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Measurement technique influences the response of transfer factor (TICO) to salbutamol in patients with airflow limitation

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Measurement technique influences the response of transfer factor (TICO) to salbutamol in patients with airflow limitation. D.J. Chinn, J. Askew, L. Rowley, J.E. Cotes.

ABSTRACT: Single-breath transfer factor obtained using a multibreath estimate of alveolar volume (TI) was measured before and after salbutamol in twenty patients with reversible airflow limitation. The effective breathholding time was calculated by four methods due respectively to Ogilvie and colleagues as modified by the American Thoracic Society (ATS), ATS Epidemiological Standardization Project (ESP), Jones and Meade in which allowance was made for the time of sample collection and a simplified method in which the allowance for sampling was in terms of volume, not time. Two patients could perform the test procedure only after salbutamol. Amongst the remainder the transfer factor calculated using a single-breath estimate of alveolar volume (TI') was on average 12% less than TI. Carbon monoxide transfer coefficient (KCO), TI and TI' were highest by the ESP method and lowest by the Ogilvie method. Inhalation of salbutamol (200γ) did not affect TI' by any method or TI and KCO by the Jones and Meade method but results by the other methods were reduced; in the case of the modified Ogilvie method the reduction was 3.9%. This error was due to overestimation of effective breathholding time by neglecting the reduction of 39% which occurred in the time of sample collection. The time of inspiration was unchanged whilst the time of deadspace washout was reduced by 16%. After bronchodilatation the absence of a change in TI' was due to the overestimation of effective breathholding time being offset by an increase in the proportion of alveolar volume measured by the single-breath procedure. It is concluded that for patients receiving bronchodilator therapy the transfer factor is best measured as TI using the Jones/Meade time correction. Use of TI' systematically underestimates the transfer factor of such patients. *Eur Respir J. 1988, 1.*

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The single-breath lung transfer factor for carbon monoxide (TICO) describes the rate of uptake of carbon monoxide from the alveoli into the pulmonary capillary blood. The rate is determined mainly by the diffusion characteristics of the lung parenchyma, the transfer gradient and the ability of haemoglobin in alveolar capillary blood to take up carbon monoxide. The related biological variables include the lung expansion, the concentration of carboxyhaemoglobin and the alveolar oxygen tension [4]. Bronchoconstriction, induced by inhalation of histamine aerosol, has been reported not to affect the transfer factor measured by the single-breath method with a separate multibreath determination of lung volume [12] and this has been confirmed [2]. By contrast the transfer factor measured by the steady state method and by the single-breath method, using the alveolar volume estimated from the dilution in the lung of the test gas, was reduced by histamine [1, 2]. The reduction was attributed to a technical artifact introduced by bronchoconstriction, rather than to an effect of histamine on gas exchange, because the response was not consistent between methods and the dose of histamine was small. On this account comparisons of measurements made before and after a change in airway calibre provide a means for validating the methodology for the single breath transfer factor including that proposed in recent reports on standardization [6, 20].

In the present paper inhalation of salbutamol has been used to increase the airway calibre of patients with chronic airflow limitation; the effect upon transfer factor of using alternative recommended procedures for estimating effective breathholding time has been examined. The procedures used were those of JONES and MEADE [10], OGILVIE *et al.* [16] and the American Thoracic Society's Epidemiological Standardization Project (ESP), [7]. The performance of an automatic apparatus (P.K. Morgan Ltd.) was also assessed. The results suggest that the effects of variation in airway calibre are minimized by the Jones and Meade procedure and to a lesser extent by the Morgan automatic apparatus. The Ogilvie and ESP procedures yielded inconsistent results.

Methods

The subjects were patient-volunteers with respiratory impairment on account of confirmed or suspected occupational lung disease; in twelve the exposure was to asbestos or other mineral, in one to vegetable dust, in seven to fumes. Of the latter one had occupational asthma due to toluene diisocyanate. All the subjects had airflow limitation which was partly reversed by salbutamol. Stature was measured using a stadiometer (Holtain) and body mass with a spring balance. Dynamic spirometry for measurement of forced expiratory volume (FEV_1), forced vital capacity and peak expiratory flow rate was performed in triplicate using a McDermott MKIII dry bellows spirometer [13]. Functional residual capacity and other subdivisions of total lung capacity were measured by the closed circuit method with helium as the indicator gas. Carbon dioxide was absorbed and oxygen added to maintain a constant resting respiratory level.

Transfer factor was measured by the single-breath carbon monoxide method (TICO,SB) using transfer test apparatus (Morgan). The initial alveolar carbon monoxide (CO) concentration was estimated from the inspired CO concentration (0.28%) adjusted for the dilution in the lung of helium in the test inspirate (14% He in air). The final CO concentration was that in an alveolar sample of 0.7 *l* collected after exhalation of a washout volume of 0.9 *l*. Prior to sample collection the bag was flushed with room air and emptied with standard suction. Allowance was made for the dilution of the collected sample which this entailed. The breathholding manoeuvre comprised exhalation to residual volume, inhalation to total lung capacity, breathholding for approximately 8 s which yielded an effective breathholding time of approximately 10 s, then exhalation to residual volume: inhalation and exhalation were required to be as rapid as possible and of duration less than 4 s. The alveolar volume during breathholding was the residual volume from closed circuit spirometry plus the volume of test gas inspired. The effective alveolar volume was calculated from the dilution in the lung of the helium present in the test breath, allowance being made for the absorption of carbon dioxide prior to analysis of helium and for the instrument and anatomical deadspaces [4]. Helium was analysed using a katharometer and carbon monoxide by an infra-red analyser. The transfer test spirometer was calibrated using a gas syringe (Mercury Electronics Ltd), the analysers by serial dilution of test gas in the closed circuit apparatus and the speed of the kymograph using a stop-watch. The kymograph speed (1 $cm \cdot s^{-1}$) was accurate to within 2% and the other measurements to within 1%. The alveolar volumes by the multibreath and single breath methods were designated respectively V_A and V_A' and the corresponding transfer factors TI and TI'. The difference between V_A' and the volume of test gas inspired into the lung (VI) was estimated residual volume. K_{CO} was expressed as transfer factor per *l* BTPS (body temperature, standard pressure saturated with water vapour) of alveolar volume. SI units were used. The start and finish of inspiration, deadspace washout and sample collection were located on the spirogram by eye and the corresponding times including that of actual breathholding (plateau time) were measured in duplicate to 0.05 s. The effective breathholding time was taken to include the plateau time together with part of the times of inspiration and of expiration as follows:

Method 1 (Jones and Meade) – two-thirds of the inspiratory time and the expiratory time up to halfway through the period of sample collection.

Method 2 (Ogilvie *et al.*) – the inspiratory time and the time of deadspace washout.

Method 3 (American Thoracic Society's Epidemiological Standardization Project) – the midpoint of inspiration by volume to the end of deadspace washout.

Method 4 (Morgan automatic apparatus) – the time during inspiration when the preset deadspace washout volume (0.9 *l*) had been inhaled to the time after breathholding when the washout volume plus half the preset sample (0.7 *l*) had been expired.

Two measurements of transfer factor were made on each occasion: to be acceptable the inspired volumes were required to agree to within 0.2 *l*, the alveolar volume (V_A) had to be within 10% of total lung capacity and the measurements of TI' by method 4 had to agree to within 5% [5]. The latter values were calculated at the time using a Hewlett-Packard 9825 calculator. Pairs of measurements which met these criteria were used for the comparison of results calculated using the effective breathholding times by the four methods. Those before salbutamol were calculated without allowance for carbon monoxide back tension; results after salbutamol were obtained after making a correction of 10 ppm which was the average increase attributable to the initial determinations in preliminary experiments. The procedures, equations and reference values are described in detail elsewhere [4].

Subjects had not smoked for at least 2 h, nor used their salbutamol inhalers for at least 4 h before the tests which were in the order dynamic spirometry, anthropometry, transfer factor and static lung volume. Subjects then inhaled 200γ of salbutamol after which the physiological measurements were repeated in the same order. The average time between the first determination of TI before and after salbutamol was 54 min. Duplicate determinations were separated by 7–10 min. The measurements were repeated at the same time of day two weeks later. The latter results, which did not differ significantly from those on the first occasion, were used to estimate the between-day variability. All flow rates and volumes were expressed at body temperature saturated with water vapour (BTPS). Hence TI/V_A (K_{CO}) had the units $mmol \cdot min^{-1} \cdot kPa^{-1} \cdot l\ BTPS^{-1}$. Mathematical analysis was performed using an IBM 370 mainframe computer and the Statistical Package for Social Sciences of the

University of Michigan [15]. Reproducibility was expressed as the coefficient of variation of a single observation; this was the standard deviation of the observation divided by the overall mean value. Percentage changes following salbutamol and percentage differences between results by the four methods were expressed in the form $100\,\Delta x/\bar{x}$ [17] and compared using paired t-tests on results calculated to four significant figures. For purposes of presentation results were rounded off to two or three figures as seemed appropriate.

Results

Nineteen men and one women were assessed. Six were smokers and the remainder exsmokers. After salbutamol all completed the tests satisfactorily but before salbutamol two subjects could not perform the measurement of transfer factor within the constraints specified. Details of the remaining 18 subjects are given in table I. The FEV_1 was on average 53% of the reference value (range 27–106%) and increased materially after salbutamol (average increase 16.5%). The residual volume was in most instances increased compared with the reference value and was reduced by salbutamol. Total lung capacity was within normal limits (mean 107% predicted, range 78–137%, table II). The transfer factor (TI) and KCO were on average 82% of predicted (range 26–148%); the values did not differ significantly between duplicates or between attendances. The transfer factor calculated using the single-breath alveolar volume (TI') was reduced compared with TI by on average 12%.

Before salbutamol the within and between-day variability of KCO, TI and TI' were on average 5% and 5.9% respectively. The variability in TI was significantly correlated with that in alveolar volume (VA). After salbutamol the variability of TI' was greater than that of KCO ($p<0.05$). Of the four methods the variability by method two was on average 5.2% and by method four it was 4.6% with the other methods intermediate. In some individual comparisons the differences reached statistical significance (table III).

The absolute results were highest by method 3 and lowest by method 2 with the other methods tending to be intermediate. Salbutamol did not alter TI by method 1 but TI by methods 2, 3 and 4 were all significantly reduced. This had the effect that, whereas before salbutamol methods 1 and 2 gave similar results, after salbutamol the results by method 2 were significantly lower by on average 3.9%. KCO behaved similarly whilst TI' was unaffected by salbutamol (table III).

The volume inspired was increased by salbutamol (table IV). Residual volume and estimated residual volume were both reduced, the latter to a lesser extent than the former (mean changes respectively 12.6 and 9.1%). The different responses had the effect that whereas VA' increased after salbutamol, VA did not. The time of inspiration was unaffected by salbutamol but the volume inspired was greater so the mean inspiratory flow rate was increased. The plateau was slightly shorter on average by 2.3%. The times of deadspace washout and sample collection were both reduced, respectively by 15.5% and 39.4%; the expiratory flow rates were increased in consequence. Overall the estimated breathholding time was reduced following salbutamol; the reduction was significantly greater for method 1 (5.3%) than the other methods (2.6–3.7%). The changes are illustrated in figure 1.

Table I. - Mean values and ranges for some indices describing the 18 subjects who completed the study. The results for ventilatory capacity ere given before and after salbutamol

	Mean	Range	Mean	Range
Age yr	63.30	44--77		
Stature m	1.70	1.54--1.84		
Body mass kg	67.20	51--85		
	before		after	
Forced expiratory volume FEV_1, *l*	1.43	0.63--3.10	1.67	0.77--3.44
Forced vital capacity FVC, *l*	3.26	2.06--4.99	3.76	2.43--5.15
FEV_1/FVC %	43.70	28.00--62.00	44.00	28.00--67.00

Table II. - Summary of the spirometric results including overall means ($\bar{x}$) standard deviation (SD) and % changes after salbutamol (100 $\Delta\bar{x}/\bar{x}$, $p<0.05$)

		$\bar{x}$	SD	% *
Forced expiratory volume	FEV_1, *l*	1.55	0.59	16.5
Forced vital capacity	FVC, *l*	3.51	0.84	15.1
Peak expiratory flow rate	PEF $l \cdot s^{-1}$	3.78	1.53	14.4
Functional residual capacity	FRC, *l*	4.39	1.15	–5.3
Vital capacity				
inspiratory	IVC, *l*	3.64	0.79	9.7
expiratory	EVC, *l*	3.56	0.79	10.5
two stage	VC, *l*	3.78	0.82	10.1
Residual volume	RV, *l*	2.90	0.91	–12.6
Total lung capacity	TLC, *l*	6.68	1.37	0.32 (NS)

* the changes were significant except where indicated as NS (not significant)

Table III. - Indices of gas transfer before and after salbutamol. Mean values (SI) and variability (%) within and between-days

		Before salbutamol			After salbutamol		
			variability			variability	
Index	Method	mean	within	between	mean	within	between
KCO	1	1.12 (4)	4.2	5.1	1.10 (2)	3.3	3.6
	2	1.12 (4)	4.9	5.8	1.08 (4)†	3.6	4.3
	3	1.21 (1)	4.6	5.3	1.16 (1)†	3.4	3.8
	4	1.14 (2)	4.3≠	5.0	1.11 (2)†	3.3	3.7
TI	1	6.99 (4)	4.8	5.9	6.91 (2)	3.8	4.8
	2	6.93 (4)	5.2	6.2	6.71 (4)†	3.9	4.9
	3	7.54 (1)	5.3	6.2	7.25 (1)†	3.8	4.9
	4	7.12 (2)	4.7≠	5.3	6.92 (2)†	3.7	4.5
TI'	1	6.20 (4)	5.4*	6.3	6.27 (2)	4.4*	5.8*
	2	6.14 (4)	5.6	6.9	6.09 (4)	4.7*	6.2*
	3	6.67 (1)	5.2	6.2	6.57 (1)	4.4*	5.8*
	4	6.30 (2)	5.3	6.3	6.28 (2)	4.3 ≠*	5.3≠

†significant change after salbutamol ($p<0.05$), ( ) significant order effect ($p<0.05$) indicated by numbers within brackets, * significantly different from variability for KCO, ≠ significant difference compared with method 2. TI and TI' transfer factors calculated from alveolar volumes respectively measured from multibreath and single breath techniques.

Discussion

The single-breath procedure for measuring transfer factor devised by FORSTER *et al.* was a minor technical masterpiece [3] but had limitations. One was that because inspiration and expiration could not be instantaneous the relationship which described gas uptake during breathholding was assumed to apply to the whole of the respiratory cycle. The alternative of treating inspiration and expiration separately was not

Table IV. - Components of transfer measurement before and after salbutamol

		Before salbutamol	variability		After salbutamol	variability	
		mean	within	between	mean	within	between
Volume inspired	*l*	3.30	3.2	5.7	3.70†	3.1	3.8
Estimated RV	*l*	2.30	6.5	4.4	2.10†	5.2	6.5
Alveolar volume VA	*l*	6.38	1.7	4.1	6.41	1.8	3.3
Alveolar volume VA'	*l*	5.61	2.7	4.1	5.79†	2.5	3.5
VA'/VA		0.88	2.7	5.6	0.90x	1.9x	3.5
Times:							
inspiration	s	2.20	16.7	20.1	2.18	12.9	19.7
plateau	s	8.00	4.4	4.5	7.82x	4.3	5.1
deadspace washout	s	0.96	12.1	23.9	0.81†	17.5	16.2
sampling	s	1.44	18.6	30.6	0.92††	19.9	16.8x
Breathholding time:							
Method 1	s	11.1 (4)	2.8	4.5	10.5 (2)††	2.8	2.1†
Method 2	s	11.2 (4)	2.3	3.1	10.8 (4)†	2.6	2.3
Method 3	s	10.3 (1)	2.2	2.7	10.0 (1)†	2.1	2.2
Method 4	s	10.9 (2)	2.5	3.2	10.5 (2)†	2.5	1.7†
Flow rates	$l \cdot s^{-1}$						
Inspiratory		1.68	16.0	19.3	1.84x	13.3	18.6
Expiratory		0.94	12.9	24.3	1.22†	16.4	9.8†
Washout		1.08	12.1	23.2	1.27†	17.5	12.9x
Sample		0.89	18.6	28.8	1.28†	19.9	16.0x

x† significant change after salbutamol ($p<0.05$ and 0.01), ( ) significant order effect, †† change after salbutamol larger than for related comparisons. VA and VA': alveolar volume measured respectively by multi breath and single breath methods.

then practicable. It can now be done [8] but few laboratories have the facilities. The difficulty was recognised by OGILVIE *et al.* [16] and a modified version of their procedure constituted the present method 2; by this method gas uptake during sample collection was assumed to be offset by an uptake deficit during inspiration. The deficit was treated differently in the related ESP method. Neither method made allowance for increased gas uptake during slow expiration as might occur in patients with airflow limitation. The Morgan transfer test apparatus (method 4) was included because it made an approximate allowance in terms of sample volume, which was simpler to apply than one based on time. Subjects with labile airflow limitation were selected for study as being likely to show up any differences between the methods. The airflow limitation was to be reduced by bronchodilatation as this mirrored the progression of disease. Bronchodilators have also been used clinically to obtain results in breathless patients, for

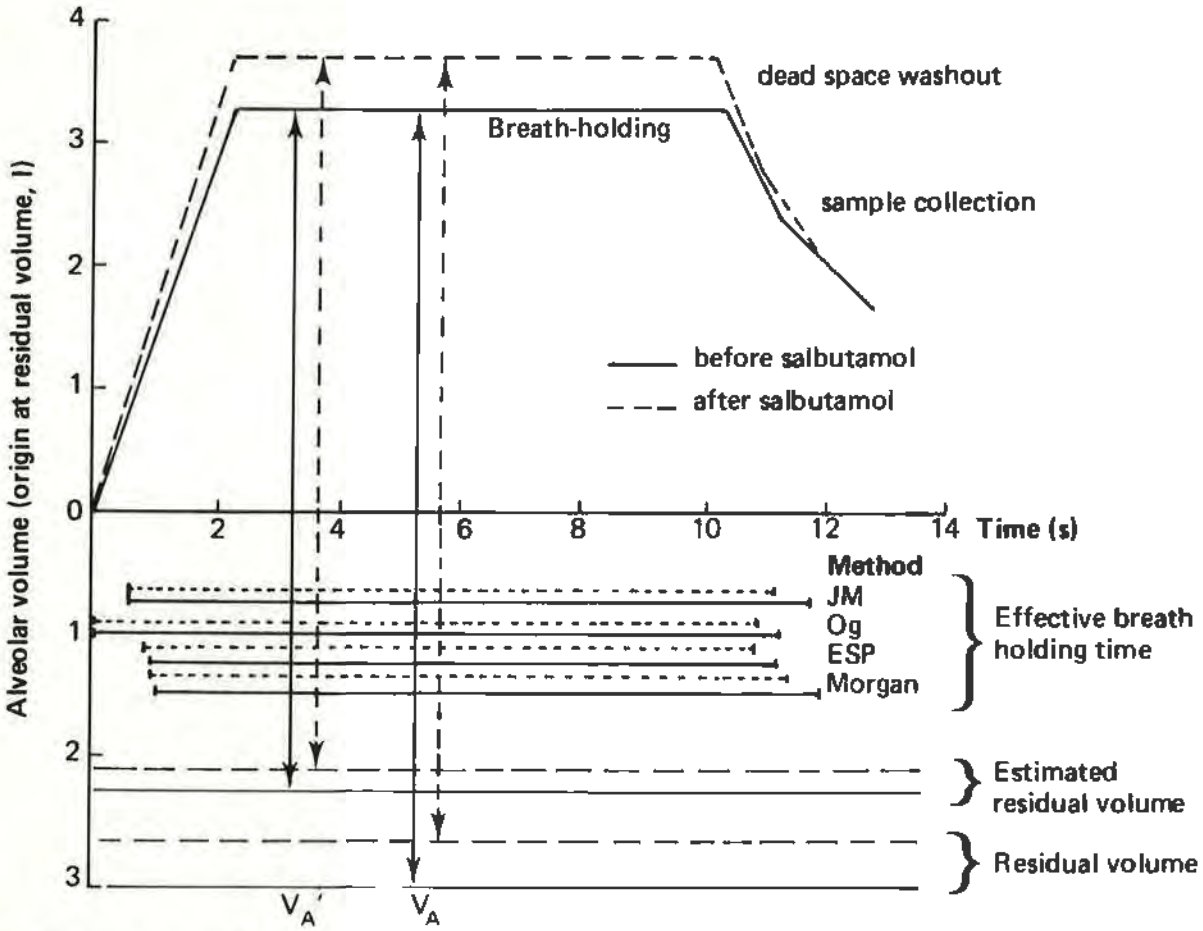

Fig. 1. The mean relationship of alveolar volume to time during the procedure for measurement of transfer factor. The mean effective breathholding times for methods 1 (Jones and Meade), 2 (Ogilvie), 3 (ESP) and 4 (Morgan) are also shown. Conditions before and after salbutamol are represented respectively by continuous and interrupted lines.

example, two of the present subjects. The apparatus and procedures conformed to the specifications of the standardization working party of the European Coal and Steel Community [20]. The experimental design enabled comparisons to be made within breaths and within subjects rather than between subjects where the spread of results was wider.

Before salbutamol methods 1 and 2 gave nearly identical results for KCO, TI and TI'; this suggested that the modified Ogilvie method effectively allowed for airflow limitation. The ESP method yielded significantly higher results; this was due to its shorter estimated breathholding time compared with the other methods [5, 9]. In the present study this disadvantage was not offset by any compensating advantages, so there is a case for abandoning the method and recalculating results based on it [11, 18].

Inhalation of salbutamol did not significantly change the transfer factor and KCO by method 1 but results by all the other methods were significantly reduced. The difference could not have been due to systematic changes in carbon monoxide back tension or cardiac output during the test procedure or to other effects of salbutamol as these would have affected all methods equally. Instead the difference was due to the salbutamol reducing significantly the time of sample collection; in addition it reduced slightly the plateau time and the time of deadspace washout. The reduction in sampling time was reflected in a significantly greater reduction in effective breathholding time by the Jones and Meade method compared with the other methods.

The discrepancy in transfer factor (TI) was due to all the factors which influenced the change in airway calibre so the result might be expected to vary between patients and within the same patients in relation to acute exacerbations or chronic deterioration. Thus whilst in the present circumstances the error in method 2 was 3.9%, in other circumstances it could be more and could interact with the other sources of error in the measurement [14]. The error affected particularly the modified Ogilvie and ESP methods. It affected the volume-corrected breathholding method of Morgan to a lesser extent. The error was avoided by use of TI'. However, the latter index was systematically lower than TI by on average 12% before salbutamol due to the residual volume of the patients being underestimated by the single-breath procedure for measurement. This was also the experience of others [19]. The underestimation was

reduced by salbutamol but the coincidence that the effect of this change was exactly cancelled by a converse change in the estimated breathholding time should not be relied on in other circumstances. These results demonstrate that for patients receiving bronchodilator therapy the transfer factor is best measured by the method of Jones and Meade with an independent estimate of residual volume. Measurements by other methods are inherently less reliable. This needs to be borne in mind when proposals for standardization of the measurement are reviewed.

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RÉSUMÉ: Le facteur de transfert calculé selon la méthode en apnée (TL), le volume alvéolaire étant obtenu par respirations multiples, a été mesuré chez 20 malades présentant une obstruction réversible des voies aériennes avant et après salbutamol. Le temps d'apnée effective a été calculé de quatre manières différentes; la méthode d'Ogilvie et coll modifiée par l'American Thoracic Society (ATS), le projet de standardisation en épidémiologie de l'ATS (ATS), la méthode de Jones et Meade prenant en compte le temps de recueil de l'échantillon et une méthode simplifiée où il est tenu compte de l'échantillonage en terme de volume et non de temps. Deux patients n'ont pu réaliser les tests demandés qu'après salbutamol. Pour les sujets restants le facteur de transfert calculé en utilisant le volume alvéolaire obtenu au cours d'une inspiration unique (TL') est en moyenne 12% plus petit que TL. Kco, TL et TL', sont les plus élevés par la méthode ESP et les plus faibles par la méthode Ogilvie. L'inhalation de 200 mcg de salbutamol ne modifie pas TL', quelle que soit la méthode utilisée, ni TL et Kco obtenus selon la méthode de Jones et Meade, tandis que avec les autres méthodes les résultats de TL et Kco sont réduits. Pour la méthode d'Ogilvie modifiéela réduction vaut 3.9%. Cette erreur est due à une surestimation du temps d'apnée effective, la réduction de 39% du temps d'échantillonage étant négligée. Le temps de l'inspiration n'est pas changé taudis que le temps de rinçage de l'espace mort est réduit de 16%. L'absence de changement du TL', après bronchodilatation est liée au fait que la surestimation du temps d'apnée effective est contrebalancée par une augmentation du volume alvéolaire mesuré au cours de l'apnée. Nous concluuns que chez des malades qui reçoivent un traitement bronchodillatateur, TL calculé selon Jones et Meade est la meileure méthode de mesure. TL', sous estime de manière systématique le facteur de transfert chez ces malades.