Noninvasive Detection and Quantification of Left-to-Right Shunts in Children Using Oxygen-15 Labeled Carbon Dioxide

DOLORES M. TAMER, M.D., Denny D. Watson, Ph.D., Peter J. Kenny, Ph.D., Warren R. Janowitz, M.D., Henry Gelband, M.D., and Albert J. Gilson, M.D.

SUMMARY A method for the detection and quantification of left-to-right intracardiac shunts is described which utilizes a single breath inhalation of oxygen-15 labeled carbon dioxide \((\text{C}^{15}\text{O}_2)\). The inhaled gas rapidly crosses the alveolar membrane and the oxygen-15 label is exchanged through the carbonic cycle to form oxygen-15 labeled water within the pulmonary capillary blood. Pulmonary indicator clearance curves are measured by external scintillation probes. A simplified method of shunt flow quantification was developed from indicator dilution principles and used for the analysis of the clearance curves. Inhilation studies were performed with 62 children on the day prior to cardiac catheterization. The presence or absence of left-to-right shunt was confirmed by contrast angiography in all cases. Twenty-six children were found to have no shunts by \(\text{C}^{15}\text{O}_2\) inhalation, oximetry or angiography. Of the 36 with shunts, 34 were detected by \(\text{C}^{15}\text{O}_2\). Two of these were designated as equivocal because they were considered to be less than the threshold of definitive detection by \(\text{C}^{15}\text{O}_2\) (having \(Qp/Qs\) less than 1.2); 32 were positive and there were two false negatives with small ventricular septal defects. There were no false positives by \(\text{C}^{15}\text{O}_2\). The correlation coefficient between \(\text{C}^{15}\text{O}_2\) and oximetry values of shunt flow for those patients with proven shunts was 0.82.

NUCLEAR MEDICAL TECHNIQUES are now widely utilized to assist in the diagnosis and evaluation of many cardiac abnormalities.\(^1\)\(^-\)\(^12\) The diagnostic information is usually derived from quantitative radionuclide angiography, performed with the aid of a scintillation camera-computer system following injection of a bolus of radioactive material into a peripheral vein. Because it is minimally invasive, this procedure has found wide acceptance in the study of congenital heart disease in children, and has been successfully employed for the detection and quantification of left-to-right intracardiac shunts.\(^13\)\(^-\)\(^14\) The computer-camera system is used to obtain a recording (activity versus time) of the initial passage of radionuclide indicator through the lungs. Left-to-right shunt flow can then be inferred from early recirculation of indicator through the shunt pathway. The accuracy of the technique, however, depends critically on the delivery of a compact bolus, and in order to obtain this, it may be necessary to sedate the child as well as inject into the external jugular vein.

This report describes a totally noninvasive method for detection and quantification of left-to-right shunts which utilizes a single breath inhalation of radioactive oxygen-15 labeled carbon dioxide \((\text{C}^{15}\text{O}_2)\), with measurement of activity versus time curves over the heart and lungs. Because the tracer is introduced at the pulmonary venous level, shunt detection is more reliable and quantification is simplified.

Methods

Sixty-two children were studied in the unsedated state by the \(\text{C}^{15}\text{O}_2\) inhalation method on the day prior to cardiac catheterization. Informed consent was obtained. The ages of the children ranged from 18 months to 16 years with modal age of 4 and median age of 6 years. Radioactive \(\text{C}^{15}\text{O}_2\) was prepared in an accelerator as previously described.\(^15\)\(^-\)\(^18\) Patients were placed supine and two collimated \(1^\circ\) thick \(× 1.2^\circ\) diameter sodium iodide detectors were positioned, one over the heart and one over the right lung as indicated in figure 1. Patients were instructed to breathe normally from a spirometer. Labeled \(\text{C}^{15}\text{O}_2\) (half-life 124 seconds) in a volume of 5 to 10 cc and in a dosage of 60 \(\mu\)Ci/kg was delivered into the spirometer mouthpiece at end tidal volume and inhaled with a tidal volume inspiratory effort. Patients who could do so were asked to hold their breath for ten seconds. The outputs from the detector ratemeters were recorded by a cathode ray tube on a photosensitive strip chart simultaneously with the ECG and spirometer tracings as indicated in figure 2. The ratemeter time constants were 0.06 sec and 0.3 sec for the heart and lung probes respectively. The maximum counting rates were in the range of 30,000 cps which was well within the range of linearity for the electronic system.

The amplitudes of the lung curve were measured at times corresponding to equivalent points on each cardiac cycle. Cardiac cycles were used in place of real time so that the normal lung clearance curve would not be distorted by time interval variations between successive heart beats. Typical curves obtained from a study indicating a moderate shunt are shown in figure 3. The amplitudes of the lung clearance curves were then plotted on semilogarithmic paper as indicated in figure 4, which illustrates the analysis of the study shown in figure 3. The initial clearance phase of the curve was extrapolated as a straight line on the semilog plot. A left-to-right shunt was indicated if the actual curve broke from the extrapolated downslope within two to four heartbeats. The appearance time, \(t_1\) (in heart beats), of the first shunt recirculation following the peak of the primary circulation was then noted in order to estimate the appearance time, \(t_2\), of the second shunt recirculation which should occur an equal time later. The peak amplitude \((h)\) of the first shunt recirculation occurred within this time interval between \(t_1\)
and \( t_2 \) as illustrated in figure 4. The arrival time of the second recirculation must be determined as described above because it usually cannot be located by visual inspection. In this way the measurement of \( h \) excludes the effects of multiple recirculation. The shunt fraction, \( f \), which is shunt flow expressed as percent of total pulmonary blood flow, was calculated according to the formula

\[
f = \frac{e}{100}
\]

which is derived in Appendix I. The shunt fraction may be expressed as pulmonary systemic flow ratio by: \( \frac{Q_p}{Q_s} = \frac{1}{1-f} \).

The studies were classified as negative for left-to-right shunt when no break from a straight line on the semi-log plots could be observed visually. When a measurable break was observed, the study was classified as positive if the quantitative analysis indicated a shunt flow of more than 20% of total pulmonary blood flow. Studies were classified as equivocal when shunt flow of less than 20% was indicated. We have observed that deviations in the lung clearance curve can occasionally be caused by unnoticed movements of the patient, forced breathing or Valsalva maneuvers. The maximum observed magnitude of such extraneous perturbations was approximately equal to that which could be caused by a 10% shunt. We therefore adopted 20% (or a \( \frac{Q_p}{Q_s} \) ratio of 1.2) as a threshold for positive shunt detection by this test in order to minimize the possibility of false positive results which could potentially label a child as having a small shunt.

Cardiac catheterization was performed using standard procedures. The children were premedicated with demerol 1.5 mg/kg, thorazine 0.5 mg/kg, and phenergan 0.5 mg/kg. Left-to-right shunt flow was calculated using oxygen saturation values of at least two paired samples from the superior vena cava and pulmonary artery. Oxygen saturation was determined by an American Optical Micro-oximeter.

Indicator dilution studies using indocyanine green dye were performed on 12 patients and were analyzed using the method of Carter et al.\textsuperscript{10}

Analysis of the \(^{14}O_2\) curves was performed without knowledge of the patients' diagnoses or clinical findings. Cardiac catheterization was done without knowledge of the \(^{14}O_2\) results. Shunt confirmation was obtained by contrast cineangiography in all cases. Correlation of the \(^{14}O_2\) data with oximetry and angiographic findings was evaluated at the end of the study period.

**Results**

Tables 1 and 2 summarize the clinical, catheterization and \(^{14}O_2\) data of the children with and without shunts, respectively. Of the 62 patients, 36 had left-to-right cardiac shunts documented by angiography and 34 were also positive by oximetry. Of these 36 cases, 34 were also detected by \(^{14}O_2\). Of the two confirmed shunts which were not detected by oximetry, one was indicated as equivocal (less than 20%) by \(^{14}O_2\) and one was classified as positive (23%) by \(^{14}O_2\). The two false negative studies by \(^{14}O_2\) both had oximetry values indicative of extremely small shunts, amounting to 16% and 23% of pulmonary blood flow.

In addition, 26 patients were included in this study who had no left-to-right shunt by oximetry or by contrast angiog-
Figure 3. Recording obtained from a patient with a small left-to-right shunt. The lung clearance curve has been darkened for emphasis. The dotted line is an extrapolation of the initial exponential clearance phase. Shunt recirculation causes a break from the extrapolated curve starting between the third and fourth heartbeats after peak concentration. The spirometer trace shows shallow spontaneous breathing during the study. This is common with younger children and does not affect the results of the test.

Figure 4. The amplitudes of the lung curve shown in figure 3 have been plotted on a log scale. The upward break of the curve caused by shunt recirculation is seen at $t_1$. The deviation of the curve from the projected line is measured at several successive points. The maximum deviation of 2.2 holds nearly constant over an interval of 1 to 2 heartbeats. The appearance of the second shunt recirculation is indicated at $t_2$.

Discussion

In recent years there has been increasing emphasis on the development of noninvasive methods which can provide reliable diagnostic information at minimal risk to the patient.
This is especially true in the area of pediatric cardiology. Reliable clinical diagnosis of certain left-to-right shunts (atrial septal defect, ventricular septal defect, patent ductus arteriosus) is usually possible by physical examination and conventional laboratory determinations. Cardiac catheterization has been the routine confirmatory study. However, in at least one center, the preoperative catheterization and angiographic procedures for a patient with findings of a typical atrial septal defect have been replaced by a battery of noninvasive tests for confirmation of the diagnosis.\(^1\) Rowe\(^2\) has cited the variability in the number of confirmatory studies required preoperatively in different centers for "typical" heart defects and has suggested that alternative noninvasive methods of cardiac diagnosis be developed and utilized where feasible. Radionuclide methods have developed sufficiently to show promise for such use.

The \(^{13}O_2\) technique may be applied to a variety of common situations in pediatric cardiology. This method is well suited for preoperative confirmation of a left-to-right shunt in the presence of the typical clinical findings of atrial septal defect or patent ductus arteriosus. In certain instances, physical findings of an innocent murmur may be confused with a small left-to-right shunt (commonly in atrial septal defect). A negative \(^{13}O_2\) study in such a case could defer a cardiac catheterization procedure. Serial measurements of ventricular left-to-right shunts during infancy and childhood could decrease the number of cardiac catheterization procedures to which a child is subjected. Additionally, the \(^{13}O_2\) method could be used postoperatively to detect residual left-to-right shunts, as well as to establish the patency of a pulmonary-to-systemic anastomosis. The basic methods described here have also been applied to an adult population by Boucher et al.\(^3\) with very similar results. The principle of using a gaseous radionuclide to "inject" an indicator through the pulmonary venous bed into the left heart in a totally noninvasive manner will hopefully justify continued research and development on other gases or inexpensive production facilities which could make the technique more widely available.

The conventional radionuclide method and the \(^{13}O_2\) method of shunt determination both employ curves obtained from the pulmonary circulation. There are, however, fundamental reasons which simplify and inherently improve the quantification of shunts with \(^{13}O_2\). The accuracy of shunt calculation depends upon the accuracy of the separation of the primary and first recirculation components of the sampled indicator dilution curves. With \(^{13}O_2\), the indicator is introduced directly into the pulmonary blood and consequently the initial pulmonary clearance is a simple exponential washout which can be easily defined as a straight line when plotted on semi-logarithmic paper, even in the presence of valvular disease or reduced cardiac output.\(^4\) This clearly defines the primary component of the indicator dilution curve which can then be separated accurately from the first shunt recirculation component. Also, there is no problem from systemic recirculation with the \(^{13}O_2\) technique.
because the labeled water is rapidly equilibrated with total body water and very little systemic recirculation occurs. Methods which use an intravenous injection require that the indicator bolus pass through the right heart and therefore undergo dilution and dispersion upstream from the sampling site. This results in a more complex indicator dilution curve which requires computer curve-fitting and some subjective judgment to insure correct curve decomposition.24

Since C\textsuperscript{14}O\textsubscript{2} has an extremely short half-life, the study can be repeated within minutes to confirm any questionable results. The radiation dose to the critical organ is lower by a factor of at least ten compared with the intravenous \textsuperscript{99m}Tc method.29,30 and lower by two to three orders of magnitude compared with angiography. Another important consideration, particularly with children, is the truly noninvasive nature of the technique. Because there is no sedation or venipuncture involved, the test is readily accepted by both parents and children. The results of this study of a pediatric population indicate that the sensitivity for shunt detection and quantitative accuracy of the C\textsuperscript{14}O\textsubscript{2} inhalation method are both comparable to oximetry at catheterization.

Acknowledgment
We wish to thank Mrs. Eileen Read and Ms. Mary Bettencourt for their excellent technical assistance.

Figure 5. Comparison of results from C\textsuperscript{14}O\textsubscript{2} and oximetry methods. The left and bottom axes express shunt flow as a fraction of pulmonary flow. The top and right axes indicate the corresponding pulmonary to systemic flow ratios. Twenty-six cases are included at the origin (0,0) having no shunt indicated by either method. The points denoted by (1) and (2) on this graph correspond respectively to patients 14 and 31. These were reported in the study as equivocal with shunts of less than 20%. The point indicated by (3) was patient 11. Both points (2) and (3) did show small shunts by angiography which were not indicated by oximetry. These points are therefore not false positives by C\textsuperscript{14}O\textsubscript{2} but rather are false negatives by oximetry. The dotted lines are ±10% from the solid identity line.

Figure 6. Illustration of a pulmonary clearance curve when a left-to-right shunt is present. The first shaded region represents recirculation from shunt flow. The second shaded area is the contribution from second recirculation through the shunt pathway which can be a significant component of this portion of the curve. Background from systemic circulation is not indicated but would begin at about the time of second shunt recirculation.

Appendix
The quantitation of left-to-right shunt flow from indicator-dilution (ID) data requires a determination of the areas (denoted respectively as A and a) under the primary circulation and first shunt recirculation components of the ID curves as illustrated in figure 6. Given these areas, it is a fundamental result that shunt flow, f, expressed as a fraction of the total pulmonary blood flow is

\[ f = \frac{a}{A} \]

or equivalently the pulmonary to systemic flow ratio is given by

\[ \frac{Q_p}{Q_s} = \frac{1}{1 - f} = \frac{A}{A - a}. \]

Direct measurement of these areas is not feasible because the curve tails are obscured by multiple recirculation and background activity from systemic circulation. However, the buildup and amplitudes of the curve components can be determined. The derivation below results in a method of estimating the areas under the curves from these parameters which can be determined easily from the ID curves.

It has been demonstrated24,31 that the lung sampled indicator dilution curves can be adequately represented by the functions

\[ C_i(t) = C_{oa} e^{-t} \left( \frac{a}{n - 1} \right) \]

which are generated from a simple tandem mixing chamber model where \( C_{i}(t) \) is the concentration of indicator as a function of time in the \( n \)-th mixing chamber. In the case of CO\textsubscript{2} inhalation, where the lung serves both as the chamber of initial injection and the chamber of sampling, the initial clearance phase follows the simple exponential form with \( n = 1 \)

\[ C_i(t) = C_{oa} e^{-t} \]

The first shunt recirculation component, which has been modified by its passage through the heart and back into the lung, can be shown to follow the functional form with \( n = 2 \)

\[ C_i(t) = C_{oa2} t e^{-t} \]

If \( H \) is the peak amplitude of the primary curve, the area can then be expressed as

\[ A = \int_0^\infty C_i(t) \, dt = H \cdot \frac{1}{\alpha} \]

(height × equivalent width)

If \( h \) is the peak amplitude of the first recirculation curve, the area of this curve can be expressed as

\[ a = \int_0^\infty C_i(t) \, dt = h \cdot \frac{e}{\alpha} \]

(height × equivalent width)
The ratio of these two areas then becomes 
\[ \frac{a}{A} = \frac{e}{H} \]
The width factors have cancelled except for the constant factor 
\[ e = 2.72. \]
The left-to-right shunt flow expressed as a percent of pulmonary blood flow is therefore 
\[ f = e \left( \frac{h}{H} \right) \times 100\% \]
and the pulmonary to systemic flow ratio is 
\[ \frac{Q_p}{Q_s} = \frac{1}{1 - e \left( \frac{h}{H} \right)} \]

The essential nature of the assumption which is built into this quantitative approach is that the width of the recirculating component will be related by a constant factor (e) to the width of the primary circulating component. The width of the primary circulating component may be altered by several variables such as cardiac output, chamber volumes, ejection fractions, and regurgitant flow; however, this will not violate the assumption which requires only that as these variables alter the first the build of indicator, they will similarly alter the shunt recirculation.

In comparison to the \( C_v/C_l \) ratio method developed by Wood,\(^5\) the above method, although quite similar, has the important technical distinction that it obviates the essential limitation of the \( C_v/C_l \) method. The \( C_v/C_l \) method is based upon the measurement of the overall curve down-slope, and any of the several variables other than left-to-right shunt which may alter the down-slope will provide potentially erroneous shunt indications.

Another more recent method by Maltz and Treves\(^7\) uses Gamma variate curve fitting to estimate the downstroke portions and consequent areas of the curves based upon the build-up curve segments. This method has been used successfully in the analysis of ID curves from intravenous injections. The \( CO_2 \) studies are amenable to this type of analysis provided that the functional forms are appropriately modified. However, we have chosen the method described above because it is much more simple in application, is objectively reproducible, and has successfully overcome the limitation of the earlier \( C_v/C_l \) ratio method.

References
Noninvasive detection and quantification of left-to-right shunts in children using oxygen-15 labeled carbon dioxide.

D M Tamer, D D Watson, P J Kenny, W R Janowitz, H Gelband and A J Gilson

Circulation. 1977;56:626-631
doi: 10.1161/01.CIR.56.4.626

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1977 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/56/4/626

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation is online at:
http://circ.ahajournals.org//subscriptions/