Quantitative Estimation by Indicator-Dilution Technics of the Contribution of Blood from Each Lung to the Left-to-Right Shunt in Atrial Septal Defect

By H. J. C. Swan, M.B., Peter S. Hetzel, M.D., and Earl H. Wood, M.D.

A method based on the initial portion of indicator-dilution curves has been used to determine the proportion of blood from each lung which drains anomalously. The results obtained appear to substantiate the derivation and permit the expression, in numerical values, of the greater proportion of anomalous drainage of blood from the right lung in the usual case of atrial septal defect. The principal assumptions pertaining to the method are discussed in some detail.

SYSTEMIC arterial dilution curves of T-1824 have been used to demonstrate the hemodynamic derangement of "anomalous drainage" of pulmonary venous blood in certain forms of acyanotic congenital heart disease characterized by a left-to-right shunt. In the usual case of atrial septal defect the proportion of blood from the right lung which drains anomalously is greater than from the left lung. This paper outlines a method for the estimation of the magnitude of the anomalous drainage from each lung.

The principal features of dilution curves obtained following injection of an indicator into the right and into the left pulmonary arteries in the usual case of atrial septal defect are evident in the example given in figure 1. The initial peak of concentrations, which occurs at 10.4 sec. and 10.0 sec. after injections of dye into the right pulmonary artery and into the left pulmonary artery respectively, is due to indicator that drains normally to the left ventricle on the first circulation. The second peak of concentration, which occurs at 14.8 sec. and at approximately 14.5 sec. following injection of indicator at each of these respective sites, represents indicator that has drained anomalously to the right atrium, and has passed, principally by way of the left pulmonary artery, to the systemic circulation following its second passage through the lungs.

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THEORETIC CONSIDERATIONS

In the absence of mitral insufficiency, or of an interventricular or aortopulmonary communication, the cavity of the left ventricle may be regarded as a final common path, in that all of a substance which enters will pass, without delay, to the systemic circulation. For reasons that are made readily apparent in a later section, quantitative analysis which involves the determination of components of dye concentration is best confined to that part of the dilution which represents the curve of increasing concentration due to dye which passes to the systemic circulation on its first circulation. The calculation of the proportion of anomalous drainage that occurs from each lung is based on a determination of the fraction of the quantity of dye injected into the right or left pulmonary artery which reaches the left ventricle on its first circulation.

Calculation of the Blood From Each Lung Which is Shunted Left-to-right. Considering arterial dilution curves obtained in a normal subject, the equation* for the determination of cardiac output, Qs, in its usual form and application is:

\[ Q_s = \frac{60 I}{C \cdot T_p} \]  

(1)

in which I is the quantity of indicator in mg., \( T_p \) is the passage time in sec., \( C \) is the average concentration in mg./L. and \( Q_s \) is the systemic

* The symbols used have been defined in a previous publication.
Fig. 1. The calculation of the magnitude of the left-to-right shunt from each lung in a patient with an atrial septal defect (case 10). In the upper panel the circulatory paths taken by indicator injected into the right and into the left pulmonary artery are represented. Beneath each diagram the dilution curves obtained in case 10 are depicted for the respective injection sites. Symbols as used in text. Beneath each dye curve are calculations of \( t \) (using equation 5) and of \( S_R \) and \( S_L \) (using equation 6) based on \( T_b \), \( C_p \), and \( Q_s \).

The dilution curve seen in the presence of a left-to-right shunt may be considered as having in its initial portion a dilution curve of normal contour due to that indicator which has reached the left ventricle on its first circulation, on which is superimposed further concentration changes due to recirculated indicator. If no recirculation were present, the magnitudes of the time and concentration components of the dilution curves would be functions of the systemic flow and the quantity of dye injected into the central circulation, all of which reaches the left ventricle. In the same manner, a relationship will exist between the systemic blood flow, \( Q_s \), the components of the initial part of the dilution curve (if no recirculated indicator obscured its dimensions) and the quantity of dye entering the left ventricle. Designating this quantity \( i \), equation 4 may be rewritten in terms of the initial dilution curve prior to its peak of concentration.

\[
i = \frac{Q_sC_pT_b}{44.5}.
\]  

In this equation, \( C_p \) and \( T_b \) pertain to the abnormal dilution curve. Equation 5 contains 2 unknown terms, \( i \) and \( Q_s \), while values for \( C_p \) and \( T_b \) can be measured from the recorded dilution curve (fig. 2). If agreement is assumed between estimates of systemic blood flow by indicator-dilution technics and by the Fick method, a value for \( Q_s \), the systemic blood flow, determined by the latter estimate may be used to permit solution of equation 5 in terms of \( i \). This value represents the number of milligrams of dye which, under these conditions, entered the left ventricle in order to produce a dilution curve with the observed values of \( C_p \) and \( T_b \).

The assumptions underlying the use of these values are discussed in a later section.

Since \( i \) represents the quantity of dye that enters the left ventricle and hence drains normally, then, if \( I_o \) is the total quantity of dye injected, \( I_o - i = \) quantity of dye draining anomalously and

\[
\frac{I_o - i}{I_o} = S_R \text{ or } S_L
\]

where \( S_R \) or \( S_L \) represents the fraction of dye, shunted from left to right through the defect, in the blood returning from the right or left lung.
following injection of dye into the right or left pulmonary artery. If uniform mixing of dye and blood is assumed, this equals the fraction of blood draining from the respective lungs to the right atrium.

If the assumption is also made that, of the total volume of blood flowing through both lungs, 48 per cent traverses the left lung, and 52 per cent the right lung, then the proportion of the pulmonary blood flow, \( S \), which drains anomalously is given by the equation

\[
S = 0.48 S_L + 0.52 S_R
\]

in which \( S \) equals the total left-to-right shunt as a fraction of the total pulmonary flow.

Calculations of Mean Pulmonary Recirculation Time and Pulmonary Blood Volume. The systemic arterial dilution curves recorded following injection of indicator into the right pulmonary artery were characterized by the presence of 2 peaks of concentration. Each of these peaks represents a maximal concentration of indicator—the first, that due to indicator passing directly to the left ventricle—the second, that due to indicator which had recirculated through the pulmonary vascular bed before entering the left ventricle. The interval between these peaks has been designated the "lung recirculation time" (LRT). A precise definition of this interval in terms of velocities, vascular path lengths and quantities of indicator is not attempted here. In general terms, the interval would appear to be related to the time taken by the average particle to traverse the pulmonary vascular bed. Adapting the formula of Hamilton and associates and using the value LRT as a mean pulmonary circulation time, the volume of blood in the lungs was calculated:

\[
PBV = \frac{LRT \times Q_F}{60 \times W}.
\]

If \( Q_F \) is the pulmonary blood flow in ml./min. (see later), \( W \) is body weight in kilograms and \( LRT \) is given in sec., then \( PBV \) is the pulmonary blood volume in ml./Kg. Theoretically, the value so derived will have the same relation to the true volume of blood within the heart and lungs as the LRT bears to the mean pulmonary circulation time.

**Methods**

Each patient was studied by the cardiac catheterization procedure. As outlined previously, arterial indicator-dilution curves following injection of T-1824 into the right and into the left pulmonary artery while the patient breathed 100 per cent oxygen were recorded by means of oximeters fastened to each ear, and simultaneously by means of a cuvette oximeter through which blood from the radial artery was allowed to flow. Since it was possible to calibrate the deflection produced by the cuvette oximeter in regard to concentration of T-1824, the dilution curves recorded utilizing this instrument are the basis for the data in this report. The dilution curves recorded by means of the ear oximeter have been reproduced for each patient previously. The numerals used refer to the same patients in each paper. Quantitative data were not obtained in case 11.

The pulmonary, \( Q_F \), and systemic, \( Q_S \), blood flows were calculated (in L./min.) from the equations:

\[
Q_F = \frac{VO_2}{C_{PVO_2} - C_{PAO_2}}
\]

\[
Q_S = \frac{VO_2}{C_{SAO_2} - C_{MVBO_2}}
\]

in which \( VO_2 \) is the value for oxygen consumption in ml./min., and \( C_{PVO_2}, C_{PAO_2}, C_{SAO_2} \) and \( C_{MVBO_2} \) represent the oxygen content (ml./L.) of the pulmonary vein blood, pulmonary artery blood, systemic artery blood, and mixed venous blood, respectively. The value for \( C_{PVO_2} \) while the patient breathed 100 per cent oxygen was taken to be equal to \( C_{SAO_2} \) and was found to exceed the oxygen capacity of arterial blood by 1.8 ml./100 ml. of blood in every instance. Values for \( C_{PAO_2} \) and \( C_{SAO_2} \) were determined by the method of Van Slyke. The value for \( C_{MVBO_2} \) was determined by the relationship

\[
C_{MVB} = \frac{2 \times C_{IVC} + C_{SVC}}{3}
\]

where \( C_{IVC} \) and \( C_{SVC} \) represent the oxygen content of inferior and superior vena cava blood respectively. Assuming no right-to-left shunt of significance to be present, the percentage of left-to-right shunt was calculated:

\[
L-R \text{ shunt} = \left( \frac{Q_F - Q_S}{Q_F} \right) \times 100.
\]

**Results**

Patients with Atrial Septal Defect. In the 11 patients with atrial septal defect the pulmonary

* Symbols modified from Pappenheimer and associates.
blood flow as measured by the Fick principle averaged 17.8 L./min. (range 9.6 to 27.0 L./min.). No patient had demonstrable arterial desaturation. The proportion of left-to-right shunt averaged 70 per cent (range 55 to 81 per cent). The indicator-dilution curves recorded following injection of T-1824 into the right pulmonary artery had average appearance and build-up times of 6.7 and 4.2 sec. Following injection into the left pulmonary artery, these values were 6.1 and 4.6 sec., respectively. The average peak concentration time for the curves recorded following injection at the former site was 10.9 sec. and at the latter injection site was 10.7 sec.

Using equations 5 and 6, the proportion of the blood traversing the right lung that drained anomalously (shunted from left to right) averaged 84 per cent (range 75 to 97 per cent), and of the blood traversing the left lung an average of 54 per cent (range 35 to 75 per cent) drained anomalously. The proportion of the total volume of the blood that drained anomalously, calculated by means of equation 7, had an average value of 70 per cent (range 63 to 80 per cent). The relation between this value calculated by means of the indicator-dilution curves (equation 7) and the value obtained by using the estimates of pulmonary and systemic blood flow (equation 9) is shown in figure 2. The average of the difference between the values determined by each of these methods was 0 and the standard deviation of these differences was 6.6 per cent. The proportion of the blood which drained anomalously, having traversed the right lung, exceeded that which drained anomalously after traversing the left lung in every instance. The average difference was 31 per cent with a wide variability (8 to 61 per cent). A consistent relationship between this difference and the magnitude of the shunt could not be demonstrated.

The "lung recirculation time" (LRT) was found to average 4.4 sec. (range 3.2 to 5.5 sec.). The volume of blood in the heart and lungs was determined according to equation 8. The average value was 23 ml./Kg. (range 12 to 36 ml./Kg.). The roentgenograms of the chest of every patient, except for patient 12, were graded according to the prominence of the pulmonary vascular markings by Dr. André Bruwer of the Section of Diagnostic Roentgenology. The relation between this grading and the values obtained by equation 8 is shown in figure 3. Except for patient 7, in whom other
abnormal findings were minimal, the agreement obtained was satisfactory.

Patients with Anomalous Pulmonary Venous Connection or with Persistent Common Atrioventricular Canal. The relevant data for these patients are given in the table.

In case 13, in which no left-to-right shunt had occurred from the left lung, the calculation based on the dye-dilution curve indicated a loss of 5 per cent of the dye that had been injected into the left pulmonary artery. In case 14, it was calculated that 15.9 mg. of T-1824 were required to produce the dilution curve recorded following injection of indicator into the right pulmonary artery (which was the artery supplying the normally connected lung in this instance). However, only 15 mg. of T-1824 had been injected, and an error known to be in excess of 6 per cent resulted. Calculations based on the dilution curves in case 15 showed good agreement between the magnitude of the shunt as determined by the dye method and from the flow values.

In the patients with persistent common atrioventricular canal, the calculations supported the impression, based on inspection of the curves, that the proportion of anomalous drainage from each lung was more nearly equal than in many cases of atrial septal defect. In 2 of the cases of atrial septal defect presented in this paper, this difference in the proportion of blood draining anomalously from each lung was equally small, but each of these patients had pulmonary recirculation of a more severe degree.

Discussion

This paper represents an attempt to express in quantitative terms a phenomenon that may be qualitatively deduced by inspection of indicator-dilution curves in patients with atrial septal defect. It is justified only if the principal assumptions are reasonable, and if the values derived thereby do not deviate substantially from estimates of the same quantities by other accepted methods. This discussion is confined to a consideration of the quantitative method, the more qualitative implications having already been presented in detail.1

The estimation of pulmonary, \( Q_p \), and systemic, \( Q_s \), blood flow is first to be considered. The oxygen content of blood samples from the inferior vena cava and superior vena cava is utilized to calculate \( C_{\text{MVO}_2} \). Any inaccuracy in these values will cause an error in \( Q_s \). However, when the difference \( (C_{\text{Sao}_2} - C_{\text{MVO}_2}) \) is considerable, small errors in either \( C_{\text{Sao}_2} \) or \( C_{\text{MVO}_2} \) are of minor significance. Concerning \( Q_p \), errors of significance appear more likely. Although only small absolute errors are likely in the estimation of \( C_{\text{Pvo}_2} \) and \( C_{\text{PaO}_2} \), an error of considerable magnitude is possible when the difference \( (C_{\text{Pvo}_2} - C_{\text{PaO}_2}) \) is small. This potential error is reduced in expressing the relative magnitude of the left-to-right shunt as a ratio

\[
\frac{Q_p - Q_s}{Q_p}.
\]

Agreement between estimates of systemic blood flow by the dye-dilution method and by the Fick method have been reported by several investigators7,8 and is not discussed further here. The standard deviation of differences between these methods found in this laboratory was ±16 per cent.11 There is also general agreement as to the division of the total volume of the pulmonary blood flow, so that approximately 52 per cent traverses the right lung and 48 per cent traverses the left lung. This division is related to the total quantity of lung tissue that comprises each lung, and, since it has been found to hold during exercise,8 it appears likely to apply also in the presence of pulmonary recirculation. Even moderate deviations from these relative proportions will affect the principal calculations but little.

The data of Hetzel and associates1 relate the value \( (C_p \times T_B) \) to the total area subtending the dilution curve obtained in normal subjects and in patients without an intracardiac shunt, the effect of indicator that has traversed the systemic capillaries having been eliminated. The variability of this relation over a wide range of values of systemic blood flow was sufficiently small to enable the total area of the dilution curve to be predicted with considerable accuracy from the values for \( C_p \) and \( T_B \). Further, in 4 normal dilution curves recorded following injection of indicator into the left ventricle or aorta, the relation of \( (C_p \times T_B) \) to
the total area of the curve (excluding the effect of systemic recirculation) was similar.

The quantitative application of indicator-dilution technics in the presence of pulmonary recirculation due to an interatrial communication is now considered. Clearly, many additional assumptions pertaining to the use of these technics, as outlined by Hamilton and associates, Zierler, and others, are implicit in the following paragraphs, in which those aspects that appear most relevant to the present problem are presented.

**Adequacy of Mixing.** Following injection of indicator into the right or the left pulmonary artery, it is assumed that the dye is representatively mixed with the blood traversing the respective lung. In practice, this may not always be attained because of difficulty in avoiding a selective injection of indicator into one or other of the branches of the right or left pulmonary artery. In some patients significant differences have been demonstrated between the drainage of blood from the upper, middle, and lower lobe pulmonary veins, in particular from the right lung. However, in the few instances in which a repeat injection of indicator has been made into a main pulmonary artery, closely similar curves have been obtained.

**Determination of T_b.** The instant at which indicator is first recognized at the sampling site, t_b,* is clearly one of the determinants of T_b. A finite concentration of indicator is necessary for recognition. Further, at any instant the concentration is a function of the total quantity of indicator that has entered the left ventricle on its first circulation. Thus, the instant at which the minimal detectable concentration of indicator can be recognized is in part dependent on the proportion of blood that drains normally. It is possible that when small quantities of indicator enter the left ventricle the true instant of appearance, t_b, may not be recognized and an error in determination of T_b may result. For the 11 patients with atrial septal defect considered in this paper, the average peak concentration times for the dilution curves recorded following injection of indicator

into the right and into the left pulmonary artery were 10.9 and 10.7 sec., and the values for T_b were 4.2 and 4.6 sec., respectively. In several patients the differences between the value of T_b for each of these injection sites were considerable (table 1). Where this was the greatest (case 3), the magnitude of S_RI was recalculated on the basis of the greater value of T_b (that is, T_b for the left pulmonary artery curve). The value for S_RI declined from 89 per cent to 85 per cent, a relative error of 4.7 per cent. When applied to the calculation of the proportion of blood draining normally, this substitution in the value of T_b resulted in an increase from 11 to 15 per cent, a relative error of 27 per cent.

The instant of peak concentration, t_p, is the second determinant of T_b. The clear identification of a peak of concentration due principally to that indicator which had drained normally was possible in every instance. The influence of recirculated indicator on the position in time of this peak is probably small, for a decline in concentration following the initial peak was usually seen before the further increase in concentration due to recirculated indicator had occurred (fig. 1). Further, the peak concentration time, PCT, from the right lung was not significantly longer than from the left lung, even in those patients in whom the proportion of the blood draining anomalously differed greatly.

**Determination of C_p.** The initial peak of concentration of indicator is taken to represent only that quantity of indicator which drains normally, and is used in equation 5 as the value for C_p. Since the average pulmonary recirculation time has been shown to be of the same order of magnitude as the average build-up time, this assumption needs further examination. First, inspection of the majority of curves recorded following injection of dye into the left pulmonary artery indicates that a relatively small quantity of dye is draining anomalously, since the change in concentration due to recirculated indicator appears only as a small deformation on the slope of declining concentration. In this instance, the absolute quantity and the relative proportion of recirculated indicator that distorts the initial

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* The use of lower case t refers to instants of time, while capital T refers to intervals of time.
TABLE 1.—Pulmonary and Systemic Blood Flows, Proportion of Anomalous Drainage from Each Lung and Estimates of Pulmonary Circulation Times in Patients with Atrial Septal Defect, Anomalous Pulmonary Venous Connection and Persistent Common Atrioventricular Canal

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<th>Case</th>
<th>Pul.</th>
<th>Sys.</th>
<th>Shunt L-R, %</th>
<th>Blood flow values, L./min.</th>
<th>Right lung</th>
<th>Left lung</th>
<th>Total shunt (both lungs), %</th>
<th>Total shunt, ml./Kg.</th>
<th>Pulmonary circulation times, sec.</th>
<th>Pulmonary blood volume, ml./Kg.</th>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>AT*</td>
<td>BT*</td>
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<td>BT*</td>
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Atrial septal defect

Anomalous pulmonary venous connection

Persistent common atrioventricular canal

* AT = appearance time.  BT = build-up time.  PCT<sub>r</sub> = peak concentration time including recirculation.  LRT = lung recirculation time.
† Agenesis of upper lobe of right lung. Calculations based on the assumption that the blood flowing into the main pulmonary artery 42 per cent traverses the right lung and 58 per cent the left lung.
‡ The value for PCT<sub>r</sub> used in these cases is the interval between the instant of injection and the instant of peak concentration (which is the first peak) following injection of indicator into the artery of the anomalously connected lung.

The peak of concentration is also likely to be small. Second, when the initial deflection itself is small, as in about half of the dilution curves recorded following injection of dye into the right pulmonary artery, it is readily apparent that no great quantity of recirculated indicator is passing to the sampling site. It could well be argued that a relatively large proportion of recirculated indicator is contributing to this initial peak. However, the slight decline in concentration which usually follows this peak implies that for this short period the concentration of indicator which has drained normally is diminishing more rapidly than the concentration due to recirculated indicator is increasing. Since the build-up slope of a normal dilution curve is more rapid than the slope of declining concentration, this suggests that the contribution of recirculated indicator to C<sub>p</sub> may not be great in this type of dilution curve.

A greater possibility of error in applying the value C<sub>p</sub> in equation 5 arises when the initial peak of concentration is intermediate in magnitude, and approximately equals the first peak of concentration due to recirculated
indicator. The considerations outlined in previous paragraphs regarding the significance of a definite decline or plateau of concentration following the initial peak suggest that the effect of recirculated indicator may not be excessive if the “lung recirculation time” is 4.5 sec. or greater. When this interval is short, as in case 16, for example, the contribution of recirculated indicator to the initial peak of concentration is probably considerable.

In each of the instances discussed in the preceding paragraphs, the effect of recirculated indicator is to increase the concentration of indicator assumed to represent the indicator draining normally—and results in a falsely low value for the magnitude of the proportion of indicator draining anomalously. The direction of this error is opposite to that which may result from an underestimate of $T_b$.

When a comparison was made between the values for the proportion of pulmonary blood shunted based on the indicator-dilution curves and the values obtained by the application of the Fick principle, a satisfactory correlation was obtained. The use of the same estimate of systemic blood flow in each determination does not appear to invalidate the significance of this comparison. The agreement found is the principal justification for the conclusion that the values obtained based on the indicator-dilution curves reflect the proportion of blood draining anomalously from each lung with a reasonable degree of accuracy—possibly of the same order as estimates of systemic blood flow by the Fick and by the dye-dilution methods.

It is perhaps of academic interest that a calculation of the proportion of the blood draining anomalously from each lung can be attempted with apparent success. The expression of a result in numerical values, however, has certain practical advantages in regard to the presentation of definitive data. Examination of certain of the assumptions that have had to be made indicates the problem of quantitative interpretation of concentration curves that may be distorted by the presence of recirculated indicator. Quantitative measurements based on concentration values following the initial peak can include several components—that due to dye which has drained normally, and those components due to dye which has recirculated through the lungs 1 or more times. It would appear that of methods of analysis based on the later portion of such dilution curves those of an empirical nature depending on relationships such as the disappearance time—build-up time ratio would be of most value.13

**Summary**

A method of analysis of indicator-dilution curves in cases of anomalous drainage of pulmonary vein blood has been derived whereby the proportion of the blood from each lung that drains anomalously may be calculated. The method utilizes measurements of build-up time and peak-concentration due to dye that drains normally, and an independent estimate of systemic blood flow. In atrial septal defect the proportion of blood draining anomalously from right and left lungs averaged 84 and 54 per cent respectively. The sums of these values agreed well with estimates of left-to-right shunt by the more conventional method

$$\frac{Q_p - Q_s}{Q_r}$$

The standard deviation of the differences between the methods was 7 per cent.

Estimates of lung recirculation time (average 4.4 sec.) indicated a very rapid pulmonary circulation in many patients. Values for pulmonary blood volume in these patients were 1.0 to 2.5 per cent of body weight in most instances.

**Summario in Interlingua**

Esseva disveloppate un metodo pro le analyse de curvas de dilution de indicator in casos de anormal drainage de sanguine pulmono-venose, permittente le calculation de proportion de sanguine veniente ab le pulmones individual. Le metodo utilisa mesura- tiones del tempore accumulatori e del concentra- tion maximal de colorantes a drainage normal insimul con un estimation indepen- dente del fluxo de sanguine systemic. In le presentia de defecto atrio-septal, le proportion de sanguine effluente de manera anomale ab le pulmones dextere e sinistre amontava, respectivamente, a valores medie de 84 e 54 pro cento. Le summa del valores esseva ben de
accordo con le proprtion \((Q_p - Q_s)/Q_p\). Le deviation standard del differentias esseva 7 pro-
cento.

Estimationes del tempore de recirculation pulmonar (valor median 4,4 sec) indicava in
multe patientes un rapidissime circulation pulmonar. Valores pro le volumele del sanguine
pulmonar (valor del casos esseva in le majori-
tate del casos 1,0 a 2,5 pro cento del peso
corporee.

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What we call sense or wisdom is knowledge, ready for use, made effective, and bears the same
relation to knowledge itself that bread does to wheat. The full knowledge of the parts of a steam
engine and the theory of its action may be possessed by a man who could not be trusted to pull
the lever to its throttle. It is only by collecting data and using them that you can get sense. One
of the most delightful sayings of antiquity is the remark of Heraclitus about his predecessors—that
they had much knowledge, but no sense.—William Osler. The Student Life. Farewell Address to
Quantitative Estimation by Indicator-Dilution Technics of the Contribution of Blood from Each Lung to the Left-to-Right Shunt in Atrial Septal Defect

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