Diagnostic Applications of Indicator-Dilution
Technics In Congenital Heart Disease

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Introduction

The diagnostic use of indicator-dilution technics in the study of congenital heart disease dates, for practical purposes, from 1950 with the nearly simultaneous description of methods for continuous recording of the concentration of Evans blue dye from Johns Hopkins University and from the Mayo Clinic. The diagnostic applications of indicator-dilution technics have been intensively applied and developed at the clinic since that time using the technics of intravascular injection of colored dyes almost exclusively. These various technics have proved of great value and for the last 10 years have, in this laboratory, been considered an indispensable tool in diagnostic studies of patients with congenital heart disease. They attain particular value when used in conjunction with various technics for catheterization of the right and left sides of the heart, and with combinations thereof. During this period more than 12,000 indicator-dilution curves of various types have been recorded in more than 3,600 patients studied in the cardiovascular laboratory.

The diagnostic as well as the investigative value of these technics has gradually received progressively widespread recognition. The rate of this progression has, however, been greatly accelerated in the last 2 or 3 years with more general availability of suitable instrumentation and particularly with the introduction of foreign gases for use as indicators in these technics. The first of these gases was nitrous oxide, the use of which was rapidly followed by the use of the radioactive gases Kr and I. The use of foreign gases as indicators in these dilution technics has contributed greatly to the ease of application of the technics by opening up a bloodless method of what in fact amounts to (1) sampling blood from the right side of the heart through the expedient of analyzing for the gas in the air equilibrated with this blood in the lungs and then expired, and (2) “injecting” the foreign-gas indicator into the left atrium by the expedient of introducing it into the inspired air where it is equilibrated in the lungs with the blood returning to the left side of the heart.

The development of miniature detectors suitable for introduction directly into the vascular system for recording of the indicator concentration in blood at desired sites in the circulatory systems has also expedited the application of these technics.

Although the advent of these new types of detectors and new indicators, particularly of the gaseous types, has in many instances greatly facilitated various applications of these technics, these applications are basically closely similar to those previously described, irrespective of the type of indicator and detector used. An important exception to this general statement is the application of gaseous indicators to the detection of blood traversing the pulmonary circulation but bypassing aerated alveoli. This type of arteriovenous shunt can be detected by dyes or other nongaseous indicators only when the transit time of the shunted blood is significantly shorter than that of blood traversing normally aerated alveoli. Since under this circumstance the transit time of the shunted blood and that of the nonshunted blood from...
The major differences from normal of dilution curves characteristic of left-to-right and right-to-left shunts are illustrated.

Top panel. The distribution of paths of differing traversal times has been simplified to a single circuit representing the normal pathway from the venous to the systemic arterial circulation. The normal dilution curve obtained from such a circulation, when the indicator is injected rapidly into the venous circulation (at arrow) and the resultant dye-blood mixture is sampled from a systemic artery, is shown at the right.

Middle panel. The circulation characteristic of increased pulmonary blood flow due to a large left-to-right shunt. Indicator is not cleared rapidly but recirculates through the central circulation via the defect. A constant fraction (dependent on the magnitude of the left-to-right shunt and the systemic flow) leaves this central pool on each circulation. The dilution curve inscribed at the right reflects this situation and may be contrasted to the normal (broken line). The maximal deflection is reduced, because the indicator is dispersed and diluted in the large volume of the central circulation and the high pulmonary flow. The disappearance phase is prolonged owing to the slow clearance of dye from the central pool.

Bottom panel. The circulation in the presence of a right-to-left shunt which is usually associated with reduced pulmonary flow. A portion of the indicator passes directly to the arterial circulation via the defect without traversing the longer, normal circulatory pathway through the lungs and arrives at the arterial sampling site before the portion that traverses the lungs. The dilution curve inscribed to the right demonstrates the early arrival of the portion of dyed blood shunted right to left the right to the left sides of the circulation may be closely similar, this type of shunt would escape detection by the usual nongaseous indicator-dilution methods.

Since with this exception the methods are basically closely similar, this discussion of the application of indicator-dilution techniques to the study of congenital heart disease will be carried out from the viewpoint of the use of an indicator dye injected at any desired site or sites in the circulation with its concentration being recorded continuously and simultaneously in the bloodstream at any other desired site or sites in the circulation. As implied above, the use of conventional dye techniques in these applications has the disadvantage that the required direct access to the injection and sampling sites in the circulation by suitable catheters or needles may, in some applications, pose considerable technical difficulty. The techniques, however, do have the advantage that methods for obtaining quantitative information as to the relative and particularly the absolute magnitudes of systemic, pulmonary and shunt flows have been developed and are for the most part more readily applicable than for the gaseous indicator and intravascular-detector techniques.

The primary disturbances in the circulation associated with congenital heart disease are of three main types: 37 (1) abnormal communications between the cardiac chambers or great vessels, (2) obstruction to blood flow through, or absence of, normal circulatory pathways, and (3) combinations of these types of abnormalities.

The most common type of obstruction to flow through normal circulatory channels is that due to abnormality of the cardiac valves. The abnormalities of the circulation produced by valvular stenosis or valvular regurgitation are fundamentally similar irrespective of whether the etiology of the valvular deformity is acquired or congenital. There-
fore, since the abnormalities of indicator-dilution curves associated with valvular regurgitation and stenosis and the diagnostic applications of these abnormalities will be covered in another section of this symposium, they will not be discussed here.

This presentation will deal primarily with the use of dilution curves to detect and localize abnormal communications between the cardiac chambers or the great vessels and their use to measure the direction and quantity of blood flow through these abnormal communications.

For the purposes of this discussion, indicator-dilution curves will be separated into arterial dilution curves and venous dilution curves. An arterial dilution curve is defined as a recording of the concentration of an indicator from any site in the arterial circulation or from the left side of the heart following injection of this indicator at another site in the circulation. A venous dilution curve is defined as a recording of the concentration of an indicator at any site in the right side of the heart or in the venous circulation following the injection of this indicator at any site in the circulation.

The importance of indicator-dilution curves in cardiovascular physiology and diagnosis is now widely recognized and perhaps can be emphasized properly by the statement that at present more information concerning the status of the circulatory system can be obtained from an indicator-dilution curve than can be obtained from the recording of any other single physiologic variable.

Before the various parameters of the circulation about which information can be obtained by means of indicator-dilution curves are discussed, it is of value to have clearly in mind the factors that are known and the factors that must be measured for the various applications of this technic. The factors that are known are (1) the dose of the indicator, (2) the site of its introduction into the circulation, and (3) the site of sampling of the resulting indicator-blood or gaseous mixture from the circulatory system. The factors that are measured directly from such a curve are only two: (1) the time at which the indicator is introduced and (2) the concentration of the indicator at the sampling site at any time during the inscriptions of the curve.

The time of arrival of indicator particles at the sampling site is determined by two factors: (1) the length of the path, that is, the distance traversed by the dye-blood mixture between the injection and sampling sites, and (2) the velocity of blood flow through this particular segment of the circulatory system under study which is determined, in turn, by the volume of blood contained in this
Method of measurement of the "forward triangles" for calculation of veno-arterial shunts from arterial dilution curves recorded from patients with cyanotic congenital heart disease. In the abnormal initial right-to-left shunt portion of the curve, the components are indicated as MC', the maximal concentration, and BT', the build-up time, of this portion of the curve. In the normal portion of the curve, that is, the second peak of concentration due to the portion of the dye-blood mixture traversing the lungs, the corresponding components are MC and BT.'

The formula for calculation of the right-to-left shunt as per cent of systemic flow is:

\[ \frac{BT' \times MC'}{(BT' \times MC') + (0.46 \times MCT \times MC')} \]

in which MCT is the maximal concentration time of the curve as illustrated in the figure and 0.46 is a factor relating MCT to BT based on measurements from a large series of normal curves.38

The upper panel is a record from a patient with a veno-arterial shunt calculated by the dye method to be 32 per cent of the systemic flow in whom the arterial oxygen saturation was 81 per cent.

The lower panel is a record from a 4-year-old boy with tetralogy of Fallot. The shunt was calculated to be 14 per cent of the systemic flow and the arterial saturation was 93 per cent. (Reproduced with permission of the publisher from Swan, H. J. C., Zapata-Diaz, J., and Wood, E. H.41)

A left-to-right shunt such as usually would occur through a ventricular or an atrial septal defect results in an increase in volume of blood flow through the pulmonary circulation so that, in this situation, the dye is diluted in a greater volume of blood and hence the peak deflection of the indicator-dilution curve, that is, the maximal concentration of the dye, is reduced below that usually encountered.
in normals. Owing to the presence of the left-to-right shunt, the dye-blood mixture continues to recirculate through the lungs so that the clearance of dye from the central circulation is delayed, thus producing the characteristic disproportionate prolongation of the disappearance phase of the dilution curve associated with a left-to-right shunt and the loss or diminution of the normally evident secondary increase in indicator concentration due to systemic recirculation.

In the presence of a right-to-left shunt a portion of the dye-blood mixture gains direct access from the right to the left side of the heart, thus bypassing the longer and normal pulmonary circulation and hence arriving at the sampling site in an abnormally short time. This results in the characteristic abnormal initial deflection of the build-up phase of the dilution curve which is characteristic of a right-to-left shunt.

Since left-to-right and right-to-left shunts are two of the most important manifestations of the presence of congenital heart disease, the association of typical contours of the dilution curves with these circulatory shunts is of evident diagnostic importance, as clearly pointed out by Nicholson and co-workers in 1951.

The relative value of various applications of indicator-dilution technics in the diagnosis and study of congenital heart disease perhaps can be properly emphasized by the following two statements: (1) recordings of arterial indicator-dilution curves obtained after injections of the indicator at selected sites on the right side of the heart provide the most sensitive practical method currently available for the detection, localization and quantification of right-to-left shunts, and (2) venous dilution curves recorded from selected sites on the right side of the heart including the expiratory airway provide the most sensitive practical method currently available for the detection, localization and quantification of left-to-right shunts.

Although indicator-dilution technics are of considerable diagnostic value as an independent method, they attain their greatest value when used in conjunction with cardiac catheterization.

Role of Indicator-Dilution Technics in Cardiac Catheterization

The procedure of diagnostic cardiac catheterization, when carried out in adequate fashion, is based on the judicious selection and the integration of several technics. The most important technics include the recording of pressures in selected sites in the cardiac chambers and great vessels and the measurement of oxygen content of blood withdrawn from these sites. In relation to the determination of blood oxygen content it is of paramount importance that a method be available for the immediate determination of blood oxygen content or saturation if the highest possible degree of accuracy is to be obtained from such measurements.
FIGURE 5
Dilution curves of T-1824 recorded by carpipe oximeters following injection of indicator into superior vena cava (left panel) and inferior vena cava (right panel) in eight patients with interatrial communication, recorded while 100 per cent oxygen was being breathed. For each dilution curve the instant of injection is represented by the vertical arrow below which the amount of dye injected is indicated. The oxygen-saturation scale to the left of each panel is a measure of the relative sensitivity of the recording instrument for each subject and the peak concentration of dye is indicated to the right of each panel. In the curves for patients 1 to 3 in the left panel, the initial break in the dilution curve indicates the shunting of a portion of superior caval blood in the right-to-left direction. In the right panel, an initial break is present in all curves, indicating that a right-to-left shunt of inferior caval blood was present in all these patients. Note that only in patient 3 does the magnitude of the shunt of superior caval blood exceed that of inferior caval blood. (Reproduced with permission of the publisher from Swan, H. J. C., Burdell, H. B., and Wood, F. H.)

diagnostic cardiac catheterization. The third technic is selective indicator-dilution studies and the fourth, selective angiocardiography. Each of these is indispensable for the performance of the best possible type of diagnostic cardiac catheterization and none of the technics should be used to the exclusion of the others. In addition, several other ancillary technics of more limited applicability such as intracardiac phonocardiography and intracardiac electrocardiography may be of great diagnostic importance in certain instances and should therefore be available for use in conjunction with routine diagnostic catheterization should the need for such technics arise during the procedure.

Angiography is, in actuality, an indicator-dilution technic, the contrast medium being the indicator and the x-ray apparatus the detector. The difference from usual indicator-dilution technics is that the output of this detector is usually a subjectively appraised visual image of a segment of the circulation rather than a quantitative record of the concentration of the indicator at a specific localized site in the circulation. External scanning methods have some similarities to angiocardiography in this regard and share with some of the advantages and disadvantages in relation to more conventional indicator-dilution technics. Despite the fact that angiocardiography is an indicator-dilution technic, no attempt will be made to cover its very important diagnostic application in this presentation. External scanning technics are covered in another section of this symposium.

A multitude of specific diagnostic and investigative applications of selective arterial and venous indicator-dilution technics has been described previously. The advent of new detectors and types of indicators, particularly of the gaseous type, have changed in some instances or facilitated the application of these technics, but for the most part these applications are basically closely similar irrespective of the type of indicator and detector used. Therefore, these applications will be discussed from the viewpoint of use of an indicator dye injected at a specific site in the circulation with its concentration being recorded in the blood stream at another site in the circulation.

First to be considered will be specific applications of arterial indicator-dilution technics.

Diagnostic Applications of Arterial Dilution Curves

One of the earliest and most important

Circulation Research, Volume X, March 1968
applications of arterial indicator-dilution techniques is their use for the detection, localization and quantitation of right-to-left shunts.\textsuperscript{4,41} (fig. 2). This technic was presaged by the description, by Benenson and Hitzig in 1938,\textsuperscript{5} of the use of ether circulation times to detect right-to-left shunts. If, in the presence of a right-to-left shunt, the cardiac catheter is advanced so that its tip lies distal to the site of the shunt and indicator is injected, a recording of the concentration of this indicator at an arterial sampling site may approach that of normal. However, if the tip of the cardiac catheter is then withdrawn to a site at or upstream to the right-to-left shunt and a second injection of indicator is made, the dilution curve recorded at the arterial sampling site will show the typical abnormal initial deflection associated with a right-to-left shunt and thus localize the site of the right-to-left shunt to the site in the circulatory system at which the indicator was injected. By equations that have been described previously by Swau and co-workers,\textsuperscript{41} it is possible, from such an indicator-dilution curve, to estimate the magnitude of the right-to-left shunt with sufficient accuracy for diagnostic purposes. This method of estimating the magnitude of a right-to-left shunt from arterial dilution curves is based on the concept of division of the indicator into two separate fractions which are proportionate respectively to the volume of blood passing to the arterial system by the normal route through the lungs, and to the volume passing by the abnormal route via the defect. This concept was presaged by Prinzmetal’s\textsuperscript{52} description of the combined use of a volatile indicator (ether) and a nonvolatile indicator (saccharin) in the detection and quantitation of right-to-left shunts.

The measurements required for application of this method can be made directly from the recorded dilution curve as illustrated in figure 3. These measurements are based on the findings of Hetzel and co-workers\textsuperscript{53} indicating that for many practical applications the initial part of a dilution curve can be regarded as a triangle for purposes of calculation of its area and that this area, so calculated with an appropriate correction factor, is representative of the total area encompassed by the curve. The area of the initial, abnormal, right-to-left shunt portion of the curve is considered to be proportional to the amount of blood traversing the right-to-left shunt, and the sum of the areas of the initial and following normal portions of the curve are considered to be proportional to the total systemic flow. The relative magnitude of the right-to-left shunt as a fraction of the systemic flow is equal to the quotient of these two values. Several assumptions upon which this method of estimation is based, such as uniform mixing of indicator and blood before separation of the dye-blood mixture into shunted and non-shunted fractions at the defect, are quite...
Comparison of values for pulmonary blood flow determined by the direct Fick method (abscissa) and from indicator-dilution curves, by use of the forward-triangle method (ordinate), in 16 patients with central arteriovenous shunts, A.S.D., V.S.D., and P.D.A. indicate patients with atrial and ventricular septal defects and patent ductus arteriosus respectively. (Reproduced with permission of the publisher from Ramirez de Arellano, A. A., Hettzel, P. S. and Wood E. H.)

certainly not strictly fulfilled. The values obtained, however, do show a reasonably close correlation with the values obtained by conventional oxygen-saturation data (fig. 4). This method, which has been in use in this laboratory since before 1953, has stood the test of time and still is the method of choice for detecting and quantitating right-to-left shunts, particularly when such shunts are of small magnitude.

The use of arterial dilution curves for demonstration of right-to-left shunts has its greatest value in localizing the site of large right-to-left shunts and in the detection and quantitation of the magnitude of relatively small right-to-left shunts some of which cannot be detected by the slight decrease in the oxygen saturation of arterial blood which they may cause. By means of this technic, it is possible to detect and to obtain some idea of the magnitude of shunts of less than 5 per cent of the systemic blood flow. In the presence of balanced pressures between the cardiac chambers or of extremely small defects, the detection of right-to-left shunts by this method frequently may be the only evidence obtained at cardiac catheterization of the presence and location of the defect in question.

Recently a modification of this method utilizing injection of a gaseous indicator on the right side of the circulation has been described. Although, as pointed out above, the modification of this technic described by Fritts and co-workers is a valuable and unique method for studying vascular shunts through the pulmonary circulation, it has no evident advantage from the viewpoint of sensitivity in detecting or localizing central right-to-left shunts and it has the apparent disadvantage that quantitation of such shunts is difficult when gaseous indicators are used. The sensitivity of the dye method and its value in elucidating the hemodynamics of blood flow through the right atrium in cases of atrial septal defect are well illustrated by the detection of a small right-to-left shunt in the majority of patients with atrial...
Correlation of the magnitude of the left-to-right shunt calculated from the data on oxygen saturation by the Fick method with the disappearance ratios of the arterial dilution curves. The regression lines are calculated from the ratios of normal subjects and patients with left-to-right shunts. The vertical bars represent the range of the 95 per cent band for normal subjects. Note that no difference is apparent when caradiogreen and Evans blue dyes were used as the indicators nor for the patients with the various types of cardiac defects. For definition of ratios, see figure 8. (Reproduced with permission of the publisher from Carter, S. A., Bajec, D. P., Yannicelli, Eduardo, and Wood, E. H.18)

Application of Arterial Dilution Curves to the Study of Left-to-Right Shunts

The characteristic abnormalities of indicator-dilution curves recorded from patients with a left-to-right shunt are well illustrated by comparing dilution curves recorded from a patient before and after surgical correction of an atrial septal defect (fig. 6). Since left-to-right shunts of less than 20 per cent of pulmonary blood flow may not produce a significant alteration in the contour of arterial dilution curves,30-40 quantitative studies of such shunts are usually best made by means of venous dilution curves as discussed in a later portion of this presentation. However, in spite of the relative lack of sensitivity of arterial dilution curves in the detection of left-to-right shunts, these curves do have some quantitative value.30-40-58 Ramirez and co-workers58 have demonstrated that the initial or "forward-triangle" portion of the arterial dilution curve recorded in the presence of a left-to-right shunt can be used to obtain a rough estimate of the magnitude of the pulmonary blood flow in such patients. This method is based on the previously mentioned finding by Hetzel and co-workers63 that in the normal circulation the forward-triangle portion of the dilution curve can be used with reasonable accuracy as a means
TABLE 1
Average and Variability of Least-Concentration to the Systemic-Recirculation Ratios ($C_L/C_R$) Obtained From Arterial Dilution Curves

<table>
<thead>
<tr>
<th>Number</th>
<th>Healthy subjects</th>
<th>Cardiac patients without left-to-right shunts</th>
<th>Patients with left-to-right shunts of:</th>
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<td>Healthy subjects</td>
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<td></td>
<td></td>
<td>Number</td>
<td>without left-to-right shunts</td>
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<td></td>
<td></td>
<td>Average</td>
<td>35 per cent or less</td>
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<td>Standard deviation</td>
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<td></td>
<td></td>
<td>Standard deviation</td>
<td>55 per cent</td>
</tr>
</tbody>
</table>

*Injection site: pulmonary artery; sampling site: radial artery.

**Patients suspected of having valvular regurgitation on the basis of clinical or surgical findings were not included.

of estimating the total area of the dilution curve and thus the cardiac output. A satisfactory correlation for most clinical purposes has been obtained between values for pulmonary flow determined by this forward-triangle indicator-dilution method and values obtained by the more conventional direct Fick method as shown in figure 7. Similarly satisfactory results have been obtained by using an empirical formula suggested by Dow and based on the close correlation between appearance time and peak concentration time of dilution curves and the area encompassed by these curves.

In addition to these arterial dilution technics for estimating pulmonary blood flow in the presence of a left-to-right shunt, an empirical method has been described by Carter and co-workers for estimation of the relative magnitude of the left-to-right shunt in relation to the pulmonary blood flow in such patients. This technic is based on the degree of distortion of the disappearance phase of the dilution curve caused by the left-to-right shunt and the high degree of internal consistency of indicator-dilution curves in relation to their various time and concentration components. The measurements required can be made directly from the curve proper without conversion to absolute units of concentration, as illustrated in figure 8, and the correlation between the left-to-right shunt values obtained by this dye method and those by the conventional oxygen-saturation methods is reasonably satisfactory for most diagnostic purposes (fig. 9). A somewhat more-sensitive method for detection of small left-to-right shunts from arterial dilution curves is provided by measurements of the ratio of least concentration to systemic recirculation concentration ($C_L/C_R$) of dilution curves recorded after injection into the pulmonary artery. The values for this ratio in patients with left-to-right shunts, normal healthy subjects and cardiac patients with stenotic valvular lesions not associated with appreciable valvular regurgitation are given in table 1. The value for the $C_L/C_R$ ratio of only one of 12 patients with left-to-right shunt of less than 35 per cent of pulmonary blood flow fell within the range of values obtained in the individuals without left-to-right shunt. This degree of sensitivity in detecting small left-to-right shunts does not compare unfavorably with that provided by the conventional cardiac-catheterization technic based on determinations of differences in blood oxygen saturations from different sites in the right side of the heart, since under the most favorable circumstances the minimal left-to-right shunt detected by this method ranges from approximately 10 to 20 per cent of the pulmonary blood flow.

**Special Applications of Arterial Indicator-Dilution Technics in Congenital Heart Disease**

Since the introduction of continuously recorded arterial dilution curves for diagnosis of cardiovascular abnormalities in 1950,
Injection into left ventricle

Normal
L-R shunt

FIGURE 10

Demonstration of the presence or absence of a left-to-right shunt of blood at or distal to the left ventricle. The route taken by the dye injected into the left ventricle is indicated by the arrows. The dilution curve inscribed immediately below each diagram is that which would be recorded from a sampling site in the systemic circulation. The vertical arrow on the dilution curve indicates the instant of injection. In the left panel the ventricular septum is intact and the resulting dilution curve is normal. In the right panel there is a ventricular septal defect with a left-to-right shunt, and the resulting dilution curve shows the abnormalities characteristic of this hemodynamic anomaly.

Many special applications of the techniques have been developed, particularly in conjunction with catheterization of the right and left sides of the heart and the arteries. These techniques utilize single and multiple injection sites alone or in conjunction with multiple sampling sites in the heart and great vessels or the pulmonary airway selected to allow the best possible demonstration or localization of the particular abnormality in question. These special applications are based both on the fundamental contours previously described as characteristic of the circulatory abnormalities associated with veno-arterial and arteriovenous shunts, valvular regurgitation or congestive failure, and on the similarity or dissimilarity of dilution curves obtained following injection or recording of indicator at sites selected especially to supply critical information in regard to the diagnostic problem under consideration. The following discussion outlines the principles underlying these special applications during diagnostic cardiac-catheterization procedures of various types and combinations thereof.

LOCALIZATION OF LEFT-TO-RIGHT SHUNTS

Left-to-right shunt of more than 15 to 20 per cent of pulmonary flow can be localized with precision by cardiac catheterization in the majority of instances, particularly with the aid of a cuvette oximeter. This is made possible by demonstrating an increase in oxygen saturation at sites at or downstream to the location of the left-to-right shunt by means of immediate and continuous photometric analysis of samples of blood drawn in rapid succession from sites upstream and at or downstream to the defect. Application of the principle of localization of the right-to-left shunt by injections of indicator downstream and upstream to the defect also can be used for localization of left-to-right shunts. But access to injection sites downstream to the origin of left-to-right shunts is difficult to attain without recourse to techniques of left-heart catheterization which are usually not applied if the information required can be obtained by simpler procedures.

During study of patients by the procedure for catheterization of the right side of the heart, the tip of the cardiac catheter may be passed into the left ventricle via an atrial septal defect or a valve-competent foramen ovale. Injection of dye into the left ventricle (fig. 10) may result in a dilution curve of normal contour, indicating absence of a left-to-right shunt at or distal to the left ventricle and competence of the aortic and mitral valves. When an abnormal dilution curve characterized by a reduced peak concentration and a prolonged or distorted disappearance slope is obtained, then a left-to-right shunt from the left ventricle or the aorta or incompetence of the mitral or aortic valve is present. Dilution curves recorded in the presence of valvular regurgitation are characterized by prolongation of the disappear-

Circulation Research, Volume X, March 1968
Localization of a left-to-right shunt via an atrial septal defect. In the left panel an injection is made into the left ventricle which is guarded by a competent valve and from which no left-to-right shunt occurs. A normal dilution curve results. In the right panel the catheter tip is in the left atrium from which there is a left-to-right shunt through an atrial septal defect. The abnormal dilution curve demonstrates the presence of a left-to-right shunt from this chamber. The measurements required to calculate the disappearance ratio for estimation of the magnitude of the left-to-right shunt from this curve are illustrated.10 (Reproduced with permission of the publisher from Fox, I. J., and Wood, E. B.)

10 sec.

Localization of a left-to-right shunt via a ventricular septal defect. In the right panel injection of dye into the aorta via a catheter placed above the valve results in a normal curve, while the curve recorded following injection into the left ventricle (left panel) shows the abnormalities characteristic of a left-to-right shunt.

To localize this shunt an injection of dye must be made at a site distal to the chamber in which the left-to-right shunt is originating and separated from it by a competent valve. The localization of the left-to-right shunt from the left atrium and the more practical objective of exclusion of a shunt distal to this chamber are illustrated in figure 11. Injection of dye into the left ventricle from which no shunt occurs results in a normal dilution curve. When the catheter tip is withdrawn to the left atrium, however, the curve obtained after injection of the dye into this chamber is distorted because of the presence of the left-to-right shunt at atrial level. This important application of dilution curves has been used to separate patients with uncomplicated atrial septal defect from those (1) with multiple anomalies as described by Callahan and co-workers in 1955,63 (2) with a ventricular septal defect associated with an atrial septal defect through which a large left-to-right shunt is occurring or (3) with a common atrioventricular canal. The value of the general principles of such applications has been confirmed by Braunwald and associates.15

To determine the presence of a left-to-
right shunt from the aorta to the pulmonary artery or to localize a left-to-right shunt to the left ventricle with certainty, an injection must be made into the aorta. This can usually be accomplished with relative ease by retrograde aortic catheterization utilizing percutaneous puncture of the femoral artery with a 15T-gauge needle which allows passage of a 5F cardiac catheter. This catheter may be advanced under fluoroscopic control to the ascending aorta just distal to the aortic valve and usually can be manipulated so as to cross the aortic valve into the left ventricle. Recording of a normal curve following injection at the root of the aorta and of an abnormal one following an injection into the left ventricle localizes the shunt to ventricular level (fig. 12). An abnormal curve following injection at the root of the aorta with a normal or nearly normal curve following injection near the origin of the left subclavian artery indicates the presence of an aortic-pulmonary window (fig. 13) or a ruptured aortic-sinus aneurysm. Closely similar curves after injection into each of these sites are characteristic of patent ductus arteriosus (fig. 14).

When an indicator is injected into a chamber or vessel from which no shunt occurs or into a vessel at a distance from a point of branching, the resulting dilution curves usually represent faithfully the flow of blood from the chamber or vessel into which the injection was made. Stated in other words, adequate mixing of blood and dye has occurred before separation of the blood-dye mixture into paths of different circulation times. When an injection is made into a chamber or vessel from which a shunt is occurring, or into a vessel close to a point of branching, the resulting dilution curve may not represent fully the over-all characteristics of the drainage of the chamber or vessel in question. This may be due to the preferential injection of dye into or away
The heart and circulation in the presence of an atrial septal defect. The right pulmonary vein passes behind the right atrium to connect normally to the left atrium. The circulatory path (solid line) from the pulmonary vein (left panel) is fundamentally different from that from the inferior vena cava (right panel). The indicator-dilution curves recorded at a systemic artery are shown below, and because of the difference in circulatory paths they show dissimilar contours.

In the left panel a considerable proportion of the blood-dye mixture passes to the left ventricle, giving rise to an initial deflection of moderate magnitude. The remainder of the blood-dye mixture is shunted left to right entering the right ventricle and pulmonary circulation and producing distortion of the disappearance phase of the curve.

In the right panel a very small proportion of the blood-dye mixture passes to the left ventricle, giving rise to an initial deflection of moderate magnitude. The remainder of the blood-dye mixture is shunted left to right entering the right ventricle and pulmonary circulation and producing distortion of the disappearance phase of the curve.

Identification of anomalous connection of the pulmonary veins

When a cardiac catheter enters the right side of the heart and then passes into a pulmonary vein, it is difficult to be certain from fluoroscopic or roentgenographic observation whether the vein entered is anomalously connected to the right atrium or to one of its tributaries or whether it is normally connected to the left atrium and the catheter has traversed an interatrial communication to enter the pulmonary vein. If the catheter is seen to enter such a vein from above the level of the slight lateral prominence of the right atrium, it is likely that the vein is draining the upper and middle lobes of the right lung and is connected to the junction of the superior vena cava and the right atrium. An associated interatrial communication located high in the atrial septum is usually associated with this type of anomalous pulmonary venous connection. When the catheter enters the middle or lower portion of the right atrium before passing into the pulmonary veins as it usually does, there may be an associated atrial septal defect, and a diagnosis of anomalous connection of the right pulmonary vein to the right atrium is seldom justified by the x-ray appearance alone.

At times, differentiation between these two conditions may be possible only from dilution curves. The principle of this differentiation is illustrated by figure 15 in which the right pulmonary vein is shown to be

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FIGURE 15

The heart and circulation in the presence of an atrial septal defect. The right pulmonary vein passes behind the right atrium to connect normally to the left atrium. The circulatory path (solid line) from the pulmonary vein (left panel) is fundamentally different from that from the inferior vena cava (right panel). The indicator-dilution curves recorded at a systemic artery are shown below, and because of the difference in circulatory paths they show dissimilar contours. In the left panel a considerable proportion of the blood-dye mixture passes to the left ventricle, giving rise to an initial deflection of moderate magnitude. The remainder of the blood-dye mixture is shunted left to right entering the right ventricle and pulmonary circulation and producing distortion of the disappearance phase of the curve.

In the right panel a very small proportion of the blood-dye mixture passes to the left ventricle, giving rise to an initial deflection of moderate magnitude. The remainder of the blood-dye mixture is shunted left to right entering the right ventricle and pulmonary circulation and producing distortion of the disappearance phase of the curve.
normally connected to the left atrium, but an interatrial communication is present in the region of the fossa ovalis. When the catheter enters the pulmonary vein, dye is injected and an arterial dilution curve is recorded. The catheter is then passed into the inferior vena cava where a second injection is made. Dissimilar dilution curves are obtained when the drainage path of the pulmonary vein differs fundamentally from the drainage of the vena cava. When an anomalous connection exists between the pulmonary vein and the right atrium as shown in the example in figure 16, the drainage patterns of the vena cava and the pulmonary veins are similar, and therefore the dilution curves are similar when dye is injected into the anomalously connected pulmonary vein and into the inferior vena cava. In practice the dilution curve obtained after injection of dye into the pulmonary vein is compared with the curves obtained after injection of dye into both the superior and the inferior vena cava, since in atrial septal defect dilution curves from these two sites may differ from each other.54, 65

An anomalous connection of a pulmonary vein, therefore, may be identified with certainty when the dilution curve obtained after injection into that vein is identical or nearly identical to the dilution curves that are representative of drainage of the systemic blood entering the right atrium. When the dilution curve from the pulmonary vein differs significantly from the caval curves, then that vein in all probability is normally connected to the left atrium and has been entered through an interatrial communication. Used in this manner, dilution curves have allowed a clear differentiation of anomalous pulmonary venous connection to the right atrium from an atrial septal defect with normally connected pulmonary veins. The occasional example of a large atrial septal defect with absence of any posterior septal tissue may show evidence of complete anomalous drainage of the right lung although, developmentally at least, the veins are probably not abnormally connected.60, 65

In cases in which the catheter does not enter a pulmonary vein, a comparison of dilution curves obtained after injection of the indicator dye into different branches of the right and left pulmonary arteries may permit the demonstration of total anomalous drainage of the blood from all or from portions of the right or the left lung.63 In the absence of an interatrial communication a diagnosis of anomalous connection of all or a portion of one lung can be made with certainty and relative ease by this technic, as illustrated diagrammatically in figure 17. In the presence of an atrial septal defect, however, this diagnosis cannot be made with such a high degree of certainty owing to the fact that the ordinary or usual type of
atrial septal defect frequently shows a strong degree of preferential drainage or left-to-right shunting from the right lung, as illustrated in figure 18. Under this circumstance a diagnosis of anomalous venous connection of a portion of the lung must be based on a careful comparison of the dilution curves recorded following injection into the arterial supply to this portion of the lung and into the vena cava.64,65 This comparison is further complicated by the frequent presence of small right-to-left shunts via the coexisting atrial septal defect.64 Therefore, a portion of the blood flowing into the right atrium via the anomalously connected pulmonary vein may actually drain normally into the left atrium by virtue of its being shunted right to left via the atrial septal defect. If these dilution curves are closely similar in contour, with the appearance time following injection into the pulmonary artery slightly longer than that following caval or right atrial injection, and if the right-to-left shunt evident on the caval curve is closely similar in magnitude to the portion of lung blood that drains normally, then a diagnosis of anomalous venous drainage of this portion of the lung can be made, and presumably therefore an anomalous pulmonary venous connection exists. Dilution curves in such a patient are illustrated in figure 19.

Parenthetically, it is of considerable hemodynamic interest that the demonstration of preferential left-to-right shunting from the
SYMPOSIUM ON INDICATOR-DILUTION TECHNICS

547

INJECTION INTO:
RIGHT PULMONARY ARTERY
LEFT PULMONARY ARTERY

FIGURE 18
The path taken by indicator dye after its injection into both the right and the left pulmonary artery, and the resultant dilution curves recorded in the systemic arterial system in a case of atrial septal defect.

a. Diagrammatic representation of the central circulation. The thick solid lines within the diagram represent the circulatory route taken by the indicator after its injection. The relative thicknesses of these lines represent the fractions of indicator passing to different locations from the left atrium. The small insert above each diagram represents the general contour of a dilution curve from each site of injection, with the instant of injection indicated by the arrow. Note the proximity of the right pulmonary veins to the location of the septal defect, which is evident from pathologic anatomic studies of this condition.

b. Systemic arterial dilution curves recorded by ear oximeter. Injections of T-1821 were made at the sites indicated to the left of the figure. The curves have been arranged vertically in relation to the instant of injection indicated by the arrow. The values for maximal concentration of dye attained in radial arterial blood recorded simultaneously are tabulated to the right and serve to indicate the sensitivity of the instrument. Note that much greater abnormality of the dilution curve recorded following right as compared to that following left pulmonary-artery injection, due to the high degree of preferential left-to-right shunting of the blood draining from the right lung. (Reproduced with permission of the publisher from Swan, S. J. C, Hetzel, P. S., Burchell, H. B., and Wood, E. H.: Relative contribution of blood from each lung to the left-to-right shunt in atrial septal defect: Demonstration by indicator-dilution tech- niques. Circulation 14:200, 1956.)

right lung in cases of atrial septal defect constitutes additional proof that complete and uniform mixing of blood in the atria does not occur. It has been clearly demonstrated both by human54 and by animal studies55 that the preferential drainage of blood from the right lung is related to the close anatomic proximity of the left atrial orifices of the right pulmonary veins to atrial septal de- fects when such defects are located in the usual position in the region of the fossa ovalis.

Circulation Research, Volume X, March 1958

DIAGNOSIS OF TOTAL ANOMALOUS PULMONARY VENOUS DRAINAGE
In cases of total anomalous pulmonary venous drainage, all right ventricular blood before gaining access to the systemic circulation must pass through the pulmonary ar- tery and pulmonary circulation and return to the right atrium, at which site a portion of it then gains egress to the left ventricle via the interatrial communication.56 Thus in this condition the right ventricle represents a site upstream from the right atrium from the functional standpoint. This hemodynamic
Preoperative and postoperative dilution curves of Evans blue obtained at cardiac catheterization. The close similarity of the dilution curves recorded following injection into the left pulmonary artery and the superior vena cava preoperatively, including the small right-to-left shunt indicated by the superior vena caval curve (left panel), demonstrates complete anomalous drainage of the left lung. The abnormal disappearance slope of the curve recorded following injection into the right pulmonary artery indicated the presence of an additional anomaly which was suspected to be an atrial septal defect.

This diagnosis was confirmed at operation during which the anomalous vein which drained the left lung vein to the superior vena cava was transected and anastomosed to the left atrium. The atrial defect was not closed, since the time of study of this case antedated development of surgical technics for this procedure.

The postoperative dilution curves indicate a large persistent left-to-right shunt via the uncorrected atrial septal defect but a normal venous drainage and hence a normal venous connection of the left lung to the left atrium.

fact may be demonstrated by indicator-dilution curves as illustrated in figure 20. These curves usually indicate the presence of a severe degree of pulmonary recirculation, and there is a close similarity between curves recorded following injections of indicator at various sites on the right side of the heart, plus the pathognomonic characteristic that the appearance time is longer for right ventricular and pulmonary-artery injections than for right atrial or caval injections. The hemodynamic basis for the similarity in contour of the curves is the common mixing of blood from the pulmonary and systemic venous systems which occurs in the right atrium or adjacent great veins. The curve recorded following injection into the left ventricle is of very different contour owing to the fact that this dye is diluted only by the systemic flow which passes directly to the systemic circulation without recirculation through the lungs (fig. 20).

IDENTIFICATION OF ANOMALOUS CONNECTION OF SYSTEMIC VEINS TO THE LEFT ATRIUM

Dilution curves have been used also to identify the rare malformation of an anomalous connection of the systemic veins to the
left atrium. In the example depicted in figure 21, the veins of the left arm drained to the left atrium while those of the right arm drained to the right atrium. This is demonstrated by the striking difference between dilution curves obtained at a systemic artery after injection of dye into each antecubital vein. Both dilution curves showed a relatively short appearance time. The portions of the curves marked “I” represent the dyed blood which passed directly to the systemic circulation, while the portion marked “II” in the upper curve, but not clearly identifiable in the lower curve, represents dye traversing the pulmonary vascular bed. These curves indicate that the blood draining from the right arm passed normally to the superior vena cava where a small portion was shunted right to left across the atrial septal defect. In contrast, the blood from the left arm traversed an anatomically dissimilar path. It passed directly to the left atrium and a large fraction entered the left ventricle while a small portion was shunted left to right. A similar dilution curve was recorded from the same patient after injection of dye into a right pulmonary vein that was anomalously connected to the persistent left superior vena cava which entered the left atrium. This pulmonary vein, therefore, in spite of its anomalous connection, actually drained normally into the left atrium. The drainage pathway of this anomalously connected vein is an excellent example of the utility and necessity for the use of the two terms “anomalous pulmonary venous connection” and “anomalous pulmonary venous drainage.”

IDENTIFICATION OF CENTRAL GREAT VESSELS

During cardiac catheterization in certain of the more complex congenital cardiac anomalies, the catheter may enter a central arterial vessel which cannot be identified with certainty to be the pulmonary artery or aorta, since neither the recorded pressure nor the oxygen saturation of blood from this vessel differs significantly from the pressure or oxygen saturation recorded from a peripheral systemic artery. When the catheter cannot be advanced so that its tip clearly enters a pulmonary or a systemic artery, certain identification of the nature of the vessel based on

FIGURE 20
Diagrammatic representation of the central circulation in total anomalous pulmonary venous drainage, illustrating the “upstream” functional relation which the right ventricle bears to the right atrium, and the demonstration of this relation by dye-dilution curves. The solid circles in the superior vena cava, the right ventricle, the pulmonary artery and the left ventricle denote the sites of an injection of dye. The dilution curves that would be obtained in the systemic arterial system following injection of dye at each of these sites are illustrated in the corners of the figure. The instant of injection for each curve is indicated by the vertical arrow. Note the similarity in contour between the curves following injection into the right ventricle, pulmonary artery and superior vena cava, all of which indicate a severe degree of pulmonary recirculation. The pathognomonic characteristic of these similar curves is that appearance time is longer following injections of dye into the right ventricle and the pulmonary artery than following injection of dye into the superior vena cava. The curve recorded following injection of dye into the left ventricle is more nearly normal in contour. See text for further comment. (Reproduced with permission of the publisher from Swan, H. J. C., and Wood, E. H.: Indicator-dilution methods. In Lusain, A. A.: Cardiology: An Encyclopedia of the Cardiovascular System. Volume 2: Methods. New York, McGraw-Hill Book Company, Inc., 1959, p. 4-160.)
FIGURE 21
Indicator-dilution curves recorded at a systemic artery following injection of T-1824 (vertical arrows) into the right and left (lower curve) antecubital veins of a 17-year-old girl with anomalous connection of the right pulmonary veins and left subclavian veins to a left superior vena cava with connection of the left superior vena cava to the left atrium. These dilution curves indicate that the venous drainage of the left arm differs markedly from that of the right arm, and are interpretable only on the basis of a direct path from the left subclavian vein to the left atrium. The initial deflections labeled "I" are caused by the portion of dye-blood mixture that entered the systemic circulation without traversing the lungs. The dye-blood mixture causing the deflection labeled "II" traversed the longer and normal right ventricular-pulmonary pathway (see text).

its position within the cardiac silhouette is impossible because of the not infrequent occurrence of transposition of the great vessels as a part of complex malformations. An arterial dilution curve obtained after injection of indicator through the catheter when the tip is lying in such a position will demonstrate the path taken by the dye-blood mixture, and thus a decision can be made as to whether this vessel is the aorta, the pulmonary artery, or an aorta from which a portion of the blood flow is directly to the lungs, as in common truncus arteriosus.

The application of the dye-dilution technic to the problem of identification of the central great vessels is illustrated diagrammatically in figure 22 by the example of transposition of the great vessels with a common ventricle. In the left panel a characteristic short appearance time and sharp deflection in the curve from the systemic artery identify the vessel into which injection was made as the aorta, while the longer appearance time and reduced deflection (right panel) identify the second vessel as a pulmonary artery. The severe disproportionate prolongation of the disappearance phase of the curve recorded after injection into the pulmonary artery indicates a high degree of pulmonary recirculation, that is, a left-to-right shunt, whereas the normality of the declining slope of the curve following injection into the aorta demonstrates absence of a left-to-right shunt distal to the aortic valve and consequently excludes an aortic-pulmonary communication. An example of the use of this technic to demonstrate the presence of transposition of the great vessels and
common ventricle in a 27-year-old man suspected of having a ventricular septal defect is illustrated in figure 23.

Other congenital cardiac anomalies in which the nature of the central vessel may be uncertain because the pressure and the oxygen saturation of the blood may not differ significantly from those of a systemic artery are as follows: tricuspid atresia, common ventricle, common truncus arteriosus, transposition of the great vessels (with atrial or ventricular septal defect), corrected transposition (with ventricular septal defect), and total anomalous pulmonary venous drainage with pulmonary hypertension.

Circulation Research, Volume X, March 1962

DEMONSTRATION OF EJECTION PATHWAYS FROM THE RIGHT VENTRICLE

During cardiac catheterization of patients with conditions in which the nature of the central vessels is uncertain, the catheter frequently may be advanced with ease from the right ventricle into the aorta through a ventricular septal defect. However, attempts to advance the catheter into a pulmonary artery may be unsuccessful, so that the existence of a direct pathway from the right ventricle to the pulmonary artery is not demonstrable. Arterial dilution curves are a great help in this situation because they will indicate whether or not a significant blood flow exists
The circulation in pulmonary atresia associated with ventricular septal defect and patent ductus arteriosus. The absence of a direct pathway from the right ventricle to the pulmonary artery is indicated by the similarity in contour of the arterial dilution curves obtained after injection of dye into the aorta and into the right ventricle.

In instances of pulmonary atresia, blood is supplied to the lungs only by way of the systemic circuits to a patent ductus arteriosus (fig. 24) or enlarged bronchial arteries. Thus all of the blood leaving the right ventricle passes directly to the aorta where it is mixed with blood which comes from the left ventricle. A portion of this blood then enters the pulmonary artery. Since the paths to the lungs from the right ventricle and from the aorta are identical, dilution curves recorded after injection at these sites have a fundamentally similar contour.

In tetralogy of Fallot, a direct pathway exists between the right ventricle and the pulmonary arteries (fig. 25). Two routes of egress from the right ventricle therefore exist, one by way of the aorta and the other by way of the pulmonary artery. The curve that is obtained after injection of indicator into the aorta has a short appearance time and a single deflection of large amplitude characteristic of this injection site. In contrast, the curve following injection into the right ventricle has two peaks of concentration. The first peak is related to blood shunted from the right ventricle to the aorta and occurs at the same time as the deflection obtained after injection into the aorta. The second peak occurs later and results from that portion of the dye which traverses the normal longer pathway through the lungs. The dissimilarity of the curves from the aorta and the right ventricle indicates the existence of a direct pathway between the right ventricle and the lungs and thereby excludes the presence of pulmonary atresia. The application of this technic during right-heart catheterization has been described.

**DIAGNOSIS OF ATRESIA OF THE TRICUSPID VALVE**

During cardiac catheterization in complex congenital cardiac anomalies, the catheter tip occasionally cannot be manipulated through the tricuspid valve but instead repeatedly traverses an interatrial communication to enter the left atrium and ventricle. In such
instances it is difficult to be certain whether or not tricuspid atresia is present. The use of indicator-dilution curves usually solves this problem by demonstrating whether or not a functional pathway does exist from the right atrium to the pulmonary artery through the right ventricle.

Figure 26 shows diagrammatically the circulatory pathway through the heart in a patient with tricuspid atresia and the route followed by indicator injection into the right atrium and left atrium. The dilution curves that would be obtained at a systemic artery are inscribed below the diagrams of the circulation. All blood must leave the right atrium through this atrial septal defect and pass into the systemic circulation in the same manner as left atrial blood. Hence dye curves recorded after injection into the right atrium and left atrium are similar in contour and time components. The similarity in contour of these curves is the feature which indicates that all of the dye-blood mixture from these two sites follows an identical vascular pathway to the lungs and to the peripheral arterial sampling site. Therefore there can be no functional right ventricular pathway, and tricuspid atresia is present.

The flow patterns in a case of severe pulmonary stenosis with an atrial septal defect and a large right-to-left shunt are shown in figure 27. This condition may be confused with tricuspid atresia when the catheter tip does not enter the right ventricle. In this instance, however, dissimilar dye curves are obtained after injection of dye into the right and left atria. Two different pathways are traversed by the dye-blood mixture leaving the right atrium, one through the tricuspid valve into the right ventricle and the lungs, and the other directly into the left atrium through the atrial septal defect. The dye curve, therefore, shows two peaks of concentration because of the interval required for the dye-blood mixture to traverse the longer (normal) pathway through the lungs. When dye is injected into the left atrium, a curve of much different contour results, consisting of a single peak of concentration corresponding in time, but of greater magnitude than, the initial peak of the preceding curve since the dye-blood mixture has a common and direct pathway to the aorta. The application of this technic during right-heart catheterization has been described.68

Use of Indicator-Dilution Curves for Selection of Site for Injection of Contrast Medium for Selective Angiocardiography

In certain types of congenital defects it is important for the surgeon to know the precise anatomic configuration of the congenital defect to enable him to better plan for its possible surgical correction. In such instances, selective angiocardiograms may be necessary in order to obtain the essential information concerning the anatomic configurations of the defects present. Preliminary recording of a series of indicator-dilution curves can be used for the basis of selecting the best possible site for injection of contrast medium for selective angiocardiography of this type in order to increase the certainty of obtaining adequate

Circulation Research, Volume X, March 1962
visualisation of the desired area in the heart or great vessels, and under certain circumstances to selectively reduce the amount of contrast medium that enters directly into the systemic circulation.

An example of this situation occurs in tetralogy of Fallot wherein it may be important for the surgeon to know the anatomic configuration of the outflow tract of the right ventricle, the proximal portion of the pulmonary artery and its main branches in order to be certain that the possibility exists for adequate surgical correction. A prerequisite in the performance of such angiography is to select, if possible, an injection site in the right ventricle from which a major portion of the contrast medium will enter the pulmonary artery. This is important for two reasons: (1) to obtain the best possible visualization of the pulmonary artery including its branches, and (2) to minimize the dangers of the procedure by allowing the minimal possible fraction of the contrast medium to shunt directly across the defect into the aorta and hence to the cerebral circulation. Since the opening of the infundibular pathway to the pulmonary artery is usually small and the pathway of preferential blood flow into it sharply localized, this desired site in the right ventricle cannot be selected by fluoroscopic observation of the position of the catheter tip alone. Indeed, use of a site which by fluoroscopic observation appears to be in an ideal position for such an injection may produce the direct opposite of the desired result, namely a strongly preferential injection into the aortic pathway from the right ventricle.

The use of indicator-dilution curves for selection of the optimal site in the right ventricle for injection of contrast medium for visualization of the pulmonary artery is illustrated in figure 28. The success of selective visualization of the pulmonary artery in this patient with tetralogy of Fallot with very severe pulmonary stenosis is illustrated in figure 29.

### Diagnostic Applications of Venous Dilution Curves

The importance of venous dilution curves in the study of congenital heart disease can be properly emphasized by the statement that this type of indicator-dilution technic provides the most sensitive and reliable known method for detecting, localizing and quantitating left-to-right shunts.

The recording of venous dilution curves requires the use of two routes to the right side of the heart: one for the injection of indicator and the other for the sampling of the resulting dye-blood mixture. These two routes may be provided by the use of conventional types of double-lumen catheters or concentric catheter assemblies, as described previously, or by the simultaneous use of two conventional-type cardiac catheters. The latter technic is usually preferred in this laboratory owing to the great flexibility of possible combinations of sampling and injection sites which can be used as required to obtain specific information necessary to establish a definite diagnosis in the various congenital conditions that may be encountered. With the increasingly common
Injection into:

SUPERIOR VENA CAVA

Femoral Artery (mg./L.)

0.17 mg./kg. Cardio-green

MID RIGHT VENTRICLE

0.17 mg./kg. Cardio-green

OUTFLOW RIGHT VENTRICLE

0.17 mg./kg. Cardio-green

FIGURE 28

Indicator-dilution curves recorded at a systemic artery during cardiac catheterization in a 6-year-old (14 kg.) boy with tetralogy of Fallot and very severe pulmonary stenosis. Roentgenograms represented at right of respective panels show positions of catheter tip during injections of dye into mid and outflow tracts of the right ventricle. The initial deflection in each curve represents dye that has shunted right to left across the ventricular septal defect, and the second deflection dye that has traversed the pulmonary circulation before entering the systemic circulation. Note preferential passage of indicator from the right ventricle into the pulmonary artery when the catheter was positioned in the outflow tract of the right ventricle as evidenced by the smaller initial deflection and larger second deflection (lower panel). This is the site of choice for injection of contrast medium if it is desired to visualize the pulmonary circulation by selective angiography. See figure 29.
Selective angiocardiograms obtained from the same patient on whom figure 28 is based. Injection site was selected by means of indicator-dilution curves recorded at a systemic artery, as illustrated in figure 28. Arrow and replica of the electrocardiogram below each panel indicate instant in which roentgen exposure was made in relation to the electrocardiogram that was recorded simultaneously. See text for discussion.

with right-heart sampling for the indicator.51-54,27 Although these technics offer very important advantages from the viewpoint of greater technical simplicity, they offer no advantage over conventional venous dilution technics from the viewpoint of sensitivity and are at some disadvantage for quantitative applications.

The characteristic normal patterns of dilution curves recorded from various sites in the right side of the heart in a patient without a right-to-left shunt and in a normal dog are illustrated in figure 30. The "mixed venous" dilution curve recorded from the right ventricle after an injection downstream to this site is a badly damped version of the dilution curve recorded from the systemic artery. The dilution curve recorded from the coronary sinus, owing to the rapidity and relatively small volume of this circulation, is similar to an arterial dilution curve. It is to be noted that, as would be expected, the dye does not appear in the right ventricular sampling site until after it has appeared at the systemic artery.

Particularly in the recording of dilution curves from the cardiac chambers and great vessels where essentially stepwise changes in indicator concentration usually occur with each heartbeat, it should be recognized that the contours of dilution curves recorded by conventional cardiac catheter-densitometer systems are badly damped versions of the actual variations in indicator concentration occurring at the tip of the cardiac catheter. This is due to the slow dynamic response of such systems,75 which is difficult to avoid when the dye-blood mixture is sampled through a long narrow-bore tube. An example of the very rapid changes in indicator concen-
Comparison of systemic arterial and venous dilution curves recorded from various sites on the right side of the heart in a patient without arteriovenous shunt (left) and a normal anesthetized dog (right). The sites in the vascular systems from which the respective dilution curves were recorded are indicated on the left of the panels, and the instant and site of dye injection are specified by the vertical arrow. Note that curves recorded from the coronary sinus of both the patient and the dog are similar to curves recorded from a systemic artery. In contrast, curves recorded from the other venous sites resemble badly damped versions of the "parent" arterial curve. Also note that the right ventricular "mixed venous curve" resembles a composite of the superior and inferior caval curves and that, as a result of the relatively much smaller blood flow from this site, the effect of the coronary-sinus curve on the "mixed venous curve" is not apparent. Dilution curves in this figure are photographs of photostats of the original photographic records which were cut out and realigned, with correction for the effect of the dead space of the sampling systems, so that the true time relationships of the dilution curves recorded at the various sampling sites are illustrated. (Reproduced with permission of the publisher from Fox, I. J., and Wood, E. H.)
Effect of variation in the dynamic response of a catheter-densitometer system on the contour of dilution curves recorded from the pulmonary artery following injections of 2.5 mg. of indocyanine green into the superior vena cava of a 25-kg. dog.

The two dilution curves shown in each panel were recorded simultaneously from the same site just downstream to the pulmonary valve by two densitometer systems. The "slow system" consisted of a 7 F. cardiac catheter 40 cm. long with an internal diameter of 1.5 mm. The volume (dead space) of the system from the catheter tip through the detecting chamber of the Waters Model X100A densitometer was 0.9 ml. The "fast system" consisted of an identical densitometer and a catheter only 8 cm. long so that the dead space of this system was reduced to 0.3 ml. and consequently its 90 per cent response time to a square-wave change in dye concentration was decreased to 0.1 second when the blood flow rate through the system was 250 ml/min. The 90 per cent response times of the slow system at approximately the different flow rates indicated on the four panels were 0.4, 0.8, 1.0 and 4.4 seconds respectively. The galvanometer trace labeled "dye syringe" is a recording of the instant and volume (1 ml.) of dye injection. The sensitivities of the two densitometers were closely similar. The peak deflections of the curves in each panel were equivalent to a dye concentration of approximately 25 mg./liter. Note that in comparison to the fast-system curve there is some damping of the slow-system curve even at the fastest flow rate of 140 ml/min. which it was possible to achieve through this 40-cm. catheter system.

Abnormal initial deflection (fig. 32). If the sampling catheter is then withdrawn to a site on the right side of the heart which is upstream to the site of the defect, in this instance the right atrium, and the pulmonary-artery injection is repeated, the dilution curve recorded from this site will not show the abnormal initial deflection. This demonstrates and localizes the site of the left-to-right shunt to the next chamber downstream to the site at which no left-to-right shunt was detected, that is, to the right ventricle in this example.

The use of this technic to demonstrate and localize a left-to-right shunt in a dog before and after creation of a ventricular septal defect is illustrated in figure 33. In this dog before creation of a ventricular septal defect, the dilution curves recorded simultaneously from the pulmonary artery and from the
femoral artery, after injection into a distal pulmonary artery, were normal in contour. After creation of the ventricular septal defect by the technic of Griffin and Essex, the dilution curves recorded in a similar fashion show a small abnormal initial deflection on the curve recorded from the pulmonary artery and thus demonstrate the presence of a left-to-right shunt. Since this abnormal initial deflection was absent from the right atrial curve, the left-to-right shunt was localized to the right ventricle. It is of interest that the magnitude of this left-to-right shunt was too small to be detected by ordinary repetitive determinations of blood oxygen saturations from various sites in the right side of the heart when a cuvette oximeter was utilized, and that the contour of the dilution curve recorded from the femoral artery in the presence of this small left-to-right shunt was not appreciably different from normal. The value of venous dilution curves for the detection and localization of left-to-right shunts has been confirmed by reports from multiple laboratories.

Dilution curves recorded simultaneously from the right side of the heart and from a systemic artery in the presence of a left-to-right shunt can be used for simultaneous determinations of the systemic blood flow, the pulmonary blood flow, and the magnitude of the left-to-right shunt by methods that have been described previously. The four measurements that are necessary from the dilution curve to make these calculations (fig. 34) can be made directly from the simultaneously recorded systemic-artery and pulmonary-artery dilution curves; they consist of the determination of the build-up time and the peak deflections of the systemic artery curve, and of these same parameters for the initial portion, that is, the left-to-right shunt portion of the pulmonary-artery curve. That it is indeed possible to obtain reasonably accurate simultaneous measurements of the pulmonary and systemic blood flow and the left-to-right shunt by means of this indicator-dilution technic is demonstrated by the data shown in figure 35. Estimations of pulmonary and systemic blood flows and the left-to-right shunt determined by the conventional Fick method have been compared with data obtained by utilizing indicator-dilution technics in the same series of patients with left-to-right shunts and in dogs with ventricular septal defects. No systematic difference between the values derived by these two separate technics is evident, and the scattering of the values determined by the two technics is no greater than what would be expected from the error which is inherent in the Fick determinations of flow and the determinations by the dye-dilution technic. Up to the present time the foreign-gas technics have not been developed.

FIGURE 32
Schematic illustration of a method for localizing a left-to-right shunt by dilution curves recorded from selected sites in the right side of the heart. Indicator is injected at a site in the right or left side of the heart that is downstream to the sampling site, but upstream to the site of origin of the left-to-right shunt. Dye curves (left) of the circulation in the presence of ventricular septal defect were recorded from a systemic artery, the right ventricle, and the right atrium after injections into a distal pulmonary artery. Note (1) that dye was detected in the right ventricle before it appeared in the systemic artery, thus demonstrating the presence of a left-to-right shunt, and (2) that early-appearing dye was not detected from the right atrium, thus localizing the site of the left-to-right shunt to the right ventricle. (Reproduced with permission of the publisher from Wood, E. H.: Use of indicator-dilution technics. In: Symposium on Congenital Heart Disease. American Association for the Advancement of Science, Washington, D.C., 1960, p. 209.)
Demonstration of the localization of a left-to-right shunt by means of dilution curves recorded simultaneously from the right side of the heart and a systemic artery during operation for creation of a ventricular septal defect in a dog. Roentgenogram shows positions of the tips of the catheters during recording of these dilution curves: A, in right atrium; B, in a distal right pulmonary artery; and C, in the main pulmonary artery. Indocyanine was injected into the distal right pulmonary artery, with sampling from the main pulmonary artery and femoral artery immediately before and after creation of the defect (panels 1 and 2 respectively) and from the right atrium and femoral artery after creation of the defect (panel 3). The instant of injection of dye is shown by vertical arrows. Note abnormally early appearance of dye in the curve recorded from the main pulmonary artery after creation of the defect; this is caused by dyed blood that has shunted left to right through the defect. The fact that no abnormally early-appearing dye was detected from the curve recorded from the right atrium indicates that the shunt is downstream to this site. The magnitude of the shunt calculated from these dilution curves from the measurements of the areas of the forward triangles indicated by the vertical broken lines (panel 2, see figure 3d) was 9 per cent of pulmonary blood flow. Note that a shunt of this size does not produce apparent distortion of the systemic arterial (femoral artery) dilution curve. (Reproduced with permission of the publisher from Wood, E. H.: Use of indicator-dilution techniques. In: Symposium on Congenital Heart Disease. American Association for the Advancement of Science, Washington, D.C. 1960, p. 209.)

to the stage of providing simultaneous quantitative estimates of the levels of systemic, pulmonary and left-to-right shunt flows.

Certain distinct advantages of indicator-dilution techniques in the measurement of these parameters should be emphasized. The measurements required for the indicator-dilution values are recorded simultaneously over a period of less than 60 seconds. Therefore, the values obtained provide an accurate comparison of the hemodynamics of the pulmonary and systemic circulations, information which may be of considerable practical value in selecting patients with intraaortic aneurysms.
possible surgical repair. The dye-dilution technics do not require blood-gas analyses or active cooperation by the patient. When a suitable indicator dye is used (indocyanine green) the method is not interfered with by the presence of foreign gases in the blood, so that the technics can be applied readily during anesthesia and during clinical surgical measures. No accessory determinations of respiratory gas exchange are required. In addition to the use of venous indicator-dilution technics for the detection and quantitation of relatively simple cardiac defects, these technics are also applicable to the elucidation of multiple or complicated congenital or acquired cardiac defects. Their use for the demonstration of a bidirectional shunt through a ventricular septal defect is illustrated in figure 36.

The technics have particular application in congenital or acquired lesions affecting the left side of the heart and not ordinarily accessible to study by conventional right-heart catheterization. By means of technics that have been developed in recent years, it is now possible to gain access to any chamber of the heart or the great vessels for either the injection of indicator or the withdrawal of the resulting dye-blood mixture. When the need arises in cases of complicated or multiple cardiac defects involving the left side of the heart, it is possible to utilize these technics in conjunction with one another with an ac-

---

**TABLE 2**

Conditions Affecting Aortic Root That Are Associated With Increased Aortic Runoff

<table>
<thead>
<tr>
<th>Without pulmonary recirculation</th>
<th>With pulmonary recirculation</th>
</tr>
</thead>
<tbody>
<tr>
<td>b. Aortic regurgitation plus mitral regurgitation</td>
<td>b. Aorticopulmonary septal defect</td>
</tr>
<tr>
<td>2. Aneurysm of aortic sinus with rupture into left ventricle or left atrium</td>
<td>c. a or b plus ventricular septal defect</td>
</tr>
<tr>
<td></td>
<td>d. a or b plus pulmonary regurgitation</td>
</tr>
<tr>
<td></td>
<td>2. Aortic regurgitation plus ventricular septal defect</td>
</tr>
<tr>
<td></td>
<td>3. Aneurysm of aortic sinus with rupture into right ventricle or atrium</td>
</tr>
<tr>
<td></td>
<td>4. Aberrant coronary artery opening into right side of heart</td>
</tr>
<tr>
<td></td>
<td>5. Various combinations of these lesions</td>
</tr>
<tr>
<td></td>
<td>6. Acquired communications from aorta to superior vena cava or pulmonary artery</td>
</tr>
</tbody>
</table>

(esyphilisic aortitis with rupture)
Comparison of flow values obtained by the dye-dilution method illustrated in figure 34 and the direct Fick method in 12 patients and 18 dogs with intracardiac shunts. Note that there is no systematic difference in the values obtained by these methods and that the magnitude of the differences between the two methods is within the margin of error for the Fick method when applied to measurement of pulmonary and systemic blood flows in the presence of a left-to-right shunt.

Demonstration of left-to-right and right-to-left shunts by dilution curves recorded simultaneously from the right side of the heart and from a systemic artery. See legend for figure 33 for additional details.

Left panel. The presence of a left-to-right shunt is demonstrated by the abnormally early initial deflection in curves recorded from the main pulmonary artery and the right ventricle, and the site of this shunt is localized to the right ventricle by the absence of this initial deflection in the curve recorded from the right atrium.

Right panel. The presence of a coexisting right-to-left shunt was demonstrated by the abnormally early initial deflection in the dilution curve recorded from the femoral artery when indicator was injected into the superior vena cava, a site which therefore was upstream to the defect. The absence of this initial deflection from the femoral-artery curve recorded after injection into the left pulmonary artery demonstrates that this site is downstream to the defect. Demonstration of an abnormal initial deflection in the femoral-artery curve after an injection into the right ventricle (curve not shown) allowed the site of the right-to-left shunt to be localized to ventricular level. (Reproduced with permission of the publisher from Wood, E. H.: Use of indicator-dilution technics. In: Symposium on Congenital Heart Disease. American Association for the Advancement of Science, Washington, D.C., 1960, p. 209.)
ceptable degree of safety. This allows study of any of the four heart valves or cardiac chambers during one procedure. This type of complicated procedure is carried out only in a small number of specially selected patients with multiple lesions of the left side of the heart and perhaps also with involvement of the right side of the heart in whom the information required to establish a diagnosis and determine the feasibility of surgical repair cannot be obtained with certainty by simpler technics.

**Special Applications of Venous Dilution Curves in Conditions With Increased Aortic Runoff and Pulmonary Recirculation**

The technic of right-heart catheterization with recording of venous dilution curves combined with aortic and left-heart catheterization has a particular diagnostic application to the elucidation of lesions of the aortic root that are associated with increased runoff of blood from the aorta. These conditions, which are listed in table 2, do not include situations that are associated with increased peripheral circulatory runoff such as is encountered in hyperthyroidism and in systemic arterial fistula and that are not associated with abnormalities of the aortic root.

Following injection of dye above the aortic valve, the immediate appearance of dye in the left ventricle is evidence for aortic regurgitation. The absence of early-appearing dye in the left atrium in such a patient is evi-

![Injection into aorta](image)

**FIGURE 37**

Demonstration by indicator-dilution technics of rapid arrival of dye in the right and left ventricles following injection of indicator into the aorta in the presence of aortic regurgitation and a ventricular septal defect. On the right is a diagram of the circulation and on the left are the dilution curves recorded simultaneously from a systemic artery and the right and left ventricles. The vertical arrows indicate the instant of injection of indicator.

Note (1) the nearly instantaneous appearance of dye in the left ventricle because of aortic regurgitation, (2) the appearance of dye in the right ventricle immediately thereafter, indicating the presence of a left-to-right shunt via the ventricular septal defect, and (3) the appearance of dye at the systemic artery later than at the ventricles, and the abnormal prolongation of the disappearance slope of the curve from the systemic artery, indicating the presence of aortic regurgitation or a left-to-right shunt occurring at or distal to the aortic valve. (Reproduced with permission of the publisher from Fox, I. J., and Wood, E. H.)

**TABLE 3**

Diagnosis Interpretation of Dye-Dilution Curves Recorded From Central Circulation Following Injection of Indicator Into Ascending Aorta

<table>
<thead>
<tr>
<th>Condition</th>
<th>Early-appearing dye in *</th>
<th>Right ventricle</th>
<th>Pulmonary artery</th>
<th>Left atrium</th>
<th>Left ventricle</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aortic regurgitation</td>
<td>+</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>+</td>
</tr>
<tr>
<td>Aortic plus mitral regurgitation</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>+</td>
</tr>
<tr>
<td>Aortic-sinus aneurysm to left ventricle</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Aortieopulmonary communication</td>
<td>+</td>
<td>—</td>
<td>+</td>
<td>—</td>
<td>+</td>
</tr>
<tr>
<td>Aortic regurgitation plus ventricular septal defect</td>
<td>+</td>
<td>—</td>
<td>+</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Aortic-sinus aneurysm to right ventricle</td>
<td>+</td>
<td>—</td>
<td>+</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

*+ = dye appears immediately; (+) = dye appears abnormally early after traversing pulmonary circulation only; and — = dye appears after traversing systemic circulation.
Injection into aorta

Sampling from:

- Systemic artery
- Left ventricle
- Right ventricle

FIGURE 38

Demonstration by indicator-dilution technics of rupture of an aortic-sinus aneurysm into the right ventricle. On the left is a diagram of the central circulation in the presence of an aortic-sinus aneurysm opening into the right ventricle, and on the right are dilution curves recorded from a systemic artery, left ventricle, and right ventricle after injection of indicator just distal to a competent aortic valve. Vertical arrows indicate the instant of injection of indicator. The almost instantaneous appearance of dye in the right ventricle, before it is recorded from the left ventricle and systemic artery, is indicative of an abnormal communication between the aortic root and the right ventricle. The curve recorded from the systemic artery shows an abnormal deflection on the disappearance slope indicative of a left-to-right shunt originating at or distal to the aortic valve. The abnormal initial deflection on the left ventricular curve is due to this left-to-right shunt. (Reproduced with permission of the publisher from Wood, E. H.: Use of indicator-dilution technics. In: Symposium on Congenital Heart Disease. American Association for the Advancement of Science, Washington, D.C., 1960, p. 209.)

Diagnosis of Ventricular Septal Defect With Aortic Regurgitation

A defect in the membranous portion of the ventricular septum may be associated with an abnormally placed or deformed aortic valve cusp adjacent to or above the defect with consequent aortic regurgitation. A schematic diagram of the central circulation in a case of ventricular septal defect with aortic regurgitation is shown in figure 37. The dilution curves accompanying this diagram illustrate nearly instantaneous detection of indicator in both the left and the right ventricle following injection of indocyanine green into the aorta above the valve, indicating the presence of aortic regurgitation and left-to-right shunt originating from the aorta and left ventricle via a ventricular septal defect. The indicator appears later at the systemic artery and then at the ventricles, and the disappearance slope of the systemic-artery curve is abnormally prolonged, indicating the presence of aortic regurgitation or a left-to-right shunt at or distal to the aortic valve.

Application of this technic during combined catheterization of the right side of the heart, puncture of the left ventricle and catheterization of the aorta has been described.81

Diagnosis of Ruptured Aortic-Sinus Aneurysm

An example of the use of technics of this type for the demonstration and estimation of
the severity of a ruptured aortic-sinus aneurysm is shown in figure 38. In the presence of an aortic-sinus aneurysm ruptured into the right ventricle, if dye is injected into the aorta just above the valve and a dilution curve is recorded from the right ventricle and the left ventricle, immediately-appearing dye will be detected in the right ventricle, and at a later period, abnormally early-appearing dye will be detected in the left ventricle because of the left-to-right shunt via the aortic-sinus aneurysm. Application of this technic during combined right and left-heart catheterization has been described. 

Summary

In summarizing the diagnostic value of the indicator-dilution technics in the study and investigation of congenital heart disease, perhaps a simple listing of the advantages and disadvantages of the technics will suffice.

The advantages are as follows: 1. The technics have a high degree of safety. In the more than 3000 cardiac patients in whom they have been utilized there have been no deaths and little or no morbidity. 2. The sensitivity of the technics for the detection and localization of right-to-left and left-to-right shunts is much superior to that of the conventional blood-gas methods. 3. Quantitative determinations of systemic and pulmonary blood flow and intrathoracic shunts by indicator-dilution methods can be made simultaneously over periods of less than 1 minute; when indicator dyes are used, these technics do not require manometric analyses, accessory respiratory-exchange studies, or active cooperation of the patient; and they are independent of foreign (anesthetic) gases in the blood. 4. The technics are versatile and can be extremely useful either for the detection and diagnosis of minimal, relatively simple defects or for the elucidation of the extremely complex types of congenital malformations. 5. The information obtained is of both a qualitative and a quantitative nature; that is, the nature and location of defects can be determined and, in addition, the magnitude and direction of flow through the defects in question as well as the levels of systemic and pulmonary blood flows can be estimated.

The disadvantages of the technics are as follows: 1. Rather complicated and sensitive recording equipment is essential. 2. Considerable technical skill is required of the persons carrying out the procedure in the placement of the necessary needles and catheters and in the proper selection of the multiple possible injection and sampling sites reached by these instruments in order to obtain the information needed to establish the diagnosis in question. 3. Correct interpretation of the diagnostic significance of the dilution curves obtained requires careful study and considerable experience by the person responsible for this phase of the investigation.

In other words, these technics entail relatively little discomfort and little danger for the patient, but require good equipment and, more important, considerable time, effort and skill on the part of the investigator and his assistants in order to obtain highly successful results.

Acknowledgment

The author is indebted to many professional and technical colleagues whose collaborative efforts made possible the observations upon which most of the material contained in this article is based. The contributions of Drs. H. J. C. Swan, H. B. Burchell, J. T. Shepherd, H. W. Marshall, Mr. W. F. Sutteror, Lucille Cronin and Mrs. Joan Frank are of particular importance.

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SYMPOSIUM ON INDICATOR-DILUTION TECHNIQUES

567


Diagnostic Applications of Indicator-Dilution Technics In Congenital Heart Disease
Earl H. Wood

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