An Improved Method for the Quantification of Left-to-Right Cardiac Shunts

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We have investigated a technique for quantifying QP/QS in left-to-right cardiac shunts. In this method, the gamma variate, which is fitted to the first-pass portion of the lung curve, is used to generate a curve, which simulates the response of a normal lung curve with systemic recirculation. The difference between this curve and the observed lung curve is then used to calculate QP/QS. This method was evaluated on a set of simulated lung time-activity curves with precisely known QP/QS values on a group of 11 patients with no clinical suspicion of cardiac shunt and on a group of 30 patients referred for cardiac shunt studies. The QP/QS in each of these studies was determined by three individuals using both the Maltz-Treves method and the new method. This method yielded QP/QS values that were more accurate on the simulated lung data and had less interobserver variation on all the studies than those obtained from the Maltz-Treves method.

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The quantitative evaluation of radionuclide cardiac shunt studies was introduced by Maltz and Treves (*1,2*). In their method, the ratio of pulmonary to systemic blood flow, QP/QS, is calculated from $A_1/(A_1-A_2)$, where A_1 is the integral of a gamma variate function fitted to the first-pass portion of the lung time-activity curve (TAC) and A_2 is the integral of a gamma variate fitted to the early recirculation peak. The recirculation peak is found by subtracting the gamma variate fit from the observed lung TAC. However, it is often difficult to select the appropriate portion of the recirculation curve for the second fitting (*3*). As a result, the calculated QP/QS is subject to the bias of the operator performing the analysis. In addition, this method has a systematic error, since it cannot distinguish between normal systemic recirculation of the tracer and shunted activity. Houser et al. (*4*) have described a technique which addresses this second problem by fitting a third gamma variate in an attempt to eliminate or reduce the systemic recirculation component. In this paper, we describe another approach to this problem. The first-pass portion of the lung TAC is used to estimate a normal lung response curve which includes normal recirculation of the tracer. The shunted activity is then calculated as the difference between this estimated curve and the actual observed lung curve.

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METHODOLOGY

Description of the Method

In our method, the normal lung curve is approximated from the sum of two functions: (1) the gamma variate which is fitted to the first-pass of the bolus through the lung and (2) the scaled and delayed integral of this gamma variate. The individual steps in the method are described below and are illustrated in Figure 1.

A gamma variate function (denoted by g(t)) is fitted to the first-pass portion of the observed lung TAC (o(t)) in a manner similar to that described by Maltz and Treves (*1*). The operator selects the start and end points of the fit corresponding respectively to the time when activity first enters the lung and the time when the shunt recirculation becomes evident. A gamma variate is fitted to this data using a least squares regression and is presented to the operator for verification. The operator can manually alter the fitting parameters at this time if the fitted curve is not optimal. Next the program calculates the expected normal recirculation based on the gamma variate fit.

After the intravenous injection of a bolus of tracer, the normal systemic recirculation of the tracer to the lung can be approximated by the time integral of the gamma variate function. The rationale for this is as follows. The circulatory system can be modeled as a set of compartments corresponding to the right heart, lungs, left heart and all the other organs in the body lumped together as the body compartment (*5*). Because the body compartment is so large relative to the heart and lungs, it acts as an integrator with an exponential rolloff. Thus, the concentration of the blood activity returning to the right heart has the functional form:

$$\exp(-t/\tau) \times \int g(t)\, dt,$$

where τ is on the order of several minutes. We have found by inspection that the observed recirculation has a slower rise time than $\int g(t)\, dt$. This is no doubt due to the fact that the body compartment also acts as a set of delay lines which stretches out the bolus. This behavior can be adequately simulated by stretching (along the time axis) the integral of g(t) by a factor of 2. This stretched integral curve will be referred to as r(t).

Before the recirculation function, r(t), is added to the gamma variate, g(t), to approximate the normal lung curve, it has to be scaled and time delayed. The scaling factor and time delay were

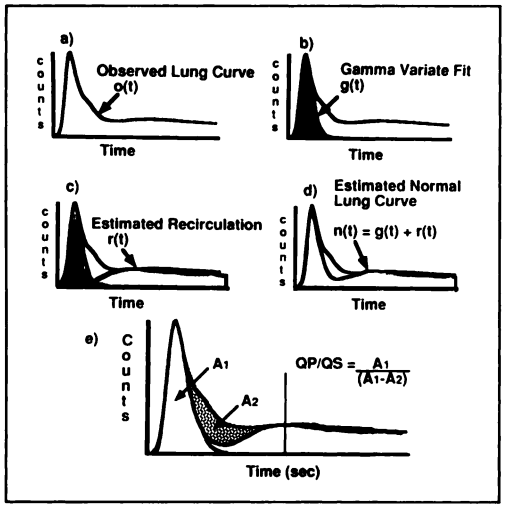

FIGURE 1. Proposed method for cardiac shunt quantification. (A) Observed lung TAC. (B) A gamma variate is fitted to the first transit portion as in the Maltz-Treves method. (C) The normal recirculation of the bolus is estimated from the initial gamma variate fit, and (D) is then added to the gamma variate to obtain the estimated normal lung curve. (E) The difference between the estimated normal lung curve and the observed lung curve is integrated to yield A_2. The QP/QS ratio is calculated from $A_1/(A_1-A_2)$, where A_1 is the integral of the initial gamma variate fit.

empirically determined by examining the lung TACs from patients with no clinical suspicion of left-to-right shunting. Values of the observed lung TAC minimum and maximum (points B and C on Fig. 2) on these patient controls were calculated as percentages of the first pass maximum (point A). The average of these values were 14% and 26%, respectively. Based on this information, the scaling is set so that the maximum of r(t) is equal to the maximum of the observed recirculation portion of the patient lung TAC as long as this does not exceed 25% of the maximum of the first-pass portion of the lung TAC. r(t) is then shifted in time with respect to g(t) so that the minimum before the recirculation peak equals 14% of the first-pass maximum when the two functions are added together. This resultant curve closely approximates a "normal" lung curve free of shunted activity, n(t). All of this is done automatically under software control without requiring operator intervention. The overlay of n(t) on the observed lung TAC is presented to the operator for validation. The scaling and shift parameters can be manually changed at this time if the operator perceives that the computer estimate is not appropriate.

At this point, the simulated normal curve, n(t) is subtracted from the observed curve, o(t). Any substantial difference between these two functions is ascribed to left-to-right shunting. This difference is integrated up to the time point where the maximum of the recirculation occurs. This area is referred to as A_2. The area under the initial gamma variate fit, A_1 is also determined. The QP/QS ratio is calculated as $A_1/(A_1-A_2)$ as shown in Figure 1E.

Evaluation of the Method

The proposed method was evaluated on three sets of data. The first set consisted of a set of simulated lung TACs with simulated cardiac shunts. The QP/QS values for these simulated curves ranged from 1.25 to 2.0 (Fig. 3). Five different curves were generated for each QP/QS with Poisson noise obtained from a pseudo random number generator.

The second set of data was obtained from radionuclide studies performed on a group of 30 patients referred to the clinic for evaluation of left-to-right cardiac shunt. The patients ranged in age from 14 to 82 yr (mean = 48 yr) and included 14 males and 16 females. The first transit of a rapidly injected bolus of ^{99}Tc-DTPA was recorded with a gamma camera positioned over the upper thorax. The images were acquired into a computer at two frames per second for 50 sec. Time-activity curves were generated from ROIs placed over the right lung and the superior vena cava.

The third set of data was obtained from first-pass radionuclide studies performed on patients with no clinical suspicion of cardiac shunts who had been referred to the nuclear medicine clinic for other studies. These studies were acquired as described in the preceding paragraph. The QP/QS ratio for each lung curve (both the simulated and patient data) was determined by three independent operators using both the proposed new method and that described Maltz and Treves as implemented on our computer system (MDS A^2 computer, MIPS version 2.0 software).

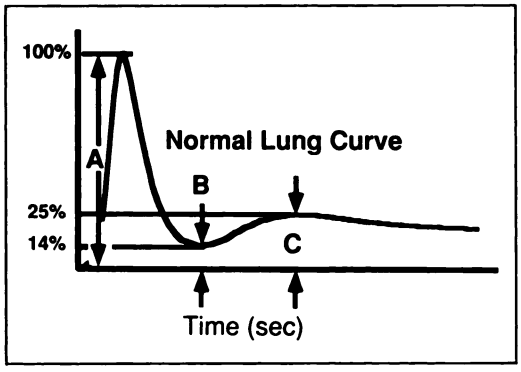

FIGURE 2. Normal lung TAC. The lung radioactivity falls as the bolus passes through the lungs and then rises as the bolus recirculates. Eleven lung TACs were examined from patients with no evidence of cardiac shunts. The values found at points B and C are shown in Table 1.

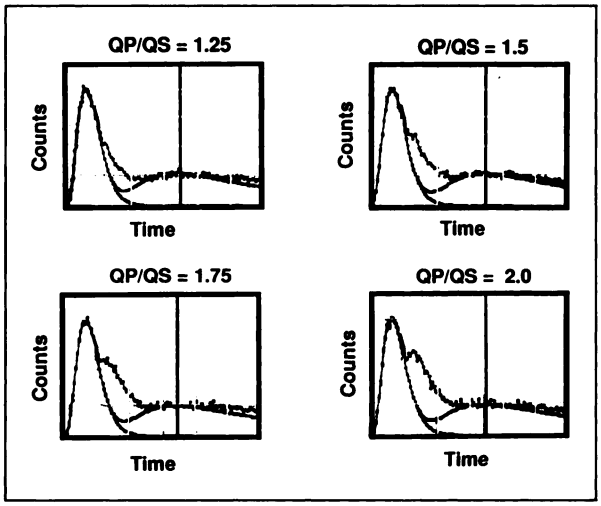

FIGURE 3. Simulated lung TACs. Lung TACs were simulated with cardiac shunts of 1.25, 1.50, 1.75, and 2.0.

TABLE 1
Normal Lung Data (B and C refer to points indicated on Figure 2)

Patient	Recirculation minimum (B)	Recirculation maximum (C)
1	11%	24%
2	17%	30%
3	15%	24%
4	13%	26%
5	11%	25%
6	16%	25%
7	15%	29%
8	12%	20%
9	17%	29%
10	19%	30%
11	12%	25%
	14.4% ± 2.7%	26% ± 3.1%

RESULTS

The analysis of the lung TACs from patients with no evidence of cardiac shunting is presented in Table 1. Points B and C are defined in Figure 2. The data in this table supports our view that normal lung curves can be reasonably estimated, since there are only small differences among the sampled curves. As a result, the normal transit of a bolus through the body can be reasonably well approximated.

The results for the simulated data are summarized in Figure 4, which shows graphs of the average QP/QS obtained by the three operators plotted as a function of the true QP/QS. Although a good correlation was obtained from the Maltz-Treves method (r = 0.9), the QP/QS was consistently overestimated as evidenced by the slope and intercept of the regression line (slope = 1.56, intercept = −0.65). There was excellent agreement between the QP/QS values found by the new method and the true QP/QS (r = 0.99, slope = 1.00 and intercept = 0.02). In addition, the scatter of points about the regression line was much less with the new method suggesting that it is more reproducible.

Figures 5 and 6 summarize the results obtained from applying the two methods to the clinical data. Figure 5 shows the correlation between the average results of the three operators with the two methods. The trend that was established in the simulated curves continues here. There is good agreement between the results of the two methods (correlation = 0.93), but the results from the Maltz-Treves method tend to overestimate the QP/QS. The interobserver variation with the two methods is illustrated in Figure 6. In this figure, plots are displayed which show the correspondence of the QP/QS obtained by different operators for each method. The average correlation between observers for the Maltz-Treves method was 0.94 while that for the new method was 0.98. While both of these are acceptable, there is less scatter about the line of identity in the plots featuring the new method.

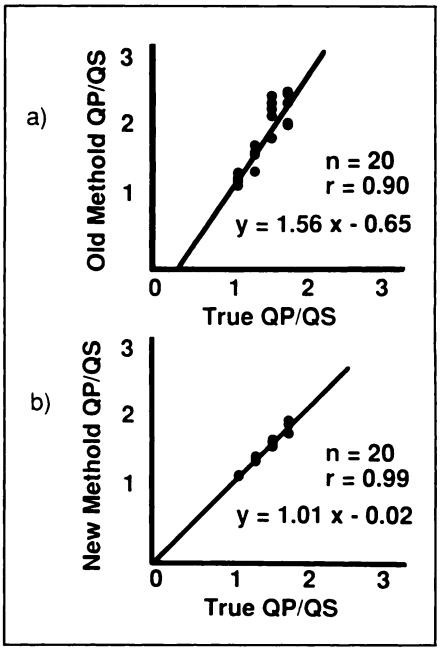

FIGURE 4. Plot of QP/QS results for simulated data. (A) The average results from the Maltz-Treves method are plotted as a function of the actual QP/QS. (B) The average results from the new method are plotted as a function of the actual QP/QS.

Fourteen of the patients in this study were also evaluated from oximetry measurements obtained during cardiac catheterization. The oximetry QP/QS values are plotted against those obtained with the radionuclide techniques in Figure 7. The measured QP/QS values from the catheterization data ranged from 1.0–3.0 (6 < 1.5, 8 > 1.5). There was a moderate correlation between the QP/QS values obtained from the catheterization procedure and the QP/QS obtained from the radionuclide studies with a slightly better correlation associated with the new method (r = 0.732 for the new method, r = 0.703 for the Maltz-Treves method).

Comparisons were made of the average QP/QS values in patients with no shunts for the Maltz and Treves method

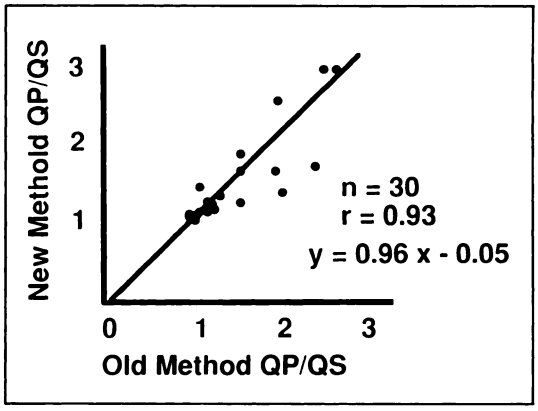

FIGURE 5. Plot of QP/QS values obtained from Maltz-Treves method versus the new method.

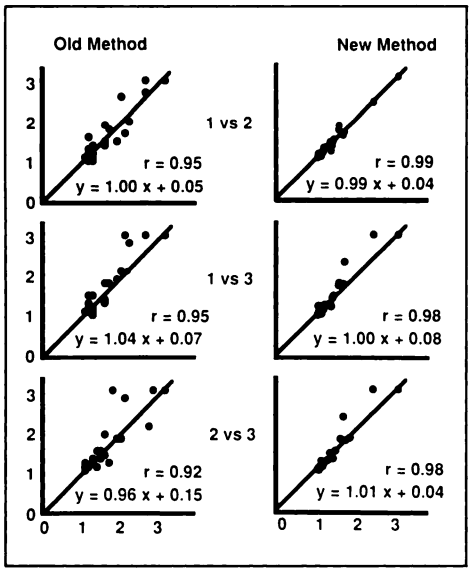

FIGURE 6. Interobserver variability plots. These plots show the correspondence of QP/QS values obtained by three operators for the Maltz-Treves and new methods on the clinical data set. The top plot shows the results of operator 1 versus operator 2, the middle plot shows operator 1 versus operator 3 and the bottom is operator 2 versus operator 3.

and the proposed methods. The mean values were 1.11 ± 0.1 and 1.04 ± 0.04, respectively. These results are consistent with the expectation that the new method better corrects for systemic recirculation and suggests that it may be more sensitive in identifying small shunts.

DISCUSSION AND CONCLUSION

The quantitative evaluation of left-to-right cardiac shunts is useful for clinical management. The Maltz-Treves method is the most widely used technique, but it can be difficult to apply because there is often no clear demarcation to guide the selection of points for the second gamma variate fit. In our method, only one gamma variate fit is required and the accuracy of the QP/QS calculation depends on how well the normal lung recirculation can be estimated. Our results indicate that this can be done with reasonable accuracy. The overlay of the estimated normal lung curve on the raw data gives substantial visual cues as to the magnitude of the shunt. This not only results in an improved correction for systemic recirculation, but provides a more reproducible determination less influenced by operator bias. It also allows the physician reading the scan to better judge the appropriateness of the computed numbers. This is an important feature since in many clinics left-to-right cardiac shunt studies are infrequently performed and are often analyzed or interpreted by individuals with a limited experience with these studies. The proposed method will be especially advantageous in these circumstances, since it requires little operator intervention.

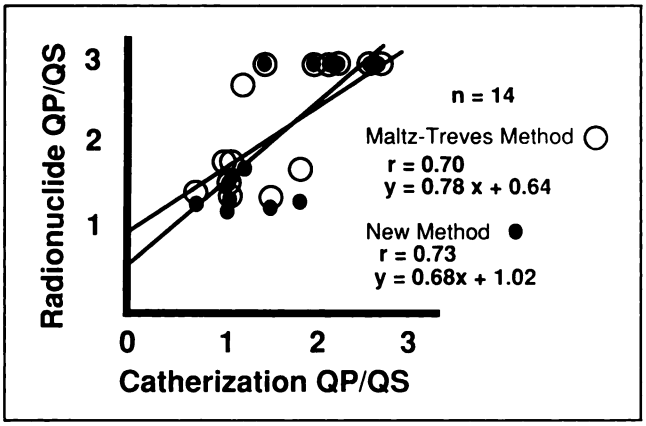

FIGURE 7. Comparison of QP/QS values obtained from cardiac catheterization with the radionuclide techniques.

The new method also provides a better compensation for systemic recirculation as evidenced by the results from the simulated lung curves and by the average values obtained on patients with no shunts. This feature should provide additional sensitivity in reliably identifying small shunts. There may be an overestimation of large shunts with this technique, since in such patients the blood is continually shunted and contributes to the early recirculation portion of the lung curve after the first pass of the radioactivity. While this contribution is negligible for small shunts, it can introduce a systematic error into the QP/QS calculated for large shunts (*3*). However, the Maltz-Treves method also suffers from this problem as well as the inability to discriminate against systemic recirculation.

It should be noted that the results of our new technique (as well as all other radionuclide techniques) will be compromised by any factors that alter validity of the lung TAC. The most important factor is the bolus input curve. If the bolus disperses either because of the injection technique or because of circulatory abnormalities in the patient such as heart failure, there will be a tendency to overestimate the magnitude of the shunting. While it may be possible to correct for the bolus dispersion (*6*), correction techniques require an exact knowledge of the bolus input function to the pulmonary vessels. If this information is not available, then the QP/QS measurement is suspect. Several investigators have reported on multiple deconvolution techniques for the quantitative evaluation of QP/QS (*3,7–10*). In these techniques, the separation between the pulmonary, systemic and shunt phases of the lung TAC is enhanced by correcting for dispersion in each compartment. However, multiple gamma variate fits are still required as well as sophisticated algorithms to perform the multiple deconvolutions.

In conclusion, a new method for determining QP/QS in cardiac left-to-right shunts has been presented. The method runs automatically and requires only one gamma variate fit. Because of this, it is not only simple and efficient, but is also substantially less subject to operator bias.

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SELF-STUDY TEST
Gastrointestinal Nuclear Medicine
ANSWERS

ture one would not expect such rapid clearance. Using the multiple swallow emptying curves, Tolin et al. were able to show differences in the degree of retention in patients with esophagitis, including both those with normal motility and those with a motor disorder. In both circumstances clearance was only mildly impaired compared with that in patients with achalasia, diffuse esophageal spasm, and scleroderma. On endoscopy this patient was found to have distal esophagitis and antral gastritis.

Although there is no documentation of wheezing along with the patient's cough, the history nonetheless raises the question of pulmonary aspiration. Pulmonary aspiration cannot be confirmed with the available images, however. One would need to obtain frequent images of the lungs with enhancement of the gray scale (by digital display) to bring out subtle focal areas of abnormal activity in the lungs. Because of the difficulties reported in visualization of pulmonary aspiration, this diagnosis cannot be excluded with a negative study but can be confirmed if positive.

Reference

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ITEMS 5–8: Gastroesophageal Scintigraphy in Children

ANSWERS: 5, T; 6, T; 7, F; 8, T

Quantification of esophageal scintigraphy is routinely performed in adults, but quantitative scintigraphy of esophageal motility in children has not been evaluated extensively. Qualitative information obtained from an evaluation of the recording of multiple swallows has been useful in infants and small children. Normally, there is a smooth progression of swallows down the esophagus with early gastric filling. Motility disorders associated with various pathologic states, such as esophageal atresia after surgical repair, achalasia of the esophagus, scleroderma, and esophagitis may be demonstrated. Older children who can cooperate can be studied by single-bolus methods, and studies can be quantified in the same fashion as in adults.

Scintigraphy is ideally suited for detecting gastroesophageal reflux, particularly because reflux occurs intermittently in most patients and monitoring can be extended over a prolonged period of time. Barium studies provide better resolution but suffer from the disadvantage that imaging is intermittent over a short period of time. The 24-hr pH probe study generally is regarded as the "gold standard." Though it is often difficult to compare studies between different centers due to lack of uniformity, it appears that scintigraphy has a sensitivity > 75%, and is generally more sensitive than the barium study (48%–80%) for detecting reflux. Manometry has proved to be a less sensitive indicator of reflux (38%–77%). An added advantage of gastroesophageal scintigraphy is that it is easy to perform, noninvasive, and can be performed on outpatients.

Although scintigraphy is capable of detecting small volumes of gastric content aspirated into the lungs, most investigators have detected pulmonary aspiration in a surprisingly small fraction of patients with reflux. This is most likely due to noncontinuous imaging of the lungs. Most imaging protocols have reported using anterior and posterior images obtained at the end of 1 hr, and have repeated these infrequently (usually at 2 and 18–24 hr). Ciliary action alone, in the absence of a cough reflex, has been shown to clear ^{99m}Tc-sulfur colloid from the upper airway with a $T_{½}$ of 1.7 hr in monkeys. With an intact cough reflex, clearance is much more rapid. Thus, with intermittent imaging, only the activity reaching the distal airway is likely to be detected, especially if there is a poor cough reflex. Despite the generally low frequency of detection of aspiration, Boonyaprapa et al. and Orellana et al. have reported higher detection rates (35%–55%) in patients with more severe pulmonary disease.

Gastric emptying of milk or formula mixed with ^{99m}Tc-sulfur colloid is easily quantified by monitoring gastric activity over at least 60 min (preferably 2 hr). Normal children have not been studied, but values in the literature suggest normal residual activity at 1 hr ranges from 36% to 70% after a milk feeding. A cow's milk formula isocaloric with human milk delays the emptying process, probably due to the different composition of the meals. It has been observed that, within limits, osmolar loads do not affect gastric emptying in infants and normal newborns. In older children, solid and liquid emptying of a standard meal may be determined with use of the same methods employed in adults.

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ITEMS 9–13: Meckel's Diverticulum in Children

ANSWERS: 9, T; 10, F; 11, F; 12, T; 13, T

The causes of lower gastrointestinal bleeding in children may be con-

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