Quantitative Radionuclide Angiocardiography

Determination of Qp : Qs in Children

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SUMMARY

A new method of determining pulmonary-to-systemic flow ratios (Qp/Qs) in patients with left-to-right shunts using radionuclide angiocardiography is described. It involves the analysis of pulmonary time-activity histograms using a gamma-variate model. It appears to be simple, relatively atraumatic, and superior to the methods using C2/C1 ratios because, in addition to accurately detecting the presence of left-to-right shunts, it permits precise quantitation. In the 35 patients studied, it was found that Qp/Qs < 1.2 could be separated from Qp/Qs > 1.2 and that when the Qp/Qs is between 1.2 and <3 the shunts could be accurately quantified.

Additional Indexing Words:
Left-to-right shunt
Ventricular septal defects
Atrial septal defects
Ejection fractions
Gamma variate
Radionuclide angiocardiography

Although detection of left-to-right shunts using nontraumatic technics may be possible, accurate quantitation of left-to-right shunts requires cardiac catheterization with oximetry or dye-dilution methods. The technics for detection used in the past included intravenous dye injection with arterial or capillary sampling and analysis of the resulting curves,1-4 and intravenous injection of radionuclides with analysis of precordial or pulmonary time-activity histograms.5-19 None of these technics permitted quantitation.

A new nontraumatic technic of quantifying left-to-right shunts is described. This method consists of intravenous injection of a radionuclide with external detection by a gamma camera. Pulmonary time-activity histograms are generated and the analysis is done using a computer program based on a least-squares fit to a gamma variate which directly generates a pulmonary-systemic flow ratio.20,24

Materials and Methods

Thirty-five patients whose diagnosis was established by previous cardiac catheterization were studied. They ranged in age from 4 months to 21 years. Among 13 without left-to-right shunts, 10 had pulmonic stenosis with pressure gradients ranging from 10 to 100 mm/Hg, and three had aortic stenosis with gradients ranging from 10 to 80 mm/Hg. Twenty-two patients had left-to-right shunts with pulmonary-to-systemic flow ratios ranging from 1.05 to 3.0 as determined by oximetry data.

A gamma scintillation camera* with a 15,000 parallel-hole collimator 2.5-cm deep was used.† The data from the camera were recorded on a magnetic tape system, in a 256 × 256 matrix format which permitted quantitative analysis.‡ The system was interfaced to a small on-line digital computer system.§ This computer can acquire and store information on a 64 × 64 matrix directly from the gamma camera or from the video tape system. The data stored can be analyzed off-line.

All patients were prepared for the study with sodium or potassium perchlorate in a dose of 6 mg/kg of body weight 3 hour before the study. An intravenous line was established in a peripheral vein, usually hand or arm, using a short-tube intravenous set with a 21- or 23-gauge needle. The patient was supine with the gamma camera above the chest. Accurate positioning was achieved by placing radioactive markers over the xyphoid and the suprasternal notch and insuring that these were centered in the gamma-camera field. The respirations of the patient were monitored to insure that

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*Nuclear Chicago HP Pho Gamma scintillation camera.
†Nuclear Chicago "high-sensitivity" collimator.
‡Nuclear Chicago data store/playback accessory.
they were quiet and regular at the time of injection. A special hand-injector system with a one-way valve was attached to the intravenous set. This allowed rapid and uniform injection of a small bolus.

50mTc pertechnetate (specific activity 10–40 mCi/ml in a dose of 200 μCi/kg) was injected. The volume of the solution injected was 0.20–1.00 ml. A minimum of 2–3 mCi was necessary to assure adequate counting statistics with our instrumentation. The images from the gamma camera, simultaneously displayed on a variable-persistence oscilloscope, were recorded on digital magnetic tape, and the length of the recording was approximately 30 sec.

By using a transparent overlay over the variable-persistence oscilloscope, an area of interest over the lung free from extrapulmonary contamination was outlined (fig. 1). The activity levels from this area of interest were read into the digital computer which produced a pulmonary time-activity histogram with points at 0.5-sec intervals. In addition to the pulmonary time-activity histogram, a second histogram was similarly obtained from an area of interest over the superior vena cava or innominate vein. By inspection of this histogram, the quality of the injected bolus could be determined and those studies with a double peak or delayed bolus could be discarded. We estimate that about 15% of our studies were discarded for this reason.

The pulmonary time-activity histogram was fed into the computer for analysis. The histogram was fitted to a gamma variate of the form: $C(t_i) = k_t \alpha e^{-t_i/\beta}$ (where $k$, $\alpha$, and $\beta$ are arbitrary parameters, $t_i$ is the $i$th time, and $C(t_i)$ is the concentration at this time) using a least-squares technique (see discussion). The limits of the fit were from 10% of the maximum activity on the upslope to 70% of the maximum on the downslope (fig. 2). The derived histogram was subtracted from the remainder of the original data to obtain a second histogram which was again fitted to the gamma function. The limits of the second fit were from 10% of a specially defined maximum on the upslope to one point after this maximum. This maximum was defined as that point above which the rise on activity failed to remain monotinous; that is, the last point on the upslope whose value was greater than 105% of the previous point. The areas of the two gamma variate-fitted histograms ($A_1$ and $A_2$) were obtained by adding the points from 10% of the maximum on the upslope to 90% of the maximum on the downslope. A ratio of these areas was obtained ($A_1/A - A_2$) which represented the $Qp/Qs$ ratio (fig. 3).

If the peak of the second derived histogram was less than 10% of the peak of the first one, or if the second peak occurred 12 sec or more after the peak which was 10% of the maximum on the upslope, the program was automatically discontinued and the $Qp/Qs$ was assumed to be 1. If the time from 10% of the maximum on the upslope to 70% of the maximum on the downslope ($T_3$) was more than twice the time from 10% of the maximum on the upslope to the maximum ($T_1$) the

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

**Figure 1**

*Normal radionuclide angiocardioam. The region of interest is shown intensified. Note the wide margin between it and cardiovascular structures necessary to prevent extrapulmonary contamination. The time listed is from first appearance of activity in the SVC.*
Figure 2
Normal pulmonary time-activity histogram and gamma function fit. The fit is close until recirculation occurs at which point the gamma function approximates a curve without recirculation.

Program was again automatically discontinued and the Qp/Qs was assumed to be greater than 3 (fig. 4).

In addition to the Qp/Qs, a modified C2/C1 ratio was obtained. This was defined in the following manner: C1 was the highest activity level on the first derived histogram; T1 was the interval from that point which was 10% of C1 on the upslope to C1; T2 was equal to T1 and originated at the peak; and C2 was the activity at time T2 on the downslope (fig. 4).

Results
The results for all patients are tabulated in table 1 and figure 5. Of the 13 normals by oximetry data, 10 were normal by this technic as well, and three others showed Qp/Qs of less than 1.12. Of the 22 patients with left-to-right shunts, two had Qp/Qs of 1.0 and 20 had Qp/Qs between 1.2 and 3.0. Linear regression analysis gave the following values: r = 0.91, SEM = 0.22, P < 0.001, regression line slope = 0.87, and intercept = 0.21.

The C2/C1 ratios are tabulated in table 1 and figures 6 and 7. There was no clear division between normals and abnormals. Linear regression analysis gave r = 0.71, SEM = 0.39, P < 0.001, regression line slope = 0.27, and intercept = 0.45.

Discussion
The analysis of the pulmonary dilution curves by this method was suggested by the work done on cardiogreen dye-dilution curves used to determine cardiac output.4 The initial passage of cardiogreen

Figure 3
Abnormal pulmonary time-activity histogram with area analysis. The two gamma function-determined areas and the method of determining the Qp/Qs ratio are shown. See text for details.
Abnormal pulmonary time-activity histogram. The points for automatic C\textsubscript{2}/C\textsubscript{1} analysis are shown as are the limits of the first gamma function fit. If T\textsubscript{3} is greater than 2 \times T\textsubscript{1}, no fit is made and the Qp/Qs is said to be greater than 3.

could be represented by a curve of concentration vs time, and the area under the curve could be related to flow. If recirculation due to left-to-right shunting occurred, there would be early reappearance of the indicator as a second curve could be related to the amount of early recirculation. The difference in these areas would represent the amount of blood not recirculated. Thus, if injection were in a peripheral vein and sampling were in the pulmonary artery, pulmonic flow, pulmonic recirculation and their difference, systemic flow, could be related to the areas under the curves. If a ratio of flows were desired, factors such as amount of indicator injected and calibration constants for concentration would not need to be taken into account providing sampling for both curves was at the same site. Thus, with a radionuclide injected into a peripheral vein and activity sampled over an area of the lungs, two curves could be obtained which, when analyzed, could yield a Qp/Qs ratio.

The problem of analysis was that curves were not distinct due to the short intrapulmonary recirculation time. A Stewart-Hamilton semilog replot technique\textsuperscript{21} could not separate these curves. It had previously been found that a gamma variate could be fitted by a least-squares method to a dye-dilution curve.\textsuperscript{20, 22, 23} The gamma function described a
Table 1

Results for Normals and Patients with Left-to-Right Shunts

<table>
<thead>
<tr>
<th>Pt no.</th>
<th>Defects</th>
<th>QP/QS ratios oximetry</th>
<th>Radioisotope data</th>
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<tr>
<td></td>
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<td>Qp/Qs</td>
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<td><strong>No L→R shunts</strong></td>
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<tr>
<td>67-18-17</td>
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<td>*†</td>
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<tr>
<td>67-02-90</td>
<td>PS &amp; PR</td>
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<td>1.00</td>
</tr>
<tr>
<td>68-69-30</td>
<td>PS</td>
<td>*</td>
<td>1.00</td>
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<td>52-69-63</td>
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<tr>
<td>72-32-26</td>
<td>ASD, postop</td>
<td>*</td>
<td>1.00</td>
</tr>
<tr>
<td>55-31-32</td>
<td>AS</td>
<td>*††</td>
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<tr>
<td>52-69-69</td>
<td>PS</td>
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<td>67-45-05</td>
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<td>*†</td>
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<td>63-73-26</td>
<td>VSD</td>
<td>1.00 - 1.10</td>
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<td>55-07-06</td>
<td>VSD</td>
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<td>64-82-81</td>
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<td>74-93-18</td>
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<td>2.15 - 2.21</td>
<td>2.18</td>
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<tr>
<td>72-32-26</td>
<td>ASD</td>
<td>2.34 - 2.68</td>
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<tr>
<td>49-77-88</td>
<td>ASD</td>
<td>2.50 - 2.74</td>
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<tr>
<td>73-08-15</td>
<td>ASD</td>
<td>2.88 - 3.12</td>
<td>3.00</td>
</tr>
</tbody>
</table>

Abbreviations: AS = aortic stenosis; PS = pulmonic stenosis; PR = pulmonic regurgitation; ASD = atrial septal defect; VSD = ventricular septal defect.

*No left-to-right shunts were demonstrated by oximetry.
†No shunt by LV angiogram.
‡No shunt by hydrogen study.

A curve with a rapid upslope, a peak, and an exponential decay, i.e. the characteristics of a dye-dilution curve. Comparison between this method and the Stewart-Hamilton method yielded consistent results. In general, the gamma-function fit was felt to be more accurate than the Stewart-Hamilton fit when cardiac output was low, i.e. when the curve is wide. We found that this gamma function could be fit to radionuclide-generated pulmonary time-activity histograms without early recirculation due to left-to-right shunting (fig. 2), and that when this recirculation occurred the curves of primary and recirculated flow could be separated and their areas obtained (fig. 3).

The results obtained indicate that this method can separate those shunts with Qp/Qs less than 1.2 from those shunts with Qp/Qs greater than 1.2 and that it can accurately quantitate the shunts when Qp/Qs is greater than 1.2 and less than 3.0. Thus, with the exception of those patients with shunts less than 1.2 who may need prophylactic antibacterial agents for subacute bacterial endocarditis, the
method can detect shunts with no clinically significant false positives or negatives, and can quantitate shunts in the clinically useful range.

The previous analysis of radionuclide pulmonary dilution curves utilized the $C_2/C_1$ ratio, with $C_1$, peak activity, $T_1$, the time from first appearance of isotope to the peak, $T_2$, a distance equal to $T_1$ from the peak and on the downslope, and $C_2$, the activity time $T_2$ (fig. 4). The criteria used to select the time of first appearance of the indicator and the time of peak activity were unclear. The determination of these points is critical in obtaining reproducible $C_2/C_1$ ratios, and the variation gave rise to the variation in limits used to distinguish normal from left-to-right shunts. Because of these limitations, we have chosen the automatic method described. It was used to determine $C_2/C_1$ ratios and gave reproducible results. Despite these attempts at uniformity, the data in our experience were in disagreement with those above and suggested that $C_2/C_1$ ratios could not be used to distinguish or quantitate shunts.

Since only those studies in which an intact bolus was delivered were included in this study, a double bolus cannot be the reason for the discrepancy between our data and those of others. Rather, the reason is probably the different "normal" population studied. In previous works, the normal groups consisted of patients who were normal from the cardiac standpoint and who usually did not undergo cardiac catheterization. All of the normal population in this paper had cardiac catheterization and intracardiac defects without shunts, including pulmonic stenosis, aortic stenosis, pulmonic regurgitation, and congestive heart failure. With any one of these defects, the $C_2/C_1$ may be high. Similarly, if left-to-right shunts and the above defects coexist, the $C_2/C_1$ may be higher than would otherwise be expected.

The theoretical basis for the inaccuracy of the $C_2/C_1$ ratio may be related to the following factors affecting the shape of the pulmonary dilution curve: (1) velocity of the blood flow, (2) pulsatile waveform, (3) time of appearance of systemic recirculation, (4) right ventricular ejection fraction, (5) uniformity of the injected bolus, and, when shunts are present, also (6) size of the shunt.
and (7) intrapulmonary recirculation time. These factors do not always interrelate and do not always equally affect the rise and fall of the time-activity histogram. This appears to occur more often when other defects are present with or without left-to-right shunting. Thus, the C₂/C₁ ratio may be altered independently of the presence, absence, or size of the shunt.

The gamma-variate fit does not depend on the interrelationship of the factors above described, or on their equal effect on ascending and descending limb of the curve. It also does not depend on their skew and spread. This is well shown by the studies on the patients with aortic stenosis, pulmonary regurgitation, and pulmonic stenosis, all of which were normal by this technic of gamma-variate analysis.

An interesting sidelight to this theoretic analysis is the notion that if the right ventricular ejection fraction is decreased the C₂/C₁ ratio will increase. In three patients with pulmonic stenosis with suprasystemic right ventricular pressures and no shunts the C₂/C₁ ratio was elevated although the Qp/Qs by our technic was 1.0. It is our hypothesis that in severe pulmonic stenosis the right ventricular ejection fraction is decreased.

In this study, the patients were not sedated and only an intravenous infusion set was used. Because of this, two sources of error appeared. These were: (a) the nonuniformity of the bolus reaching the heart and (b) crying or irregular respirations. The first could create double or multiple peaks or an extremely prolonged curve. The second could create irregular variation in activity over the lung due to changes in pulmonary blood volume caused by sudden and irregular changes in intrathoracic pressure. If either of these errors was large, the studies were deleted. However, it is probable that when either of these was present, no obvious errors in Qp/Qs ratios were produced. It seems that elimination of these errors and increase in accuracy can be obtained by the routine use of sedation and an indwelling venous catheter.

The analysis of the curves depends on the assumption that the partition of the flow to the lungs from the right ventricle is not altered during recirculation. This assumption does not hold in patients with patent ductus arteriosus, and different shunt ratios may be calculated over each lung. This may reflect the true hemodynamics. Perhaps these data can be compared to the total shunt by oximetry data to yield greater understanding on this condition.

Although the method described was developed using a gamma camera and an on-line computer, similar results could be obtained more simply. For example, data from a single probe over one lung connected to a scaler and a buffered digital printer could be fed into any digital computer for analysis.

**References**

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Quantitative Radionuclide Angiocardiography: Determination of Qp : Qs in Children
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_Circulation_. 1973;47:1049-1056
doi: 10.1161/01.CIR.47.5.1049

_Circulation_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

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