Use of Factor Analysis in the Evaluation of Left to Right Cardiac Shunts

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We have compared two methods of data processing for the quantitation of left-to-right cadiac shunts using first-pass radionuclide angiography. These two methods are used for curve generation in the deconvolution analysis. The standard method involves manual definition of regions of interest. A newer method—factor analysis—provides automatic curve generation and is therefore more operator-independent. Both techniques yield curves of the venous input, lung, and background. The venous input curve is deconvolved by the lung curve, and the resultant unit impulse response is fitted by the gamma variate method to quantitate the left-to-right shunt fraction. Both techniques—factor analysis and regions of interest (ROIs)—separated the shunt patients (n = 16) from the control subjects (n = 20) with a $p < 0.001$. There was less interobserver variability with the curves obtained by factor analysis than with those obtained by regions of interest. The coefficient of correlation of factor analysis results with oximetry, r, was 0.90. High sensitivity and specificity, each 94%, was achieved with curves generated by factor analysis. Time vs. activity curves generated by ROIs can achieve high sensitivity and low specificity, or vice versa, depending on the cutoff level defined for separation of the left-to-right shunt patients from the control group.

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A left-to-right (L-R) cardiac shunt may be diagnosed and quantitated by analysis of the lung time versus activity curves from first-pass radionuclide angiography (FPRNA). A diagnosis of L-R shunt may also be obtained from equilibrium gated cardiac studies using the stroke volume ratio (*1,2*). The gated method has several limitations related to geometry and location of the L-R shunt. Furthermore, the equation to quantitate the shunt flow varies according to the presence of right or left ventricular overload.

This study was designed to assess the efficacy of factor analysis (FA), an automatic method to generate time vs. activity curves, for the diagnosis of L-R shunts from FPRNA, and to compare the results with the standard method of drawing regions of interest (ROIs) to obtain these curves.

FA is a method to generate curves and images from a dynamic study. The factors obtained correspond to dynamic processes and are not constrained by anatomic structures. It can separate partially overlapping structures, with the advantage of requiring minimal operator intervention. A description in detail of FA can be found in (*3–6*). We used the lagged normal deconvolution algorithm (*11*). The input is the venous curve and the output is the lung curve. The analysis was done on the resultant unit impulse response (UIR) curve using the gamma area ratio method (*12*).

MATERIALS AND METHODS

Study Population

We studied 16 patients with a L-R shunt quantitated by oximetry using standard techniques (*7*) and 20 control subjects who underwent catheterization for evaluation of coronary artery disease (Table 1). None of the L-R shunt patients nor the control subjects had clinical or catheterization evidence for tricuspid or pulmonary regurgitation.

All L-R shunt patients underwent hydrogen gas inhalation tests, green dye dilution tests, and oximetry. The final diagnoses were eight atrial septal defects, seven ventricular septal defects and one traumatic fistula of Valsalva (right atrium communicating with aorta). The

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TABLE 1
Study Population and FPRNA Quality Control Data*

	Mean			Mean transit times (sec)	
	Total	Male	Age (yr)	Input†	Lung
Shunt patients	16	8	38 ± 21.6	3.2 ± 1.4	12.6 ± 3.7
Control subjects	20	9	41 ± 10.9	3.2 ± 1.6	10.7 ± 3.5

*Sex, age and radionuclide quality control data were similar for 16 L-R shunt patients and 20 control subjects.
†Input = venous time vs. activity curve.

indocyanine dye dilution test gave a rough estimate of the magnitude of the shunt flow, but only oximetry was used (*7,8*) to calculate the pulmonic to systemic flow (Qp/Qs). The shunt fractions measured by oximetry ranged from 0.23 to 0.68, corresponding to Qp/Qs values from 1.3 to >3 (Table 2). Over half the patients had a small L-R shunt and stringent criteria were required to separate them from the control group.

Data Acquisition

The FPRNA was performed with an antecubital intravenous bolus injection of 15–20 mCi [^{99m}Tc]pertechnetate followed by a 20 cc normal saline flush. The study was acquired in list mode for 25 sec in the anterior projection. An all-purpose, low-energy, parallel hole collimator was used with a digital gamma camera that was interfaced to a dedicated minicomputer*. A portable camera with an acquisition computer was used for the study of the control subjects. The FPRNA was performed <1 hr prior to the catheterization study. The list mode was acquired onto a hard disk and was stored on floppy disks to be transferred later to the main computer* for analysis.

Preprocessing and Quality Control

Frames were created from list mode, at a framing rate of 0.5 sec. No time or spatial smoothing techniques were used. The innominate vein (or right subclavian vein) mean transit time (t) was calculated at the 0.369 level of the maximum value. The superior vena cava ROI was avoided because it frequently generates a curve contaminated by other great vessels or the lungs. The presence of a L-R shunt can be simulated by an improper bolus injection, and the deconvolution of the output curve by the input corrects for bolus imperfections. Prolonged bolus transit (t >4 sec) was observed in 4/20 control subjects and 3/16 shunt patients. The quantitation of these studies could only be achieved by using a deconvolution algorithm.

TABLE 2
Size of L-R Shunts as Determined by Oximetry*

Size	Shunt fraction (%)	Qp/Qs	No.
Small	0.17–0.37	1.2–1.6	9
Medium	0.38–0.67	1.7–<3	6
Large	>.68	>3	1
			Total = 16

*Oximetry quantification of pulmonary to systemic flow ratio (Qp/Qs) shows that 9/16 patients had small L-R shunt.

Processing

Factor analysis with deconvolution and gamma variate curve fitting. The only step which requires simple operator intervention in the generation of curves by FA is electronically masking out the heart and most of the venous input image in order to exclude them from the analysis (Fig. 1). This procedure decreases the number of factors obtained and shortens the computer processing time to ~6 min.

FA was used with three factors, the trixel size was 4 pixels × 4 pixels and the 30 most active trixels were analyzed (*1–4*).

Three images and curves were obtained which correpond to venous input, lungs and background (Fig. 2).

The lung curve was deconvolved by the venous input curve using a lagged normal algorithm as described by Kuruc et al. (*11*). The outcome of this deconvolution was the UIR (unit impulse response) curve of the right heart. The UIR is constrained to be a non-negative sum of a set of scaled lagged normal curves.

The gamma variate method was used to quantitate the L-R shunt (*10,11*). A gamma variate was fitted on the UIR, defining an area under the curve (Fig. 3, curve A). The limits of the fit are defined at 10% of the maximum activity on the upslope and 70% on the downslope (*10*). The gamma curve obtained was substracted from the UIR curve; the resultant curve was also gamma fitted. The limits of this second gamma fit were defined as detailed by Maltz and Treves (*12*). The second gamma fit is constrained to have the same alpha value as the first. The area under the second gamma function (Fig. 3, curve B) is proportional to the L-R shunt flow.

Two parameters were calculated from the areas under the first and second gamma curves:

$$\text{Shunt fraction (SF) \%} = B/A;$$

$$\text{Pulmonary to systemic flow ratio (Qp/Qs)} = A/A-B.$$

This formula used by Maltz and Treves (*10*) is defined as a mathematic model in (*11*). Qp/Qs values higher than 3 were considered as 3 for further calculations and correspond to very large shunts (*10,12*). The relationship of the SF to the Qp/Qs is

$$SF\ \% = 1 - 1/(Qp/Qs),$$

where curves are created by ROIs, deconvolution, and gamma variate curve fitting.

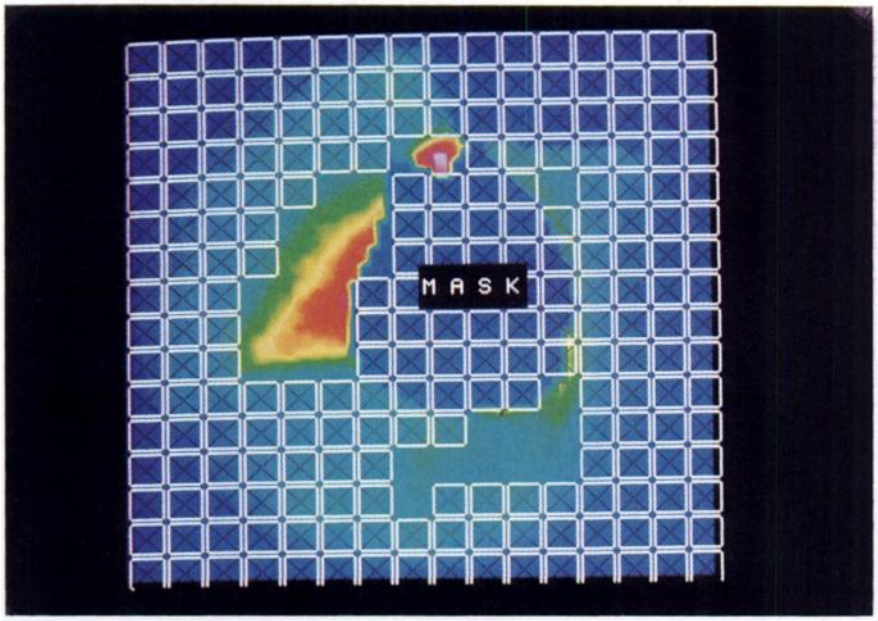

FIGURE 1
Wide mask is positioned over heart and most of injected arm in order to exclude them from FA. Trixels are rectangular with size of 4 × 4 pixels. Thirty most active trixels are analyzed

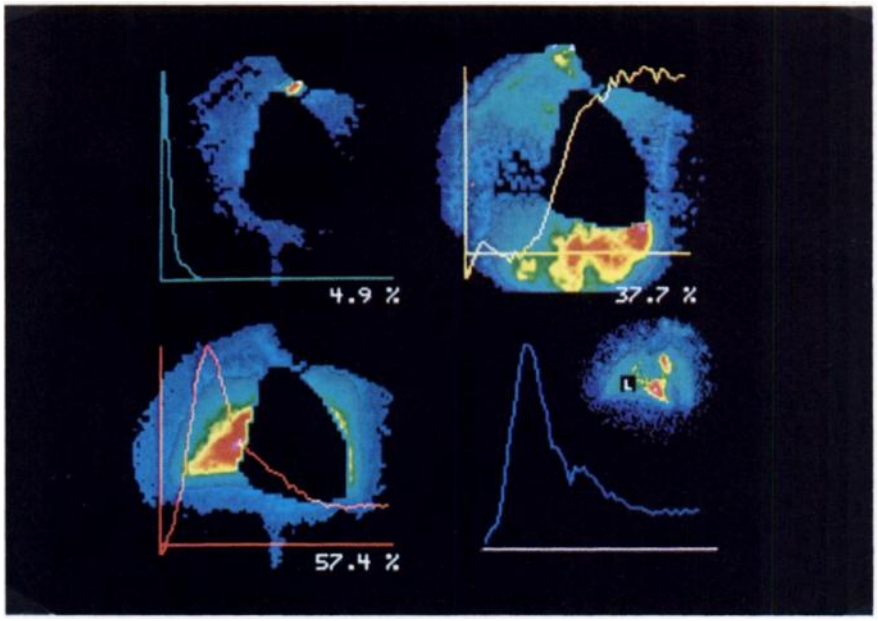

FIGURE 2
Using FA, three images and curves are obtained from dynamic series. They correspond to venous input, background, and lung factor. Note that in this example, lung factor takes in over 50% of counts available in study. Curve in right lower quadrant is obtained by positioning rectangular ROI over right lung

This method requires the selection of ROIs over the venous input, the lung, and the ascending aorta. A 6 × 10 pixel lung ROI was positioned on the middle third of the lung, preferentially the right lung, avoiding overlap with the heart, liver, or injection arm. The venous input and aortic ROIs were 3 × 3 pixels each. Time vs. activity curves with 50 points were generated for each ROI. The lung curve was deconvolved by the venous input curve, using the lagged normal algorithm, and the UIR was obtained. Two gamma functions were fitted on this curve. The aortic curve was used as a reference to define the peak of the second gamma function. The shunt fraction and Qp/Qs were calculated as described in the preceding section.

Statistical Analysis

The Student's t-test for unpaired data was used to calculate the level of significance (p) between the SF and Qp/Qs in the shunt patients and in the control group. P values >0.05 were considered nonsignificant. Linear regression analysis was used to obtain the correlation coefficient (r) and the standard error of the

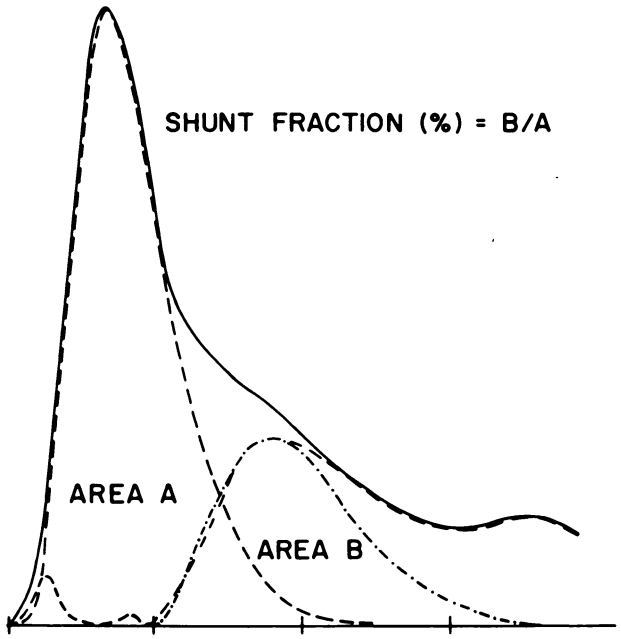

FIGURE 3
Area under gamma function A corresponds to systemic flow, and area under gamma function B corresponds to L-R shunt flow. Definition of beginning and end of second gamma function was clearly defined when generating curves with FA. $Q_p/Q_s = A/A-B$

estimate (s.e.e.) from the nuclear medicine and oximetry shunt fractions (or Qp/Qs); it was also used to test the interobserver variability.

RESULTS

The results of the shunt fraction and Qp/Qs calculations, and the correlation with oximetry appear in Tables 3 and 4 and Figs. 4 and 5.

The sensitivity and specificity of the two methods changed according to the cutoff level selected to separate the L-R shunt patients from the control group, (Fig. 6). The optimal cutoff value was found to be SF = 0.25 (Qp/Qs = 1.33) using the FA technique and SF = 0.27 (Qp/Qs = 1.37) for the ROI method. The simultaneous attainment of high sensitivity (94%) and high specificity (94%) could only be achieved when using FA at the optimal cutoff value. When using a different cutoff value, e.g., a Qp/Qs of 1.2, the sensitivity is 94% for FA and ROIs but the specificity falls to 71% for FA and to 50% when using ROIs (Fig. 6).

The comparison of both the FA and ROI methods to generate curves demonstrates that both methods can separate the shunt patients from the control group, p <0.001. The correlation coefficients with oximetry of shunt patients only are r = 0.66 for FA and r = 0.63 for ROIs. The interobserver variability was r = 0.87 for FA and r = 0.78 for ROIs.

TABLE 3
Results Obtained by Two Observers Expressed as Qp/Qs, Generating Curves with FA and ROIs

	Oximetry (Qp/Qs)	Radionuclide data (Qp/Qs)					
		Obs. 1		Obs. 2			
		FA	ROI	FA	ROI	B/A	C2/C1
L-R shunt patients							
1 ASD	1.5	2.92	2.57	1.38	1.42	1.4	1.3
2 VSD	1.4	2.27	2.06	1.79	2.56	2	1.7
3 VSD	1.4	1.69	1.73	1.94	1.89	1.4	1.4
4 *	1.5	1.92	1.93	1.79	1.34	1.4	1.6
5 VSD	1.4	2.24	2.57	1.92	1.81	1.2	1
6 ASD	1.5	1.4	2.48	1.67	1.21	1.2	1.2
7 ASD	2.1	3	3	1.55	3	2.6	1.7
8 ASD	1.3	1.13	1.17	1.13	1.19	1	1
9 VSD	1.7	2.33	2.47	1.51	3	1.1	2.1
10 ASD	3	3	3	3	3	1.9	1.7
11 ASD	2	1.57	2.72	2.02	1.44	1.6	1.8
12 ASD	2.7	3	3	3	3	3	3
13 VSD	1.7	1.8	1.8	1.54	1.75	1	1
14 VSD	1.5	1.82	1.73	1.45	2.33	1.4	1.2
15 ASD	2.2	2.69	2.5	1.62	1.92	1.8	1.8
16 VSD	1.4	2.1	2.78	1.89	1.59	1.1	1
Mean	1.77	2.18	2.34	1.82	2.03	1.57	1.53
s.d.	0.49	0.61	0.55	0.50	0.66	0.56	0.51
Control subjects							
1 CAD	—	1.07	1.38	1.05	1.13	1.5	1.2
2 CAD	—	1.02	1.08	1.11	1.08	1	2.4
3 CAD	—	1.08	1.18	1.09	1.13	1	1
4 CAD	—	1.63	1.53	1.42	1.11	1	1
5 CAD	—	1.05	1.32	1.02	1.13	1	1
6 CAD	—	1.21	1.16	1.09	1.12	1	1
7 CAD	—	1.12	1.03	1.13	1.12	1	1
8 CAD+MR	—	1.07	1.09	1.15	1.17	1	1
9 CAD+MR	—	1.25	1.10	1.04	1.09	1	3
10 CAD+MVP	—	1.11	1.25	1.03	1.08	1	1
11 CAD+MS+MI	—	1.09	1.23	1.02	1.02	1	3
12 CAD	—	1.26	1.21	1.08	1.35	1	1
13 CAD	—	1.18	1.25	1.03	1.01	1	1
14 CAD	—	1.34	1.37	1	1	1	1
15 CAD+MR+MS	—	1.06	1.11	1.04	1.01	1	1.9
16 CAD	—	1.16	1.31	1.04	1.04	1	1
17 CAD	—	1.06	1.08	1.01	1.02	1	1
18 CAD+MR	—	1.07	1.05	1.03	1.05	1	1
19 CAD+AS+AI	—	1.01	1.13	1.01	1.05	1	
20 CAD	—	1	1.05	1.03	1.51	1.1	2.6
Mean		1.14	1.20	1.07	1.11	1.03	1.46
s.d.		0.14	0.13	0.09	0.12	0.11	0.71

* Fistula of Valsalva.

TABLE 4
Results Expressed as Shunt Fractions (SF) and Qp/Qs*

Curve generation method	Control Group SF x ± sx	Control Group Qp/Qs x ± sx	Shunt Patients SF x ± sx	Shunt Patients Qp/Qs x ± sx	p, SF	p, Qp/Qs
FA	0.12 ± 0.09	1.14 ± 0.14	0.50 ± 0.15	2.18 ± 0.61	<0.001	<0.001
ROIs	0.15 ± 0.09	1.20 ± 0.13	0.55 ± 0.13	2.34 ± 0.55	<0.001	<0.001

*Generation of curves by FA and by ROIs coupled with lagged normal deconvolution and gamma variate analysis separate L-R shunt patients from control subjects with p <0.001.

DISCUSSION

The invasive diagnosis of L-R cardiac shunts is performed with procedures such as oximetry, dye or thermal dilution or inert gas inhalation (*5,6,15–18*). Oximetry is the most widely used technique, despite its lower sensitivity when compared with other techniques. For example, a L-R shunt at the atrial level would need to have a minimal Qp/Qs ratio between 1.5 to 1.9 in order to be detected (*19*).

The nuclear medicine approach has been based mainly on the first-pass analysis. Initially the studies were performed with gamma probes and later with the gamma camera or positron detecting devices. Many approaches have been tested and validated.

Inhalation of radioactive gases and determination of their concentration in blood sampled from the right side of the heart or detected in the lungs is a very sensitive technique. Studies have been done with krypton-85m (*23–24*), iodine-131 methyl iodide (*5*) and oxygen-15-labeled carbon dioxide (*26–28*).

In order to avoid contamination of the left heart chambers in a first-pass study, iodine-125 with cardiac probes was used. The low energies of 25–35 keV have a half value layer of 2 cm in water. Because of the anterior anatomic position of the right heart, curves of right heart activity were obtained which were uncontaminated by activity from the left heart (*30*). Another way to avoid interference from the left-sided chambers and from recirculation when measuring right heart activity has been to use a very short-lived radionuclide such as iridium-191m ($T_{\frac{1}{2}}$ = 5 sec), with the added advantage of giving a very low radiation absorbed dose (*31*).

Three common analytic techniques have been described to study the lung time versus activity curve. The C2/C1 ratio described in 1962 by Folse and Braunwald (*32*) is similar to the empiric formula used for dye

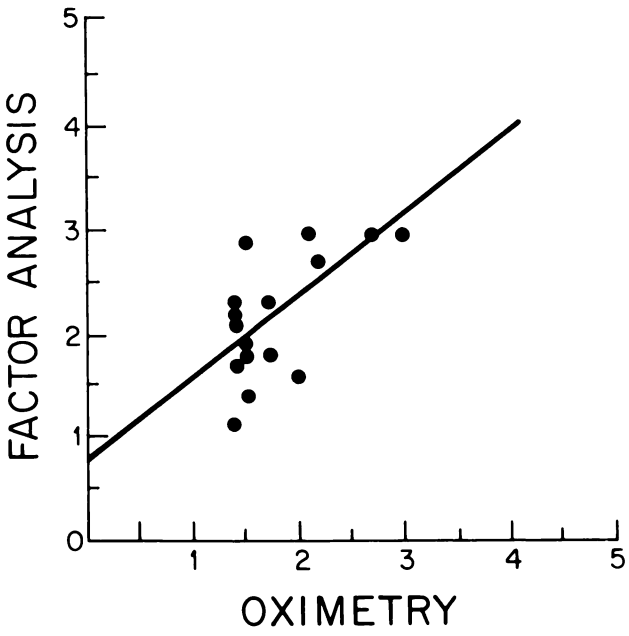

FIGURE 4
Correlation of Qp/Qs obtained by oximetry and by lung time vs. activity curves generated by FA. Y = 0.79X + 0.77; R = 0.655; s.e.e. = 0.47; N = 16

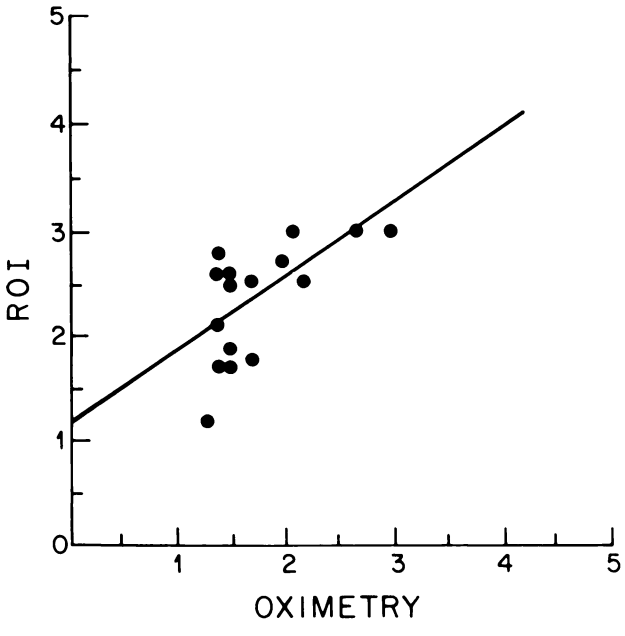

FIGURE 5
Correlation of Qp/Qs obtained by oximetry and by lung time vs. activity curves generated by ROIs. Y = 0.68X + 1.14; R = 0.626; s.e.e. = 0.44; N= 16

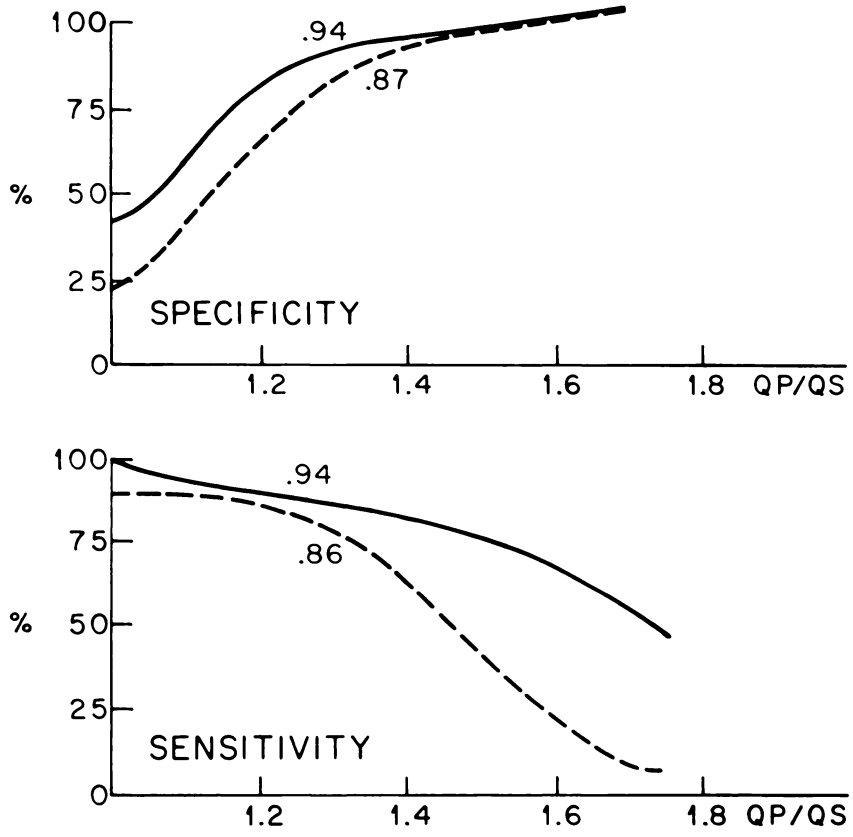

FIGURE 6
Sensitivity and specificity as function of Qp/Qs value selected to separate normal subjects from L-R shunt patients. For instance, if Qp/Qs of 1.2 is selected as cutoff value, specificity using FA will be 71%, while specificity using ROIs will be 50%; sensitivities will both be 93–94%. Optimal cutoff value of Qp/Qs using FA was 1.33 with sensitivity and specificity of 94%. FA.A 1.33 (—); ROIs 1.37 (---)

dilution studies in the catheterization laboratory, described in 1960 by Carter et al. (*33*). A ratio between the peak concentration and at two and three buildup times is calculated. The buildup time is defined as the time of appearance of the dye to its peak concentration. This technique will detect shunts with a Qp/Qs over 1.33 (*31*). Previous studies have reported significant inaccuracy of the C2/C1 ratio when studying children (*10*). Anderson (*34*) described a method to analyze the pulmonary curve by the logarithmic extrapolation of the initial portion of the downslope to a point 1% from the peak activity, defining two areas; the ratio of these areas define the shunt flow. Maltz and Treves proposed the gamma variate method described above which, compared with the other methods, gave better results.

Our results show that both curve-generating techniques, FA and ROIs, separate the L-R shunt patients from the control group with a $p < 0.001$. However, the use of FA resulted in a significant improvement in interobserver variability compared with ROIs. This is because the operator intervention in the generation of the curves using FA is minimal, limited to the positioning of the mask over the heart and most of the venous input. Furthermore, the lung factor extracted corresponds to an average of 48% of the total counts whereas a 6 pixel × 10 pixel ROI positioned over the lung analyzes only 1.6% of the total area of a 64 × 64 frame. Therefore, the statistical significance of a curve generated by FA is much higher than that obtained by using a ROI.

In conclusion, we believe that the best method for quantitating L-R shunts at the present time utilizes FPRNA, curves generated by FA, and an excellent deconvolution algorithm and gamma variate analytic technique. FA, which automatically generates uncontaminated curves and is relatively free of operator intervention, plays an important role in the high degree of accuracy and reproducibility reported here. An added advantage of this method is that we may use [^{99m}Tc] pertechnetate for our studies. This provides convenience, economy, and low radiation absorbed dose to patients.

FOOTNOTE

* Simis 5 Sopha computer and Sopha dedicated acquisition computer, Sopha Medical, Baltimore, MD.

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