Red cell distribution and the recruitment of pulmonary diffusing capacity

CONNIE C. W. HSIA,1 ROBERT L. JOHNSON, JR.,1 AND DIPEN SHAH2
1Department of Medicine, University of Texas Southwestern Medical Center, Dallas 75235; and 2HLA Engineers Incorporated, Dallas, Texas 75206

Hsia, Connie C. W., Robert L. Johnson, Jr., and Dipen Shah. Pulmonary diffusing capacity and the recruitment of pulmonary diffusing capacity. J. Appl. Physiol. 86(5): 1460–1467, 1999.—The distribution of red blood cells in alveolar capillary segments is typically nonuniform, as shown by intravital microscopy and in alveolar tissue fixed in situ. To determine the effects of red cell distribution on pulmonary diffusive gas transport, we computed the uptake of CO across a two-dimensional geometric capillary model containing a variable number of red blood cells. Red blood cells are spaced uniformly, randomly, or clustered without overlap within the capillary. Total CO diffusing capacity (DLCO) and membrane diffusing capacity (DmCO) are calculated by a finite-element method. Results show that distribution of red blood cells at a fixed hematocrit greatly affects capillary CO uptake. At any given average capillary red cell density, the uniform distribution of red blood cells yields the highest DmCO and DLCO, whereas the clustered distribution yields the lowest values. Random nonuniform distribution of red blood cells within a single capillary segment reduces diffusive CO uptake by up to 30%. Nonuniform distribution of red blood cells among separate capillary segments can reduce diffusive CO uptake by >50%. This analysis demonstrates that pulmonary microvascular recruitment for gas exchange does not depend solely on the number of patent capillaries or the hematocrit; simple redistribution of red blood cells within capillaries can potentially account for 50% of the observed physiological recruitment of DLCO from rest to exercise.

pulmonary diffusing capacity; membrane diffusing capacity; capillary model; finite-element analysis

IT IS KNOWN THAT PULMONARY diffusing capacity progressively increases about two- to threefold from rest to exercise without reaching an upper limit, even as peak exercise is approached (2, 12). It is unclear from where these large reserves of diffusing capacity arise from rest to exercise. It is known that with exercise the increase in lung volume and the number as well as volume of patent capillaries can augment pulmonary gas transfer (3, 18). In addition, our group and other investigators (1, 6, 10, 11, 19) have shown that physical properties of the red blood cell (RBC) can also alter the diffusive process in important ways. Utilizing a finite-element analysis and principles of heat exchange, we simulated the diffusive uptake of CO in the lung (DLCO) across a geometric model of a pulmonary capillary segment and used this analysis to validate the conceptual framework underlying the physiological and morphometric techniques of estimating DLCO as well as its components: membrane diffusing capacity (DmCO) and capillary blood volume (10). We found that DmCO and, hence, DLCO are sensitive to changes in the spacing of RBCs within the capillary, i.e., capillary hematocrit (10), as well as to changes in red cell shape (11). As spacing intervals between red cell centers increase, effective capillary surface area for diffusive gas exchange decreases; hence, DLCO and DmCO per unit capillary segment length should decrease. The relationship between DLCO of a capillary segment and the spacing intervals between red cell centers is such that changing spacing intervals between red cell centers has a greater effect on DLCO at a low hematocrit than at a high hematocrit (10, 11). Consequently, for a given capillary segment length containing a fixed number of RBCs, the decrease in DLCO caused by an increase in the spacing between red cell centers in one region of the capillary will not be completely compensated by a corresponding decrease in the spacing in another region in the absence of any change in red cell numbers. The potential effect of uneven distribution of RBCs within and among open capillaries on DLCO has never been examined.

Because of the above observations we ask the question: How much of the increase in DLCO from rest to exercise can be explained by improving the uniformity of red cell distribution within and among already patent pulmonary capillaries in the absence of any structural change in the capillary bed? We hypothesize that, for a fixed average red cell density, uneven spacing will significantly impair diffusive gas exchange, relative to uniform spacing. This is an important issue that is difficult to address by physiological studies but that can be approached from a theoretical standpoint. In the present study, we utilized the same geometric model and finite-element analysis as described previously (10) to determine the possible magnitude by which nonuniform red cell distribution can alter diffusive uptake of CO across the lung.

METHODS

Geometric model. The capillary model consists of a cross-section (thickness 1 µm) through the long axis of a pulmonary capillary segment (length 90 µm). The capillary segment was divided into 12 equal pockets; each pocket can accommodate one circular-shaped RBC (diameter 7.5 µm). One to twelve RBCs are placed single-file within the capillary in different distributions: uniformly spaced (equal distance between neighboring red cell centers), randomly spaced (unequal distance between neighboring red cell centers), or clustered (distance between adjacent RBC centers = 7.5 µm and lateral RBC membranes touch one another) (Fig. 1). Adjacent RBCs do not overlap. Dimensions and constants employed (7, 9, 15) are listed in Table 1.
Finite-element analysis. Analysis using the finite-element method (FEM) was performed on the entire 90-µm capillary. We assume an infinite reservoir of CO in the alveolar air space. The RBCs represent infinite sinks for CO \( [\text{partial pressure of CO (PCO)}] \) within RBCs \( [\text{specific rate of CO uptake by RBCs (} u_{\text{CO}})\] \). The red cell component of CO uptake, including reaction with hemoglobin \( [1/\text{RBC}] \), is modeled as a resistance to CO diffusion across a thin red cell membrane; the resistance is varied in accordance with the assumed alveolar O2 tension (in mmHg) to accurately mimic the values of \( u_{\text{CO}} \) measured by Holland et al. (9) in dog RBCs at 39°C.

\[
\frac{1}{\theta_{\text{CO}}} = 0.929 + 0.0042 \text{PO}_2 \tag{1}
\]

We assume that the flux of CO is due entirely to tension gradients of CO driving CO diffusion into RBCs and that CO tension gradients reach steady state immediately. Diffusive transport is described by the Laplace equation

\[
|\alpha D_{\text{C0}} \nabla^2 \text{PCO}| = 0 \tag{2}
\]

where \( \alpha \) is Bunsen solubility coefficient in lung tissue and plasma \( (\text{mmHg}^{-1}) \); \( D_{\text{C0}} \) is diffusion coefficient (\( \mu m^2/s \)); \( \text{PCO} \) is in mmHg; and \( \nabla \) is gradient operator \( (i \partial /\partial x + j \partial /\partial y + k \partial /\partial z) \) (\( \mu m^{-1} \)).

The boundary conditions are that \( \text{PCO} = 1 \) mmHg in the alveolar phase 5 µm above the air-tissue interface and \( \text{PCO} = 0 \) mmHg at the inner membrane surface of the RBCs. Because RBCs may not be equally spaced and, hence, the capillary model may not be symmetrical, we analyzed the entire capillary segment for each asymmetric distribution. The model is divided into 3,724 connecting quadrilateral and triangular elements and 3,805 nodal points, each with its own respective diffusion properties in air, tissue, and plasma (Fig. 2, A and B). Through this discretization process, Eq. 2 is transformed into 3,381 simultaneous algebraic equations (excluding boundary constraints) from which the \( \text{PCO} \) at each nodal point can be solved in the same manner as described previously (10). The matrix equation has the form

\[
\{D|\theta| = \text{flux}\} \text{ or } \{\text{Diffusive properties}|\theta_{\text{CO}}| = \text{CO flux}\} \tag{3}
\]

Once the distribution of \( \text{PCO} \) is determined, the diffusive flux of CO for each element is computed as

\[
\text{CO flux (} \mu m/s) = \alpha D_{\text{CO}} \frac{\partial \text{PCO}}{\partial n} \tag{4}
\]

where \( \partial \text{PCO}/\partial n \) denotes \( \text{PCO} \) gradients evaluated along the normal direction from a constant \( \text{PCO} \) surface. The total CO flow, equivalent to \( D_{\text{CO}} \) of each typical region, is obtained by

<table>
<thead>
<tr>
<th>Table 1. Dimensions and constants of capillary model</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Length of capillary segment</strong></td>
</tr>
<tr>
<td><strong>Alveolar septal thickness</strong></td>
</tr>
<tr>
<td><strong>Thickness of tissue barrier</strong></td>
</tr>
<tr>
<td><strong>Internal capillary diameter</strong></td>
</tr>
<tr>
<td><strong>RBC diameter</strong></td>
</tr>
<tr>
<td><strong>Thickness of RBC membrane</strong></td>
</tr>
<tr>
<td><strong>PACO</strong></td>
</tr>
<tr>
<td><strong>CO diffusion coefficient in air</strong></td>
</tr>
<tr>
<td><strong>D_{\text{CO}} tissue and D_{\text{CO}} plasma</strong></td>
</tr>
<tr>
<td><strong>Bunsen solubility coefficient</strong></td>
</tr>
<tr>
<td><strong>( \theta_{\text{CO}} ) (at 80 Torr)</strong></td>
</tr>
<tr>
<td><strong>( \theta_{\text{CO}} ) (at 560 Torr)</strong></td>
</tr>
</tbody>
</table>

RBC, red blood cell; PACO, alveolar CO tension; \( D_{\text{CO}} \), diffusion coefficient of CO; \( u_{\text{CO}} \), specific rate of gas uptake by RBCs. *Values taken at a temperature of 39°C. †Assuming \( 5.1 \times 10^9 \) RBCs per ml of blood.
summing the flow along the boundary surface of air-tissue barrier for all the elements

\[ D_{\text{LCO(FEM)}} = \sum \text{flow} = \frac{\sum \text{flux} \cdot \Delta \text{(area)}}{P_{\text{ACO}}} \] (5)

where \( P_{\text{ACO}} \) is the alveolar \( P_{\text{CO}} \) at the air-tissue interface. For symmetric distributions, a typical repeating unit is analyzed as above. The \( D_{\text{LCO}} \) of the entire capillary segment is obtained by multiplying \( D_{\text{LCO}} \) of a typical unit by the number of repeating units in the geometric model. The membrane diffusing capacity, \( D_{\text{mCO(FEM)}} \), is computed as

\[ D_{\text{mCO(FEM)}} = \frac{\text{Total CO flow}}{\left( P_{\text{ACO}} - \text{mean } P_{\text{CO}} \text{ over outer surface of RBC membrane} \right)} \] (6)

A commercial software package (ANSYS 5.3) was employed for this analysis. We computed \( D_{\text{LCO}} \) for different numbers of RBCs per capillary segment and at two different alveolar \( O_2 \) tensions (80 and 560 mmHg). Interaction at the ends of the capillary model was accounted for by joining the ends in a loop.

RESULTS

Effect of RBC distribution on diffusing capacity within a 90-µm capillary. The pattern of CO flux over the red cell surface is shown in examples of a uniform, nonuniform random, and clustered distribution in Fig. 3, A-C. The magnitude of flux is represented by the length of the vector. Figures 4 and 5 show the effect of red cell distribution on \( D_{\text{mCO}} \) and \( D_{\text{LCO}} \), respectively. At a given red cell density, the uniform distribution yields the highest values, whereas the clustered distribution yields the lowest. Other nonuniform distributions yield intermediate results. The magnitude of the effect of cell distribution on \( D_{\text{LCO}} \) is shown in Fig. 6. A simple rearrangement of RBCs at a given red cell density within a single capillary segment can change \( D_{\text{LCO}} \) by up to 33%. Red cell distribution has the greatest effect on \( D_{\text{LCO}} \) when there are between three and seven cells
per capillary segment, corresponding to a hematocrit of 18–43%.

Estimation of DLCO for capillaries with uneven RBC spacing. The estimation of DLCO by finite-element analysis in a capillary with uniformly spaced RBCs is simplified by symmetry. Because of the symmetry of the model and flux distributions, finite-element analysis is required on only one quadrant of an RBC to describe the entire capillary. Using the results obtained assuming uniform spacing of RBC at different hematocrits, we calculated the relationship of DLCO per unit capillary segment length between red cell centers and spacing intervals, as shown in Fig. 7.

Assuming there is no interaction between CO fluxes generated on either side of unequally spaced RBCs, data from Fig. 7 can be used to approximate DLCO of a

---

**Fig. 4.** Relationship of total membrane diffusing capacity for CO (DMCO) (A) and DMCO per RBC (B) to no. of RBCs arranged in the different distributions. FEM, finite-element method. At any given red cell no., uniform distribution yields the highest and clustered distribution the lowest DMCO; other random nonuniform distributions yield intermediate results.

**Fig. 5.** Relationship of total lung diffusing capacity for CO (DLCO) (A) and DLCO per RBC (B) to no. of RBCs arranged in the different distributions. At any given red cell no., uniform distribution yields the highest and clustered distribution the lowest DLCO; other random nonuniform distributions yield intermediate results.
capillary with uneven red cell spacing intervals and compared with the DLCO in a capillary containing the same number of uniformly distributed RBCs. For example, for a 90-µm capillary segment containing four RBCs with uneven spacing intervals of 7.5, 22.5, 7.5, and 52.5 µm, the DLCO would be the sum of the products of each (spacing interval) \( \times (\text{the corresponding DL/µm}) \), based on the data in Fig. 7, i.e. \( (2 \times 7.5 \times 0.0511) + (22.5 \times 0.0260) + (52.5 \times 0.0115) = 1.955 \mu m^3 \cdot min^{-1} \cdot mmHg^{-1} \). For the same number of RBCs with uniform spacing of 22.5 µm, DLCO would be given by \( (4 \times 22.5 \times 0.0260) = 2.34 \mu m^3 \cdot min^{-1} \cdot mmHg^{-1} \). By this comparison, efficiency of CO uptake would be reduced 16.5% by the nonuniform RBC distribution.

On the other hand, if significant interaction between CO fluxes generated on either side of unequally spaced RBCs develops, errors may result in this comparison. To determine the magnitude of this potential error, we carried out finite-element analysis on 12 sets each of representative random distributions of three, six, and nine RBCs in a 90-µm capillary at O2 tensions of 80 and 560 Torr (a total of 72 comparisons). The resultant comparison (Fig. 8) of DLCO, obtained by direct analysis of nonuniformly distributed RBCs and corresponding indirect estimates made by using the data in Fig. 7, demonstrates a correlation so close to the line of identity that we can neglect this potential source of error. Hence, all of our subsequent analyses of the effects of nonuniform red cell spacing on diffusive uptake of CO are based on data from Fig. 7.

Effect of RBC distribution among five 90-µm capillary segments. Data from a single capillary segment were extended to estimate the effect of random distributions of a selected number of RBCs among five separate capillary segments of the same dimension. The generation of random red cell distributions within a given capillary and among separate capillaries is described in detail in the APPENDIX. Results of finite-element analysis are shown in Fig. 9. For a given total number of RBCs, improvement in the uniformity of cell distribution among five capillary segments significantly increased total DLCO. Capillary hematocrit in the lung has been estimated to lie between 60 and 90% of that in the peripheral circulation (16); hence, for this model, physiological hematocrit would be reflected by between 20 and 35 RBCs distributed among five 90-µm long capillaries. The potential increase in DLCO that could be explained by improving the uniformity of RBC distribution from clustered to uniform spacing within and among these capillaries would range from 30 to 50%. More than one-half of this increase could be explained by a change from random spacing to uniform spacing.

**DISCUSSION**

Summary of findings. The present theoretical analysis provides the first quantitative evidence that uneven distribution of RBCs at a fixed hematocrit or red cell

---

**Fig. 6**. Magnitude of possible increase in DLCO by redistributing a given no. of RBCs within a capillary segment from a clustered to a random distribution and from a random to a uniform distribution.

**Fig. 7**. Relationship between DLCO per micrometer of capillary length (vertical axis) and distance between red cell centers when RBCs are uniformly distributed in capillary.

**Fig. 8**. Comparison of DLCO (µm³·s⁻¹·mmHg⁻¹) calculated by 2 methods for a capillary containing a random distribution of RBCs: indirectly from data for uniform distributions in Fig. 7 or directly, by finite-element analysis, of entire capillary.
density significantly affects diffusive uptake of CO in pulmonary capillaries. For a given red cell density, uniform spacing of RBCs is associated with a higher \( D_{mCO} \) and \( D_{LCO} \) than is nonuniform spacing; clustering of cells is associated with the lowest \( D_{mCO} \) and \( D_{LCO} \). The magnitude of this effect is influenced by the average red cell density, being greatest at a density equivalent to a capillary hematocrit of 18%. Simple rearrangement of RBCs within a single capillary segment can change \( D_{LCO} \) by up to 33%. For a given red cell number, improvement in the uniformity of RBC distribution among five separate patent capillary segments can potentially increase \( D_{LCO} \) by over 50%. In the physiological range of capillary hematocrit ranging from 25 to 43% (equivalent to between 25 and 35 RBCs, respectively, distributed among five 90-µm capillaries), improvement in red cell distribution from a clustered to a uniform pattern could increase \( D_{LCO} \) by 30–50%.

Effect of red cell characteristics on diffusing capacity. The particulate nature of RBCs leads to an inherently nonuniform distribution of hemoglobin that creates a mismatch between the gas-exchange surfaces of the red cell and the septal tissue. Distribution of RBCs within capillaries is determined by various factors, including the physical properties of RBCs and the capillary network, local flow dynamics, as well as the sequestration of capillary leukocytes (14). Changes in the static and dynamic properties of RBCs can alter diffusive gas exchange in important ways. For instance, in isolated perfused rabbit lungs, diffusing capacity for \( O_2 \) (\( D_{LCO} \)) is lower when the lung is perfused with red cell suspensions than with hemoglobin solutions (6), suggesting that a uniform distribution of hemoglobin facilitates \( O_2 \) uptake. A decrease in the deformability of RBCs in isolated rabbit lungs reduces \( D_{LCO} \) (1). This effect may be due to a thicker unstirred layer around undeformed RBCs flowing at low velocities; the unstirred layer is thinner around deformed RBCs flowing at higher speed because of better mixing. Alternatively, the loss of red cell deformability may also lead to a nonuniform distribution of capillary flow resistance, resulting in nonuniform regional hematocrits (17). The deleterious effect of deformation on diffusive uptake may be offset by the simultaneous improvement in hydrodynamics of the deformed cells, which might lead to greater homogeneity in the distribution of capillary RBCs. These opposing effects highlight the complex structure-function interaction between the red cell and the capillary network, complicating the interpretation of physiological data.

Wang and Popel (19) simulated the deformation of RBCs from a circular to parachute shape and reported that deformation results in a 26% decline of \( O_2 \) flux, the effect being inversely related to the capillary transit time of the red cell. We reached a similar conclusion by finite-element analysis of CO flux in a geometric model of the pulmonary capillary containing circular or parachute-shaped RBCs (11). We found that the lower \( D_{LCO} \) associated with parachute-shaped RBCs is due to a more heterogeneous distribution of CO flux over the red cell surface, and the effect is greater as capillary red cell density is reduced. Thus, in addition to capillary red cell volume, the mean spacing between adjacent RBCs, the geometry of the RBC, and regional red cell distribution are all important factors that affect \( D_{LCO} \).

Red cell distribution and recruitment of diffusing capacity. From rest to exercise there is a nearly twofold increase of \( D_{LCO} \) in a linear relationship with respect to cardiac output (2, 13). Up to peak exercise, there is no evidence of an upper limit being reached in this relationship, indicating the existence of large physiological reserves in diffusing capacity. It is believed that recruitment of diffusing capacity reserves occurs because the increased pulmonary perfusion opens previously collapsed capillaries and distends patent capillaries, resulting in a higher pulmonary capillary blood volume as well as a larger red cell-endothelial interface for diffusion. In highly aerobic animals that possess a large splenic reservoir of blood, i.e., horses and dogs, autotransfusion by splenic contraction is an additional factor that further augments \( D_{LCO} \) on exercise by increasing total blood volume and hematocrit (20). Theoretical analyses suggest that an increase in capillary hematocrit from 10 to 50% can potentially increase \( D_{LCO} \) and \( D_{LDO} \) more than threefold (5, 10). Although it has been suggested that a more uniform regional red cell distribution may also contribute to increasing \( D_{LCO} \) during exercise, this effect has not been previously demonstrated. At rest, red cell distribution among pulmonary capillaries is markedly heterogeneous; there is a wide range of transit times through the capillary bed (8, 16). As perfusion increases, both the mean and the relative dispersion of red cell transit time distribution decrease, suggesting a more homogeneous red cell distribution, which mitigates the decline in mean red cell transit time and maintains a minimum transit time just above the theoretical threshold required for complete saturation with \( O_2 \) (16). The improved homogeneity of red cell distribution can potentially augment
DLCO by another 30–50% without further change in the number of perfused capillaries.

We thus conclude that changes in the distribution pattern of capillary RBCs can account for a large component of the recruitment in DLCO observed physiologically from rest to exercise.

**APPENDIX**

How a Random Distribution of Cells Is Defined Within a Single Capillary

We define a random distribution of red cells within and among capillaries the same as the spatial distribution of particles in statistical mechanics. Space is subdivided into small pockets or cells; assumptions are made about the relative probability of a pocket being filled, whether particles and pockets are distinguishable, and how many particles can exist in the same pocket. We assume the following.

1. A 90-µm capillary is subdivided into 12 pockets, the width of each is the diameter of a red cell (7.5 µm). The capillary is circularized to eliminate discontinuities at the ends.
2. Each pocket has an equal probability of being occupied.
3. RBCs are indistinguishable from one another.
4. Pockets are distinguishable from one another only by occupancy or lack of occupancy.
5. No more than one RBC can occupy a pocket at a given time.
6. Multiple capillaries are distinguishable only if occupancy patterns are different.

The random distribution of a given number of RBCs ($q$) in $n$ pockets follows a Fermi-Dirac statistic (4). The number of possible ways ($N$) that $q$ cells can be arranged in 12 pockets is given by

$$N = \frac{12!}{q!(12 - q)!} \quad (A1)$$

The spacing interval between cell centers is by definition discrete, i.e., multiples of the red cell diameter (7.5 µm); hence, cell centers in adjacent pockets are one diameter unit apart (7.5 µm); red cell centers separated by one empty pocket are two diameter units apart (15 µm), etc. The sum of (total spacing units × 7.5 µm) in a given arrangement of RBCs must equal the length of the capillary (90 µm). Thus, in the example of four RBCs distributed randomly in 12 pockets (Fig. 1, middle), there are two spacing intervals of one diameter unit, one of three diameter units, and one of seven diameter units, i.e., $(1 + 1 + 3 + 7) \times 7.5 = 12 \times 7.5 = 90$ µm. The total number of permutations of this specific combination (C) of spacing intervals is

$$C = \frac{12 \times (q - 1)!}{2!1!1!} \quad (A2)$$

The factorial in the denominator derive from the fact that one spacing interval is present twice and the remaining two

**Table 2. Possible combinations of cell occupancy; an example of $q = 30$ cells and $n = 5$ capillaries**

<table>
<thead>
<tr>
<th>Combination</th>
<th>$n_1$</th>
<th>$n_2$</th>
<th>$n_3$</th>
<th>$n_4$</th>
<th>$n_5$</th>
<th>$D_1$</th>
<th>$D_2$</th>
<th>No. of Permutations</th>
<th>Probability</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>12</td>
<td>12</td>
<td>6</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>2</td>
<td>30</td>
<td>1/17,151</td>
</tr>
<tr>
<td>2</td>
<td>12</td>
<td>12</td>
<td>5</td>
<td>1</td>
<td>0</td>
<td>2</td>
<td>0</td>
<td>60</td>
<td>2/17,151</td>
</tr>
<tr>
<td>3</td>
<td>12</td>
<td>12</td>
<td>4</td>
<td>2</td>
<td>0</td>
<td>2</td>
<td>0</td>
<td>60</td>
<td>1/17,151</td>
</tr>
<tr>
<td>4</td>
<td>12</td>
<td>12</td>
<td>4</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td>2</td>
<td>30</td>
<td>1/17,151</td>
</tr>
<tr>
<td>5</td>
<td>11</td>
<td>11</td>
<td>9</td>
<td>5</td>
<td>3</td>
<td>2</td>
<td>0</td>
<td>120</td>
<td>2/17,151</td>
</tr>
<tr>
<td>6</td>
<td>11</td>
<td>11</td>
<td>9</td>
<td>4</td>
<td>4</td>
<td>2</td>
<td>2</td>
<td>60</td>
<td>1/17,151</td>
</tr>
<tr>
<td>7</td>
<td>11</td>
<td>11</td>
<td>9</td>
<td>4</td>
<td>2</td>
<td>4</td>
<td>2</td>
<td>60</td>
<td>1/17,151</td>
</tr>
<tr>
<td>8</td>
<td>11</td>
<td>11</td>
<td>9</td>
<td>4</td>
<td>2</td>
<td>4</td>
<td>2</td>
<td>60</td>
<td>1/17,151</td>
</tr>
<tr>
<td>9</td>
<td>11</td>
<td>11</td>
<td>9</td>
<td>4</td>
<td>2</td>
<td>4</td>
<td>2</td>
<td>60</td>
<td>1/17,151</td>
</tr>
<tr>
<td>10</td>
<td>11</td>
<td>11</td>
<td>9</td>
<td>4</td>
<td>2</td>
<td>4</td>
<td>2</td>
<td>60</td>
<td>1/17,151</td>
</tr>
<tr>
<td>11</td>
<td>11</td>
<td>11</td>
<td>9</td>
<td>4</td>
<td>2</td>
<td>4</td>
<td>2</td>
<td>60</td>
<td>1/17,151</td>
</tr>
<tr>
<td>12</td>
<td>11</td>
<td>11</td>
<td>9</td>
<td>4</td>
<td>2</td>
<td>4</td>
<td>2</td>
<td>60</td>
<td>1/17,151</td>
</tr>
<tr>
<td>13</td>
<td>10</td>
<td>11</td>
<td>9</td>
<td>5</td>
<td>3</td>
<td>2</td>
<td>0</td>
<td>120</td>
<td>2/17,151</td>
</tr>
<tr>
<td>14</td>
<td>10</td>
<td>11</td>
<td>9</td>
<td>5</td>
<td>3</td>
<td>2</td>
<td>0</td>
<td>120</td>
<td>2/17,151</td>
</tr>
<tr>
<td>15</td>
<td>10</td>
<td>11</td>
<td>9</td>
<td>5</td>
<td>3</td>
<td>2</td>
<td>0</td>
<td>120</td>
<td>2/17,151</td>
</tr>
<tr>
<td>16</td>
<td>10</td>
<td>11</td>
<td>9</td>
<td>5</td>
<td>3</td>
<td>2</td>
<td>0</td>
<td>120</td>
<td>2/17,151</td>
</tr>
<tr>
<td>17</td>
<td>10</td>
<td>11</td>
<td>9</td>
<td>5</td>
<td>3</td>
<td>2</td>
<td>0</td>
<td>120</td>
<td>2/17,151</td>
</tr>
<tr>
<td>18</td>
<td>10</td>
<td>11</td>
<td>9</td>
<td>5</td>
<td>3</td>
<td>2</td>
<td>0</td>
<td>120</td>
<td>2/17,151</td>
</tr>
<tr>
<td>19</td>
<td>10</td>
<td>11</td>
<td>9</td>
<td>5</td>
<td>3</td>
<td>2</td>
<td>0</td>
<td>120</td>
<td>2/17,151</td>
</tr>
<tr>
<td>20</td>
<td>10</td>
<td>11</td>
<td>9</td>
<td>5</td>
<td>3</td>
<td>2</td>
<td>0</td>
<td>120</td>
<td>2/17,151</td>
</tr>
<tr>
<td>21</td>
<td>10</td>
<td>11</td>
<td>9</td>
<td>5</td>
<td>3</td>
<td>2</td>
<td>0</td>
<td>120</td>
<td>2/17,151</td>
</tr>
<tr>
<td>22</td>
<td>10</td>
<td>11</td>
<td>9</td>
<td>5</td>
<td>3</td>
<td>2</td>
<td>0</td>
<td>120</td>
<td>2/17,151</td>
</tr>
<tr>
<td>23</td>
<td>10</td>
<td>11</td>
<td>9</td>
<td>5</td>
<td>3</td>
<td>2</td>
<td>0</td>
<td>120</td>
<td>2/17,151</td>
</tr>
<tr>
<td>24</td>
<td>10</td>
<td>11</td>
<td>9</td>
<td>5</td>
<td>3</td>
<td>2</td>
<td>0</td>
<td>120</td>
<td>2/17,151</td>
</tr>
<tr>
<td>25</td>
<td>10</td>
<td>11</td>
<td>9</td>
<td>5</td>
<td>3</td>
<td>2</td>
<td>0</td>
<td>120</td>
<td>2/17,151</td>
</tr>
<tr>
<td>26</td>
<td>10</td>
<td>11</td>
<td>9</td>
<td>5</td>
<td>3</td>
<td>2</td>
<td>0</td>
<td>120</td>
<td>2/17,151</td>
</tr>
<tr>
<td>27</td>
<td>10</td>
<td>11</td>
<td>9</td>
<td>5</td>
<td>3</td>
<td>2</td>
<td>0</td>
<td>120</td>
<td>2/17,151</td>
</tr>
<tr>
<td>28</td>
<td>10</td>
<td>11</td>
<td>9</td>
<td>5</td>
<td>3</td>
<td>2</td>
<td>0</td>
<td>120</td>
<td>2/17,151</td>
</tr>
<tr>
<td>29</td>
<td>10</td>
<td>11</td>
<td>9</td>
<td>5</td>
<td>3</td>
<td>2</td>
<td>0</td>
<td>120</td>
<td>2/17,151</td>
</tr>
<tr>
<td>30</td>
<td>10</td>
<td>11</td>
<td>9</td>
<td>5</td>
<td>3</td>
<td>2</td>
<td>0</td>
<td>120</td>
<td>2/17,151</td>
</tr>
<tr>
<td>Total</td>
<td>125</td>
<td>125</td>
<td>125</td>
<td>125</td>
<td>125</td>
<td>125</td>
<td>125</td>
<td>17,151</td>
<td>1</td>
</tr>
</tbody>
</table>

Columns $n_1$–$n_5$ represent the 5 capillaries. Each row represents a combination of occupancies by RBCs. Columns $D_1$ and $D_2$ give no. of duplicate occupancies in each combination. See APPENDIX for further description.

Fig. 10. Probability of contribution from different spacing intervals to total capillary length for a random deployment of 4 RBCs in a 90-µm capillary. DLCO per micrometer of capillary length for the above distribution = $\Sigma p_k(DLCO/\mu m)$, where $p_k$ is the probability of unit spacing interval $k$. Term ($DLCO/\mu m$) is obtained from Fig. 7. A unit spacing interval = 7.5 µm between RBC centers; hence, $k = 1$ indicates a spacing interval of 7.5 µm and $k = 9$ indicates a spacing interval of $9 \times 7.5 = 67.5$ µm.

Fig. 11. Random probability distribution for 30 cells in and among 5 capillaries. DLCO per micrometer of capillary length for the above distribution = $\Sigma p_i(DLCO/\mu m)$, where $p_i$ represents the probability of $i$ cells in a capillary and (DLCO/µm) is the DLCO for a random distribution of $i$ cells in a capillary; e.g., DLCO for a random distribution of 4 cells in a capillary was given as $0.0233 m^3 \cdot s^{-1} \cdot mmHg^{-1} \cdot \mu m$ of capillary length$^{-1}$. For a completely uniform distribution of 30 cells within and among 5 capillaries, it would be $0.0355 m^3 \cdot s^{-1} \cdot mmHg^{-1} \cdot \mu m$ of capillary length$^{-1}$. 

![Graph of DLCO per µm of capillary](image-url)
only once each. For four cells in a 12-pocket capillary, Eq. A1 gives a total of \( N = 495 \) possible different permutations; out of these, the total number of ways of obtaining the combination of spacing intervals \((1, 1, 3, 7)\) is given by Eq. A2, i.e., \( C = 36 \). Thus the overall probability of this spacing arrangement is \( P = 36/495 = 0.073 \). The expected fraction of capillary length occupied by different spacing intervals between RBC centers for a random deployment of four RBCs in a 90-μm capillary is shown in Fig. 10.

How a Random Distribution of Cells Is Defined Among Multiple Capillaries

The random distribution of \( q \) indistinguishable cells among \( n \) capillaries follows Bose-Einstein statistics (4), with the added restriction that no more than 12 RBCs can be present in a given capillary. One can generate by hand or by computer all the possible combinations of cell occupancy; Table 2 gives an example of \( q = 30 \) cells and \( n = 5 \) capillaries.

In Table 2, the number of permutations \( (P) \) of each combination \((i)\) is calculated as follows

\[
P_i = \frac{5!}{D_1!D_2!} \tag{A3}\]

The probabilities of the combinations are listed in the last column of Table 2, calculated as \( P_i / P \).

Note that the completely uniform distribution of six cells each in all five capillaries (combination 252) has the lowest probability. An example of the random probability distribution for 30 cells in 5 capillaries is shown in Fig. 11.

The authors gratefully acknowledge the statistical assistance of Dr. William H. Frawley of Academic Computing Services, University of Texas Southwestern Medical Center.

This project was supported by National Heart, Lung, and Blood Institute Grants R01-HL-40070, R01-HL-54060, and R01-HL-45716. C. C. W. Hsia was supported by an Established Investigator Award from the American Heart Association. Parts of this work have been published in abstract form in FASEB J. 12: A498, 1998.

The referees are thanked for their critical reviews of the manuscript.

REFERENCES


