制不良相关，但目前指南尚缺少小气道管理相关内容。本文就小气道功能障碍与哮喘控制关系做一综述，以期提升对小气道功能障碍在哮喘控制中作用的认知水平，为哮喘指南的完善提供支持性证据。

关键词

哮喘控制，小气道功能障碍

Small Airway Dysfunction and Asthma Control

Liangqin Yi[1,2,3,4], Zhengxiu Luo[1,2,3,4*]

[1]Department of Respiratory, Children's Hospital of Chongqing Medical University, Chongqing
[2]National Clinical Research Center for Child Health and Disorders, Chongqing
[3]Ministry of Education Key Laboratory of Child Development and Disorders, Chongqing
[4]Chongqing Key Laboratory of Pediatrics, Chongqing

Received: Feb. 17th, 2023; accepted: Mar. 14th, 2023; published: Mar. 21st, 2023

Abstract

Asthma is a common chronic airway disease. Inflammation in asthma can involve the entire tra-

*通讯作者。

文章引用: 易良琴, 罗征秀. 小气道功能障碍与哮喘控制[J]. 临床医学进展, 2023, 13(3): 4129-4135.
DOI: 10.12677/acm.2023.133593

chea-bronchial tree. Recent years, small airways have been accepted to be the main site of inflammation and major reason of airflow obstruction. And small airway dysfunction is confirmed as a characteristic of persistent asthma, which is related to exacerbation and control. However, in asthma guidelines, little information is stressing the role of small airway. In this review article, we focused on the relationship between small airway dysfunction and asthma control, pointed out the influence of small airway dysfunction in poor asthma control and stressed the importance of its management, in order to provide supporting evidence for asthma guideline.

Keywords

Asthma Control, Small Airway Dysfunction

1. 引言

哮喘是一种常见的慢性呼吸道疾病，影响全球约 3.39 亿人，其患病率逐年上升[1] [2]。尽管表明哮喘控制是一个可实现的目标，但在临床及研究发现，相当一部分哮喘患者仍处于哮喘控制不佳状态[3] [4]，我国哮喘控制率约 28.5%，低于发达国家哮喘控制水平[5]。哮喘控制不佳与患者病情加重、生活质量受损和个人医疗保健负担增加相关[6] [7]，了解影响哮喘控制不佳的危险因素并及时干预对实现哮喘最佳临床控制至关重要。既往研究已经证实患过敏性鼻炎、治疗依从性差和吸入治疗方法错误等是导致哮喘控制不佳的危险因素[8] [9] [10] [11]。近年来，越来越多的证据提示小气道功能障碍与哮喘发作及恶化相关[12] [13] [14]。研究表明在哮喘早期阶段小气道已有不同程度受累，持续性小气道炎症是导致哮喘控制不佳的重要危险因素[12] [13] [14] [15]，然而现有哮喘指南并未提及小气道功能障碍(small airway dysfunction, SAD)在哮喘中的作用及如何对其管理[11] [16] [17] [18]。因此，本文就目前关于小气道功能障碍对哮喘控制水平的影响做一综述，以期为识别小气道功能障碍在哮喘控制中的重要性提供依据。

2. 小气道功能障碍

小气道被定义为气管内径 ≤ 2 mm，壁上不含软骨，从第 8 级支气管延伸至周围肺组织的气道[19]。正常情况下，小气道对气道阻力的贡献很小，在成人中小气道阻力仅占总气道阻力的 10%~20%，通常被称为肺的“沉默区”[20]。然而小气道面积大，受炎症累及时，可提供相当大的气道阻力。小气道功能障碍的患病率因生理评估手段不同而呈现差异，总体而言，成人哮喘中小气道功能障碍患病率约 50%~60% [21]，儿童哮喘中约为 20%~30% [22] [23]。多项研究表明，重度哮喘患者小气道功能障碍患病率最高[12]，且与更严重气道高反应性、更差的哮喘控制水平、更频繁的哮喘病情恶化有关[12] [13] [14]。

3. 小气道功能的评估方法

目前尚缺乏标准化、统一化小气道测量方法，SAD 也缺乏评估金标准。全球哮喘倡议(GINA)提出常规肺通气功能仍是评价肺功能的首选方法，第 1 秒用力呼气容积(FEV_1)是评估患者气道阻塞的金标准[11]，然而，FEV_1 不能敏感地评估小气道功能。用力呼出 50%肺活量时的瞬间呼气流量(FEF 50%)，用力呼出 75%肺活量时的瞬间呼气流量(FEF 75%)和用力呼出 25%~75%肺活量间的平均呼气流量(FEF 25%~75%，也称最大呼气中期流量，MMEF)是常用来反应小气道功能指标[24]，此三项指标中有两项低于正常值下

限(<65%预计值)可提示 SAD [24]。近年来，随脉冲震荡试验(Impulse oscillometry, IOS)、体积描记法(Body plethysmography)、呼出气一氧化氮(Fractional exhaled nitric oxide, FeNO)、重复呼吸氮冲洗法(Multiple breath nitrogen washout test, MBNW)、影像学等专业测试在临床实践中陆续开展，发现 IOS 能更敏感地识别小气道功能障碍，更有潜力运用于临床监测[25] [26]。

IOS 是通过脉冲波在不同振动频率下检测呼吸道不同部位气道阻力，在 5 Hz 时的气道阻力(R5)代表总气道阻力，20 Hz 时的气道阻力(R20)代表中心气道阻力，R5~R20 代表小气道阻力，5 Hz 时的电阻抗(X5)和电抗下面积(AX)也是反应小气道功能的重要参数，当小气道出现阻塞时其值可显著增加[27] [28]。在成人，当 R5~R20 > 0.07 kPa/L·s 提示有 SAD [13]，部分研究也以 R5~R20 > 0.03 kPa/L·s 作为成人 SAD 评估标准[29]；在儿童中，R5~R20 的界限值因不同年龄段而呈现出差异[23] [30]，目前尚无统一判定 SAD 的 IOS 标准。

体积描记法是一种静态评估肺过度充气和空气滞留的方法，小气道狭窄引起气流阻塞，气道过早关闭导致空气滞留，因此残气量(residual volume，RV)增加和 RV/肺总量(total lung capacity, TLC)升高(>0.3)提示存在 SAD，当慢肺活量(slow vital capacity)-用力肺活量(forced vital capacity, FVC) > 10%可提示小气道的过早关闭[31] [32]。

FeNO 是一种有效的非侵入性检测 Th2 介导的气道炎症的方法，可根据数学模型分为支气管 NO 和肺泡 NO(CaNO)两部分，CaNO 被认为与小气道的炎症有良好相关性[33]，但目前这一数学模型的准确性和应用行仍存在争议。

MBNW 可用于评估小气道通气异质性，通过受试者重复吸入纯氧至 TLC，再呼气至残气位，多次分析每一阶段呼出氮气浓度的变化，从而计算出通气不均及肺清除率指标。气道传导通气不均指标 Scond 和气体交换肺腺泡通气不均指标 Sacin 的升高以及反应肺清除率的肺清除指数(LCI)的降低可提示小气道病变，其中 LCI 被认为是一种最稳定反小气道功能的参数[34] [35]。

4. 小气道功能障碍与哮喘的进展相关

哮喘患者中，气道炎症和结构改变是引起气流受限的重要因素，由于小气道提供的阻力相对小，在哮喘早期尤其未出现典型临床症状前，已有的小气道阻塞可能未被临床检测出，提示临床对 SAD 的识别不够，这可能是哮喘进展的危险因素之一[36]。出生队列研究证实[37]，在儿童期肺功能下降发生成年期哮喘患者中，FVC 和 FEV_1 处于正常水平时，FEF 25%~75%已出现了不同程度降低。横断面研究发现[38]，从儿童期即有持续性哮喘的患儿比成年期发病的哮喘患者病情更严重，肺功能水平更差，有更多 SAD 的证据，提示持续性炎症反应对小气道累及更重。小气道功能障碍能成功预测学龄前喘息发生青春期哮喘，其中 IOS 相关小气道功能指标降低与青春期持续性肺功能异常相关[39]。Skylogiann 等发现中重度过敏性鼻炎患儿支气管舒张试验后存在小气道功能障碍，是随访 5 年内哮喘发生的有效预测指标[40]。在无哮喘症状且 FEV_1 及支气管激发试验正常的哮喘患儿中，SAD 是未来哮喘恶化的危险因素[41]。以上研究表明，小气道功能障碍可在大气道功能下降前出现，其可独立于大气道的影响并长期存在，持续的小气道功能障碍加速了哮喘患者的肺功能下降，使得哮喘病情更加严重，症状频繁发作。

5. 小气道功能障碍与哮喘控制相关

们使用不同检测手段来评估小气道功能障碍与哮喘控制之间关系。Takeda 等[42]使用 IOS 评估了哮喘患者小气道功能障碍，并探讨其与哮喘症状及哮喘控制的关系，发现 R5~R20 增加与更频繁的呼吸困难独立相关，X5 与哮喘控制不佳相关。Shi 等[30]发现 R5~R20 和 AX 可用来区分哮喘控制和未控制患者，当前哮喘控制稳定的学龄儿童中 R5~R20，AX 降低，在未来的 8~12 周内有哮喘控制不佳风险。Galant

等发现[43]，由 R5~R20，AX，X5 定义的 SAD 与患儿发生哮喘控制不佳一致相关，存在 SAD 也提示患儿有哮喘控制不佳风险。Farah 的研究[44] [45]表明了哮喘控制不佳组患者的 Scond 和 Sacin 值高于控制良好组的哮喘患者，Scond 和 Sacin 值的增加与一年内哮喘加重的次数显著相关，是哮喘控制不佳的独立危险因素。Puckett 等人[46]将学龄期－青春期的哮喘儿童根据肺泡和支气管 NO 的浓度将其分组研究，发现在各组间 FEV_1 的值未见差异，但肺泡 NO 水平升高的患者比肺泡和支气管 NO 水平正常的患者或仅支气管 NO 水平升高的患者哮喘控制更差，此外肺泡 NO 水平升高的患者出现更频繁的哮喘恶化。也有研究者在使用大剂量吸入性糖皮质激素(inhaled corticosteroids, ICS)治疗的患者中观察到肺泡 NO 浓度与哮喘控制之间的并无相关性，这可能与大剂量 ICS 抑制呼出气 NO 水平有关[47]。ATLANTIS 这项最大的多国研究中证明了 SAD 对哮喘的作用[12]：91%的哮喘患者均发现有异常的小气道功能指标，SAD 存在于所有按 GINA 哮喘病情严重程度分级中，以常规肺通气功能和 IOS 等指标形成的 SAD 结构方程评分与哮喘控制，恶化，病情严重程度显著相关，其一年随访数据[14]表明通过 FEF 25%~75%，IOS，MBNW 等测量的 SAD 与哮喘控制、恶化和生活质量纵向相关。

总的来说，上述证据提示随着小气道受累越重，哮喘控制不良的比率增多，哮喘恶化也更加频繁，同时也证实在 SAD 的检出上除常规肺通气功能外，使用 IOS 和其他检测手段重要性。

6. 小气道功能障碍的治疗对哮喘控制的影响

哮喘的治疗主要是控制气道炎症，ICS 是哮喘患者抗炎治疗的基石[11] [18]，然而大多数吸入疗法不能充分到达小气道。针对小气道功能障碍的治疗通常是增加 ICS 的剂量或联用舒张支气管的药物以使 ICS 沉积到远端气道，或使用小颗粒二丙酸倍氯米松氢氟烷吸入器(HFA)，以期增加药物的肺部沉积率，或联合白三烯受体拮抗剂(LTRA)治疗，从而最大程度的改善气道的炎症，达到哮喘控制[48] [49] [50]。

Farah 等人[45]研究影响哮喘控制变化情况的因素，发现小气道功能障碍是 ICS 剂量上调后哮喘控制良好或 ICS 剂量下调后哮喘控制不佳的独立危险因素；在对重度难治性哮喘患儿行肌注皮质类固醇治疗 4 周后，LCI 和 FeNO 指标得到明显改善，且两者改善呈一致性关系，而其他肺通气功能参数无明显改变，这提示了小气道炎症可能是常规 ICS 治疗无反应哮喘患儿气流阻塞的主要原因[51]。与大颗粒 ICS 治疗相比，使用 HFA 联合超细颗粒二丙酸倍氯米松/福莫特罗(ICS/LABA)治疗的哮喘患者，其哮喘控制良好的比例更高，哮喘症状恶化的频率更低[52] [53] [54]。对使用超细颗粒 ICS/LABA 治疗的哮喘患者随访 3 个月，发现 IOS 相关小气道功能指标及哮喘控制水平得到明显改善[55] [56]。与安慰剂相比，使用孟鲁司特治疗的哮喘患儿，症状的好转与肺残气量、肺泡 NO 降低和 AX 的改善相关，与 FEV_1，FEV_1/FVC 无关[57]。最近一项对接受至少一月孟鲁司特维持治疗的轻度持续性哮喘控制良好的学龄期儿童中，在停用孟鲁司特两周后，并未观察到哮喘控制不佳比例增加、IOS 相关的小气道功能指标恶化及 FENO 增加的变化[58]，但该项研究仅随访了短时间内肺功能及哮喘症状变化，仍需相关纵向研究随访评估小气道功能改变情况与哮喘控制之间的关系。

7. 结论

综上，SAD 与哮喘患者的症状恶化、控制不佳相关，对病情发展有重要影响。尽管有有效的治疗方法，部分哮喘患者病情仍然控制不佳，这可能与 SAD 在哮喘中作用认识不足有关。除常规肺通气功能外有很多适用于评估 SAD 的方法，IOS 在评估 SAD 与哮喘控制及治疗方面较常规肺功能更好，研究结果也较多，能更好地用于检测小气道功能。目前哮喘指南尚缺少针对小气道功能管理这部分内容，似乎需迫切完善相关建议与实施，提高临床医生对 SAD 的认识，从而早期识别和针对性地治疗，达到哮喘控制的目的和减少病情恶化的发生。

参考文献

[1] Enilari, O. and Sinha, S. (2019) The Global Impact of Asthma in Adult Populations. *Annals of Global Health*, **85**, 2.

[2] 张偲莹, 高宗石, 吴丽宏, 田蓓蓓, 刘蒙, 陶芳标, 吴修龙. 中国1990-2019年儿童青少年哮喘疾病负担变化趋势[J]. 中国学校卫生, 2022, 43(1): 123-128.

[3] Braido, F., Brusselle, G., Guastalla, D., *et al*. (2016) Determinants and Impact of Suboptimal Asthma Control in Europe: The International Cross-Sectional and Longitudinal Assessment on Asthma Control (Liaison) Study. *Respiratory Research*, **17**, 51. https://doi.org/10.1186/s12931-016-0374-z

[4] Neffen, H., Chahuàn, M., Hernández, D.D., *et al*. (2020) Key Factors Associated with Uncontrolled Asthma—The Asthma Control in Latin America Study. *Journal of Asthma*, **57**, 113-122. https://doi.org/10.1080/02770903.2018.1553050

[5] 农英, 林江涛, 王文巧, 等. 我国城区支气管哮喘患者疾病认知与控制水平关系的多中心调查[J]. 中华医学杂志, 2017, 97(18): 1425-1429.

[6] World Health Organization. Asthma 2021. https://www.who.int/zh/news-room/fact-sheets/detail/asthma

[7] 林江涛, 邢斌, 唐华平, 等. 2013-2014 年我国城区支气管哮喘急性发作住院患者的临床特征及住院费用的回顾性调查[J]. 中华结核和呼吸杂志, 2017, 40(11): 830-834.

[8] Mulugeta, T., Ayele, T., Zeleke, G., *et al*. (2022) Asthma Control and Its Predictors in Ethiopia: Systematic Review and Meta-Analysis. *PLOS ONE*, **17**, e0262566. https://doi.org/10.1371/journal.pone.0262566

[9] Nordlund, B., Melén, E., Schultz, E.S., *et al*. (2014) Risk Factors and Markers of Asthma Control Differ between Asthma Subtypes in Children. *Pediatric Allergy and Immunology*, **25**, 558-564. https://doi.org/10.1111/pai.12271

[10] Ghanname, I., Chaker, A., Cherkani Hassani, A., *et al*. (2018) Factors Associated with Asthma Control: MOSAR Study (Multicenter Observational Study of Asthma in Rabat-Morocco). *BMC Pulmonary Medicine*, **18**, 61. https://doi.org/10.1186/s12890-018-0624-6

[11] Report G (2022) Global Strategy for Asthma Management and Prevention.

[12] Postma, D.S., Brightling, C., Baldi, S., *et al*. (2019) Exploring the Relevance and Extent of Small Airways Dysfunction in Asthma (ATLANTIS): Baseline Data from a Prospective Cohort Study. *The Lancet Respiratory Medicine*, **7**, 402-416. https://doi.org/10.1016/S2213-2600(19)30049-9

[13] Cottini, M., Licini, A., Lombardi, C., *et al*. (2020) Clinical Characterization and Predictors of IOS-Defined Small-Airway Dysfunction in Asthma. *The Journal of Allergy and Clinical Immunology*: *In Practice*, **8**, 997-1004.e2. https://doi.org/10.1016/j.jaip.2019.10.040

[14] Kraft, M., Richardson, M., Hallmark, B., *et al*. (2022) The Role of Small Airway Dysfunction in Asthma Control and Exacerbations: A Longitudinal, Observational Analysis Using Data from the ATLANTIS Study. *The Lancet Respiratory Medicine*, **10**, 661-668. https://doi.org/10.1016/S2213-2600(21)00536-1

[15] Abdo, M., Trinkmann, F., Kirsten, A.M., *et al*. (2021) Small Airway Dysfunction Links Asthma Severity with Physical Activity and Symptom Control. *The Journal of Allergy and Clinical Immunology*: *In Practice*, **9**, 3359-3368.e1. https://doi.org/10.1016/j.jaip.2021.04.035

[16] Expert Panel Report 4 (EPR-4) Working Group (2018).

[17] 中华医学会儿科学分会呼吸学组,《中华儿科杂志》编辑委员会. 儿童支气管哮喘诊断与防治指南(2016年版) [J]. 中华儿科杂志, 2016, 54(3): 167-181.

[18] 中华儿科杂志编辑委员会, 中华医学会儿科学分会呼吸学组, 中国医师协会儿科医师分会儿童呼吸专业委员会. 儿童支气管哮喘规范化诊治建议(2020年版) [J]. 中华儿科杂志, 2020, 58(9): 708-717.

[19] Macklem, P.T. and Mead, J. (1967) Resistance of Central and Peripheral Airways Measured by A Retrograde Catheter. *Journal of Applied Physiology*, **22**, 395-401. https://doi.org/10.1152/jappl.1967.22.3.395

[20] Mead, J. (1970) The Lung's "Quiet Zone". *The New England Journal of Medicine*, **282**, 1318-1319. https://doi.org/10.1056/NEJM197006042822311

[21] Usmani, O.S., Singh, D., Spinola, M., *et al*. (2016) The Prevalence of Small Airways Disease in Adult Asthma: A Systematic Literature Review. *Respiratory Medicine*, **116**, 19-27. https://doi.org/10.1016/j.rmed.2016.05.006

[22] Tirakitsoontorn, P., Crookes, M., Fregeau, W., *et al*. (2018) Recognition of the Peripheral Airway Impairment Phenotype in Children with Well-Controlled Asthma. *Annals of Allergy*, *Asthma & Immunology*, **121**, 692-698. https://doi.org/10.1016/j.anai.2018.08.023

[23] Shi, Y., Aledia, A.S., Galant, S.P., *et al*. (2013) Peripheral Airway Impairment Measured by Oscillometry Predicts Loss of Asthma Control in Children. *Journal of Allergy and Clinical Immunology*, **131**, 718-723.

https://doi.org/10.1016/j.jaci.2012.09.022

[24] 中华医学会呼吸病学分会肺功能专业组. 肺功能检查指南(第二部分)——肺量计检查[J]. 中华结核和呼吸杂志, 2014, 37(7): 481-486.

[25] Mcnulty, W. and Usmani, O.S. (2014) Techniques of Assessing Small Airways Dysfunction. *European Clinical Respiratory Journal*, **1**, Article No. 25898. https://doi.org/10.3402/ecrj.v1.25898

[26] Zimmermann, S.C., Tonga, K.O. and Thamrin, C. (2019) Dismantling Airway Disease with the Use of New Pulmonary Function Indices. *European Respiratory Review*, **28**, Article ID: 180122. https://doi.org/10.1183/16000617.0122-2018

[27] King, G.G., Bates, J., Berger, K.I., *et al*. (2020) Technical Standards for Respiratory Oscillometry. *European Respiratory Journal*, **55**, Article ID: 1900753.

[28] 《中华实用儿科临床杂志》编辑委员会. 儿童肺功能系列指南(三): 脉冲振荡[J]. 中华实用儿科临床杂志, 2016, 31(11): 821-825.

[29] Anderson, W.J., *et al*. (2012) Are We Overlooking Persistent Small Airways Dysfunction in Community-Managed Asthma? *Annals of Allergy*, *Asthma & Immunology*, **109**, 185-189.e2.

[30] Shi, Y., Aledia, A.S., Tatavoosian, A.V., *et al*. (2012) Relating Small Airways to Asthma Control by Using Impulse Oscillometry in Children. *Journal of Allergy and Clinical Immunology*, **129**, 671-678. https://doi.org/10.1016/j.jaci.2011.11.002

[31] Mahut, B., Peiffer, C., *et al*. (2010) Gas Trapping Is Associated with Severe Exacerbation in Asthmatic Children. *Respiratory Medicine*, **104**, 1230-1233.

[32] Perez, T., Chanez, P., *et al*. (2013) Small Airway Impairment in Moderate to Severe Asthmatics without Significant Proximal Airway Obstruction. *Respiratory Medicine*, **107**, 1667-1674.

[33] 中华医学会儿科学分会呼吸学组肺功能协作组, 《中华实用儿科临床杂志》编辑委员会. 儿童肺功能及气道非创伤性炎症指标系列指南(七): 呼出气体一氧化氮监测[J]. 中华实用儿科临床杂志, 2017, 32(21): 1622-1627.

[34] Cherrez-Ojeda, I.A., *et al*. (2022) Current Needs Assessment for Using Lung Clearance Index for Asthma in Clinical Practice. *Current Allergy and Asthma Reports*, **22**, 13-20.

[35] 黄懿洁, 艾涛. 小气道功能障碍的测定及其临床意义[J]. 中国实用儿科杂志, 2021, 36(6): 420-425.

[36] 刘传合, 李硕, 邵明军. 支气管哮喘患儿肺功能改变的特征[J]. 中国实用儿科杂志, 2021, 36(6): 412-416.

[37] Arshad, S.H., Hodgekiss, C., Holloway, J.A.-O., *et al*. (2020) Association of Asthma and Smoking with Lung Function Impairment in Adolescence and Early Adulthood: The Isle of Wight Birth Cohort Study. *European Respiratory Journal*, **55**, Article ID: 1900477. https://doi.org/10.1183/13993003.00477-2019

[38] To, M., Tsuzuki, R., Katsube, O., *et al*. (2020) Persistent Asthma from Childhood to Adulthood Presents a Distinct Phenotype of Adult Asthma. *The Journal of Allergy and Clinical Immunology*: *In Practice*, **8**, 1921-1927.e2. https://doi.org/10.1016/j.jaip.2020.01.011

[39] Lajunen, K., Kalliola, S., *et al*. (2018) Abnormal Lung Function at Preschool Age Asthma in Adolescence? *Annals of Allergy*, *Asthma & Immunology*, **120**, 520-526. https://doi.org/10.1016/j.anai.2018.03.002

[40] Skylogianni, E., Triga, M., Douros, K., *et al*. (2018) Small-Airway Dysfunction Precedes the Development of Asthma in Children with Allergic Rhinitis. *Allergologia et Immunopathologia*, **46**, 313-321. https://doi.org/10.1016/j.aller.2017.09.025

[41] Schulze, J., Biedebach, S., *et al*. (2016) Impulse Oscillometry as a Predictor of Asthma Exacerbations in Young Children. *Respiration*, **91**, 107-114. https://doi.org/10.1159/000442448

[42] Takeda, T., Oga, T., Niimi, A., *et al*. (2010) Relationship between Small Airway Function and Health Status, Dyspnea and Disease Control in Asthma. *Respiration*, **80**, 120-126. https://doi.org/10.1159/000242113

[43] Galant, S.P., Fregeau, W., Pabelonio, N., *et al*. (2020) Standardized IOS Reference Values Define Peripheral Airway Impairment-Associated Uncontrolled Asthma Risk across Ethnicity in Children. *The Journal of Allergy and Clinical Immunology*: *In Practice*, **8**, 2698-2706. https://doi.org/10.1016/j.jaip.2020.03.040

[44] Farah, C.S., King, G.G., Brown, N.J., *et al*. (2012) The Role of the Small Airways in the Clinical Expression of Asthma in Adults. *Journal of Allergy and Clinical Immunology*, **129**, 381-387. https://doi.org/10.1016/j.jaci.2011.11.017

[45] Farah, C.S., King, G.G., Brown, N.J., *et al*. (2012) Ventilation Heterogeneity Predicts Asthma Control in Adults Following Inhaled Corticosteroid Dose Titration. *Journal of Allergy and Clinical Immunology*, **130**, 61-68. https://doi.org/10.1016/j.jaci.2012.02.015

[46] Puckett, J.L., Taylor, R.W., Leu, S.Y., *et al*. (2010) Clinical Patterns in Asthma Based on Proximal and Distal Airway Nitric Oxide Categories. *Respiratory Research*, **11**, 47. https://doi.org/10.1186/1465-9921-11-47

[47] Mahut, B., Trinquart, L., Le Bourgeois, M., *et al*. (2010) Multicentre Trial Evaluating Alveolar NO Fraction as a

Marker of Asthma Control and Severity. *Allergy*, **65**, 636-644. https://doi.org/10.1111/j.1398-9995.2009.02221.x

[48] Usmani, O.S., Baldi, S., Warren, S., *et al*. (2022) Lung Deposition of Inhaled Extrafine Beclomethasone Dipropionate/Formoterol Fumarate/Glycopyrronium Bromide in Healthy Volunteers and Asthma: The STORM Study. *Journal of Aerosol Medicine and Pulmonary Drug Delivery*, **35**, 179-185. https://doi.org/10.1089/jamp.2021.0046

[49] Lavorini, F., Pedersen, S. and Usmani, O.S. (2017) Dilemmas, Confusion, and Misconceptions Related to Small Airways Directed Therapy. *Chest*, **151**, 1345-1355. https://doi.org/10.1016/j.chest.2016.07.035

[50] Sonnappa, S., Mcqueen, B., Postma, D.S., *et al*. (2018) Extrafine versus Fine Inhaled Corticosteroids in Relation to Asthma Control: A Systematic Review and Meta-Analysis of Observational Real-Life Studies. *The Journal of Allergy and Clinical Immunology*: *In Practice*, **6**, 907-915.e7. https://doi.org/10.1016/j.jaip.2017.07.032

[51] Irving, S., Fleming, L., Ahmad, F., *et al*. (2020) Lung Clearance Index and Steroid Response in Pediatric Severe Asthma. *Pediatric Pulmonology*, **55**, 890-898.

[52] Díaz-García, R., Flores-Ramírez, G. and Ramírez-Oseguera, R.T. (2020) Effect of Extrafine Formulation of BDP/FF Inhaler on Asthma Control, Small Airway Function and Airway Inflammation among Mexican Asthmatic Patients. A Retrospective Analysis. *Respiratory Medicine*, **165**, Article ID: 105932. https://doi.org/10.1016/j.rmed.2020.105932

[53] Barnes, N., Price, D., Colice, G., *et al*. (2011) Asthma Control with Extrafine-Particle Hydrofluoroalkane-Beclometasone vs. Large-Particle Chlorofluorocarbon-Beclometasone: A Real-World Observational Study. *Clinical & Experimental Allergy*, **41**, 1521-1532. https://doi.org/10.1111/j.1365-2222.2011.03820.x

[54] Carpagnano, G.E., Scioscia, G., Lacedonia, D., *et al*. (2020) Treatment Response According to Small Airways Disease Status: The Effects of High-Strength Extrafine pMDI Beclomethasone Dipropionate/Formoterol Fumarate in Fixed Dose Combination in Moderate Uncontrolled Asthmatic Patients. *Pulmonary Pharmacology & Therapeutics*, **60**, Article ID: 101879. https://doi.org/10.1016/j.pupt.2019.101879

[55] Price, D., Martin, R.J., Barnes, N., *et al*. (2010) Prescribing Practices and Asthma Control with Hydrofluoroalkane-Beclomethasone and Fluticasone: A Real-World Observational Study. *Journal of Allergy and Clinical Immunology*, **126**, 511-518.e1-10. https://doi.org/10.1016/j.jaci.2010.06.040

[56] Allegra, L., Cremonesi, G., Girbino, G., *et al*. (2012) Real-Life Prospective Study on Asthma Control in Italy: Cross Sectional Phase Results. *Respiratory Medicine*, **106**, 205-214. https://doi.org/10.1016/j.rmed.2011.10.001

[57] Nakaji, H., Petrova, G., Matsumoto, H., *et al*. (2013) Effects of 24-Week Add-On Treatment with Ciclesonide and Montelukast on Small Airways Inflammation in Asthma. *Annals of Allergy*, *Asthma & Immunology*, **110**, 198-203.e3. https://doi.org/10.1016/j.anai.2012.12.016

[58] Kim, J.H., Lee, S., Shin, Y.H., *et al*. (2020) Airway Mechanics after Withdrawal of a Leukotriene Receptor Antagonist in Children with Mild Persistent Asthma: Double-Blind, Randomized, Cross-Over Study. *Pediatric Pulmonology*, **55**, 3279-3286. https://doi.org/10.1002/ppul.25085