Evaluation of Valvular Regurgitation by Factor Analysis of First-Pass Angiography

Laurent Philippe, Ismael Mena, Jacques Darcourt, and William J. French

Divisions of Nuclear Medicine and Cardiology, Harbor-UCLA Medical Center, Torrance, UCLA School of Medicine, Los Angeles, California

We have evaluated left ventricular regurgitation by means of factor analysis of ^{99m}Tc first-pass radionuclide angiography (FPRNA) and time-activity curve deconvolution. The FPRNA regurgitant fraction (RF) was computed in 26 individuals: 13 patients (eight mitral, three aortic, and two mitral-aortic) and 13 controls. The reference method was contrast ventriculography (CV) performed within 1 hr after FPRNA. In 19 patients, CV was preceded by the determination of cardiac output, using indocyanine green dye (n = 16) or thermodilution technique (n = 3), to determine a catheterization regurgitant fraction (CATH-RF). Lung and left ventricular (LV) time-activity curves were gathered by factor analysis and the FPRNA regurgitant fraction assessed by a lagged normal deconvolution of these curves. In valvular regurgitation, the LV deconvolved curve demonstrates the appearance of a long transit time component that is amenable to quantification. The presence of regurgitation was determined by contrast ventriculography. With a 10% RF as an acceptable upper limit of normal for nonregurgitant patients, FPRNA yielded one false-negative and no false-positive studies (n = 26), while CATH-RF yielded two false-negative and four false-positive determinations (n = 19). The following are results of quantitative determination of RF (mean ± s.d.): FPRNA 0.39 ± 0.19 (n = 13 Valvular), 0.01 ± 0.03 (n = 13 Controls); CATH 0.34 ± 0.24 (n = 11 Valvular), 0.13 ± 0.12 (n = eight controls). FPRNA was able to differentiate ($p < 0.001$) between control patients (CV grading 0) and mild/moderate regurgitation (CV grading 1+ or 2+) and severe regurgitation (3+ or 4+) ($p < 0.025$).

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Demonstration of valvular regurgitation has been accomplished by several noninvasive procedures, including ultrasound, cine-computed tomography (CT) (*1*), and nuclear magnetic resonance (NMR) (*2*). Furthermore, quantification of valvular regurgitation is possible by noninvasive radionuclide techniques using several approaches (*3*). Gated equilibrium blood-pool studies have compared right and left ventricular stroke volumes with the following assumptions: absence of right ventricular valvular insufficiency (pulmonary or tricuspid), absence of atrial septal defect, similar counting efficacy for both ventricular chambers, and regular cardiac rhythm. These assumptions, in particular the similar counting efficacy for right ventricle (RV) and left ventricle (LV), are inaccurate in many patients and may explain the high stroke index ratio for normal patients. A significant advantage of the noninvasive first-pass radionuclide angiography (FPRNA) method is that it does not assume normal right heart valve competence, similarity of geometric conditions and can be performed even in the presence of arrhythmias.

In order to assess the existence and quantification of regurgitant flow with FPRNA, we analyzed the unit impulse response (UIR) of the left heart obtained by deconvolution of the LV and pulmonary time-activity curves. These curves are gathered with factor analysis of the FPRNA. The UIR is related to the distribution of transit times through the left heart and reveals a long transit time component associated with valvular regurgitation. We report quantification results comparing them to contrast angiography with and without quantification.

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For reprints contact: I. Mena, MD, Director, Division of Nuclear Medicine, Harbor-UCLA Medical Center, 1000 W. Carson St., Torrance, CA, 90509.

*Present address: CHU Trousseau - Div. Nuclear Medicine. 37044 Tours, France.

MATERIAL AND METHODS

Patient Population

The study series consisted of 26 patients, 12 men and 14 women, aged 20 to 79 yr, who consented to cardiac catheter-

ization for evaluation of valvular abnormalities and/or coronary artery disease. Thirteen of the 26 patients had contrast proven valvular insufficiency involving the mitral valve (eight patients), the aortic valve (three patients), or both mitral and aortic valves (two patients). The remaining 13 patients without contrast evidence of valvular regurgitation were considered as control patients. Coronary artery disease was present in 10 control patients and in four valvular patients. Three valvular patients were in atrial fibrillation (Table 1). There was no significant difference in age between the valvular and the control patients: 51 yr (range 39–68) for the controls and 51 yr (range 20–79) for the valvular patients.

In 19 patients, cardiac output was determined by indocyanine green dye dilution technique (in 16 cases) or by thermodilution (three cases). Forward stroke volume (FSV) in milliliters was computed by dividing the cardiac output by the heart rate. All patients underwent, within 1 hr, FPRNA and biplane LV contrast ventriculography (CV) and/or aortic root angiography. The 26 patients also underwent coronary angiography. The end-diastolic and end-systolic volumes (EDV and ESV) were calculated from cineangiography and the total stroke volume (TSV) of the LV derived from TSV= EDV − ESV.

The regurgitant fraction (RF) was calculated by comparison of the FSV and TSV: RF = (TSV-FSV)/TSV. A semiquantitative grading of the magnitude of valvular insufficiency was performed by using a standard 0 to 4+ scale for contrast cineangiogram (*4*).

First-Pass Radionuclide Angiography—Data Acquisition

The patient was in the supine position, and a 19-gauge needle was placed into a basilic vein and connected to a 3-ml volume external catheter. Twenty millicuries (740 MBg) of technetium-99m (^{99m}Tc) pertechnetate, were injected in a volume of < 1 ml and rapidly hand-flushed with 30 ml of saline or dextrose solution. Imaging was performed with a conventional mobile analog camera (General Electric, Milwaukee, WI) equipped with a low-energy, high-sensitivity, parallel-hole collimator. The camera detector was positioned in a 20-degree RAO projection.

Immediately postinjection, a 40-sec acquisition was begun in list mode and recorded directly into an acquisition mobile microprocessor. The information was transferred later via floppy disks to the main computer (Sopha Medical). During direct acquisition total field count rates of 50,000–80,000 cps were recorded.

First-Pass Radionuclide Angiography—Data Processing

The list mode was framed in a 64 × 64 format at the same rate as the heart rate in order to filter the high frequency oscillations related to the cardiac contractions. The lungs and LV time-activity curves were gathered by Factor Analysis (FA) using the algorithm developed by Barber (*5*) and DiPaola and

TABLE 1
Clinical, Angiographic, and Isotopic Characteristics of Patients

				Dilution SV		Contrast Ventriculography				FPRNA			
Patient No.	Angio Findings	Sex	Age	GDD*	TD	EDV	EF	TSV	RF	EF	RF #1	RF #2	RF m
1	Infarct	M	49	73	·	108	0.60	65	0	0.64	0	0.22	0.11
2	Infarct	F	44	68	·	153	0.56	86	0.21	0.43	0	0	0
3	CAD	M	45	87	·	200	0.46	92	0.05	0.42	0	0	0
4	Infarct COPD	F	56	49	·	112	0.59	66	0.26	0.34	0	0	0
5	CAD	M	48	84	·	103	0.71	73	0	0.72	0	0.07	0.04
6	CAD COPD P.HTN	F	60	89	·	95	0.83	79	0	0.76	0	0	0
7	Infarct	M	44	63	·	119	0.69	82	0.23	0.62	0	0	0
8		M	48	108	·	199	0.77	154	0.30	0.77	0	0	0
9	Normal	F	39	–		108	0.62	67	–	0.68	0	0	0
10	CAD	M	44	–		–	0.72	114	–	0.71	0	0	0
11	Normal	F	63	–		110	0.82	90	–	0.69	0	0	0
12	CAD	F	56	–		99	0.67	66	–	0.70	0	0	0
13	CAD	M	68	–		–	–	–	–	0.38	0	0	0
14	4+ MR AF	F	44	39	·	167	0.77	129	0.69	0.61	0.56	0.52	0.54
15	4+ MR	F	20	74	·	178	0.54	97	0.24	0.64	0.56	0.56	0.56
16	2+ MR	F	59	72	·	153	0.61	94	0.24	0.64	0.44	0.38	0.41
17	1+ MR CAD	F	59	97	·	132	0.44	58	0	0.37	0	0.12	0.06
18	2+ MR CAD AF PHTN	F	44	72	·	232	0.28	66	0	0.31	0.47	0.44	0.45
19	2+ AI AS	F	79	64	·	131	0.84	110	0.42	0.85	0.48	0.38	0.43
20	4+ AI	M	24	64	*	227	0.44	99	0.34	0.52	0.45	0.21	0.33
21	4+ MR MS	F	32	35	*	85	0.67	57	0.39	0.65	0.45	0.44	0.44
22	3+ MR MS 1+AI AF	M	49	81	*	155	0.72	112	0.59	0.51	0.47	0.68	0.57
23	1+ AI AS	F	60	42	·	74	0.69	51	0.18	0.79	0	0	0
24	3+ AI AS 1+MR	M	51	44	·	230	0.61	139	0.68	0.55	0.57	0.44	0.51
25	1+ MR CAD	M	74	–		99	0.66	65	–	0.56	0.21	0.29	0.25
26	2+ MR CAD	M	63	–		166	0.43	71	–	0.67	0.27	0.23	0.25

SV = effective LV stroke volume; GDD = Green dye solution; TD = Thermodilution; EDV = LV end-diastolic volume; EF = LV ejection fraction; TSV = Total stroke volume; RF = Regurgitant fraction; #1 = First observer; #2 = Second observer; m = mean; Infarct = Myocardial infarct; CAD = Coronary artery disease; COPD = chronic pulmonary disease; PHTN = Pulmonary hypertension; AF = Atrial fibrillation; MR = Mitral reguritation; MS = Mitral stenosis; AI = Aortic insufficiency; and AS = Aortic stenosis.

Bazin (*6,7*), and used for gated blood-pool studies by Cavailloles (*8*) and Pavel (*9*). Factor analysis provides images and curves which correspond to the various functions of a dynamic study, without constraint to an anatomic model for the spatial data and to a mathematic model for the time-activity curves. For example, a four-factor analysis applied to FPRNA will automatically separate the right chambers, lungs, left chambers, and general circulation or background. A factor image is associated with each curve allowing identification of the time-activity curve. Factor analysis is processed automatically with minimal operator intervention. Nevertheless, three parameters seem to influence the result: (1) the number of factors should correspond to the number of functions that occur in the area analyzed; (2) the trixel size should be chosen according to the count rate and to the size of the structure to be analyzed, (Trixel = area of observation unit, usually 4 × 4 pixels); (3) the number of trixels influences the processing time. Therefore, in practice the number of factors to extract depends on the area analyzed. In order to reduce the processing time while extracting the significant factors, and because we were not concerned with the right heart, we masked-off the first segment of the FPRNA (superior vena cava, right atrium, right ventricle, and pulmonary artery) thus achieving factor analysis with only three factors. This mask is performed using an isocontour defined on the integrated frame corresponding to the first segment of the FPRNA and ending at the time of visualization of the pulmonary artery. The left atrium was masked-off at the same time because of its superimposition with the right atrium in the RAO projection. Finally, the abdominal aorta was manually masked-off (Fig. 1).

Factor analysis with three factors provided three compartments: lungs, LV, and the general circulation (background, BKGD, Fig. 1). The parameters used for the FA were the following:

1. Three factors.
2. The trixels dimension was 4 × 4 pixels.
3. Thirty-five trixels were analyzed.
4. Positive constraint.
5. Iterations were stopped at four negative alphas.

The curves were fitted before deconvolution. The end of the downslope of the lungs curve was exponentially extrapolated in order to avoid counts originating from recirculation. Furthermore, the LV curve was fitted with a gamma variate using fixed fit limits for all patients (fit limits: 40% of the maximum of activity on the upslope to 70% of the maximum on the downslope).

The left heart unit impulse response (UIR) was determined by deconvolution of the LV curve (output function) by the lungs curve (input function). We used the lagged normal deconvolution algorithm as described by Kuruc (*10*). The calculated UIR is constrained to be a nonnegative sum of a set of scaled lagged normal curves. In normal patients, this UIR is unimodal, while in valvular patients it is multimodal (Fig. 2). The second component of the UIR represents a fraction of the flow with prolonged transit time through the left heart and therefore appears to be related to valvular regurgitation. The same principle used by Maltz and Treves (*11*) for the calculation of the Qp/Qs ratio in shunt evaluation is applied for the calculation of the RF (Fig. 3). The first UIR component is gamma fitted and the gamma curve obtained (area A1) is subtracted from the total UIR curve. The difference curve is also gamma fitted (area A2) using a constraint assuming a similar shape as the first gamma fit. The area A1 represents the total flow through the left heart, and the area A2 the long transit time component flow. Therefore, the RF is calculated (RF = A2/A1).

Statistical Analysis

All results are expressed as mean and standard deviation. We used the unpaired t-test to compare the means of the different groups of patients. The Bonferroni adjustment is

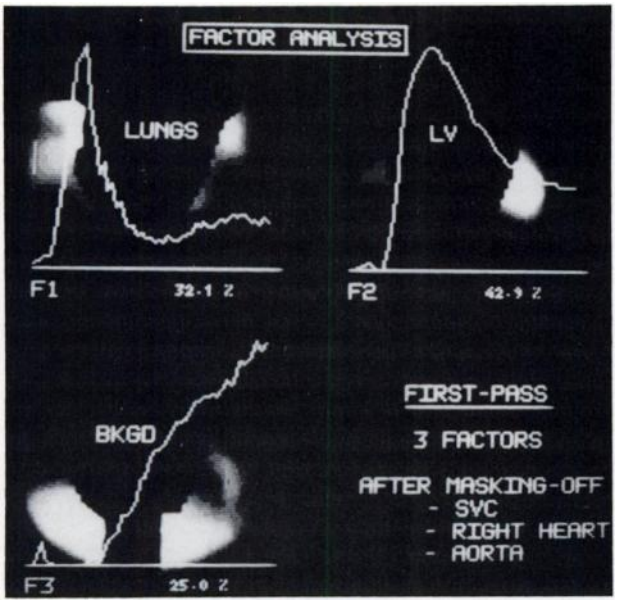

FIGURE 1
FPRNA analyzed with a three-factor analysis, after masking-off the right heart. Each curve is superimposed with the corresponding image. F1 represents the lungs, F2 the LV, and F3 the general circulation.

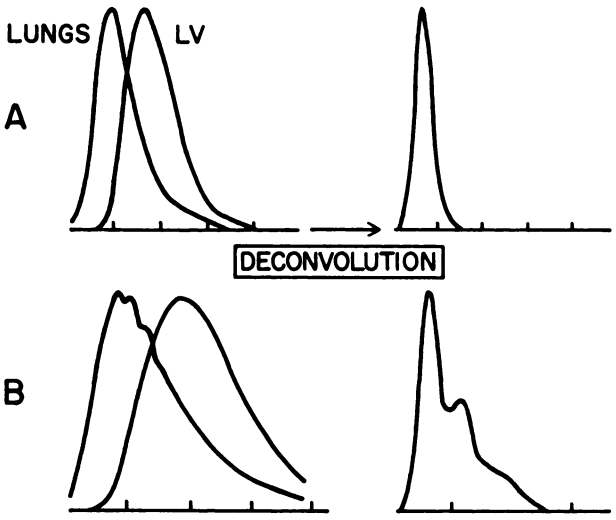

FIGURE 2
Left heart UIR obtained after deconvolution of LV curve by pulmonary curve for a control patient (upper right quadrant) and for a valvular patient (lower right quadrant). Notice the multimodal aspect of the UIR for valvular patient.

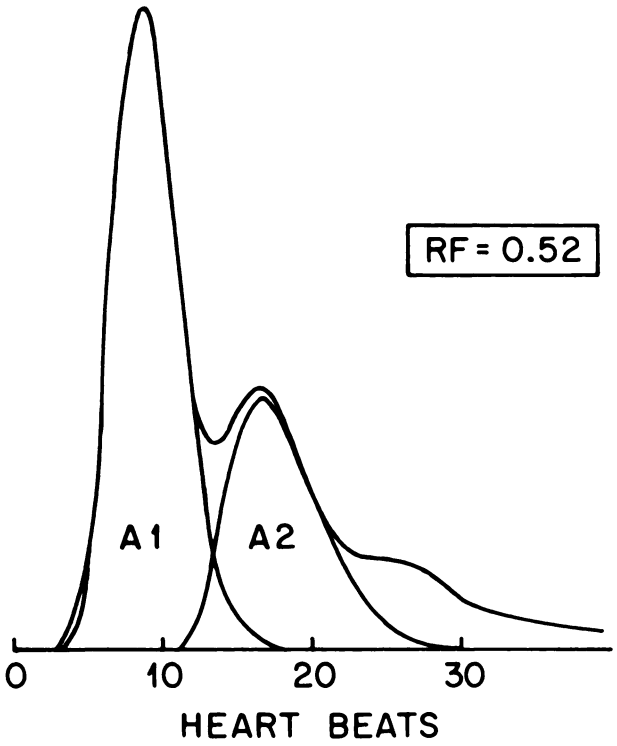

FIGURE 3
Quantification of the regurgitation: calculation of the RF using the UIR. A gamma variate fit of the 1st component defines area A1. The residual curve is also gamma fitted defining area A2. Regurgitant fraction is calculated as the ratio RF = A2/A1. Here is an example of the UIR for a patient with a 4+ mitral regurgitation (Patient 14).

used for taking account of multiple comparisons: the new significance level is obtained by dividing the desired simultaneous significance level for each group (0.05) by the number of tests being made (for two t-tests, then $p < 0.025$). Linear correlations were calculated and results expressed as the correlation coefficient (r), the standard error of the estimate (s.e.e.), and the regression equation.

RESULTS

Cardiac Catheterization Data

Eight patients had pure mitral insufficiency, including two with grade 1+, three with grade 2+, and three with grade 4+. Three patients had aortic insufficiency, including one with grade 1+, one with grade 2+, and one with grade 4+. One patient had a 1+ aortic insufficiency associated with a 3+ mitral insufficiency, and one patient had a 1+ mitral insufficiency associated with 3+ aortic regurgitation. Regurgitant fractions has been computed for the 19 patients who underwent determination of cardiac output. The RF ranged between 0 and 30% for the control patients (n = 8, 0.13 ± 0.12) and between 0 and 69% for the valvular patients (n = 11, 0.34 ± 0.24) ($p < 0.05$). Calculation of the LV stroke volume (SV) by contrast ventriculography (CV) and by green dye dilution for the control patients yielded a correlation coefficient r = 0.74 (y = 0.46x + 37, s.e.e. = 13, n = 8, $p < 0.05$).

The left ventricular ejection fraction (LVEF) was 0.59 ± 0.15 (range 0.28–0.84) for the valvular patients, and 0.67 ± 0.11 (range 0.34–0.83) for the control patients (p = N.S.). The end-diastolic volume was 156 ± 51 ml (range 74–232) for the valvular patients and 128 ± 37 ml (range 95–200) for the controls (p = N.S.).

First-Pass Radionuclide Angiography Data

The RF ranged between 0 and 6% (0.01 ± 0.03) for the control patients, and between 0 and 57% (0.39 ± 0.19) for the valvular patients ($p < 0.001$). To test the interobserver variability of the method, the radionuclide RF was computed independently by two observers. The correlation was r = 0.92, and the interobserver variability 9.2%. To diminish the operator dependence of these results, the RF was expressed as the mean of two observers (Table 1).

Comparison Between FPRNA and Catheterization Data (CATH)

The 26 patients were divided into three groups, according to the CV grading of the severity of the insufficiency: group A (control patients), group B corresponding to mild/moderate regurgitation (grades 1+ or 2+ by CV), and group C with severe regurgitation (4+, and the two bivalvular patients 3+/1+). The values are summarized in Table 2 and Figure 4. There were significant FPRNA RF differences between the three groups (A versus B: $p < 0.001$, B versus C: $p < 0.025$. The RF calculated by CATH was not able to separate low and mild regurgitation from the control patients (A versus B: NS, V versus C: $p < 0.025$.

The ability to detect regurgitation was compared for the two methods (CATH versus FPRNA). Contrast visualization of regurgitant flow is considered the gold standard. To characterize the performances of a quantitative test, it is necessary to set a threshold between normal and abnormal values. The number of true-

TABLE 2
Regurgitant Fraction by Catheterization and by FPRNA Compared to the Angiographic Grading of Insufficiency

Angiographic grading	CATH-RF (m ± s.d.)	FPRNA RF (m ± s.d.)
0	0.13 ± 0.12	0.01 ± 0.03
1+ & 2+	0.17 ± 0.16	0.27 ± 0.16
3+ & 4+	0.49 ± 0.10	0.49 ± 0.08
	Statistical difference	
0 vs. (1+, 2+, 3+, 4+)	$p < 0.05$	$p < 0.001$
0 vs. (1+, 2+)	N.S.	$p < 0.001$
(1+, 2+) vs. (3+, 4+)	$p < 0.025$	$p < 0.025$

positives, false-positives, true-negatives and false-negatives has been calculated for different levels using various cut-off limits between controls and valvular patients (Table 3). A 10% RF threshold yielded a good separation between the two populations: one false-negative and 0 false-positive for the FPRNA (n = 26), 2 false-negatives and four false-positives for the CATH-RF method (n = 19).

The sensitivity and the specificity for different values of RF threshold between 0 and 35% (Table 3) were also computed. For a 10% RF threshold between control and valvular patients, the sensitivity was 92% for FPRNA-RF and 82% for CATH-RF, and the specificity was 100% for FPRNA-RF and 50% for CATH-RF. These results are presented in a receiver-operating characteristic curve (Fig. 5).

For the 11 valvular patients (with CATH-RF calculated), the RF correlation between CATH and FPRNA was $r = 0.60$ ($y = 0.47 + 0.23$, S.E.E. = 0.16, $p < 0.05$).

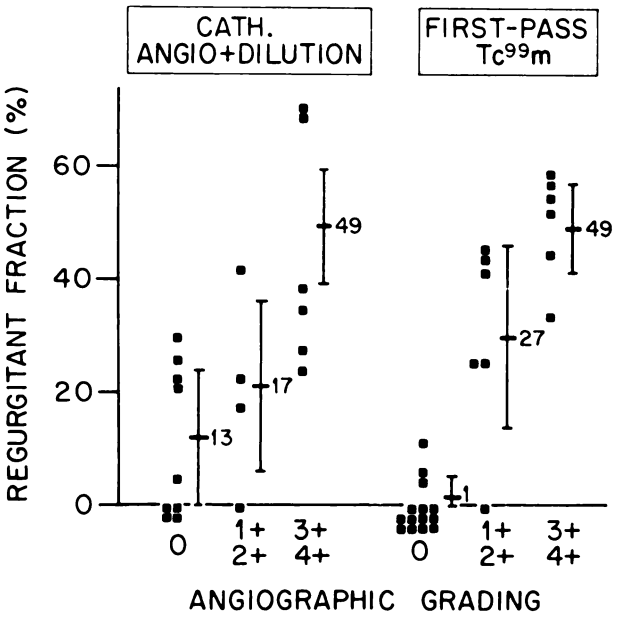

FIGURE 4
The regurgitant fractions calculated by catheterization (left panel) and by FPRNA (right panel) are displayed according to the severity of regurgitation as assessed by contrast angiography (semi-quantitative grading 0–4+). There is better separation between control patients (Group 0) and mild regurgitant patients (Group 1+ and 2+) for FPRNA than for catheterization. (All the dots plotted on and below the X-axis represent patients with RF = 0.)

DISCUSSION

This study demonstrated the capability of FPRNA to noninvasively quantitate valvular regurgitation. Analysis of the left heart UIR allowed separation of patients with and without regurgitation, as well as to quantitate the severity of the regurgitation.

Other Noninvasive Techniques

Doppler echocardiography is frequently used for assessing valvular insufficiency, especially aortic regurgitation. It is able to evaluate semi-quantitatively the

TABLE 4
Experimental Values (Duplicate) of Pump Unit Response Curves Displayed in Figure 7

	RF* PUMP	(%) FP†
#1	0	0
	0	2
#2	17	6
	17	5
#3	29	26
	29	25
#4	36	36
	36	27
#5	50	51
	50	50
#6	70	61
#7	70	63

* RF = Regurgitant fraction.
† FP = First-pass study.

TABLE 3
Performances of FPRNA and Catheterization for the Detection of Valvular Regurgitation

RF (%) Normal Upper Limit	TP* (n)		FN (n)		TN (n)		FP (n)		SENS† (%)		SPE† (%)	
	FP	Cath	FP	Cath	FP	Cath	FP	Cath	FP	Cath	FP	Cath
0	12	9	1	2	11	3	2	5	92	82	85	38
5	12	9	1	2	12	4	1	4	92	82	92	50
10	12	9	1	2	13	4	0	4	92	82	100	50
15	11	9	2	2	13	4	0	4	85	82	100	50
20	11	8	2	3	13	4	0	4	85	78	100	50
25	9	6	4	5	13	6	0	2	69	55	100	75
30	9	6	4	5	13	8	0	0	69	55	100	100
35	8	5	5	6	13	8	0	0	62	45	100	100

* TP = True positive; FN = False-negative; TN = True-negative; FP = False-positive; SENS = Sensitivity; SPE = Specificity; Cath = Catheterization; and FP = First-pass.
† Sensitivity and specificity are computed for different levels of upper normal RF value.

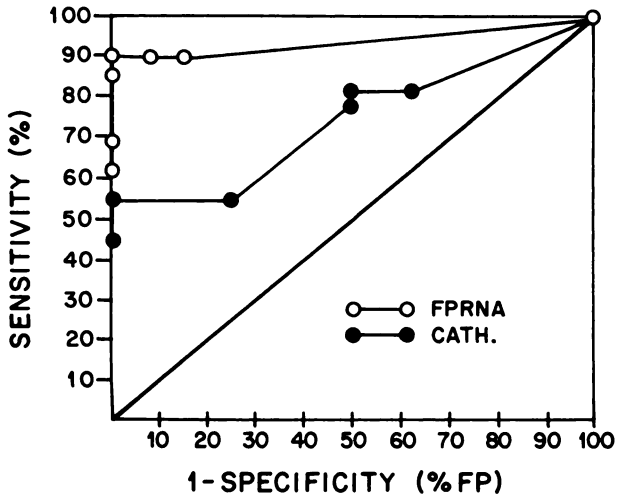

FIGURE 5
Receiver-operating characteristic curves for the detection of valvular regurgitation by catheterization (RF assessed by angiography and dilution) and by FPRNA. The existence of regurgitation is here assessed by means of the RF quantitation. Contrast cineangiography is the reference (visualization of the regurgitant flow). The FPRNA method yields better results. A 10% RF threshold between control and valvular patients yields a sensitivity of 92% of FPRNA, 82% for CATH, and a specificity of 100% for FPRNA and 50% for CATH.

severity of the regurgitation, but it is very sensitive to the presence of other pathologic lesions. Kitabatake et al. (*12*), using a new Doppler approach that compared the pulmonary and the aortic flows, was able to demonstrate a correlation of RF only in patients with aortic regurgitation in the absence of right valvular insufficiency. Recently, Ohlsson et al. (*13*) used an interesting combined CO_2-rebreathing method and echocardiography to evaluate aortic and mitral regurgitation but could not separate controls from patients with mild regurgitation.

The usual way to assess valvular insufficiency by radionuclide studies involves gated nuclear angiography (GNA) as described by Rigo et al. (*14*). Since this first work, many adjustments have been made in order to improve the accuracy and the reproducibility of the method, but the main problem is still the high stroke index ratio for the control patients (index ratio up to 1.62 (*15*), 2.05 (*16*) and 2.9 (*17*), corresponding respectively to RF of 38%, 51%, and 66%). This results in an overlap between normal individuals and patients with mild valvular regurgitation. In addition, the GNA technique assumes a right ventricular valvular competence. Furthermore, GNA cannot be performed with accuracy in patients with irregular rhythms because of the ECG gating technique.

The FPRNA method has also been used to quantify valvular insufficiency using the same concept expressed for the gated method, i.e., the comparison between right and left ventricular stroke volumes (*18,19,20*), or by analytical technique after injection of a bolus in the left atrium (*21*). Weber et al. (*22*) used a method similar to the invasive method by comparing the forward cardiac output with the total LV stroke volume. Steele et al. (*23*) and Glass et al. (*24*) assessed regurgitation using the concept of forward ejection fraction (FEF). Steel injected the radionuclide through a wedged pulmonary artery catheter and then computed the FEF on the downslope of the LV curve as described by Donato (*25, 26*). Glass performed i.v. injection and, in order to assess the FEF, used a least-square deconvolution algorithm (deconvolution of LV by lungs) to correct for the bolus shape, constraining the UIR to a monoexponential decay curve, and afterwards computing its slope in order to define also the rate of LV washout. Both authors calculated the RF by comparing the FEF to the global LVEF.

Factor Analysis Method

Factor analysis has many advantages over other methods because of the following characteristics: (1) pulmonary and LV time-activity curves are generated by FA; (2) lagged normal deconvolution was used without constraint on the UIR downslope shape; and (3) UIR was analyzed with definition of early and delayed flow components. Thus there is no consideration of the slope of the UIR for our calculation.

The advantage of FA over region of interest (ROI) determination is the definition of less raw nonfitted contaminated curves. This is demonstrated by a slower washout of the downslopes of the curves gathered by ROI reflecting contamination of this curve segment. The upslopes are similar with both methods.

The lungs perfusion is modified in patients with left sided regurgitation (*27*). In such cases, while it would be difficult to choose a ROI location representing global pulmonary dynamics, FA produces an operator independent pulmonary curve.

Superimposition of both ventricular chambers in RAO projection can lead to right ventricular contamination of the beginning of the curve in spite of the previous masking off of right chambers (especially in small LV). If so, a four-factor analysis can extract the right ventricular component as a fourth factor and provides a LV curve with a better upslope. The determination of the masking ROI is not critical, especially for an analysis with four factors: in this case the only area we have to mask is the venous input and the superior vena cava. Secondly, in many patients, especially with severe valvular insufficiency, there was imperfect definition transition between the end of the LV and the beginning of recirculation. This "smearing effect" has been ascribed to the elongation of the injected tracer as it passes through blood vessels and mixing chambers of various volumes (*28*). Therefore, the LV

curve had to be fitted. Thompson et al. (*29*) showed that indicator transit time curves may be considered equivalent to a modified gamma variate and expressed this as $C(t) = Kta \exp(-t/b)$. The downslope limit for this gamma fit was set at 70% of the maximum as suggested by Maltz and Treves (*11*) for pulmonary curves in shunt evaluation, and this method provided very good and reproducible fitting.

These fitted curves were deconvolved using a lagged normal algorithm. This deconvolution with constraint was preferred to point-by-point exact deconvolution because the constrained solutions produce impulse responses that remain smooth with noisy data (*30*). Furthermore, as the constraint is chosen according to the physiologic model, the unit impulse response is directly interpretable. For evaluation of RF, Glass et al. (*24*) used a mono-exponential constrained deconvolution, assuming a mono-exponential washout of the UIR. This is not the case in valvular patients because of the interference of the left atrium (LA), which is an intermediate reservoir with a different washout rate when compared to the LV. We used a lagged normal deconvolution algorithm as described by Kuruc et al. (*10*) that constrains the unit impulse response (UIR) to be a nonnegative sum of a set of scaled lagged normal curves. This deconvolution seems to be well suited for flow analysis (*31,32*) and does not assume any constraint on the UIR downslope.

Strictly, the UIR is the time-activity curve which would be obtained after an instantaneous pulmonary pulse injection. The UIR is a composite function of the left atrial transfer function and of the LV residual impulse curve. Therefore, this UIR is not representative of the LV only, but also probably that of the left atrium since the input function is taken upstream of the left heart.

This UIR was different in control and valvular patients. In control patients, there was no (or minimal) second component suggesting an homogeneous transit through the LV. For valvular patients, the UIR was multimodal. This pattern is related to the appearance of long transit time components. In both mitral or aortic regurgitation the insufficiency effect is to prolong transit times through the left heart (LA and LV) while the lung input is not significantly affected. In patients with mitral insufficiency, the additional fraction of stroke volume regurgitated is stored in the LA which is more compliant than the pulmonary vessels. The reservoir function of the LA is expanded in such case (*33*). In aortic insufficiency, the lungs and LA washouts are not affected by the regurgitation, but the LV washout definitely is affected.

We quantitated the RF using a method similar to Maltz and Treves (*11*) quantification of left-to-right shunt (Qp/Qs). We considered that the regurgitant flow was proportional to the area corresponding to the slow UIR component while the total flow was represented by the first component. We validated this method by applying it to an experimental pulsatile flow model (please see Appendix).

Angiographic Correlation

In our study, the reference or gold standard was the cardiac catheterization (CV and dilution techniques). It has been demonstrated that there was not good correlation between the semi-quantitative grading (0 to 4+) and the CATH-RF (*34*). Furthermore, the value of the green-dye dilution technique has been investigated by several authors and its accuracy seems to be problematic especially for valvular patients (*35*). We found a poor correlation between the stroke volumes computed by dilution method and by angiography for control patients ($r = 0.74$). For this reason, the assessment of the FPRNA-RF quantification becomes difficult because the "gold standard" itself was not perfectly reliable.

The regurgitant volume itself is influenced by several hemodynamic factors. Although there was a small time interval between the FPRNA and the catheterization, the injection of contrast can still increase the LV end-diastolic filling pressure and alter afterload, modifying instantly the basal RF (*36*).

Of importance, the poor RF correlation between CATH and FPRNA (Table 1) reveals two patients with significant disagreement. The first patient (No. 18) had 2+ mitral insufficiency: the RF was 0 by CATH and 45% by FPRNA. The second patient (No. 15) had 4+ mitral insufficiency with a 24% RF by CATH and 56% by FPRNA.

Our method provides a reliable noninvasive determination of valvular regurgitation. In this study, there was a significant difference between the patients with severe 3+/4+ and with mild/moderate 1+/2+ regurgitations, and between the patients with grade 1+/2+ and the control patients. The results correlated also closely with experimental simulations ($r = 0.98$).

Compared to other radionuclide techniques, the RF is directly assessed without the need of any other hemodynamic parameters (cardiac output, LVEF, RVEF, etc). The limitations of this method are the other causes for prolonged LV transit times such as an intracardiac shunt, a prolonged pulmonary transit time, or a major wall motion abnormality leading to an overestimation of the regurgitation.

Repeated sequential RF evaluations can be performed using ultra-short lived radionuclides (^{195m}Au, half-life: 30 sec (*37*). This makes this measurement amenable for exercise or pharmacologic interventions.

We conclude that the proposed FPRNA method produces a satisfactory quantitative estimation of the severity of the regurgitation (aortic and mitral). The technique is simple, fast and reproducible, and allows detection of mild to severe regurgitation.

APPENDIX

An experimental pulsatile flow model was used to assess the accuracy of the lagged normal deconvolution and of the regurgitant fraction quantitation. The model consisted of an open circuit including a water reservoir (input), two parallel tubings, an elastic balloon, a pump, and a collecting reservoir. The pre-load was maintained constant in the input reservoir. The pulmonary resistance was simulated by a system of two parallel tubings. The LA was an elastic balloon. The pump was a physiologic pulsatile perfusion pump (Medical Engineering Consultants, Los Angeles, CA) with two plastic tricuspid valves simulating the aortic and mitral valves, allowing accurate adjustment of the pump rate and of the stroke volume.

The volumes were ~ 50 ml for the "lungs," 20–40 ml for the "left atrium," and 20 ml for the pump in end-diastole. In this experiment, the pump rate was 60/min and the total stroke volumes were 10 and 15 ml. The experimental valvular regurgitation was measured by comparing the effective output in the collecting reservoir with the total pump stroke volume.

With the model under the gamma camera, an injection of 2 mCi of [^{99m}Tc]pertechnetate (in a volume of 2 ml flushed by 10 ml) was performed in the tubing upstream to the "lungs." A list mode acquisition of 30–60 sec was then recorded into the computer.

Twelve experiments were acquired, including two acquisitions with competent valves and 10 with insufficient mitral valves. Five different levels of insufficiency were obtained by damaging the plastic tricuspid valve. These studies were processed using the same lagged normal deconvolution algorithm and the same RF quantitation as for the patients.

As the valvular insufficiency increased, the pump time-activity curve demonstrated a slower washout. We deconvolved the pump curve by the "pulmonary" curve to get the pump UIR. The more incompetent was the valve, the larger was the second component of the UIR (Fig. 6). The RF correlation between the computed value and the experimental measured value was r = 0.98, y = 0.96x −0.03, s.e.e. = 0.05. (Fig. 7).

This experiment has been set up to test the method for mitral insufficiency. The same model can be used for testing aortic insufficiency. Indeed, the consequence of the aortic regurgitation will be to delay again the washout of the pump activity when compared to the "pulmonary" activity, which would not be affected. For mitral insufficiency, the presence of a "left atrium" in the model is necessary to prevent backflow to the "lungs," this is not the case in aortic insufficiency.

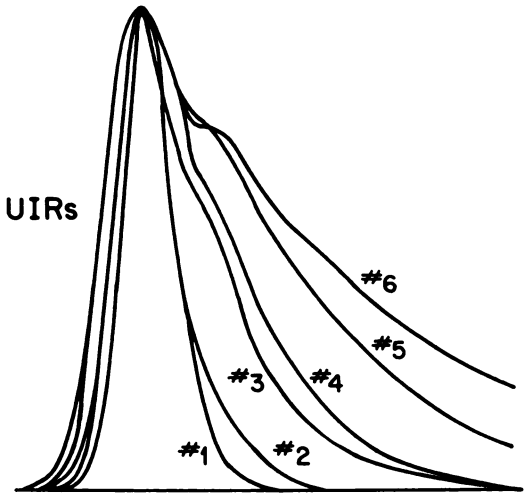

FIGURE 6
Superimposition of six-pump unit impulse responses (PUMP UIR) for different levels of regurgitation. The importance of the secondary component of the UIR increases with the severity of the regurgitation (Curves 1–6, with 6 equal to maximal regurgitation. The experimental values are displayed with the corresponding curve numbers, with two consecutive experiments for each level of insufficiency (see Table 4).

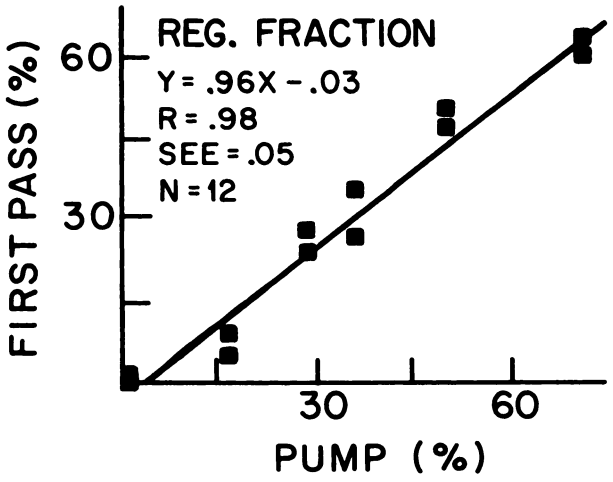

FIGURE 7
Correlation between the pump regurgitant fraction computed by the first-pass method (X-axis). There is excellent linear correlation with a regression line close to the identity line. (r = 0.98 and y = 0.96x − 0.03).

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