Volumetric Capnography to Assess Functional Respiratory Disturbances in Patients with Bronchial Asthma

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Spirometry, which implies carrying out forced expiration procedure, frequently, presents a problem, especially in patients with severe asthma, providing no idea of small airways condition. Volumetric capnography has no limitations typical for spirometry.

The aim of the investigation was to study the capabilities of volumetric capnography to determine functional respiratory disturbances in patients with bronchial asthma.

Materials and Methods. 171 male and female patients were examined, including 46 patients with severe bronchial asthma and 42 patients with moderate bronchial asthma. A control group consisted of 83 apparently healthy volunteers. All the subjects under study underwent a clinical examination. In addition, their spirometry and volumetric capnography findings were evaluated using an ultrasound computed spirograph SpiroScout (Ganshorn, Germany) capable of volumetric capnography. In addition, body plethysmography was carried out.

Results. Volumetric capnography revealed the following changes in bronchial asthma patients compared to the controls: phase III inclination angle increase (g/mol·L), which indicates heterogeneity of lung periphery ventilation and perfusion due to small airways pathology, and an emphysema index characterizing pulmonary hyperinflation. Phase III inclination angle alterations were significant in different bronchial asthma severity degrees. A post-bronchodilator test with Salbutamol (400 μg) in the patients with bronchial asthma were found to show an increase in anatomical dead space (ml) and phase II inclination angle decrease (g/mol·L). Phase III inclination angle and an emphysema index of volumetric capnography demonstrated a correlation relationship with spirometry and body plethysmography parameters.

Conclusion. Volumetric capnography extends the concept of the nature and degree of an impaired respiratory function in bronchial asthma. It enables to assess small airways function and determine the presence and extent of lung hyperinflation in patients with bronchial asthma.

Key words: bronchial asthma; volumetric capnography; spirometry; body plethysmography; emphysema index; small airways.

A combined examination of patients suffering from bronchial asthma (BA) involves the evaluation of complaints, anamnestic data, clinical evidence and respiratory function. Respiratory function study is a required technique to analyze ventilatory disturbances, which determine clinical presentation characteristics and the severity degree [1, 2]. Currently, it is spirometry that is of higher priority when assessing respiratory disturbances in such patients, since spirometry includes a bronchodilatory test.

Spirometry is the most common technique for functional diagnostics and monitoring in obstructive respiratory failures in BA patients [1, 3, 4]. The technique has no absolute contraindications; however, carrying out forced expiration procedure, frequently, presents a problem, especially in patients with severe BA [5–7]. Small airways (SAW) dysfunction has been found to be of great importance in airway resistance formation in BA [8–10]. A severe BA phenotype characterized by a high risk of fatality, as well as a phenotype with persisting bronchial obstruction have been suggested to be associated with marked SAW inflammation, obstruction and impaired relationship with alveoli resulting in respiratory disturbances [11–13]. In BA pathogenesis, an emphasis is laid on lung hyperinflation, especially in exacerbations and during asthma attacks. Spirometry fails to verify SAW hyperinflation and obstructive alterations. It raises the necessity to study and introduce other respiratory function assessment tools.

Currently, body plethysmography is used for these

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purposes [14]. Capnography is an integral part of respiratory failure diagnostics, it being used to measure carbon dioxide (CO_2) level in expired air. When studying a capnographic curve, in particular, the inclination angle alteration of an ascending part of capnogram (Van Merten index: RCO_2), one can reveal obstructive respiratory disease [15].

One of promising techniques of functional diagnostics of respiratory disorders is volumetric capnography [15, 16]. In contrast to a traditional technique, it estimates CO_2 changes referring to respiratory volume [15] followed by the calculation of a number of parameters: dead space, phase II and III inclination angles, emphysema index [17]. There are several devices used to record volumetric capnograms, among them there is an ultrasound computed spirograph SpiroScout (Ganshorn, Germany) with volumetric capnography function.

Each phase of a volumetric capnogram has its physiological significance (Figure 1).

Phase I shows CO_2 concentration exhaled from upper airways (i.e. carbon dioxide of anatomical dead space); phase I increase indicates the growth of anatomical dead space ventilation (VD_{aw}).

Phase II presents CO_2 from airways with gas impurities from alveoli, and indicates perfusion alterations; phase II decrease can be indicative of perfusion reduction.

Phase III, or alveolar plateau, presents data on CO_2 released from alveoli, and characterizes gas distribution, the lung periphery ventilation and perfusion [18], which in its turn indicates SAW condition and pulmonary hyperinflation [18–21].
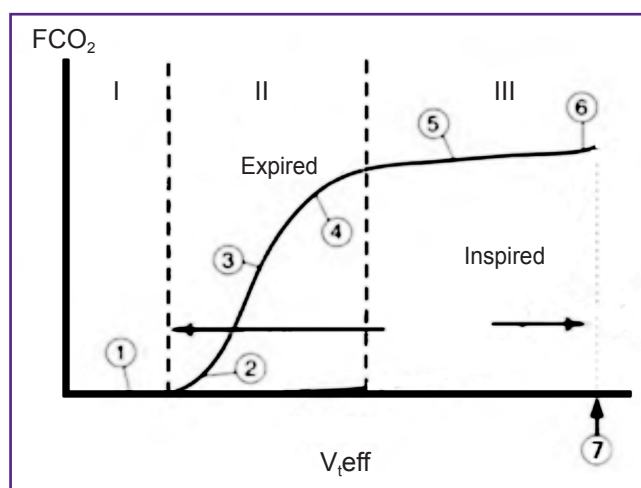

Figure 1. Volumetric capnogram [17]:
I–III: capnogram phases; (*1*) dead space volume; (*2*) transition of phase I to phase II; (*3*) phase II inclination; (*4*) alpha angle (transition of phase II to phase III); (*5*) phase III inclination; (*6*) expiration end; (*7*) released CO_2 volume (area between the curves); FCO_2: fractional carbon dioxide in the expired air; $V_t$eff: effective respiratory volume

The calculated parameters of volumetric capnography will enable to determine the dead space volume, respiratory volume, the amount of released CO_2, as well as assess the lung periphery condition (ventilation-perfusion ratio inhomogeneity). At the same time, the technique enables to estimate the presence of hyperinflation (emphysema) in patients with obstructive respiratory diseases. The use of a pulmonary functional test ("emphysema test") that helps determine an integral parameter — slope of the regression line of mixed air index — is original [18, 22]. In lung emphysema, mixed air volume containing from 25 to 50% maximum CO_2 concentration ($Vm_{25–50}$) undergoes the greatest changes. The parameter is called an 'emphysema index'. It depends on inspiratory volume (VT_{ins}), therefore, $Vm_{25–50}$ to VT_{ins} ratio is used to diagnose emphysema.

Among the advantages of volumetric capnography, special mention should be made of the informativity, noninvasiveness, easiness of use, as well as no need to perform forced respiration that is significant for patients with severe BA. The device to perform the procedure is portable and low cost.

In literature there are enough reports of the studies demonstrating the capabilities of clinical use of volumetric capnography in anesthesiology and intensive care [21, 23, 24–27] to diagnose thromboembolia of pulmonary artery [28–32] and respiratory distress syndrome [33, 34], and there are just a few reports devoted to the assessment of volumetric capnography variations in patients with BA [19, 35] and COPD [20, 36–38], it causing the necessity of further studies of the method.

The aim of the investigation was to study the capabilities of volumetric capnography to determine functional respiratory disturbances in patients with bronchial asthma.

Materials and Methods. It was a cohort and non-interventional study. 88 male and female patients were examined. Among them there were 46 patients with severe BA and 42 patients with moderate BA, with a different extent of disease control. A control group involved 83 apparently healthy volunteers. BA diagnosis was made according to GINA 2015 criteria [1].

BA patients and the controls were similar in age, sex and anthropometrical data (Table 1).

The study complies with the Declaration of Helsinki (the Declaration was passed in June 1964, Helsinki, Finland, and revised in October 2000, Edinburgh, Scotland) and was performed following approval by the Ethic Committee of Ryazan State Medical University named after Academician I.P. Pavlov. Written informed consent was obtained from every patient.

To record volumetric capnography and spirometry findings, we used an ultrasound computed spirograph SpiroScout (Ganshorn, Germany) with volumetric capnography function (Figure 2). Spirometry was performed in accordance with ATS/ERS standards. Body plethysmography was carried out using a body plethysmograph Q-box (COSMED, Italy).

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Table 1

Anthropometric data of patients with bronchial asthma and a control group (M±σ)

Parameters	Bronchial asthma group (n=88)	Control group (n=83)
Age (years)	59.5±1.6	57.4±1.6
Sex (male/female)	28/60	20/63
Height (cm)	165.3±8.4	165.5±0.9
Mass (kg)	82.2±2.1	78.2±1.6
Body mass index	30.20±5.50	28.53±0.54

Figure 2. SpiroScout spirograph with volumetric capnography function (Ganshorn, Germany)

Functional respiratory study included the assessment of spirography and body plethysmograph findings, which were compared with those of volumetric capnography. The respiratory parameters of BA patients were recorded twice: before and 20 min after the inhalation of a short-acting bronchodilator (Salbutamol, 400 µg).

Body plethysmography was performed in 32 controls and 30 patients with BA. All BA patients used no long-acting bronchial spasmolytics 12 h before the examination and short-acting bronchial spasmolytics 6 h before the examination.

The findings were statistically processed using a software package Statistica 10.0 (StatSoft Inc., USA). The results are presented as a mean ± standard deviation for Gaussian samples, and as a median with 25–75% interquartile range for samples different to Gaussian samples. The differences were considered significant if $p < 0.05$, Spearman's rank correlation coefficient being used.

Results and Discussion. Table 2 shows the findings of spirometry, body plethysmography and volumetric capnography.

According to spirometry, BA patients compared to a control group were found to have a significant decrease of respiratory function parameters: forced expiratory volume per during the first second (FEV1, % of reference value), forced vital lung capacity (FVLC, % of reference value), modified Tiffeneau index (Gaenslar index) (FEV1/FVLC, %). Moreover, the patients with different severity degrees demonstrated the significant difference in FEV1 values (% of reference value) between themselves and compared to a control group: 46.40±10.25 in severe BA, 68.47±0.92 in moderate BA, and 98.98±1.26 in the controls. FEV1 increased significantly in BA patients after bronchial spasmolytic inhalation (Table 3).

Table 2

Spirometry, volumetric capnography and body plethysmography findings in patients with bronchial asthma and a control group

Parameter	Bronchial asthma group (n=88)	Control group (n=83)
Spirometry		
FEV1 (% of reference value)	59.50±1.72*	98.98±1.26
FVLC (% of reference value)	74.91±2.08*	102.86±1.29
FEV1/FVLC (%)	76.22±2.45*	109.67±2.47
Body plethysmography		
	Bronchial asthma group (n=30)	Control group (n=32)
PRV (% of reference value)	166.5 (136.5; 291)*	110.5±6.22
PRV/TLC (%)	65.75±6.4*	58.75±4.82
R_{aw} (kPa s/L)	200.3±46.73*	83.58±8.95
Volumetric capnography		
VD_{Fowler} (ml)	126 (106; 154)*	154 (126; 189)
dMM/dV2 (g/mol·L)	2.78 (2.1; 3.44)	2.55 (1.9; 3.31)
dMM/dV3 (g/mol·L)	0.26 (0.19; 0.36)*	0.19 (0.11; 0.26)
Alpha s2s3 (degrees)	127 (117; 135)*	124 (119; 128)
dMMmax (g/mol)	0.42±0.01*	0.37±0.01
Vm_{25-50}/VT_{ins}	35.64 (12.8; 75.9)*	18.43±1.47

* Significant difference with controls, $p < 0.05$. FEV1: forced expiratory volume during the first second; FVLC: forced vital lung capacity; FEV1/FVLC: Gaenslar index; PRV: pulmonary residual volume; PRV/TLC: the ratio of pulmonary residual volume to total lung capacity; R_{aw} (kPa s/L): bronchial resistance index; VD_{Fowler}: dead space volume according to Fowler; VT_{ins}: respiratory volume; dMM/dV2: phase II inclination; dMM/dV3: phase III inclination; Alpha s2s3: alpha angle between phase II and III; dMM_{max}: maximum molar mass of total CO_2 released during the expiration related to the volume; Vm_{25-50}/VT_{ins}: emphysema index.

Table 3

Pre- and post-bronchodilatory indices of spirometry and volumetric capnography in patients with bronchial asthma

Parameter	Pre-bronchodilation (n=88)	Post-bronchodilation (n=88)
Spirometry		
FEV1 (% of reference value)	59.50±1.72*	67.31±1.75
FVLC (% of reference value)	74.91±2.08*	81.28±1.89
FEV1/FVLC (%)	76.22±2.45	77.82±1.79
Volumetric capnography		
VD_{Fowler} (ml)	126 (106; 154)	131 (112; 158)
dMM/dV2 (g/mol·L)	2.78 (2.1; 3.44)*	2.38 (1.73; 2.85)
dMM/dV3 (g/mol·L)	0.26 (0.19; 0.36)	0.24±0.01
Alpha s2s3 (degrees)	127 (117; 135)	128.39±0.93
dMM_{max} (g/mol·L)	0.42±0.01*	0.37±0.01
Vm_{25-50}/VT_{ins}	35.64 (12.8; 75.9)*	25.2 (11.09; 57.9)

* Significant difference of values with post-bronchodilatation indices. FEV1: forced expiratory volume during the first second; FVLC: forced vital lung capacity; FEV1/FVLC: Gaenslar index; dMM/dV2: phase II inclination; dMM/dV3: phase III inclination; Alpha s2s3: alpha angle between phase II and III; dMMmax: maximum molar mass of total CO_2 released during the expiration related to the volume; Vm_{25-50}/VT_{ins}: emphysema index

According to body plethysmography, compared to the controls, BA patients were found to have an increase in pulmonary residual volume (PRV) (as % of reference value) and the ratio of pulmonary residual volume to total lung capacity (PRV/TLC) (as %) that was caused by an air cushion effect. In addition, R_{aw} (kPa s/L) — airways resistance index — also increased in BA patients compared to the controls due to bronchial obstruction (See Table 2).

The analysis of volumetric capnography indices showed the anatomical dead space volume (VD_{Fowler}) in a BA group to be significantly lower than in a control group due to bronchial obstruction.

No reliable differences of phase II inclination angle values (dMM/dV2) were found in BA patients and the controls. However, its decrease in BA patients after taking Salbutamol indicates indirectly the change of dead space amount in response to bronchodilation (Table 3). The findings are consistent with those by Almeida et al. [19], who studied volumetric capnography in children with controlled persisting BA. The correlation dependence of dMM/dV2 with body plethysmography indices PRV (r=0.68) and R_{aw} (r=0.74) was found.

Phase III inclination angle (dMM/dV3) characterizes the condition of the lung periphery ventilation and perfusion [18]. In healthy subjects with minimal ventilation inhomogenuity this curve phase is flat. In patients with SAW pathology, phase III has a slope proportional to ventilation inhomogenuity. dMM/dV3 value was significantly higher in BA patients compared to the controls that is consistent with the data obtained by Almeida [19]. Romero et al. [37] when estimating the capabilities of the method in examining patients with COPD also found the index increase. Thus, phase III inclination angle change in BA patients compared to the controls indicates ventilation inhomogenuity due to distal airway pathology (Figure 3). In addition, the parameter values differed significantly in patients with moderate (0.25±0.02) and severe BA (0.32±0.004). The assessment of dMM/dV3 before and after Sulbutamol showed no reliable difference that can be due to irreversible changes of distal airways [17]. The parameter had correlation dependence with FEV1 of spirometry (r=–0.47) and R_{aw} of body plethysmography (r=0.55).

An inclination angle between phases II and III (Alpha s2s3) was significantly higher in BA patients compared to the controls due to irregular "emptying" of alveoli breathing out in bronchial obstruction [18]. There was found the correlation of the parameter with FEV1 of spirometry (r=–0.36) and PRV/TLC of body plethysmography (r=–0.32).

Maximal molar mass of total CO_2 (dMM_{max}) released during the expiration, and related with the volume was significantly higher in BA patients compared to the controls; after bronchial spasmolytic inhalation the parameter reduced that can be due to expiratory volume change.

The lung hyperinflation in the subjects under study was determined using an emphysema test (Figure 4). BA patients had significantly higher Vm_{25-50}/VT_{ins} index compared to a control group. Vm_{25-50}/VT_{ins} correlated

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Capnography	Reference value	Curve 1	Curve 2	Curve 3	Curve 4	Curve 5	Mean
$VD_{threshold}$ .... ml	-	94	98	101	93	98	97
VD_{Bohr} .... ml	-	198	228	197	214	191	206
VD_{Fowler} .... ml	-	139	147	143	138	156	144
dMM/dV2 .... g/mol·L	-	2.55	2.63	2.51	2.25	2.78	2.55
dMM/dV3 .... g/mol·L	-	0.16	0.20	0.12	0.19	0.09	0.15
Alpha s2s3	-	120	122	119	125	115	120
f 1/min	-	-	-	-	-	-	24
VT L	-	-	-	-	-	-	0.65

a

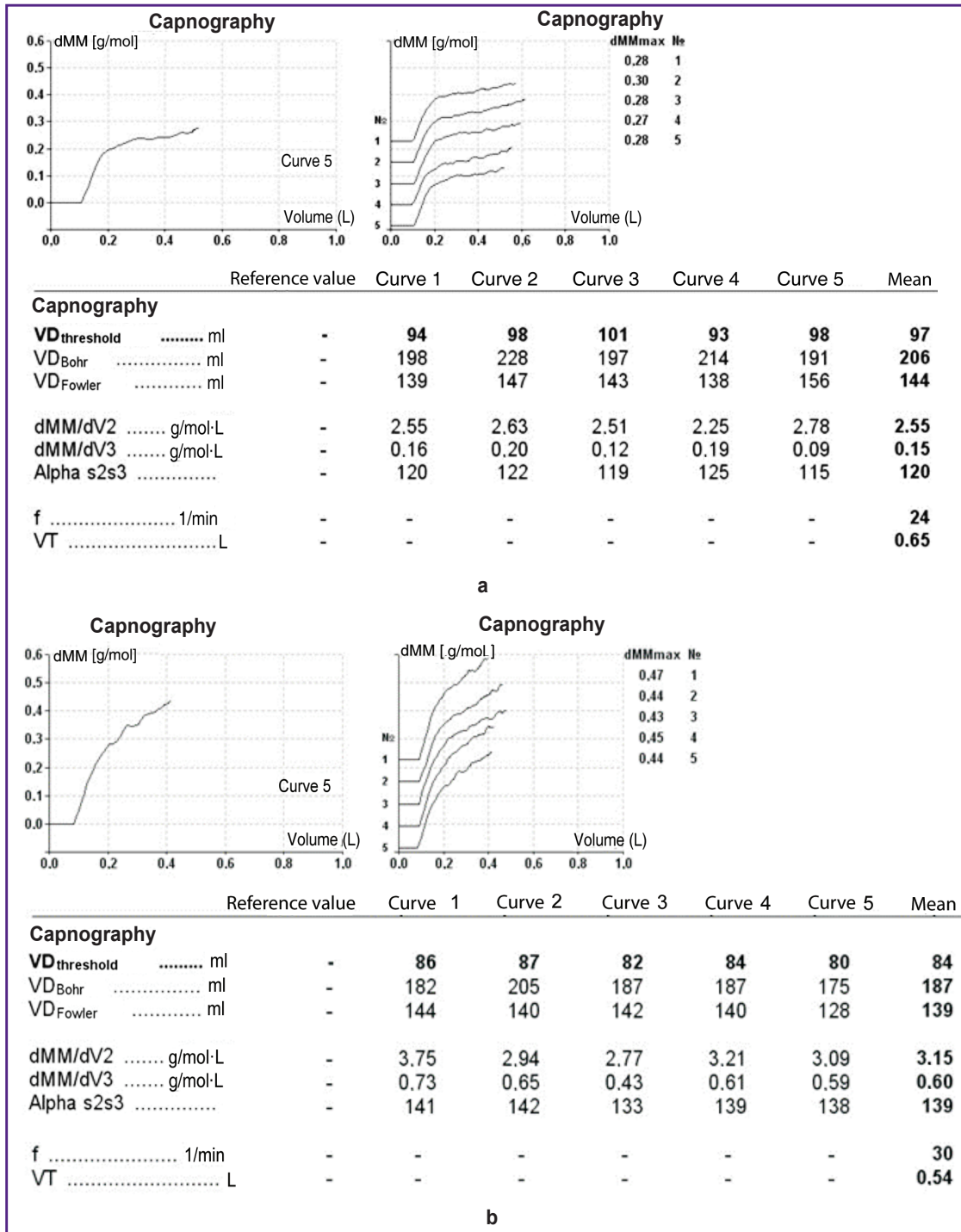| Capnography	Reference value	Curve 1	Curve 2	Curve 3	Curve 4	Curve 5	Mean
$VD_{threshold}$ .... ml	-	86	87	82	84	80	84
VD_{Bohr} .... ml	-	182	205	187	187	175	187
VD_{Fowler} .... ml	-	144	140	142	140	128	139
dMM/dV2 .... g/mol·L	-	3.75	2.94	2.77	3.21	3.09	3.15
dMM/dV3 .... g/mol·L	-	0.73	0.65	0.43	0.61	0.59	0.60
Alpha s2s3	-	141	142	133	139	138	139
f 1/min	-	-	-	-	-	-	30
VT L	-	-	-	-	-	-	0.54

b

Figure 3. Volumetric capnogram: normal (a) and in respiratory obstruction (b):
$VD_{threshold}$: dead space determined by a threshold method; VD_{Bohr}: dead space determined according to Bohr technique; VD_{Fowler} dead space determined according to Fowler technique; dMM/dV2: phase II inclination; dMM/dV3: phase III inclination; Alpha s2s3: alpha angle (transition of phase II to phase III); f: respiration rate; VT: respiratory volume; dMM_{max}: maximum molar mass of total CO_2 released during the expiration related to the volume

to FEV1 of spirometry (r=–0.32) and to PRV of body plethysmography (r=0.50).

Thus, the analysis of volumetric capnography findings showed the anatomic dead space volume (VD_{Fowler}) in a BA group was significantly lower than in the control group. BA patients after Salbutamol taking had a decrease of phase II inclination angle (dMM/dV2), an increase in phase III inclination angle (dMM/dV3), and
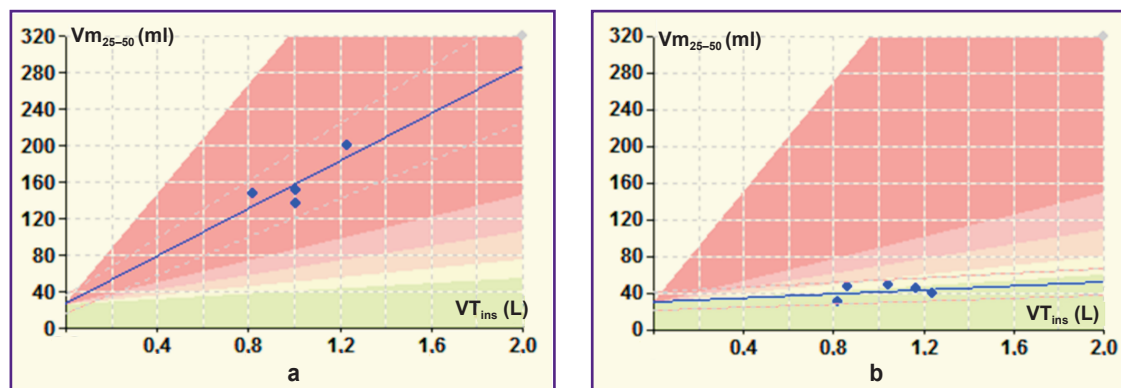
Figure 4. Emphysema test:
(a) in a patient with lung hyperinflation (Vm_{25-50}/VT_{ins}-130.43); (b) in a control patient (Vm_{25-50}/VT_{ins}-10.62)

inclination angle between phase II and III (Alpha s2s3) and emphysema index (Vm_{25-50}/VT_{ins}) compared to the controls. Moreover, phase III inclination angle had significant differences in patients with moderate and severe BA and in those with severe BA. Volumetric capnography parameters — phase III inclination angle and emphysema index — demonstrated the clearest correlation relation with forced expiratory volume during the first spirometric second, as well as with the volumes of the lungs and bronchial resistance index determined by body plethysmography.

Conclusion. Volumetric capnography extends the concept of the nature and degree of the impaired respiratory function in BA, since it enables to assess small airways function and determine the presence and extent of lung hyperinflation. The method enables to undertake a study of pulmonary function in patients with severe bronchial asthma, it being of great importance especially in cases, when spirometry is infeasible.

Conflict of Interests. The authors have no conflict of interests to disclose.

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