Determination of Blood Volume in the Heart and Lungs and the Cardiac Output through the Injection of Radiophosphorus

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The dilution curve of the specific activity of the erythrocytes in the arterial blood after intravenous injection of labeled erythrocytes with P32 has been treated mathematically. It is possible with the help of the dilution curve to calculate the minute volume of the heart and the thoracic pool (the residual blood of the heart + the blood content of the lungs). The values of the thoracic pool amount to about 30 per cent of the total circulatory blood-volume.

THIS REPORT describes a method for the estimation of the cardiac output and the blood volume of the heart and lungs (referred to as the Pool Volume) by the use of red cells labeled with radioactive phosphorus (P32). A theoretic analysis of the experimentally obtained data has led to the development of a formula for the cardiac output exhibiting a certain similarity to earlier formulas reported by Kinsman, Moore and Hamilton.4

METHOD

A sample of venous blood, taken from the patient to be studied, is incubated with radiophosphorus in the form of sodium acid phosphate. The red blood corpuscles in the sample are consequently labeled with P32 according to the method of Hevesy and associates.1–3 A given quantity of the labeled material is re-injected into the antecubital vein. Arterial blood is then serially sampled at short intervals. The concentration of radiophosphorus in the extracted samples having been ascertained, a curve (referred to as the Dilution Curve) may be plotted of the arterial concentration, c, as a function of time. The characteristics of such dilution curves under normal and abnormal circumstances have been reported in more detail previously.3–4 Such a dilution curve is illustrated in figure 1.

Examination of this figure will show: (1) That maximum concentration at Point A of the curve is derived from the concentration of the injected indicator which for the first time passes the testing point (here called the primarily circulating indicator). (2) That maximum concentration at Point L is derived partly from the concentration of the indicator passing through the body for the second time (after having followed the shortest possible course through the body) and partly from the primarily circulating indicator. (3) That the recirculation at Point B of the curve sets in before the whole volume of indicator has passed the testing point for the first time. At Point L of the curve the concentration is derived partly from the respective concentrations of the recirculating indicator (E) and the primarily circulating indicator (F).

Because of the impossibility of distinguishing E from F by direct determination, a method must be developed to do this mathematically. That is to say, one must know the equation of the curve GB to be able to extrapolate the curve beyond the Point B.

In order to examine whether the curve has an exponential form, the logarithm of the concentration (log c) has been drawn as a function of time (Fig. 2). It then appears that the curve segment GB has the character of a straight line with the equation

\[ \log c = -\lambda t + \alpha \]  

(1)

where \(-\lambda = \) the slope of the line, \(t = \) the time, \(c = \) the concentration, \(\alpha = \) a constant. It therefore seems practically justifiable to give the equation of this segment of the curve as:

\[ c = c' e^{-\lambda t} \]  

(2)

* A glossary of symbols used in text, figures and equations is given in the Appendix, page 83.
where $e$ = the base of the natural log. system (appr. = 2.72), and $c'$ = a constant.

If the perpendicular axis of a diagram like that of figure 2 is logarithmic, it seems rather probable that part of the curve thus obtained will assume, more or less, the character of a straight line even in those cases where the original curve noticeably diverges from the exponential form.

It thus seems justifiable to try to analyze the mixing conditions from a more theoretic point of view. We will therefore examine the mixing process in a system of receptacles through which a fluid is allowed to flow. A quantity of indicator is then injected at Point A$_1$ (fig. 3). This system of receptacles has been designed so as to resemble the circulatory system of heart and lungs.

The quantity of indicator which per unit time passes Point B$_1$ of the system of receptacles is a function of time $[=f_1(t)]$, as is also the quantity of indicator which per unit time passes C$_1$=[=f$_2$(t)].

Thus, $\frac{dm}{dt} = f_1(t) - f_2(t)$  \hspace{1cm} (3)

where $m$ = the amount of indicator in the receptacles.

When the greater part of the indicator has passed the testing point, D$_1$ (fig. 3), and before the recirculation has set in, it may, with fair approximation, be assumed that $f_1(t) = 0$, as practically all the indicator must then have passed Point B$_1$. Further, $f_2(t) = Xc'_1$
where \( c'_1 \) = concentration at Point \( C_1 \) in the receptacles (fig. 3), and \( X = \) rate of flow (in liters per minute)

Thus, \( \frac{d}{dt}m = -Xc'_1. \)

The rate of flow through the receptacles is constant. The mean concentration \( c_m \) in the receptacles (excluding the recirculating indicator) is necessarily smaller than the concentration \( c'_1 \). Therefore it may be assumed that

\[ c'_1 = S \cdot c_m \]

where \( S \) is a factor greater than 1.

Thus, \( \frac{d}{dt}m = -XSc_m = -Xc'_1 \frac{m}{V} \) \( \Rightarrow \frac{d}{dt}m = -Xc'_1 \frac{m}{V} \) \( \Rightarrow \frac{d}{dt}m = -Xc'_1 \frac{m}{V} \) \( \Rightarrow \frac{d}{dt}m = -Xc'_1 \frac{m}{V} \)

where \( V = \) volume of the receptacles in liters. Integration of Equation 4 gives

\[ m = m_0 e^{-(X/S)Vt} \]

FIG. 3.—EQUIVALENT HYDRODYNAMIC SYSTEM.

where \( m_0 = \) the integration constant. Hence from Equation 5 we get by differentiation:

\[ \frac{d}{dt}m = -m_0 \cdot \frac{XS}{V} \cdot e^{-(X/S)Vt} \]

In this equation every symbol refers to the conditions in the receptacles. Equation 6 may be compared with Equation 2 which was derived from practical determinations.

Equation 2 gives the concentration at a point corresponding to Point \( D_1 \) in Fig. 3. Through multiplication of Equation 2 by the cardiac output, \( X_1 \), we get

\[ X_1c = X_1c'_1 e^{-Mt} \]

but \( X_1c = -\frac{d}{dt}m_1 \) where \( \frac{d}{dt}m_1 \) = the amount of indicator passing the testing point per unit time.

\[ \therefore \frac{d}{dt}m_1 = -X_1c'_1 e^{-Mt} \]

A comparison between the practically obtained Equation 7 and the mathematically obtained Equation 6 shows that both are of exponential form. Therefore, the circulatory conditions in the body may be expressed in the following form:

\[ \frac{d}{dt}m_1 = -X_1c'_1 e^{-(X_1S_1/Vp)t} \]

where \( V_p = \) the pool volume.

\( S_1 = \) a factor > 1, illustrating the ratio of the concentration at the test point to the mean concentration of the primarily circulating indicator in heart and lungs during the time interval \( HN \) (fig. 1).

As further support for the correctness of Equations 7 and 8 the works of Kinsman, Moore, and Hamilton, who reached the same result, may be cited. These workers built up a mechanical system of the type shown in figure 3, which reproduced as closely as possible the actual conditions existing in the heart and lungs. The indicator injected at a point corresponding to \( A_1 \) in figure 3 was conveyed by means of a pumping system through the receptacles and past the testing point. By an arrangement such as this, disturbances from the recirculating indicator may be avoided and the dilution curve may be followed during a considerably longer period than is possible in the human body.

**Calculation of Cardiac Output**

From a curve of the type shown in figure 1 the cardiac output may be estimated, since there are two expressions for the total quantity of indicator:

\[ h_{iV}c_i = \int_0^\infty cX_1h \, dt \]

where \( h_i = \) the hematocrit of the injected sample, \( v_i = \) volume of injected labeled blood, \( c_i = \) concentration of indicator of the injected
sample, \( h \) is the hematocrit of the circulating blood.

Since it may be assumed that the cardiac output and the hematocrit of the circulating blood are constant under constant conditions, we may write

\[
h_i v_i c_i = X_1 h \int_0^\infty c \, dt
\]

Thus,

\[
X_1 = \frac{h_i v_i c_i}{h \cdot \int_0^\infty c \cdot dt}
\]

where \( \int_0^\infty c \, dt \) is the area limited by the curve DAGBJ (fig. 1) and the time-axis. Of this area the part DAGH (= \( R \)) must be determined graphically. The area below GBJ is determined as follows:

\[
\int_H^\infty c e^{-\lambda t} \, dt
\]

Therefore

\[
X_1 = \frac{v_i c_i}{h_i} \cdot \frac{h_i}{R + \int_H^\infty c e^{-\lambda t} dt}
\]

All time units expressed in minutes, all volumes in liters. \( c' \) and \( \lambda \) are constants to be determined from the curve segment GB. Suppose we have two points on GB: \( P_2 (c_2 t_2) \) and \( P_3 (c_3 t_3) \).

Then

\[
\begin{align*}
  c_2 &= c' e^{-\lambda t_2} \\
  c_3 &= c' e^{-\lambda t_3}
\end{align*}
\]

Thus,

\[
\begin{align*}
  \lambda &= \frac{\ln c_2 - \ln c_3}{t_2 - t_3} \quad (11) \\
  c_3 &= c' e^{-\lambda t_3} \quad (12)
\end{align*}
\]

Here only \( \lambda \) and \( c' \) are unknown.

**DETERMINATION OF THE BLOOD VOLUME OF THE HEART AND LUNGS (\( V_p \)).**

The time \( \Delta t \) (fig. 1) is the average time taken for the blood to travel from the point of injection to the testing point, that is, from the vein of one arm to the artery of the other. \( X_1 \cdot \Delta t = \) the quantity of blood found in the heart, lungs, arteries and veins from the heart to the elbow and to points equidistant to the elbow. The blood in the coronary arteries and veins is not included in the volume \( X_1 \cdot \Delta t \).

A comparison of Equations 7 and 8 shows that

\[
\frac{X_1 S_1}{V_p} = \lambda
\]

\[
\therefore V_p = S_1 \frac{X_1}{\lambda}
\]

Thus,

\[
V_p > \frac{X_1}{\lambda}
\]

Set:

\[
\frac{X_1}{\lambda} = V_2
\]

We have accordingly here established an upper limit \( V_1 = X_1 \cdot \Delta t \) and a lower limit \( V_2 = \frac{X_1}{\lambda} \).

The time \( \Delta t \) is usually considerably greater than the transit time through heart and lungs; in other words \( X_1 \Delta t \) is considerably greater than \( V_p \). On the other hand,

\[
V_p = S_1 \frac{X_1}{\lambda}
\]

where \( S_1 \) is the ratio between the concentration at the testing point and the mean concentration of the primarily circulating indicator in heart and lungs. Here \( S_1 \) is normally appreciably greater than 1, and hence \( V_p \) is much greater than \( \frac{X_1}{\lambda} \).

If one therefore puts \( V_0 = \frac{V_1 + V_2}{2} \) the divergence of the mean value \( V_0 \) from the real value \( V_p \) will be considerably lower than \( V_0 - V_1 \), respectively \( V_0 - V_2 \).

The total blood volume of the body has been determined from the horizontal part of the curve. This determination was made twenty to sixty minutes after injection. Due to the fact that after this period of time the blood has become homogeneously mixed with the indicator, the following equation has been obtained:

\[
V_t = \frac{c_1 v_1 k h_1}{c_0 h}
\]

where \( V_t \) is total blood volume of the body, and \( c_0 = \) concentration of the samples taken between twenty and sixty minutes after injection.

In some cases there has been difficulty in determining the injected amount \( V_i \). In these cases a constant \( K_1 \) has been introduced for the total blood volume; and the amounts of
$X_1, V_1,$ and $V_2$ have been calculated as percentages of the total volume, $K_1$.

**RESULTS**

The results are epitomized in tables 1 to 4 (see also figs. 4 to 7).

**Table 1.—Cardiac Output, Pool Volume of the Chest and Total Circulatory Blood Volume in Normal Subjects and in Patients with Heart Disease.**

<table>
<thead>
<tr>
<th>Case</th>
<th>Cardiac output ($X_1$) (liters)</th>
<th>Pool Volume</th>
<th>Total blood volume in the body ($V_3$) (liters)</th>
<th>% of total blood volume</th>
<th>Mean value of $V_4$ = $V_1 + V_2$ (liters)</th>
<th>Lower limit ($V_1 + V_2$) (liters)</th>
<th>Upper limit ($X_1 + X_2$) (liters)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3.7</td>
<td>2.9</td>
<td>2.85</td>
<td>33</td>
<td>8.6</td>
<td>2.2</td>
<td>4.0</td>
</tr>
<tr>
<td>2</td>
<td>4.4</td>
<td>2.2</td>
<td>1.3</td>
<td>32</td>
<td>5.5</td>
<td>1.9</td>
<td>2.5</td>
</tr>
<tr>
<td>3</td>
<td>5.0</td>
<td>1.9</td>
<td>1.2</td>
<td>34</td>
<td>4.5</td>
<td>1.1</td>
<td>2.3</td>
</tr>
<tr>
<td>4</td>
<td>2.3</td>
<td>1.3</td>
<td>1.1</td>
<td>29</td>
<td>4.2</td>
<td>1.2</td>
<td>2.5</td>
</tr>
<tr>
<td>5</td>
<td>1.35K</td>
<td>0.45K</td>
<td>0.15K</td>
<td>30</td>
<td>K</td>
<td>0.30K</td>
<td>K</td>
</tr>
<tr>
<td>6</td>
<td>1.60K</td>
<td>0.41K</td>
<td>0.29K</td>
<td>35</td>
<td>K</td>
<td>0.35K</td>
<td>K</td>
</tr>
<tr>
<td>7</td>
<td>0.79K</td>
<td>0.42K</td>
<td>0.21K</td>
<td>32</td>
<td>K</td>
<td>0.32K</td>
<td>K</td>
</tr>
<tr>
<td>8</td>
<td>1.10K</td>
<td>0.43K</td>
<td>0.17K</td>
<td>30</td>
<td>K</td>
<td>0.30K</td>
<td>K</td>
</tr>
</tbody>
</table>

**Table 2.—Roentgenologic Heart Volume and Hematocrit in Normal Subjects and in Patients with Heart Disease (Same Cases as in Table 1).**

<table>
<thead>
<tr>
<th>Case</th>
<th>Diagnosis</th>
<th>Roentgenologic heart volume (liters)</th>
<th>Body weight (Kg)</th>
<th>Hematocrit (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>mitral stenosis</td>
<td>3.1</td>
<td>70</td>
<td>44.5</td>
</tr>
<tr>
<td>2</td>
<td>&quot;</td>
<td>1.8</td>
<td>72</td>
<td>36.0</td>
</tr>
<tr>
<td>3</td>
<td>aortic insufficiency</td>
<td>0.85</td>
<td>69</td>
<td>43.0</td>
</tr>
<tr>
<td>4</td>
<td>orthostatic hypotension</td>
<td>—</td>
<td>60</td>
<td>50.0</td>
</tr>
<tr>
<td>5</td>
<td>normal case</td>
<td>0.60</td>
<td>66</td>
<td>—</td>
</tr>
<tr>
<td>6</td>
<td>&quot;</td>
<td>1.35</td>
<td>50</td>
<td>51.5</td>
</tr>
<tr>
<td>7</td>
<td>aortic insufficiency</td>
<td>1.72</td>
<td>45</td>
<td>59.0</td>
</tr>
<tr>
<td>8</td>
<td>&quot;</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

As seen from table 2, tests have been made on normal as well as pathologic cases. As a means of comparison, heart volumes determined through roentgen rays, according to the method of Liljestrand, Lysholm, Nylin and Zachrisson,7 have been given.

Heart volume = $K_2 \cdot \frac{4}{3} \pi \cdot \frac{a_2 \cdot a_3 \cdot a_4}{8} \quad (13)$

where $a_2$ = the largest diameter, $a_3$ and $a_4$ = the largest diameters perpendicular to $a_2$ and to each other, $K_2$ = a proportionality constant.

The heart volumes thus obtained consist not only of the blood volume of the heart but also of the muscle tissues of the heart. In the cases where the heart volume determined by x-ray gives a higher value than the blood volume in heart and lungs, these values do not contradict each other.

As appears from table 1, the blood volume
of heart and lungs seems to vary from 29 to 35 per cent of the total blood volume.

There is a certain correlation between the roentgenologic heart volume and the blood volume of heart and lungs. This is quite natural as there is reason to expect that a dilatation of the heart should be followed by a considerably increased quantity of residual blood in the heart.

Considering case 1, which afterwards went to autopsy, the quantity of residual blood of the heart during life was determined with the guidance of the ante- and postmortem roentgenologic determination of the heart volume and by the postmortem quantity of residual

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**Fig. 4.** X-ray of the Heart, Normal Subject (Case 5).

**Fig. 5.** Dilution Curve, Normal Subject (Case 5).

**Fig. 6.** X-ray of the Heart, Case 1. Heart volume = 3.1 liters.
blood. As a control, the displacement volume of the extracted heart was determined.

The following results were obtained: roentgenologic heart volume in vivo, 3.1 liters; roentgenologic heart volume after death, 2.2 liters; residual blood of the heart: 1.1 liters; displacement volume of the extracted heart, 2.2 liters.

It is evident from these results (1) that the roentgen volume diminished 0.9 liter at the moment of death, and 0.9 liter of blood must accordingly then have been pressed out of the heart, as it cannot be imagined that the heart muscle should have undergone such a considerable reduction; (2) that the blood volume of the heart in vivo had been 2.0 liters, and as the stroke volume is of the size 0.1 liter there is evidently here a very large quantity of residual blood.

The values of cardiac output, obtained by this method are as a rule higher than those obtained with the Fick method, as an arterial puncture cannot be executed under as quiet circumstances as a determination according to the gas-analytical method. As to the determination of the pool volume, this increase is at least partly compensated by a decrease of the time Δt and an increase of the constant λ. The injection has generally taken place five to fifteen minutes after the arterial puncture to create at least as quiet circumstances as possible. The results of the original measurements for two of the cases are to be found in tables 3 and 4. Corresponding curves and x-ray of the heart are found in figures 4-7.

**ERROR OF CALCULATION**

From equation 10 we get through logging and differentiation:

\[
\frac{dX_i}{X_i} = \frac{dv_i}{v_i} + \frac{dc_i}{c_i} - \frac{dn_i}{n_i} + \frac{dh_i}{h_i} - \frac{dh}{h}
\]

where \( n_i \) = the denominator = \( R + \int_{H}^{\infty} e^{\lambda t} dt \)

\[
\frac{dv_i}{v_i} = 2 \text{ per cent} \quad \frac{dc_i}{c_i} < 2 \text{ per cent} \quad \frac{dh_i}{h_i} = \frac{dh}{h} < 1 \text{ per cent}
\]

\( \frac{dn_i}{n_i} \), depending both on \( R \) and the integral. \( R \) can be determined with fairly good accuracy. However, concerning the integral, even small variations in \( \lambda \) may cause rather great variations of the integral value. The uncertainty of the integral value amounts to some 10 per cent.

For the above stated cases

in the normal case: \( \frac{dn}{n} = 5 \text{ per cent} \)

in Case 1: \( \frac{dn}{n} = 6 \text{ per cent} \)

\( \frac{dX_i}{X_i} = 10 \text{ per cent} \). That is, the uncertainty in determining the cardiac output amounts to about 10 per cent.

**SUMMARY**

An indicator substance, \( P^{32} \), has been injected into an arm vein. Immediately afterward blood samples have been taken at about three-second intervals from the artery of the opposite arm. The concentration of indicator of the obtained samples has been drawn up as a function of time. A formula has been given for estimating the cardiac output from the obtained curve. Moreover, formulas have been given for estimating the upper as well as the lower limit of the blood volume in heart and lungs. It seems that 29 to 35 per cent of the total blood volume is contained in heart and lungs according to the measurements obtained.
APPENDIX: Symbols

A Point in fig. 1
A₁ Point in fig. 3
a₂ The largest diameter in Equation 13
a₁ and a₄ The largest diameters perpendicular to a₂
and to each other
B Point in fig. 1
B₁ Point in fig. 3
c Indicator concentration at testing point (variable)

c' Constant in Equation 2
C₁ Concentration at Point C₁
C₂ Mean pool concentration at the time N (fig. 1);
derived from primarily circulating indicator
cₐ Concentration in samples taken twenty to sixty
minutes after injection
cᵢ Concentration of injected material

cᵅ Mean concentration in the receptacles
cₜ Concentration at Point P₁
D Point in fig. 1
D₁ Point in fig. 3
E Length in fig. 1
e Base of the natural log. system (appr. 2.72)
F Length in fig. 1
f₁ A function
f₂ A function
G Point in fig. 1
H Point in fig. 1
h Hematocrit in the body
hᵢ Hematocrit in the injected material
J Point in fig. 1
K Point in fig. 1
K₁ Total blood volume in the body (used in table 1)
K₂ Constant in Equation 13
L Point in fig. 1
m Amount of indicator in the receptacles
m₀ Integration constant
m₀ Amount of primarily circulating indicator in
heart and lungs at the time interval H-N (fig. 1)
N Point in fig. 1

P₁ Point in fig. 1

P₂ Point in fig. 1

P₄ Point in fig. 1

R Area between segment DAGH and t-axis

S A factor (> 1) = cᵅ

S₁ A factor (> 1) = cᵅ

t General time nomenclature
t₁ Time in fig. 1
t₂ Time in fig. 1
Δt Time interval in fig. 1

V Volume of the receptacles

Vₚ Pool volume

V₁ Total blood volume in the body

V₀ Mean value of V₁ and V₂

V₂ Upper limit of pool volume

V₃ Lower limit of pool volume

v Volume of injected blood

X Rate of flow in receptacles

X₁ Cardiac output

a Constant in Equation 1

λ Slope of the line in Equation 1

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