Pulmonary gas exchange capacity is reduced during normovolaemic haemodilution in healthy human subjects

Charles Le Merre MD,* Michel Dauzat MD,†
Patrice Poupard MD,‡ Rémi Targhetta MD PhD,*
Christine Fabre MD,* Stéphane Bouges MD,§
Jean-Jacques Eledjam MD,‡ Pierre Balmès MD*

Purpose: *To test the hypothesis that a physiological compensatory mechanism maintains respiratory gas exchange during normovolaemic haemodilution.*

Methods: *Pulmonary gas exchange capacity was evaluated in seven healthy subjects by measuring the lung diffusion of carbon monoxide (DLCO). During the measurement, various breath-holding times, inspiratory volumes, and sitting or supine positions, were randomly selected in an attempt to alter pulmonary capillary perfusion. KCO was calculated as the percentage of theoretical values of the ratio of DLCO by alveolar volume and normalized by sex, age, and height. Normovolaemic haemodilution (NH) was performed by bleeding an average blood volume of 1 L with simultaneous Dextran 60 replacement to obtain an haematocrit below 35%.*

Results: *After NH, haemoblogin concentration [Hb] decreased from 14.94 ± 0.96 to 12.5 ± 0.98 $g \cdot dl^{-1}$ ($P < 0.001$). KCO decreased ($P < 0.02$) but remained closely correlated to [Hb] at every lung volume ($P < 0.02$). Breathholding time and body position had no effect.*

Conclusion: *Moderate NH impairs pulmonary gas exchange capacity in awake, resting healthy subjects. There is no evidence of any compensatory mechanism since the KCO vs [Hb] relationship is unchanged.*

But: *Vérifier l'hypothèse d'un mécanisme physiologique compensateur maintenant la capacité d'échanges respiratoires lors de l'hémodilution normovolémique.*

Méthodes: *Nous avons évalué les échanges gazeux respiratoires par la mesure du transfert du CO (DLCO) chez sept sujets sains au cours d'une hémodilution normovolémique (NH). Différents temps d'apnée, volumes inspiratoires, et postures ont été sélectionnés aléatoirement afin de modifier la perfusion capillaire pulmonaire. Les résultats ont été normalisés en fonction de l'âge, du sexe, et de la taille par l'expression en pourcentage des valeurs théoriques du KCO (rapport de DLCO sur le volume alvéolaire). La NH a été réalisée par soustraction d'une quantité moyenne de 1 L de sang, remplacée par du Dextran 60.*

Résultats: *Après NH, le taux d'hémoglobine [Hb] a diminué de 14,94 ± 0,96 à 12,5 ± 0,98 $g \cdot dl^{-1}$ ($P < 0,001$). KCO diminuait ($P < 0,02$) mais restait étroitement corrélé à [Hb] ($P < 0,02$) quelque soit le volume pulmonaire. Le temps d'apnée et la position étaient sans effet.*

Conclusion: *La NH modérée diminue la capacité d'échanges respiratoires chez le sujet sain, éveillé et au repos. Il ne paraît pas exister de mécanisme compensateur, puisque la pente de la relation entre KCO et [Hb] n'est pas modifiée.*

Key words
LUNG:
TRANSFUSION:

From the Pneumology Unit, Internal Medicine A*, Vascular Laboratory†, Department of Anaesthesia and Intensive Care‡, and the Department of Biostatistics§, University Hospital, Nîmes, France.

Address correspondence to: Dr. C. Le Merre, Pneumology - Internal Medicine A, University Hospital - BP 26, 30 029 - Nimes (France).

Phone: (33) 66 27 32 21. Fax: (33) 66 26 32 13.

E-Mail: dauzat@zeus.sc.univ-montp1.fr

Accepted for publication 17th March, 1996.

Several reports in the early 1970s provided the incentive for the clinical use of normovolaemic haemodilution (NH).[1-4] There is now renewed interest for the technique because of the risks associated with blood transfusion, and because of the beneficial effects of NH that have been demonstrated in a number of clinical situations. Nevertheless, the widely acknowledged assertions by Messmer that respiratory gas transport is optimal at a haematocrit of 30%[2] disagree with earlier results from several authors,[5-7] and the mechanisms involved in producing the effect remain to be clarified. The aim of our study was to determine the influence of moderate NH on respiratory gas exchange at the pulmonary level in

TABLE I Individual data: initial pulmonary function tests

Name	Sex	Age (years)	TLC (%th)	FEV_1 (%th)	D_{LCO} (%th)	Haemoglobin ($g \cdot dl^{-1}$)		Haematocrit (%)	
						Before NH	After NH	Before NH	After NH
CL	M	37	111	114	97.8	14.4	12.3	42.5	37.6
CR	M	33	110	111	109.7	16.0	11.9	46.8	33.8
CF	F	36	98	107	89.9	13.7	11.4	40.2	33.4
JCM	M	30	101	99	131.5	15.5	14.4	45.6	43.2
MD	M	37	99	115	122.5	14.7	11.9	43.7	36.4
RT	M	36	103	116	104.8	16.1	13.5	45.9	40.9
JMJ	M	45	113	107	96.5	14.2	12.1	44.6	38.6
Mean ± SD		36.3 ± 4.6	105 ± 6.2	109.9 ± 6	107.2 ± 15	14.9 ± 0.9	12.5 ± 10.6	44.2 ± 2.3	37.7 ± 3.6

(TLC: total lung capacity; FEV1: forced expiratory volume in one second; DLCO: transfer lung capacity of CO); Haemoglobin and haematocrit levels before and after normovolaemic haemodilution (NH). %th: percentage of theoretical values.

healthy humans. We measured the diffusion capacity of carbon monoxide (DLCO) which is widely used for the assessment of alveolar capillary gas exchange, and has been demonstrated to correlate with haemoglobin concentration.[15]

Methods

Seven healthy volunteers from the medical staff, aged from 26 to 45 yr, gave informed consent to this study, which was conducted according to the ethical guidelines of the 1975 Declaration of Helsinki and the ethical standards of our institution. The subjects had normal respiratory function, and had no history of pulmonary disease. One subject was a moderate smoker (Table I). Normovolaemic haemodilution was performed in the intensive care unit. An average of one litre of blood was removed and simultaneously replaced with an equal quantity of Dextran 60,[8] to achieve an haematocrit between 30 and 35%. Blood volume was preserved by maintenance of pulse rate and arterial blood pressure.

The diffusion capacity of carbon monoxide (DLCO) was measured by the single breathholding method, a few days (two to five) before, and two hours after NH, using the same protocol on each occasion, and in accordance with the European recommendations.[9] We used a "Transfer Test C" from Morgan Ltd (UK), the inspired gas being CO 0.27%, He 13%, O_2 21%, and N_2. The washout volume was 0.7 L; the sample volume was 0.6 L, and the standard breathholding time was nine seconds.

Six DLCO measurements were performed in random order, with a 20 min interval between each manoeuvre. The alveolar CO concentration was checked at each step, and the end-expiratory fraction was kept < 0.02%. Measurements were performed on the seven subjects in the sitting position at various pulmonary volumes: total lung capacity (TLC), 70% of TLC, and functional residual capacity (FRC). In addition, three breathholding times (5, 9, and 15 sec), and two body positions (sitting and supine) were tested. As it was not possible to carry out all measurements in the same subjects within the limited time when a steady state could be expected results were obtained with various breathholding times in the first four subjects and the effect of position was determined in the last three subjects.

The ratio of DLCO to alveolar volume (DLCO/VA or KCO) was calculated, and results were expressed as a percentage of theoretical values, to exclude the effect of age, sex, and height.[10,11] Haematocrit and haemoglobin concentration [Hb] were measured before and three hours after NH, i.e. during the six consecutive DLCO measurements.

Statistics

Statistical calculations were performed using the SAS system software (SAS Institute Inc., version 6.0, Cary, NC, USA). The coefficients of variation of inspiratory volumes and breathholding times were calculated relative to their preset values. The between and within subjects effects of [Hb] and/or VA on KCO were evaluated by multivariate analysis of variance, exact F test statistics (Wilk's Lambda), and Student's t test. The relationships between KCO and [Hb], for the different lung volumes and breathholding times (tBH), and posture, were represented graphically by linear regression.

Results

The main functional respiratory and haematological variables appear in Table I. All subjects completed the examination protocol. The coefficient of variation was 3.7% ± 1.1% (range 2.9 to 5.8%) for volumes, and 3.8 ± 2.8% for breathholding time (range 0.6 to 10.9%).

The KCO was different at TLC, 70% TLC, and FRC, before as well as after NH (Table II). Normovolaemic

TABLE II Ratio of transfer capacity of carbon monoxide (DLCO) to alveolar volume (VA) for TLC, 70% of TLC, 5" and 15" breathholding time, and in supine position, expressed as percentage of theoretical values (%th).

	n	*Before NH*	*After NH*	*P*
Haemoglobin ($g.l^{-1}$)	7	149.4 ± 9.3	125.0 ± 10.6	0.00039
DLCO/VA at TLC (%th)	7	91.3 ± 10.8	75.5 ± 13.4	0.0012
DLCO/VA at 70%TLC (%th)	7	104.5 ± 15.5	88.5 ± 13.7	0.02
DLCO/VA at FRC (%th)	7	130 ± 20.2	107.6 ± 13.4	0.0066
DLCO/VA, 5" (%th)	4	92.1 ± 13.7	77.5 ± 14.1	NC
DLCO/VA, 15" (%th)	4	87.1 ± 14	75 ± 15.1	NC
DLCO/VA supine (%th)	3	102.9 ± 14.8	79.7 ± 7.1	NC

Number of patients (*n*). Mean ± standard deviation. Hb = Haemoglobin concentration; TLC = total lung capacity; NH = normovolaemic haemodilution. NC: not calculated.

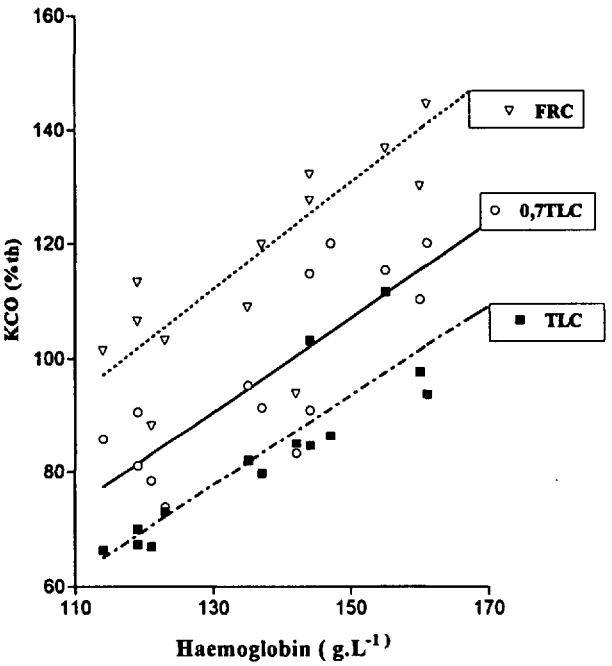

FIGURE 1 KCO versus haemoglobin concentration before and after normovolaemic haemodilution, at various lung volumes (FRC = functional residual capacity; TLC = total lung capacity) : individual data and regression lines.

haemodilution produced a mean decrease in [Hb] of 2.44 $g \cdot dl^{-1}$. For a given lung volume, KCO decreased when [Hb] was decreased by NH (Figure 1, Table II). At a given [Hb], increasing the lung volume decreased KCO (Figure 1, Table III). Breathholding times between 5 and 15 sec did not alter the relationship between KCO and [Hb] (Figure 2). Changing from the sitting to the supine position did not change the KCO versus [Hb] relationship (Figure 3).

Multivariate analysis of variance demonstrated a within subject effect of VA on DLCO (P = 0.0001) independently of the presence or absence of haemodilution (P = 0.83), and a between subject effect of [Hb] on DLCO (P = 0.022) independently of VA.

Discussion

This study of the effect of NH on the diffusion capacity of CO is the first to be performed in normal volunteers under physiological circumstances, i.e., whilst awake and breathing air. Our results demonstrate that pulmonary gas exchange is impaired after even moderate NH. Although obtained over a smaller range of NH, our results are in agreement with previous studies.[14-19]

We chose DLCO to evaluate pulmonary gas exchange capacity because the affinity of haemoglobin for CO is so high that most of the gas combines with haemoglobin and little is carried away as a dissolved gas by the circulation. Moreover, DLCO measurement is a non-invasive technique, and DLCO is closely and linearly correlated to the haemoglobin concentration, over the range of physiological values.[14] The relative importance of the rate of gas diffusion across the pulmonary membrane, and of gas uptake by red cells, in the determination of the overall rate of alveolar capillary gas exchange, is expressed by the following equation: DLCO-1 = DM-1 + θVC-1 where DM is the membrane diffusing capacity, VC is the average volume of blood in the pulmonary capillary bed, and θ is the rate of blood combination with CO. Membrane diffusing capacity is not affected by haemoglobin concentration[15,17] and VC does not change after bleeding[15,20] while θ is reduced, probably because of the decreased number of red cells in the pulmonary capillary bed.[15]

The disappearance of CO from mixed alveolar gas is a function of breatholding time. Low lung volumes ensure complete filling of the pulmonary capillary bed while the supine position increases capillary blood volume. Therefore, performing breathholding manoeuvres

TABLE III Differences of KCO values, expressed as percentage of theoretical values (%th), between measurements performed at TLC, 70% of TLC, and FRC.

		Before NH			*After NH*		
KCO (%th)	*n*	*Value*	*t*	*P*	*Value*	*t*	*P*
(KCO at TLC)-(KCO at 70%TLC)	7	-13.20	-2.77	0.03	-13.03	-4.84	0.003
(KCO at TLC)-(KCO at FRC)	7	-38.73	-5.19	0.002	-32.16	-11.24	<0.001
(KCO at 70%TLC)-(KCO at FRC)	7	-25.53	-7.04	<0.001	-19.13	-6.05	0.001

n = number of patients; t = Students' t test, and *P* = signification against 0 of differences.

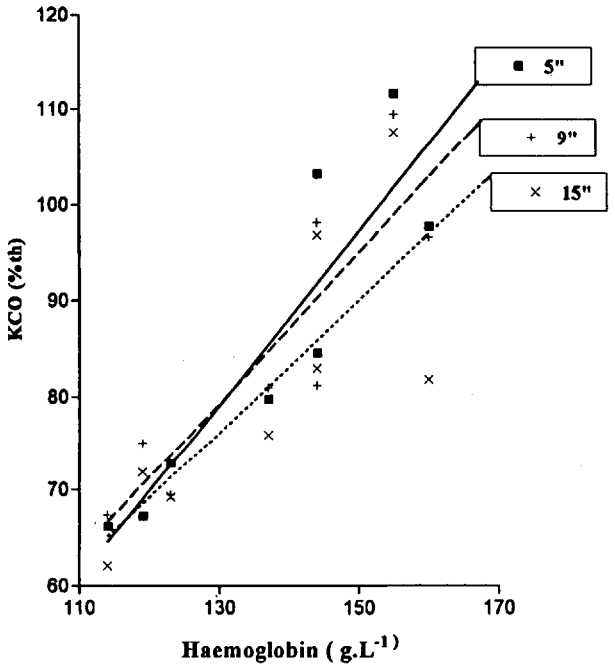

FIGURE 2 KCO versus haemoglobin concentration before and after normovolaemic haemodilution, for various breathholding times (s) : individual data and regression lines.

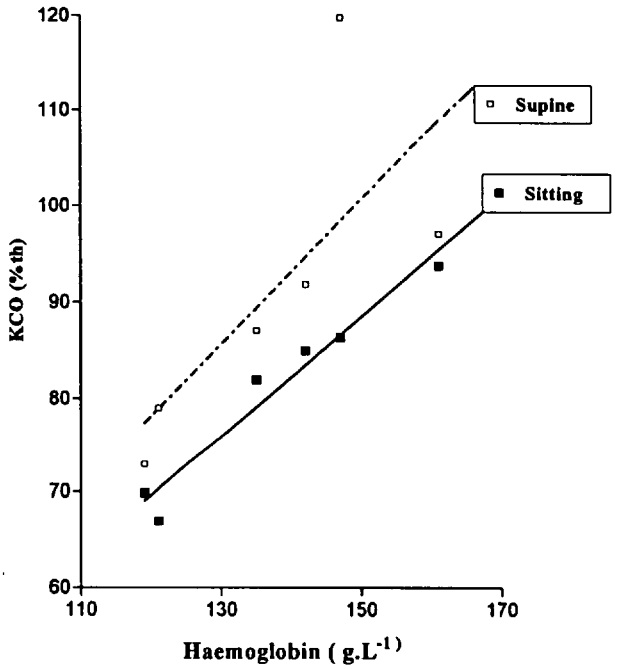

FIGURE 3 KCO versus haemoglobin level before and after normovolaemic haemodilution, at various positions (supine or seated) : individual data and regression lines.

of variable duration, with various inflation levels, in the sitting and in the supine position, enabled us to alter both DLCO and pulmonary perfusion.[21-24] As DLCO was expressed as KCO, the only variable allowed to change was pulmonary perfusion and its distribution. The KCO increase was inversely proportional to the inspiration level (Figure 1). Also, KCO increased slightly when changing from the sitting to the supine position (Figure 3). On the contrary, there was no change in KCO with a change in the breathholding duration in the 5 to 15 sec range (Figure 2), contrary to Riepl's results.[21] We believe that the improvement in CO diffusion that we observed with posture and inspiration level was the result of better filling of the capillary bed, because of a decreased alveolar inflation and a reduced hydrostatic gradient in the supine position. Moreover, modifying the inspiration manoeuvre did not change the KCO and [Hb] relationship after NH. Therefore, NH-induced changes appeared to be the result only of the [Hb] decrease. No compensating change in pulmonary gas exchange could be demonstrated, in spite of the expected rheological improvement of the pulmonary capillary circulation.

Systemic oxygen transport (SO_2T) corresponds to the amount of oxygen delivered to the body in the systemic circulation per unit time, and is calculated as $SO_2T = \dot{Q} \cdot CaO_2$ where $\dot{Q}$ is cardiac output and CaO_2 is arterial oxygen content. Some authors, supporting the clinical use of NH, argued that SO_2T is maintained at its normal level during NH by an increase in cardiac output result-

ing from decreased blood viscosity, thus compensating for a decreased CaO_2. Messmer et al.[2] and Sunder-Plasmann[1], supporting Hint's results,[11] suggested that the optimal SO_2T could be obtained with a haematocrit of 30%. This theoretical concept was supported by global haemobiological measurements which did not take into account the singularity of regional circulations. In particular, these studies referred to haematocrit values measured in the general, systemic circulation, while several authors[12,13] have demonstrated that different haematocrit values can be found in different organs. Rheological microcirculatory studies demonstrated that blood viscosity is lower in vessels smaller than one mm in diameter than in larger vessels, because of an axial arrangement of red cells with a peripheral plasma sheath (the Fahraeus-Linqvist phenomenon). Therefore, the "dynamic" haematocrit observed in such vessels is lower than the "systemic" haematocrit.[22] Fung[25] demonstrated that pulmonary capillary blood flow is unsteady and variable, because of the changing circulatory resistance of the capillary segments, resulting in separate changes in plasma and red cells flows: the plasma flows through the whole capillary network, while red cells are flowing in its less resistive parts. Recently, Johnson and Hsia,[26] discussing the functional recruitment of pulmonary capillaries, termed this mechanism "plasma skimming." Moreover, the stability of blood volume appears to be an essential methodological requirement. In our study, we replaced the subtracted volume of blood by an equal volume of dextran and waited two hours before starting KCO measurements, in order to ensure a relatively steady state with normo- or slightly hypervolaemic conditions.[8] Studies performed in strict normovolaemic conditions demonstrated a decrease in SO_2T.[5–7] Even, with a 12% increase in blood volume, Laks *et al.*[3] found a slight decrease in SO_2T. Therefore, the interpretation of the SO_2T improvement observed by Rosberg[4] should take into account the concomitant 25% increase in pulmonary blood volume.

On the contrary, increasing blood volume should result in increased capillary recruitment that appears to be the main physiological factor for improvement of respiratory exchange and CO transfer.[21] As suggested above, the only result of the increase in cardiac output elicited by NH should be, at the alveolar level, an increase in plasmatic flow. Therefore, oxygen should be involved only in its dissolved fraction, that accounts for no more than 1/30th of the total oxygen transport.

On the other hand, the impaired pulmonary capillary gas exchange capacity that we observed during NH should not preclude the improved oxygen extraction at the tissue level[7] that represents one of the main beneficial effects of NH.

We conclude that respiratory gas exchanges are decreased by NH, even moderate, because of a limitation of the haemoglobin quantity available at the pulmonary capillary level.

Acknowledgments

We thank Hervé Guénard and Kevin Cheeseman for their advices and editorial assistance.

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