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Serum periostin reflects dynamic hyperinflation in patients with asthma

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ABSTRACT

Introduction: Dynamic hyperinflation (DH) is sometimes observed and is associated with impaired daily life activities of asthma. We assessed the relationship between DH and asthma biomarkers (blood eosinophil, fractional exhaled nitric oxide (F_{eNO}) and serum periostin) in patients with asthma.

Methods: Fifty patients with stable asthma were prospectively recruited and underwent blood test, F_{eNO} measurement, spirometry and metronome-paced tachypnoea (MPT) test to assess DH. In MPT tests, inspiratory capacity (IC) was measured at baseline and after 30 s of MPT with breathing frequencies of 20, 30 and 40 breaths·min^{-1}. DH was assessed by the decline of IC from baseline, and maximal IC reduction $\geqslant 10\%$ was considered as positive DH.

Results: Thirty patients (60%) showed positive DH. Patients with positive DH showed higher serum periostin levels (107.0±30.7 ng·mL^{-1}) than patients with negative DH (89.7±23.7) (p=0.04). Patients in Global Initiative for Asthma treatment steps 4–5 (n=19) showed higher serum periostin levels (p=0.01) and more severe IC reduction after MPT (p<0.0001) than patients in steps 1–3 (n=31). Maximal IC reduction after MPT was significantly correlated with asthma control test score (r=−0.28, p=0.05), forced expiratory volume in 1 s (r=−0.56, p<0.0001), and serum periostin levels (r=0.41, p=0.003).

Conclusion: Serum periostin may have the possibility to reflect DH in patients with stable asthma.

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Serum periostin level as a marker of dynamic hyperinflation in patients with asthma https://bit.ly/3djKTeQ

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Introduction

Asthma is characterised by various respiratory symptoms and inflammatory phenotypes [1]. A subset of patients with asthma experience exercise intolerance, which sometimes limits daily life activities [2]. Exercise intolerance has mainly been attributed to airway obstruction or bronchoconstriction, which provokes increased airway resistance. However, pathogenesis of exercise intolerance is complex, and many other factors are also involved. During exercise or tachypnoea, decreased expiratory time due to tachypnoea provokes lung hyperinflation, and a progressive reduction of inspiratory capacity (IC) consecutively occurs. This phenomenon is referred to as dynamic hyperinflation (DH) and is recognised as one of the key determinants of maximal exercise capacity. DH is often observed in chronic obstructive pulmonary disease (COPD) patients. Little had been known about DH in other respiratory diseases; however, recent studies highlighted the existence of DH in patients with asthma. VAN DER MEER et al. [2] emphasised high prevalence of DH in moderate-to-severe asthma (81%), which was associated with poor overall health and impaired daily life activities. LAVENEZIANA et al. [3] also showed that DH, as well as airway obstruction, was one of the best predictors of dyspnoea during a methacholine challenge test or cardiopulmonary exercise test (CPET) in patients with asthma.

Chronic type 2 airway inflammation contributes to uncontrolled asthma symptoms. Type 2 inflammation leads to oedema of small airway mucus production, smooth muscle contraction and impairment of small airway function [4]. These pathological changes have a potential to promote DH. Among type 2 airway inflammation, it is speculated that downstream of interleukin (IL)-13 has an important role in the development of DH via airway fibrosis and remodelling [5, 6].

Periostin, a 90-kD matricellular protein, is one of the key molecules of type 2 inflammation in asthma [7–9]. Expression of periostin is upregulated in fibroblasts and airway epithelial cells in response to the type 2 cytokine families, IL-4 and IL-13, and periostin is involved in the remodelling process of the airways. In patients with asthma, serum periostin level is elevated and related to fixed airway obstruction [8, 9]. Considering that periostin is involved in both processes of airway type 2 inflammation and airway remodelling, it can be hypothesised that serum periostin would become a promising biomarker of DH in patients with asthma. In the present study, we evaluated the relationship between serum periostin and DH in patients with asthma.

Methods

Subjects

Fifty patients with asthma (age: 20–80 years) were prospectively recruited from the Tohno Chuo Clinic (Gifu, Japan) between June and August 2019. All patients were on regular treatment with inhaled corticosteroids (ICS), combined with or without long-acting β-agonists or other controllers for $\geqslant 3$ months according to the Global Initiative for Asthma (GINA) guideline [10]. Patients who required step 4 or 5 treatment, defined by the GINA guideline [10] to achieve optimal asthma control were considered as having severe asthma. All patients had stable asthma without exacerbations in the past 3 months before inclusion and were nonsmokers or ex-smokers (smoking history <10 pack-years). None of the patients was under systemic corticosteroid treatment at the time of enrolment. Patients who had experienced respiratory infection in the past 4 weeks, and those who had, or were suspicious of having interstitial lung disease, bronchiectasis or COPD were excluded. Atopy was defined as the presence of at least one positive allergen-specific IgE test result (IgE$\geqslant 0.35$ kU·L^{-1}).

Study design

Written informed consent was obtained from all the patients before entering the study. The study was approved by the Shinagawa East One Medical Clinic Ethical Review Board (2019031401).

All the subjects underwent fractional exhaled nitric oxide F_{eNO}, pulmonary function tests, blood test, and metronome-paced tachypnoea (MPT) test. All measurements were performed at one visit. Bronchodilators (short- and long-acting β2-agonist, long-acting muscarinic antagonist and theophylline) were withheld for 24 h prior to testing.

Questionnaire

All subjects completed the asthma control test (ACT) [11]. ACT was validated in patients with asthma, focusing on asthma control levels. The ACT score ranges from 5 (poor control) to 25 (complete control).

Fractional exhaled nitric oxide

F_{eNO} was measured using a portable nitric oxide analyser (NIOX VERO®) at an exhalation flow rate of 50 mL·s^{-1} (Chest Corp, Tokyo, Japan) [12].

Pulmonary function tests
Spirometry was performed with SP-790COPD® (Fukuda Denshi, Tokyo, Japan) according to the American Thoracic Society/European Respiratory Society recommendations [13]. Patients were told to abstain from bronchodilators (short- and long-acting β2-agonist, long-acting muscarinic antagonist and theophylline) were withheld for 24 h prior to testing.

MPT test
DH was assessed using an MPT technique, which was validated in previous studies [2, 14–16], using a spirometer (SP-790COPD®).

First, subjects performed maximum inspiration followed by gradual maximum expiration after quiet and stable breathing, and resting IC (IC_{rest}) was measured. Then, subjects were asked to breathe at a rate of 20 breaths per minute (bpm) for 30 s, immediately followed by a maximal inspiratory manoeuvre (IC_{20}). In the same manner, subjects were asked to breathe at 30 bpm for 30 s and 40 bpm for 30 s, and the IC was measured (IC_{30} and IC_{40}). ΔIC (%) was defined as the reduction percentage of IC from IC_{rest} for each breathing frequency (ΔIC_{20}, ΔIC_{30} and ΔIC_{40}). ΔIC_{max} (%) was defined as the maximal reduction percentage of IC from IC_{rest} throughout the MPT procedure. We stratified patients into two groups: negative DH, ΔIC_{max} (%) <10% and positive DH, ΔIC_{max} (%) ⩾10 [2].

Blood samples
As well as blood eosinophil count, serum periostin levels were measured using an ELISA by the Shino-Test Corp. (Kanazawa, Japan) as described previously [8, 9].

Statistical analysis
Data are expressed as mean±SD. A comparison between the two groups was performed by a Chi-squared test, and unpaired t-test, wherever appropriate. Associations between two valuables were analysed using the Pearson correlation test. Associations between serum periostin and ΔIC (%) were also assessed using multivariable linear regression models (adjusted by factors found to be significant). Data with non-normal distribution were analysed after log transformation. A p-value <0.05 was considered to be statistically significant.

Results
Patient characteristics
Fifty patients were enrolled in this study. Patient characteristics are shown in table 1. All patients were treated with ICS therapy with the average dose equivalent to fluticasone propionate at 387.6±176.2 µg·day^{-1}. Only three patients had smoked previously. The average serum periostin level was 96.3±29.8 ng·mL^{-1}. Average ΔIC for each breathing frequency were as follows: ΔIC_{20} (%): 4.7±6.2, ΔIC_{30} (%): 9.6±8.3 and ΔIC_{40} (%): 12.5±9.3 (figure 1). Ten patients (20%) showed positive DH ($\Delta IC \geqslant 10\%$) at 20 bpm, 22 patients (44%) at 30 bpm and 30 patients (60%) at 40 bpm, respectively. All patients completed MPT tests safely, and no patients complained about severe dyspnoea during the test.

We stratified patients according to the degree of maximal IC reduction (with and without DH, table 1). Patients with DH were older, and had significantly higher body mass index (BMI) and serum periostin levels than patients without DH. In contrast, there were no differences between the groups in atopic status, ICS daily dose, blood eosinophil count or F_{eNO}.

Relevance of DH and clinical indices
Serum periostin levels, as well as FEV_1 (% predicted), showed good correlation with ΔIC (%) at each MPT frequency (table 2, figure 2). After adjusted by parameters, which showed significant differences between patients with and without DH in table 1 (age, BMI and FEV_1 % predicted), serum periostin remained associated with each ΔIC (%) (ΔIC_{20} (%): β=0.062 (95% CI=0.007–0.117), p=0.03; ΔIC_{30} (%): 0.087 (0.023–0.152), p=0.009; ΔIC_{40} (%): 0.072 (0.002–0.142), p=0.04). In contrast, there was no association between ΔIC and blood eosinophil or F_{eNO} (table 2).

Relevance of asthma severity and clinical indices
Table 3 compared the clinical indices between patients in the GINA treatment steps 1–3 (n=31) and those in steps 4–5 (n=19). Patients in GINA treatment steps 4–5 showed lower FEV_1 (% predicted), higher ΔIC for each frequency, and higher serum periostin levels than patients in steps 1–3.

Discussion
In the present study, we showed that DH is a common feature of asthma, which accounted for 60% of all patients. To the best of our knowledge, this study is the first to evaluate a relationship between DH and

TABLE 1 Patient characteristics

	Negative DH	Positive DH	p-value
Number of patients	20	30	
Age years	53.3±8.7	63.7±10.9	0.001
Sex males/females[#]	4/16	5/25	0.76
Atopic predisposition n (%)[#]	16 (80)	24 (80)	1.00
BMI kg·m^{-2}	21.3±2.7	24.7±3.8	0.001
Treatment step according to GINA (2/3/4/5)[#]	1/14/5/0	2/14/13/1	0.33
Disease duration years	8.8±10.4	11.5±12.4	0.43
ICS daily maintenance dose FP equivalent μg	345.5±120.1	415.7±202.4	0.17
ACT	24.0±1.5	23.1±2.2	0.15
Blood eosinophil %	4.1±2.8	4.3±2.5	0.78
Serum periostin ng·mL^{-1}[¶]	89.7±23.7	107.0±30.7	0.04
F_{eNO} ppb[¶]	29.1±15.8	38.1±31.9	0.24
FVC % predicted	108.7±9.9	94.8±13.3	0.0002
FEV$_1$/FVC %	77.0±6.0	73.2±11.5	0.18
FEV$_1$ % predicted	101.0±13.0	85.9±21.0	0.006
IC baseline mL	2277.5±538.6	2140.7±93.5	0.11
ΔIC$_{20}$ %	1.0±5.6	7.2±5.4	0.0003
ΔIC$_{30}$ %	2.7±4.6	14.2±7.0	<0.0001
ΔIC$_{40}$ %	3.8±3.8	18.3±6.9	<0.0001

Data are presented as n or mean±SD, unless otherwise stated. A comparison between the two groups was done by a Chi-squared test or unpaired t-test. BMI: body mass index; GINA: Global Initiative for Asthma; ICS: inhaled corticosteroid; FP: fluticasone propionate; ACT: asthma control test; FeNO: fractional exhaled nitric oxide; FVC: forced vital capacity; FEV$_1$: forced expiratory volume in 1 s; IC: inspiratory capacity; ΔIC: the reduction percentage of IC from baseline (IC$_{rest}$) for each breathing frequency (ΔIC$_{20}$, ΔIC$_{30}$ and ΔIC$_{40}$); DH: dynamic hyperinflation; Negative DH: patients with the maximal reduction percentage of IC <10%; Positive DH: patients with the maximal reduction percentage of IC ⩾10%. [#]: Chi-squared test; [¶]: analysed after log transformation.

clinical inflammatory biomarkers in patients with asthma. We found that serum periostin level was associated with DH induced by MPT. This finding suggests that serum periostin is useful for evaluating DH in patients with asthma. Assessment of DH is time-consuming and has a potential to induce shortness of breath especially in patients with uncontrolled conditions. Therefore, our result might be valuable for evaluating DH in patients with asthma in clinical practice.
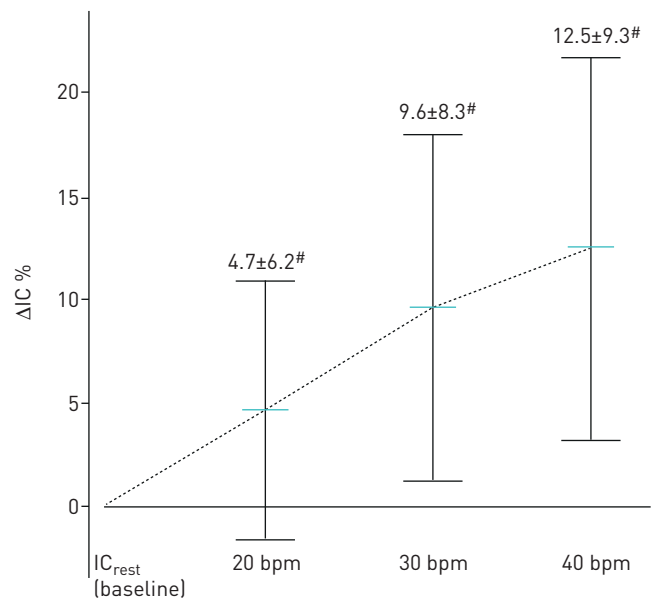

FIGURE 1 ΔIC for each breathing frequency (20, 30 and 40 bpm). ΔIC: the reduction percentage of inspiratory capacity (IC) from baseline (IC$_{rest}$) for each breathing frequency (ΔIC$_{20}$, ΔIC$_{30}$ and ΔIC$_{40}$); bpm: breaths per minute. [#]: p<0.0001 from baseline.

TABLE 2 The association between ΔIC (%) and clinical indices			
	ΔIC_{20} %	ΔIC_{30} %	ΔIC_{40} %
ACT	r=−0.24, p=0.09	r=−0.34, p=0.02	r=−0.28, p=0.05
FEV$_1$ % predicted	r=−0.37, p=0.008	r=−0.51, p=0.0001	r=−0.56, p<0.0001
Blood eosinophil %	r=0.05, p=0.72	r=0.12, p=0.90	r=0.02, p=0.91
Serum periostin ng·mL^{-1}	r=0.37, p=0.008	r=0.43, p=0.002	r=0.41, p=0.003
F_{eNO} ppb	r=0.003, p=0.98	r=0.11, p=0.45	r=0.22, p=0.12

ACT: asthma control test; FEV$_1$: forced expiratory volume in 1 s; F_{eNO}: fractional exhaled nitric oxide; ΔIC: the reduction percentage of inspiratory capacity from baseline (IC$_{rest}$) for each breathing frequency (ΔIC$_{20}$, ΔIC$_{30}$ and ΔIC$_{40}$).

Several factors contribute to the development of DH. First, it is well known that smoking history influences the development of DH [17]. Serum periostin level is also influenced by smoking history [18]. Therefore, we excluded smokers (current and ex-smokers with smoking history ⩾10 pack-years) prior to the study. In the present study, DH was found to be influenced by low pulmonary function, age, BMI, and serum periostin levels (table 1). The association between low FEV$_1$ and DH has already been demonstrated in the previous study [17], and the present study also confirmed this observation. Considering that DH is a passive consequence of expiratory flow limitation, this association seems appropriate (table 2). However, it has been discussed that FEV$_1$ does not fully explain DH, and other constitutional factors also contribute to DH. The association between age and DH is mainly explained by declines of pulmonary function and airway remodelling across the ages. A previous study showed that obesity contributed to the development of DH [19]. Likewise, our study also showed that high BMI was related to positive DH. These factors (age, BMI and lung function) were also associated with serum periostin levels [18]. Therefore, these factors become cofounding factors when evaluating the association between serum periostin level and DH. Hence, we also certificated this association using multivariable linear regression models. Therefore, the association between serum periostin level and DH was not merely the result of airway obstruction as assessed by FEV$_1$ (% predicted) and other cofounding factors.

Among biomarkers for type 2 inflammation of asthma (blood and sputum eosinophil counts, F_{eNO} and serum periostin) [8, 9, 20, 21], previous studies support the superiority of serum periostin for reflecting airway flow limitation [8, 22, 23]. KANEMITSU et al. [8] demonstrated that serum periostin, but not blood eosinophils, was associated with greater decline of FEV$_1$. TAKAHASHI et al. [22] showed that serum periostin level was more closely associated with fixed airflow limitation than F_{eNO} or blood eosinophil counts. Moreover, HOSHINO et al. [23] showed the association between serum periostin and airway wall thickness in patients with steroid-naïve asthma. As DH occurs as a consequence of expiratory flow limitation, it is plausible to speculate that factors that associate with airflow limitation and airway remodelling also contribute to the development of DH. In this study, we demonstrated a significant association between the magnitude of DH and serum periostin levels. As serum periostin is considered a good reflector of type 2 inflammation [7–9], our result implies the possibility that ongoing type 2 airway inflammation, mainly IL-4 and IL-13, underlies in the pathogenic process of DH in patients with asthma.
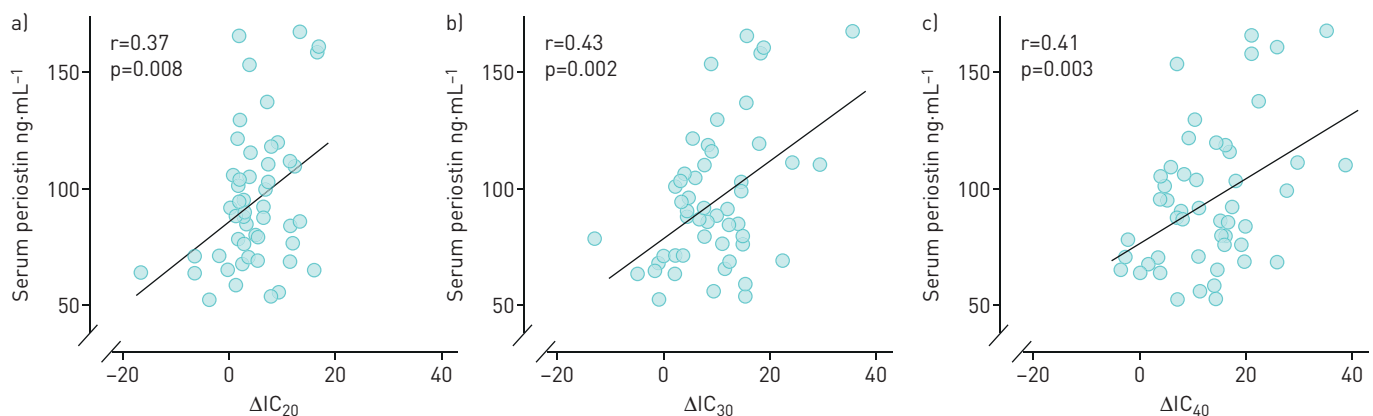

FIGURE 2 Relationship between serum periostin level and ΔIC for each breathing frequency (ΔIC$_{20}$, ΔIC$_{30}$ and ΔIC$_{40}$). ΔIC: the reduction percentage of inspiratory capacity from baseline (IC$_{rest}$) for each breathing frequency (ΔIC$_{20}$, ΔIC$_{30}$ and ΔIC$_{40}$); bpm: breaths per minute.

TABLE 3 The association between asthma severity and clinical indices			
	GINA 1–3	**GINA 4–5**	**p-value**
Number of patients	31	19	
Blood eosinophils %	4.2±2.9	4.3±2.2	0.98
Serum periostin ng·mL^{-1}	87.6±20.1	114.9±34.6	0.01
F_{eNO} **ppb**	28.8±16.8	43.1±40.0	0.06
FEV$_1$ % predicted	99.3±15.4	80.9±20.3	0.0007
ΔIC$_{20}$ %	1.86±5.4	9.0±4.8	<0.0001
ΔIC$_{30}$ %	5.6±6.5	15.6±7.3	<0.0001
ΔIC$_{40}$ %	8.2±7.2	19.0±8.2	<0.0001
Positive DH n (%)	16 (52)	14 (74)	0.12

GINA: Global Initiative for Asthma; FEV$_1$: forced expiratory volume in 1 s; F_{eNO}: fractional exhaled nitric oxide; ΔIC: the reduction percentage of inspiratory capacity from baseline (IC$_{rest}$) for each breathing frequency (ΔIC$_{20}$, ΔIC$_{30}$ and ΔIC$_{40}$); DH: dynamic hyperinflation; Positive DH: patients with the maximal reduction percentage of IC⩾10%.

Potential mechanisms exist which explain the involvement of periostin in the pathogenic process of airway remodelling and DH. When activated, type 2 inflammatory cells release IL-4 and IL-13, which in turn activate expression of POSTN, the gene that encodes periostin [7]. Pathological changes of the airway subsequently occur in relation to expression of periostin [24]. Periostin promotes collagen production in fibroblasts, differentiation of fibroblasts to myofibroblasts, and enhances fibrosis by binding to other extracellular matrix proteins. Significant association between expression of periostin and the thickness of the airway basement membrane has also been demonstrated. These structural changes increase airway resistance, and consequently provoke DH. Airway hyperresponsiveness (AHR) also explains the occurrence of DH in patients with asthma [25]. AHR refers to the predisposition of the airways to narrow excessively in response to stimuli, such as allergens, environmental irritants, and exercise. IL-13 and IL-4 are considered to provoke AHR of airway smooth muscle [26], and the association between serum periostin and AHR has been demonstrated in asthmatic children [27]. Therefore, AHR via IL-4 and IL-13 pathway including periostin may also be involved in the development of DH.

DH impairs exercise capacity and daily life activities of asthma [2]. In addition, severe DH is associated with increased emergency visits [2]. Moreover, DH itself has a potential to stimulate proinflammatory effects through cellular stretching or tissue damage [28]. Considering the negative impacts of DH on regular daily activities and the inflammatory process of asthma, DH should be included not only as a target of measurement, but also as a target of treatment. Actually, a recent study showed the effectiveness of omalizumab on DH, as well as exercise capacity in severe asthma [29]. This study implies that type 2 inflammation might be involved in the development of DH. If so, other anti-inflammatory treatments might also have a potential to ameliorate exercise capacity by reducing DH. Intriguingly, serum periostin has been proposed as a biomarker to predict response to treatment. Previous studies showed that patients with high serum periostin levels had a tendency to receive clinical benefits (symptoms, lung function, and exacerbation rate) from anti IL-13 (lebrikizumab) [30] and Ig-E treatments (omalizumab) [31]. It would be interesting if serum periostin also reflects patients who are likely to show the improvement of DH after these treatments. Further research is needed in this area.

In patients with asthma, high breathing rates, which may progress DH, are sometimes observed in stressed conditions, such as exercise or asthma exacerbations. A recent survey revealed high prevalence of MPT-induced DH (81%) in patients with moderate-to-severe asthma [2]. We also found a high proportion of patients who developed DH after MPT (20% of patients showed positive DH at 20 bpm, 44% at 30 bpm and 60% at 40 bpm, figure 1), although most patients were in stable conditions (mean ACT score: 23.5±2.0). Although we did not compare results directly, the magnitude of ΔIC for each frequency in patients with asthma in the present study (figure 1) seemed higher than healthy volunteers (ΔIC$_{20}$ (%): 2.1±3.1; ΔIC$_{30}$ (%): 2.8±2.9; and ΔIC$_{40}$ (%): 3.3±2.9) in the previous study [16], in which the same protocol of MPT was used. Additionally, patients with GINA treatment steps 4–5 showed higher ΔIC than patients in steps 1–3 for each frequency (table 3). This finding may be explained by the previous finding that showed a significant association between the degree of remodelling and asthma severity [32].

This study has several limitations. First, we excluded patients who had experienced asthma exacerbations in the past 3 months. Also, we did not include patients who could not stop bronchodilators prior to testing. Therefore, our results might not be applicable in patients with uncontrolled asthma. Additionally,

the number of patients was small. To make our findings confirmative, further studies of larger cohorts, including patients with uncontrolled asthma would be required. Secondly, the present study was only designed to elucidate the clinical relationship between serum periostin and DH, but not the direct mechanisms of it. It would be interesting to explore the direct mechanisms in the following pathophysiological studies. Finally, some patients might not be stressed enough during MPT. IC reduction rate depended on the intensity of tachypnoea (figure 1) [14], and no patients expressed severe dyspnoea throughout the MPT test. However, compared to CPET [15], the MPT test is less strenuous and noninvasive [33]. Therefore, it is more suitable in the clinical field. Previous studies clearly supported good accuracy of the MPT test for detecting DH as CPET [15, 31, 34]. Besides, the present study found that DH became evident after MPT despite no apparent symptoms. This finding was in line with the previous report ,which detected DH during exercise in patients with asthma with normal lung function and little or no apparent symptom [35]. A low sensation of dyspnoea, which is often observed in patients with asthma, may explain the discrepancy between perception of dyspnoea and DH [35]. Considering that asymptomatic patients with normal lung function may also show reduced exercise capacity and the development of DH, evaluating DH is meaningful not only for patients who take notice of exercise intolerance, but also for patients who lack clinical symptoms.

In conclusion, we have demonstrated MPT-induced DH in patients with stable asthma. The association between serum periostin and IC reduction after MPT may imply the potential of serum periostin as a biomarker of DH in patients with stable asthma.

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