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Does phase 2 of the expiratory P_{CO_2} *versus* volume curve have diagnostic value in emphysema patients?

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ABSTRACT: It has been postulated that serial inhomogeneity of ventilation in the peripheral airways in emphysema is represented by the shape of expiratory carbon dioxide tension *versus* volume curve. We examined the diagnostic value of this test in patients with various degrees of emphysema.

The volumes between 25–50% ($V_{25–50}$) and 25–75% ($V_{25–75}$) of the expiratory carbon dioxide tension *versus* volume curve were determined in 29 emphysematous patients (20 severely obstructed and 9 moderately obstructed), 12 asthma patients in exacerbation of symptoms, and 28 healthy controls. Discriminant analysis was used to examine whether these diagnostic groups could be separated.

With regard to phase 2 of the expiratory CO_2 *versus* volume curve (mixture of anatomic deadspace and alveolar air), a plot of intercept *versus* slope of the relationships of ($V_{25–50}$) and ($V_{25–75}$) *versus* inspiratory volume (V_I) from functional residual capacity (FRC), obtained during natural breathing frequency, proved to be most discriminating in the separation between healthy controls and severely obstructed emphysema patients. Separating healthy controls and severely obstructed emphysema pat- ients on the basis of the discriminant line for $V_{25–50}$, 9 of the 12 asthma patients in exacerbation were classified as normal, and only 5 of the 9 moderately obstructed emphysema patients as emphysematous. For $V_{25–75}$ involvement of phase 3 of the curve (alveolar plateau) in asthma patients in exacerbation caused a marked overlap with the severely obstructed emphysema patients. In the healthy controls, a fixed breathing frequency of 20 breaths·min^{-1} led to an increase of both volumes. For $V_{25–50}$, this resulted in an overlap with the severely obstructed emphysematous patients.

We conclude that $V_{25–50}$ and $V_{25–75}$ are not useful in the diagnosis of emphysema. This indicates that the ventilatory inhomogeneity as reflected by Phase 2 of the expiratory carbon dioxide tension *versus* volume curve is not sensitive enough for diagnostic application.

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During expiratory capnography 3 phases can be observed: phase 1 with air from the anatomic deadspace of the airways without CO_2, followed by phase 2 showing a rapid rise in CO_2, leading to phase 3: the alveolar plateau. The abnormal shape of the expiratory carbon dioxide tension (P_{CO_2}) *versus* time curve in emphysema patients has often been studied [1–5] and has been attributed to serial, as well as parallel, inhomogenity of ventilation. The time between 25–75% of the end-tidal P_{CO_2} [4], and the minimum radius of curvature [5], resulted in abnormally high values in emphysema patients compared to asthma patients and healthy controls. The dependence of the expiratory P_{CO_2} *versus* time curve on expiratory flow has led to the use of the P_{CO_2} *versus* volume curve [6–8].

WORTH [7, 8] focused on phase 2, and determined the volume expired between 25–50% ($V_{25–50}$), and 25–75% ($V_{25–75}$) of the inspiratory to end-tidal partial pressure differences for He, SF_6, O_2 and CO_2. He found that the slopes of the relationships between $V_{25–50}$ or $V_{25–75}$ and inspiratory volume (V_I) for these gases increased more in emphysema than in healthy controls and asthma patients, which he explained on basis of serial ventilatory inhomogeneity due to a different airway morphology.

The aim of the present study was to further evaluate the diagnostic value of $V_{25–50}(CO_2)$ and $V_{25–75}(CO_2)$ *versus* V_I by comparing at first severely obstructed emphysema patients with healthy controls (as has been done in earlier studies), and subsequently, on basis of the former results, investigating whether emphysema patients with less airway obstruction could be separated from healthy controls, and whether asthma patients in exacerbation could be distinguished from emphysema patients.

Moreover, we investigated the influence of breathing pattern on $V_{25–50}$ and $V_{25–75}$ in the first 10 severely obstructed emphysema patients and healthy controls who entered the study. Breathing pattern was characterized

by inspiratory volume (V_I), expiratory volume (V_E) inspiratory time (T_I), expiratory time (T_E) mean inspiratory and expiratory flow (V_I/T_I and V_E/T_E), and end-tidal P_{CO_2} (P_{ET,CO_2}), respectively. The relationship of V_{25-50} and V_{25-75} at a fixed inspiratory volume of 1 *l* with height, and the influence of a fixed breathing frequency, was evaluated in all healthy controls.

Methods

Study population

The healthy controls were 28 persons with no history of disease from cardiopulmonary origin. The patient group consisted of 12 asthma patients in exacerbation of symptoms and 29 emphysema patients, 20 of the latter being severely obstructed (forced expiratory volume in one second (FEV_1) values below 1.4 *l*) and 9 moderately obstructed. In 5 of the asthma patients, the investigations were repeated after recovery. Mean values for anthropometric data, including age, sex, length and body mass index (BMI: weight in kg/length in m^2) are reported in table 1. The controls had a relatively high weight and normal spirometric values, although residual volume (RV) and functional residual capacity (FRC) values were relatively low. The asthma patients, however, were younger and mostly female. The moderately obstructed emphysema patients were comparable in age and weight with the severely obstructed emphysema patients, but had better FEV_1 values, which were in the same range as those of the exacerbation asthma patients. The severely obstructed emphysema patients were mostly men, characterized by a relatively low body weight, reflected by their BMI. They had severe obstruction and hyperinflation. Both groups of emphysema patients showed only slight and comparable improvement after bronchodilator inhalation (0.75 mg terbutaline by metered-dose inhaler (MDI). Mean improvements in % of initial FEV_1 were 6.1% (SD 5.5%) and 5.9% (SD 6.7%) for the severely and moderately obstructed emphysema patients, respectively. Blood gas values indicated primarily hypoxaemia, without an overall alveolar hypoventilation.

Clinical diagnosis

For the diagnosis of emphysema the American Thoracic Society (ATS) criteria for chronic obstructive pulmonary disease (COPD) [9] and the X-ray criteria described by PRATT [10] were used: the latter are based on signs of hyperinflation and tissue loss on the posteroanterior and lateral chest X-ray. On the posteroanterior X-ray two signs may be present: 1) depression and flattening of the diaphragm with blunting of costophrenic angles; and 2) irregular radiolucency of lung fields. On the lateral X-ray there are also two signs: 1) abnormal retrosternal space; and 2) flattening, or even concavity, of the diaphragm. Emphysema was diagnosed if two or more of these criteria were present. Asthma was diagnosed according to the ATS criteria: a clinical syndrome characterized by increased responsiveness of the tracheobronchial tree to a variety of stimuli, with symptoms of paroxysmal dyspnoea, wheezing and cough, and, as a physiological manifestation of this hyperresponsiveness, variable airways obstruction [9]. Only those patients in whom the airways obstruction was completely reversible after recovery were selected for this study.

All healthy controls older than 50 yrs underwent chest X-ray to exclude pulmonary pathology.

Pulmonary function tests

Pulmonary function tests in the patient group included spirometry, with estimation of total lung capacity TLC, FRC, RV, vital capacity (VC), and FEV_1. FRC was estimated using the closed circuit helium dilution method. Arterial blood gas analysis was performed in all severely obstructed patients in a stable phase. Mean values (and SD) of the pulmonary function variables are presented in table 1. Reference values for spirometry were European Community for Coal and Steel (ECCS) values [11].

Table 1. – Characteristics of subject groups

	Healthy controls		Exacerbation asthma patients		Moderately obstructed emphysema patients		Severely obstructed emphysema patients	
M/F n	17/11		4/8		7/2		18/2	
Age yrs	51	(17)	36	(14)*	54	(10)	60	(12)
Height m	1.72	(0.10)	1.72	(0.13)	1.78	(0.08)	1.73	(0.08)
BMI $kg \cdot m^{-2}$	24.8	(2.7)	23.7	(2.9)	21.7	(2.9)*	21.1	(3.5)*
TLC % pred	102	(8)	103	(11)	132	(15)*	123	(11)*
FRC/TLC % pred	88	(12)	101	(15)*	118	(9)*	126	(14)*
RV/TLC % pred	87	(6)	101	(22)*	138	(22)*	150	(34)*
VC % pred	114	(13)	89	(18)*	106	(13)	87	(16)*
FEV_1 % pred	106	(11)	57	(17)*	61	(12)*	29	(11)*
FEV_1/VC % pred	74	(7)	53	(9)*	44	(6)*	25	(7)*
Pa_{O_2} kPa							8.8	(0.9)
Pa_{CO_2} kPa							5.6	(0.7)

Data are presented as mean, and SD in parenthesis. M: male; F: female; BMI: body mass index; TLC: total lung capacity; FRC: functional residual capacity; RV: residual volume; FEV_1: forced expiratory volume in one second; Pa_{O_2}: arterial oxygen tension; Pa_{CO_2}: arterial carbon dioxide tension.

Measuring equipment

The measuring equipment consisted of a CO_2 analyser (Hewlett Packard, 47210A capnometer) in series with a pneumotachometer head (Jaeger, Würzburg, Germany) connected to a Validyne transducer, model P46 (Validyne Corp., Northridge, CA, USA). A pneumotachometer was used in view of its dynamic properties, thus avoiding distortion of phase 2 and synchronization difficulties, which are to be expected when a spirometer system is used. Both signals, P_{CO_2} and flow, were sampled with a frequency of 50 Hz and analysed by the lung function computer network at our laboratory [12]. Flow was integrated to volume. A time delay, inherent to the capnograph, of 160 ms was needed to synchronize the CO_2 signal with the flow signal. The pneumotachometer head was maintained at a constant temperature of 37°C. As the humidity and temperature of the gas in the pneumotachometer head are difficult to estimate, a humidity of 50% and a mean temperature of 30°C were assumed. From these values and the current barometric pressure a body temperature and pressure saturated with water vapour (BTPS) correction was made for the inspired air. For the expiratory gas, BTPS conditions were present. Before each measurement, calibration with a 1 *l* syringe was carried out.

Because volume integration was performed over a relatively large number of breaths in series, a correction had to be made for volume drift. Assuming an unchanged RV during the test, a correction factor was established based on RV level after maximal expiration at the beginning and end of the procedure (fig. 1). The accuracy of the volume estimation was verified with a spirometer in series. The volume measured by the pneumotachometer was slightly (but randomly) different from the volume measured by the spirometer, and within a range of about 5%.

The dead space volume of mouthpiece, CO_2 analyser and pneumotachometer head was 50 ml.

Experimental protocol

Each test consisted of a series of 40–80 consecutive breaths with natural breathing frequency. With intervals of 3–5 normal breaths, the subject took a voluntary deep breath from FRC, returning to FRC (fig. 1). The controls repeated these manoeuvres at fixed frequencies of 10, 15 and 20 breaths·min^{-1}. For each breath the following characteristics were determined: T_I, T_E, V_I, V_E, and P_{ET,CO_2}.

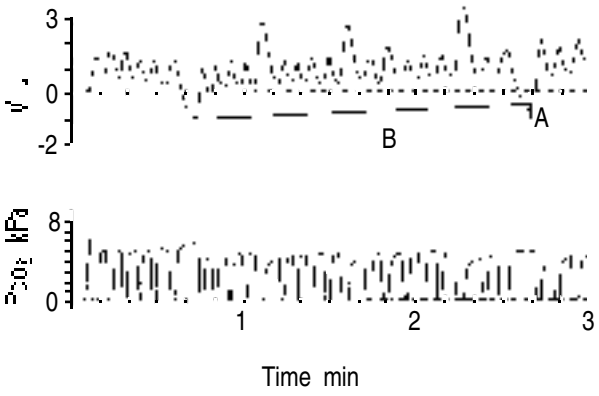

Fig. 1. – Example of a recording of volume *vs* time and carbon dioxide tension (P_{CO_2}) *vs* time. A: represents extent of baseline drift (ml) over time (B).

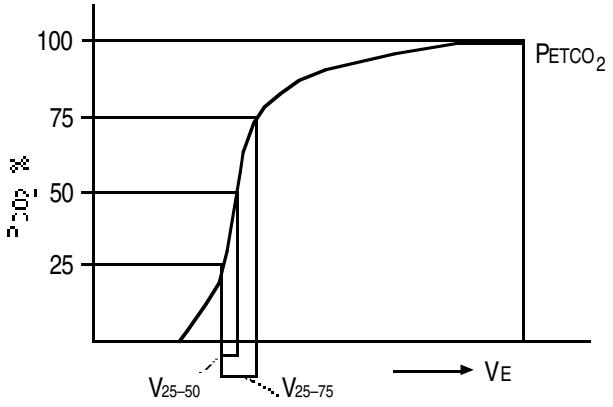

Fig. 2. – Variables $V_{25–50}$ and $V_{25–75}$ derived from the expiratory P_{CO_2} *vs* volume curve. $V_{25–50}$ and $V_{25–75}$: volume expired between 25–50% and 25–75% of the P_{ET,CO_2}, respectively; P_{ET,CO_2}: end-tidal carbon dioxide tension.

An expiratory P_{CO_2}/V_E curve was plotted (fig. 2). Variables derived from this curve were: 1) $V_{25–50}$: the volume expired between 25–50% of the P_{ET,CO_2}; and 2) $V_{25–75}$: the volume expired between 25–75% of the P_{ET,CO_2}.

Analysis of the variables was performed on all breaths starting at FRC level. A breath was rejected if the difference between inspiratory and expiratory volume exceeded 300 ml, or if inspiratory or expiratory volume was less than 300 ml.

Statistical methods

Linear regression analysis was used to determine the linear relationship and correlation coefficient (r) of $V_{25–50}$ and $V_{25–75}$ with V_I and the other breath characteristics. Multiple linear regression analysis was used to investigate whether a second breath characteristic (the first being V_I) could improve the linear relationships (expressed as r^2, the coefficient of determination). Discriminant analysis was applied to investigate whether two groups could be separated on the basis of intercept and slope of the linear relationships. Unpaired and paired t-tests were applied to detect differences between and within groups, respectively.

For statistical analysis, the commercial computer programs Statgraphics and Statistical Package for the Social Sciences (SPSS) were used.

Results

$V_{25–50}$ and $V_{25–75}$ versus *V_I in the study groups*

Examples of the relationship between $V_{25–50}$ and V_I, and $V_{25–75}$ and V_I with their regression lines for a healthy control and severely obstructed emphysema patient are

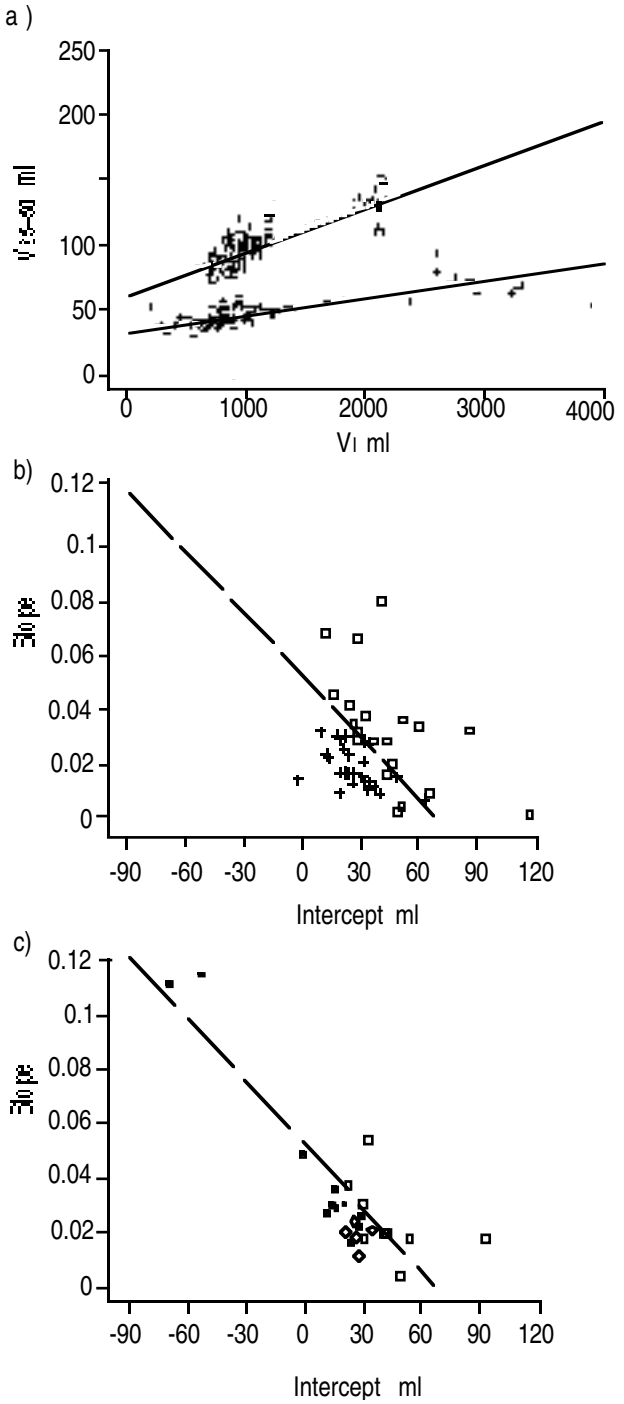

Fig. 3. – a) Examples of V_{25-50} *vs* V_I with regression lines, in one severely obstructed emphysematous patient and one healthy control. ❒ : severly obstructed emphysema patient; + : healthy control; ——— : linear regression lines for both groups. b) Slope *vs* intercept of linear regression lines of V_{25-50} *vs* V_I in 20 severely obstructed emphysema patients and 28 healthy controls. ❑ : severely obstructed emphysema patient; + : healthy control; —— —— : discriminant line. c) Slope *vs* intercept of linear regression lines of V_{25-50} *vs* V_I in 9 moderately obstructed emphysema patients (❒); in 12 exacerbation asthma patients (■); and in 5 asthma patiens after recovery (◆). —— ——: discriminant line from 3b. V_I: inspiratory volume. For further abbreviations see legend to figure 2.

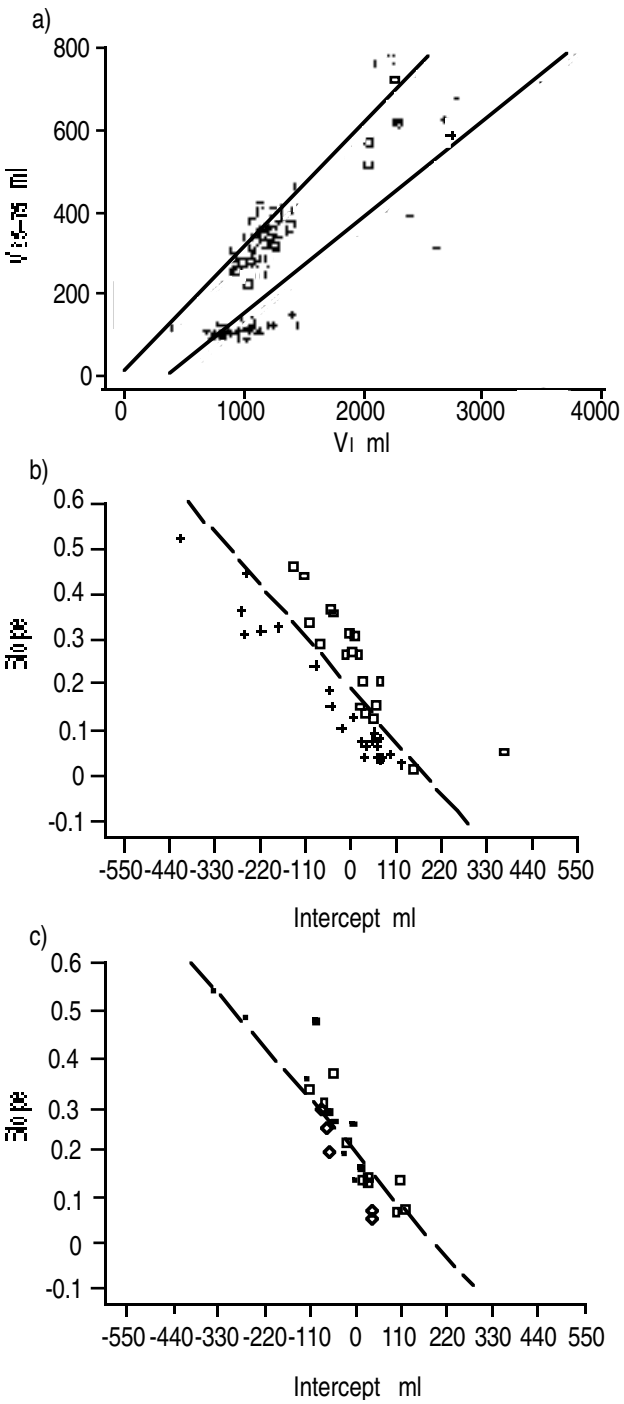

Fig. 4. – a) Examples of V_{25-75} *vs* V_I with regression lines in one severely obstructed emphysema patient and one healthy control; ❒ : severely obstructed emphysema patient; + : healthy control; ——— : linear regression lines for both groups. b) Intercept *vs* slope of linear regression lines of V_{25-75} *vs* V_I in 20 severely obstructed emphysema patients and 28 healthy controls; ❑ : severely obstructed emphysema patient; +: healthy control; —— —— : discriminant line. c) Slope *vs* intercept of linear regression lines of V_{25-75} in 9 moderately obstructed emphysema patients (❒); in 12 exacerbation asthma patients (■); and in 5 asthma patients after recovery (◆). —— —— : discriminant line from 4b. For abbreviations see legend to figures 2 and 3.

shown in figures 3a and 4a, respectively. The X-Y-plots of intercept *versus* slope of the individual regression lines of all healthy controls and severely obstructed emphysema patients showed that the two groups had only a slight overlap (figs 3b and 4b). Discriminant lines (determined by discriminant analysis) are drawn in these

figures. These lines yielded a sensitivity of 80–90% for both volume indices, and a specificity of 89% for V_{25-50} *versus* V_I and 100% for V_{25-75} *versus* V_I relationship.

In figures 3c and 4c, the discriminant lines separating healthy controls and severely obstructed emphysema patients were drawn (taken from 3b and 4b), together with plots of intercept and slope of the regression lines for the asthma patients in exacerbation and the moderately obstructed emphysema patients. In figure 3c the symbols, representing intercept and slope of the regression lines for the asthma patients in exacerbation were predominantly on the "control" side of the discriminant line. In the case of V_{25-75} *vs* V_I there was more overlap with the emphysema patients, which disappeared after recovery in 2 of the 5 asthma patients, who repeated the test after recovery (fig 4c). Only 5 of the 9 moderately obstructed emphysema patients were located on the emphysema side of the discriminant lines.

Influence of breathing frequency in the controls

Fixed breathing frequencies of 10, 15 and 20 breaths·min^{-1} in the healthy controls generally showed an increase of V_{25-50} and V_{25-75} in relation to V_I with increase of breathing frequency (figs 5 and 6). At a breathing frequency of 20 breaths·min^{-1} the position of intercepts and slopes of the regression lines of V_{25-50} showed a marked overlap with those of the severely obstructed emphysema patients.

Influence of breath characteristics and height

In the 10 controls, in all cases V_{25-50} and V_{25-75} were significantly correlated with V_I, but also with V_E, V_I/T_I and V_E/T_E, the last variables representing mean inspiratory and mean expiratory flow, respectively. The correlation coefficients (r) were in the range 0.80–0.90 with a mean SD of 0.10. However, multiple regression analysis did not show an appreciable increase of r^2 or reduction of residual variance when either of the other characteristics (T_I, T_E, V_E, V_I/T_I, V_E/T_E or P_{ET,CO_2}) was added as a second variable (the first being V_I).

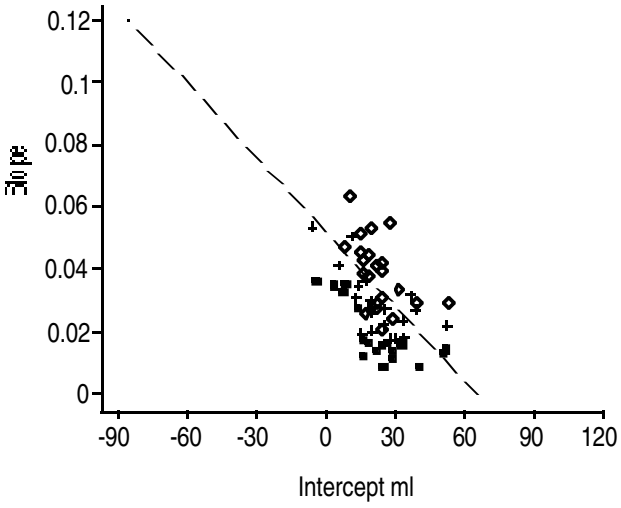

Fig. 5. – Slope *versus* intercept of linear regression lines of V_{25-50} *vs* V_I in 28 healthy controls with different breathing frequencies. ■ : 10 breaths·min^{-1}; + : 15 breaths·min^{-1}; ◆ : 20 breaths·min^{-1}; —— ——: discriminant line as in figure 3b.

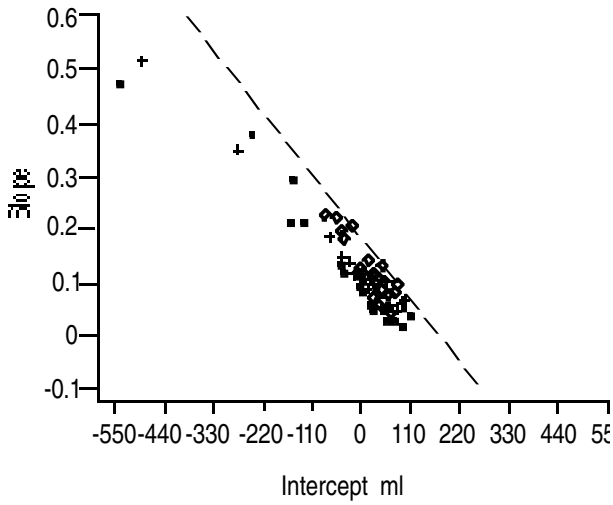

Fig. 6. – Slope *versus* intercept of linear regression lines of V_{25-75} *vs* V_I in 28 healthy controls with different breathing frequencies. ■ : 10 breaths·min^{-1}; + : 15 breaths·min^{-1}; ◆ : 20 breaths·min^{-1}; —— ——: discriminant line as in figure 4b. For abbreviations see legnd to figures 2 and 3.

In the 10 severely obstructed emphysema patients, V_{25-50} and V_{25-75} were significantly correlated with V_I in eight cases, two patients showing no significant correlation with r<0.30. This was why the mean correlation coefficients were lower, with values of 0.59 (SD 0.28) and 0.73 (SD 0.30) for V_{25-50} and V_{25-75}, respectively. Because, in the two patients mentioned above, a significant correlation of V_{25-50} existed only with T_I and V_I/T_I, a multiple regression analysis adding these variables, increased r^2. At a fixed inspiratory volume of 1 *l*, there was a positive correlation of V_{25-50} and V_{25-75} with height in the 28 controls, with correlation coefficients of 0.56 (p=0.002) and 0.43 (p=0.022), respectively.

Discussion

This study was aimed at determining the diagnostic value of phase 2 indices of the P_{CO_2} *versus* volume curve in pulmonary emphysema. The results showed that severely obstructed emphysema patients could be separated from healthy controls and asthma patients after recovery on the basis of a plot of intercept *versus* slope of the relationships of V_{25-50} or V_{25-75} *versus* V_I. Separation of asthma patients in exacerbation and severely obstructed emphysema patients was only possible for the relationship of V_{25-50} *versus* V_I. Moderately obstructed emphysema patients showed a marked overlap with healthy controls; and increasing breathing frequency in healthy controls caused an overlap with the severely obstructed emphysema patients for the relationship of V_{25-50} *versus* V_I. Finally, in healthy controls both V_{25-50} and

V_{25-75} showed a positive correlation with height at an inspiratory volume of 1 *l*.

Our clinical diagnosis of emphysema may be subject to criticism. Emphysema is histologically diagnosed [9], and diagnosis of this disease is often difficult in its early stage. Use of computed tomography (CT) [13–15] and, more recently, high resolution CT [16–19], with estimation of density, is currently the gold standard. These techniques enable the disease to be diagnosed at an earlier stage, but are costly and no standardized procedure has yet been established [20]. Characteristic chest X-ray abnormalities usually develop in a later stage of the disease [21]. Diagnostic chest X-ray criteria related to histological findings were described by PRATT [10] in 1987, who claimed good sensitivity and specificity. Although chest X-ray signs were not detected in some emphysema patients in his study, this is a well-known disadvantage of the chest X-ray [20]; X-ray signs were never positive in normal lungs, and positive signs of emphysema always coincided with histologically proven emphysema. The positive predictive value can, thus, be considered as 100%; and this has never been disproved by the new gold standard, the high resolution CT scan.

Although increased lung compliance and reduced pulmonary diffusion capacity are considered to be the most indicative pulmonary function indices for emphysema [22–25], they were not performed in all patients for technical reasons (single-breath diffusion capacity test requires a minimum FEV_1 of 1 *l*) and due to burdening of the patients (compliance).

Since a late stage of the disease is accompanied by severe airways obstruction, chest X-ray and FEV_1 were chosen to characterize the patients and, thus, defined the severely obstructed emphysema group. Some patients, however, were clearly less obstructed and were separated at the beginning of the study to serve as a second emphysema group, with moderate emphysema. As airways obstruction also occurs in asthma patients, our second check on the validity of the test as a diagnostic test for emphysema was made using this group of asthmatics with exacerbation of symptoms. They had normal FEV_1 and VC values after recovery, with no signs of emphysema on chest X-ray, and were considered to have no emphysema.

For the alveolar plateau of the capnograph, it is generally accepted that primarily parallel ventilation-perfusion inhomogeneity, in combination with sequential emptying of the lung units, defines its value, slightly modified by the ongoing CO_2 excretion [6]. The alveolar plateau slope values and P_{ET,CO_2} undoubtedly influence the magnitude of V_{25-50} and V_{25-75}, which means that these mechanisms also contribute to the values.

WORTH [7, 8] postulated that serial inhomogeneity in a trumpet model was the main determining mechanism. Thus, increased serial inhomogeneity due to morphological changes in peripheral airways in emphysema patients provides an explanation for the increase both of V_{25-50} and V_{25-75}; and, moreover, for the increase of these variables with increasing V_I. The findings of WORTH [7, 8] have been extended in the present study by enlarging the number of patients, and using not only the change with V_I, but both the intercept and slope of the relationships.

For the discrimination of severely obstructed emphysema patients and controls it appeared from our data that a plot of slope *versus* intercept of the relationship of either V_{25-50} or V_{25-75} *versus* V_I gave most discrimination, if compared with the slope alone (fig. 3b and 4b). Both for the V_{25-50} and V_{25-75} *versus* V_I relationships, we found on average a twofold smaller increase in slope in emphysema patients compared to controls than WORTH [7, 8]. The differences between our results and those of WORTH [7, 8] could be due to difference in study populations, our study group being three times larger and, moreover, age-matched with the controls, which was not the case in Worth's study.

The results in the nine moderately obstructed emphysema patients did not support the discriminatory value of slope and intercept, and the asthma patients in exacerbation were only classified properly for the V_{25-50} *versus* V_I relationship. If morphological lesions alone were responsible for the observed differences, as found in the severely obstructed emphysema patients, it was to be expected that the nine emphysema patients with less airways obstruction could also be discriminated from the healthy controls. In asthma patients in exacerbation of symptoms airways obstruction is expected to occur, with narrowing of peripheral airways, which explains the lack of difference compared to controls for V_{25-50}. The lesser discriminatory power for the V_{25-75} *versus* V_I relationship in the case of asthma, may be explained by the influence of an increased slope of the alveolar plateau on this volume, causing extension of V_{25-75} into the alveolar phase. This same mechanism may explain the fact that in severely obstructed emphysema patients *versus* controls, V_{25-75} was slightly better than V_{25-50}.

Influence of breathing characteristics, breathing frequency and height

The first 10 healthy controls and first 10 severely obstructed emphysema patients who entered the study, confirmed that during natural breathing frequency (and fixed breathing frequencies in the controls) V_{25-50} and V_{25-75} were dependant mainly on V_I. Thus, the discriminatory power of the relationships with V_I will not increase if more breathing characteristics are taken into account. Fixed breathing frequency with varying V_I implies higher inspiratory and expiratory flows; whereas, during natural breathing the respiratory cycle time increased with increasing V_I. The increase of V_{25-50} and V_{25-75} *versus* V_I with increase of frequency is in agreement with the results in Worth's controls and can be attributed physiologically to movement of the diffusion front in a peripheral direction by increased inspiratory flow, which results in an increased cross diameter of this front [7, 8]. The increased cross diameter causes an increase in phase 2 volumes.

WORTH [7, 8] found no relationship between the slopes of V_{25-50} and V_{25-75} *versus* V_I and height in controls. However, at a fixed inspiratory volume chosen because

of the volume dependence, we found a significantly positive correlation of V_{25-50} and V_{25-75} with height in the controls, which is a new finding. This linear correlation is certainly based, as for the anatomical dead space [26], on the relationship with the anatomical dimensions of the bronchial tree, being body size-dependent.

In conclusion, the results of our study make the use of phase 2 indices for the diagnosis of emphysema, as suggested previously [7, 8], doubtful. Moderately obstructed emphysema patients could not be distinguished sufficiently from healthy controls, as was the case for the asthma patients in exacerbation of symptoms *versus* severely obstructed emphysema patients if V_{25-75} was considered. Most probably, the explanation of differences between patient groups, on the basis of serial inhomogeneity in a trumpet model of the lung, means an oversimplification of the complex interaction with parallel ventilation perfusion inhomogeneity and asynchronization.

The variables are not sensitive enough for further diagnostic application, and certainly the use of more refined clinical indices for emphysema, as obtained by for instance a high resolution CT scan, will not influence this conclusion.

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