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呼出气一氧化氮对儿童支气管哮喘急性发作期的诊断价值及对病情的评估价值

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[摘要] 目的：探讨呼出气一氧化氮(fractional exhaled nitric oxide, FeNO)对儿童支气管哮喘的诊断及病情评估价值。方法：共收集德阳市人民医院2017年3月至2018年6月儿科收治的80例支气管哮喘急性发作期患儿，记为急性期组($n=80$)，急性期患儿根据病情程度进一步分为轻度组($n=32$)和中重度组($n=48$)；选取同期收治的35例支气管哮喘非急性发作期患儿作为参照，记为非急性期组($n=35$)。检测上述患儿FeNO浓度、第一秒用力呼气容积占预计值百分比(percentage of predicted forced expiratory volume in one second, FEV1%pred)、第1秒用力呼气容积占用力肺活量(forced vital capacity, FVC)百分比(forced expiratory volume in 1 second/forced, FEV1/FVC%)和炎症因子白介素-6(interleukin 6, IL-6)、C反应蛋白(C-reaction protein, CRP)水平，采用Pearman法分析急性期组FeNO浓度与FEV1%pred, FEV1/FVC%, IL-6, CRP的相关性，采用受试者工作特征(receiver operating characteristic, ROC)曲线分析FeNO诊断小儿支气管哮喘急性发作期的诊断效能。结果：所有受检患儿完成相关检测，急性期组患儿FeNO浓度和血清IL-6和CRP水平均高于非急性期组，FEV1%pred, FEV1/FVC%明显低于非急性期组，差异均有统计学意义($P<0.001$)；轻度组和中重度组患儿FeNO浓度，FEV1%pred, FEV1/FVC%, IL-6, CRP比较，差异有统计学意义($P<0.001$)。Spearman线性相关分析提示：急性期患儿FeNO浓度与FEV1%pred, FEV1/FVC%呈负相关，与炎症因子IL-6和CRP呈正相关。ROC曲线提示FeNO诊断急性发作期支气管哮喘患儿的最佳截断点为39.84 ppb，敏感度、特异度分别为82.36%，88.74%。结论：支气管哮喘急性发作期患儿FeNO浓度与肺功能和炎症水平有较好相关性，加强FeNO监测有助于诊断急性期早期和评估病情程度，对指导起始治疗有一定参考价值。

[关键词] 支气管哮喘急性期；儿童；呼出气一氧化氮；炎症因子；诊断

Diagnostic value of exhaled nitric oxide in children with acute attack of bronchial asthma

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Abstract **Objective:** To explore the value of fractional exhaled nitric oxide (FeNO) in the diagnosis and evaluation of

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children's asthma in acute stage. **Methods:** A total of 80 children with acute attack of bronchial asthma admitted to our hospital from March 2017 to June 2018 were recorded as acute group ($n=80$). According to the severity of the disease, children in acute stage were further divided into mild group ($n=32$) and moderate severe group ($n=48$). Thirty-five children in non-acute attack of bronchial asthma admitted at the same period were selected as reference and recorded as non-acute group ($n=35$). FeNO, FEV1% pred, FVC, IL-6 and CRP were measured in all asthmatic children. The correlation between FeNO concentration and FEV1% PRED, FEV1/FVC, IL-6, CRP in acute stage group was analyzed by Pearman method, and the diagnostic efficacy of FeNO in acute stage of childhood asthma was analyzed by receiver operating characteristic (ROC) curve. **Results:** All the children were tested. The levels of FeNO, IL-6 and CRP in the acute group were higher than those in the non-acute group, FEV1% pred and FEV1/FVC% were significantly lower than those in the non-acute group ($P<0.001$). There were significant differences in FeNO concentration, FEV1% pred, FEV1/FVC%, IL-6 and CRP between mild group and moderate group ($P<0.001$). Spearman linear correlation analysis showed that FeNO concentration was negatively correlated with FEV1% pred and FEV1/FVC%, and positively correlated with IL-6 and CRP. ROC curve suggested that the best cut-off point of FeNO in the diagnosis of asthma in children with acute attack was 39.84 ppb, with sensitivity and specificity of 82.36% and 88.74%. **Conclusion:** There is a good correlation between FeNO concentration and pulmonary function and inflammatory level in children with acute attack of asthma. Strengthening the monitoring of FeNO is helpful for the early diagnosis and assessment of the degree of disease in the acute stage, and has a certain reference value for guiding the initial treatment.

Keywords acute stage of bronchial asthma; children; exhaled nitric oxide; inflammatory factors; diagnosis

支气管哮喘是儿科常见疾病，多在夜间或清晨发作、加剧，主要表现为胸闷、咳嗽、喘息等临床症状，若诊治不及时，随病程延长可产生气道不可逆性缩窄和气道重塑，对患儿身心健康和日常学习产生消极影响^[1]。目前临床主要根据临床症状、体征观察和肺功能检测等诊断评估病情，但上述手段并不能直接反映患儿气道炎症情况，操作主观性较强^[2]。虽然支气管镜下支气管灌洗液和内膜活检可直接检测气道炎症，但该方法有创或操作要求较高，不宜被患儿家属接受，临床推广应用较为困难^[3]。呼出气一氧化氮(fractional exhaled nitric oxide, FeNO)是近些年支气管哮喘气道炎症研究领域的热点，FeNO检测方便、无创和重复性好，对支气管哮喘的辅助诊断价值得到公认，但FeNO诊断支气管哮喘急性期患儿的报道偏少，最佳阈值点尚无权威定论，与病情严重程度有无内在关联仍需深入探讨^[4]。本研究旨在探讨FeNO浓度检测对儿童支气管哮喘急性发作期的诊断及病情程度评估价值。

1 对象与方法

1.1 对象

研究对象为2017年3月至2018年6月期间德阳

市人民医院儿科收治的支气管哮喘急性发作期患儿，记为急性期组($n=80$)。纳入标准：1)患儿年龄5~12岁，因喘息、气急、胸闷等症状就诊，诊断均符合中华医学会儿科学分会呼吸学组《儿童支气管哮喘诊断与防治指南(2016年版)》^[5]；患儿多因过敏体质发病；2)就诊入组前1周未使用糖皮质激素或支气管扩张剂；3)患儿家属对本研究知情同意。排除标准：1)患儿1个月内有全身变态反应表现或急性上下呼吸道感染史者；2)合并慢性肺部疾病、全身系统疾病等；3)合并鼻炎、湿疹；4)患儿依从性较差、难以配合相关检测者。纳入患儿中男43例，女37例；年龄5~12(7.15 ± 0.96)岁；根据指南评估病情程度，轻度32例，中度37例，重度11例，因重度例数偏少，故将中、重度合并，将急性期组患儿分为轻度组($n=32$)和中重度组($n=48$)，轻度组与中重度组患儿资料比较差异无统计学意义($P>0.05$)。选取同期收治的35例非急性发作支气管哮喘患儿作为参照，记为非急性期组($n=35$)，排除合并鼻炎、严重感染和慢性肺部疾病等。非急性发作期男21例，女14例；年龄3~12(5.70 ± 2.11)岁。急性期与非急性发作期患儿性别和年龄相较差无统计学意义($P>0.05$)，均衡可比。本研究经德阳市人民医院医学伦理委员会审核批准。

1.2 方法

1.2.1 FeNO 浓度检测

采用纳库仑NO分析仪, 检测前由受试者家属和专门的医护人员与受试者进行沟通, 讲解FeNO检测的基本操作, 对于年龄较小的患儿, 由患儿家属、检测者轻柔耐心安抚, 直至顺利接受检查。检查时, 受试患儿取端坐位, 用力呼气后用嘴唇含紧过滤器, 用力吸气约5 s后, 用均匀平稳的流速呼气, 呼气时间持续8~10 s, 60 s后可读取FeNO浓度值。每例受检患儿检测3次, 取平均值作为最终FeNO浓度值。

1.2.2 肺功能指标检测

采用德国AEGER公司生产的Mastre Screen肺功能检测仪, 由专门检测人员严格按照说明书操作。采用肺量测定法获得受试者最大气流-容积曲线, 检测指标包括第一秒用力呼气容积占预计值百分比(FEV1%pred)。每例受检者检测3次, 取平均值作为最终肺功能指标记录值。

1.2.3 血清炎症因子检测

抽取受检者空腹静脉血3 mL, 常规3 000 r/min离心15 min后收集血清样本, 置于-80 ℃冰箱内储存待检。采用ELISA检测血清CRP和IL-6水平, 均严格按照试剂盒说明书操作。

1.3 统计学处理

采用SPSS22.0统计软件进行数据分析, 正态分布计量资料用均数±标准差($\bar{x} \pm s$)表示, 组间数据相较行独立t检验, 偏态分布剂量资料用中位数[四分位数间距]表示, 组间比较行Mann-Whitney U检验; 采用Pearman法分析急性期组患儿FeNO浓度与肺功能、血清炎症因子指标之间的关系; 绘制ROC曲线分析FeNO诊断支气管哮喘急性发作期

患儿的最佳诊断界值。以 $P < 0.05$ 为差异有统计学意义。

2 结果

2.1 急性期组和非急性期组患儿 FeNO 浓度和肺功能、炎症因子水平比较

所有患儿成功完成FeNO浓度和肺功能指标检测, 急性期组FeNO浓度和血清IL-6和CRP水平明显高于非急性发作期组, FEV1%pred显著低于轻度组, 差异均有统计学意义($P < 0.05$, 表1)。

2.2 急性期组不同病情程度患儿 FeNO 浓度和肺功能、炎症因子水平比较

中重度组患儿FeNO浓度和血清IL-6, CRP水平高于轻度组, FEV1%pred显著低于非急性发作期组, 差异均有统计学意义($P < 0.05$, 表2)。

2.3 急性期组患儿 FeNO 浓度与肺功能、炎症因子相关性

支气管哮喘急性期患儿FeNO浓度与FEV1%pred呈负相关($r = -0.736$, $P < 0.05$), 与血清IL-6和CRP水平呈正相关($r = 0.748$, 0.729 ; $P < 0.05$), 即急性期患儿随病情加重, FeNO浓度升高, FEV1%pred逐渐下降, 血清IL-6和CRP水平明显升高。

2.4 FeNO 浓度对支气管哮喘急性期患儿的诊断效能

以支气管哮喘指南为指导的临床诊断结果为金标准, FeNO浓度诊断支气管哮喘急性期患儿的ROC曲线下面积为0.897, 最佳阈值点为39.84 ppb(95%CI: 0.869~0.937), 敏感度82.36%, 特异度88.74%。

表1 急性期组和非急性发作期FeNO浓度及相关检测指标比较($\bar{x} \pm s$)

Table 1 Comparison of FeNO concentration and related detection indexes between the acute stage group and the non-acute stage group ($\bar{x} \pm s$)

组别	n	FeNO/ppb	FEV1%pred/%	IL-6/(pg·mL ⁻¹)	CRP/(mg·L ⁻¹)
非急性期组	35	32.41 ± 5.84	84.42 ± 9.01	2.32 ± 0.51	2.98 ± 0.74
急性期组	80	53.27 ± 7.01	53.58 ± 8.57	4.37 ± 1.05	5.09 ± 1.23
t		15.410	17.482	10.978	9.417
P		<0.001	<0.001	<0.001	<0.001

表2 不同病情支气管哮喘患儿FeNO浓度和CRP水平比较($\bar{x} \pm s$)Table 2 Comparison of FeNO concentration and CRP level in children with asthma of different conditions ($\bar{x} \pm s$)

组别	<i>n</i>	FeNO/ppb	FEV1%pred/%	IL-6/(pg·mL ⁻¹)	CRP/(mg·L ⁻¹)
轻度组	32	44.63 ± 5.30	57.42 ± 6.38	2.97 ± 0.64	4.16 ± 0.55
中重度组	48	59.03 ± 6.57	51.02 ± 7.12	5.30 ± 0.96	5.71 ± 0.78
<i>t</i>		10.349	4.103	12.048	9.734
<i>P</i>		<0.001	<0.001	<0.001	<0.001

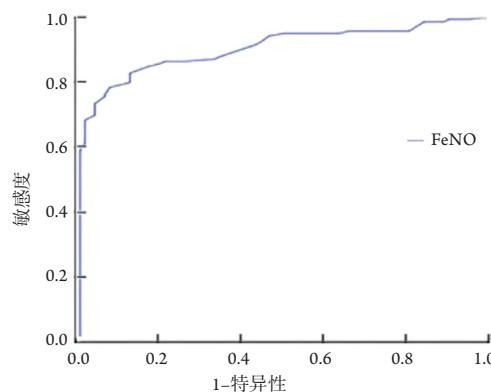


图1 FeNO浓度诊断支气管哮喘急性期患儿的ROC曲线图
Figure 1 ROC curve of FeNO concentration in the diagnosis of acute stage of bronchial asthma

3 讨论

目前普遍认为支气管哮喘与呼吸道病毒感染、气道慢性炎症、机体应急变态反应等有关，其本质为气道炎症，急性期患儿血清IL-6和CRP等炎症因子水平异常升高^[6-7]。儿童由于机体发育不成熟、呼吸系统屏障功能和免疫抵抗力低等特点，是此症的高发人群。据第3次中国城市儿童哮喘流行病学调查结果^[8](2009年9月至2010年8月)显示发病率高达3.02%，2年现患率达2.32%，已接近发达国家水平，同时不同地区、年龄的儿童患病情况也各有特点，给临床诊治带来诸多难题。气道炎症和儿童支气管哮喘发病及病情进展息息相关，但以往评价气道炎症的方法操作繁琐、有创或准确度偏低，比如支气管内膜活检、诱导痰检测及生化检测(血Eos和IgE水平)等，不易在临床推广应用。

医学上将FeNO称为“炎症尺度”，原因在于呼吸道上皮可在炎性细胞因子诱导下持续产生NO，可作为气道嗜酸粒细胞炎性反应的标志物^[9-10]，美国胸科协会(American Thoracic Society,

ATS)和全球哮喘防治创议(Global Initiative for Asthma, GINA)均充分肯定FeNO检测对支气管哮喘临床诊疗的参考价值。较多报道^[11-12]指出支气管哮喘患儿受气道炎症损伤影响，上皮细胞诱导的NO合成酶(nitric oxide synthase, NOS)活性增高，导致呼出气体中NO水平也随之升高，通过检测FeNO浓度可直观、准确掌握受检患儿气道的炎症水平，对临床诊断和病情评估提供参考。此外FeNO检测具有操作简单、耗时短、可重复等优点，受到临床的充分重视^[13]。但关于FeNO浓度对支气管哮喘急性期患儿的诊断报道较少，急性期患儿病情程度差异较大，不同病情程度患儿的FeNO浓度检测价值尚需深入探讨。

本研究为减少受检患儿年龄过小对FeNO浓度检测结果的影响，年龄段选择为5~12岁。结果显示急性期组患儿FeNO浓度明显高于非急性期组，血清IL-6和CRP也异常较高，FEV1%pred明显降低，可见支气管哮喘急性期和非急性发作期患儿的FeNO浓度、气道炎症程度和肺功能存在较大差异，急性期患儿病情和文献[14]结论相吻合，提示FeNO浓度对支气管哮喘急性期的诊断及病情评估有积极作用。FeNO浓度和FEV1%pred分别从气道炎症和气道通气功能2个不同角度进行评估，二者变化可能并不平行。既往报道^[15-16]和临床经验表明：较多支气管哮喘非急性发作期患儿FeNO浓度有异常升高，而肺功能检测正常或趋于正常，也较好解释了FeNO浓度和FEV1%pred的关系。但支气管哮喘患儿急性期病情加剧，FeNO浓度随之异常升高，气道高反应性明显，易引起患儿气流受限和气道阻塞，导致气道通气功能障碍，表现为FEV1%pred下降，因此FeNO浓度仅作为支气管哮喘的辅助诊断，不能替代肺功能检测，二者联合诊断效果更佳^[17-18]。本研究显示：中重度组FeNO浓度、FEV1%pred和血清IL-6，CRP水平与轻度组比较也有显著差异；且Pearman法分析显示：急性

期组患儿FeNO浓度与FEV1%pred呈负相关，与血清IL-6和CRP水平呈正相关，表明FeNO浓度能较好反映急性期患儿气道炎症水平和气道通气障碍程度，有助于评估病情程度和指导治疗^[19-20]。目前医学对FeNO浓度辅助诊断儿童支气管哮喘急性发作期的最佳阈值点无明确定论，资料缺乏，已有报道多为成人支气管哮喘急性期的诊断评估。本研究ROC曲线分析提示FeNO浓度诊断儿童支气管哮喘急性期的最佳阈值点为39.84 ppb，敏感度、特异度分别为82.36%，88.74%，可为临床诊断提供参考。

本研究也存在些许不足，比如受准备时间仓促、精力有限影响，难免存在些许疏漏和主观偏差。此外FeNO浓度检测对于鉴别小儿支气管哮喘和咳嗽变异性哮喘的价值也可进一步深入探讨等^[20]。总的来说，FeNO浓度检测为临床诊断儿童支气管哮喘急性期和评估病情程度提供了有效途径，操作简单、方便和敏感性好等优点，易推广应用。相信随着医学对FeNO认识水平的不断加深和相关检测说明的不断完善，其检测运用价值将日益凸显。

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