Radionuclide Angiocardioography

Improved Diagnosis and Quantitation of Left-to-Right Shunts Using Area Ratio Techniques in Children

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SUMMARY
A comparison of several reported methods for detection and quantitation of left-to-right shunts by radionuclides was performed in 50 children. Count ratio (C2/C1) techniques were compared with the exponential extrapolation and gamma function area ratio techniques. C2/C1 ratios accurately detected shunts and could reliably separate shunts from normals, but there was a high rate of false positives in children with valvular heart disease. The area ratio methods provided more accurate shunt quantitation and a better separation of patients with valvular heart disease than did the C2/C1 ratio. The gamma function method showed a higher correlation with oximetry than the exponential method, but the difference was not statistically significant. For accurate shunt quantitation and a reliable separation of patients with valvular heart disease from those with shunts, area ratio calculations are preferable to the C2/C1 ratio.

Additional Indexing Words:
- Atrial septal defects
- Cardiac catheterization
- C2/C1 ratio
- Exponential extrapolation techniques
- Valvular heart disease
- Ventricular septal defects
- Congenital heart disease
- Gamma function

Radionuclide angiocardioography can provide valuable diagnostic assistance in the evaluation of congenital heart disease. The studies are noninvasive, rapid, and expose the patient to a relatively low radiation dose. Circulatory dynamics are not disturbed and no exposure to radiographic contrast media is necessary.

Prinzmetal et al. introduced the technique of precordial angiocardioography in 1949 using 24Na and a Geiger-Mueller tube. However, the presence of both cardiac chambers within the detector's field of view led to complex curves and made analysis difficult. In 1962, Folse and Braunwald showed that left-to-right (L-R) shunts could be diagnosed from the pulmonary vascular dilution curve obtained with a single detector over a peripheral lung field. They used 131I-diodrast as a tracer, and suggested calculation of the C2/C1 ratio as a simple index for detection of L-R shunts.

Subsequently, count ratio methods have been widely investigated. Using 99mTc-pertechnetate as a tracer, these studies have demonstrated adequate discrimination of patients with shunts from normals and from patients with other types of congenital heart disease. However, it has recently been suggested that the C2/C1 ratio is unreliable and cannot adequately distinguish patients with shunts from those with valvular heart disease. In order to more easily distinguish these patients and to provide more accurate quantitation of L-R shunts, two area ratio techniques have been developed. These techniques calculate shunt size from a ratio of areas under the pulmonary time-activity curve. The areas are defined by fitting a mathematical function to the original data. One method employs gamma function fitting of the pulmonary activity curve, while the other uses a Stewart-Hamilton extrapolation of the downslope of the curve. Both methods are reported to be highly accurate.

Since knowledge of the relative accuracy of these methods would be helpful in planning the evaluation of a patient with congenital heart disease, we have compared results obtained with each of these methods to those of standard oximetry determinations.

Methods
Radionuclide angiocardioograms were performed on 61 patients aged three months to 18 years (mean, 7.5 years).
Fifty-three were in-patients at St. Louis Children's Hospital who underwent cardiac catheterization and angiography within two days of their radionuclide study. Eight patients were normal young adults (16-18 years old) referred to the nuclear medicine service for brain scans. The radioangiographic study was performed on these patients at the time of $^{99m}$Tc-pertechnetate injection. Informed consent was obtained from the parents of all patients.

All studies were performed with the patient in the supine position under a Searle Radiographic-HP gamma camera interfaced to a small PDP-12 digital computer. A high sensitivity parallel hole collimator was used. A rapid intravenous injection of $^{99m}$Tc-pertechnetate (215 $\mu$Ci/kg) was made using the saline flush technique. The left antecubital fossa was the usual site of injection, but the external jugular vein was used in infants if a suitable arm vein could not be located.

Digitized data frames were collected at 0.4 sec intervals and stored on magnetic tape. A summed image of the venous and arterial phases of the study was presented on the computer output oscilloscope and an area of interest was outlined over the peripheral lung fields. The cardiac blood pool and the venous structures containing the bolus activity were excluded from the area of interest. Since cardiac activity obscured some portions of the left lung, the area of interest usually contained more of the right lung than the left. A pulmonary time-activity curve was generated from the outlined region.

A smaller area of interest was placed over the superior vena cava to evaluate the adequacy of the injection. Studies which showed a prolonged (> 2.4 sec) or double-peaked bolus were discarded. This occurred in 11 of 61 patients (18%). A poor bolus was often noted in children who cried during injection and in those who resisted venipuncture by moving their elbow or arm excessively during the injection. Indwelling catheters were not used and patients were not sedated because our pediatric cardiologists preferred that these techniques not be employed.

The remaining 50 patients comprise the study group. The radionuclide angiocardiogram of each patient was subjected to each of the methods of shunt quantitation described below, so that results obtained from the same raw data base could be compared. The studies in these patients showed a mean bolus duration of 2.0 sec (range 1.2-2.4). Thirty patients had isolated L-R shunts (13 VSDs, 10 ASDs, 7 PDAs). Three of these patients had coexistent valvular heart disease; one had severe mitral insufficiency and a small VSD, one had severe pulmonic stenosis and a small VSD, and one had mild pulmonic stenosis and a 2.1 ASD. Of the remaining 20 patients, eight were normal (this includes five of the normal volunteers), while 12 had angiographically demonstrated cardiac abnormalities but no shunts. These 12 patients had the following lesions: mitral insufficiency (3); mitral stenosis (3); pulmonary valvular stenosis (1); aortic stenosis (1); coarctation of the aorta (1); and corrected transposition of the great vessels (1).

Count ratio calculations were performed in the standard method originally described by Folse and Braunwald (C2/C1 ratios). Count rate C1 was obtained at the peak of the pulmonary activity curve, and the build-up time $T_b$ was determined. C2 was defined as the count rate occurring at time $T_d$, a time after the peak equal to $T_b$ (fig. 1A). The ratio of C2 to C1 was determined and expressed as a percentage. The onset of the initial rise of pulmonary activity was determined in several ways. When simple inspection of the curves was used, three criteria had to be satisfied. 1) The starting point was chosen as the first point which had an activity greater than 50 counts/0.4 sec, and 2) which also contained at least twice the activity of the preceding frame. 3) As an additional check against this rise in counts being due to scatter from the bolus in the subclavian vein or superior vena cava, right heart activity had to be present. The arrival of the bolus in the heart was always discrete, and not difficult to detect. If right heart activity was not present in the initial frame fulfilling the first two criteria, the frame in which right heart activity first appeared was chosen as the starting point.

The C2/C1 ratio was also calculated by choosing the

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

*Figure 1*

The pulmonary time-activity plot of a patient with an oximetrically determined 1:8:1 shunt is shown. In A an artist has added arrows to indicate C1 (the peak point) and C2. In B and C the computer has superimposed the fitted functions on the real data and displayed them together. In A the C2/C1 ratio was 50%, and the QP/QS ratio determined from the regression equation was 1:6:1. In B exponential fitting resulted in an X/Y area ratio of 1.94 and calculated a QP/QS ratio of 1.8:1. In C gamma function fitting calculated a QP/QS ratio of 1.7:1.
starting point as the first frame in which activity was equal to or exceeded 10% of peak activity. In addition, the C2/C1 ratio was calculated automatically by the formula developed as part of the Maltz and Treves algorithm. This formula defined the C2/C1 ratio as follows: C1 was the activity of the real data point which occurred at the same time as the fitted maximum of the first pulmonary transit. T1 was the time from the beginning of the fitted curve to C1. T2 was equal to T1 and originated at the peak. C2 was the activity of the real data point at T2. Regression equations were calculated relating these three types of C2/C1 ratios to oximetrically determined QP/QS ratios.

The area ratio calculation of Anderson et al. was performed by a FOCAL-12 algorithm which required operator interaction. A pulmonary time-activity curve was inspected by the operator, who selected the peak point. He then inspected the downslope to determine how many points after the peak would be included in the exponential fit. By including the maximum number of data points in the fit, we felt the reliability of the fitted line and the shunt calculation would be increased. This would not be true, of course, if points in the terminal portion of the descending limb changed the slope of the fitted line. We avoided this by carefully inspecting time-activity curves and numerical printouts of the data, and excluding terminal points which caused the initial downslope to be altered. When both the peak and the number of points to be fit in the downslope were determined, the algorithm performed a least squares fit to the log of the data and exponentially extrapolated the fitted line from the peak to 1% of the peak value. This divided the area beyond the peak of the pulmonary curve into two sections (fig. 1B). Area Y is bordered superiorly by the fitted line extrapolated to 1% peak value, inferiorly by the base line, and on its left side by a line extending perpendicular to the base line upward to the curve peak. Area X is bordered superiorly by the original pulmonary activity curve, inferiorly by the extrapolated line, and on its right by a line perpendicular to the base line extending upward from the 1% level. The algorithm then calculates area X, area Y and the area ratio of X/Y.

This analysis is based on the assumption that normal pulmonary clearance will follow a single exponential decline. Area Y represents this theoretical normal area. Area X includes the original data curve, and will increase in proportion to the degree in which the real data deviate from a single exponential decline. Therefore, it will theoretically increase in proportion to the shunt flow. The ratio of the areas (X/Y) can then be related to the QP/QS ratio determined by oximetry. This method will be referred to as the exponential fitting method.

Minor curve fitting problems were encountered with this method. Fitting a straight line to the downslope of activity from the peak was sometimes difficult. This was especially true when the region of peak activity was not discrete. However, this problem occurred in only five of 50 cases. In patients with large shunts (QP/QS by oximetry ≥ 2.5), another problem occurred. The shunt recirculation curve often disrupted the exponential decline of the pulmonary activity curve quite soon after peak activity. Therefore, fewer data points were available to fit the straight line. However, in no case did we have to fit the line to less than three data points, and this occurred in only eight of 50 cases. The mean number of data points available for fitting the downslope of the pulmonary activity curve was 5.3 (range 3–9).

The gamma function method was performed using the algorithm developed by Maltz and Treves. Their original FOCAL-11 program had to be adapted to our FOCAL-12 format, but identity of the two versions was verified by testing our program on the raw data* of ten patients from the Boston Children's Hospital Medical Center. The QP/QS calculations with the two programs were identical.

Using a least squares technique, the first transit pulmonary activity curve is fitted with a gamma variate function of the form: C(t) = K1e−C2t. The limits of the first transit fit are from 10% of maximum activity on the upslope to 70% maximum activity on the downslope (fig. 1C). The area under this fitted curve (A) is felt to represent a normal first pulmonary transit. This fitted curve is then subtracted from the real data to obtain the difference of the real and fitted curves. A second derived data set is then formed by finding the maximum point in the difference curve (defined as the last point on the upslope whose value is greater than 105% of the previous point). Then a gamma function is fit from 10% on the upslope of the difference curve to one point after the maximum. This second derived histogram is felt to represent the time-activity plot of the shunted blood. The area under this curve (B) is then calculated. The ratio (A/B) is felt to be a direct representation of the QP/QS ratio.

The calculated QP/QS ratio is limited to the range from 1:1 to 3:1. When a shunt is very large and the pulmonary time activity curve falls very slowly from the peak, the algorithm will automatically calculate a greater than 3:1 shunt without actually deriving a recirculation area. This happens whenever the 70% level on the downslope of the first pulmonary transit occurs at a time more than twice the time it took to reach the peak. Similarly, when the difference between the fitted first transit curve and the real data is sufficiently small, the algorithm will automatically calculate a QP/QS of 1.0. This method will be referred to as the gamma function method.

Curve fitting problems were also encountered with this algorithm. Although the fit to the high count rate first transit curve was good, there were definite problems in fitting the recirculation curve. The count rate was much lower and statistical fluctuations of the data were likely to influence the point chosen as the maximum. This led to errors in the calculated second transit area and the QP/QS ratio. Similar difficulties have been encountered by Maltz and Treves (S. Treves, personal communication). They have overcome the problems by allowing the computer operator to interact with the algorithm, and correct errors by subjectively determining the fit of the second transit curve. Subroutines of the Maltz and Treves algorithm which would allow such interaction were made available to us, but we chose to attempt a less subjective approach in which the algorithm would detect and correct errors without operator intervention.

The Maltz and Treves algorithm defines the limits of the fitted second curve to include one point after the maximum point. In most cases, this point after maximum had less than the maximum value, and the peak portion of the shunt recirculation curve had a shape similar to that of the first curve. However, by definition of this algorithm, the point after the maximum of the second transit curve can actually be greater than the maximum (i.e., it can be as much as 1.04 times maximum). We developed a subroutine to print out the value of the raw data points in the second transit curve, and to identify which of these points was defined as the fitted

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*Kindly supplied by Dr. S. Treves.

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maximum. In six of the 30 patients with shunts the point after maximum was larger than the fitted maximum. This caused the least squares fitting technique to continue the fitted curve upward for some time before returning it to baseline, and resulted in overestimation of the area of the shunt recirculation curve and the QP/QS ratio. The effect which the value of the point after maximum has upon the calculation of the QP/QS ratio is shown in figure 2. Using this fact, we developed a subroutine which allowed us to alter the area of the recirculation curve. The computer substituted the value of the point preceding maximum for the point after maximum whenever this latter value was greater than maximum. This resulted in a smaller recirculation area and a smaller QP/QS ratio.

In two additional cases, an obviously incorrect, very large recirculation area was determined by the algorithm. The point after maximum in these cases was less than the defined maximum, and the time-activity curves were those of a small shunt. The calculated QP/QS ratios in these cases were 3.5:1 and 3.9:1. We used our subroutine to reduce the area under the recirculation curve, and found that the value of the second point preceding maximum had to be substituted for the point after maximum to obtain a QP/QS ratio less than 3:1. We then included this arbitrary modification as a separate subroutine in our algorithm, so that any case demonstrating the time-activity curve of a small shunt, but a calculated QP/QS of greater than 3:1, could be corrected in this fashion.

These alterations of the original Maltz and Treves algorithm allowed us to avoid overcalculation errors and improved the relation of the calculated QP/QS ratio to oximetry. This method will be called the modified gamma function and will be the method compared with count ratios and exponential fitting unless otherwise stated.

**Results**

Both area ratio methods and the C2/C1 method detected all shunts with an oximetry ratio of greater than 1.2:1. Detection of shunts less than 1.2:1 occurred in some cases, but all methods were inconsistent at this level. Therefore, a calculated QP/QS ratio greater than 1.2:1 was considered evidence for a shunt. Using this criterion, the relative ability of the methods to detect shunts and separate other cardiac lesions from shunts was compared and is shown in figure 3. The false negative rate for shunt detection was 6.6% (2/30) for both the count ratio and exponential methods. It was somewhat higher (13%) (4/30) with the gamma function method. It should be noted that two patients with small angiographically visible VSDs were missed by all methods. These patients had no evidence of a shunt by oximetry. Two additional shunts were missed by the gamma function method, and both had oximetry shunts of 1.2:1. The correlations of the results of each method with oximetry are given in table 1. For this analysis, the results have been separated into groups containing only patients with shunts, normal patients and those with shunts, and all patients, including those with cardiac abnormalities but no shunts.

The count ratio methods provided sensitive shunt detection and good separation of patients with shunts from normals. For the C2/C1 ratio determined by inspection, the mean normal value was 26% (± 5.2% s.d.) with a range of 18–35%. When the 10% method was used, the time from the initial (10%) point to peak was less than the build-up time of the inspection method. Therefore, C2 occurred earlier on the downslope and C2/C1 ratios were slightly higher. The mean normal value with this method was 30 ± 7.6% with a range of 25–42%. There was little difference between these two methods in the 30 patients with shunts. By inspection, the C2/C1 of these 30 cases averaged 59 ± 16%, while the 10% method yielded an average C2/C1 of 60 ± 15%. The algorithm calculations of C2/C1 ratios correlated strongly with both the inspection ($r = 0.93$)

![Figure 2](http://circ.ahajournals.org/)

**Figure 2**

Four QP/QS ratios have been calculated using the gamma function algorithm. A) QP/QS = 1.4:1, B) QP/QS = 2.1:1, C) QP/QS = 4:1, and D) QP/QS = a negative number. The original data calculation is B above. In A, C, and D, the only difference is the value of the point after maximum in the recirculation curve, which has been changed by a FOCAL-12 subroutine. In A the value was decreased 10% from its original value. In C it was increased 10% and in D it was increased 20%.
Table 1

Correlation of Count Ratio and Area Ratio Methods with Oximetry

<table>
<thead>
<tr>
<th>Method</th>
<th>Shunts only (N = 30)</th>
<th>Shunts and normals (N = 38)</th>
<th>All patients (N = 50)</th>
</tr>
</thead>
<tbody>
<tr>
<td>C2/C1 ratio:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inspection</td>
<td>0.76 (±0.40)</td>
<td>0.84 (±0.35)</td>
<td>0.84 (±0.34)</td>
</tr>
<tr>
<td>10%</td>
<td>0.72 (±0.42)</td>
<td>0.81 (±0.38)</td>
<td>0.80 (±0.38)</td>
</tr>
<tr>
<td>Algorithm</td>
<td>0.76 (±0.39)</td>
<td>0.83 (±0.36)</td>
<td>0.84 (±0.35)</td>
</tr>
<tr>
<td>Gamma function</td>
<td>0.74 (±0.41)</td>
<td>0.82 (±0.38)</td>
<td>0.85 (±0.34)</td>
</tr>
<tr>
<td>Modified gamma</td>
<td>0.88 (±0.29)</td>
<td>0.92 (±0.20)</td>
<td>0.93 (±0.25)</td>
</tr>
<tr>
<td>Exponential fit</td>
<td>0.84 (±0.33)</td>
<td>0.89 (±0.31)</td>
<td>0.86 (±0.33)</td>
</tr>
</tbody>
</table>

*Values given are the correlation coefficient ± the standard error of estimate.

The ability of each of the methods to separate normals from patients with shunts and those with other cardiac lesions is shown. The dotted line represents a QP/QS ratio of approximately 1.2:1, the level at which the separation of patients with shunts from others was reliably made. Normal patients are represented by clear circles (○), patients with valvular heart disease or other cardiac abnormalities are dark circles (●), while patients with shunts appear as crosses (+).

and 10% (r = 0.92) methods. Normal patients had C2/C1 ratios ranging from 18–34% with a mean C2/C1 ratio of 26 ± 7.4%. The 30 patients with shunts showed an average C2/C1 of 55 ± 14%. The over-all correlation of C2/C1 ratios (inspection) with oximetry was 0.84 (± 0.34 SEE) (table 1). The resulting regression equation was QP/QS = 2.79 (C2/C1) + 0.21 (fig. 4).

The C2/C1 method occasionally resulted in false positive studies. Four of ten patients (40%) with valvular heart disease but no shunt had false positive studies. Three of these patients had severe mitral valve disease (two had mitral insufficiency, one had mitral stenosis) and were in clinically obvious congestive heart failure at the time of the study. The other patient had peripheral pulmonic stenosis with a gradient of 50 mm Hg between the main and peripheral pulmonary artery. This patient was asymptomatic at the time of the study. Two other patients with valvular pulmonary stenosis had normal C2/C1 ratios. One of these had a pressure gradient of less than 50 mm Hg, but the other had a gradient of 148 mm Hg. The time activity curves of these patients showed a slow rise to a peak value. The long build-up times forced the C2 value farther along the downslope of activity into lower count areas, and resulted in a normal C2/C1 ratio.

When the exponential fitting method was used, all normal patients were found to have an X/Y ratio less than 0.7, while all patients with left-to-right shunts had X/Y ratios in excess of 0.8 (mean, 1.41 ± 0.43). Patients with cardiac abnormalities but no shunts had ratios ranging from 0.25 to 1.33 (mean, 0.63 ± 0.36). Two of ten patients with valvular heart disease had false positive studies (X/Y ratios of 1.32, 1.33). Both had severe mitral insufficiency and were in congestive heart failure at the time of their study. The remaining eight patients with valvular heart disease and no

![Figure 3](https://example.com/figure3.png)

The ability of each of the methods to separate normals from patients with shunts and those with other cardiac lesions is shown. The dotted line represents a QP/QS ratio of approximately 1.2:1, the level at which the separation of patients with shunts from others was reliably made. Normal patients are represented by clear circles (○), patients with valvular heart disease or other cardiac abnormalities are dark circles (●), while patients with shunts appear as crosses (+).

![Figure 4](https://example.com/figure4.png)

The linear regression analysis of the C2/C1 ratio vs oximetry data is shown.

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shunts were correctly diagnosed. This method showed a significantly better correlation with oximetrically determined shunts than C2/C1 ratios (P < 0.05) (table 1). The best correlation of the data with oximetry was provided by a linear regression equation, \( \frac{Q_P}{Q_S} = 1.01X + 0.45 \) (fig. 5). Quadratic equations, such as the one used by Anderson et al., were evaluated, but did not provide as strong a correlation as this linear regression equation.

The gamma function method gave only one false positive result. This was in one of the two patients with severe mitral insufficiency and congestive heart failure. This patient was incorrectly diagnosed by every method. The gamma function method correctly calculated a \( \frac{Q_P}{Q_S} \) of 1.0 in another patient with severe mitral insufficiency while the exponential fitting results and count ratio were falsely positive. The ten normal patients and the other 11 patients with cardiac disease but no shunts were diagnosed correctly by the gamma function method.

The over-all correlation of the unmodified gamma function algorithm with oximetrically determined shunts was disappointing (table 1). With the scatter introduced by the relatively large errors occurring in a minority (8 of 30) of cases, the method did not show significantly better quantitation than the C2/C1 ratio. However, when these large errors were avoided by using the modification subroutine, the correlation of the gamma function \( \frac{Q_P}{Q_S} \) values with oximetry in shunts was significantly better than C2/C1 ratio (P < 0.01) and exceeded the correlation obtained by the exponential method (table 1). However, the difference between the exponential and gamma function methods was not statistically significant. The regression equation for the modified gamma function was \( \frac{Q_P}{Q_S} = 0.88X + 0.14 \) (fig. 6).

The results of the two area ratio methods correlated reasonably well with each other \( (r = 0.80 \pm 0.25 \text{ see, } P < 0.001) \), and nearly half (14/30) of the shunts were calculated within \( \pm 0.2 \) units by the two methods. However, in a nearly equal number (12), calculated shunts varied by more than \( \pm 0.5 \).

When L-R shunts coexisted with valvular heart disease (three patients in this study), reasonably accurate shunt quantitation was obtained. One patient with severe mitral insufficiency and a small 1.2:1 VSD was falsely negative by the gamma function technique. Otherwise, all three methods detected shunts and provided reasonably good quantitation (mean error \( \pm 0.2 \) units). Two small shunts (1.2:1) which were associated with severe valvular disease were slightly overestimated by the count ratio and exponential fitting methods.

The ability of the count ratio and area ratio methods to accurately separate patients with shunts smaller than 1.5:1 from those with shunts greater than 1.5:1 was also evaluated. This was done because our pediatric cardiologists will often follow a patient with an ASD or VSD having a shunt less than 1.5:1 without performing catheterization or angiography. Patients with an ASD or VSD and larger shunts are usually managed by catheterization, angiography, and surgical correction. We found that it was rare for a patient to have a shunt greater than 1.5:1 and a radionuclide \( \frac{Q_P}{Q_S} \) less than 1.5:1. This happened in only one of 20 patients (a patient with a 1.9:1 shunt by oximetry) using the count or gamma function methods, and it did not occur with the exponential method. It was slightly more common to calculate a shunt greater than 1.5:1 for a patient with an oximetry

The linear regression analysis of the modified gamma function vs oximetry is shown. The total number of points is less than 30 because identical results occurred in several cases and are superimposed (see fig. 3).
shunt less than 1.5:1. Ten patients had shunts of less than 1.5:1, and four had a calculated shunt greater than 1.5:1 using the count ratio method. This occurred in two patients when the exponential fitting or the gamma function methods were used. Thus, defining a radionuclide shunt ratio of 1.5:1 as a criterion for further studies, the false positive rate was 20% (2 of 10) with exponential fitting and the gamma function, and 40% for the count ratio. The more important false negative rate was 5% (1 of 20) for the count ratio and gamma function methods, and zero for exponential fitting.

Discussion
Recently the use of the C2/C1 method for shunt detection and quantitation has been criticized. Criticisms center mainly on the occurrence of false positive results in patients with valvular heart disease who do not have shunts. Patients with valvular heart disease have been termed normals in some studies and it has been stated that the C2/C1 ratio cannot separate normals from patients with shunts. In the current study we have attempted to separate the normals from patients with shunts or other cardiac abnormalities. The C2/C1 ratio separated patients with shunts from normals without difficulty. However, the studies of four of ten patients with valvular heart disease and no shunt were false positives. Three of these patients were in congestive heart failure at the time of their study, while one was asymptomatic (the patient with peripheral pulmonic stenosis). Therefore, the C2/C1 ratio appears to be unreliable in patients with valvular heart disease, especially when this disease is severe enough to make the patient symptomatic.

Area ratio techniques provide a more reliable separation of patients with shunts from those who have other cardiac lesions but no shunts. The fact that the normal first transit area of both techniques is influenced by the shape of the pulmonary activity curve seems important. In conditions which are associated with a diminished right or left heart ejection fraction and a slow pulmonary transit time, the pulmonary activity curve will be broad and its descent will be slowed. Therefore, the calculated first transit area will increase. Area Y of the exponential method will increase and decrease the probability that the X/Y ratio will be abnormal. Similarly, the first transit area \( A \) of the gamma function algorithm will increase and diminish the chances that an abnormal recirculation peak will be detected or that a calculated \( \frac{A}{A-B} \) ratio will be abnormal.

Anderson et al. have reported that the exponential fitting method is adversely affected by severe mitral or aortic insufficiency. In the current study, three children had severe mitral insufficiency with congestive heart failure, and the exponential method gave false positive results in two of them. Seven other patients had less severe valvular disease, including three with mitral stenosis, and the exponential method did not give false positive results. Therefore, although the exponential fitting method is superior to C2/C1 ratio in separating valvular heart disease and shunts, it does seem to be adversely affected when congestive failure and/or severe mitral valve disease is present. The gamma function provided slightly better discrimination of the three patients with severe mitral disease and congestive failure, but did give one false positive result.

The area ratio methods appear to provide reasonably accurate quantitation of shunts even when significant valvular heart disease coexists. In our limited experience (three patients) the count ratio method also seemed accurate. However, in the two patients with small shunts (1.2:1) it is difficult to know whether the C2/C1 ratio was elevated because of the small shunt or because of the severe valvular disease. Further study of patients with coexistent valvular disease and L-R shunts is needed.

The study demonstrated that the methodology used in calculating the C2/C1 ratio had no significant bearing on its ability to quantitate shunts. The C2/C1 correlation with oximetry for the inspection method \( r = 0.84 \) slightly exceeds that previously reported by Hagan et al. However, if only patients with shunts are considered, the value is lower \( r = 0.76 \). This agrees with Hagan's conclusion that the shunt detection capabilities of the C2/C1 ratio exceed its abilities of shunt quantitation.

Although the two area ratio techniques were calculated in very different ways, they were not significantly different in their ability to quantitate shunts. However, both techniques provided significantly better shunt quantitation than the C2/C1 ratios. This improved ability may relate to the fact that statistical fluctuations of data are present in pulmonary activity curves. When a method uses only two points (C2/C1) for calculation of shunt size, these data fluctuations will lead to variability. By considering many data points in determining the areas used by the exponential or gamma function methods, the adverse effects of statistical fluctuations are diminished.

Both area ratio methods and the C2/C1 methods had low false positive and false negative rates when a QP/QS of 1.5:1 was chosen as a criterion for further diagnostic studies. Because of false positives, a few patients with nonsurgical shunts could be subjected to catheterization and angiography, but it is unlikely that a shunt requiring surgical correction would not be detected. Therefore, these methods seem quite
RADIONUCLIDE MEASUREMENT OF L-R SHUNTS

useful for precatheterization screening of pediatric patients with murmurs. Application of these methods may help avoid catheterization and angiography in children with valvular heart disease or functional murmurs. The methods may also be of use in documenting the success of a surgical shunt correction or following the physiologic closure of a small VSD.

This study has demonstrated the limitations of count ratio methods in diagnosing and quantitating L-R cardiac shunts in children. Area ratio methods provide better quantitation of shunts and give less false positive diagnoses in patients with valvular heart disease who do not have shunts. The exponential fitting method has the advantage of being more easily implemented than the gamma function technique. In fact, if used in its original manual format, it does not require a computer. Curve fitting is relatively easy with this technique, and should provide no problems. The method yields answers in terms of an X/Y area ratio, and therefore requires external calibration from oximetrically determined QP/QS ratios. The tendency, reported by Anderson et al.\textsuperscript{13} and confirmed in this study, for this method to give false positive results in patients with severe mitral heart disease is a drawback.

The gamma function algorithm is more complex and requires a computer to extract the shunt recirculation curve from the raw data. The method yields answers in terms of a QP/QS ratio, and does not require external calibration in this sense. However, the results are not identical to those of oximetry. To make maximum use of the information one should determine the relationship of the gamma function QP/QS to locally performed oximetry determinations. Curve fitting problems can lead to occasional large errors with this technique, but these can be avoided by using a subroutine such as utilized in the current study or by operator intervention (S. Treves, personal communication).

Although the gamma function method gave a higher correlation with oximetry and one less false positive than exponential fitting, the differences in the results were not statistically significant. Exponential fitting resulted in less false negative studies, but this difference was also insignificant. Both area ratio methods were superior to count ratio methods in shunt detection and quantitation, and their use is recommended. The gamma function method seems desirable for those hospitals with appropriate computer facilities while the exponential fitting method provides a useful alternative to others.

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