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Pulmonary gas exchange in elderly subjects

H. Guénard, R. Marthan

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ABSTRACT: Although important alterations in structure and function develop with age, the hypothesis that the lungs are capable of maintaining adequate gas exchange for the maximum human life span is generally accepted.

This hypothesis was examined by measuring arterial oxygen and carbon dioxide tension (P_{a,O_2} and P_{a,CO_2}) alveolo-arterial differences in oxygen and carbon dioxide tension ($P_{A\text{-}a,O_2}$ and $P_{a\text{-}A,CO_2}$), steady state transfer capacity of the lung for carbon monoxide ($T_{L,CO,ss}$) as well as the gas exchange ratio (R) in a series of 74 healthy subjects aged more than 68 yrs (69–104 yrs). In addition, P_{a,O_2} and P_{a,CO_2} were measured in a series of 55 young healthy subjects, who acted as controls.

In the elderly subjects, except for $T_{L,CO,ss}$, there was no significant correlation between any of the other variables and age. However, for a given P_{a,CO_2}, P_{a,O_2} was always lower in the group of elderly subjects than in the group of young control subjects. $T_{L,CO,ss}$, as well as $T_{L,CO,ss}$/minute ventilation (V'_E) ratio, was correlated with age, according to the following regression equations: $T_{L,CO,ss}$ (mL·min^{-1}·kPa^{-1}) = 126-0.90 × age (yrs), and $T_{L,CO,ss}/V'_E$ (kPa^{-1}×10^3) = 13.5-0.085 × age, respectively.

These results show that arterial oxygen tension did not decrease with age in this series of elderly subjects. However, the decrease in steady-state transfer capacity of the lungs for carbon monoxide with age indicates that oxygen transport could be diffusion-limited in elderly subjects, at least when oxygen consumption is increased.

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Laboratoire de Physiologie, Université de Bordeaux II, Bordeaux, France.

Correspondence: H. Guénard
Laboratoire de Physiologie
Faculté de Médecine Victor Pachon
Université de Bordeaux II
146 rue Léo Saignat
33076 Bordeaux cedex
France

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Ageing is usually thought to be accompanied by a progressive decline in arterial oxygen tension (P_{a,O_2}) and transfer capacity of the lungs for carbon monoxide ($T_{L,CO}$) [1]; whereas, arterial carbon dioxide tension (P_{a,CO_2}) remains constant [2] and ventilation meets, at least at rest, the CO_2 excretion demand. However, data establishing these relationships are often either obtained in small samples of aged subjects or extrapolated from those measured in younger subjects. Therefore, it seemed of interest to measure gas exchange in a large sample of aged healthy subjects to avoid any extrapolation. From these data, the possibility of a limitation in lung O_2 transport as well as its determinants could be examined.

Methods

Subjects

Seventy four subjects aged more than 68 yrs (range 69–104 yrs) were selected for this study. Two thirds of this population were female (table 1). The mean age was 82 yrs. The subjects were recruited from a retirement home with the assistance of the local consultant physician, who reviewed their medical record. None of them had a history of chronic or acute pulmonary or cardiac disease, none of the females was a smoker or ex-smoker, but 16 out of 25 of the males were ex-smokers. They were all able-bodied and did not suffer from obesity. At the time of the study, their complete physical examination, chest radiograph and electrocardiogram were within the normal range. All of the subjects gave informed consent. All measurements were performed on subjects in the sitting position, breathing quietly in steady state. All measurements needing a forced manoeuvre were excluded to avoid the bias of poor co-operation, which is an age-dependent factor [3].

Table 1. – Age, weight and body skin area of the population studied

	Age yrs	Weight kg	Body skin area m^2
Female (n=49)	82 (69–104)	53 (32–84)	1.47 (1.39–1.74)
Male (n=25)	81 (70–97)	60 (44–78)	1.63 (1.38–1.87)

Values are presented as mean, and range in parenthesis.

Protocol

The measured data, including steady state transfer capacity of the lung for carbon monoxide ($T_{L,CO,ss}$), P_{a,O_2}, P_{a,CO_2}, pH, alveolo-arterial differences in oxygen and carbon dioxide tension $P_{A\text{-}a,O_2}$ and $P_{a\text{-}A,CO_2}$, were obtained as follows. The subject was first asked to breath normally through a mouthpiece connected to a low resistance valve (0.25 hPa pressure loss for 0.25 L·s^{-1}) with a Fleisch No. 2 pneumotachograph (PTG) (0.08 hPa

pressure loss for 0.25 L·s^{-1}) on the expiratory arm. After a 5 min adaptation period, the inspiratory arm of the valve was connected *via* a two-way tap, to a rubber bag filled with a mixture of 21% O_2 and 0.1% CO in N_2. The subject breathed quietly for another 5 min. Tidal volume (V_T) and instantaneous expired CO fraction ($F_{E,CO}$) (Cosma Rubis 3000 France) were displayed on a graphic recorder (HP 740A, USA) for 2 min. Meanwhile, expired gas was collected in a rubber bag (50 L) and later analysed for $F_{E,CO}$. After calibration of the recorded parameters, V_T as well as mean alveolar carbon monoxide tension ($P_{A,CO}$) were calculated. $P_{A,CO}$ was taken as the mid-plateau value of the instantaneous P_{CO} recording. Mean $P_{A,CO}$, V_T and respiratory frequency (f_R) were calculated during the 2 min of analysis. From these data, minute ventilation (V'_E), CO consumption (V'_{CO}) and $T_{L,CO,ss}$ were derived. At completion of $T_{L,CO,ss}$ measurement, the subject was allowed to rest for 10 min. An arterial blood sample was then slowly withdrawn from the humeral artery and analysed for P_{a,O_2}, P_{a,CO_2} and pH with an IL 613 analyser (Instruments Laboratory, USA), which was calibrated before each measurement. Simultaneously, instantaneous expired O_2 (Beckman OM11, USA) and CO_2 fractions (Jaeger CO_2 test, Germany) were recorded to measure alveolar oxygen and carbon dioxide tensions (P_{a,O_2} and P_{a,CO_2}). Meanwhile, expired gas was collected for later analysis of O_2 and CO_2 fractions. Respiratory gas exchange ratio (R), $P_{A\text{-}a,O_2}$ and $P_{a\text{-}A,CO_2}$ were also calculated.

Control group

To provide reference values for blood gas tensions measured using the same techniques as in the laboratory, blood gas values were obtained in a series of 55 young healthy subjects. Medical students aged 26±4 yrs, registered for a postgraduate course in physiology, acted as control subjects. In order to mimic the actual ventilatory condition observed in the elderly subjects, 20 of these control subjects were asked to slightly hyperventilate, so that their P_{a,CO_2} value ranged 4–4.5 kPa (see Results).

Statistical analysis

Linear regressions were calculated between main gas exchange data and age using a robust regression software (NCSS, USA). Statistical significance was accepted at the 95% confidence level ($p<0.05$). Mean P_{a,O_2} values between elderly and control subjects were compared using unpaired Student's t-test, and a p-value of 0.05 was considered significant.

Results

Table 2 presents mean values of the main gas exchange data in the elderly subjects. In 77% of the subjects, gas exchange ratio (R-values) were 0.7–1. As expected, some subjects (19%) had a trend to hyperventilate when connected to the mouth piece as shown by R-values above 1. Three subjects (4%) had R-values below 0.7 and were suspected of hypoventilating.

Neither P_{a,O_2} nor P_{a,CO_2} were correlated with age in the group of elderly subjects (fig. 1). There was also no correlation between either $P_{A\text{-}a,O_2}$ or $P_{a\text{-}ACO_2}$ and age (fig. 2).

Table 2. – Main gas exchange data in elderly subjects

P_{a,O_2} kPa	11.2±1.0
P_{a,CO_2} kPa	4.6±0.6
$P_{A\text{-}a,O_2}$ kPa	4.4±1.3
$P_{a\text{-}A,CO_2}$ kPa	0.7±0.4
$T_{L,CO,ss}$ mL·min^{-1}·kPa^{-1}	53.9±16.3
V'_{O_2} mL·min^{-1}	215.4±49.6
V'_{CO_2} mL·min^{-1}	186.7±47.2
R	0.83±0.27

Values are presented as mean±SD. P_{a,O_2}: arterial oxygen tension; P_{a,CO_2}: arterial carbon dioxide tension; $P_{A\text{-}a,O_2}$: alveolo-arterial difference in oxygen tension; $P_{a\text{-}ACO_2}$: alveolo-arterial difference in carbon dioxide tension; $T_{L,CO,ss}$: steady-state transfer capacity of the lung for carbon monoxide; V'_{O_2}: oxygen consumption; V'_{CO_2}: carbon dioxide production; R: gas exchange ratio.

P_{a,O_2} values are compared between the young and elderly subjects in table 3. As mentioned above, to take into account the ventilatory status of the subjects, the comparison was performed according to the P_{a,CO_2} value. In both series of subjects (*i.e.* young and elderly), three groups of an approximately similar size were characterized as follows: P_{a,CO_2} 4–4.5 kPa; P_{a,CO_2} 4.5–5 kPa; and P_{a,CO_2} >5 kPa. The very few subjects whose P_{a,CO_2} was lower

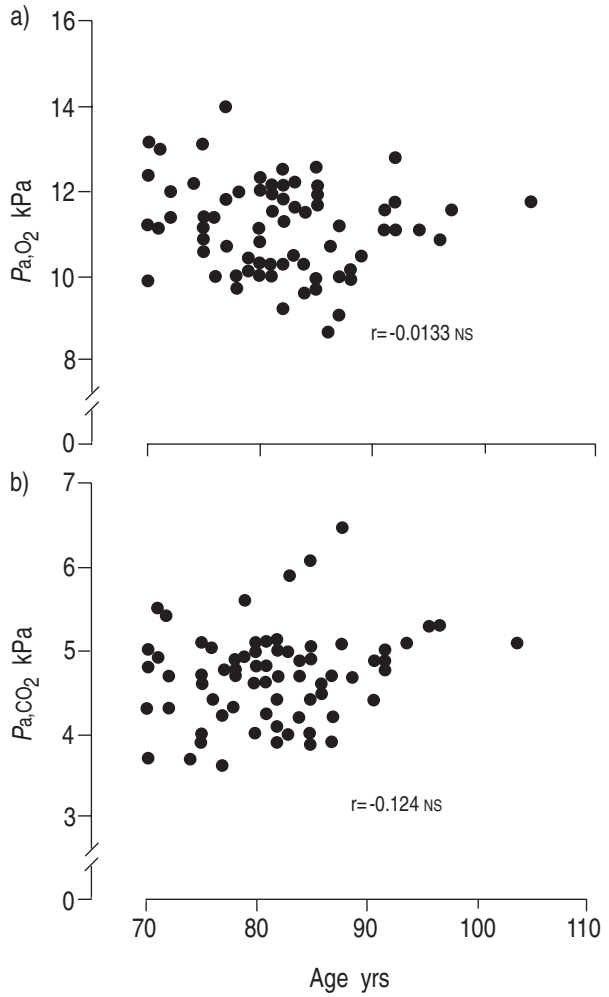

Fig. 1. – a) P_{a,O_2}; and b) P_{a,CO_2} as a function of age. The solid lines indicate the regression lines according to equations in each graph. There was no correlation between arterial blood gas tensions and age. P_{a,O_2}: arterial oxygen tension; P_{a,CO_2}: arterial carbon dioxide tension.

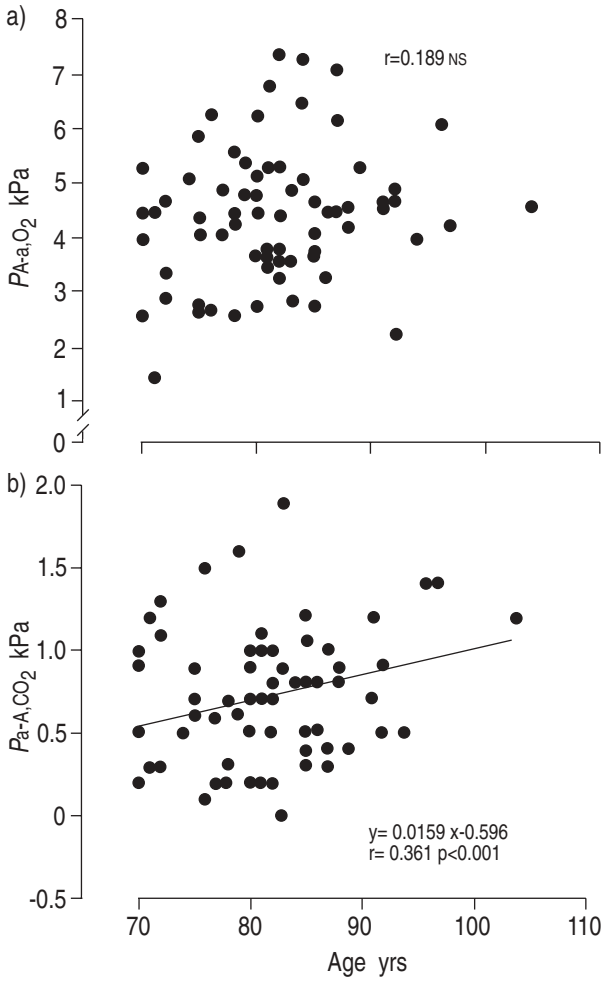

Fig. 2. – a) Alveolo-arterial difference in oxygen tension ($P_{A\text{-}a,O_2}$); and b) alveolo-arterial difference in carbon dioxide tension ($P_{a\text{-}ACO_2}$) as a function of age. The solid line indicates the regression line according to the equation in the graph.

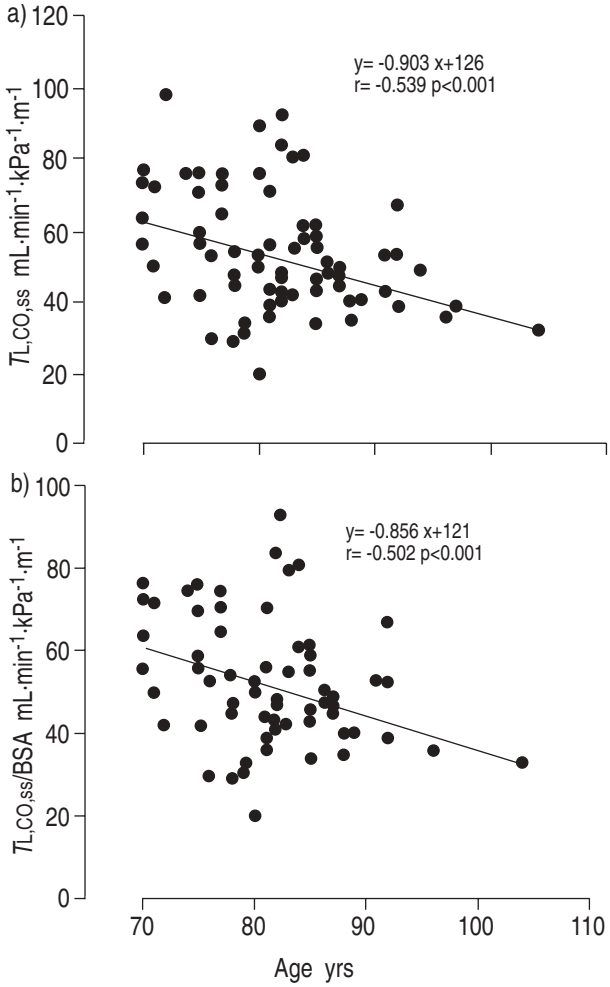

Fig. 3. – $T_{L,CO,ss}$ and $T_{L,CO,ss}$/BSA as function of age. The solid lines indicate the regression lines according to equations in each graph. $T_{L,CO,ss}$ was negatively correlated to age. $T_{L,CO,ss}$: steady-state transfer capacity of the lungs for carbon monoxide; $T_{L,CO,ss}$/BSA: ratio of $T_{L,CO,ss}$ to body surface area.

than 4 kPa were discarded (four individuals in both series). Table 3 shows that P_{a,O_2} was always significantly lower in the elderly than in the young subjects, whatever the range of P_{a,CO_2}. This table also shows that, unlike young subjects, in the elderly the P_{a,O_2} did not increase with the decrease in P_{a,CO_2}. As a consequence, for the group with the highest P_{a,CO_2} values (*i.e.* >5 kPa), the difference in P_{a,O_2} between the elderly and young subjects was very small (approximately 0.6 kPa), although significant.

Table 3. – P_{a,O_2} values (kPa) in the two populations studied subdivided into three subgroups according to P_{a,CO_2} values

	P_{a,CO_2}		
	4–4.5 kPa	4.5–5 kPa	>5 kPa
Elderly (n=70)			
P_{a,O_2} kPa	11.4±1.16 (n=20)	10.9±0.97 (n=27)	11.2±0.82 (n=23)
Young (n=51)			
P_{a,O_2} kPa	13.6±1.27 (n=19)	12.9±1.08 (n=17)	11.8±0.96 (n=15)
p-value	<0.001	<0.01	<0.05

Values are presented as mean±SD. The last line indicates the p-value (unpaired Student's t-test) between mean P_{a,O_2} in the elderly and young for each P_{a,CO_2} subgroup. P_{a,O_2}: arterial oxygen tension; P_{a,CO_2}: arterial carbon dioxide tension.

$T_{L,CO,ss}$ decreased significantly with age, although the results were scattered (fig. 3). The linear regression equation was: $T_{L,CO,ss}$ (mL·min^{-1}·kPa^{-1})=126-0.90×age (yrs) (r=0.54; p<0.001). None of the subjects in this series had a $T_{L,CO,ss}$ value lower than 20 mL·min^{-1}·kPa^{-1}. As $T_{L,CO,ss}$ depends on ventilation, $T_{L,CO,ss}$ /V'_E ratios were calculated. These ratios were correlated to age: $T_{L,CO,ss}$/V'_E (kPa^{-1}×10^3)=13.5-0.085×age (r=0.44; p<0.001). The linear regression equation of the ratios of $T_{L,CO,ss}$ to body surface area (BSA) was: $T_{L,CO,ss}$/BSA (mL·min^{-1}·kPa^{-1}·m^{-1}) =121-0.86 (r=0.50; p<0.001).

Discussion

This study shows that blood tensions were not correlated with age in this series of elderly subjects; although, for a given P_{a,CO_2}, P_{a,O_2} is slightly lower in elderly than in control young healthy subjects. $T_{L,CO,ss}$ significantly decreases with age and the lowest value observed in this series was 20 mL·min^{-1}·kPa^{-1}. As the number of subjects above 90 yrs was relatively small, it could be suggested that some bias in the interpretation of the regression equations of the variables *versus* age has been introduced;

however, when the data from subjects above 90 yrs were discarded, although slopes and ordinates of regression equations were slightly altered, the correlation coefficients remained close to those obtained for the whole series.

Blood gas values

The apparatus used for measuring blood gas values was automatically checked for calibration with calibrated gas mixtures. In addition, whole blood tonometry was performed once a week and samples, the P_{O_2} and P_{CO_2} of which were unknown to the laboratory staff, were analysed. On 21 samples, the relationship between measured P_{O_2} (y) and true P_{O_2} (x) was y=1.009×+0.03 kPa (r=0.992). As a consequence, no correction factor was used for the measured values.

It is generally accepted that during life, at least until the age of 70 yrs, P_{a,O_2} progressively decreases leading to a physiological hypoxaemia that has been ascribed to age-induced increase in V'_A/Q' mismatch [4]. Reference values for P_{a,O_2} in subjects older than 70 yrs are, however, usually obtained by extrapolation from measurements performed in subjects mainly in the adult age range, with no, or very few, elderly people. For example, SORBINI *et al.* [5] studied 152 subjects, including 24 above 60 yrs of age with a median age of 71 yrs, and only 10 above 70 yrs. In this latter group, mean P_{a,O_2} was 9.9±0.6 kPa, *i.e.* lower than in the present series. More recent studies have reported similar values of P_{a,O_2} (*i.e.* approximately 10 kPa) in aged subjects [6, 7], whereas higher values (*i.e.* 11.5 kPa) close to those in the present study were reported by CONWAY *et al.* [8], MELLEMGAARD [9], DELCLAUX *et al.* [10] and CERVERI *et al.* [11]. Reasons that could account for these discrepancies in the above-mentioned studies include differences in the inclusion criteria of the subjects, body position during the measurements, technical and methodological aspects of measurement of blood gas values. The former explanation is difficult to study thoroughly. The latter are discussed in the next paragraphs.

As arterial puncture may induce hyper- or hypoventilation [12], gas exchange ratios were measured during the arterial sample, and in most subjects (77%) R-values were within the normal range. It should be noted that, in the literature, R-values are not commonly given, and therefore systemic error due to hypo- or hyperventilation during arterial blood withdrawal could be suspected. P_{a,CO_2} values can also be taken as a criterion of hypo- or hyperventilation. For SORBINI *et al.* [5], mean P_{a,CO_2} in the 24 subjects aged over 60 yrs was 5.3±0.28 kPa, and did not vary whatever the age group. In the present work, mean P_{a,CO_2} was lower (*i.e.* 4.6±0.6 kPa). If V'_A/Q heterogeneity in aged subjects was moderate, this difference in P_{a,CO_2} (*i.e.* 0.7 kPa) should be accompanied by a similar but opposite difference in P_{a,CO_2} [13]. As a consequence, the higher P_{a,O_2} value observed in the present study may only reflect a difference in ventilation between the two populations. However, unlike young healthy subjects (table 3), P_{a,O_2} in elderly subjects with low P_{a,CO_2} was not higher than that in elderly subjects with higher P_{a,CO_2}. Thus, it is likely that hyperventilation worsens the distribution of V'_A/Q' in these subjects. This hypothesis seems to be supported by the fact that both $P_{A\text{-}a,O_2}$ and $P_{a\text{-}A,CO_2}$, are higher in old people than in young subjects. For example, KANBER *et al.* [14] have reported a twofold increase in $P_{A\text{-}a,O_2}$ between 34 and 72 yrs of age.

Another possible factor which could alter the blood gas values is related to the resistance through which the subjects are breathing. In the present study, the subjects breathed through the mouth and were relieved from nasopharyngeal resistances; but, simultaneously, they breathed through a valve chamber and a PTG, the overall pressure loss of which for a 0.25 $L \cdot s^{-1}$ flow, was 0.35 hPa, *i.e.* the resistance was 1.4 $hPa \cdot L^{-1} \cdot s$. Both effects could compensate one for the other. Changes in resistance alter the pattern of intra-alveolar pressure. A slight increase in end-expiratory pressure could avoid airway closure and improve gas exchange. However, in most studies, the route of breathing is not indicated and it is, therefore, difficult to assess its effect on P_{a,O_2}. It is noteworthy that many freely breathing subjects change their route of breathing during the arterial puncture, which could be a cause of scatter of normal P_{a,O_2}, at least in elderly people.

Changes in body position induce alterations in P_{a,O_2}, due to changes in the V'_A/Q' distribution partially linked to the direct effect of gravity [15], but also to changes in lung volume and, therefore, closing volume [16]. In young subjects, the distribution of V'_A/Q' is less heterogeneous in a supine than in an erect posture, as in older subjects this phenomenon is hindered by the effect of airway closure in the dependent part of the lung, decreasing V'_A/Q' values. In the long-term, a supine position may lead to atelectasis. Therefore, one possible explanation for the discrepancies among results in the literature is that data have been obtained in different postures. In fact, the data of SORBINI *et al.* [5] were obtained in supine subjects and the reported decrease in P_{a,O_2} with age was sharp; whilst in the studies by DELCLAUX *et al.* [10] and CERVERI *et al.* [11], and in the present study data were obtained in the sitting position and there was no decline in P_{a,O_2} with age in elderly people. Therefore, in clinical practice, attention should be paid to body position when interpreting blood gas values in elderly subjects.

CO transfer in the elderly

The decline in $T_{L,CO}$ with age is a well-established relationship, starting very early in adult life. In young subjects aged 20–40 yrs, $T_{L,CO,ss}$/BSA is about 60 $mL \cdot min^{-1} \cdot kPa^{-1} \cdot m^{-2}$, according to the results of FILLEY *et al.* [17] BATES and PEARCE [18] and GUÉNARD *et al.* [19]. In the present study, the value of $T_{L,CO,ss}$/BSA was about 35 $mL \cdot min^{-1} \cdot kPa^{-1} \cdot m^{-2}$, corresponding to approximately one half that observed in young subjects. The result is in agreement with that of GEORGES *et al.* [20], who used the single-breath method. The decrease in single-breath $T_{L,CO}$ ($T_{L,CO,sb}$) is linear for CRAPO and MORRIS [1], and MUIESAN *et al.* [2]. GEORGES *et al.* [20] have reported a nonlinear decrease in $T_{L,CO,sb}$ with age, which has been ascribed to the fact that the rate of decline in the pulmonary capillary blood volume (Q_c) increases sharply above the age of 60 yrs.

In the present study, we could not measure the two components of the lung transfer capacity factor, *i.e.* diffusing capacity of the alveolocapillary membrane (D_m) and Q_c. However, if one assumes that the reduction in the two components is similar, the lowest $T_{L,CO}$ value observed in the present series corresponds to approximately 40

mL·min^{-1}·kPa^{-1} and 12 mL for Dm and Qc, respectively, in agreement with the calculated lowest value of Qc, *i.e.* 13 mL from the data of GEORGES *et al.* [20]. The following structural changes may account for these functional alterations. On the one hand, the density of lung capillaries decreases with age [21], although data in subjects older than 60 yrs are still lacking. Moreover, there is evidence that pulmonary capillary pressure increases with age, at least during moderate muscular exercise [22], which suggests that the recruitment of pulmonary capillaries is also limited in elderly subjects. On the other hand, according to VERBEKEN *et al.* [23], the "senile lung" is characterized by "a homogeneous enlargement of the alveolar airspaces, without fibrosis or destruction of their walls". This enlargement is associated with a reduction in surface, which reduces Dm. Moreover, Dm could be further reduced by the increased thickness of the gas phase. GRAHAM *et al.* [24] have shown that TL,CO,sb depends on the duration of the apnoea in patients with obstructive diseases, either asthma or emphysema, and that this dependency is a function of the overdistension of the lungs, *i.e.* alveolar spaces. Therefore, a limitation of the diffusion of CO in the gas phase is also likely to contribute to the decrease in Dm in elderly people.

The decrease in TL,CO value with age may indicate that O_2 transport could be diffusion-limited in elderly subjects. The lowest value of TL,CO observed in this series corresponds to very low values of Dm (approximately 40 mL·min^{-1}·kPa^{-1}) and Qc (about one fifth of that in young adults, *i.e.* 15 mL). These figures appear critical for O_2 transport [25, 26], if not at rest, at least when oxygen consumption is increased, such as during muscular activity or fever. In conclusion, although there was no correlation between blood gas values and age in this series of elderly subjects, the decrease in transfer capacity of the lung for carbon monoxide suggests that oxygen transport may be diffusion-limited in ageing.

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