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ORIGINAL RESEARCH

Bronchodilator Response Assessed by Surface Respiratory Muscle EMG in Children

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Background: An increase of ≥ 12% in forced expiratory volume in the first second (FEV_1) after inhalation of bronchodilator indicates airway reversibility. However, it is difficult to measure FEV_1 in children. The aim of the study is to determine whether respiratory muscle electromyograms recorded from chest wall surface electrodes can be used to distinguish children with uncontrolled asthma from healthy subjects.

Methods: Fourteen children with uncontrolled asthma [aged 6.1 (3 ~ 13) years] and 28 healthy children [aged 7.6 (3 ~ 13) years] were recruited. Uncontrolled asthma was defined as having poorly controlled symptoms, along with an increase in FEV_1 of at least 12%, or presenting with a wheezing symptom that improved after inhaling a bronchodilator. Diaphragm electromyogram (EMG_{di}), parasternal intercostal EMG (EMG_{para}), airflow, FEV_1, and wheezing were recorded before and after inhalation of bronchodilator.

Results: Good-quality EMG_{di} and EMG_{para} could be recorded in all subjects. However, 18 of 42 children could not perform the spirometer properly. Changes in EMG_{di} [−24.6% (−43.5 ~ −12.4%) vs −0.1% (−13.2 ~ 16.9%), $p<0.001$] and EMG_{para} [−11.2% (−31.5 ~ 32.4%) vs −0.5% (−24.9 ~ 13.0%), $p<0.05$] in children with asthma were, respectively, significantly larger than those in healthy subjects during bronchodilator response. The area under the receiver operating characteristic curves for the changes of EMG_{di} and EMG_{para} were 0.995 (95% CI 0.906 to 1.000) and 0.755 (95% CI 0.598 to 0.874).

Conclusion: Surface respiratory muscle EMG could be feasible and useful to assess bronchodilator response to differentiate children with uncontrolled asthma from healthy subjects.

Keywords: respiratory muscle electromyogram, bronchodilator test, spirometry, children asthma

Introduction

Asthma is characterized by episodic and reversible lower airway obstruction.[1] The post-bronchodilator airway reversibility could offer useful objective information for a diagnosis of asthma and evaluating response to therapy.[1,2] An increase of ≥ 12% in forced expiratory volume in the first second (FEV_1) after inhalation of bronchodilators indicates airway reversibility.[3] However, measuring FEV_1 can be challenging due to difficulties in meeting quality control standards, and it has limitations, such as requiring forced maximal inhalation and exhalation maneuvers, which can affect airway calibre.[4–6]

Compared to adults, the success rate of conducting spirometry is lower in children, particularly in preschool-aged children, where the success rate is less than half.[7] Moreover, the baseline lung function of children can be also affected by multiple factors such as previous lower respiratory tract infections, the timing of previous wheeze,[8] which in turn impacts the evaluation of the results of bronchodilator response (BDR). In many healthcare settings, asthma in children is

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a clinical diagnosis based on parental reported symptoms,[9] but this approach carries a significant risk of misdiagnosis,[10,11] resulting in over- and undertreatment of asthma, poor symptom control, and in delayed commencement of asthma treatment.[12]

Since respiratory muscle EMG reflects the work of breathing, the overall stiffness or compliance of the lungs induced by changes in the airway smooth muscle activity, EMG could be used to reflect change in load or increase in compliance after bronchdilation.[13–16] Our previous studies showed that respiratory muscles electric activities recorded from chest wall surface electrodes are a noninvasive technique, requires minimal active cooperation. Moreover, it could offer objective information that indirectly reflect the changes in the lower airway resistance induced by histamine provocation test[17] or exercise[18] in adults. However, no data are available on surface respiratory muscle EMG and BDR in children with acute asthma. The aims of the present study were to determine whether surface respiratory muscle EMG could be feasible and used to assess the BDR and differentiate children with acute asthma from healthy subjects.

Methods

Subjects

A case–control study was performed on uncontrolled asthmatic children matched by age to healthy controls recruited from the community. Uncontrolled asthmatic children aged 3–14 years were recruited in the department of pediatrics of the first affiliated hospital of Guangzhou Medical University. These asthmatic children were diagnosed by a pediatric physician based on history of recurrent attacks of dyspnea with perceptible wheezing and one of the objective tests (eg, IgE, FeNO, or methacholine provocation test), and meeting the 2022 Global Initiative for Asthma,[1] and remained in an uncontrolled state at this visit. The uncontrolled state was defined as having poorly controlled symptoms, along with an increase in FEV_1 of at least 12%, or presenting with a wheezing symptom that improved after inhaling a bronchodilator. The history of respiratory conditions for asthma children were also collected during this visiting. This study protocol was reviewed and approved by ethic committee of the first affiliated Hospital of Guangzhou Medical University, approval number [2020 K-123], and written informed consent was obtained from participants' parent to participate in the study.

Measurement

All subjects were asked to lay on the bed to measure diaphragm electromyogram (EMG_{di}), parasternal intercostal EMG (EMG_{para}) and airflow. EMG_{di} was simultaneously recorded from two pairs of electrodes (3M Health Care, D-41453 Neuss, Germany) on the right side as described by previous studies.[17–20] EMG_{para} was recorded using bipolar electrodes placed bilaterally 3 cm from the midpoint of the sternum in the second intercostal space.[21] Airflow was recorded by a digital flow meter (Siargo, Inc. Santa Clara, CA 95054, USA) via mask further connected to an additional tube which was 2 cm in diameter and 7 cm in length to increase inspiratory load to improve EMG_{di} quality. The EMG_{di} and airflow were recorded by the respiratory signal processor (RA-16, Respiratory Medical Science Co. Ltd, Guangzhou, China) simultaneously. The subjects were lied down throughout the test to minimize influences caused by posture changes.

Spirometry measurements (Cosmed Micro Quark, Cosmed Italy) were performed based on the recommendation of ATS/ERS.[22] Sufficient time was offered to the subjects for practicing maneuvers of the forced spirometry to ensure quality of the pulmonary function test. For FEV_1 repeatability, the difference between the largest and the next largest FEV_1 is <0.150 L for those older than 6 years of age and <0.100 L or 10% of the largest FEV_1, whichever is greater, for those aged 6 years or younger.[22] A minimum of two technically acceptable measurements were required for those who are able to perform spirometry in both healthy group (Healthy-A) and asthma group (Asthma-A) but not for those who are unable to perform spirometry after more than ten manoeuvres or twenty minutes practice in both healthy group (Healthy-U) and asthma group (Asthma-U).

Protocol

Surface respiratory muscle EMG, FEV_1 and wheezing were successively recorded before and after the inhalation of salbutamol. EMG signals and airflow were systematically recorded before spirometry to avoid the effect produced by forced spirometry maneuvers on bronchial tone. It is difficult for children to maintain stable breathing for 3 minutes;

therefore, brief interruptions were allowed during EMG signal recording. Salbutamol was delivered via a mouthpiece chamber: 2 puffs (200 µg) for children aged 3–5 years and 4 puffs (400 µg) for those older than 5 years. Timing between salbutamol and EMG measurements was at least 15min. The recording time for surface respiratory muscle EMG and FEV_1 was collected, respectively, for the former including preparation and recording sufficient analyzed EMG signals, for the latter from the beginning of training to obtaining three valid measurements.

Data and Statistical Analysis

Respiratory muscle EMG signal was automatically converted to Root Mean Square (RMS) by the respiratory signal processor (RA-16, Respiratory Medical Science Co. Ltd, Guangzhou, China).[23–25] Peak value of RMS of EMG free from ECG was selected. Tidal volume (V_T) was calculated from integrated flow and was further standardized with body weight (mL/kg). Data from fifteen breathing cycles during tidal breaths were averaged for each time points (before and after the inhalation of salbutamol). EMG_{di} and EMG_{para} combined with V_T were expressed as EMG_{di}/V_T and EMG_{para}/V_T. The changes of FEV_1 ($\Delta FEV_1\%$), EMG_{di} ($\Delta EMG_{di}\%$), EMG_{para} ($\Delta EMG_{para}\%$), EMG_{di}/V_T ($\Delta EMG_{di}/V_T\%$) and EMG_{para}/V_T ($\Delta EMG_{para}/V_T$) before and after inhalation of bronchodilator were selected for further analysis. EMG_{di} recorded from one pair representing better signal-to-noise ratio and less baseline variation was regarded as the primary signal for analysis. For each subject, the same pair of electrodes were used consistently before and after inhalation of salbutamol.

All parameters were assessed for normality by the Shapiro–Wilk test. Normally distributed data was presented as mean (standards or range), while data distributed non-normally was represented with mean (minimum ~ maximum). Wilcoxon Signed rank test and Mann–Whitney *U*-test were used for statistical analysis of two independent or paired groups. For categorical variables, contingency tables were used (2 with Fisher exact test). ROC (Receiver Operating Characteristic) curves were used to evaluate the diagnosis value of $\Delta EMG_{di}\%$, $\Delta EMG_{para}\%$, $\Delta EMG_{di}/V_T\%$ and $\Delta EMG_{para}/V_T\%$ for asthma, and the difference between each two area under ROC curves (AUC) among those were compared with the method of DeLong et al.[26] $P<0.05$ was considered statistically significant.

Results

Thirty-two healthy children from community who agreed to participate in the study were classified as healthy; four were excluded (two presented an acute respiratory tract infection and two refused to perform spirometry). Therefore, data from 28 healthy children and 14 asthmatics were available for analysis. Most demographic characteristics showed no significant differences, but there was a statistically significant difference in gender ratio between the two groups (p=0.047; Table 1). As anticipated, the prevalence of rhinitis and eczema was significantly higher among children with asthma compared to healthy controls.

In this study, eighteen out of forty-two children were unable to perform the spirometry procedure correctly. All healthy participants underwent spirometry for the first time, whereas 6 asthmatic children had prior experience with the test. The proportion of healthy subjects unable to obtain valid lung function results (15 out of 28) was significantly higher than that for asthmatic children (3 out of 14), but these participants were all under six years of age. Among those who performed FEV_1 maneuver and obtained valid results, the duration of EMG recording was significantly shorter compared to that of the pulmonary function tests (8 ± 1 min vs 15 ± 4 min, $p < 0.01$). Furthermore, the timing for subjects who were able to perform the pulmonary function tests was comparable to that of those who could not (8 ± 1 min vs 9 ± 1 min).

Table 1 Demographic Characteristics of Healthy and Asthmatic Children

	Healthy Group n=28	Asthma Group n=14	*p*-value
Age (years), mean (range)	6.1 (3 ~ 13)	7.6 (3 ~ 13)	0.14
Sex, (male/female), n/n	13/28	11/14	0.047
Height (cm), mean (±SD)	118 ± 20	127 ± 20	0.16
Weight (kg), mean (±SD)	24.2 ± 12.0	27.4 ± 13.5	0.44
Rhinitis or eczema, n (%)	6 (21%)	12 (86%)	< 0.001

Table 2 Changes in Diaphragm EMG (EMG_{di}), the Ratio of EMG_{di} to Tidal Volume (EMG_{di}/VT), Parasternal Intercostal EMG (EMG_{para}) and the Ratio of EMG_{para} to Tidal Volume (EMG_{di}/VT) Before and After Inhaled Salbutamol

	Healthy Group (n=28)				Asthma Group (n=14)			
	Before	After	Δ%	*p*-value	Before	After	Δ%	*p*-value
EMG_{di} (μV)	22.6 (5.1 ~ 46.5)	22.8 (4.9 ~ 50.0)	−0.1 (−13.2 ~ 16.9)	0.893	27.3 (9.6 ~ 50.1)	20.0 (7.9 ~ 36.6)	−24.6 (−43.5 ~ −12.4)*	0.001
EMG_{di} /V_T (μV·kg/mL)	2.4 (0.3 ~ 11.0)	2.4 (0.3 ~ 11.7)	−0.4 (−9.9 ~ −56.7)	0.479	6.4 (1.0 ~ 48.9)	2.6 (0.8 ~ 8.6)	−29.2 (−82.5 ~ 7.4)*	0.002
EMG_{para} (μV)	10.2 (3.7 ~ 20.2)	10.2 (3.4 ~ 19.4)	−0.5 (−24.9 ~ 13.0)	0.703	11.7 (4.2 ~ 25.1)	10.0 (3.6 ~ 17.3)	−11.2 (−31.5 ~ 32.4)*	0.028
EMG_{para} /V_T (μV·kg/mL)	1.0 (0.4 ~ 3.4)	1.1 (0.4 ~ 5.3)	−0.6 (−26.3 ~ 54.4)	0.166	2.5 (0.5 ~ 16.4)	1.3 (0.3 ~ 3.5)	−16.0 (−78.8 ~ 36.5)	0.099
V_T (mL/kg)	11.6 (3.8 ~ 19.0)	11.7 (3.3 ~ 18.6)	1.2 (−36.4 ~ 14.0)	0.338	8.4 (1.0 ~ 11.9)	8.8 (3.3 ~ 12.1)	21.5 (−30.6 ~ 222.6)	0.432

Notes: Data was represented with mean (minimum ~ maximum); Δ%=(After-Before)/Before×100%; *p <0.05 in Δ% between two groups.

EMG_{di}, EMG_{para} and EMG_{di}/V_T all exhibited a statistically significant reduction following the administration of salbutamol in patients with uncontrolled asthma, except for EMG_{para}/V_T that showed non-significant reduction (Table 2). Conversely, no significant alterations were detected in EMG_{di}, EMG_{para} and EMG_{di}/V_T, and EMG_{para}/V_T in healthy subjects before and after salbutamol inhalation. Importantly, the changes in $\Delta EMG_{di}\%$, $\Delta EMG_{para}\%$ and $\Delta EMG_{di}/V_T\%$, with the exception of $\Delta EMG_{para}/V_T\%$, post-salbutamol inhalation were significantly greater in asthmatic patients compared to healthy controls (Table 2). Figure 1 presents ROC curves for $\Delta EMG_{di}\%$, $\Delta EMG_{para}\%$, $\Delta EMG_{di}/V_T\%$ and $\Delta EMG_{para}/V_T\%$. The optimal cut-off values for these indices, along with their corresponding sensitivities and specificities for differentiating uncontrolled asthmatics from healthy children, are detailed in Table 3. Notably, the ROC analysis indicated that a BDR of 12.4% in $EMG_{di}\%$ provided the highest discriminative capacity, achieving a sensitivity of 100% and a specificity of 96% (Table 3).

In sub-group analysis, there were no significant differences in EMG_{di}, EMG_{para}, EMG_{di}/V_T and EMG_{para}/V_T before and after inhalation of salbutamol in both the Healthy-A and Healthy-U groups in healthy children. There were also no significant differences in $\Delta EMG_{di}\%$, $\Delta EMG_{para}\%$, $\Delta EMG_{di}/V_T\%$ and $\Delta EMG_{para}/V_T\%$ between the Healthy-A and Healthy-U groups (Figure 2). Regarding asthmatic patients, obvious difference in EMG_{di}, EMG_{para}, EMG_{di}/V_T and EMG_{para}/V_T before and after inhalation of salbutamol were observed in both the Asthma-A and Asthma-U groups (Figure 2), and the trend was consistent for both sub-groups. However, ΔEMG_{di}, ΔEMG_{para}, $\Delta EMG_{di}/V_T$ and $\Delta EMG_{para}/V_T$ in the Asthma-U group were larger than those in the Asthma-A group (Figure 2).

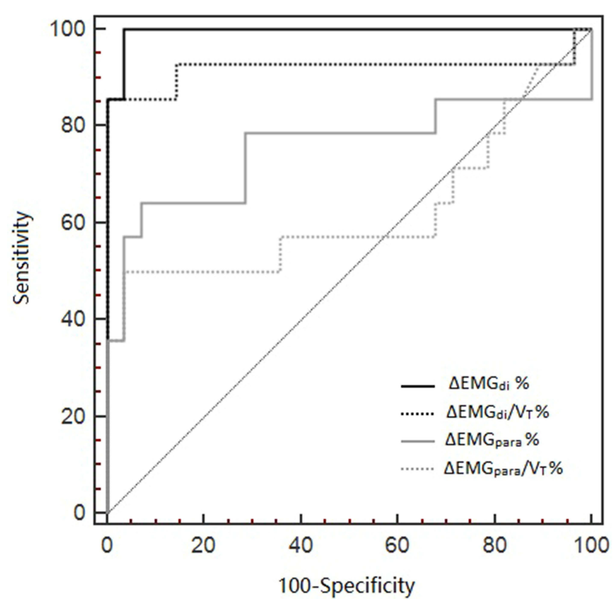

Figure 1 ROC curves for $\Delta EMG_{di}\%$, $\Delta EMG_{para}\%$, $\Delta EMG_{di}/V_T\%$, and $\Delta EMG_{para}/V_T\%$. $\Delta EMG_{di}\%$, $\Delta EMG_{para}\%$ and $\Delta EMG_{di}/V_T\%$ could distinguish asthmatics from the healthy using ROC curves, but the highest value was the bronchodilator response of 12.4% in ΔEMG_{di} with 100% of sensitivity, 96% of specificity.

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Table 3 Area Under Receiver Operating Characteristic (ROC) Curves (AUC), Sensitivity and Specificity of Bronchodilator Response (Calculate as % of Change From Basal) Using ROC

Variable	AUC (95% CI)	*p*-value	Cut-off	Sensitivity (%)	Specificity (%)
ΔEMG_{di} %	0.995 (0.906 to 1.000)[a,b]	<0.001	−12.4	100	96
$\Delta EMG_{di}/V_T$ %	0.921 (0.795 to 0.982)[c]	<0.001	−11.5	86	100
ΔEMG_{para} %	0.755 (0.598 to 0.874)	0.012	−10.8	64	93
$\Delta EMG_{para}/V_T$%	0.624 (0.461 to 0.768)	0.270	−24.0	50	96

Notes: [a]p <0.05 between ΔEMG_{di} and ΔEMG_{para}; [b]p <0.05 between ΔEMG_{di} and $\Delta EMG_{para}/V_T$; [c]p <0.05 between $\Delta EMG_{di}/V_T$ and $\Delta EMG_{para}/V_T$.

Abbreviations: ΔEMG_{di}, changes of diaphragm EMG (EMG_{di}) before and after inhalation of bronchodilator; $\Delta EMG_{di}/V_T$, changes of the ratio of EMG_{di} to tidal volume before and after inhalation of bronchodilator; ΔEMG_{para}, changes of parasternal intercostal EMG (EMG_{para}) before and after inhalation of bronchodilator; $\Delta EMG_{para}/V_T$, changes of the ratio of EMG_{para} to tidal volume before and after inhalation of bronchodilator.

Four asthmatics in Asthma-A group showed mild-to-moderate airway obstruction, while all healthy children in Healthy-A group had normal lung function. The results of FEV_1, FVC, FEV_1/FVC and $FEF_{25\text{-}75\%}$ before and after BDR were presented in the Table 4. ΔFEV_1% in the Asthma-A group was larger than that in the Healthy-A group (17.6±5.4% vs 5.5±3.7%, p<0.001). There was a significant relationship between ΔFEV_1% and ΔEMG_{di}% (r=0.762, p<0.001) and between ΔFEV_1% and $\Delta EMG_{di}/V_T$% (r=0.603, p<0.01), but no correlation was found with ΔEMG_{para} and $\Delta EMG_{para}/V_T$.

Discussion

In this study, all participants were able to record high-quality EMG_{di} and EMG_{para} signals; but 18 of them were unable to complete the pulmonary function tests. Among those who successfully underwent pulmonary function assessment, the duration of surface EMG recording was significantly shorter than the time required for the pulmonary function procedures. Both EMG_{di} and EMG_{para} could differentiate the healthy from uncontrolled asthmatics through assessing the BDR, but EMG_{di} is more useful.

Consistent with previous studies,[27,28] our data indicate that the age at which pulmonary function test could not be performed is under 6 years. The proportion of healthy subjects who were unable to perform pulmonary function tests was higher than that of asthma patients. This may be attributed to the fact that nearly half of the asthma patients in this study had prior experience with pulmonary function procedures. Early exposure to pulmonary function testing might enable children to be familiar with the correct techniques of deep breathing and rapid exhalation, thus increasing the odds of a successful test.

This study is the first to compare the duration of EMG signals recording with that of pulmonary function testing. Our data indicate that the time required to record EMG signals is significantly shorter than the time needed to collect FEV_1 results. Although the analysis of EMG_{di} still requires some time, it is possible to achieve automatic removal of ECG and then automatic analysis for EMG_{di} with the improvement of technology.[29] The advantage in operation time could provide more possibilities for the future clinical promotion of this technology.

To improve the signal-to-noise ratio of the EMG signals, a 7 cm tubing was used, which is shorter than the 15 cm typically used for adults.[17] This adjustment was made primarily due to the lower tidal volume in children, as longer tubing could lead to an increased risk of dead space ventilation. Additionally, the choice to use the right for recording EMG_{di} is intended to minimize interference from the ECG. If the EMG_{di} signal of the right diaphragm could not be obtained, EMG_{para} can be used as a substitute.[30,31] Our data showed that ΔEMG_{para} could also distinguish asthmatic children from the healthy, although its AUC is significantly smaller than that of ΔEMG_{di}.

Our previous data found that EMG_{di} expressed as a function of tidal volume ($\Delta EMG_{di}/V_T$) has higher discriminative power during the challenge test than ΔEMG_{di} alone in adults, although it failed to reach statistical significance.[17] However, there was an opposite trend in children's data, which showed the ROC area from ΔEMG_{di} was higher than that from $\Delta EMG_{di}/V_T$. This may be because mask leakage is more common in children than in adults. In addition, tidal volume in children is smaller than that of adults, so slight fluctuations are more likely to cause data bias. Therefore, extra caution should be taken if using a mask to record airflow in children.

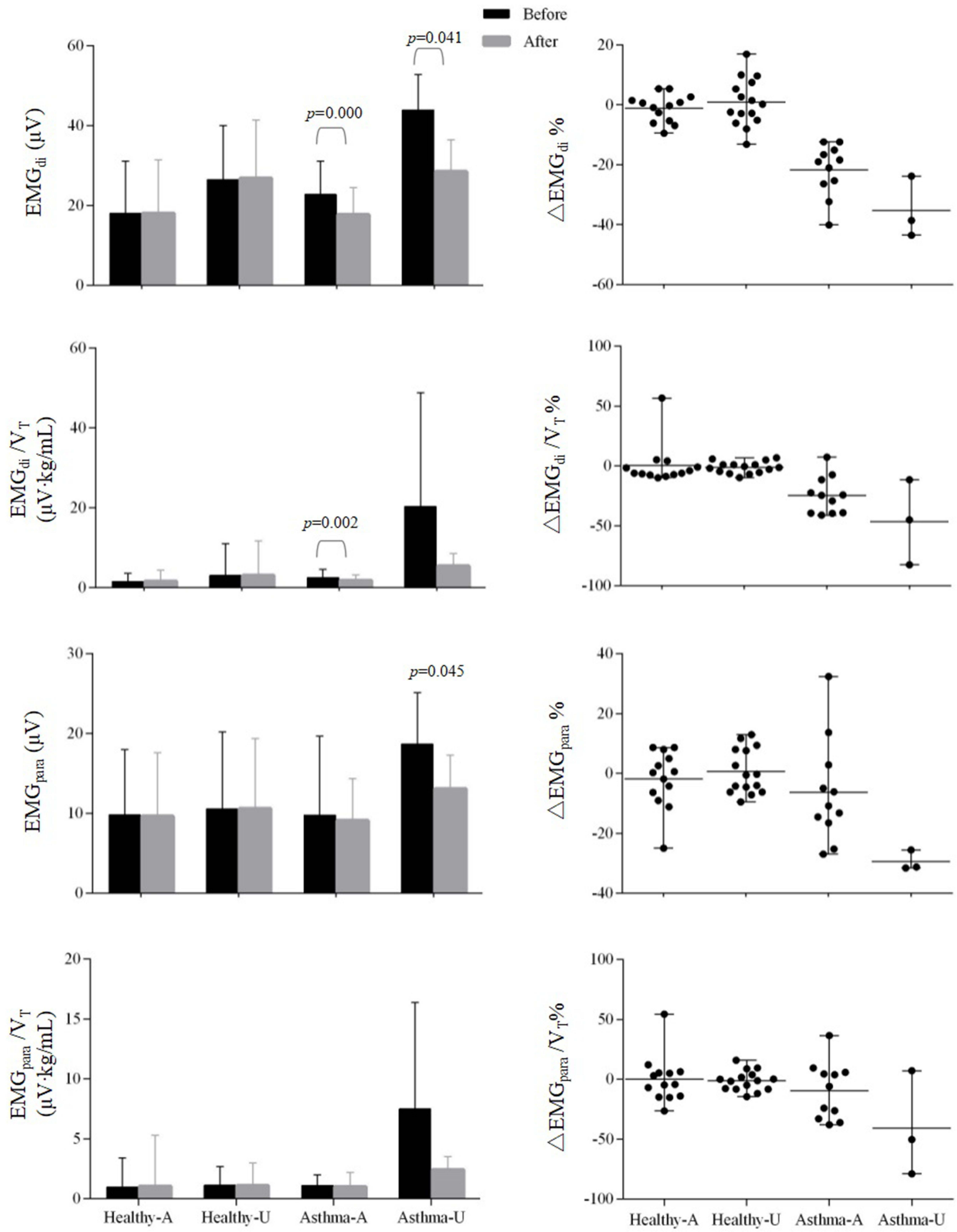

Figure 2 Comparison between participants able and unable to perform spirometry. In healthy group, two sub-groups were divided based on whether spirometry are able (Healthy-A, n=13) or unable (Healthy-U, n=15) to be performed; similarly, two sub-groups were divided based on whether spirometry are able (Asthma-A, n=11) or unable (Asthma-U, n=3) to be performed in the asthma group. In subgroup analysis, the trend and degree of change in EMG_{di}, EMG_{para} before and after inhalation of bronchodilator between Healthy-A and Healthy-U subgroups were both consistent. In relation to asthmatic subjects, the trend of change in EMG_{di}, EMG_{para} before and after inhalation of bronchodilator between Asthma-A and Asthma-U groups was consistent, but the changes in the Asthma-U group were larger than those in the Asthma-A group.

Table 4 Changes in Forced Vital Capacity (FVC), Forced Expiratory Volume in 1 second (FEV_1), the FEV_1 /FVC Ratio, and Forced Expiratory Flow During the Middle Half of the Forced Vital Capacity ($FEF_{25-75\%}$) Before and After Inhaled Salbutamol

	Control Group (n=13)				Asthma Group (n=11)			
	Before	After	Δ%	*p-value*	Before	After	Δ%	*p-value*
FVC, L	1.84 ± 0.86	1.91 ± 0.89	4 ± 6	0.057	1.82 ± 0.72	1.98 ± 0.82	8 ± 7	0.018
FEV_1, L;	1.62 ± 0.66	1.71 ± 0.70	6 ± 4	0.001	1.35 ± 0.42	1.59 ± 0.49	18 ± 5*	< 0.001
FEV_1/FVC, %	91 ± 10	92 ± 9	2 ± 2	0.012	76 ± 8	83 ± 10	9 ± 6*	0.001
$FEF_{25-75\%}$, L	2.15 ± 1.01	2.42 ± 1.07	15 ± 14	0.001	1.15 ± 0.25	1.61 ± 0.47	40 ± 30*	0.001

Note: *p <0.05 in Δ% between two groups.

Maarsing et al's study demonstrated that even when asthmatic children exhibited distinct clinical symptoms—including wheezing, persistent cough, prolonged expiration, or increased respiratory rate—at the end of the challenge test, no significant differences in EMG_{di} or EMG_{para} values were observed between these symptom groups.[32] However, in our study, when asthmatic children exhibited two distinct response patterns during BDR—improvement in FEV_1 and improvement in wheezing symptoms—significant differences were observed in their corresponding EMG_{di} and EMG_{para} values (see Figure 2). This may be related to the varying degrees of improvement in airway resistance during BDR under these two response patterns. However, the more pronounced changes in EMG_{di} and EMG_{para} following bronchodilator administration in the Asthma-U group suggest that surface respiratory muscle EMG may be useful in distinguishing patients with asthma from those without, particularly in individuals who are unable to perform spirometry.

Our study has several limitations. The sample size was relatively small, especially in the asthma group. In addition, not all participants were able to complete spirometry, including FEV_1, which limited our ability to compare changes in respiratory EMG with FEV_1 across all subjects. Finally, we did not compare respiratory EMG changes with airway resistance measured by body plethysmography, which could have offered additional insights into airway dynamics.

In conclusion, surface respiratory muscle EMG signal is feasible in children even for those who are unable to perform FEV_1 during BDR. EMG_{di} and EMG_{para}, rather than those combined with V_T, could be useful to assess the BDR and differentiate uncontrolled asthma from healthy in children during BDR.

Data Sharing Statement

The original data are available upon request. Please contact the corresponding author at y.m.luo@vip.163.com to request access.

Statement of Ethics

This study protocol was reviewed and approved by the ethics committee of the first affiliated Hospital of Guangzhou Medical University, approval number [2020 K-123], and written informed consent was obtained from participants' parent to participate in the study.

Author Contributions

He, Li, and Liu are co-first authors who contributed equally to the study design, data acquisition, data interpretation, and manuscript writing. Luo supervised the study and contributed to the conception, design, execution, data interpretation, and manuscript preparation. All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors have no conflicts of interest to declare for this work.

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