

Perceived effect on shortness of breath of an acute inhalation of saline or terbutaline: variability and sensitivity of a visual analogue scale in patients with asthma or COPD

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ABSTRACT: The purpose of the study was to validate a bipolar visual analogue scale (VAS) to assess the perceived effect on shortness of breath of an acute inhalation and to search for differences in perception between asthmatics and subjects with chronic obstructive pulmonary disease (COPD).

Thirty two subjects with airway obstruction and a diagnosis of either asthma (n=16) or COPD (n=16) received three consecutive inhalations of isotonic saline, followed by two inhalations of 400 µg terbutaline.

Saline was perceived by asthmatics as a slight improvement: VAS (median, 95% confidence interval) 9%, 0-18% of line length. COPD subjects could be separated into two subgroups: "high perceivers" (n=8, VAS 43%, 33-53%) and "low perceivers" (n=8, VAS 5%, 3-7%). The median intrasubject coefficient of variation of the three post-saline VAS ratings was 19.4% (asthma), 12.5% (COPD high perceivers), and 14.5% (COPD low perceivers). After terbutaline, asthmatics had, by selection, a larger increase in forced expiratory volume in one second (FEV₁) than COPD subjects. However, for other indices (expiratory specific resistance, inspiratory vital capacity and maximal inspiratory flow at 50% forced vital capacity) the changes were smaller in COPD low perceivers than in both asthmatics and COPD high perceivers. The parallel improvement in VAS was 24%, 20-39% (asthma), 15%, 6-25% (COPD high perceivers) and 1%, -1-8% (COPD low perceivers).

The most sensitive index was FEV₁ in asthmatics, vital capacity in COPD subjects, VAS being among the most sensitive indices in the former, but among the least sensitive in the latter.

We conclude that the sensitivity of this VAS to bronchodilation is better in asthmatics than in COPD subjects. The latter can however be separated into subgroups with high and low level of perception.

Eur Respir J, 1992, 5, 1043-1053.

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Keywords: Asthma
lung diseases
obstructive
perception
visual analogue scale

Received: July 23 1991
Accepted for publication May 25 1992

Despite a growing interest in recent years in the assessment of respiratory sensations, the perception of acute bronchodilation in the lung function laboratory has so far received little attention. The influence of a single dose salbutamol inhalation on breathlessness at rest was studied in 93 subjects with chronic obstructive pulmonary disease (COPD) by WOLKOVE *et al.* [1]. These authors used a Borg scale to evaluate dyspnoea and were faced with the problem that 28 of their patients claimed not to be breathless at all at baseline. As a consequence, any subjective post-bronchodilator improvement was impossible to rate in these subjects. Lung function being assessed by spirometry, the authors reported a subjective improvement despite no increase in forced expiratory volume in one second (FEV₁) in 17 out of 65 breathless

subjects, but they admitted that the absence of a placebo arm was a weakness of their study.

Our first concern was to select an appropriate tool for magnitude estimation of acute changes in airway obstruction. Asking subjects to assign line lengths to represent the sizes of apparent differences is a procedure known as "interval estimation" in the psychophysical literature [2]. We hypothesized that a bipolar visual analogue scale (VAS), including a no change midpoint, would be adequate for this purpose. Such a scale was originally used by LEWIS *et al.* [3] to assess the subjective change in breathing in a study focused on suggestion-induced asthma. A second matter of concern was to evaluate inspiratory *versus* expiratory lung function indices. Indeed, dyspnoea perceived by subjects with asthma is a predominantly

inspiratory sensation [4] and several bronchodilator studies focused on the work of breathing in patients with airflow limitation have suggested that inspiratory indices are potentially more relevant as they are free from any collapse artefact [5, 6].

The purpose of the present study was, firstly, to validate in patients with airway obstruction the bipolar VAS to assess a change in shortness of breath following an inhaled agent, the subjects being given standardized neutral information. We particularly focused on the reproducibility of the ratings obtained on such a scale and on their sensitivity to an acute bronchodilation. Secondly, as there is some evidence that asthmatics and COPD subjects do not have the same ability to perceive added resistive loads [7], we hypothesized that the perception of an acute modification in intrinsic airway obstruction might be different between asthmatics and COPD subjects.

Patients and methods

Patients

Thirty five out-patients (22 men, 13 women) attending the Chest Clinic agreed to participate in a study concerning respiratory sensations at rest. All had a FEV_1 <60% predicted and a FEV_1 /inspiratory vital capacity (IVC) ratio <65%. A condition for entry into the study was that lung function testing, including a bronchodilation test with 200 µg inhaled salbutamol, had previously been performed at least three times (with at least one week interval) over a time span of at least three months. Their anthropometric features were (mean(SEM)): age 62.6(1.7) yrs, height 166.8(1.5) cm, weight 69.3(2.2) kg. They were classified as having either asthma or COPD on the basis of the following criteria. Firstly, a clinical history of episodic breathlessness and wheeze in a lifetime nonsmoking subject was suggestive of asthma, whilst a history of chronic cough, sputum production and dyspnoea on exertion in a smoker or ex-smoker (no smoking for at least six months) was suggestive of COPD. Secondly, functional records of the patients were examined. The diagnosis of asthma was retained provided an increase in FEV_1 , exceeding 15% predicted [8], had been obtained at least once. Similarly, the diagnosis of COPD was retained provided none of the ΔFEV_1 values in the subject's record exceeded 10% predicted. Subjects labelled as having asthma or COPD on clinical grounds but not fulfilling the functional criteria were not retained for the study. Eighteen subjects (9 men, 9 women) were considered as having asthma, 17 (13 men, 4 women) as having COPD. COPD patients were predominantly ex-smokers with a median interval since smoking cessation of 4 yrs (range 0.5–20 yrs). Maintenance drug therapy included (by decreasing frequency) inhaled steroids (n=15), inhaled sympathomimetics (n=14), oral theophylline (n=8), oral steroids (n=7) and inhaled

anticholinergics (n=6) in the asthma group, inhaled sympathomimetics (n=9), inhaled steroids and oral theophylline (n=7) and inhaled anticholinergics (n=6) in the COPD group. Two COPD subjects had no regular therapy.

Study design

All subjects gave informed consent and the study protocol was approved by the Ethics Committee of the Hôpital Universitaire Brugmann. The study consisted of three consecutive inhalations of isotonic saline followed by two inhalations of terbutaline. In every case, the subject was ignorant of which agent he would inhale, whilst the investigator was aware. All sessions started at 1500 h and all subjects were asked to abstain from inhaled bronchodilators from 0700 h that morning. Oral theophylline preparations were withheld 48 h before testing. Oral and inhaled steroids were not withheld. After arrival in the lung function laboratory, each subject comfortably rested on a chair for 10 min and full explanation was given about the scaling method. Baseline lung function was subsequently measured. The patient was then given the first inhalation and, thereafter, rested in the sitting position. After a 2 min interval, the subject was invited to rate the change in shortness of breath and lung function was measured again. The subsequent inhalations were given and the procedure of subjective response rating and lung function measurement was repeated at each step. No attempt was made to monitor side-effects from the aerosols, but spontaneous comments were recorded.

Dosage of inhaled agents

A Mefar MB3 dosimeter (Medicali, Brescia, Italy) activated by the subject's inspiratory manoeuvre was used [9]. The subjects were instructed to have the mouthpiece above the tongue and to slowly inspire from functional residual capacity (FRC) up to total lung capacity (TLC) whilst wearing a noseclip. The volume of solution in each nebulizer was 3 ml at room temperature. Each nebulizer was calibrated, the mean output being $12.5 \mu\text{l}\cdot\text{s}^{-1}$.

Isotonic saline was used for the first three steps and the commercially available $10 \text{ mg}\cdot\text{ml}^{-1}$ terbutaline solution for the subsequent two inhalations (cumulated terbutaline doses 0, 0, 0, 400 and 800 µg). The inhalation time (0.8 s) and the number of inhalations (four) were the same at each step.

Visual analogue scale

At the beginning of the session the patient was given the following neutral information: "During this session, you will receive several consecutive inhalations which may modify your respiratory comfort.

After each inhalation, you will be asked whether you feel less short of breath, equally short of breath or shorter of breath, in comparison with the beginning of the session and you will be invited to rate the change on the scale". Questions such as: "Which agent shall I inhale?", "Is it the same agent at each step?" or "Is the concentration of the agent the same at each step?" were not answered. The experimenter simply repeated, if necessary, the standardized information detailed above. Subsequently, the VAS used in the study was shown to the patient. It was a 40 cm horizontal line labelled "very much worse" at the left end, "very much better" at the right end, and "no change" in the middle [3]. We ensured, in each case, that the subject understood that this scale offered three possibilities in rating, *i.e.* improvement, no change or worsening. Each subject was instructed to mark the line at any point he wished, and ratings were expressed as % of line length, the range being -100% (very much worse) to +100% (very much better). Patients were instructed to rate even the slightest perceptible change in shortness of breath, the smallest measurable difference in line length being 0.1 cm (0.5%). We also carefully recommended the subjects to rate only shortness of breath and to ignore other sensations such as cough, chest tightness, nasal irritation or throat irritation.

Lung function

A Jaeger (Wurzburg, Germany) Bodytest plethysmograph was used. Airflow at the mouth was displayed against box pressure and their relationship was computed according to an automated procedure. Signals were digitized over a period of five breaths with a sampling rate of 50 Hz. After correction for the thermal drift induced by the subject's heat production, a loop was obtained and midpoints at flows of +0.5 (point A), 0 (point B) and -0.5 $l \cdot s^{-1}$ (point C) were considered. Two straight lines were obtained, the first one between points B and A defining the specific inspiratory resistance (sRin), the second one between points B and C defining the specific expiratory resistance (sRex). At least two technically satisfactory five breath-loops were obtained at each step and the reported sRin and sRex were arithmetical means. After a shutter had been closed in order to measure the FRC, expiration to residual volume followed by a slow and smooth IVC manoeuvre was performed. The door of the box was then opened and flow-volume curves were obtained. The subject was instructed to slowly inspire up to TLC, to subsequently expire a forced vital capacity (FVC_{ex}) and finally to inspire a forced vital capacity (FVC_{in}). In all subjects, two to three technically acceptable curves were obtained for the baseline evaluation as well as at each step following terbutaline or saline inhalation. Optimization of the reading of the expiratory curves was performed as recommended by PESLIN *et al.* [10]. Similarly, the inspiratory curves were superimposed at residual

volume (RV) and a composite curve was obtained. The maximal flows retained for analysis were those at 50% of the FVC_{ex} (MEF₅₀) and at 50% of the FVC_{in} (MIF₅₀); after saline or terbutaline the 50% level was calculated from the baseline pre-inhalation FVC_{ex} and FVC_{in} values, in agreement with the most common recommendations [11-13]. Static and dynamic lung volumes were reported as % predicted [13], sRin and sRex as $cmH_2O \cdot s$, MEF₅₀ and MIF₅₀ as $l \cdot s^{-1}$.

Statistical analysis

Samples were described as either mean (SEM) or median (range). The terbutaline and saline-induced variations were described in terms of 95% confidence interval of the post-800 μg terbutaline minus the third post-saline, and the mean post-saline minus the baseline value, respectively. A non-parametric analysis was used to calculate the confidence intervals [14]. The Wilcoxon signed rank test and rank sum test were used to compare, respectively, paired and independent samples. Subjects exhibiting marked variation either between successive baseline measurements or between post-saline and baseline measurements were excluded from the analysis, a marked variation being defined as a $\Delta FEV_1 > 15\%$ predicted and/or a $\Delta sRin > 15 cmH_2O \cdot s$.

Intrasubject variability was assessed by calculating, for each subject, the intrasubject coefficient of variation (CV) of the three post-saline measurements. Sensitivity to bronchodilation was subsequently evaluated in each subject as the difference between the post-terbutaline value minus the third post-saline value, divided by the subject's CV. To calculate the sensitivity index (SI) so defined, the post-terbutaline value used was the best value, obtained after either 400 or (more frequently) 800 μg . A rank order of sensitivity was established in the asthmatics and in the COPD subjects on the basis of decreasing median SI values.

Results

Baseline and post-saline measurements

Three subjects were excluded from the analysis according to the criteria defined in the methods section. One asthmatic woman exhibited progressive deterioration over the successive expirations for baseline evaluation (sRin 9.3-26.2 $cmH_2O \cdot s$), interpreted as a typical maximum respiratory manoeuvre-induced bronchoconstriction [15]. Two men, one with asthma (sRin 33.2-52.3 $cmH_2O \cdot s$; FEV₁ 45.3-22.6% predicted), the other with COPD (sRin 36.9-58.4 $cmH_2O \cdot s$) developed bronchoconstriction after inhaled saline. All the results presented in the following text involve the 32 remaining subjects, who had a baseline predicted FEV₁ % of 47.7 (2.7)% in the

asthma group ($n=16$) and 37.0 (2.2)% in the COPD group ($n=16$).

Individual VAS ratings obtained after inhaled saline are shown in figure 1. A wide intersubject range of subjective response to saline was observed. In the asthma group, two subjects rated a post-saline worsening in shortness of breath (mean post-saline changes in FEV₁ -0.7 and +0.1% predicted in these two subjects), whilst the others reported some degree of improvement. The VAS estimate of the perception of saline inhalation was (median, 95% confidence interval) 9%, 0–18%. In the COPD group, the response had a bimodal distribution, with eight subjects reporting minimal improvement and eight subjects reporting a 24–67.5% of line length improvement. The difference was so striking that it was decided to consider two subgroups, further designated as "high perceivers" ($n=8$) and "low perceivers" ($n=8$), and to analyse their results separately. The VAS rating was (median, 95% confidence interval) 43%, 33–53% in high perceivers, 5%, 3–7% in low perceivers. The VAS estimates of the perception of saline were significantly lower in asthmatics and low perceivers than in high perceivers ($p<0.01$), and lower in low perceivers than in asthmatics ($p<0.05$). Group values of VAS rating and lung function are represented in figures 2 and 3 as median and range. As shown in table 1, inhaled isotonic saline produced only minimal changes in lung function indices.

Analysis of post-saline variability

The rank order of variability is shown in table 2 in terms of within-subject CVs. In the three groups (asthma, COPD high and low perceivers), median CVs were found to range from 1.6–5.4% for volume and flow indices (except for MEF₅₀) and from 6.9–11.5% for sRin, sRex and MEF₅₀. The variability of MIF₅₀ was significantly lower than that of MEF₅₀ in asthmatics ($p<0.01$) as well as in COPD high perceivers ($p<0.01$) and low perceivers ($p<0.02$).

The VAS ratings for assessment of the change in shortness of breath were found to have the largest variability, with median CVs as high as 19.4% (asthma), 12.5% (COPD, high perceivers) and 14.5% (COPD, low perceivers) (difference between asthma and the two COPD subgroups significant, $p<0.05$).

Post-terbutaline measurements and subjects' comments

After inhaled terbutaline, a parallel improvement in lung function indices and in shortness of breath was observed (figs 2 and 3). As shown in table 3, a statistically significant (Wilcoxon signed rank test) improvement was achieved in all lung function indices studied in the asthma group, in all but FRC in the COPD high perceivers, and in all but FRC, IVC and MIF₅₀ in the COPD low perceivers.

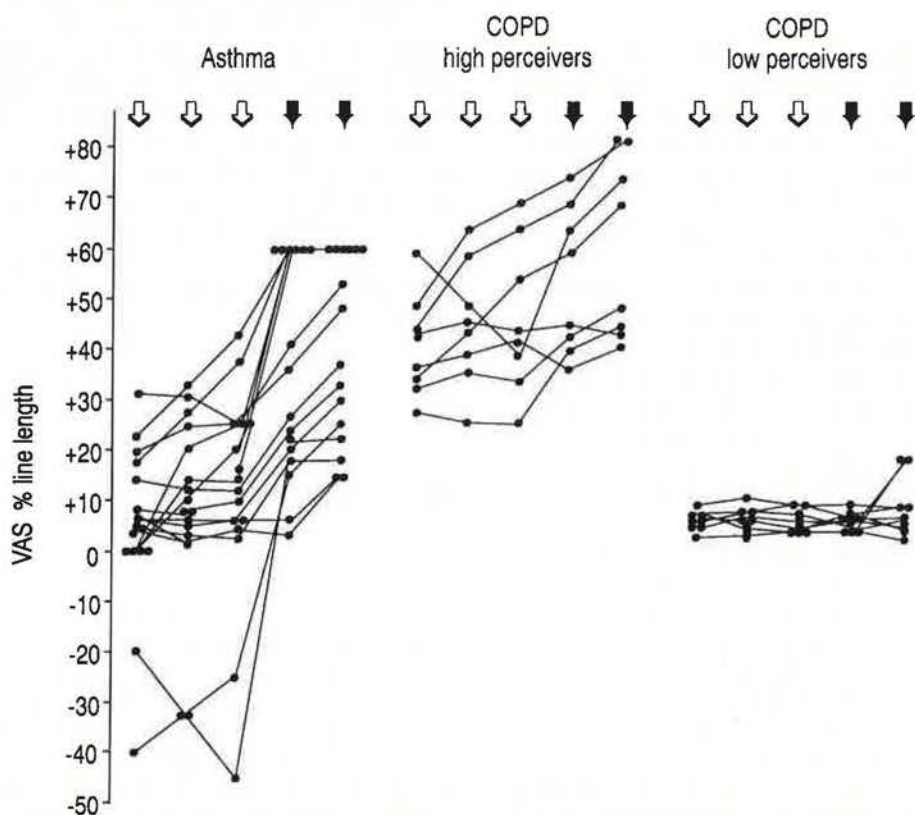


Fig. 1. – VAS estimates of the change in shortness of breath in 16 patients with asthma (left) and 16 patients with COPD (middle: "high perceivers", $n=8$; and right: "low perceivers", $n=8$). VAS ratings are expressed as % of line length (range -100 to +100%). For each individual, five ratings are represented, three after inhaled saline (white arrows) and two after inhaled terbutaline (black arrows). COPD: chronic obstructive pulmonary disease; VAS: visual analogue scale.

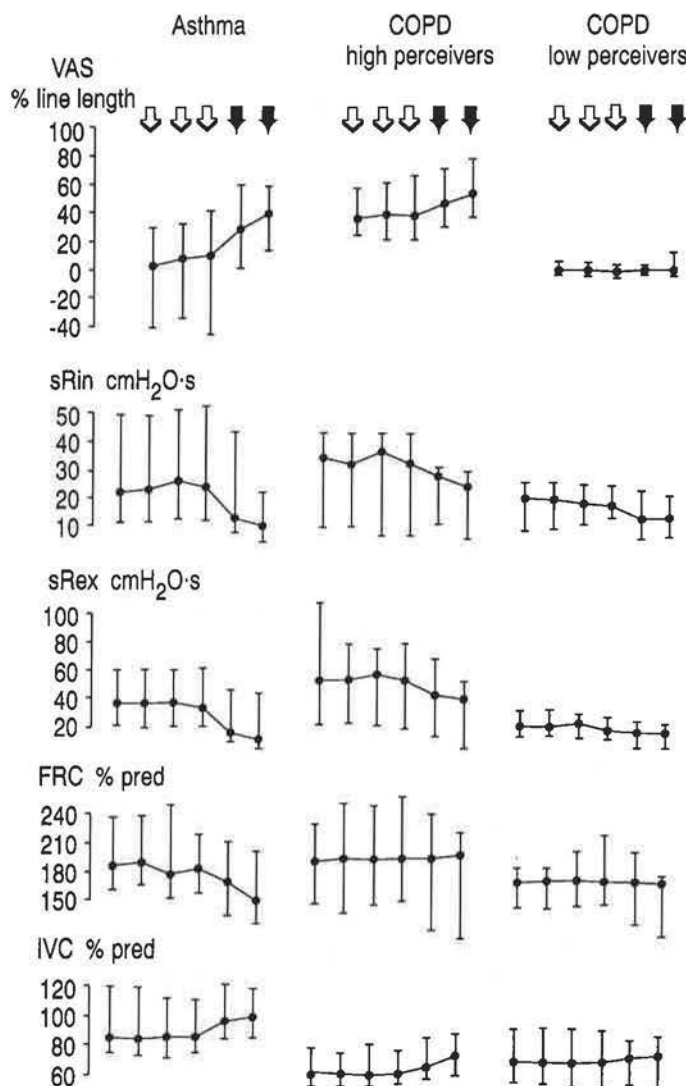


Fig. 2. — VAS rating of the change in shortness of breath, specific resistances and static lung volumes (median and range) in 16 subjects with asthma (left) and 16 subjects with COPD (middle: high perceivers, $n=8$; and right: low perceivers, $n=8$). Measurements were made at baseline, after inhaled isotonic saline (three measurements: white arrows) and after 400 µg and 800 µg terbutaline (black arrows). sRin: specific inspiratory resistance; sRex: specific expiratory resistance; FRC: functional residual capacity; IVC: inspiratory vital capacity. For further abbreviations see legend to figure 1.

The post-terbutaline subjective improvement reached significance in the asthmatics and in the COPD high perceivers. The terbutaline-induced changes are shown in table 4. The only change in lung function that was significantly larger in the asthmatics than in the two COPD subgroups was ΔFEV_1 . Three indices, sRex, IVC and MIF_{50} showed a response larger in both the asthmatics and the COPD high perceivers than in the COPD low perceivers. The amount of perceived improvement in shortness of breath (ΔVAS) was (95% confidence interval) 20–39% in asthmatics *versus* 6–25% (COPD high perceivers) and -1–8% of line length (COPD low perceivers). The VAS was the only parameter studied with three significant between-group differences: asthma > COPD high perceivers > COPD low perceivers. In the asthma group, the VAS rating obtained after the first 400 µg dose was higher than the mean post-saline rating in 15 subjects (and

lower in one), whilst all 16 subjects had a higher post-800 µg than mean post-saline VAS (fig. 1). Half of the subjects (8 out of 16) gave a higher rating after 800 µg than after the first dose. In the COPD group, the proportion of subjects with higher post-terbutaline than mean post-saline rating was only 9 out of 16 after 400 µg, and 12 out of 16 after 800 µg (fig. 1). The terbutaline-induced changes in VAS ratings and those in FEV_1 , were unrelated in the COPD subjects, whilst a modest correlation was found in the asthma group ($r=0.43$, $p=0.10$). Post-terbutaline side-effects in the asthma group were reported in two subjects as a bad taste and palpitations (first inhalation), and in two subjects as a bad taste (first inhalation) and throat irritation (second inhalation). Two COPD subjects mentioned nervousness (first inhalation) and two perceived a bad taste (second inhalation).

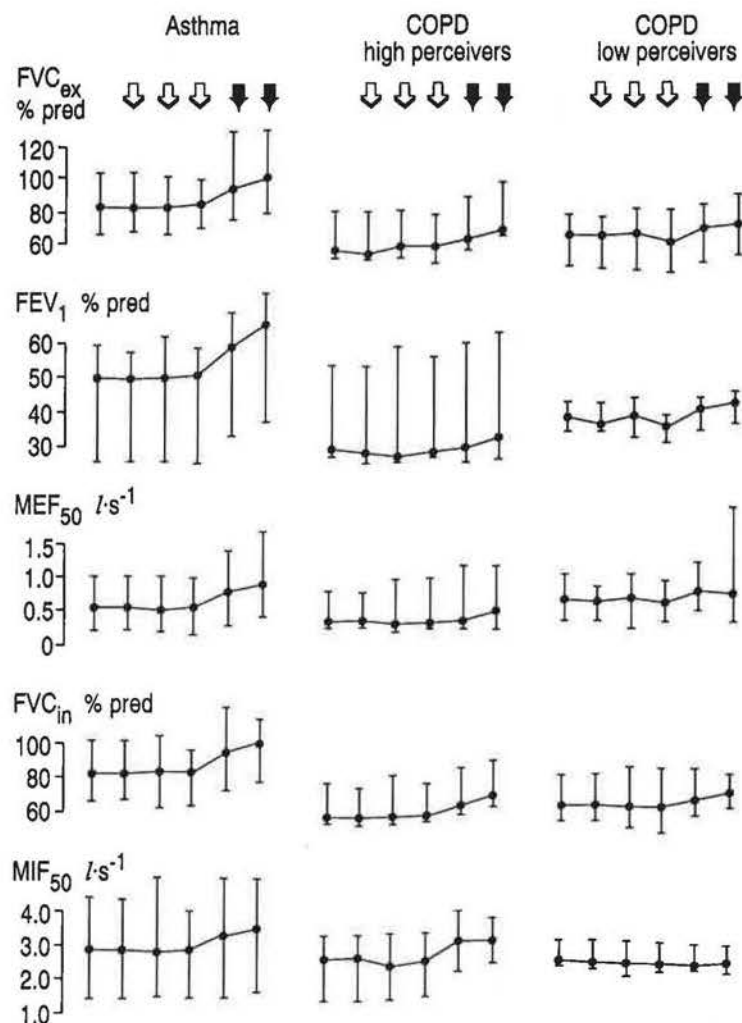


Fig. 3. — Indices derived from a forced expiration manoeuvre, followed by a forced inspiration manoeuvre (median and range) in 16 subjects with asthma (left) and 16 subjects with COPD (middle: high perceivers, $n=8$; and right: low perceivers, $n=8$). For further details see legend to figure 2. FVC_{ex} : forced expiratory vital capacity; FEV_1 : forced expiratory volume in one second; MEF_{50} : maximal expiratory flow at 50% of FVC_{ex} ; FVC_{in} : forced inspiratory vital capacity; MIF_{50} : maximal inspiratory flow at 50% FVC_{in} ; COPD: chronic obstructive pulmonary disease.

Table 1. — Post-saline (mean of three values) minus baseline measurements in 32 subjects with airway obstruction

		Asthma $n=16$	COPD high perceivers $n=8$	COPD low perceivers $n=8$
ΔsR_{in}	$cmH_2O \cdot s$	0.8 (-0.4–2.3)	-0.9 (-2.1–0.3)	-1.4 (-1.6–0.3)
ΔsR_{ex}	$cmH_2O \cdot s$	0.8 (-1.7–2.0)	-2.5 (-9.6–2.7)	-1.5 (-2.5–0.6)
ΔFRC	% pred	-1.1 (-5.3–3.2)	3.4 (-3.0–11.7)	3.2 (0.6–10.5)
ΔIVC	% pred	-1.5 (-3.4–3.2)	0.4 (-1.2–2.6)	-0.6 (-1.5–0.1)
ΔFVC_{ex}	% pred	0.6 (-4.0–2.9)	1.4 (-1.2–2.5)	0.4 (-1.0–2.2)
ΔFEV_1	% pred	-0.3 (-0.9–0.5)	-0.7 (-2.0–1.2)	-1.3 (-3.0–0.1)
ΔMEF_{50}	$l \cdot s^{-1}$	0 (-0.05–0.03)	-0.02 (-0.03–0.04)	-0.02 (-0.07–0.03)
ΔFVC_{in}	% pred	-0.6 (-3.9–3.2)	1.6 (0.4–1.9)	-0.1 (-2.5–1.7)
ΔMIF_{50}	$l \cdot s^{-1}$	-0.01 (-0.07–0.06)	-0.02 (-0.11–0.08)	-0.03 (-0.11 to -0.01)

Median difference with 95% confidence interval in parenthesis (non-parametric analysis). sR_{in} : specific inspiratory resistance; sR_{ex} : specific expiratory resistance; FRC: functional residual capacity; IVC: inspiratory vital capacity; FVC_{ex} : forced expiratory vital capacity; FEV_1 : forced expiratory volume in one second; MEF_{50} : maximal expiratory flow at 50% forced vital capacity; FVC_{in} : forced inspiratory vital capacity; MIF_{50} : maximal inspiratory flow at 50% forced vital capacity; COPD: chronic obstructive pulmonary disease.

Table 2. — Variability of lung function indices and VAS rating of the change in shortness of breath: assessment on three post-saline measurements in 32 subjects with airway obstruction ranked by increasing variability

	Asthma n=16	COPD high perceivers n=8	COPD low perceivers n=8
FVC _{ex}	2.3 (0.3–6.2)	IVC 3.3 (1.0–4.3)	IVC 1.6 (0.8–8.2)
IVC	2.7 (0.6–8.6)	FVC _{ex} 3.4 (1.0–4.2)	MIF ₅₀ 2.9 (1.1–4.4)
FEV ₁	3.1 (1.2–5.5)	FRC 3.6 (2.6–7.6)	FRC 3.3 (0.7–12.2)
FVC _{in}	3.3 (0.3–7.5)	FVC _{in} 3.8 (2.4–7.0)	FVC _{in} 3.4 (2.0–11.6)
MIF ₅₀	3.9 (1.0–15.7)	MIF ₅₀ 4.3 (1.4–7.0)	FVC _{ex} 3.9 (3.2–4.2)
FRC	4.6 (3.5–7.3)	FEV ₁ 4.6 (2.3–5.9)	FEV ₁ 5.4 (3.8–10.0)
MEF ₅₀	9.5 (3.0–16.0)	sRin 8.7 (0.4–24.6)	sRin 6.9 (0.4–24.2)
sRex	9.7 (1.4–14.9)	sRex 10.3 (3.4–10.9)	sRex 11.3 (9.4–15.1)
sRin	10.0 (1.8–16.4)	MEF ₅₀ 11.4 (10.3–15.6)	MEF ₅₀ 11.5 (5.0–19.3)
VAS	19.4 (9.1–100.0)	VAS ₅₀ 12.5 (2.7–23.5)	VAS ₅₀ 14.5 (10.8–24.8)

Within-subject coefficients of variation, median (range in parenthesis). VAS: visual analogue scale. For further abbreviations see legend to table 1.

Table 3. — Statistical evaluation of the post-800 µg terbutaline versus the third post-saline value in 32 subjects with airway obstruction

	Asthma n=16	COPD high perceivers n=8	COPD low perceivers n=8
VAS	<0.01	0.05	—
sRin	<0.01	0.01	0.01
sRex	<0.01	0.01	0.01
FRC	<0.01	—	—
IVC	<0.01	0.01	—
FVC _{ex}	<0.01	0.01	0.01
FEV ₁	<0.01	0.05	0.01
MEF ₅₀	<0.01	0.02	0.05
FVC _{in}	<0.01	0.01	0.05
MIF ₅₀	<0.01	0.01	—

All p values ≤0.05 are given (Wilcoxon signed rank test). —: not significantly different. For abbreviations see legend to tables 1 and 2.

Table 4. — Post-terbutaline (800 µg) minus post-saline (third value) measurements in 32 subjects with airway obstruction

	Asthma n=16	p (1)	COPD high perceivers n=8	p (2)	COPD low perceivers n=8	p (3)
ΔVAS % line length	24 (20–39)	<0.01	15 (6–25)	<0.01	1 (-1–8)	<0.01
ΔsRin cmH ₂ O·s	-8.4 (-6.1 to -24.5)	—	-7.1 (-1.3 to -14.3)	—	-4.8 (-3.3 to -6.3)	<0.01
ΔsRex cmH ₂ O·s	-20.0 (-7.4 to -28.3)	—	-12.1 (-11.5 to -19.5)	<0.01	-4.1 (-2.2 to -7.9)	<0.01
ΔFRC % pred	-23.8 (-8.6 to -38.5)	—	-26.1 (5.2 to -42.8)	—	-19.3 (0.1 to -41.7)	—
ΔIVC % pred	12.2 (9.3–15.2)	—	12.5 (7.8–15.4)	<0.01	1.7 (-3.0–6.0)	<0.01
ΔFVC % pred	19.6 (6.6–27.3)	—	15.4 (9.4–20.6)	—	10.0 (9.1–10.9)	—
ΔFEV ₁ % pred	15.2 (7.3–19.3)	<0.02	2.5 (0.3–7.5)	—	5.9 (5.3–7.6)	<0.05
ΔMEF ₅₀ l·s ⁻¹	0.47 (0.20–0.70)	<0.05	0.15 (0.05–0.25)	—	0.15 (0–0.70)	—
ΔFVC _{in} % pred	15.4 (6.9–21.4)	—	12.5 (8.1–16.7)	—	8.7 (1.8–13.7)	—
ΔMIF ₅₀ l·s ⁻¹	0.50 (0.20–1.00)	—	0.65 (0.35–1.15)	<0.01	0.03 (-0.05–0.08)	<0.01

Median differences with 95% confidence interval in parenthesis (non-parametric analysis). p (1) p (2) p (3): significance level for the comparison asthma versus COPD high perceivers p (1), COPD high perceivers versus COPD low perceivers p (2), COPD low perceivers versus asthma p (3). For abbreviations see legends to table 1 and 2.

Table 5. — Sensitivity index (post-800 µg terbutaline minus third post-saline measurement, divided by the subject's post-saline CV) in 32 subjects with airway obstruction

	Asthma n=16		COPD high perceivers n=8		COPD low perceivers n=8
FEV ₁	10.4 (0.3–43.6)	FVC _{ex}	6.0 (2.9–20.5)	FVC _{ex}	4.1 (2.5–7.9)
MEF ₅₀	9.8 (2.3–26.8)	FVC _{in}	5.2 (1.3–15.4)	ICV	3.7 (-5.4–6.6)
VAS	7.4 (1.3–31.8)	MIF ₅₀	5.2 (3.4–23.0)	FVC _{in}	3.6 (-0.2–5.5)
sRex	7.1 (0–38.4)	IVC	4.4 (3.0–24.0)	FEV ₁	2.9 (2.5–6.1)
FVC _{ex}	6.7 (0.4–97.0)	sRex	3.9 (1.8–9.7)	sRin ₁	2.2 (1.9–119.1)
sRin	6.6 (1.5–34.0)	FRC	3.0 (-3.0–5.6)	VAS	1.9 (0–29.7)
FVC _{in}	5.8 (1.2–35.7)	sRin	2.6 (0.5–73.3)	FRC	1.5 (-5.3–7.0)
IVC	5.6 (1.8–36.7)	MEF ₅₀	2.4 (0–4.8)	sRex	1.4 (0.8–4.4)
MIF ₅₀	4.2 (1.5–20.7)	VAS	1.6 (0–16.9)	MEF ₅₀	1.3 (0–14.8)
FRC	3.5 (1.0–5.3)	FEV ₁	1.5 (-0.6–6.6)	MIF ₅₀	0.7 (0–1.8)

Data are given as median (range in parenthesis). For abbreviations see legends to tables 1 and 2.

Analysis of sensitivity to bronchodilation

The rank order of sensitivity of the indices studied is shown in table 5. In the asthmatics, the VAS rating of the change in shortness of breath was ranked among the most sensitive indices. All of the indices studied had a median index >4, except for FRC. In the COPD subjects, the vital capacity measured as FVC_{ex}, FVC_{in} or IVC had the best sensitivity, in the high as well as in the low perceivers, whilst the VAS rating showed poor sensitivity, with a median index <2 in both subgroups. The difference in sensitivity between asthma and the two COPD subgroups was significant ($p<0.05$) for FEV₁, MEF₅₀ and VAS. VAS sensitivity index individual values in the subjects who reported terbutaline-induced side-effects were 2.1, 4.0, 4.3 and 6.1 (asthma), 1.1 and 13.3 (COPD high perceivers) 0 and 1.9 (COPD low perceivers).

Discussion

In the present study, we have compared, in 32 subjects with airflow limitation, the subjective perception of acute changes in airway obstruction, assessed as a change in shortness of breath on a VAS, and conventional lung function indices in terms of variability and sensitivity. Variability was evaluated in each subject on measurements made after three consecutive isotonic saline inhalations, expected to be a neutral intervention, whilst sensitivity was evaluated on measurements made after inhaled terbutaline, a sympathomimetic agent, expected to be beneficial to subjects with airway obstruction. The main findings were: firstly, that saline exerted a placebo effect on shortness of breath, which was particularly marked in some COPD subjects (high perceivers); secondly, that the VAS ratings had a large post-saline variability; and thirdly, that they showed a very weak sensitivity to bronchodilation in COPD subjects, whilst they proved to be very sensitive in subjects with asthma.

Several features of the study design dealing with the rating procedure deserve particular attention. The first point is the choice of a bipolar VAS, devised for an interval estimation. This scale has a slight disadvantage, namely the loss of the rating of the degree of shortness of breath at baseline, but has a major advantage in allowing subjects who claim not to be breathless at all at baseline (30% [1] to 50% [16] of patients with moderate to severe airway obstruction) to report some improvement or worsening after a therapeutic intervention. A second point is the decision to study the variability on measurements obtained after inhaled saline. We observed, as have other investigators [17, 18], that a few subjects with either asthma or COPD may develop significant bronchoconstriction after nebulized isotonic saline. However, these individuals were excluded according to well-defined criteria and the variability analysis involved subject samples in whom inhaled saline proved to be a neutral intervention. A third point is avoidance of any bias in rating due to the subject's expectation of the nature of the inhaled agent. In the present study every effort was made to keep the subject unaware of the nature of the aerosols. The information given about the aerosols was strictly standardized and neutral, which is in our opinion mandatory. Indeed, whilst suggestion-induced bronchoconstriction in asthmatics has remained controversial [3, 18–20], it is clear that suggestion does influence the subjective perception of airway response recorded on a VAS [3]. The nebulizers used throughout the protocol were indistinguishable from each other and inhalation time, number of inhalations, and interval between inhalation and measurement of response were identical at each step of the protocol. The shift from saline to terbutaline was probably perceived as inhaling something different by a few subjects who reported some symptom after the first terbutaline inhalation (6 out of 32, two out of six being regular users of inhaled sympathomimetics). The awareness of a change in the nature of the aerosol is less clear in two other

subjects, who commented about some symptom only after the last inhalation. Despite these limitations to the subject's blinding, we do not think our results were significantly affected. Indeed, in eight subjects (four with asthma and four with COPD), who reported terbutaline-induced side-effects, sensitivity index values for the VAS rating were not particularly high, with seven out of eight values less than or equal to the median of their group.

The choice of the lung function indices being studied also deserves comments. Using body plethysmography we decided to focus on the specific resistance, which is usually not affected [21] by artefactual increases in thoracic gas volume measurements [22]. We measured specific inspiratory and expiratory resistance separately, mainly because in some subjects with severe obstruction, expiratory flow plateaus occur at flow rates as low as $0.5 \text{ l}\cdot\text{s}^{-1}$, so that specific resistance measurements in these subjects may be influenced by increased collapsibility of large airways [12]. Static lung volumes (FRC, IVC) were included to account for the existence of isolated volume responders among severely obstructed patients, as emphasized by RAMSDELL and TISI [23]. We analysed the inspiratory as well as the expiratory limb of the flow-volume curve; indeed, indices derived from a forced inspiratory manoeuvre, although not evaluated in most previous studies assessing bronchodilator response [24–26], are potentially very sensitive to bronchodilation [27, 28].

Inhaled isotonic saline, whilst it produced very small, clinically nonsignificant, changes in lung function in the 32 subjects retained for analysis, was perceived as an improvement by all subjects, except for two asthmatics. The median response on the VAS was small in the asthma group (+9%), even smaller in a subgroup of eight COPD subjects (+5%) but large in the eight other COPD subjects (+43%). These values may be considered as the placebo effect of inhaled saline on shortness of breath at rest, in different groups of patients with airway obstruction. To the best of our knowledge, the only previous study concerning the perception of inhaled saline was performed by LEWIS *et al.* [3] on healthy subjects and on asthmatics. However, these authors provided the subjects a written neutral or bronchoconstrictive suggestion and focused their study on the effect of suggestion, whilst in the present study, the information given to the subjects was strictly neutral in every case. Our results in terms of post-saline variability including median CVs around 2–5% for volumes and flows (except for MEF_{50}) and around 10% for sRin, sRex and MEF_{50} , with little difference between asthmatics and COPD subjects, compare well with the findings of other groups on within-day variability in patients with airflow limitation [25, 26, 29]. The CVs reflecting short-term variability are about half of those found in studies focused on long-interval variability, including one study from our own laboratory [25, 30]. The subjective perception was found to have the largest variability among the indices studied,

with median CVs of 19.4% (asthma), 12.5% (COPD high perceivers) and 14.5% (COPD low perceivers).

The analysis of the terbutaline-induced changes revealed two major findings. Firstly, the only clear difference between the asthmatics and the subjects from the two COPD subgroups was the size of the FEV_1 response; this was expected, as it simply reflects the criterion used for categorization of the subjects in this study. Secondly, both the asthmatics and the COPD high perceivers were characterized by a larger improvement in sRex, IVC and MIF_{50} . The finding concerning IVC and MIF_{50} is particularly interesting, as a predominant influence of inspiratory function on shortness of breath was one of our initial hypotheses. Our results suggest that the perception of an airway response by COPD subjects may depend either on a larger degree of bronchodilation, or, as previously suggested by BELLAMY and HUTCHISON [31], more specifically on a larger responsiveness of inspiratory indices. The fact the subjects labelled as high perceivers in this study felt already improved at the time that they had inhaled only saline could be ascribed to an anticipation effect in patients used to perceiving effective bronchodilation in everyday life. The analysis of the sensitivity to bronchodilation yielded very different results in asthmatics and COPD subjects. In the asthma group, all of the indices did well, except for FRC, the VAS rating being ranked immediately after FEV_1 and MEF_{50} . In the two COPD subgroups, only the vital capacity proved to be sensitive, whilst subjective perception assessed on the VAS had a poor sensitivity. The superiority of FEV_1 and MEF_{50} over sRin and sRex in the asthma group was somewhat surprising, as it is known that in some obstructed subjects a marked post-bronchodilator decrease in specific resistance may be accompanied by only a small increase in forced expiratory flows, a phenomenon initially described in normals and ascribed to either increased collapsibility of large airways [32] or decreased lung elastic recoil [33]. Like other investigators [24], we found, however, that when the post-bronchodilator change is divided by the inherent variability, the FEV_1 has the highest true sensitivity in asthmatics. In the two COPD subgroups, the best test, as judged from its sensitivity index, was FVC, followed by IVC. Other investigators have emphasized the potential of the FVC as a bronchodilation test [34, 35], or have shown IVC to be more sensitive than FEV_1 [31] in COPD subjects. A condition for the differences that we have found between asthma and COPD subjects to be relevant is that our discrimination between asthma and COPD was basically correct. Clinical as well as functional criteria were taken into account. In assessing the reversibility of airway obstruction, we were careful to choose a ΔFEV_1 threshold of sufficient specificity for the diagnosis of asthma [8, 36] and to consider the results of repeated testing, as bronchodilator responsiveness is known to vary over time in the same subjects with asthma [37] as well as with COPD [38].

Data available in the literature about the subjective perception of acute bronchodilation by subjects with asthma or COPD are scarce and mainly limited to qualitative studies. OREHEK *et al.* [16], studying 19 asthmatics with baseline obstruction, reported that 10 out of 19 claimed not to perceive salbutamol-induced bronchodilation. In COPD subjects, BOUSHY [12], as well as BELLAMY and HUTCHISON [31], described perceivers and non-perceivers after acute administration of a bronchodilator agent. The latter authors reported that 14 out of 20 subjects with emphysema were able to distinguish inhaled salbutamol from inhaled placebo and suggested that this ability was associated with a salbutamol-induced increase in vital capacity. In the only quantitative study, by WOLKOVE *et al.* [1] 20 out of 65 COPD subjects did not rate any improvement on a Borg scale after 200 µg inhaled salbutamol. In the present study, we evaluated, using a bipolar VAS, asthmatics and COPD subjects. We found that half of the COPD subjects had high post-saline and post-terbutaline ratings, whilst the others had low ratings throughout the protocol. The amount of perceived improvement after terbutaline (Δ VAS) decreased in the order: asthmatics > COPD high perceivers > COPD low perceivers. In the COPD group, high perceivers were found to share with the asthmatics a larger responsiveness to terbutaline than the low perceivers, involving mainly inspiratory indices, whilst the sensitivity analysis suggested that all COPD subjects, high as well as low perceivers, were characterized by an insensitivity of the VAS to terbutaline, the VAS ratings being sensitive in asthmatics. Whether the high post-saline ratings obtained in COPD high perceivers represent an anticipation of bronchodilation in subjects used to being perceivers, or reflect a true inability to distinguish between a neutral and a bronchodilator agent, remains to be elucidated. We wish to emphasize that in this study, focused on variability and sensitivity, we did not attempt to systematically study the relationship between perception assessed on the VAS and the changes in lung function indices. Indeed, we considered that, as the VAS is to be used on a within-subject basis [39], the use of only two terbutaline doses precluded such an analysis. Dose-response studies during progressive bronchodilation are needed to evaluate potential correlations between perception and lung function. Such investigation is also needed, to evaluate whether subjects with either asthma or COPD differ in their ability to perceive acute pharmacologically-induced changes in airway obstruction.

Acknowledgements: The authors thank J.P. Carpiaux, E. Driessens and R. Moens for technical help, V. de Maertelaer for statistical assistance, M. Telerman for his support and Astra Belgium for supplying terbutaline solution.

References

1. Wolkove N, Dajczman E, Colacone A, Kreisman H. - The relationship between pulmonary function and dyspnea in obstructive lung disease. *Chest*, 1989; 96: 1247-1251.
2. Stevens SS. - Issues in psychophysical measurement. *Psychol Rev*, 1971; 78: 426-450.
3. Lewis RA, Lewis MN, Tattersfield AE. - Asthma induced by suggestion: is it due to airway cooling? *Am Rev Respir Dis*, 1984; 129: 691-695.
4. Morris MJ. - Asthma-expiratory dyspnoea? *Br Med J*, 1981; 283: 838-839.
5. Miller JM, Gall G, Sproule BJ. - Work of breathing before and after bronchodilators in patients with emphysema. *Dis Chest*, 1965; 48: 458-463.
6. Jenne JW, Siever JR, Druz WS, Solano JV, Cohen SM, Sharp JT. - The effect of maintenance theophylline therapy on lung work in severe chronic obstructive pulmonary disease while standing and walking. *Am Rev Respir Dis*, 1984; 130: 600-605.
7. Gottfried SB, Altose MD, Kelsen SG, Cherniack NS. - Perception of changes in airflow resistance in obstructive pulmonary disorders. *Am Rev Respir Dis*, 1981; 124: 566-570.
8. Nicklaus TM, Burgin WW, Taylor JR. - Spirometric tests to diagnose suspected asthma. *Am Rev Respir Dis*, 1969; 100: 153-159.
9. Balzano G, Delli Carri I, Gallo C, Cocco G, Melillo G. - Intrasubject between-day variability of PD₂₀ methacholine assessed by the dosimeter inhalation test. *Chest*, 1989; 95: 1239-1243.
10. Peslin R, Bohadana A, Hannhart B, Jardin P. - Comparison of various methods for reading maximal expiratory flow-volume curves. *Am Rev Respir Dis*, 1979; 119: 271-277.
11. Afschrift M, Clement J, Peeters R, Van de Woestijne KP. - Maximal expiratory and inspiratory flows in patients with chronic obstructive pulmonary disease. Influence of bronchodilation. *Am Rev Respir Dis*, 1969; 100: 147-152.
12. Boushy SF. - The use of expiratory forced flows for determining response to bronchodilator therapy. *Chest*, 1972; 62: 534-541.
13. Quanjer PhH ed. - Standardized lung function testing. *Bull Eur Physiopathol Respir*, 1983; 19 (Suppl. 5): 22-27 and 45-51.
14. Campbell MJ, Gardner MJ. - Calculating confidence intervals for some non-parametric analyses. In: Gardner MJ, Altman DG, eds. *Statistics with confidence. Confidence intervals and statistical guidelines*. London, 1989; pp. 71-79.
15. Gayraud P, Orehek J, Grimaud C, Charpin J. - Bronchoconstrictor effects of a deep inspiration in patients with asthma. *Am Rev Respir Dis*, 1975; 111: 433-439.
16. Orehek J, Beaupre A, Badier M, Nicoli MM, Delpierre S. - Perception of airway tone by asthmatic patients. *Bull Eur Physiopathol Respir*, 1982; 18: 601-607.
17. Olivenstein R, Wolkove N, Cohen C, Frank H, Kreisman H. - A comparison of responses to albuterol delivered by two aerosol devices. *Chest*, 1986; 90: 392-395.
18. Pastorello EA, Codecassa LR, Pravettoni V, *et al.* - The role of suggestion in asthma. I. Effects of inactive solution on bronchial reactivity under bronchoconstrictor or bronchodilator suggestion. *Ann Allergy*, 1987; 59: 336-338.
19. Spector S, Luparello TJ, Kopetzky MT, Souhrada J, Kinsman RA. - Response of asthmatics to methacholine and suggestion. *Am Rev Respir Dis*, 1976; 113: 43-50.
20. Neild JE, Cameron IR. - Bronchoconstriction in response to suggestion: its prevention by an inhaled anticholinergic agent. *Br Med J*, 1985; 290: 674.

21. Tattersfield AE, Keeping IM. - Assessing change in airway calibre: measurement of airway resistance. *Br J Clin Pharmacol*, 1979; 8: 307-319.
22. Rodenstein DO, Stanescu DC, Francis C. - Demonstration of failure of body plethysmography in airway obstruction. *J Appl Physiol: Respirat Environ Exercise Physiol*, 1982; 52: 949-954.
23. Ramsdell JW, Tisi GM. - Determination of bronchodilation in the clinical pulmonary function laboratory. Role of changes in static lung volumes. *Chest*, 1979; 76: 622-628.
24. George RB, Conrad SA, Light RW. - Relative value of tests used to measure bronchodilator response. *Chest*, 1978; 73: 989-990.
25. Pennock BE, Rogers RM, McCaffree DR. - Changes in measured spirometric indices. What is significant? *Chest*, 1981; 80: 97-99.
26. Demedts M. - The assessment of reversibility: what physiological tests? *Eur Respir J*, 1990; 3: 1084-1087.
27. Connellan SJ, Gough SE. - The effects of nebulized salbutamol on lung function and exercise tolerance in patients with severe airflow obstruction. *Br J Dis Chest*, 1982; 76: 135-142.
28. Denison DM, Waller JF, Turton CWG, Sopwith T. - Breathing in and breathing out. *Br J Dis Chest*, 1982; 76: 237-252.
29. Garcia JG, Hunninghake GW, Nugent KM. - Thoracic gas volume measurement. Increased variability in patients with obstructive ventilatory defects. *Chest*, 1984; 85: 272-275.
30. Nosedá A, Carpioux JP, Prigogine T, Schmerber J. - Lung function, maximum and submaximum exercise testing in COPD patients: reproducibility over a long interval. *Lung*, 1989; 167: 247-257.
31. Bellamy D, Hutchison DCS. - The effects of salbutamol aerosol on lung function in patients with pulmonary emphysema. *Br J Dis Chest*, 1981; 75: 190-196.
32. Bouhuys A, Van de Woestijne KP. - Mechanical consequence of airway smooth muscle relaxation. *J Appl Physiol*, 1971; 30: 670-676.
33. McFadden ER, Newton-Howes J, Pride NB. - Acute effects of inhaled isoproterenol on the mechanical characteristics of the lungs in normal man. *J Clin Invest*, 1970; 49: 779-790.
34. Girard WM, Light RW. - Should the FVC be considered in evaluating response to bronchodilator? *Chest*, 1983; 84: 87-89.
35. Gove RI, Shepherd J, Burge PS. - Variability and reversibility of the slow and forced vital capacity in chronic airflow obstruction. *Br J Dis Chest*, 1987; 81: 182-185.
36. Meslier N, Racineux JL, Six P, Lockhart A. - Diagnostic value of reversibility of chronic airway obstruction to separate asthma from chronic bronchitis: a statistical approach. *Eur Respir J*, 1989; 2: 497-505.
37. Freedman BJ. - Patterns of response to bronchodilators in asthma. *Br J Dis Chest*, 1978; 72: 95-107.
38. Anthonisen NR, Wright EC and the IPPB Trial Group. - Bronchodilator response in chronic obstructive pulmonary disease. *Am Rev Respir Dis*, 1986; 133: 814-819.
39. Stark RD. - Dyspnoea: assessment and pharmacological manipulation. *Eur Respir J*, 1988; 1: 280-287.