Partition of Xenon and Iodoantipyrine among Erythrocytes, Plasma, and Myocardium

RONALD CARLIN and SHU CHIEN

SUMMARY A new method was developed for determining directly the distribution of $^{133}$Xe between red cells and plasma in vitro without an air-fluid interface; the partitioning of $^{133}$Xe and $^{131}$I-iodoantipyrine between blood and myocardium was investigated in the dog in situ. The red cell-plasma partition coefficient for $^{133}$Xe is defined as $\lambda_{cp} = C_{cp}/C_{p}$. The cell-plasma partition coefficient ($\lambda_{cp}$) for $^{131}$I-iodoantipyrine and $^{133}$Xe was 2.27 ± 0.07 (mean ± SD) for human blood and 3.31 ± 0.06 for dog blood. The blood-plasma partition coefficient for $^{133}$Xe was 0.75 ± 0.04 for human blood and 0.97 ± 0.03 for dog blood. The results support the concept of a three-compartment partition of the indicator among erythrocytes, plasma, and myocardium. The mean values (± SD) of the hematocrit-independent plasma-tissue partition coefficients in the left ventricle for $^{133}$Xe and $^{131}$I-iodoantipyrine were 1.08 ± 0.16 and 1.54 ± 0.20 g/ml, respectively.

The equilibration of an indicator between blood and tissue may be considered in terms of three components: red blood cells (RBC), plasma, and tissue, where the indicator concentrations are $C_{c}$, $C_{p}$, and $C_{t}$, respectively. The indicator concentration in the blood ($C_{b}$) can be calculated as

$$C_{b} = HC_{c} + (1 - H) C_{p}$$

where $H$ is the volume fraction of RBC in blood. The blood-tissue partition coefficient ($\lambda_{bt}$, in g/ml) is defined as

$$\lambda_{bt} = C_{b}/C_{t}$$

The plasma-tissue partition coefficient ($\lambda_{pt}$, in g/ml) is defined as

$$\lambda_{pt} = C_{p}/C_{t}$$

The cell-plasma partition coefficient ($\lambda_{cp}$) is defined as

$$\lambda_{cp} = C_{cp}/C_{p}$$

Combining Equations 1 through 4 yields

$$\lambda_{bt} = \lambda_{cp} [1 + (\lambda_{cp} - 1)H].$$

Therefore, for an indicator with $\lambda_{cp}$ significantly different from unity, $\lambda_{bt}$ would vary with $H$ at given values of $\lambda_{pt}$ and $\lambda_{cp}$.

Two indicators commonly used in washout studies are $^{125}$Xe, a lipophilic substance, and radioiodinated antipyrine, a more hydrophilic compound. In the present investigation $\lambda_{cp}$ values for $^{133}$Xe and $^{131}$I-iodoantipyrine were...
determined in human and dog blood. A new incubating and sampling technique has been developed for the measurements of $^{133}$Xe activities in RBC and in plasma without exposing samples to air. The results of these studies demonstrate that $\lambda_{cap}$ of $^{133}$Xe is substantially greater than unity and that $\lambda_{cp}$ of $^{131}$I-iodoantipyrine is much closer to unity.

Because Xe has a higher affinity for RBC than plasma, a decrease in hematocrit would reduce the relative affinity of blood vs. tissue for the indicator, and therefore decrease the rate of $^{133}$Xe washout at a given blood flow. Since $^{131}$I-iodoantipyrine has similar affinities for RBC and plasma, hematocrit variations should have minimal effects on its partition between blood and tissues or its washout from tissues at a given rate of blood flow. In the present experiments, the partitioning of $^{133}$Xe and $^{131}$I-iodoantipyrine between blood and the myocardium was determined after equilibration of the indicators in vivo. By performing the experiments at various hematocrits in different dogs, it was possible to test the theoretical predictions that variations in red cell concentration lead to changes in $\lambda_{cp}$.

**Methods**

**DETERMINATION OF CELL-PLASMA PARTITION COEFFICIENTS**

$^{133}$Xe

The $^{133}$Xe (Diagnostic Isotopes) used in this study was the gas dissolved in pyrogen-free 0.9% NaCl solution. The partition coefficient of $^{133}$Xe between RBC and plasma ($\lambda_{cap}$) was determined on freshly drawn heparinized whole blood. A test tube containing a small amount of mercury was completely filled with blood and sealed free of air bubbles with a rubber stopper. $^{133}$Xe dissolved in saline was added to the tube by displacing an equal volume of blood and without introducing any gaseous phase. The content of the tube was then mixed and centrifuged. Plasma and packed red cell samples were drawn from the tube into counting vials that had been prepared from 2-ml disposable plastic syringes, filled with mercury, and stopped. The sample drawn from the tube was replaced by an equal volume of mercury (Fig. 1). Therefore, the sampling procedure involved the use of a continuous system consisting of only the sample and mercury, and there was no gaseous phase at any time. Three to five samples (0.4-0.8 ml each) of plasma and packed red cells were obtained in each run.

The $^{133}$Xe activity of the plasma or packed cell sample was determined in the well-type scintillation counter of a three-channel gamma ray spectrometer system (Packard Instrument Co.). Total activity in counts/min (cpm) of $^{133}$Xe in each counting vial was recorded on channel 1 (40-120 keV) of the spectrometer system and denoted as $Q_{cx}$ and $Q_{cp}$ for the packed cell and plasma samples, respectively. After counting, the sample weight was determined to the nearest hundred of a milligram. Sample weights were converted to sample volumes ($V_{cs}$ and $V_{p}$ for cell and plasma samples, respectively) by use of the appropriate density values. The density ($\rho$) of cell samples was found to be a linear function of the hematocrit value.

$$\rho = 1.027 + 0.063 H.$$  \hspace{1cm} (6)

where 1.027 is the plasma density and $H$ is the volume fraction of red cells in the sample calculated from the hematocrit value after correcting for incomplete centrifugal packing.

$^{133}$Xe activity per unit volume of plasma ($C_{px}$ in cpm/ml) was calculated as

$$C_{px} = Q_{px}/V_{p}.$$  \hspace{1cm} (7)

The following equation was used to calculate the $^{133}$Xe activity in the packed cell sample due solely to RBC ($Q_{cx}$), with subtraction of the activity due to trapped plasma

$$Q_{cx} = Q_{px} - C_{px} V_{cs} (1 - H).$$  \hspace{1cm} (8)

The $^{133}$Xe activity per milliliter of RBC was calculated as

$$C_{cx} = Q_{cx}/(V_{cs} H)$$  \hspace{1cm} (9)

and the cell-plasma partition coefficient for $^{133}$Xe was obtained as

$$\lambda_{cap} = C_{cx}/C_{px}.$$  \hspace{1cm} (10)

$^{131}$I-Iodoantipyrine

The $^{131}$I-iodoantipyrine (New England Nuclear) used in this study was dissolved in 0.9% pyrogen-free NaCl solution at a pH of 7.4. All determinations of $\lambda_{cap}$ for $^{131}$I-iodoantipyrine ($\lambda_{cp}$) were made on freshly drawn heparinized whole blood. Approximately 15 ml of blood were

![Figure 1](http://circres.ahajournals.org/)

**Figure 1** Diagrams showing the sampling system before (diagram A) and after (diagram B) withdrawing $^{133}$Xe-labeled plasma from the test tube into the counting vial (V). The test tube containing a mixture of $^{133}$Xe, blood, and mercury was centrifuged to give three layers: plasma, packed cells, and mercury. A withdrawal needle (N) (formed by joining two needles with a two-way stopcock) and a replacement needle (connected to a syringe, R) are inserted into the test tube through its rubber stopper. The counting vial and the replacement syringe are filled with mercury. The entire system is free of gaseous phase. When mercury is drawn from the counting vial into the withdrawal syringe (W), plasma enters the counting vial via N, and its volume in the test tube is replaced quantitatively by mercury entering from R.
placed in a test tube and 131I-iodoantipyrine (approximately 0.1 μCi) was added. After mixing, the test tube was centrifuged and 1-ml plasma samples were pipetted for counting. After removal of buffy coat the packed red cells were mixed, a hematocrit value was taken, and 1-ml samples were pipetted for 131I counting.

The 131I-iodoantipyrine activity (in cpm) of the plasma and packed cell samples was recorded on channel 3 (230–430 keV) of the spectrometer system and denoted as Qp and Qpc for plasma and packed cell samples, respectively.

Using equations analogous to Equations 7, 8, and 9 the 131I-iodoantipyrine activities per unit volume of plasma and RBC (Cpl and Cpr, respectively, in cpm/ml) were calculated, and the cell-plasma partition coefficient for 131I-iodoantipyrine is

\[
\lambda_{cp} = \frac{C_p}{C_{pl}} = \frac{Q_p/V_p}{Q_{pl}/V_{pl}}
\]

\[
= \frac{V_p}{Q_{pl}} = \frac{C_{pl} V_{pl} (1 - H)}{(Q_p/V_p) V_{pl} H). \tag{11}
\]

**DETERMINATION OF PLASMA-ORGAN AND BLOOD-ORGAN PARTITION COEFFICIENTS**

**Surgical Preparation**

Mongrel dogs (15–30 kg) were anesthetized by intravenous administration of sodium pentobarbital (22.5 mg/kg) and α-chloralose (25 mg/kg). The dog was ventilated with a mixture of room air and oxygen to ensure an arterial O2 saturation of over 95%. The right femoral artery was cannulated for monitoring blood pressure. After a left thoracotomy, the pericardium was opened. The hematocrit levels in the dog were changed by an isovolumic exchange procedure. Either fresh, heparinized packed RBC or fresh, heparinized plasma from donor dogs were infused into the left external jugular vein, and whole blood was simultaneously withdrawn from the right common carotid artery at the same rate (approximately 25 ml/min).

**Administration of Isotopes**

133Xe solution (approximately 2 μCi/ml) was infused via a 21-gauge needle inserted into the left auricle (14 dogs) or the left ventricle (three dogs) at a rate of 0.72 ml/min. The duration of the infusion before stopping the heart was approximately 80 minutes.

To determine the contribution of any 133Xe remaining inside the coronary vasculature to the activity found in heart samples, in four experiments 51Cr-labeled RBC were injected intravenously approximately 50 minutes after the start of the 133Xe infusion.

Because of its relatively slow rate of elimination, 131I-iodoantipyrine was administered to nine dogs by a single intravenous injection (120 μCi). The heart was stopped 5 minutes after the injection. The 131I-iodoantipyrine was passed through an anion-exchange resin (Bio-Rad) prior to its injection to remove 131I that may have separated from the antipyrine molecule.8,9

**Determination of Isotope Activity in Blood**

Blood samples were drawn from the descending aorta, pulmonary artery trunk, left pulmonary vein, and coronary sinus. Radioactivity of the samples was determined in a three-channel gamma ray spectrometer in which the energy spectra were set at 40–120 keV for channel 1, 240–360 keV for channel 2, and 230–430 keV for channel 3, encompassing the peak energies of 133Xe, 51Cr, and 131I, respectively. The count rate of the blood sample in each channel (in cpm, background subtracted) was divided by the volume of the blood sample (Vb, in ml) to yield the activity per unit volume (Cbx, in cpm/ml) for 133Xe activity. The background per unit volume (Cbx, in cpm/ml) for 51Cr activity recorded in channel 1 by using the count ratios in channels 1 and 2 for a 51Cr standard.

**Determination of Isotope Activity in Myocardium**

After approximately 80 minutes of 133Xe infusion the heart was stopped by application of electrical stimuli [40 V, 50 cycles/sec(cps)]. The infusion was stopped at exactly the time the stimuli began. The heart was removed, its blood content was drained, and sampling of the ventricles was begun within 1–2 minutes after stopping the heart. Extracorporeal monitoring of the excised heart showed that only approximately 1% of the 133Xe activity was lost in 30 minutes after stopping the heart. Tissue samples, varying in weight from 0.2 to 1.0 g, were transferred to previously labeled and weighted counting vials. The vials were immediately sealed and the isotope activity was determined. The total sampling time was generally less than 10 minutes.

Blood-tissue partition coefficients showed no significant difference between the initial and late samples.

The abbreviations used follow the same format as that used above for blood, except that the subscript b (blood) is replaced by t (tissue). The activity of each isotope (in cpm, background subtracted) in the myocardial sample was divided by the tissue sample weight (Wt, in grams) to yield the activity per unit weight (Cbt, Cbt1, and Cbt2 for 133Xe, 51Cr, and 131I, respectively, in cpm/g). In studies involving 133Xe and 51Cr, Cbt was corrected for the 51Cr activity present in channel 1.

**Determination of Water and Lipid Contents in Myocardium**

The tissue sample weight was determined after counting. The samples were then placed in an electric oven at 90°C for approximately 100 hours for the determination of water content. Chloroform was added to the desiccated sample to extract lipids. After approximately 48 hours the chloroform was aspirated and replaced with fresh chloroform; 48 hours later the chloroform was again aspirated and the samples were placed in an oven to evaporate any residual solvent. The extracted sample was weighed to determine the weight of lipid in each sample.

**Calculation of Blood-Tissue Partition Coefficients**

The blood-tissue partition coefficient for 133Xe (λbxt) and that for 131I-iodoantipyrine (λbxt) were calculated from Equation 2. The radioactivities per unit volume of blood (Cbx and Cbt) were obtained by averaging the values in coronary sinus and arterial blood. Radioactivities per unit
weight of myocardium (C\textsubscript{X} and C\textsubscript{N}) were obtained from samples without visible fatty tissue or large blood vessels.

**Correction of Myocardial Activity for Blood Content**

The weight fraction of blood (\(w_b\), in g/g) remaining in each myocardial sample was calculated from the \(^{51}\)Cr activity per unit weight of myocardial tissue, the \(^{51}\)Cr activity per unit volume of blood, and the appropriate blood density value (\(\rho\)) for the particular hematocrit:

\[
\phi_b = \frac{W_b}{W_t} = \rho C_{51X}/C_{51B}.
\]

(12)

The \(^{133}\)Xe or \(^{131}\)I-iodoantipyrine activity recorded for any myocardial sample (\(Q\)), in cpm) is the sum of the true tissue activity (\(Q_t\), in cpm) plus the activity due to any blood remaining in the coronary vasculature (\(Q_b\), in cpm), hence

\[
Q' = Q_t - Q_b.
\]

(13)

Since each of these activities is the product of the activity per unit weight (in cpm/g) and the component weight.

\[
C_i = \frac{(C_i - C_{51X})(1 - \phi)}{(C_i - C_{51B})(1 - \phi)}.
\]

(14)

The blood-tissue partition coefficient corrected for trapped blood is obtained as

\[
\lambda' = \frac{C_i}{C_t} = \frac{1 - \phi}{(1/\lambda - \phi/\rho)}.
\]

(15)

**Calculation of Plasma-Tissue Partition Coefficients**

The plasma-tissue partition coefficient for \(^{133}\)Xe (\(\lambda_{ptX}\)) and for \(^{131}\)I-iodoantipyrine (\(\lambda_{ptI}\)) were calculated from Equation 5, using the mean \(\lambda_{ba}\) value. Similarly, values of the plasma-tissue partition coefficient corrected for trapped blood (\(\lambda'_{pt}\), in g/ml) were calculated as

\[
\lambda'_{pt} = \frac{\lambda'_{pt}}{1 + (\lambda_{pt} - 1)}.
\]

(17)

The \(\lambda_{pt}\) value for 35°C was used in the calculation of \(\lambda_{pt}\) and \(\lambda'_{pt}\), since this was the temperature measured in the inferior vena cava of the open-chest dog.

**Results**

**EFFECT OF TEMPERATURE ON CELL-PLASMA PARTITION COEFFICIENTS IN DOG BLOOD**

\(\lambda_{ptX}\) values were determined on dog blood at 5°C, 21°C, and 37°C. Values of \(\lambda_{ptX}\) were found to decrease with an increase in temperature (Table 1A). Regression analysis of the variation of \(\lambda_{ptX}\) with the temperature yielded the following equation:

\[
\lambda_{ptX} = 4.061 - 0.020 \, ^\circ \text{C}.
\]

(18)

The standard error of estimate is 0.106, and the coefficient of correlation is -0.917 (\(P < 0.001\)).

The xenon solubilities in aqueous and lipid materials are known to vary inversely with temperature. The \(^{133}\)Xe solubility in dog RBC (\(S_{X}\), ml/ml) may be calculated as

\[
S_{X} = \lambda_{ptX} S_{XX}.
\]

(19)

where \(S_{XX}\) is \(^{133}\)Xe solubility in dog plasma and is equal to 0.12 ml/ml at 37°C. Assuming that the temperature-dependence of \(S_{XX}\) is parallel to that of xenon solubility in albumin solutions, we may calculate from Equation 19 the \(S_{XX}\) values at various temperatures (Fig. 2). The calculated \(S_{XX}\) decreases with temperature such that the slope is slightly greater than that for plasma, and this may account for the observed decrease in \(\lambda_{ptX}\) with increasing temperature (Table 1A).

\(\lambda_{pt}\) values were determined on dog blood at 5°C, 26°C, and 38°C (Table 1B). Regression analysis of the variation of \(\lambda_{pt}\) with temperature yielded the following equation:

\[
\lambda_{pt} = 0.937 + 0.001 \, ^\circ \text{C}.
\]

(20)

The standard error of estimate is 0.100, and the coefficient of correlation is +0.416 (0.025 < \(P < 0.05\)). These results indicate that \(\lambda_{pt}\) shows very slight changes with temperature and the correlation is only of borderline sig-
nificance. For practical purposes, \( \lambda_{cp} \) may be considered as temperature-independent within physiological range.

**EFFECT OF INITIAL HEMATOCRIT ON CELL-PLASMA PARTITION COEFFICIENTS IN DOG BLOOD**

Since \( \lambda_{cp} \) represents the ratio of concentrations of an indicator in RBC and plasma, values of \( \lambda_{cp} \) should not change when one varies the hematocrit of the blood sample used for the determination.

Sixteen determinations of \( \lambda_{cp} \) were carried out at \( 37^\circ C \) on dog blood. In eight of the determinations the hematocrit was altered by removing or adding plasma to the blood, resulting in initial hematocrits ranging from 20% to 72% prior to the addition of \( ^{133}\text{Xe} \). Variations in the initial hematocrit did not result in any significant change in \( \lambda_{cp} \) (Fig. 3). The coefficient of correlation between \( \lambda_{cp} \) and initial hematocrit is not significant: \( r = +0.457 \), \( (0.05 < P < 0.1) \).

Thirty-two determinations of \( \lambda_{pl} \) were carried out on dog blood. In seven of the determinations the hematocrit was altered over a range of 32–67% prior to the addition of \( ^{133}\text{Xe} \). Variation in initial hematocrit did not result in a significant change in \( \lambda_{cp} \) (Fig. 3). Regression analysis on \( \lambda_{pl} \) and initial hematocrit yielded a coefficient of correlation of \(-0.133 \), which is not significant \((0.4 < P < 0.5)\).

**EFFECT OF PENTOBARBITAL ANESTHESIA ON CELL-PLASMA PARTITION COEFFICIENT IN DOG BLOOD**

Measurements of \( \lambda_{cp} \) were made on blood taken from unanesthetized dogs and from the same dogs 20–60 minutes after intravenous administration of sodium pentobarbital \((30 \text{ mg/kg body weight})\). At \( 37^\circ C \) the \( \lambda_{cp} \) \((3.23 \pm \text{ SD 0.06}) \) and \( \lambda_{pl} \) \((1.00 \pm \text{ SD 0.01}) \) values in the anesthetized dogs were not significantly different from the corresponding results obtained in the unanesthetized state \( \lambda_{cp} = 3.28 \pm 0.03, \lambda_{pl} = 0.98 \pm 0.02 \).

**COMPARISON OF CELL-PLASMA PARTITION COEFFICIENTS BETWEEN HUMAN AND DOG BLOOD**

At temperatures of 37–38°C, human blood showed an average \( \lambda_{cp} \) of 2.27 ml/ml \((\text{SD 0.07})\) and a mean \( \lambda_{pl} \) of 0.75 ml/ml \((\text{SD 0.04})\). Both of these values are significantly different from the corresponding data in the dog (Table 2, \( P < 0.001 \)).

**BLOOD, WATER, AND LIPID CONTENTS OF MYOCARDIAL TISSUE**

The weight fractions of residual blood, water, and lipid in myocardial samples which contained no visible fatty tissue or large blood vessels are listed in Table 3. Statistical analysis shows a significant difference in trapped blood content between left ventricle and right ventricle (Student’s t-test, \( P < 0.002 \)), but the water and lipid contents of the two ventricles are not significantly different.

**TIME-CONCENTRATION CURVES IN BLOOD WITH \( ^{133}\text{Xe} \) INFUSION**

Blood levels of \( ^{133}\text{Xe} \) at different points in the circulation during the isotope infusion are shown in Figure 4. At the steady levels, the concentrations in the aorta and

<table>
<thead>
<tr>
<th>Species</th>
<th>No. of samples</th>
<th>( \lambda_{cp} ) (ml/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Human blood A: ( ^{133}\text{Xe} )</td>
<td>6</td>
<td>2.27 ± 0.07</td>
</tr>
<tr>
<td>Dog blood</td>
<td>8</td>
<td>3.31 ± 0.06</td>
</tr>
<tr>
<td>Human blood B: ( ^{131}\text{I} )-idoantipyrine</td>
<td>4</td>
<td>0.75 ± 0.04</td>
</tr>
<tr>
<td>Dog blood</td>
<td>13</td>
<td>0.97 ± 0.03</td>
</tr>
</tbody>
</table>

Values given for \( \lambda_{cp} \) are means ± SD; temperature = 37–38°C; mean hematocrit = 44–46%.

**Figure 3** Independence of cell-plasma partition coefficient \( \lambda_{cp} \) (ordinate, ml/ml) from initial hematocrit levels \((\text{abscissa})\) Individual values of the cell-plasma partition coefficient for \( ^{133}\text{Xe} \) \((\lambda_{cpx})\) are shown as dots. The range of values for \( ^{131}\text{I} \)-idoantipyrine \((\lambda_{cp})\) are grouped by the open ovals and circles with the numbers of measurements indicated.
Contents of Trapped Blood, Water, and Lipid in Dog Ventricles

<table>
<thead>
<tr>
<th></th>
<th>Weight fractions (g/g)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Left ventricle</strong></td>
<td></td>
</tr>
<tr>
<td>Trapped blood</td>
<td>0.052 ± 0.012 (31)</td>
</tr>
<tr>
<td>Water</td>
<td>0.7965 ± 0.0098 (110)</td>
</tr>
<tr>
<td>Lipid</td>
<td>0.0101 ± 0.0063 (110)</td>
</tr>
<tr>
<td><strong>Right ventricle</strong></td>
<td></td>
</tr>
<tr>
<td>Trapped blood</td>
<td>0.040 ± 0.005 (12)</td>
</tr>
<tr>
<td>Water</td>
<td>0.7975 ± 0.0164 (33)</td>
</tr>
<tr>
<td>Lipid</td>
<td>0.0138 ± 0.0105 (33)</td>
</tr>
</tbody>
</table>

Values given are means ± s.d. Numbers in parentheses denote number of samples analyzed. Blood content was determined in four dogs. Water and lipid contents were determined in 10 dogs.

Fatty tissues do not show a significant correlation with the lipid content. However, when measurements on samples with visible fatty tissues are included, the \(\lambda_{\text{ptX}}\) values in the left ventricle then show an inverse relation with the lipid content (Table 5).

**BLOOD-TISSUE PARTITION COEFFICIENT AND PLASMA-TISSUE PARTITION COEFFICIENT FOR \(^{131}\text{I-iodoantipyrine}\)**

The \(\lambda_{\text{ptX}}\) values for different samples from the same dog showed relatively small variations, with the standard deviation generally being less than 10% of the mean values. The mean value in the left ventricle for nine dogs was 1.48 ± 0.19. The \(\lambda_{\text{biX}}\) values in the left ventricle, corrected for trapped blood averaged 1.52 ± 0.21. The \(\lambda_{\text{biX}}\) and \(\lambda_{\text{ptX}}\) values in the left ventricle were 1.50 ± 0.18 and 1.54 ± 0.20, respectively. There was no significant difference in \(\lambda_{\text{ptX}}\) between the two ventricles.

**Discussion**

Previous studies\(^{1,2,3,14-15}\) have shown that Xe has different affinities for RBC and plasma. In these previous studies, the partitioning of Xe between RBC and plasma was determined indirectly by equilibrating each of the components through an air phase with a solution. Such a procedure necessitates a prolonged period of equilibration, and the air-plasma or air-blood interface may cause undesirable alterations in plasma proteins and/or RBC. In the present investigation a new technique has been developed for the direct determination of the cell-plasma partition coefficient for \(^{133}\text{Xe}\) without air interfaces. The use of such a direct procedure not only avoids the possible damaging effect of an air interface, but also makes possible rapid equilibration of Xe between RBC and plasma under conditions similar to the physiological situation in vivo. Our results of \(\lambda_{\text{ptX}}\) (ml/ml) on human blood at 37°C gave a mean value of 2.27 (Table 2A) which is in excellent agreement with the value of 2.25 reported by Ladefoged and Anderson.\(^{15}\)

The \(\lambda_{\text{ptX}}\) value for dog blood at 37°C was 3.31. Thus, the RBC have a higher affinity for Xe than does plasma; and this difference in affinity is more pronounced in the dog than in man.

Antipyrine and iodoantipyrine have long been recognized as highly diffusible indicators. For this reason they have often been used in the determination of total body water content\(^{5,16,17}\) and the rate of blood flow.\(^{18-20}\) Because \(^{131}\text{I-iodoantipyrine}\) has a volume of distribution in tissues similar to that of urea, deuterium oxide, and tritiated water,\(^{5,20,21}\) it is reasonable to expect \(\lambda_{\text{ptX}}\) to be similar to the ratio of volume fractions of water between

![Figure 4](http://circres.ahajournals.org/)

**Figure 4** Semilogarithmic plot of \(^{133}\text{Xe}\) blood activities (ordinate, logarithm \(C_{\text{bi}}, \text{cpm/ml}\)) during the course of the isotope infusion (abscissa, minutes). Changes in \(^{133}\text{Xe}\) activity are shown for blood sampled from the coronary sinus (CS), descending aorta (A), pulmonary artery (PA), and pulmonary vein (PV).

![Figure 5](http://circres.ahajournals.org/)

**Figure 5** Variation in the corrected blood-tissue partition coefficient for \(^{133}\text{Xe}\) in the dog left ventricle (ordinate, \(\lambda_{\text{biX}}, \text{g/ml}\)) with hematocrit (abscissa, %). The regression line (solid line) fitted to the experimentally determined values of \(\lambda_{\text{biX}}\) shows good agreement with the theoretical change in \(\lambda_{\text{biX}}\) calculated with the use of the mean corrected plasma-tissue partition coefficient (\(\lambda_{\text{ptX}}\)) for left ventricle, the cell-plasma partition coefficient for \(^{133}\text{Xe}\) at 35°C (\(\lambda_{\text{ptX}}\)), and Equation 17 (broken line). Ventrical bars represent sd of determinations in individual dogs.
TABLE 4  Plasma-Tissue Partition Coefficient for $^{133}$Xe ($\lambda_{ptx}$) and $^{131}$I-Iodoantipyrine ($\lambda_{ptx}$) in Dog Ventricles

<table>
<thead>
<tr>
<th></th>
<th>Left ventricle</th>
<th>Right ventricle</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>A: $^{133}$Xe</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Uncorrected $\lambda_{ptx}$</td>
<td>1.02 ± 0.14 (17)</td>
<td>1.38 ± 0.24 (15)</td>
</tr>
<tr>
<td>Corrected $\lambda_{ptx}$</td>
<td>1.08 ± 0.16 (17)</td>
<td>1.49 ± 0.29 (15)</td>
</tr>
<tr>
<td><strong>B: $^{131}$I-Iodoantipyrine</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Uncorrected $\lambda_{ptx}$</td>
<td>1.50 ± 0.18 (9)</td>
<td>1.57 ± 0.33 (9)</td>
</tr>
<tr>
<td>Corrected $\lambda_{ptx}$</td>
<td>1.54 ± 0.20 (9)</td>
<td>1.61 ± 0.36 (9)</td>
</tr>
</tbody>
</table>

Values given are means ± SD; numbers in parentheses denote the number of dogs studied.

RBC and plasma. The water content of the human RBC has been found to be 0.63 g/g,\textsuperscript{26} or 0.72 ml/ml,\textsuperscript{22} and human plasma water content has been reported as 0.91 g/ g,\textsuperscript{26} or 0.93 ml/ml.\textsuperscript{25} Therefore, the human RBC to plasma water content ratio is 0.69 g/g, or 0.77 ml/ml. This value of 0.77 ml/ml is in excellent agreement with the experimentally determined value of $\lambda_{pbt}$ for human blood (Table 2B). Therefore, the present study indicates that $^{131}$I-Iodoantipyrine is distributed in human blood in accordance with its water-solubility. This finding is in agreement with previous studies using antipyrine.\textsuperscript{4,5}

Water content in dog blood is approximately 0.64 ml/ml in RBC and 0.93 ml/ml in plasma.\textsuperscript{24} These values were confirmed in the present investigation by experimental desiccation of dog plasma and packed cells at 90°C for 72 hours. Based on these water contents and the assumption that iodoantipyrine distributes itself solely on the basis of its water-solubility, $\lambda_{pbt}$ for dog blood should have a value of approximately 0.69 ml/ml. The experimentally determined $\lambda_{pbt}$ for dog blood differed substantially from this value, having a mean value of 0.97 ml/ml at 38°C (Table 2B). This discrepancy indicates that, as previously reported by Effros and Chinard,\textsuperscript{26} $^{131}$I-Iodoantipyrine is found in the dog RBC beyond what is accountable on the basis of intracellular water content.

The present study on blood-myocardium partition coefficients of $^{133}$Xe differs from previous investigations in that (1) the indicator equilibration was achieved in vivo, (2) correction has been made for any blood $^{133}$Xe activity in tissue, (3) correlation has been made with tissue lipid content, and (4) the experiments were carried out over a wide range of hematocrit values.

Since $^{133}$Xe is eliminated rapidly in the lungs, a constant infusion is needed to maintain steady concentrations in blood and in tissue for the equilibration studies. The time-concentration curves for blood levels of $^{133}$Xe in coronary sinus and arterial samples during 80-minute infusions (Fig. 4) indicate that this objective was achieved in the present study. The in vivo equilibration of indicator delivered to the tissue via the circulation provides a much more physiologic condition than in vitro studies on homogenized specimens.

With the use of $^{51}$Cr-labeled red cells, the weight fraction of blood was found to average 5.2% in the left ventricle. This value represents the blood trapped in the myocardium after partial drainage of vascular content during dissection. Because the trapped blood had a higher $^{133}$Xe activity per unit weight than the myocardium, its inclusion would give a falsely low blood-tissue partition coefficient. This error, which can be calculated as $100(\lambda_{pbt} - \lambda_{pbt})/\lambda_{pbt}$, averages 5% for the left ventricle. Since the difference in blood and myocardial activities for $^{131}$I-Iodoantipyrine is smaller, the error introduced by ignoring the correction for trapped blood is only 2%.

The inverse correlation of $\lambda_{ptx}$ with tissue lipid content (Table 5) reflects the lipophilic nature of $^{133}$Xe. Thus, regions with a high lipid content have low values for $\lambda_{ptx}$ and $\lambda_{pbt}$, and this would lead to a sluggish $^{133}$Xe washout in flow measurements.

The experimental values of $\lambda_{ptx}$ in left ventricle showed a significant correlation with hematocrit (coefficient of correlation = 0.72, $P < 0.01$). This provides direct evidence for the theoretical prediction based on the high affinity of red cells for $^{133}$Xe in comparison to plasma.

Since the red cells probably do not equilibrate directly with the tissue but rather indirectly through the plasma, $\lambda_{ptx}$ may be considered as the primary partition coefficient. The mean $\lambda_{ptx}$ for left ventricle was $1.08 \pm 0.16$ g/ml (Table 4) and, as expected, it showed no significant correlation with hematocrit ($P > 0.20$). Because $\lambda_{ptx}$ is independent of hematocrit it is possible to use this mean value of all experiments and the $\lambda_{ptx}$ at 35°C of 3.37 ml/ml to back calculate $\lambda_{pbt}$ at various hematocrits (Eq. 17). As shown by the broken line in Figure 5, this back-calculated

<table>
<thead>
<tr>
<th>No. of samples</th>
<th>Lipid content (g/g)</th>
<th>$\lambda_{ptx}$ (g/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myocardium with no visible fat</td>
<td>110</td>
<td>0.010 ± 0.006</td>
</tr>
<tr>
<td>Myocardium with lipid content &gt; 50%</td>
<td>10</td>
<td>0.732 ± 0.075</td>
</tr>
</tbody>
</table>

Values given are means ± SD.
\( \lambda_{\text{fast}} \) line agrees rather well with the experimental data. Because \(^{131}\)I-iodoantipyrine is not eliminated in the lungs, a single intravenous injection was made instead of constant infusion. \(^{131}\)I-iodoantipyrine is metabolized in the dog at a significant rate.\(^4\)\(^-\)\(^8\)\(^-\)\(^20\) The 5-minute equilibration period was chosen as a compromise between the need for adequate mixing of the indicator and the avoidance of significant metabolic degradation. The ratio of \(^{131}\)I-iodoantipyrine activity in arterial blood to that in coronary sinus blood just prior to stopping the heart was not significantly different from unity (mean \( \pm \) SD = 0.94 \( \pm \) 0.07). A previous study\(^19\) which allowed only 2 minutes for an equilibrium of distribution of the injected indicator, showed a significant difference between arterial coronary and sinus concentrations of \(^{131}\)I-iodoantipyrine.

As the \( \lambda_{\text{fast}} \) value is close to unity, \( \lambda_{\text{hit}} \) is not significantly affected by hematocrit and its mean value in the left ventricle of 1.52 g/ml is not markedly different from the \( \lambda_{\text{hit}} \) value for left ventricle of 1.54 g/ml. Since \(^{131}\)I-iodoantipyrine has a volume distribution in the human body similar to that of water,\(^17\) it is of interest to compare the experimentally determined \( \lambda_{\text{hit}} \) value with that predicted on the basis of relative water content in blood and myocardium.\(^21\)\(^-\)\(^27\) Our data on the water content of the canine left ventricle (0.7965 g/g, Table 3) is in good agreement with the data reported by others.\(^28\)\(^-\)\(^30\) Utilizing this value of left ventricular water content and the plasma water content of 0.93 g/ml, an indicator distributed solely in accordance with the water content should have a plasma-left ventricle partition coefficient of only 1.17 g/ml; therefore, our experimental \( \lambda_{\text{hit}} \) value in the left ventricle is higher than that predicted on the basis of relative water content in blood and myocardium. The \( \lambda_{\text{hit}} \) value of the right ventricle is similarly higher than that predicted on the basis of relative water contents.

The present investigation has demonstrated that, when an indicator has a \( \lambda_{\text{CP}} \) considerably different from unity (e.g., \(^{123}\)Xe), changes in hematocrit may cause significant variations in \( \lambda_{\text{hit}} \). Failure to use the proper \( \lambda_{\text{CP}} \) for the appropriate hematocrit may give rise to errors in blood flow calculations. Such errors become insignificant for indicators with \( \lambda_{\text{CP}} \) close to unity (e.g., \(^{131}\)I-iodoantipyrine). The effect of hematocrit variations on coronary blood flows calculated from the washout of these two indicators is presented in the next paper.\(^31\)

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Partition of xenon and iodoantipyrine among erythrocytes, plasma, and myocardium.

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