Transfer Function Analysis of the Ventricular Function: A New Method for Calculating Right Ventricular Ejection Fraction

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The relationship between the ventricular transfer function and ejection fraction has been investigated by the routine procedure of first-pass radionuclide angiocardiography. Ejection fraction has been shown to equal $1 - e^{-b}$, where b is the ratio of the R-R interval over the mean transit time difference between ventricular and atrial time-activity curves. To evaluate the effect of region of interest (ROI) on the right ventricular ejection fraction (RVEF), the results of the transfer function analysis (TFA) technique using precise ROI, TFA using rectangular ROI, and the routine method were compared. Regression analyses among RVEFs obtained from the above ROI methods yielded good correlations. Reliable RVEFs have been obtained even in the case of an improper bolus injection. Thus, the TFA technique is a new, simple, and reliable method for calculating RVEF without needing to outline the right ventricle precisely.

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First-pass radionuclide angiocardiography (FPRNA) is a clinically accepted procedure for calculating the ejection fraction (EF) that is the most widely used parameter for measuring cardiac function. However, FPRNA has been criticized for its poor counting statistics because of the generation of the ventricular time-activity curves (TACs) with a sampling interval of 0.03–0.07 sec. The difficulty in precisely outlining the ventricular boundary and the poor counting statistics lead to large inter- and intraobserver variations in the calculation of the EF. Therefore, an attempt was made to solve the above problems, using a simple mathematical model to analyze ventricular function. The relationship between the ventricular transfer function and the EF has been evaluated. It can be demonstrated that ventricular EF is equal to $1 - e^{-b}$, where b is the decay constant of the ventricular transfer function (in units of heart beat). In general, certain deconvolution procedures have to be applied in order to measure the ventricular transfer function. Further analysis from the convolution theory shows that the mean transit time technique can be undertaken instead. Computational complexity can be tremendously reduced. As we demonstrate in this paper, a precise region of interest (ROI) is not necessary for getting accurate results. The sampling time interval for TAC is ten to twenty times longer so that the counting statistics can be significantly improved. A portion of this work has been published earlier in abstract form (*1*).

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MATERIALS AND METHODS

Mathematical Basis of Transfer Function Analysis

The radionuclide transit of FPRNA can be formulated as a linear system (Fig. 1) where SVC = superior vena cava, RA = right atrium, RV = right ventricle, PA = pulmonary artery, LG = lung, LA = left atrium, LV = left ventricle, AO = aorta, and SC = systemic circulation. Suppose that the TAC of chamber j can be described by function f_j and the transfer function of chamber j is h_j, then $f_j = f_{j-1} * h_j$, where * denotes the convolution operator. Let us focus on the ventricular area for the moment:

$$f_v = f_a * h_v,$$

where f_v is the ventricular output function, f_a is the atrial output function, and h_v is the ventricular transfer function. Let F and F^{-1} be the Fourier transform and the inverse Fourier transform operators, respectively, then:

$$h_v = F^{-1}\left(\frac{F(f_v)}{F(f_a)}\right).$$

In other words, the transfer function can be calculated directly from the known input and output functions using the Fourier transform and inverse Fourier transform functions. In practice, unavoidable errors in the measured values of both the input and output functions can result in physically unreasonable values of the transfer function, e.g., negative values or rapid oscillatory behavior (*2*). Thus, indirect techniques are preferred (*3–5*). However, both approaches suffer from large computational complexities. Accordingly, we analyze the ven-

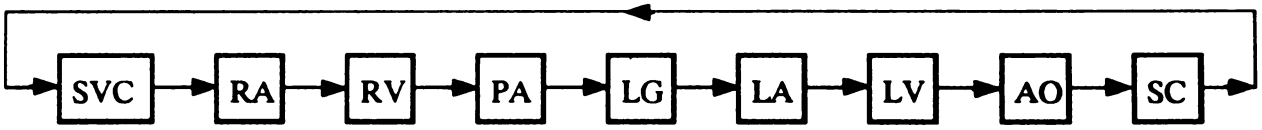

FIGURE 1
Linear system for transfer function analysis. See Materials and Methods for definitions.

tricular function from the physiologic point of view. Two circumstances of radionuclide input, as described below, are impulse response and a sequence of radionuclide input.

Impulse Response: An Instantaneous Radionuclide Input

In the first situation, we measure the variation for the remaining radioactivity in the ventricle after an instant injection with a quantity, Q, of radioactivity. Four assumptions are made here: (a) a constant EF k ($0 < k < 1$), (b) a constant end-diastolic volume (EDV), (c) injection at the end-diastolic instant, and (d) no radioactivity in the blood entering the right ventricle during the diastolic phase. In other words, the analysis is valid only before the recirculation occurs. Such a model is shown in Figure 2.

The quantity of radioactivity at any end-diastolic instant can be observed as follows:

$$Q_0 = Q,$$

$$Q_1 = Q_0(1 - k),$$

$$Q_2 = Q_1(1 - k),$$

$$\ldots$$

$$Q_i = Q_{i-1}(1 - k).$$

Thus, the quantity of the remaining radioactivity at the i-th end-diastolic time instant after the injection is:

$$\begin{aligned} Q &= Q_{i-1}(1 - k) \\ &= Q(1 - k)^i \\ &= Qe^{-ib}, \end{aligned}$$

where $b = \ln(1/1 - k) > 0$. As a result, it can be observed that the ventricular transfer function follows a simple exponential decay and the decay constant b equals $\ln(1/1 - k)$. The EF k is then equal to $1 - e^{-b}$.

A Sequence of Radionuclide Input [I_i]

In the second situation, the assumptions are made as follows: (a) a constant EF k, (b) a constant EDV, (c) no time delay between the ventricular and atrial functions, and (d) the atrial function as a discrete time sequence I_i. The subscript i is counted in number of heart beats. The radioactivity measured at the end-diastolic instant of each heart beat can then be expressed as follows:

$$Q_0 = I_0,$$

$$Q_1 = Q_0(1 - k) + I_1,$$

$$Q_2 = Q_1(1 - k) + I_2,$$

$$\ldots$$

$$Q_i = Q_{i-1}(1 - k) + I_i.$$

Thus, the quantity of the remaining radioactivity at the i-th beat is:

$$\begin{aligned} Q_i &= Q_{i-1}(1 - k) + I_i \\ &= I_0(1 - k)^i + I_1(1 - k)^{i-1} + \ldots + I_i \\ &= \sum_{j=0}^{i} I_j(1 - k)^{i-j}. \end{aligned}$$

As we initially suggested, the ventricular function is equal to the convolution of the atrial function and a transfer function h. Using the discrete notation, $h_i = (1 - k)^i = e^{-i\ln(1/1-k)}$. Again, the ventricular transfer function follows a simple exponential decay and the decay constant b equals $\ln(1/1 - k)$. The EF k also equals $1 - e^{-b}$ as is the case with the impulse response condition.

Methods of Calculating Right Ventricular Ejection Fraction

Ninety-five patients with good bolus injection, i.e., the mean transit time of the superior vena cava being <4 sec, were randomly chosen from the routine FPRNA study. In our laboratory, the routine FPRNA procedure was modified from that of Jengo et al. (*18*). Data were acquired in list mode using right anterior oblique projection for 33 sec after intravenous injection of 20 mCi of technetium-99m-pertechnetate. Patients were divided into 2 groups. One study with 50 patients was done by linking a digital camera (Elscint APEX 410, Haifa, Israel) to a minicomputer (Informatek Simis 5, Buc, France), and the other with 45 patients was performed by linking an analog camera (Pho Gamma IV) to another minicomputer (Informatek Simis 3). For the routine procedure, list mode data were reframed into one second images and the representative images for right heart, lung and left heart were chosen. Regions of interest were then manually defined. As in the left ventricular phase, right ventricular TAC was generated in units of 40-msec time intervals. The right ventricular ejection fraction (RVEF) was calculated by averaging 2 to 3 peak-valley pairs chosen from the right ventricular TAC as suggested by Jengo et al. (*18*).

For comparison, a rectangular ROI was placed within the right ventricular area in addition to the routine precise ROI.

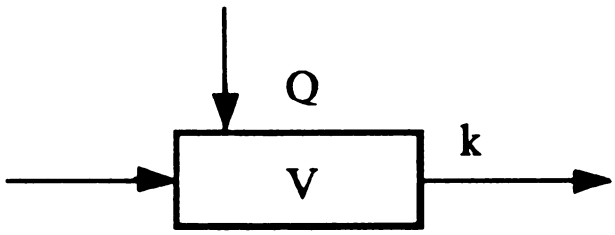

FIGURE 2
A transfer function analysis model for impulse response.

The TACs generated from the ROIs were gamma fitted to get rid of nontarget activities. The gamma fitted TACs were treated as the function of right atrium and ventricle. The mean transit times of the gamma fitted curves were then measured and the EFs were calculated from the equation described earlier in this section. The sampling interval of TACs was equal to the R-R interval, the atrial TAC was generated by a time delay of a fraction of the R-R interval, i.e., the interval of the diastolic phase, and the ventricular transfer function was described by the simple exponential decay function with decay constant b and the EF equal to $1 - e^{-b}$. The decay constant can be obtained by an exponential fit of the transfer function solved by the deconvolution technique. However, the direct solution using Fourier transform has some practical difficulties (*2*). Accordingly, we solve the problem in another way. According to the convolution theory, it can be proved that, if $g = f * h$, then $MTT(g) = MTT(f) + MTT(h)$, where MTT(g) is the mean transit time of the function g. It can also be proved that, if $h = ae^{-bt}$, then $MTT(h) = 1/b$. Since the TACs of both atrium and ventricle are known, calculation of mean transit times can be easily obtained (*8,9*). As a result, the decay constant of the ventricular transfer function can be expressed as R-R interval/MTT(h) where the R-R interval and MTT(h) were all counted in units of seconds.

RESULTS

In the experiment, the RVEF from the "precise" ROI method was compared with that from the routine manual first-pass (MFP) method. The correlation coefficient was 0.91 for the digital camera group and 0.90 for the analog camera group. The correlation coefficients of RVEF from the "rectangular" ROI method and from the MFP procedure were all 0.90 for both groups. There were high correlations between the "rectangular" ROI method and the "precise" ROI method with r = 0.96 and 0.98 for the digital and analog groups, respectively. The regression plots of the above relationships for the digital group are shown in Figure 3 and those for the analog group are illustrated in Figure 4. After the determination of the transfer function, it could be reconvolved with the gamma fitted atrial curve. The reconvolved curve was then compared with the gamma fitted ventricular curve. An example is shown in Figure 5.

In addition, seven patients with both rapid and slow injections were studied to show the effect of injection rate on the results. The results are shown in Table 1. Poor correlation (r = 0.58, s.e.e. = 12.8) between both rapid and slow injections was found for MFP method whereas good correlations were obtained for both TFA methods (r = 0.98, s.e.e. = 0.30 for precise ROI TFA method and r = 0.98, s.e.e. = 0.26 for rectangular ROI TFA method).

DISCUSSION

The use of the low frequency isotope dilution curve in calculating the RVEF has been described by other authors (*6,7,15–17*). Their analyses have focused on the down slope of the right ventricular time-activity curve (RV TAC), and the results depend on the quality of the bolus injection. A deconvolution process was recommended in their procedures for a poor bolus injection since their model could be applied to the ideal situation only, namely, the impulse response condition. In contrast, RVEF was calculated from the transfer function instead of the RV TAC in our study. Accordingly, RVEFs, as shown in Table 1, are relatively independent of the bolus injection since the deconvolution effect is embedded in the transfer function analysis technique. Glass et al. (*15,16*) used down slope transfer function analysis for calculating left ventricular ejection fraction (LVEF). The deconvolution process is done with Fourier and/or Laplace transforms. Their model uses pulmonary TAC as input which is not adequate in our model. As for the compartmental model described by Konstantinow et al. (*13*), there is delay and spread factor for tracer in each compartment. If the input for the ventricular function is not atrial TAC, MTT difference will be relatively increased with a resultant underestimation of the EF. Villanueva-Meyer et al. (*17*) also

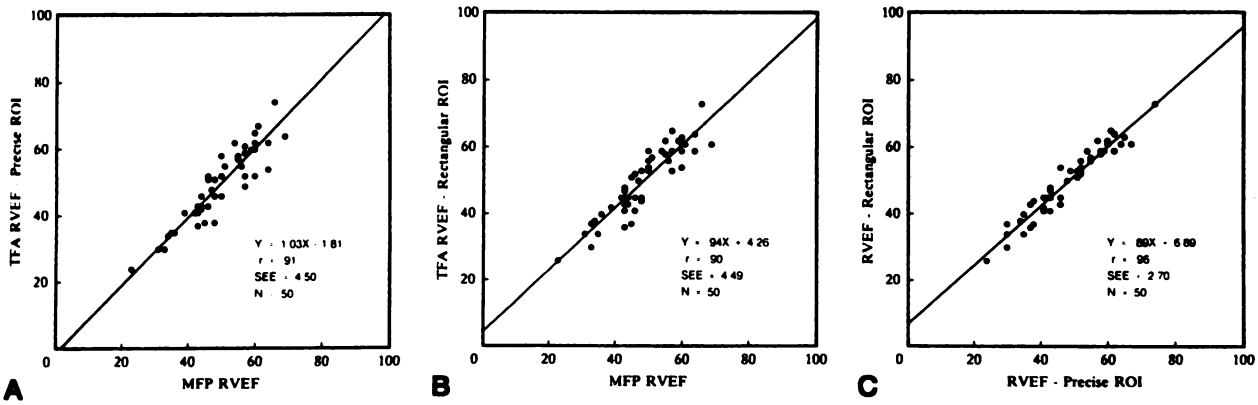

FIGURE 3
Correlations of digital camera group between RVEF as calculated from (A) TFA precise ROI method and routine MFP ROI method, (B) TFA rectangular ROI and MFP ROI, and (C) both TFA ROIs.

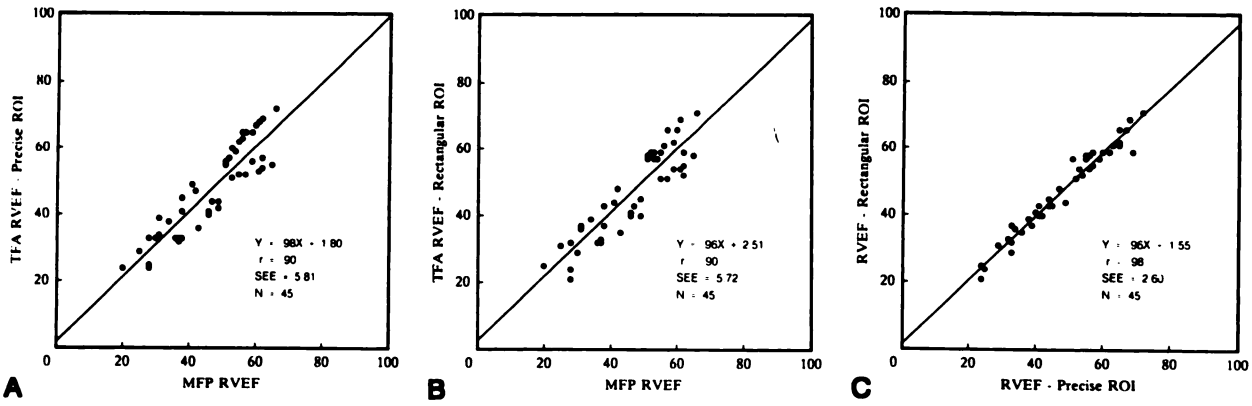

FIGURE 4
Correlations of analog camera group between RVEFs as calculated from (A) TFA precise ROI method and routine MFP ROI method, (B) TFA rectangular ROI and MFP ROI, and (C) both TFA ROIs.

chose the ideal case as their model, using the superior vena cava TAC as input and pulmonary artery TAC as output. The use of pulmonary TAC as output function is not adequate in our model since the pulmonary TAC includes the transfer function of pulmonary artery, which will increase the MTT difference between input and output functions and result in the underestimation of the EF.

From the results shown in the previous section, there is a good correlation in RVEFs between the procedures of the transfer function analysis technique and the routine procedure. The advantages gained from this technique include ROI independence, good sampling statistics, simplicity, and reliable results. No obvious discrepancy in RVEF occurs between the two methods with the precise ROI and the rectangular ROI, respectively, as evidenced by their high correlation (r = 0.96 and 0.98 for the digital and analog groups, respectively). Since the procedure for gamma fitting has been automated, the good correlation here means low inter- and intraobserver variations. With this technique, the criticism of low count rate in the FPRNA study can be avoided because the sampling time of TACs is about 10–20 times longer than that used routinely. Furthermore, no significant difference exists between the use of the digital cameras and analog cameras. A similar conclusion has been obtained by Aswegen et al. (*6*). Pitfalls of the inverse Fourier transform for deconvolution can be avoided also because it is not necessary to consider the effect of time delay between the ventricular and atrial functions in the MTT technique. The sampling time interval is not restricted to the R-R

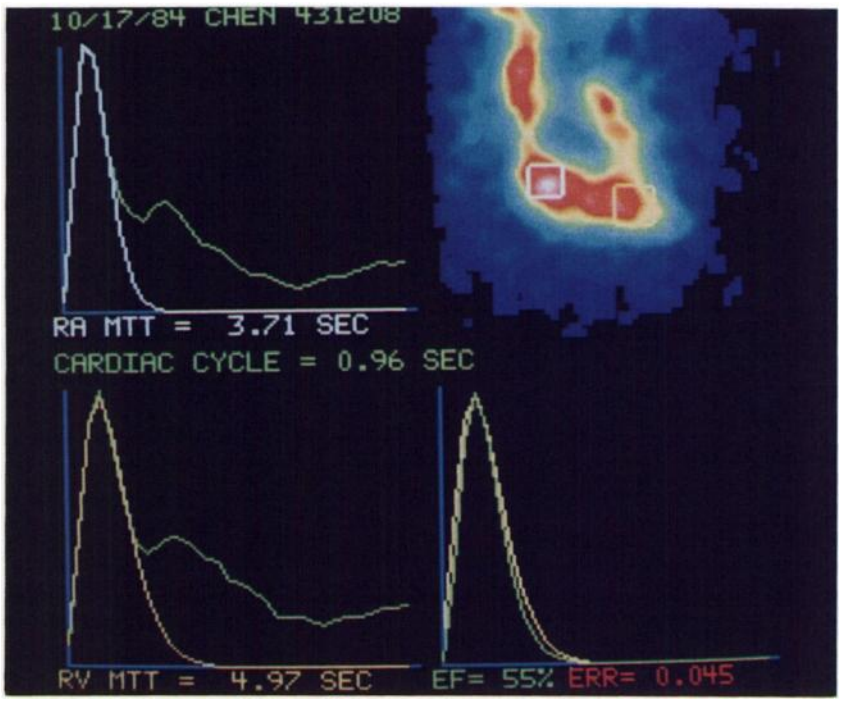

FIGURE 5
Example of transfer function analysis of RVEF. Atrial TAC on upper-left quadrant and ventricular TAC on lower-left quadrant are gamma fitted. One-second image and ROIs drawn are shown on upper-right quadrant. Atrial TAC is reconvolved (displayed in green) and compared with ventricular TAC (in yellow) on lower-right quadrant.

TABLE 1
Effect of Injection on Results of RVEFs Obtained from MFP, TFA Precise ROI, and TFA Rectangular ROI Methods

	1st injection				2nd injection			
Patient	SMTT*	EF1†	EF2‡	EF3§	SMTT*	EF1†	EF2‡	EF3§
1	1.9	23	26	25	4.9	33	29	27
2	2.8	55	50	51	4.1	54	52	52
3	2.4	43	49	53	5.1	27	46	47
4	2.7	22	20	21	9.9	37	22	24
5	3.4	40	38	36	23.1	56	42	37
6	1.7	45	46	50	4.9	46	43	49
7	3.4	55	58	54	4.5	45	60	53

* SMTT = mean transit time of SVC.
† EF1 = RVEF from MFP procedure, r = 0.51 between injections, s.e.e. = 12.8.
‡ EF2 = RVEF from TFA precise ROI method, r = 0.98, s.e.e. = 3.0.
§ EF3 = RVEF from TFA rectangular ROI method, r = 0.98, s.e.e. = 2.6.

interval either. This makes the algorithm fairly simple. The reliable results as shown in Table 1 can be obtained for some cases of the prolonged bolus injection. If the bolus has more than one peak, the result of the current method is not satisfactory either. The results would be similar to those obtained by deconvolution techniques (*10–12*).

Of course, two problems can occur with the current procedure. First, the gamma fitting technique cannot remove nontarget activities; second, the current procedure does not work for patients with severe valvular disease because of the incorrect curve fitting. To overcome the effect of overlapping in organs, the algorithm described by Konstantinow et al. (*13*) could be helpful. It eliminates crosstalk iteratively. Factor analysis technique (*14*) could be another choice, but it is difficult to distinguish the ventricular activities from the atrial activities. Inadequate mixing of the radionuclide bolus with blood introduces a potential source of error for calculating RVEF (*19*). Although such an effect hinders the homogeneous mixing assumption of our model and other washout models, clinical experience has shown the feasibility and usefulness of the transfer function analysis in the assessment of RVEF (*6,7,15–17*).

In theory, the current analysis should work for the left heart. However, some practical difficulties do exist. In the right anterior oblique projection used by FPRNA routinely, the ROI of the left atrium cannot be reliably drawn. The use of pulmonary TAC, as discussed above, is not adequate for the estimation of LVEF. Furthermore, the background factor is greater in the left heart than in the right heart. Thus, the validity of applying this technique to the determination of LVEF needs further investigation. Such an investigation is now in progress in our laboratory.

In conclusion, the transfer function analysis technique is a new, simple, and reliable method for calculating RVEF, in which RVEF is not dependent on accurate ROI and a good bolus injection.

REFERENCES

1. Wu LC, Yeh SH, Chen Z, et al. Transfer function analysis of ventricular function: a new method for the calculation of right ventricular ejection fraction. *J Nucl Med* 1985; 26:P73–P74.
2. Gamel J, Rousseau WF, Katholi CR, et al. Pitfalls in digital computation of the impulse response of vascular beds from indicator-dilution curves. *Circ Res* 1973; 32:516–523.
3. Kuruc A, Caldicott WJH, Treves S. An improved deconvolution technique for the calculation of renal retention functions. *Comput Biomed Res* 1982; 15:46–56.
4. Knopp TJ, Dobbs WA, Greenleaf JF, et al. Transcoronary intra-vascular transport functions obtained via a stable deconvolution technique. *Ann Biomed Eng* 1976; 4:44–59.
5. Nakai M. Computation of transport function using multiple regression analysis. *Am J Physiol* 1981; 240:H133–H144.
6. Aswegen AV, Herbst CP, Otto AC, et al. Determination of right ventricular ejection fraction utilising a radionuclide washout technique. *Eur J Nucl Med* 1983; 8:477–481.
7. Taki J, Shiire Y, Bunko H, et al. Determination of right ventricular ejection fraction using first transit clearance technique. *Jpn J Nucl Med* 1986; 23:221–225.
8. Oldendorf WH. Measurement of mean transit time of cerebral circulation by external detection of an intravenously injected radioisotope. *J Nucl Med* 1962; 3:381–398.
9. Maseri A, Caldini P, Permutt S, et al. Frequency function of transit times through dog pulmonary circulation. *Circ Res* 1970; 26:527–543.
10. Alderson PO, Douglass KH, Mendenhall KG, et al. Deconvolution analysis in radionuclide quantitation of left-to-right cardiac shunts. *J Nucl Med* 1979; 20:502–506.
11. Ham HR, Dobbeleir A, Viart P, et al. Radionuclide quantitation of left-to-right cardiac shunts using deconvolution analysis. *J Nucl Med* 1981; 22:688–692.
12. Brendel AJ, Commenges D, Salamon R, et al. Deconvolution analysis of radionuclide angiocardiography curves. Problems arising from fragmented bolus injections. *Eur J Nucl Med* 1983; 8:93–98.
13. Konstantinow G, Pizer SM, Jones RH. Decontamination of time-activity curves in first-pass radionuclide angiocardiography. In: Esser PD, ed. *Emission computed tomography: current trends.* New York: The Society of Nuclear Medicine; 1983:251–262.
14. Di Paola R, Bazin JP, Aubry F, et al. Handling of dynamic sequences in nuclear medicine. *IEEE Trans Nucl Sci* 1982; 29:1310–1321.
15. Glass EC, Cohon HA, Mena I. Deconvolution of first-pass

radionuclide angiograms for determination of forward ejection fraction. *Am J Cardiol* 1982; 49:1032.
16. Glass EC, Cohon HA, Berens SC, et al. Functional evaluation of left heart by first-pass deconvolution analysis. *J Nucl Med* 1982; 23:P79.
17. Villanueva-Meyer J, Darcourt J, Philippe I, et al. Measurement of right ventricular ejection fraction in myocardial infarction by means of transfer function analysis. *J Nucl Med* 1986; 27:968.
1986; 27:968.
18. Jengo JA, Mena I, Blanfuss A, et al. Evaluation of left ventricular function (ejection fraction and segmental wall motion) by single pass radioisotope angiography. *Circulation* 1978; 57:326–332.
19. Wackers FJ. First-pass radionuclide angiocardiography. In: Gerson MC, ed. *Cardiac nuclear medicine.* New York: McGraw-Hill Book Co.; 1987:53–66.