Lower pulmonary diffusing capacity in the prone vs. supine posture

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Peces-Barba, G., M. J. Rodríguez-Nieto, S. Verbanck, M. Paiva, and N. González-Mangado. Lower pulmonary diffusing capacity in the prone vs. supine posture. J Appl Physiol 96: 1937–1942, 2004; 10.1152/japplphysiol.00255.2003.—We evaluated the effect of prone positioning on gas-transfer characteristics in normal human subjects. Single-breath (SB) and rebreathing (RB) maneuvers were employed to assess carbon monoxide diffusing capacity (DL CO ), its components related to capillary blood volume (Vc) and membrane diffusing capacity (Dm), pulmonary tissue volume (Vti), and cardiac output (Qc). Alveolar volume (VA) was significantly greater prone than supine, irrespective of the test maneuver used. Nevertheless, DL CO was consistently lower prone than supine, a difference that was enhanced when appropriately corrected for the higher VA prone. When adequately corrected for VA, diffusing capacity significantly decreased by 8% from supine to prone [SB: DL CO cor supine vs. prone: 32.6 ± 2.3 (SE) vs. 30.0 ± 2 ml·min⁻¹·mmHg⁻¹ STPD; RB: DL CO cor supine vs. prone: 30.2 ± 2.2 (SE) vs. 27.8 ± 2.0 ml·min⁻¹·mmHg⁻¹ STPD]. Both Vc and Dm showed a tendency to decrease from supine to prone, but neither reached significance. Finally, there were no significant differences in Vt or Qc between supine and prone. We interpret the lower diffusing capacity of the healthy lung in the prone posture based on the relatively larger space occupied by the heart in the dependent lung zones, leaving less space for zone 3 capillaries, and on the relatively lower position of the heart, leaving the zone 3 capillaries less engorged.

body posture; pulmonary capillary volume; membrane diffusing capacity; heart position

THE IMPROVED GAS EXCHANGE observed in patients with acute lung injury with prone positioning has motivated several studies into the underlying pathophysiological mechanisms (4, 6, 20, 21, 31). In normal human subjects, the effect of supine and prone postures has been investigated on perfusion distribution, on ventilation distribution, and on ventilation-perfusion relationships. Perfusion distribution was found to be more homogeneous prone than supine (19) or similar in both recumbent postures (11, 18). Ventilation distribution was found to be more homogeneous prone than supine (11, 18) or similar in both recumbent postures (26). However, measurements of ventilation-perfusion consistently showed similar distribution between prone and supine postures (17, 18). Taken together, these measurements do not provide a clear-cut physiological basis for potential improvement of gas exchange in the prone vs. supine posture.

Pulmonary diffusing capacity (DL CO ) provides complementary information about the capillary bed in functional contact with ventilated alveoli in either recumbent posture. Its two determinants, membrane diffusing capacity (Dm) and capillary blood volume (Vc), have been seen to be affected by different postural positions with respect to the gravity field. In microgravity, where DL CO was increased by 28%, both Dm and Vc were shown to be significantly increased (23). This was attributable to an extensive capillary recruitment and more uniform capillary filling throughout the lung. By contrast, with a postural change from standing to supine in normal gravity, some degree of heterogeneity between dependent and nondependent lung region persists, only Vc was seen to be increased, and not Dm, for an overall DL CO increase of 15%. This was thought to reflect a larger portion of the lungs in the dependent region with capillaries in zone 3 condition in the supine vs. upright posture (32). Although one might not have expected any modification in diffusing capacity in normal subjects from supine to prone, the present findings show that there is a definite difference, and we speculate how this could affect diffusing capacity in patients with diffuse alveolar disease after prone positioning.

MATERIALS AND METHODS

Fourteen healthy subjects who never smoked were instructed to perform single-breath diffusing capacity maneuvers (SB-DL CO ) and 10 of these 14 subjects also performed a rebreathing diffusing capacity maneuver (RB-DL CO ). The Center Ethical Committee approved the protocol, and all the participants agreed by signing the informed consent. The SB-DL CO maneuver was carried out with two test gas mixtures, one with a high-O2 content and one with a normal-O2 content, to determine the diffusing capacity components Dm and Vc. The RB-DL CO maneuver was performed with only one test gas mixture, from which cardiac output (Qc) and tissue volume (Vti) could also be determined. Each SB-DL CO or RB-DL CO maneuver was performed with the subjects in sitting, supine, and prone postures (the prone posture with shoulders and hips resting on foam cylinders, ensured freely moving abdomen and chest wall). Three valid tests for each maneuver were obtained on each subject in each body posture, separating any two subsequent tests in the same subject by at least 10 min. Tests were performed after we positioned the subject in each posture under study for 3–5 min.

The SB-DL CO maneuver was performed according to the American Thoracic Society standardized SB technique (2) but using CH4 as insoluble inert gas instead of helium. In fact, two test gas mixtures were employed: 0.3% CO, 0.3% CH4, 21% O2, and balance N2 (normal-O2 mixture) and 0.3% CO, 0.3% CH4, 60% O2, and balance N2 (high-O2 mixture). The breathing maneuver involved expiration to residual volume, a vital capacity inspiration of the test gas mixture, and not Dm, for an overall DL CO increase of 15%. This was thought to reflect a larger portion of the lungs in the dependent region with capillaries in zone 3 condition in the supine vs. upright posture (32). Although one might not have expected any modification in diffusing capacity in normal subjects from supine to prone, the present findings show that there is a definite difference, and we speculate how this could affect diffusing capacity in patients with diffuse alveolar disease after prone positioning.

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DIFFUSING CAPACITY IN PRONE POSITION

followed by a 10-s breath hold, and expiration back to residual volume. A continuous fast infrared gas analyzer was used for CO and CH₄ recordings (Cosmed Quark PFT, Rome, Italy) with a response time on both gases <200 ms. A bidirectional digital turbine flowmeter with a flow range of 0.03–20 l/s (Cosmed Quark PFT) was used for volume measurement. After gas and flow calibrations before each experimental session, all calibrated data were collected at 25 Hz during each maneuver. For the diffusing capacity computation, CO and CH₄ concentrations were assessed in a sample volume of 1 liter of the expired volume obtained by discarding the beginning of the expiration until phase II was completely washed out. Calculations of the effective breath-hold time were performed according to specifications by Jones and Mead (12). Finally, Vc and Dm were estimated from diffusing capacity obtained with high- and normal-O₂ test gas mixtures according the method of Roughton and Forster (28). The alveolar partial pressure of O₂ when using a test gas mixture containing 60% O₂ was computed for each test maneuver in each subject and taken into account in the diffusing capacity computations.

For the RB-DLCO maneuver, the test gas mixture contained an inert blood- and tissue-soluble gas (C₂H₂), an inert insoluble gas (Ar), and a hemoglobin-specific gas (CO): 0.9% C₂H₂, 0.3% C¹⁸O, 9% Ar, 21% O₂, and balance N₂. The isotopic C¹⁸O was chosen to allow the recording of CO in the presence of N₂ when using a mass spectrometer (Marquette Gas Analysis, St. Louis, MO). For this maneuver, a rebreathing bag was filled with a volume corresponding to 20% of the subject’s total lung capacity (TLC). After a period of normal air breathing at functional residual capacity, a valve was switched to the rebreathing bag, and the subject emptied and refilled the bag ~10 times within ~20 s. Volume was recorded by a dry-sealed-displacement spirometer (Morgan, UK). For the rebreathing maneuver, data were collected at 100 Hz. From the logarithmic plot of C₂H₂ concentrations (normalized by corresponding Ar concentration), Qc and Vti could be determined according to the method of Sackner et al. (29), including the time 0 correction. The C¹⁸O signal was used for application of the Sackner time 0 correction on Qc and Vti, and direct computation of diffusing capacity.

Because of the measurement maneuver (SB or RB) or intrinsic to postural changes for any given maneuver, diffusion capacity measurements were made at different alveolar lung volumes (VA). Therefore, we accounted for the effect of possible VA differences on diffusion capacity in two different ways. First, we computed the most commonly used KCO as the ratio of DLCO and VA. However, it has been demonstrated experimentally that KCO increases with decreasing VA in the same subject (14). Alternatively, it is possible to obtain a corrected DLCO value (DLCOcorr) by dividing the measured DLCO by a VA-weighted coefficient Z = [2⁻¹f(VA/TLCpred)]⁻¹[1 + 1⁻¹f(VA/TLCpred)], where TLCpred is the predicted TLC for each subject (9). All statistics were done using Statistica 5.5 (StatSoft, Tulsa, OK). Normal distribution of all variables was tested with a Kolgomorov-Smirnov test. Two-way repeated-measures ANOVA [with maneuver (SB or RB) and posture (sitting, supine, or prone) as independent factors] with post hoc Bonferroni adjustment were used for comparison of diffusing capacity measurements obtained on the same 10 subjects. For comparison between sitting, supine, and prone on all parameters, obtained on either 10 or 14 subjects (depending on the maneuver), one-way repeated-measures ANOVA with post hoc Bonferroni adjustment was used. Significance was accepted at P < 0.05.

RESULTS

Anthropometric characteristics and lung volumes for all 14 subjects are summarized in Table 1. Figure 1 represents the diffusing capacity measurements obtained on the 10 subjects performing both the SB and RB maneuver. Figure 1A shows significantly higher DLCO values for the SB than for the RB maneuver across all postures. This maneuver-dependent difference was inverted when simply dividing DLCO by VA, with KCO for RB now being greater than for SB. Finally, Fig. 1C shows a more adequate VA-weighted DLCOcorr, which also retains the same units as DLCO. With the latter VA normalization, any maneuver-dependent DLCO difference for any given body posture totally disappeared.

For the 10 subjects of Fig. 1 who performed both RB and SB maneuvers, the VA corresponding to the SB maneuver averaged 5.21 ± 1.16 (SD) liters (sitting), 5.05 ± 1.18 liters (supine), 5.26 ± 1.32 liters (prone), and the VA corresponding to the RB maneuver were 3.46 ± 0.90 liters (sitting), 3.16 ± 0.80 liters (supine), and 3.56 ± 0.82 liters (prone). A two-way repeated-measures ANOVA on VA in these 10 subjects confirmed significant VA differences between RB and SB maneuvers (P < 0.01 for the RB-SB comparison for any given posture). When VA was compared between postures for any given maneuver, only one VA difference was significant, i.e., between supine and prone for the RB maneuver (3.16 vs. 3.56 ml; P = 0.005). Despite the tendency for a decreased VA in the supine vs. sitting or prone postures, which could have led to an artificially decreased diffusing capacity supine if not appropriately VA corrected. Fig. 1 showed a consistent pattern of greatest DLCO, KCO, and DLCOcorr in the supine vs. both sitting and prone postures.

Table 1. Anthropometric characteristics and lung volumes in the sitting posture

<table>
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<tr>
<th>Subject No.</th>
<th>Gender</th>
<th>Age, yr</th>
<th>Height, cm</th>
<th>Weight, kg</th>
<th>TLC, liters</th>
<th>FRC, liters</th>
<th>VC, liters</th>
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TLC, total lung capacity; FRC, functional residual capacity; VC, vital capacity. *Performed only single breath DLCO maneuver.
Table 2 displays all SB- and RB-derived variables obtained on all 14 (SB) and 10 (RB) subjects in the sitting, supine and prone postures. First, the SB data in Table 2 show an expected pattern of a significantly increased diffusing capacity, capillary volume, and Qc supine vs. sitting. Second, the SB data in Table 2 confirm the significantly decreased diffusing capacity prone vs. supine as depicted in Fig. 1. This is true when considering DLCO (P = 0.002) and is reinforced, in the presence of a significant VA increase from supine to prone, by a similar DLCO corr decrease from supine to prone (P < 0.001). Of the DLCO components, Vc and Dm, which both showed a tendency to decrease, neither showed a significant decrease. The RB measurements showed essentially similar results in that DLCO corr was significantly decreased prone with respect to supine. However, because the VA difference between the two postures was relatively greater for the RB than for the SB maneuver (Table 2), the greater VA prone was associated with a greater uncorrected DLCO so that the difference in DLCO between supine and prone no longer reached significance. Finally, the RB data in Table 2 show a marked Qc increase from sitting to supine but no change in Qc or Vt prone vs. supine.

**DISCUSSION**

**Upright vs. supine.** The transition from upright to the supine posture caused DLCO to rise by 8 and 14%, respectively, with the SB-DLCO and RB-DLCO maneuvers (Fig. 1). These changes are in line with earlier observations of a 15% SB-DLCO increase in four healthy subjects upright to supine (23) or a 10% RB-DLCO increase in six male subjects (15) and consistent with a picture of recruitment of lung capillary bed on transition from upright to supine. Accordingly, our observations of an increased Vc without Dm change (Table 2) is also in line with observations by others (23). Nevertheless, a number of other studies had displayed marked intersubject variability in postural dependence of DLCO (13, 22), and several confounding factors in the DLCO response to postural change have been identified: age (5, 30), alterations in the capillary bed (8), and mean pulmonary arterial pressure (7). In particular, an in-
increased rigidity of lung capillaries attenuates the $D_{LCO}$ increase from upright to supine (5, 30), and $D_{LCO}$ was shown to only increase from upright to supine in subjects with normal mean pulmonary arterial pressure (7). Finally, the lack of Vc increase from upright to supine has been indicated as a sign of the presence of microangiopathy involving pulmonary small vessels bed (8). In summary, only in healthy subjects with a normal vascular bed do we expect a clear-cut $D_{LCO}$ increase from upright to supine, which is then directly attributable to gravity-dependent preferential filling of capillaries in the dependent lung regions.

Supine vs. prone. The transition from supine to the prone posture caused diffusing capacity to be lower, and, when appropriately corrected for a greater $V_A$ in the prone vs. the supine posture, the resulting $D_{LCO,corr}$ decrease was 8%, with use of either the SB or RB maneuver (Fig. 1). This result contrasts with the absence of change in volume-corrected diffusing capacity between supine and prone postures published by Rohdin et al. (27) at the time of writing. Our Table 2 provides a hint that the relatively greater $V_A$ changes associated with the RB than with the SB maneuver could indeed be responsible for this discrepancy between our corrected diffusing capacity and theirs. Rohdin et al. performed a linear $V_A$ correction method based on data by Stam et al. (30) in the $V_A$ range between 50 and 100% TLC. However, a linear correction leads to increasing underestimation of actual corrected diffusing capacity as $V_A$ drops further below 50% TLC (i.e., greater underestimation of corrected $D_{LCO}$ supine than prone). This could explain the discrepancy between our corrected $D_{LCO}$ results supine vs. prone and those in Rohdin et al. (27) where $V_A$ was presumably well below 50% TLC for the subjects under study. Unfortunately, $D_{LCO}$ measurements were unavailable in the upright posture (27), which could have enabled further comparison of both $V_A$ correction methods. The fact that totally independent breathing maneuvers RB and SB, performed on independent calibrated setups, yield the same $D_{LCO,corr}$ on our 10 subjects (Fig. 1) does provide us with a reasonable confidence that there is a true postural effect on diffusing capacity between prone and supine.

The SB diffusing capacity decrease was paralleled by a tendency to a decreased $Dm$ and $Vc$, although neither reached significance (Table 2). The use of 60% $O_2$ in the high-$O_2$ mixture test gas could have been responsible for a wider dispersion of the $Dm$ and $Vc$ values. Nevertheless, the differential $Dm$ and $Vc$ behavior on transition from upright to supine, which confirmed experimental observations by others (13), indicates that we could reliably measure these $D_{LCO}$ components. Possibly, the observed $D_{LCO}$ changes between supine and prone were too small to obtain a statistically significant differentiation between $Dm$ and $Vc$ behavior.

The posture-dependent change in $D_{LCO}$ between supine and prone was of the same order of magnitude as that observed on transition from sitting to supine, although both gravity-dependent pressure gradients as well as conformational changes are expected to behave very differently on moving from upright to supine as opposed to from supine to prone. If the gravity-dependent pressure gradient and its effect on capillary filling were the only determinant of overall $D_{LCO}$, the similar lung height between supine and prone postures would not a priori predict a $D_{LCO}$ difference between these two recumbent postures. However, a more detailed inspection of the conformational arrangement of lung zones with respect to the heart in either recumbent body posture could provide some explanation for the present findings.

Figure 2 shows the lung contours drawn from typical computed tomography slices at the level of the heart, obtained by Albert and Hubmayr (1) in a normal subject supine (A) and prone (B). Icons representing zone 1, 2, and 3 capillary filling (31) were drawn on dependent and nondependent lung zones within these contours. Because the purpose of the Albert and Hubmayr study was to assess the area of the lungs situated under and compressed by the heart, this study reported no quantification of the proportion of lung volume in dependent vs. nondependent lung regions in either posture (above or below the horizontal dotted line in Fig. 2 for the sake of simplicity). However, inspection of the computed tomography images clearly indicate that the space occupied by the heart and the shape it is taking in the prone vs. supine posture, leads to significantly less lung volume in the dependent lung zone available for zone 3-type capillaries. In addition, the vertical position of the heart in the line of gravity is at the level of the dependent lung zone in the prone posture, whereas in the supine posture the heart is situated well above the level of the dependent region. Hence, the larger number of blood capillaries in the dependent regions of the supine subject is expected to also be more engorged than in the prone posture. Both these effects could have contributed to a higher diffusing capacity in the supine vs. the prone posture.

In recent years, animal studies have emerged to suggest the presence of important intraregional perfusion heterogeneities in the mammalian lung (16). Any such heterogeneities in normal human subjects are expected to occur in addition to the
long-established interregional perfusion differences between the top and bottom of the lungs (32). Even the most recent electron beam computed tomography data obtained by Jones et al. (11) clearly show a greater perfusion in dependent lung regions of healthy human subjects both in prone and supine postures. The single-photon-emission computed tomography perfusion images in Nyren et al. (19) also show that perfusion is generally higher in lung units of the dependent zone in either prone or supine postures but that there is simply less of the lung volume in the dependent zone when normal human subjects are prone. In this respect, the interregional model of perfusion heterogeneity superimposed on the lung conformation supine and prone (Fig. 2) is compatible with the lower DLCO we observed in the prone posture. To what extent interregional perfusion heterogeneities could contribute to the explanation of the observed DLCO differences between the prone and supine posture in the normal human lung is as yet obscure.

Qc did not change significantly between prone and supine postures (Table 2). A previous study in normal subjects has shown how any potential change in cardiac index between supine and prone posture is so crucially dependent on the shape of the physical support for the prone posture, with a flat surface leading to no change and a convex surface to a decreased cardiac index in the prone posture (33). These authors speculated that the decreased cardiac index when prone could be due to the mechanical impact of the physical support on the chest. A recent study in normal subjects (25) found a decreased stroke volume in the prone vs. supine posture and also attributed this to a mechanical compression of the thorax. In patients with acute lung injury, placed prone with the entire body in contact with the bed, Blanch et al. (4) did not observe any significant changes in Qc between supine and prone postures.

Despite the absence of significant change between Qc supine vs. prone, there was a tendency to a decreased Qc in the prone posture accompanying the decreased DLCO in that posture. Taken together with the increase of both DLCO and Qc from sitting to supine (Table 2), it is tempting to suggest that there is a relationship between DLCO and Qc. Hsia et al. (10) have previously observed linear correlations between DLCO and Qc by comparing normal subjects at rest and during exercise (derived from data with Qc ranging 5 to 30 l/min). We can apply their proposed physiological explanations for a causal relationship between DLCO and Qc to the prone and supine postures as follows: if Qc were larger supine, this would increase Vc, which would indeed affect the Vc component of DLCO. If distribution of red cell transit time is more evenly distributed due to a larger Qc supine, both Vc and Dm components of DLCO would be affected. This alternative explanation of increased Qc as the underlying reason of a greater DLCO supine still requires a reason why Qc should be increased in the supine posture. We speculate that this could be linked to the larger number of more engorged capillaries supine, due to the proposed conformational changes in terms of the space and location occupied by the heart in supine and prone postures.

The lower diffusing capacity prone than supine is in apparent contradiction with a potential for gas-exchange improvement in the prone posture, at least in normal subjects. However, in those patients with adult distress respiratory syndrome in whom diffuse alveolar disease occurs, the posture that puts the largest portion of Vc in dependent lung zones would increase the level of shunt and would show the worst gas exchange. In this sense, we speculate that the prone posture with a relatively lower portion of the lungs in the dependent zone is expected to effectively decrease the portion of the lungs subject to shunt. Other authors have suggested mechanisms of how redistribution of blood flow away from unventilated areas to regions with normal ventilation-perfusion ratios or recruitment of previously atelectatic regions (4, 20) could be responsible for an improved arterial oxygenation. Considering also studies in patients with unilateral disease, the general idea of positioning the healthy portion of the lung in the dependent position appears to be widely accepted (3, 24). Obviously, those patients with adult respiratory distress syndrome with a disease pattern predominantly in the dorsal region when supine will also benefit from positioning the healthy portion in the most perfused lung zone, even if this implies that a smaller volumetric portion of the total lung is dependent in that posture. As pointed out by Blanch et al. (4), the beneficial effect of prone positioning depends on the progression (and concomitant distribution) of the disease, and the above arguments should be considered accordingly.

Critique of the diffusing capacity measurement method. The use of both RB and SB washout techniques to assess diffusing capacity was done to make sure that the outcome was not due to possible artifacts from the DLco measurement maneuver or lung volume. Indeed, VA was significantly greater in the prone vs. supine posture, irrespective of whether SB or RB maneuver was used (Table 2). As the different panels of Fig. 1 illustrate, the simple division of DLCO by VA is inappropriate (B), and only a slightly more complex VA normalization to obtain a DLCOcorr abolishes the difference in diffusing capacity obtained with either maneuver (C). In view of future diffusion capacity measurements in adult respiratory distress syndrome patients prone and supine, such a VA normalization may be particularly relevant when assessing the intrinsic diffusion properties of the gas-blood barrier.

In conclusion, we interpret the lower diffusing capacity in the prone posture as a consequence of the relative heart position in the thorax, changing from top when supine to bottom when prone. In the latter posture, the space occupied by the heart occurs at the expense of a lesser portion of the alveolar blood capillaries in zone 3 condition in the dependent lung zone. In addition, these zone 3 capillaries are also less engorged because of a smaller difference in vertical distance between the heart and the dependent lung in the line of gravity in the prone posture.

GRANTS

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