Impact of Altered Alveolar Volume on the Diffusing Capacity of the Lung for Carbon Monoxide in Obesity

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Key Words

Alveolar volume • Body mass index • Diffusion capacity of the lung • Lung volume • Obesity • Waist circumference

Abstract

Background: Studies on the diffusing capacity of the lung for carbon monoxide (DL_{CO}) in obese patients are conflicting, some studies showing increased DL_{CO} and others unaltered or reduced values in these subjects. **Objectives:** To compare obese patients to controls, examine the contribution of alveolar volume (VA) and CO transfer coefficient (K_{CO}) to DL_{CO} , and calculate DL_{CO} values adjusted for VA. **Methods:** We measured body mass index (BMI), waist circumference (WC), spirometry and DL_{CO} in 98 adult obese patients without cardiovascular or smoking history and 48 healthy subjects. All tests were performed in the same laboratory. **Results:** Using conventional reference values, mean DL_{CO} and VA were lower (–6%, $p < 0.05$, and –13%, $p < 0.001$, respectively), and K_{CO} was higher (+9%, $p < 0.05$) in obese patients than in controls. VA decreased whereas K_{CO} increased with increasing BMI and WC in the obese group. Patients with lower DL_{CO} had low K_{CO} in addition to decreased VA. In contrast, some obese patients maintained normal VA, which, coupled with high K_{CO} , result-

ed in higher DL_{CO} . The main result is that diffusion capacity differences between obese patients and controls disappeared using reference equations adjusting DL_{CO} for VA. **Conclusions:** Using conventional reference equations, our obese patients show slightly lower mean DL_{CO} , lower mean VA and higher mean K_{CO} than controls, but with a large range of DL_{CO} values and patterns. Adjusting DL_{CO} for VA suggests that low lung volumes are the main cause of low DL_{CO} and high K_{CO} values in obese patients.

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Introduction

The impairment of the respiratory function in obesity has long been recognized [1]. However, while the effects of obesity on spirometric variables are well established, studies on the diffusing capacity of the lung for carbon monoxide (DL_{CO}) in obese patients are conflicting. Some studies found increased DL_{CO} values [2–4]. In contrast, others found that DL_{CO} was unaltered or reduced in obese subjects [5–10]. The earliest study concluded that, in the case of low-normal DL_{CO} , loss of the pulmonary capillary bed should be suspected in obese patients [3]. Part of

these discrepancies may be explained by the lack of control subjects in some of these series, the measured DL_{CO} being compared to predicted values. In addition, medical history, especially smoking history, was not taken into account in all studies.

The calculation of single-breath DL_{CO} requires measurement of two variables, the permeability factor (k_{CO} , Krogh factor) and the alveolar volume (VA). k_{CO} is measured as the exponential decay in fractional concentration of CO over the breath-holding period. VA is measured using the gas dilution method. The k_{CO} converts to K_{CO} or DL_{CO}/VA by dividing by the STPD to BTPS conversion and by the barometric pressure term, and DL_{CO} is the product of K_{CO} and VA [11]. Consequently, low DL_{CO} results from low K_{CO} and/or low VA . Only a few studies on obesity reported K_{CO} and/or VA values [2, 4, 5, 10]. Interpreting these variables in obese patients should contribute to understanding the discrepancies between the published studies, and identifying the role of low lung volumes [6] or increased K_{CO} [2, 3] in DL_{CO} variations. Furthermore, the low VA values observed in some series can also explain at least part of the high K_{CO} reported in some obese patients. In normal subjects, K_{CO} increases when VA decreases. Consequently, DL_{CO} is lower and K_{CO} is higher at lower lung volumes compared with reference values estimated at total lung capacity [12, 13]. Reference equations have been published to adjust DL_{CO} and K_{CO} for lung volume [12–16]. Obtaining normal DL_{CO} values with these equations would support that DL_{CO} changes in obese patients result mainly from altered lung volumes.

Considering the above, the aims of this study were: (i) to compare the DL_{CO} of obese patients to those of controls obtained in the same laboratory; (ii) to examine the contribution of VA and K_{CO} to DL_{CO} values, especially in obese patients with higher DL_{CO} or lower DL_{CO} , and (iii) to compare the DL_{CO} values of obese patients to reference values adjusted for VA .

Subjects and Methods

We retrospectively reviewed the medical records of adult patients (>18 years) who were referred to our department for pulmonary function tests before weight reduction surgery between January 2003 and June 2008. Patients were reassessed in our department. Patients with smoking history, diabetes, obesity hypoventilation syndrome, cardiopulmonary and chest wall abnormalities, revealed by a complete medical history, physical examination and chest radiograph, were excluded.

Control subjects were technicians, nurses, physicians or students from our department, and healthy subjects referred for assessment before exercise training protocols. All of them denied

cardiopulmonary history or symptoms and smoking history, and allowed us verbally to put their data in our database in an anonymous manner. This study has been approved by the Institutional Review Board of the French Learned Society for Respiratory Medicine – Société de Pneumologie de Langue Française (CEPRO 2008–022).

Pulmonary Function Tests

Lung volumes, flow-volume curves and single-breath DL_{CO} tests were measured using a MS-PFT device (Jaeger USA Master-screen Diffusion TP, VIASYS Healthcare, Yorba Linda, Calif., USA), and following the ATS/ERS recommendations [17–20]. Functional residual capacity was determined using the helium dilution technique. For DL_{CO} measurement, we paid particular attention to equipment quality control and test acceptability [18]. Equipment and protocols were unchanged during the 5.5-year period and tests were performed by experienced technicians. Reference equations for spirometry and DL_{CO} used in our laboratory are those published by the European Respiratory Society in 1993 [17, 21]. Predicted VA is predicted total lung capacity – anatomic dead space (150 ml) [17, 18]. Reference values used to adjust DL_{CO} or K_{CO} for VA are those published by Chinn et al. [14], Frans et al. [12], Johnson [16], Stam et al. [13] and Filley et al. [15]. DL_{CO} values of patients were corrected for hemoglobin (Hb) [18]. Results are expressed as absolute values and percentage of predicted values.

Height and weight were measured and body mass index (BMI) was calculated. Waist circumference (WC) was quantified by placing a measuring tape around the waist at the midpoint between the lowest rib margin and the upper point of the iliac crest at the end of expiration. WC was measured by experienced personnel from the Internal Medicine and Nutrition Department.

Analysis

Student's *t* test was used to compare the variables of patients and controls. One-way analysis of variance (ANOVA) was performed to compare $DL_{CO}\%$, $K_{CO}\%$ or $VA\%$ of controls and obese patients grouped by $DL_{CO}\%$ (>mean $DL_{CO}\%$ of the control group or <90% mean $DL_{CO}\%$ of the control group). When the *F* value indicated significant differences, a Student-Neuman-Keuls test for multiple comparisons was performed. Linear regression between $DL_{CO}\%$, $K_{CO}\%$ or $VA\%$ and either BMI or WC were assessed, and the Pearson correlation coefficients were calculated. Data are given as mean $\pm$ standard deviation. Statistical significance required a *p* < 0.05.

Results

Subject Characteristics

A total of 98 of 265 obese patients (37%) referred to our department met the inclusion criteria. Data from 48 controls were also analyzed. The demographic and anthropometric characteristics are presented in table 1. The mean age of control males was lower than that of obese males (32 ± 11 vs. 40 ± 11 years, *p* < 0.05), the range of values being not very different (21–60 years in controls, and 21–65 years in obese patients). Since DL_{CO} was ex-

Table 1. Baseline characteristics and pulmonary function results

	Males			Females		
	controls (n = 15)	obese (n = 25)	p	controls (n = 33)	obese (n = 73)	p
Age, years	32 ± 11	40 ± 11	<0.05	37 ± 14	39 ± 11	NS
Height, cm	178.6 ± 4.8	175.8 ± 7.5	NS	164.7 ± 6.6	161.9 ± 7.5	NS
Weight, kg	71.7 ± 6.3	150.8 ± 32.4	<0.01	57.7 ± 6.1	119.9 ± 21.6	<0.01
BMI	22.5 ± 1.8	48.6 ± 8.5	<0.01	21.6 ± 1.84	46.0 ± 8.9	<0.01
WC, cm		139.9 ± 16.9 ^a			124.5 ± 18.4 ^a	
VC, liters	5.5 ± 1.0	4.6 ± 0.8	<0.01	3.9 ± 0.9	3.5 ± 0.8	NS
VC%	109.5 ± 15.2	92.9 ± 13.9	<0.01	108.8 ± 14.6	103.8 ± 18.6	NS
FEV ₁ , liters	4.7 ± 0.9	3.6 ± 0.8	<0.05	3.2 ± 0.8	2.9 ± 0.7	NS
FEV ₁ %	108.5 ± 11.9	92.5 ± 15.8	<0.05	107.5 ± 11.5	102.9 ± 15.1	NS
FRC, liters	3.5 ± 0.7	2.4 ± 0.5	<0.01	2.8 ± 0.7	1.9 ± 0.5	<0.001
FRC%	103.0 ± 13.9	71.6 ± 14.0	<0.01	101.2 ± 14.9	70.2 ± 14.8	<0.001
TLC, liters	7.1 ± 1.2	5.9 ± 1.3	<0.01	5.1 ± 0.9	4.6 ± 1.1	<0.05
TLC%	101.7 ± 15.1	83.2 ± 18.3	<0.01	103.4 ± 15.6	92.1 ± 16.1	<0.05
DL _{CO} , ml·min ⁻¹ mm Hg ⁻¹	34.1 ± 6.2	29.3 ± 4.6	<0.05	23.0 ± 4.1	21.6 ± 3.3	NS (0.07)
DL _{CO} %	97.5 ± 14.5	91.4 ± 17.0	NS	87.9 ± 15.3	84.0 ± 10.9	NS
K _{CO} , ml·min ⁻¹ mm Hg ⁻¹ l ⁻¹	5.1 ± 1.0	5.3 ± 0.9	NS	4.6 ± 0.7	5.1 ± 0.7	<0.001
K _{CO} %	104.5 ± 16.3	113.5 ± 15.7	NS (0.08)	89.0 ± 12.8	98.2 ± 12.7	<0.001
VA, liters	6.9 ± 0.7	5.6 ± 0.8	<0.001	5.0 ± 0.6	4.3 ± 0.7	<0.001
VA%	98.1 ± 8.4	82.5 ± 11.8	<0.001	101.7 ± 8.4	89.0 ± 10.6	<0.001

Results are presented as mean ± SD. NS = Not significant; BMI = body mass index; WC = waist circumference; VC = vital capacity; FEV₁ = forced expiratory volume in 1 s; TLC = total lung capacity. The pulmonary function values are given as absolute values and percentage of the predicted value.

^a Obtained in 39 patients.

pressed in percent of predicted values based on age and height, this did not preclude comparisons between obese and control males. The Hb values of obese patients were 14.7 ± 1.3 in males and 13.4 ± 1.1 g·dl⁻¹ in females. Therefore, there was no difference between the corrected and the uncorrected DL_{CO} values, which are calculated by the device with default Hb values of 14.6 in males and 13.5 in females.

DL_{CO}, VA and K_{CO} in Obese Patients and Controls Using Conventional Reference Values

Mean DL_{CO}% and VA% were significantly lower in obese patients than in controls (−6%, $p < 0.05$ and −13%, $p < 0.001$, respectively). In contrast, K_{CO}% was higher in the obese group (+9%, $p < 0.05$; table 1). The 23 obese patients with higher DL_{CO}% (>mean DL_{CO}% of the control group) had VA% of 97 ± 9% of predicted values, not different from that of controls, and K_{CO}% of 112 ± 15% of predicted values, higher than that of controls ($p < 0.01$). The 33 obese patients with lower DL_{CO}% (<90% mean DL_{CO}% of the control group) had VA% of 81 ± 12% of

predicted values, lower than that of controls ($p < 0.01$) and K_{CO}% of 95 ± 15% of predicted values, not different from that of controls.

Relationship between DL_{CO}, K_{CO} or VA and BMI or WC

In the obese group, VA% was inversely correlated with BMI ($r = -0.38$, $p < 0.001$; fig. 1). K_{CO}% was correlated with BMI ($r = 0.32$, $p < 0.005$). There was no correlation between DL_{CO}% and BMI. In obese men, VA% was inversely correlated with BMI ($r = -0.60$, $p < 0.005$), K_{CO}% was not correlated with BMI, and DL_{CO}% tended to be inversely correlated with BMI ($r = -0.38$, $p = 0.06$). In obese women, VA% was inversely correlated with BMI ($r = -0.28$, $p < 0.05$). K_{CO}% was correlated with BMI ($r = 0.38$, $p < 0.05$), and there was no correlation between DL_{CO}% and BMI. In the control group, there was no correlation between BMI and either DL_{CO}%, K_{CO}% or VA%.

VA% was inversely correlated with WC ($r = -0.45$, $p < 0.01$). K_{CO}% was correlated with WC ($r = 0.60$, $p < 0.0001$). There was no correlation between DL_{CO}% and WC.

Fig. 1. Relationship between VA, K_{CO} or DL_{CO} (expressed in percentage of ERS predicted values [17]), and body mass index (BMI) in 98 obese patients.

DL_{CO} Values Adjusted for VA

Results are presented in table 2. There was no difference between obese patients and controls using these reference equations. Using the equations of Chinn et al. [14], 10% of obese women and 16% of obese men had DL_{CO} adjusted for VA of <80%, and 4% of women and 8% of men had DL_{CO} adjusted for VA of >110%. Using the equations of Stam et al. [13], 18% of obese women and 20% of obese men had K_{CO} adjusted for VA of <80%, and 2% of women and 4% of men had K_{CO} adjusted for VA of >110%.

Discussion

DL_{CO}, K_{CO} and VA in Obese Patients and Controls Using Conventional Reference Values

In our group of 98 obese patients, mean DL_{CO}% was slightly but significantly lower (–6%) than that in the control group. A low VA% (–13% compared to controls) likely explains the lower DL_{CO}% in our obese patients. This hypothesis is supported by several studies in which DL_{CO} and VA were measured in obese patients at rest [22], during exercise [23] or after weight loss [10]. Although VA was inversely correlated with BMI (fig. 1), we found no correlation between DL_{CO} and BMI. This is likely the result of the positive correlation between K_{CO} and BMI and the inverse correlation between VA and BMI (fig. 1). The impact of VA on DL_{CO} could be identified as this series included a large proportion of very obese patients who demonstrate the largest loss of VA. Indeed, 77 of 98 pa-

Table 2. DL_{CO} values adjusted for alveolar volumes

	DL _{CO} %			K _{CO} %		
	Chinn et al. [14]	Johnson et al. [16]	Frans et al. [12]	Frans et al. [12]	Stam et al. [13]	Filley et al. [15]
Obese males	91.1 ± 13.8 (63.3 – 121.9)	108.3 ± 6.0 (98.3 – 123.5)	95.3 ± 14.9 (64.3 – 131.7)	103.1 ± 15.9 (66.8 – 138.9)	86.9 ± 11.9 (62.6 – 110.3)	88.6 ± 8.3 (67.5 – 102.3)
Control males	91.9 ± 14.2 (72.0 – 128.8)	101.7 ± 3.1 (96.0 – 106.9)	97.5 ± 14.4 (77.1 – 135.5)	102.1 ± 16.0 (83.5 – 142.2)	89.9 ± 14.1 (70.4 – 126.5)	97.7 ± 4.3 (90.5 – 105.5)
Obese females	92.9 ± 10.0 (68.1 – 118.0)	105.0 ± 4.8 (95.1 – 115.6)	86.0 ± 9.8 (63.0 – 111.5)	92.4 ± 11.5 (61.0 – 120.2)	91.9 ± 10.7 (65.9 – 118.9)	93.1 ± 6.7 (78.5 – 106.8)
Control females	91.4 ± 13.6 (70.8 – 126.7)	99.4 ± 3.5 (94.4 – 108.6)	86.6 ± 13.5 (68.3 – 122.8)	96.8 ± 3.2 (86.9 – 99.6)	89.4 ± 14.6 (69.6 – 124.7)	100.8 ± 4.9 (88.2 – 107.8)

Results are expressed as mean ± standard deviation (range). The reference values used to adjust DL_{CO} or K_{CO} for VAs are those published by Chinn et al. [14], Frans et al. [12], Johnson et al. [16], Stam et al. [13] and Filley et al. [15].

tients (79%) had a BMI of >40 . Interestingly, obese patients presented with a large range of $DL_{CO}\%$ values, from 65 to 114%. Our 33 patients with lower $DL_{CO}\%$ had low $VA\%$, and these low $VA\%$ were not, as was expected, coupled with high $K_{CO}\%$. On the other hand, the 23 obese patients with higher DL_{CO} showed a high $K_{CO}\%$ together with $VA\%$ very close to our control $VA\%$. Whether the preservation of normal lung volume in obese patients is associated with specific fat distribution deserves to be investigated. Taken as a whole, these results illustrate that, using conventional reference equations, obese patients can present with a variety of DL_{CO} values and patterns.

DL_{CO} and K_{CO} in Obese Patients and Controls Using Reference Values Adjusted for VA

Several reference equations have been established to adjust DL_{CO} and K_{CO} for lung volume. We used some of these equations [12–16] in our series and found that mean adjusted DL_{CO} values were similar in the obese and control groups. This suggests that altered lung volumes explain most of DL_{CO} variations in obese patients. This conclusion, however, is based on the assumption that the K_{CO} – VA relationship does not differ significantly in normal subjects and in obese patients, since the VA effects on DL_{CO} were derived from studies in normal subjects with submaximal inspiratory volumes. Increased abdominal pressure and mechanical constraint placed on the chest wall by fat accumulation are the main mechanisms leading to low lung volumes in obesity [23]. No structural pulmonary abnormalities have been described, and normalization of lung function after weight loss has been reported. Therefore, one may hypothesize that the K_{CO} – VA relationship is not significantly modified in obesity. To further investigate this hypothesis, studying the contribution to lung diffusion capacity of the distribution of gas and perfusion in the lungs of obese patients, especially in basal lung areas [24], should be of interest. In this view, comparing Krogh factors and lung volumes measured with the re-breathing and single breath methods at the same inspired volume should allow correcting diffusion for the effects of unequal ventilation in obese subjects [25, 26].

After adjustment of DL_{CO} or K_{CO} for lung volume, 10–20% of obese patients, according to the chosen equation, had values of $<80\%$ of predicted. This may suggest that, in addition to low lung volumes, obesity-associated disorders may contribute to decrease diffusing capacity in some patients. In a recent study, 40% of obese patients with reduced DL_{CO} presented with moderate or severe diastolic dysfunction, which may trigger disruption of

the alveolar-capillary barrier [9]. Type 2 diabetes, which reduces alveolar microvascular reserves and lung volumes, may also impair diffusing capacity in obese patients [27].

Using adjusted $DL_{CO}\%$ or $K_{CO}\%$ values for VA , we found very few obese patients (2–8% according to the reference equation) with high $DL_{CO}\%$ or $K_{CO}\%$ values. High K_{CO} in obesity has been attributed to larger total circulating blood volume that increases pulmonary vascular recruitment [28]. The last assumption has received particular attention and was supported by the finding of an increased capillary volume in severely obese patients using the Roughton and Forster method [8]. Another author achieved similar conclusions using the diffusing capacity for nitric oxide [10]. However, both authors found diminished membrane diffusion that counterbalanced the high capillary volume and lead to normal DL_{CO} values in their obese patients.

Limitations of the Study and Perspectives

Larger series of obese patients are needed to study the role of fat distribution on VA and DL_{CO} . In this view, WC may be a better predictor of DL_{CO} than BMI since it reflects central adiposity [29, 30]. In addition, the small sex-related differences we observed (tendency of DL_{CO} to decrease with BMI and lack of correlation between K_{CO} and BMI in men, in contrast to women) suggest that there may be a larger loss of lung function in obese men compared to women which deserves to be confirmed [31, 32]. In further series, particular attention should also be paid to patients >60 years, since VA dependence of DL_{CO} has been found to be larger in younger subjects [13].

In conclusion, using conventional reference equations, our series of very obese patients shows slightly lower DL_{CO} , lower VA and higher K_{CO} than controls, with subtle gender differences. However, the range of DL_{CO} values is large, from low DL_{CO} characterized by low VA and K_{CO} , to high-normal DL_{CO} characterized by normal VA and high K_{CO} . Using reference equations adjusting DL_{CO} for VA , the differences between the obese and the control groups disappear, suggesting that low lung volumes are the main cause of low DL_{CO} and high K_{CO} values in obese patients. These results may help to better understand lung function in very obese patients in clinical situations of increasing frequency, such as pre-bariatric surgery assessment.

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