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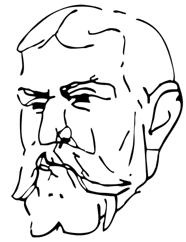

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SPIS TREŚCI

COMPREHENSIVE ASSESSMENT OF AUTONOMIC DYSFUNCTION IN PATIENTS WITH ASTHMA USING THE REGULATORY SYSTEMS ACTIVITY INDEX

KOMPLEKSOWA OCENA DYSFUNKCJI UKŁADU AUTONOMICZNEGO U CHORYCH Z ASTMĄ PRZY WYKORZYSTANIU WSKAŹNIKA RSAI

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ABSTRACT
The regulatory systems activity index (RSAI), proposed by RM Bayevsky, can be used as an integral measure of the functional stress of the autonomic nervous system in patients with asthma. RSAI values of 8-10 should be used as a criteria for maladaptive and prognostically unfavorable course of asthma. Autonomic dysfunction at these RSAI levels is characterized by a pronounced reduction in total power of the spectrum of heart rate variability (HRV) (TP<1000ms), significant predominance of humoral-metabolic waves (VLF> 65%), increased activity of the sympathetic nervous system(LF/HF> 3.0), and high index of centralization (IC > 8).

KEY WORDS: asthma, autonomic dysfunction, heart rate variability, regulatory systems activity index.

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INTRODUCTION
Bronchial asthma (BA) is a multifactorial disease [9] that involves a dysfunction of the autonomic nervous system (ANS) as one of the key elements in its pathogenesis [2,4,6.7]. Because autonomic disturbancesunderlie the disruption of the mechanisms of patient's adaptation to the disease, methods for characterizing the autonomic dysfunction draw considerable attention[2,10,]. During the last decade, clinical practice has experienced a wide implementation of the analysis of heart rate variability (HRV), a highly informative method for assessing the functional stateof the ANS and autonomic adaptation [1,8,12,13], as well as of the Regulatory Systems Activity Index(RSAI), an integral indicator of the adaptive capacity of the bodyproposed by RM Bayevsky [1]. Here, we propose to use RSAI for assessing the degree of stress of the regulatory systems and the adaptive capacity of the body. Three functional states, also referred to as the "Traffic Light" system, can be distinguished based on RSAI: the green zone denotes the normal state, or the state of satisfactory adaptation; yellow zone signifies strain or overstrainof adaptation mechanisms; and finally, red zone indicates the failure of adaptation. Recently there has been a growing interest in the use of RSAI in clinical medicine and rehabilitation[1,3,4,5], because it allows characterizing not only the degree of stress of the adaptation mechanisms and initial functional condition of the body, but also its adaptive capacity during changes in environmental conditions. Furthermore, this indicator is useful for comprehensive assessment of the stressful effect of aggravating factors on the human body.

Currently there is a lack of information in literature regarding the assessment of adaptive capacity of the ANS in patients with asthma involving RSAI.

THE AIM
The aim of the study was to determine the functional state of the ANS in patients with asthma using RSAI and to investigatethe relationship between the functional state of the ANS and the clinical course of asthma.

MATERIALS AND METHODS
108 patients with moderately severe persistent bronchial asthma in the unstable remission phase were evaluated. The average age of patients was 40.2 ± 2.43 years. The patients had no comorbidities that could influence the autonomic regulation of the heart rhythm. The control group (CG) consisted of 20 healthy individuals of similar sex and age.

The functional state of the ANS was evaluated by cardiointervalography (CIG) followed by the analysis of statistical and spectral measures of heart rate variability (HRV) using the "Cardiolab ANS", a combined hardware-software system thatenables quantitative assessmentof the functional state of the bodyin arbitrary units (points) of the regulatory systems activity index.

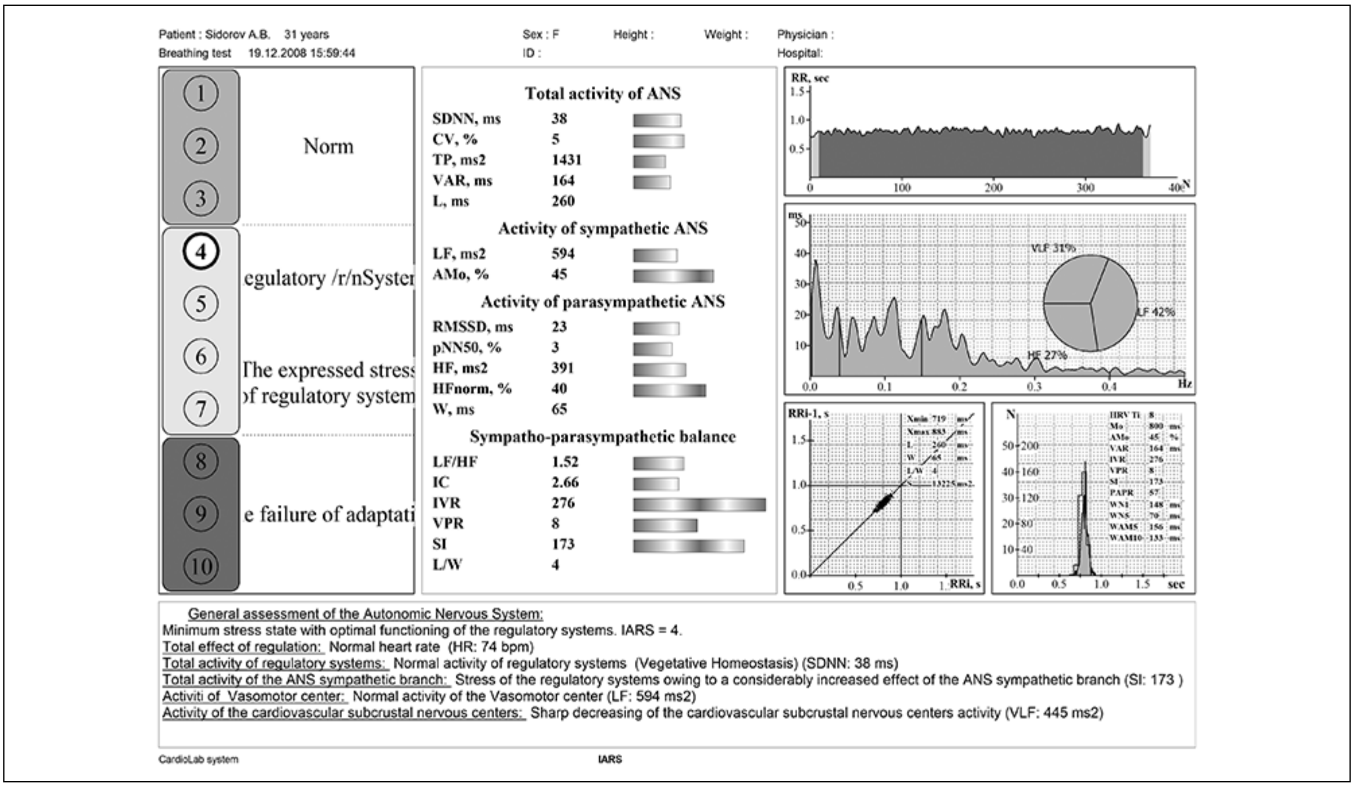

Figure 1. Computer processing of the heart rate variability recording of the patient B., 46 years old, using the "Cardiolab ANS" device

Recording and computer analysis of HRV was performed in accordance with accepted international standards [11], as well as according to RM Baevsky [1]. 5-minute ECG recording in standard lead II was used for HRV analysis. Becausemost patients used bronchodilators, which have a pronounced stimulating effect on the sympathetic tone, to reduce the impact of these drugs on HRV the patients were recommended to abstain from using short-acting bronchodilators for 6 hours before the study and long-acting bronchodilators for 24 hours before the study. Patients did not consume coffee, tea,or alcohol for 24 hours before the study.

ECG was recorded in the morning at physiological rest in supine position. ECG recordings began after a 10-15-minute rest allowing for appropriate adaptation to the conditions of the evaluation.

Statistical and spectral measures of HRV were determined (Figure 1).

The evaluated statistical parameters of HRV included:
- SDNN, ms, (standarddeviationoftheNNinterval), which reflects the cumulative effect of the autonomic regulation of circulation.
- RMSSD, ms, (the square root of the mean squared differences of successive NN intervals). The value of this index is determined predominantly by the influence of the parasympathetic branch of the autonomic regulation;
- NN50 - the number of pairs of successive R-R intervals whose durations differ by more than 50 ms;
- pNN50 (%) - percentage of NN50 among all analyzed R-R intervals.

In addition, indicators of autocorrelation analysis of HRV per RM Baevsky were used [1]:
- AMo,% - mode of amplitude, the number of cardiointervals equal to Mo as a fraction of the total number of detected cardiocycles. This is an indicator of the activity of the sympathetic branch of regulation.
- IN, arbitrary units, - an index of stress of the regulatory systems proposed by RM Baevsky. This parameter reflects the shift of the heart rhythm regulation from peripheral to central nervous structures.

The wave structure of heart rhythm was evaluated using:
- TP, ms^2 (Total Power) –the total power of the spectrum of HRV;
- VLF% (Very Low Frequency) –activity of the higher suprasegmental centers of the autonomic regulation and humoral-metabolic influences;
- LF% (Low Frequency) –activity of the sympathetic modulators;
- HF% (High Frequency) – associatedwith vagal influences;

LF / HF –sympathetic-vagal balance;
- IC - index of centralization.

A comprehensive assessment of autonomic homeostasis was performed by the regulatory systems activity index (RSAI), which is calculated by a specificalgorithm that considers the following 5 groups of criteria:
1. The total effect of regulation according to the heart rate.
2. The total activity of regulatory mechanisms using TP and SDNN.
3. Autonomic balance using IN.
4. Activity of the vasomotor center using LF and AMo.
5. Activity of the suprasegmental levels of regulation using VLF andIC.

Table I. Mean values of HRV parameters in patients with asthma and controls at rest (M±m)

Parameters	Controls (n=20)	Patients with asthma (n=88)
Parametersoftemporalandautocorrelation analysis		
Mo	*0.84±0.02*	*0.81±0.02*
AMo	34.4±2.5	42.5±3.2*
SDNN, ms	44.56±1.71	40.24±2.31
RMSSD, ms	36.16±2.52	29.91±2.17*
pNN50, %	21.96±3.2	18.68±1.90
IN	134.3±17.3	218.4±25.51**
Parameters of spectral analysis		
IC	2.7±0.4	6.1±0.5**
TP, ms2	3348.42±242.4	2930.5±202.58
VLF, ms2	1161.22±115.41	1569.9±104.56*
VLF%	34.7±3.32	53.8±2.4**
LF, ms2	1260.44±92.24	962.05±83.33*
LF%	38.6±2.4	31.1±1.9*
HF, ms2	926.69±92.73	440.92±38.54**
HF%	26.7±2.70	14.4±1.8**
LF/HF	1.44±0.23	2.31±0.21*

Notes: * - significant intergroup differences between controls and patients with asthma at p <0.05 and ** at p <0.01.

RESULTS

HRV analysis in the control group was characterized by values typical for healthy individuals [8,11] with an optimal balance of regulatory systems.

HRV analysis allowed to reveal the specific features of autonomic regulation in patients with asthma (Table I). Analysis of the temporal parameters of HRV showed that patients with asthma at rest have significant differences in measures characterizing sympathetic influences compared to controls. Thus, the AMo index was significantly higher in patients with asthma (42.5 ± 3.2 in patients with asthma vs 34.4 ± 2.5 in controls, p <0.05). The integral indicator IN was also increased in asthma patients (218.44 ± 25.51 vs 134.3 ± 17.3 in controls, p <0.01), which points to the stress of adaptive mechanisms. As for the activity of the parasympathetic parts of the regulation, only the RMSSD index was significantly reduced in patients with asthma (29.91 ± 2.17) compared to controls(36.16 ± 2.52, p <0.05). There were no significant differences between the groups in any other studied measures.

Spectral analysis of HRV revealed a statistically significant decrease in sympathetic and parasympathetic parts of the spectrum in patients with asthma compared to controls. Thus, the HF (ms^2) parameter was reduced by 52.5% (p <0.01), and the index of LF (ms^2) was reduced by 23.6% (p <0.05) in asthma patients relative to controls. Along with the decrease in absolute values, relative measures LF% and HF% were also significantly decreased (LF%: 31.2 ± 1.9% in patients with asthma vs 38.6 ± 2.4% in controls, p <0.05; HF%: 14.4 ± 1.8% in patients with asthma vs 26.7 ± 2.7% in controls, p<0.01). At the same time, the contribution of humoral-metabolic effects (VLF%) to the total power of spectrum (TP), which reflects the activation of the suprasegmental division of the ANS, was increased in patients with asthma (53.9 ± 2.4% vs 34.7 ± 3.3% in controls, p <0.01).

In this case, the activity of both parts of the ANS was reduced. However, the reduction of the tone of the parasympathetic branch was more significant, leading to a relative predominance of sympathetic activity at the segmental levels of the ANS.

The TP index, which reflects the overall level of activity of regulatory systems, remained effectively unchanged (2930.5 ± 202.58 in patients with asthma vs 3348.42 ± 242.4 in controls, p>0.05).

To summarize, the analysis of baseline HRV indicators in the state of physiological rest revealed a disturbance of neurohumoral regulation of heart rhythm in patients with asthma. The initial autonomic tone in patients with asthma is characterized by reduced levels of vagal indicators (significant reduction in RMSSD, HF and HF%, and the downward trend in pNN50, compared to controls), moderate sympathetic influences (significant increase in IN, AMo, and LF/HF), and severe humoral-metabolic effects (significant increase in IC and VLF). Thus, the relationship among the effects of the ANS branches on heart rate can be presented as VLF>LF>HF in patients with asthma, and as LF≥VLF≥HF in controls. This illustrates that the pathways of the regulatory processes in patients with asthma are altered from those in healthy controls and are implemented mainly through humoral-metabolic influences with excessive centralization of heart rhythm regulation (IC =6.1 ± 0.5

Table II. Distribution of the subjects based on RSAI values

RSAI-based adaptive capacity	Controls (n=20)		Patients with asthma (n=108)	
	n	%	n	%
The state of satisfactory adaptation (A)	11	55	21	20,3
The state of stress or overload of the adaptation mechanisms (B)	9	45	57	52,7
The state of unsatisfactory adaptation (C)	-	-	30	27,7

Table III. Spectral parameters of the HRV in asthma patients with different adaptive capacities (M±m)

Parameter	Satisfactory adaptation (n=21 1A	Stressed adaptation (n=57) 2B	P 1-2	Unsatisfactory adaptation (n=30) 3C	P 1-3	P 2-3
TP, ms²	3557.7±315.2	3263.9±374.1	-	827.92±96.9	<0.01	<0.01
VLF, ms²	1255.9±161.1	1915.8±170.3	<0.05	570.44±80.8	<0.01	<0.01
VLF, % below	34.8±2.0	58.3±2.3	<0.01	68.5±2.5	<0.01	<0.05
LF, ms²	1401.6±170.5	1002.9±111.8	<0.05	206.19±44.5	<0.01	<0.01
LF, %	39.8±2.5	30.6±1.9	<0.05	23.8±1.8	<0.01	<0.05
HF, ms²	897.32±73.3	344.3±55.8	<0.01	62.2±3.8	<0.01	<0.001
HF, %	25.1±1.6	11.1±1.3	<0.01	7.5±0.9	<0.01	<0.05
LF/HF	1.56±0.1	2.6±0.2	<0.01	3.2±0.3	<0.01	-
IC	2.97±0.3	7.4±0.6	<0.05	11.8±1.3	<0.05	<0.05

Notes: P1-2 –p-values for the differences between groups 1A and 2B; R1-3 - p-values for the differences between groups 1A and 3C; R2-3 -p-values for the differences between groups 2B and 3C.

in patients with asthma vs 2.7 ± 0,4 in controls, p <0.01).

A comprehensive assessment of adaptation reserves in the examined groups using RSAI showed that its average value in patients with asthma was significantly higher than in controls and equaled 6.2 ± 0.7 points, indicating an increased stress of the regulatory systems and reduced adaptation reserves. At the same time, the RSAI in controls was 3.4 ± 0.5 points, indicating satisfactory adaptation and the optimal state of the regulatory systems.

Based on the obtained RSAI values all subjects were divided into 3 groups (zones), which are also known as the “Traffic Light” system (Table II):

Group “A” (green zone) – subjects with a satisfactory adaptation and optimal state of the regulatory systems (RSAI =1-3 points), group “B” (yellow zone) –subjects in the state of functional stress of the regulatory systems (RSAI =4-5 points) and overload of the regulatory mechanisms (RSAI = 6-7 points), and group “C” (red zone) – subjects with unsatisfactory adaptive capacity, whereby the activity of the regulatory mechanisms is insufficient for maintaining homeostasis.

A comprehensive assessment of adaptation reserves based on RSAI revealed a state of satisfactory adaptation mechanisms in most control subjects, while the majority of patients with asthma were in the state of stress or failure of the adaptive mechanisms (Table II).

This distribution of patients based on RSAI revealed the features of autonomic regulation that were specific to each group of patients (Table III).

In patients with satisfactory adaptation (group A) none of the spectral parameters of HRV were significantly different from those in controls. In addition, high level of TP (TP>2500) and a relative balance of regulatory systems (LF≥VLF≥HF) was found in this group. Furthermore, activity of the peripheral branch of the ANS (LF% + HF% > 50%) dominated over humoral-metabolic effects in the autonomic regulation of heart rhythm in patients of this group at rest (Figure 1). Among the autonomic effects, sympathetic activity dominated in the spectral power structure. However, the values of the sympathetic-vagal balance point to initial euthony in this group of patients (LF / HF = 1.58; Figure 2).

In patients with stress adaptation (group B), the functional state of the ANS was characterized by high levels of total spectrum power (TP = 3224 ± 350), which, however, was accompanied by the reorganization of the heart rhythm modulation (VLF> LF> HF; Figure 1). A more significant reduction of parasympathetic effects, compared with reduction in sympathetic activity, produced a shift in the LF / HF parameter towards sympathicotony (LF / HF = 2.6). All absolute and relative values of the spectrum components were significantly different from similar indicators in group “A” patients.

In patients with unsatisfactory adaptation (Group C), HRV measures revealed a decrease in total spectrum power

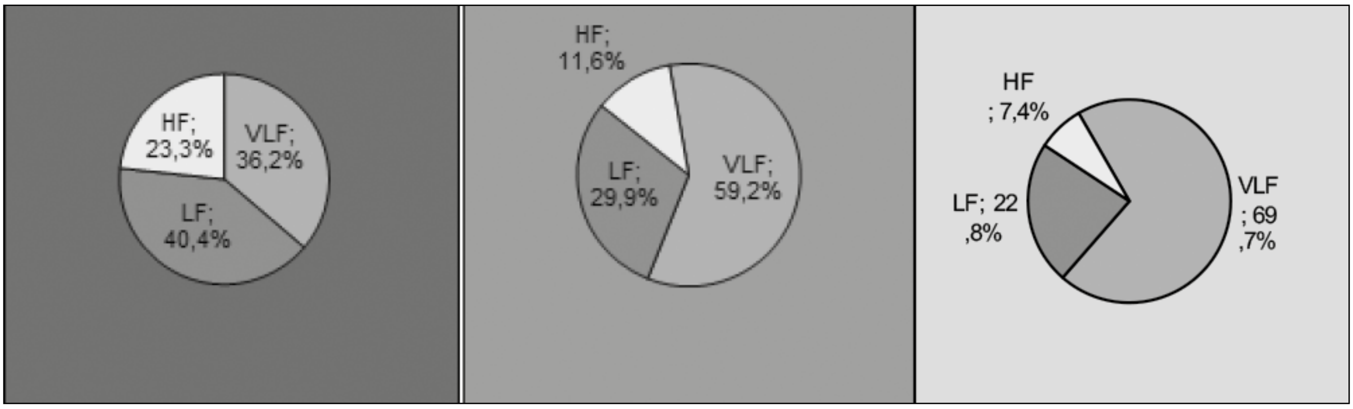

Figure 2. Changes in pathways regulating the heart rhythm in asthma patients with different adaptive potential

Table IV. The relationship between RSAI and clinical course of asthma

Measures	Satisfactory adaptation (n=21)	Stressed adaptation (n=57)	Unsatisfactory adaptation (n=30)
Mean duration of asthma (years)	6.3±1.4	8.2±1.2	14.1±2.1
Frequency of in-patient treatment (times/year)	1.4±0.3	2.2±0.3	2.3±0.3
Frequency of out-patient treatment (times/year)	2.0±0.4	2.4±0.5	2.9±0.5
Severity of asthma symptoms (points)	8.2±0.7	11±0.9	11.7±0.9
Degree of bronchial obstruction (FEF_{25-75}, %)	70.3±4.4	63.1±3.2	59.2±3.3
Daily intake of bronchodilators (fraction of patients)	35%	50%	80%

(TP<1000 ms^2) due to statistically significant decrease in all components of the spectrum, expressed in absolute terms - VLF, LF, HF. In the spectrum structure, humoral-metabolic effects (VLF% = 70%) were significantly overrepresented, while the parasympathetic activity was dramatically decreased. Spectral ratio was characterized as VLF >> LF >> HF (Figure 1). The index of the sympathetic-vagal balance averaged 3.2 ± 0.2, which corresponded to the initial hypersympatheticotony.

Distribution of patients into groups according to RSAI revealed that the features common to the general population of asthma patients become more pronounced as the stress of the adaptation mechanisms increases. Thus, in patients with unsatisfactory adaptation, the total HRV spectrum power, as well as the power of all its frequency domains, is reduced, the level of humoral-metabolic influences reaches maximum values, and the sympathetic-vagal ratio is increased. All of these parameters are different from the same measures both in control group and in patients with satisfactory adaptation with high significance (p<0.001). This indicates a marked ANS dysregulation with depletion of the compensatory abilities of the sympatho-adrenal system and development of asthenia of adaptive mechanisms, which can be considered as predictors of an increased risk of failure of compensatory mechanisms and of the emergence of maladjustment reactions to stress factors.

The study of clinical features of asthma course in groups A, B, and C revealed a relationship between the RSAI values and clinical manifestations of the disease. Thus, the analysis of questionnaire data revealed that the average frequency of in-patient treatment of patients examined in the last year was 1.9 ± 0.3 per year, while patients with a satisfactory adaptation potential required in-patient treatment significantly less frequently (p <0.05) than patients with stressed and unsatisfactory adaptation. In contrast, no significant differences in the frequency of outpatient treatment in the studied groups were detected. Despite the presence of clinical symptoms of asthma in all surveyed patients, the intensity of symptoms was significantly lower in group A patients with satisfactory adaptation. This can be explained by the presence of mostly distal bronchial obstruction (Forced Expiratory Flow $[FEF]_{25-75} \geq 70\%$, but $FEF_{75-85} < 60\%$ of normal values) in these patients, while in group B with stressed adaptation and in group C with unsatisfactory adaptation a combined bronchial obstruction was detected ($FEF_{25-75} < 70\%$ and $FEF_{75-85} < 60\%$ of normal values), resulting in more severe clinical manifestations of asthma (Table IV).

Regarding the frequency of sympathomimetic use, we found a statistically significant relationship between the fraction of patients using sympathomimetics, regularity of their use, and the degree of stress of the autonomic regulation of functions.

Thus, 80% of patients with unsatisfactory adaptation required broncholytics daily, while only 35% of patients with satisfactory adaption did. This points to a reliably less severe disease course in the latter group compared with the former.

CONCLUSIONS

1. The regulatory systems activity index (RSAI) can be used as an integral measure ofmaladjustment in patients with asthma. RSAI within 8-10 points, characterized by substantial reductions in total HRV spectrum power (TP <1000ms), significant predominance of humoral-metabolic waves (VLF> 65%), hypersympathicotony (LF / HF> 3.0), and high index of centralization (IC> 8), should be considered as maladaptive and prognostically unfavorable course of asthma
2. The distribution of patients with asthma based on RSAI revealed that an increase in stress of the adaptation mechanisms is accompanied by increased influence of suprasegmental levels of regulation (VLF%, p<0.01) with centralization of heart rhythm regulation(IC, p<0.01) anddecreased activity of segmental autonomic effects: sympathetic- AMo, LF%, p <0.05 and especially parasympathetic - HF%, p <0.01, as indicated by initial sympathicotony.
3. A relationship between the increase in the degree of autonomic dysfunction, degree of clinical manifestation of the disease, worsening of ventilation dysfunction, duration of asthma and frequency of relapses was found.

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