LETTER TO THE EDITOR

The Importance of
Surface Area/Volume Ratio to the Rate
of Oxygen Uptake by Red Cells

Dear Sir:

Holland and Forster (1966) demonstrated experimentally that velocity constants for initial rates of oxygen uptake by fully reduced erythrocytes (k'_c) are inversely related to mean corpuscular volume (MCV) (Table I). They based k'_c upon measurements of the rate of hemoglobin saturation with oxygen, so that the entire process included oxygen diffusion through the cell membrane, diffusion through the cell interior, and the chemical reaction of oxygen with hemoglobin. Cell thickness was considered the most obvious factor to account for decrease in k'_c as cell volume increases. However, when they used an infinite sheet as a cell model, they did not establish a clear relationship between k'_c and thickness. An inverse relationship was demonstrated between k'_c and the radius (r) of a hypothetical sphere used as a cell model. Related material has been reviewed by Forster (1964).

The present analysis is based upon the data in Table I. Average diameters (d) of sheep, rabbit, and human cells in plasma were taken from Ponder (1948); the other diameters are of dried cells (Altman and Ditmer, 1971) multiplied by 1.08 to correct for cell shrinkage. Red cell shape is considered to be that of a cylindrical disc, which differs little from a prolate spheroid and is easier to work with mathematically; thickness is taken as mean corpuscular thickness (MCT) as calculated by Wintrobe (1967). Surface area (S) and surface to volume ratio (S/V) are calculated as for a disc. All pairings between variables in Table I yield highly significant ($P < 0.001$) correlation coefficients, indicating that all of these characteristics are closely interrelated.

If the calculations of MCT in Table I are accepted, then the increase of ~50% in cell thickness appears inadequate to account for a major portion of the 34-fold increase in cell volume, or the decrease in k'_c to one-eighth of the maximal value. From Table I, we can see that increase in cell diameter is primarily responsible for the increase in MCV.

The correlation coefficients which involve k'_c show that its best correlation is with S/V ($r = 0.92$), followed by d ($r = -0.83$), MCT ($r = -0.76$), S ($r = -0.76$), and MCV ($r = -0.73$). For these experiments, we believe that decreasing S/V has the critical role in limiting rate of oxygen uptake as cell size increases. Apparently the rate of hemoglobin saturation is limited primarily by the surface area through which oxygen can diffuse in relation to the cell volume (and hemoglobin content), which must become saturated, rather

than by the thickness through which intracellular diffusion must occur. Partial correlations also show the relative importance of S/V and volume to K_c. The partial correlation coefficient for K_c and S/V is 0.83 ($P < 0.001$), whereas the partial correlation coefficient for K_c and MCV is -0.31 ($P < 0.30$). These coefficients show that S/V has a highly significant correlation to K_c when MCV is constant, but the relationship between K_c and cell volume is minor when the effect of cell shape (S/V) is held constant.

TABLE I

MEASUREMENTS AND RATIOS AMONG RED CELLS OF SELECTED VERTEBRATES

Species	$K_c(37°C)$*	MCV*	Diameter‡§	MCT‖	S‖	S/V‖
		μm^3	μm	μn	μm^2	
Goat	158	20	4.3	1.38	47.6	2.38
	133	20	4.3	1.38	47.6	2.38
Sheep	137	33	5.2	1.55	67.8	2.05
Horse	109	43	5.9	1.58	83.9	1.95
	93	45	5.9	1.65	85.2	1.89
Rabbit	79	66	7.5	1.49	123.5	1.87
	76	74	7.5	1.67	127.7	1.73
Dog	67	68	7.5	1.54	124.7	1.83
	69	71	7.5	1.61	126.3	1.78
	64	66	7.5	1.49	123.5	1.87
	67	66	7.5	1.49	123.5	1.87
Man	77	90	8.5	1.59	155.9	1.73
	85	90	8.5	1.59	155.9	1.73
Bullfrog	19	680	20.0	2.17	764.4	1.12
	19	680	20.0	2.17	764.4	1.12

* Holland and Forster (1966).
‡ Ponder (1948).
§ Adjusted from Altman and Dittmer (1971).
‖ Calculated values.

It is important to use a cell model of an appropriate shape to assess properly the effect of S/V. This can be shown by comparison of three membraneless models of equal volume: in an infinite sheet with thickness of 2 μm, a disc-shaped (but rimless) portion 8 μm in diameter would have S of 100 μm^2 and V of 100 μm^3, for S/V of 1; a disc of similar dimensions (but with a rim) would have S of 150 μm^3 and V of 100 μm^3 for S/V of 1.5; a sphere ($d = 5.85$ μm) has S of 107 μm^2 and V of 100 μm^3 for S/V of 1.07. Of these models, the disc has the greatest S/V and should have the highest rate of oxygen saturation, when other conditions are equal. The use of a sphere or infinite plate as a model underestimates S/V of a disc by about 30%.

A cell model may limit or predetermine the development of concepts related to the model. For instance, if the red cell is considered an infinite sheet, it is logical to assume that an increase in volume is dependent upon an increase in thickness, since there is no other dimension which can increase. Similarly, an increase in volume of a sphere must accompany an increase in radius. However, the volume of a discoidal red cell is a function of thickness and diameter. This is also true of S/V for a disc, where t is substituted for MCT:

$$S/V = (\pi d^2/2 + \pi dt)/(\pi d^2 t/4)$$

$$= 2/t + 4/d.$$

Although Table I shows little variation in MCT, there is a very high correlation ($r = 0.95$) between MCT and d. Linear regression analysis yields the equation

$$MCT = 1.23 + 0.047d,$$

which shows that the discoidal shape is maintained in cells of different sizes, but large cells are proportionately thinner than small cells. Since the strongly correlated dimensions of d and MCT determine the proportions of a disc, it is not surprising that d has such high correlations with surface area ($r = 0.99$), volume ($r = 0.98$), and their ratio ($r = -0.93$).

The data in Table I indicate that larger cells have lower rates of oxygen uptake because of their lower surface-to-volume ratios, which are determined partly by thickness, but largely by diameter. It may be noted that the coefficients used by Holland and Forster (1966) in the proportionalities of K_c, for an infinite sheet ($1/b$, which is equal to $2/t$) and for a sphere ($3/r$), can be taken as the S/Vs for those models. The corresponding coefficient for a disc is its S/V ($2/t + 4/d$), which can be simplified to $1/d$ if t is considered constant. Thus, we come to the proportionality, $K_c \propto 1/d$, which is very similar to $K_c \propto 1/r$ recognized by Holland and Forster (1966) for their spherical model.

We do not believe that the effect of cell thickness upon intracellular diffusion is the rate-limiting factor for the experiments cited, but we do acknowledge that this factor (or any of several other factors) may be rate-limiting under other circumstances. It would be interesting to test the importance of S/V as the rate-limiting factor of K_c through studies of oxygen uptake by cells which are similar in volume, but different in S/V (e.g., comparison of discoidal red cells with ellipsoidal red cells of camels, salamanders or others).

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