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Expiratory capnography in asthma:

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Expiratory capnography in asthma: evaluation of various shape indices. B. You, R. Peslin, C. Duvivier, V. Dang Vu, J.P. Grilliat. ©ERS Journals Ltd 1994.

ABSTRACT: The shape of the capnogram is modified by airway obstruction, and the evaluation of this deformation, using measurable indices, could allow an indirect measurement of bronchial patency. A previous study undertaken in asthmatic subjects showed a good correlation between a capnographic index (end-tidal slope) and a spirometric parameter (forced expiratory volume in one second as a percentage of predicted (FEV_1 %pred)) and suggested the study of other indices.

The correlations between capnographic and spirometric indices were measured in 10 healthy subjects and 30 asthmatic patients. The usefulness of eight descriptive indices, analysing the successive phases of the capnogram, was assessed by measuring their reproducibility and their sensitivity to airway obstruction. The intra-individual and interindividual variabilities (Vi and VI) and the noise/signal ratio (Vi/VI) were measured by comparing the results of two successive capnographic measurements in 14 asthmatic subjects. The results show an increasing noise/signal ratio along the expiration (between 23 and 62%).

Significant correlations between spirometry and capnography were found with all indices, but the strongest were observed with indices analysing the intermediate phase of the capnogram, that is the angle between the ascending phase (E2) and the alveolar plateau (E3).

The correlations show that the analysis of the capnogram's shape is a quantitative method for evaluating the severity of bronchospasm. This ability, added to specific advantages (noninvasiveness, effort-independency, measurements during tidal breathing) opens new fields of application to capnography, such as measurement of bronchospasm in children and computerized monitoring of asthma.

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The capnogram is the curve obtained by continuous recording of the carbon dioxide partial pressure (P_{CO_2}) in a sample of expiratory air (P_{ECO_2}). The normal capnogram (fig. 1a) has a square wave pattern, marked by alternating inspiratory (P_{ICO_2} equals zero) and expiratory phases [1–3]. Expiration itself consists of three successive phases: 1) a latency phase, "E1", corresponding to expiration of the anatomical dead space (P_{ECO_2}=0), indistinguishable from the preceding inspiration; 2) phase "E2", marked by a very rapid rise in P_{ECO_2}, corresponding to expiration of mixed air; and 3) plateau phase, "E3", reflecting the elimination of alveolar air (slightly increasing P_{ECO_2}) resulting in a peak at the end of tidal expiration (P_{ETCO_2}, close to alveolar carbon dioxide tension (P_{ACO_2})), which immediately precedes the start of the following inspiration. These three phases are separated by two, normally, well-defined transitions: angles "P" and "Q".

This almost rectangular shape depends on the homogeneity of the gas distribution and alveolar ventilation [4–6]. In the absence of obstructive syndrome, the verticality of E2 indicates a regular separation front between the absolute dead space and the alveolar air. As all of the territories are ventilated homogeneously, the elimination of their alveolar air is synchronous, and this is reflected by a very sudden rise in P_{ECO_2} (E2), followed by the expiration of alveolar air with a homogeneous P_{ACO_2}, as indicated by the almost horizontal plateau, E3.

Bronchial obstruction is associated with regional decreases in the airflow, and consequently alveolar ventilation, responsible for "parallel heterogeneity" of the ventilation/perfusion ($\dot{V}_A/\dot{Q}$) ratio. Each bronchopulmonary territory is characterized by its own $\dot{V}_A/\dot{Q}$, determining its P_{ACO_2}. During expiration, there is a desynchronization of the various territories, which are evacuated at different times depending on their $\dot{V}_A$. On the capnogram the highest level of P_{ACO_2} in the most poorly ventilated territories combined with their lower airway conductance, induces a deformation of the curve marked by a loss of verticality of E2, flattening and opening of angle Q, and shortening and inclination of E3. In severe cases, the capnogram takes on a "shark's fin" appearance (fig. 1b).

Several studies, conducted in subjects with chronic bronchitis or emphysema [7, 15], have demonstrated the existence of a significant correlation between indices

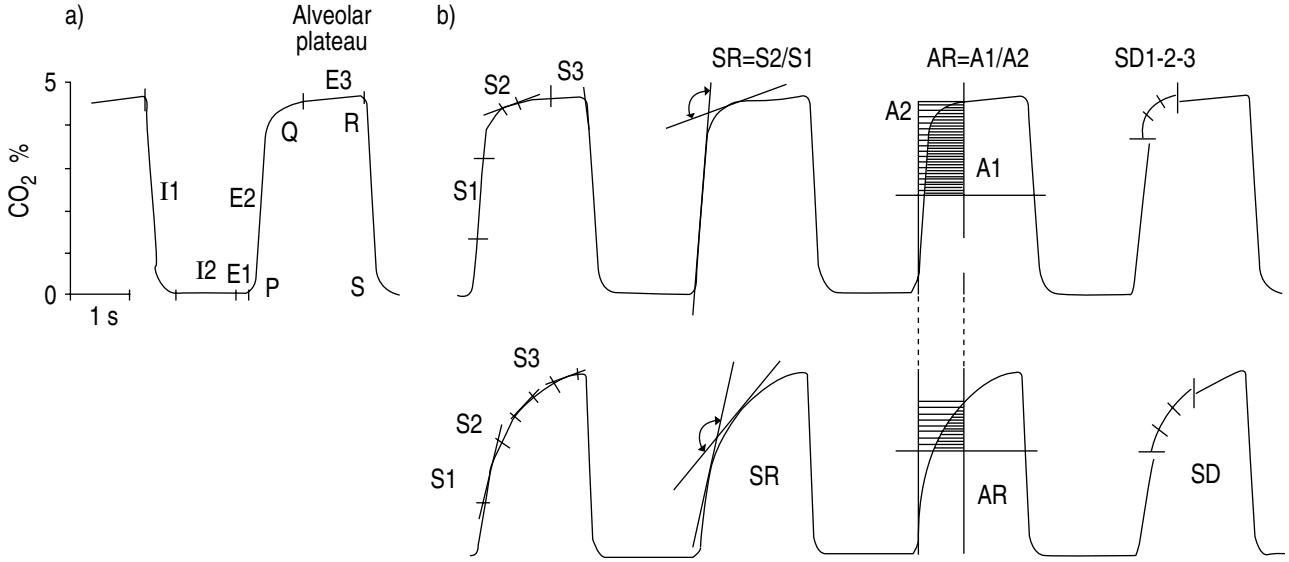

Fig. 1. – Description of the capnogram and of its indices in normal and obstructive conditions. a) The inspiratory (I1 and I2) and expiratory phases (E1, E2. E3) of a normal capnogram. b) Schematic description of the capnographic indices measured on a normal (upper) and on an obstructive (lower) capnogram. S1-2-3: slopes measured at different phases; SR: slope ratio; AR: area ratio; SD1-2-3: indices measured from the second derivative. See text for details.

describing the shape of the capnogram and the usual spirometric parameters. These observations are of great interest since, contrary to forced respiratory manoeuvres, capnographic measurements do not require the patient's co-operation, or even wakefulness, and could, therefore, be used for monitoring airway patency in a number of clinical situations. In a preliminary study conducted in asthmatic subjects [16], we demonstrated the existence of a very good correlation ($p<0.001$) between a capnographic index (the end-tidal slope (ETS) of the alveolar plateau) and a spirometric parameter (forced expiratory volume in one second as a percentage of predicted (FEV_1 % pred)). This capnographic index was selected since it can be easily measured by hand, but this study also suggested the probable existence of other, more reproducible indices that are even more representative of bronchial obstruction.

As a continuation of this preliminary study, the objectives of the present work were: 1) to define new capnographic indices; 2) to validate them in terms of sensitivity in relation to the usual spirometric measurements, and in terms of reproducibility, both in healthy subjects and in asthmatic subjects; and 3) depending on the results obtained, to select indices suitable for application to the monitoring of asthmatic patients.

Methods

Measurements

The capnographic measurements were performed with an aspirative capnograph (Datex Normocap®; response-time 250 ms; weekly calibration with a reference gas mixture (5% CO_2)); the sample collection catheter (length 1.8 m; diameter 0.9 mm; aspiration rate 150 ml·min^{-1}; pure delay 1 s) was fixed to the upper lip and inserted a few millimeters into the nostril. The analogue fraction of expired carbon dioxide ($FECO_2$) signal was digitized, with a sampling rate of 30 Hz for periods of 60 s, using an analogue-digital conversion card (Digimetrie Digimetrix®), and was processed by an Apple IIe computer system.

Maximal expiratory flow-volume curves were recorded with a computerized spirometer (Gauthier Spirometric®) which met the European Coal and Steel Community (ECSC) technical requirements [17].

To quantify the deformation of the time-related capnogram, we computed the variations in a number of shape parameters, each exploring one or several components of this deformation. They were defined in relation to the visible onset of expiration (T0), *i.e.* - on the capnographic curve - from the start of phase "E2". In this study, T0 was defined by the passage of the $FECO_2$ above a threshold of 0.2%.

Eight shape indices were tested (fig. 1b):
Three indices measured the slope of the capnogram during the various phases of expiration. Each phase was defined by the times of its onset and completion, expressed in seconds from T0. The slopes were obtained by linear regression of $FECO_2$ *versus* time and expressed as %·s^{-1}: "S1", initial slope measured from 0 to 0.2 s (E2); "S2", intermediate slope measured from 0.8 to 1.2 s (beginning of E3); and "S3", terminal slope measured at the end of expiration during the half second preceding the end-expiratory peak (end of E3).

Two indices indirectly measured the opening of Q: 1) the slope ratio (SR) between the intermediate and the initial slopes (S2/S1) × 100; 2) the area ratio (AR) of the area under the curve at angle Q (A1) to the area of the rectangle in which it is inscribed (A2) (A1/A2) × 100. A1 and A2 were calculated above a threshold of 2.5% of CO_2 between times 0.2 and 1 s. The threshold of 2.5% of CO_2 was chosen because every capnogram oversteps

this threshold, and because this level usually marks the beginning of angle Q in severe attacks.

Three indices used the second derivative of the capnographic curve; they indicated its curvature at its various points: "SD1", value of the maximum negative peak of the second derivative close to angle Q (expressed as $\%\cdot s^{-2}$); "SD2", mean value of the second derivative between the time where it is zero (inflection of E2) and the time at which the slope becomes less than 0.75 $\%\cdot s^{-1}$; and "SD3", mean value of the second derivative between its zero value and the time at which it becomes larger than -0.03 $\%\cdot s^{-2}$ (E3 almost linear). SD1, SD2 and SD3 are negative but, for simplicity, their sign has been ommitted in the rest of this presentation.

Inadequate cycles were excluded on various criteria: expiration lasting less than 0.8 s or more than 3 s, end-tidal F_{ECO_2} less than 3%, severe deformation by artefacts (see below). The eight indices (S1, S2, S3, SR, AR, SD1, SD2 and SD3) were measured on each accepted cycle, and their mean values were taken and compared to spirometric indices.

Patients and protocol

Two studies were performed independently in asthmatic subjects who exhibited differing degrees of dyspnoea at the time of tests, but whose bronchial obstruction had been clinically stable for several hours.

The reproducibility of the capnographic indices was studied in 14 asthmatic subjects (7 women and 7 men, mean±SD age 40.3±13.6 yrs), suffering from bronchial asthma based on usual clinical criteria, and having evidence of bronchial hyperresponsiveness (carbamylcholine bronchial challenge). They had experienced no signs of bronchial infection for more than one month and continued their usual treatments (bronchodilator±corticoids). The measurements were performed more than 4 h after the last administration of $beta_2$-mimetic spray. The values of the eight capnographic indices were measured and compared for two successive recordings at an interval of 10 min. The reproducibility of each index was evaluated by calculating the "intraindividual variability" (Vi) defined by the ratio of the difference to the mean (m) of the successive measurements ($Vi=(m_1-m_2)\times 2/(m_1+m_2)$). The noise/signal ratio of the index was then characterized by relating the mean Vi in the group to the "interindividual variability"(VI) (coefficient of variation in the group: $VI=(\sigma 1/m1+\sigma 2/m2)/2$), where $\sigma 1$ and $\sigma 2$ are the standard deviations of the first and second measurements in the group.

The correlation between capnographic and spirometric parameters was studied in 10 control subjects (6 women and 4 men; mean±SD age 44.3±13.9 yrs), nonsmokers and free of any bronchopulmonary disease, and in 30 asthmatic subjects. The latter (15 men and 15 women, mean±SD age 43.1±16.3 yrs) were selected using the same criteria as in the reproducibility study. All subjects underwent, successively, tidal volume capnography lasting 60 s and spirometric recordings during forced expiration. The eight capnographic indices and the spirometric parameters (FEV_1 %pred, peak expiratory flow (PEF) %pred, forced mid-expiratory flow (FEV_{25-75}) %pred) [17] were measured and compared by calculating their correlation coefficients.

The asthmatic group was divided into three subgroups, according to the severity of the bronchospasm: subgroup A1 with $FEV_1 \geq 80$ %pred; subgroup A2 with FEV_1 40–79 %pred; and subgroup A3 with FEV_1 <40 %pred.

Results

Reproducibility study

Large differences were seen among the indices (table 1). The intraindividual variabilities were low (Vi <10%) with indices describing the initial part of the capnogram (S1, AR, SD1, SD2). The results were poor for intermediate indices (SD3, SR and S2) and worst for S3. A large between-subjects variability, suggesting a high sensitivity to airway obstruction, was seen for intermediate and terminal slopes (S2, S3, SR), followed by SD1, SD2, SD3, and the lowest ranges were seen with S1 and SR.

For Vi/VI which is an index of the noise/signal ratio, the best results, *i.e.* the lowest values, were obtained with SR, AR and SD2; good results were found with S1, S2 and SD1; and poor results with SD3 and S3.

Table 1. – Reproducibility of the capnographic indices and their correlations to the spirometric indices

	S1	S2	S3	SR	AR	SD1	SD2	SD3
Vi %	6.4	15.5	27.4	15.4	3.3	9.3	7.7	11.5
VI %	18.2	44.0	44.4	54.6	14.3	23.5	30.9	21.8
Vi/VI %	35.1	35.2	61.7	28.2	23.3	39.4	24.9	52.6
FEV_1 %pred	0.73	0.89	0.90	0.89	0.85	0.82	0.93	0.90
PEF %pred	0.75	0.84	0.86	0.89	0.81	0.82	0.87	0.85
FEV_{25-75} %pred	0.59	0.89	0.087	0.87	0.71	0.69	0.84	0.78

All the correlations (r) between the capnographic and spirometric indices are significant ($p<0.001$); linear regressions for AR and SD1–3, semi-logarithmic regressions for S1–3 and SR. FEV_1: forced expiratory volume in one second; PEF: peak expiratory flow; FEV_{25-75}: forced mid-expiratory flow; S1-2-3: slopes measured at different phases; SR: slope ratio; AR: area ratio; SD1-2-3: indices measured from the second derivative; Vi: intraindividual variability; VI: interindividual variability; Vi/VI: noise/signal ratio.

Table 2. – Spirometric and capnographic data in healthy control subjects and in asthmatic patients

	Control subjects		Total asthmatic subjects		Asthmatic subgroups					
					A1 FEV_1 ≥80%		A2 40%≤ FEV_1 <80%		A3 FEV_1 <40%	
	n=10		n=30		n=10		n=10		n=10	
FEV_1 %pred	104±7.7	(7.4%) ***	62±26.4	(42.7%)	89±7.09	***	67±10.16	***	29±6.44	
PEF %pred	108±13.1	(12.1%) ***	68±29.6	(43.6%)	99±6.3	***	71±16.06	***	34±12.91	
FEV_{25-75} %pred	97±15.5	(16%) ***	38±29.3	(61.2%)	65±16.07	*	44±15.44	***	16±5.50	
S1 $\%\cdot s^{-1}$	15±1.87	(12.5%) ***	11.4±2.34	(20.5%)	13.4±1.98	*	11.5±1.19	**	93±1.72	
S2 $\%\cdot s^{-1}$	0.23±0.06	(26.1%) ***	0.55±0.30	(54.5%)	0.31±0.09	NS	0.45±0.21	***	0.90±0.18	
S3 $\%\cdot s^{-1}$	0.16±0.05	(31.7%) ***	0.35±0.22	(62.9%)	0.18±0.04	NS	0.28±0.12	**	0.59±0.21	
SR %	1.6±0.49	(31.4%) ***	5.5±3.95	(71.7%)	2.4±0.95	*	4.0±1.96	**	10.1±3	
AR %	88±3	(3.4%) ***	78±9	(11.5%)	86±6	*	79±6	**	65±9	
SD1 $\%\cdot s^{-2}$	38.1±4.67	(12.3%) ***	27.2±7.92	(29.1%)	34.8±6.04	NS	26.9±3.73	**	20.0±5.57	
SD2 $\%\cdot s^{-2}$	18.2±2.04	(11.2%) ***	11.2±4.30	(38.5%)	15.3±2.5	*	12.2±2.47	***	6.5±1.89	
SD3 $\%\cdot s^{-2}$	12.3±2.2	(17.9%) ***	8.4±2.12	(25.2%)	10.3±1.35	*	8.9±0.98	***	6.0±1.27	

Data are presented as mean±SD, with coefficient of variation in parenthesis. Significances of the differences between control and asthmatic subjects, and between the three subgroups of asthmatic subjects A2 *versus* A1, and A3 *versus* A2; *: p<0.05; **: p<0.01; ***: p<0.001. For abbreviations see legend to table 1.

Correlation study

Comparison of control and asthmatic subjects. The two populations of subjects could be clearly distinguished on the basis of spirometric results (table 2). While control subjects had values closely grouped around the mean (standard deviation/mean, σ/m=7.4–16%), the asthmatic subjects showed marked interindividual differences, reflecting a great diversity in the severity of the bronchospasm (σ/m = 42.5–61.2%). Ten asthmatics subjects had normal or subnormal spirometric values, with FEV_1 %pred ranging from 80–100%, 10 showed moderate (FEV_1=40–79 %pred) and 10 marked signs of obstruction (FEV_1=16–39 %pred). The variance analysis showed that all the capnographic indices were significantly different (p<0.001 in all cases) between control and asthmatic groups. In spite of lower subgroup sizes, most of the indices were also different between the three subgroups, notably between A2 and A3.

Correlations between capnography and spirometry. In general, the capnographic indices were strongly correlated to the spirometric parameters (p<0.001 in every case) (table 1 and fig. 2). In some instances, slightly better correlations were found using semi-log adjustment. The highest correlations were usually observed with FEV_1 %pred rather than with PEF %pred. Those with FEV_{25-75} %pred were consistently lower than with the other spirometric indices. Intermediate and terminal indices were often more closely correlated to maximal flows than initial indices (S1, AR, SD1). The best results were obtained with the mean second derivatives, especially SD2. For the slopes, no improvement was seen when relating S2 to S1.

Discussion

KELSEY and OLDHAM [18] described four kinds of shapes in normal and obstructive capnograms. Since their report, various theoretical approaches have been used in order

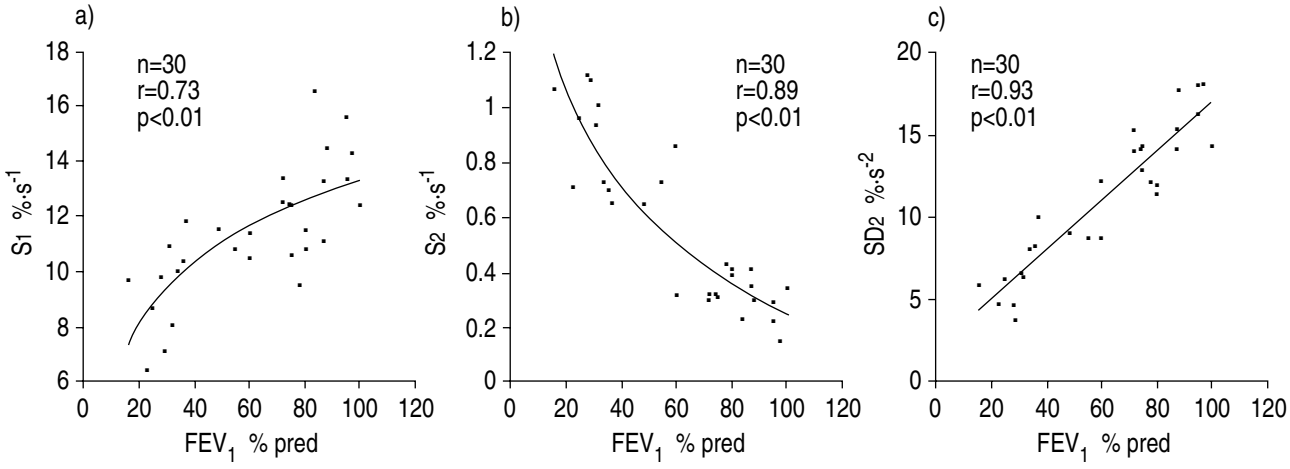

Fig. 2. – Relationship between three capnographic indices and FEV_1 %predicted. These indices were chosen for their sensitivity to airway obstruction (S2 and SD2) and for their ability to be measured in "worst conditions" (S1). FEV_1 forced expiratory volume in one second. For further abbreviations see legend to figure 1.

to quantify these deformations [2, 7–9, 19, 20], and several capnographic indices have been assessed in chronic obstructive lung disease (COLD): 1) the slope of the alveolar plateau which can be related to the P_{ETCO_2} [1, 10, 11]; 2) the radius of minimal curvature of angle Q [7– 9, 12, 21]; 3) the time necessary to pass from 25 to 75% of the P_{ETCO_2} [4, 13]; and 4) the angle between "E2" and "E3" measured manually or computed from the ratio of their slopes [14, 22, 23]. In all the validation studies [10–12, 14] significant correlations were found between the usual spirometric measurements and the values of the capnographic indices used.

Four studies focused on the capnogram in asthmatics. The first three [23–25] were conducted in children, and showed changes in E2 and E3 slopes after bronchial challenge. The fourth [16], performed by ourselves, was conducted in adult asthmatics. The value of the end-tidal slope (ETS), measured manually, was compared to FEV_1 %pred. A good correlation was observed between these two parameters, but this preliminary study suggested a computerization of capnogram analysis and then the evaluation of new indices not possessing the disadvantages encountered with the use of ETS (see below).

Selection of cycles

From a methodological point of view, the physiological irregularities of respiration require the selection of good quality cycles according to criteria of duration, amplitude and, when possible, regularity of the curve. In this study, we systematically eliminated cycles which did not meet the following criteria: 1) expiration lasting between 0.8 and 3 s; 2) maximal amplitude above 3.5%; and 3) good regularity of E2 and E3.

Furthermore, within these limits, certain indices require, according to their definitions, that a cycle satisfy specific requirements of duration and shape. These particular requirements are responsible for an automatic rejection rate, specific to each index, and increasing with the severity of bronchospasm (short cycles preventing the measurement of the latest indices).

Factors influencing the data

Some indices may be altered by factors inducing a deformation of the capnogram unrelated to bronchial obstruction.

The shape of the capnogram may depend first upon methodological factors, namely the dynamic characteristics of the analyser. In this respect, one should distinguish between the response-time and the pure delay introduced by the sampling catheter. The latter does not alter the shape of the signal, but a long response-time will filter out its fast components. In this study, the 90% response-time of the instrument was of 250 ms, with the sampling flow of 150 $ml \cdot min^{-1}$. Assuming first-order behaviour, this corresponds to a time-constant of about 100 ms. We tried to numerically correct the data for that instrumental response, and studied the influence of doubling the response-time: it resulted in a decrease of all the indices which, however, remained correlated to the spirometric parameters ($p<0.01$ for all indices, except $p<0.05$ for S1 and $p<0.02$ for SR). We conclude that an increased response-time modifies capnographic indices, but does not erase their diagnostic value.

In time-related capnography, the expiratory flow rate also determines the general shape of the capnogram, as the P_{ECO_2} is related more to the expired volume than to the expiratory time. An emotional rise in the expiratory flow rate can be responsible for and underestimation of the bronchospasm. On the other hand, during sleep, stage related decreases of the ventilation flow rate (rapid eye movement (REM) phases) can induce pseudo-obstructive deformations of the capnogram. This is the price to be paid when a spirogram is not simultaneously recorded. In the same way, the arterial carbon dioxide tension (Pa_{CO_2}) determines the overall amplitude of the capnogram, and slightly influences the indices.

The duration of the expiratory phase profoundly influences the latest indices, by shortening or lengthening the terminal part of the capnogram the slope of which decreases. In some conditions (expiration <1.5 s or >2.5 s) a late index (S3) may, therefore, greatly over- or underestimate bronchospasm. This may explain the large intraindividual variability of such indices.

Lastly, the alveolar plateau may be altered by artefacts derived from the upper airways (nasal obstruction, pulsatile waves of carotid origin) which prevent the analysis of 5% of the recordings. These different pitfalls require criteria for adequate use and interpretation of aspirative capnography; the most important, in clinical use, are strict resting conditions (which excludes exercise challenge).

Variability and relationship to spirometric indices

The assessment of capnographic indices must consider firstly their noise/signal ratio (Vi/VI), and secondly their correlation to spirometric indices. In terms of Vi/VI, the initial indices have the lowest noise (Vi <10%) and show evidence of sturdiness, whilst the latest indices (S3 and SD3) have a high noise/signal ratio (Vi/VI >50%) which prohibits their clinical use. Inversely, the intermediate and terminal indices show the best correlations to spirometric parameters. Therefore, along the expiration, the capnogram appears to be more and more sensitive to bronchial obstruction but less and less reproducible.

The good results of the correlation study are confirmed by measurements performed during bronchial challenge. In the literature, modifications of different capnographic indices during inhalative bronchial challenges were found in two studies conducted in children [23, 24]. In one of our previous works [16], a high correlation ($p<0.001$) was found between the variations of a capnographic index (ETS) and one of the FEV_1 produced by salbutamol. In another study (unpublished) conducted in six asthmatic children (mean age±SD age 5.0±2.2 yrs), the values of SD2 were compared to those of respiratory impedance obtained by forced oscillations. Measurements, performed during an acetylcholine challenge and then after salbutamol, showed a good correlation ($p<0.01$) between the variations of the two indices. These results prompted us to use on-line monitoring of the capnographic indices, the trend curves of which give a dynamic, time-related, view of the bronchial response to any drug [26].

Monitoring of asthma has not yet become part of clinical practice; several functional methods have been used [27–35] because of the lack of a universally acknowledged sensitive, reliable and noninvasive method. The absence of constraints (noninvasiveness and co-operation-independency), combined with a satisfactory sensitivity (high correlations to spirometric parameters), allows capnography to be proposed for this application. The computerized measurement of the indices, their memorization and visualization in the form of trend curves, could constitute a useful tool for asthma monitoring. Capnography can be used in awake and sleeping subjects and could allow various new applications to be envisaged: monitoring of status asthmaticus, detection of nocturnal attacks, evaluation of the duration of action of bronchodilator drugs, intra- and postoperative monitoring of asthmatic patients, and dynamic bronchial provocation tests, especially in children.

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