

哮喘发作期 FeNO 升高儿童肺功能舒张试验的特点分析

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摘要: **目的** 分析不同呼出气一氧化氮(fractional concentration of exhaled nitric oxide, FeNO)水平哮喘发作期儿童肺功能指标支气管舒张试验(bronchial dilation test, BDT)后变化特点。**方法** 选取2022年1月至2023年12月就诊于山东第一医科大学附属省立医院小儿呼吸科门诊5~12岁哮喘发作期儿童为研究对象,按患儿FeNO结果分为FeNO正常组与FeNO升高组。比较两组儿童各项肺功能参数及BDT后肺功能参数改善率,并分析FeNO与肺功能参数及其舒张后改善率的相关性。**结果** 共纳入哮喘发作期儿童268例,其中211例(78.74%)FeNO升高。两组哮喘儿童肺功能主要参数第1秒用力呼气容积(forced expiratory volume in one second, FEV₁)、第1秒用力呼气容积占用力肺活量比值(forced expiratory volume in one second to forced vital capacity ratio, FEV₁/FVC)、最大呼气流量(peak expiratory flow, PEF)、用力呼气50%肺活量的瞬间流量(forced expiratory flow at 50% vital capacity, FEF₅₀)、用力呼气75%肺活量的瞬间流量(forced expiratory flow at 75% vital capacity, FEF₇₅)、最大呼气中期流量(maximum midexpiratory flow, MMEF)中位水平差异无统计学意义($P>0.05$)。BDT后,FeNO升高组FEV₁、FEF₅₀、MMEF改善率中位水平均显著高于FeNO正常组($P<0.05$);FeNO升高组儿童FEF₅₀、FEF₇₅、MMEF改善率阳性人数占比显著多于FeNO正常组儿童($P<0.05$)。FeNO与FEV₁、FEV₁/FVC弱负相关($P<0.05$);FeNO与BDT后FEV₁、PEF、FEF₅₀和MMEF改善率正相关($P<0.05$)。**结论** 多数哮喘发作期儿童FeNO水平升高,表明儿童哮喘发作以II型炎症为主。FeNO升高的急性发作期哮喘儿童BDT后改善显著增加,尤其以小气道功能改善为主要特点。此外,FeNO与FEV₁、FEF₅₀和MMEF舒张后改善率正相关。

关键词: 儿童; 支气管哮喘; 呼出气一氧化氮; 肺通气功能; 支气管舒张试验

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Analysis of the characteristics of bronchial dilation test in children with FeNO elevation during asthma exacerbation

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Abstract: Objective To analyze the improvement of pulmonary function indices after the bronchial dilation test (BDT) in children with asthma at different levels of fractional concentration of exhaled nitric oxide (FeNO).

Methods This study included children with asthma exacerbation aged 5-12 who visited the Pediatric Respiratory Clinic of Shandong Provincial Hospital Affiliated to Shandong First Medical University from January 2022 to December 2023. They were divided into the normal FeNO group and the high FeNO group based on their fractional concentration of FeNO results. Then the pulmonary function indices between the two groups of children were compared, as well as the improvement rate of pulmonary function indices after BDT, and the correlation between FeNO and pulmonary function indices and their improvement rate was analyzed. **Results** A total of 268 children with asthma exacerbations were included, of whom 211 (78.74%) had elevated FeNO. The median values of forced expiratory volume in one second (FEV_1), forced expiratory volume in one second to forced vital capacity ratio (FEV_1/FVC), peak expiratory flow (PEF), forced expiratory flow at 50% vital capacity (FEF_{50}), forced expiratory flow at 75% vital capacity (FEF_{75}) and maximum midexpiratory flow (MMEF) were not significantly different between the two groups ($P>0.05$). The median improvement rates of FEV_1 , FEF_{50} and MMEF in the high FeNO group were higher than those in the normal FeNO group ($P<0.05$). The proportion of children with positive FEF_{50} , FEF_{75} , and MMEF improvement rates in the high FeNO group was significantly higher than that in the normal FeNO group ($P<0.05$). FeNO was weakly negatively correlated with FEV_1 , FEV_1/FVC ($P<0.05$); FeNO was positively correlated with FEV_1 , PEF, FEF_{50} and MMEF improvement rate after BDT ($P<0.05$). **Conclusion** Most children with asthma during the exacerbation period have elevated levels of FeNO, indicating that type II inflammation is the main cause of childhood asthma exacerbation. The improvement of BDT in children with exacerbation of asthma with elevated FeNO is significantly increased, especially characterized by the improvement of small airway function. FeNO is positively correlated with bronchial dilation test improvement rates in FEV_1 , FEF_{50} , and MMEF.

Key words: Children; Bronchial asthma; Exhaled nitric oxide; Spirometry; Bronchial dilation test

支气管哮喘是儿童时期常见的慢性呼吸道疾病,其特征主要表现为气道炎症、气道高反应性和可逆性气流受限。呼出气一氧化氮(fractional concentration of exhaled nitric oxide, FeNO)检测无创,儿童配合程度高,近年来已逐渐成为儿童哮喘气道炎症评估重要辅助手段^[1]。支气管舒张试验(bronchial dilation test, BDT)阳性是儿童哮喘重要诊断标准之一^[2]。近几年部分学者开始关注气道炎症类型对BDT影响^[3-5],目前国内外儿童不同FeNO水平下的BDT相关的文献较少,本研究将比较不同FeNO水平哮喘儿童肺功能指标BDT后变化特点,探讨FeNO升高对哮喘儿童BDT的影响。

1 资料与方法

本研究遵循《赫尔辛基宣言》,纳入儿童监护人均签署知情同意书,通过山东第一医科大学附属省立医院医学伦理审查委员会批准(SWYX:NO.2022-581)。

1.1 研究对象

本研究纳入2022年1月至2023年12月就诊于山东第一医科大学附属省立医院小儿呼吸科门诊的5~12岁哮喘发作期儿童。

1.1.1 纳入标准

①符合《儿童支气管哮喘规范化诊治建议

(2020年版)》^[6]中哮喘诊断标准;②5岁患儿处于轻度哮喘发作,6~12岁患儿处于轻、中度哮喘发作;③近1周末使用吸入糖皮质激素(inhaled corticosteroids, ICS)及全身糖皮质激素治疗;④患儿均行肺通气功能和FeNO检查;⑤患儿药物使用符合《儿童肺功能系列指南(五):支气管舒张试验》^[7]中BDT各类药物停用时间要求;⑥征得法定监护人知情同意。

1.1.2 排除标准

①胸部异常,如鸡胸、漏斗胸、肋缘外翻等;②合并以下疾病之一者:处于肺结核、呼吸道感染等疾病急性传染期,合并肺大疱、支气管扩张等肺部疾病,先天性心脏病、心律失常等其他系统原发疾病;③生活环境暴露于严重污染有害气体或烟雾中;④不能配合完成肺通气功能与FeNO检查者。

1.2 方法

1.2.1 FeNO

采用纳库伦一氧化氮分析仪(型号:SV-O2,中国无锡尚沃生物科技有限公司)对样品气进行在线测定,参照《儿童肺功能及气道非创伤性炎症指标系列指南(七):呼出气一氧化氮监测》^[8]进行FeNO检测。所有儿童均首先进行FeNO测定。

参照《儿童呼出气一氧化氮检测及临床应用专家共识(2021版)》^[9]中FeNO界值判读标准,按照患儿FeNO测定值,12岁儿童以20ppb为切点,11岁及以下儿童年龄每减少1岁切点值降低1ppb,

将患儿分为 FeNO 升高组与 FeNO 正常组。

1.2.2 肺功能测定

使用肺功能仪(型号: Master Screen, 德国耶格公司)进行肺功能测定,在 FeNO 检测后行肺通气功能检测,并记录舒张试验后肺功能参数变化率。

1.2.2.1 肺通气肺功能测定

参照 2022 年 ATS/ERS 联合发表常规肺功能检查技术标准^[10]与《儿童肺功能检测及评估专家共识》^[11]进行肺通气功能检测。记录患儿 BDT 前后第 1 秒用力呼气容积(forced expiratory volume in one second, FEV₁)、第 1 秒用力呼气容积占用力肺活量比值(forced expiratory volume in one second to forced vital capacity ratio, FEV₁/FVC)、最大呼气流量(peak expiratory flow, PEF)、用力呼气 50%肺活量的瞬间流量(forced expiratory flow at 50% vital capacity, FEF₅₀)、用力呼气 75%肺活量的瞬间流量(forced expiratory flow at 75% vital capacity, FEF₇₅)、最大呼气中期流量(maximum midexpiratory flow, MMEF)等指标。根据指南,以 FEV₁ 占预计值百分比<80%, FEV₁/FVC 占预计值百分比<92%, FEF₅₀ 占预计值百分比、FEF₇₅占预计值百分比、MMEF 占预计值百分比<65%为降低标准^[12]。

1.2.2.2 支气管舒张试验

核对患儿支气管舒张剂及白三烯受体拮抗剂等

表 1 两组儿童年龄、性别、身高、体质量、BMI 比较

Table 1 Comparison of age, gender, height, weight and BMI between the two groups

项目	FeNO 正常组	FeNO 升高组	$\chi^2/Z/t$	<i>P</i>
人数/例(%)	57(21.3)	211(78.7)		
年龄/岁	7.0(6.0,8.5)	8.0(6.0,9.0)	-1.626	0.104
男性/例(%)	40(70.2)	135(64.0)	0.760	0.383
身高/m	1.29±0.15	1.33±0.14	-1.937	0.054
体质量/kg	32.96±16.53	33.68±14.60	-0.322	0.747
BMI	17.35(15.51,20.73)	16.83(15.13,20.34)	-0.594	0.552

2.2 患儿肺功能指标比较

2.2.1 基础肺功能比较

FeNO 正常组与 FeNO 升高组儿童 FEV₁、

表 2 两组儿童肺通气功能参数比较/ $M(P_{25}, P_{75})$

Table 2 Comparison of spirometry indices between the two groups/ $M(P_{25}, P_{75})$

肺功能参数 实预比	FeNO 正常组	FeNO 升高组	<i>Z</i>	<i>P</i>
FEV ₁ /%	94.90(79.15,103.80)	90.50(82.30,98.60)	-1.182	0.237
FEV ₁ /FVC/%	89.70(85.65,93.10)	89.50(83.30,94.60)	-0.503	0.615
PEF/%	82.00(74.05,95.40)	82.30(74.20,90.70)	-0.581	0.561
FEF ₅₀ /%	58.70(47.80,73.50)	57.00(48.20,66.30)	-0.767	0.443
FEF ₇₅ /%	46.80(30.80,60.15)	42.60(33.20,53.20)	-0.539	0.590
MMEF/%	57.10(44.05,71.60)	54.00(44.20,63.50)	-0.633	0.527

相关药物的停用时间。在患儿进行肺通气功能检查后,给予硫酸特步他林雾化溶液,雾化 15 min 后再次行肺通气功能检测^[7,13]。

根据指南,以 BDT 后 FEV₁ 改善率≥12%,PEF 改善率≥15%,FEF₅₀、FEF₇₅、MMEF 改善率≥30%为 BDT 阳性标准^[7,13-15]。

1.3 统计学处理

应用 SPSS 26.0 统计软件。肺通气功能检测参数以占正常预计值百分比表示。对纳入分析所有参数进行正态性检验,计量资料采用 $\bar{x}\pm s$ 或 $M(P_{25}, P_{75})$ 表示,组间比较使用独立样本 *t* 检验或 Mann-Whitney *U* 检验。计数资料采用频数(构成比)表示,组间比较使用 χ^2 检验。相关性分析采用 Spearman 相关。检验水准 $\alpha = 0.05$ 。

2 结果

2.1 一般资料

研究共纳入 268 例哮喘发作期儿童,FeNO 正常组 57 例(21.3%),FeNO 升高组 211 例(78.7%)。肺通气功能及其 BDT 后改善率均呈非正态分布。两组儿童年龄、性别、身高、体质量、体质量指数(body mass index, BMI)差异均无统计学意义($P > 0.05$)。见表 1。

FEV₁/FVC、PEF、FEF₅₀、FEF₇₅、MMEF 差异均无统

计学意义($P > 0.05$)。见表 2。

对患儿各肺功能参数降低人数比例进行统计分析,两组儿童肺功能降低人数比例差异均无统计学意义($P>0.05$)。见表 3。

表 3 两组儿童肺通气功能参数降低人数所占比例比较/ n (%)Table 3 Comparison of the proportion of children with decreased spirometry indices between the two groups/ n (%)

肺功能参数降低人数	FeNO 正常组 ($n=57$)	FeNO 升高组 ($n=211$)	总体 ($n=268$)	χ^2	P
FEV ₁	15(26.32)	42(19.91)	57(21.27)	1.101	0.294
FEV ₁ /FVC	39(68.42)	131(62.09)	170(63.43)	0.777	0.378
FEF ₅₀	36(63.16)	152(72.04)	188(70.15)	1.690	0.194
FEF ₇₅	49(85.96)	187(88.63)	236(88.06)	0.302	0.583
MMEF	38(66.67)	165(78.20)	203(75.75)	3.249	0.071

2.2.2 支气管舒张后各肺功能参数变化率的比较 改善率显著高于 FeNO 正常组($P<0.05$)。见表 4。

FeNO 升高组 BDT 后 FEV₁、FEF₅₀、MMEF 的

表 4 两组儿童 BDT 后肺通气功能参数改善率比较/ $M(P_{25},P_{75})$ Table 4 Comparison of the improvement rate of spirometry indices after BDT between the two children groups/ $M(P_{25},P_{75})$

肺功能参数改善率	FeNO 正常组	FeNO 升高组	Z	P
FEV ₁ /%	12.10(4.90,14.90)	13.50(8.40,17.60)	-2.359	0.018
PEF/%	9.20(2.30,16.40)	10.60(5.00,18.30)	-1.323	0.186
FEF ₅₀ /%	29.20(13.30,54.35)	42.60(24.40,61.40)	-2.526	0.012
FEF ₇₅ /%	46.60(18.30,78.10)	59.00(34.70,86.10)	-1.911	0.056
MMEF/%	39.20(16.50,61.40)	48.80(30.30,66.90)	-2.495	0.013

对患儿 BDT 后肺功能参数阳性占比进行分析,肺通气功能指标中,FeNO 升高组儿童 FEF₅₀、FEF₇₅、MMEF 改善率阳性儿童人数占比显著多于 FeNO 正常组儿童($P<0.05$)。见表 5。

表 5 两组儿童肺通气功能参数 BDT 阳性人数所占比例比较/ n (%)Table 5 Comparison of the proportion of BDT positive of spirometry indices between the two children groups/ n (%)

肺功能参数 BDT 阳性人数	FeNO 正常组 ($n=57$)	FeNO 升高组 ($n=211$)	总体 ($n=268$)	χ^2	P
FEV ₁ BDT	29(50.88)	130(61.61)	159(59.3)	2.143	0.143
PEF BDT	18(31.58)	76(36.02)	94(35.07)	0.388	0.533
FEF ₅₀ BDT	28(49.12)	141(66.82)	169(63.1)	6.037	0.014
FEF ₇₅ BDT	34(59.65)	168(79.62)	202(75.4)	9.643	0.002
MMEF BDT	34(59.65)	159(75.36)	193(72.0)	5.493	0.019

2.3 FeNO 与肺功能有关指标相关性分析

2.3.1 FeNO 与肺功能参数相关性分析

FeNO 与 FEV₁ 和 FEV₁/FVC 弱负相关($r_s = -0.194, -0.150; P<0.05$)。见表 6。

表 6 哮喘发作儿童 FeNO 与肺通气功能参数的相关性

Table 6 Correlation between FeNO and spirometry indices in children with asthma exacerbation

肺功能参数 实预比	r_s	P
FEV ₁	-0.194	0.001
FEV ₁ /FVC	-0.150	0.014
PEF	-0.064	0.300
FEF ₅₀	-0.106	0.083
FEF ₇₅	-0.079	0.199
MMEF	-0.095	0.121

2.3.2 FeNO 与 BDT 后肺功能参数相关性分析

FeNO 与 BDT 后 FEV₁、PEF、FEF₅₀ 和 MMEF 改善率正相关($P<0.05$)。见表 7。

表 7 哮喘儿童 FeNO 与 BDT 后肺通气功能参数改善率的相关性

Table 7 Correlation between FeNO and improvement rate of spirometry indices after BDT in children with asthma

肺功能参数 改善率	r_s	P
FEV ₁	0.167	0.006
PEF	0.163	0.008
FEF ₅₀	0.140	0.022
FEF ₇₅	0.062	0.315
MMEF	0.124	0.043

3 讨论

常规通气肺功能检查可以反映患儿肺容积和通气功能的情况,是国内外指南推荐的儿童哮喘诊断与病情监测评估的重要手段^[2,6,15]。本研究中超60%患儿存在 FEV₁/FVC、FEF₅₀、FEF₇₅与 MMEF 水平降低,表明哮喘发作期儿童存在肺功能下降,与既往研究一致^[16]。

儿童支气管哮喘多数为过敏性哮喘,主要内型为 II 型炎症^[1,17]。急性发作期,气道 NO 水平升高会加重气道炎症与组织损伤,表现气道高反应性^[18],因此 FeNO 是重要的 II 型气道炎症生物标志物,可用于儿童哮喘监测,识别哮喘急性发作风险^[19]。

本研究纳入的哮喘发作期儿童中,78.74% FeNO 水平升高,表明儿童哮喘发作主要以气道 II 型炎症为主,与李硕等的研究结果一致^[20]。FeNO 水平能辅助评估哮喘急性发作炎症类型及对激素治疗的反应,FeNO 升高儿童气道 II 型炎症较重,其对抗炎治疗要求更高, Schneider 等^[21]的前瞻性队列研究发现,FeNO 升高增强了 ICS 反应的可能,《儿童呼出气一氧化氮检测及临床应用专家共识(2021 版)》指出,对于 12 岁以下儿童若 FeNO 值高于 35 ppb,多数情况下对 ICS 治疗的反应较为理想。而基线值超过 50 ppb 的儿童,在治疗后若 FeNO 值较基线下降超过 10 ppb,即可视为 ICS 治疗有效^[9]。因此 FeNO 水平升高儿童应加强 ICS 抗炎治疗。

本研究发现,吸入支气管舒张剂后,FeNO 升高组 FEV₁、FEV₁/FVC、FEF₅₀与 MMEF 改善率中位水平显著高于 FeNO 正常组儿童,同时 FEF₅₀、FEF₇₅、MMEF 改善率阳性人数占比显著高于 FeNO 正常组,进一步对 FeNO 水平与 BDT 后改善率进行相关性分析,发现 FeNO 水平与 BDT 后 FEV₁^[3]、PEF、FEF₅₀和 MMEF 改善率正相关。Ghobain 等对成人哮喘患者进行研究,发现高 FeNO 人群 FEV₁ 更低,且吸入支气管扩张剂后可逆性更高,FeNO 与支气管可逆性呈弱正相关。此外,Skov 等^[4]对哥本哈根哮喘儿童前瞻性研究母子队列进行分析,也发现高 T2 型哮喘儿童较低 T2 型患儿 BDT 后气道阻力(specific airway resistance, sRaw)与 FEV1 改善率更高,气道可逆性更高,与本研究结果相似。FeNO 升高组儿童多数暴露于过敏原,可破坏气道上皮屏障功能,激活以 Th2 及 II 型固有淋巴细胞(Group 2

innate lymphoid cell, ILC2) 为主导的 II 型炎症反应,IL-5 水平升高可动员嗜酸性粒细胞(Eosinophil, EOS)活化并激发其脱颗粒,进而促进 EOS 在气道浸润,诱发过敏性炎症,IL-4 与 IL-13 分泌升高共同促进气道上皮 NO 表达增加,激活 EOS、嗜碱性粒细胞与淋巴细胞等炎症细胞并促进其募集^[22],此外,FeNO 升高可引起亚硝酸盐等物质生成增加,进一步加重气道炎症^[23]。持续慢性气道炎症又加重哮喘儿童气道高反应性,当遇到物理、化学、感染等诱因时,哮喘儿童会频繁出现咳嗽、喘息等呼吸道症状^[24]。因此,FeNO 升高患儿 BDT 改善率更高,对支气管舒张剂反应更敏感。

小气道管腔直径虽小,但体积占肺总体积的 98.8%,是哮喘儿童气流受限的主要部位^[25]。本研究发现 FeNO 升高组儿童 BDT 后 FEF₅₀、FEF₇₅、MMEF 改善率阳性人数占比显著高于 FeNO 正常组,FeNO 升高儿童小气道功能改善阳性率更高。高 FeNO 水平会导致气道炎症加重,更易引起小气道功能障碍,既往研究表明,小气道功能障碍与更严重的气道高反应性、更差的哮喘控制与更多的急性发作有关^[26],总之,FeNO 升高组小气道指标改善率更高。

因此,在临床实践中,FeNO 检测不仅为评估气道炎症提供便捷高效的手段,而且能够初步预测哮喘儿童对支气管舒张剂的敏感性。对于那些 FeNO 水平升高且病情较重的哮喘儿童,暂时无法进行肺功能检测,亦可在加强抗炎治疗的基础上,积极施用支气管舒张剂,并持续监测肺功能,特别是小气道功能的逐步改善。

综上所述,多数哮喘发作期儿童 FeNO 水平升高,表明儿童哮喘发作以 II 型炎症为主;FeNO 升高的急性发作期哮喘儿童 BDT 后改善显著增加,尤其以小气道功能改善为主要特点;此外,FeNO 与 FEV₁、FEF₅₀和 MMEF 舒张后改善率正相关。

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