First-Third Ejection Fraction: Is the First-Pass Radionuclide Method Accurate?

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Previous reports have suggested that left ventricular first-third ejection fraction (EF) can be obtained from the left ventricular time-activity curve derived from first-pass radionuclide angiography based on Anger camera data. The validity of this technique was assessed by: (a) a study of beat-to-beat variations in data from 15 patients in which electrocardiographic data were simultaneously recorded, and (b) a computer simulation incorporating the application of Poisson statistics to appropriate count rate data. The results of patient studies showed no consistent trend in any first-third parameter obtained from consecutive beats in individual subjects, and unacceptably high statistical uncertainty in the calculation of the first-third ejection fraction. The weighted standard deviation of the first-third ejection fraction in each of 15 patients studied averaged 7.5 EF units, while first-third ejection fraction averaged 22.9 EF units. The relative error averaged 32%. The computer simulation indicated a high relative error of 47% associated with the first-third ejection fraction at typical end-diastolic count rates of 200 per frame from 1,000 computer Poisson randomizations of an appropriate analog volume curve. The results render the first-pass radiocardiographic method invalid for determining first-third ejection fraction.

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Accurate assessment of cardiac function is a critically important task in the evaluation and management of patients with apparent or suspected cardiac disease. Although there is no absolute hemodynamic or mechanical measurement of contractility, ejection phase indices have been proposed as capable of detecting depressed contractility in the basal state, and as being preferable to isovolumic phase indices. Even though ejection phase indices are markedly influenced by acute changes in afterload, they are believed to be the most reliable and sensitive indices of changes in contractility (*1*).

These considerations prompted the study of the first-third ejection fraction by Johnson (*2*) and later by Slutsky (*3*) using contrast angiography. They demonstrated that the first-third ejection fraction at rest showed subtle abnormalities of left ventricular function in patients with coronary artery disease (CAD), and accurately predicted significant coronary stenoses, which were not recognized by holosystolic ejection fraction alone. More recently, Slutsky (4–6) developed another method to obtain first-third ejection fraction using first-pass radionuclide angiography, and demonstrated a high correlation between first-third ejection fractions calculated from high frequency time-activity curves and from contrast angiography in the same patients. In their series, the radionuclide method also identified subtle abnormalities of left ventricular function at rest in more than 90% of patients with proven CAD with normal ejection phase parameters, including holosystolic ejection fraction, obtained by conventional contrast angiography (*4*). However, there are two major potential limitations to the use of the high frequency, left ventricular time-activity curve, particularly as they affect the credibility of first-third ejection fraction calculations. The first derives from Poisson counting errors, and the second from the lack of total and constant identification of the signal with true left ventricular volume variations. By considering these limitations, the present work addresses the potential limits of accuracy of radionuclide determinations of the first-third ejection fraction.

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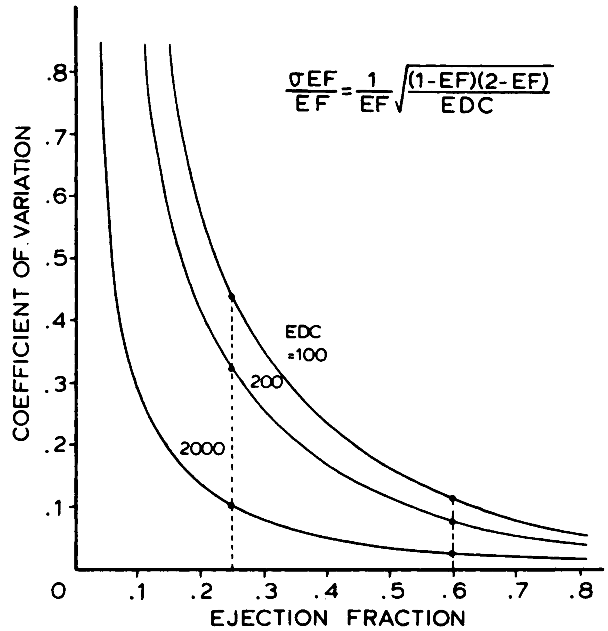

FIGURE 1
Influence of Poisson counting errors on uncertainty of calculated ejection fraction at different count rates (for abbreviation, see text)

Theoretical considerations

The statistical variance from Poisson counting errors associated with the total count within any time interval is equal to that count itself, assuming that data in the interval is not correlated with that of other intervals (note that temporal smoothing or filtering correlates data with that of other intervals). Since the ejection fraction (EF) may be derived from end-diastolic counts (EDC) and end-systolic counts (ESC), the variance associated with ejection fraction may also be determined from these counts:

$$V_{EF} = \left(\frac{\delta_{EF}}{\delta_{EDC}}\right)^2 \times V_{EDC} + \left(\frac{\delta_{EF}}{\delta_{ESC}}\right)^2 \times V_{ESC}$$

where V_{EF}, V_{EDC}, and V_{ESC} are the variances associated with EF, EDC, and ESC, respectively. Allowing only for Poisson counting errors, the variance associated with EDC and ESC may be set equal to these counts themselves. The variance thus associated with ejection fraction has a simple mathematical form when expressed in terms of ejection fraction and end-diastolic counts:

$$V_{EF} = \frac{(1 - EF)(2 - EF)}{EDC}.$$

The coefficient of variation associated with ejection fraction is expressed as

$$\frac{\sigma_{EF}}{EF} = \frac{1}{EF}\sqrt{\frac{(1 - EF)(2 - EF)}{EDC}}$$

where σ_{EF} is the standard deviation associated with ejection fraction (7). The same equations are applicable when first-third ejection fraction is substituted for holosystolic ejection fraction.

Figure 1 is a parametric graph of the uncertainty of calculated ejection fraction due to counting statistics alone, at different end-diastolic count rates for uncorrelated (unfiltered) data. A relative error of 9% or 5 EF units is shown for 60% ejection fraction at an end-diastolic count rate of 200 per 40 msec (typical of our technique, using a dose of 20 mCi for 70 kg). From the same curve, a 32% relative error or 8 EF units is associated with either a 25% holosystolic or a 25% first-third ejection fraction at the same end-diastolic count rate of 200. In contrast, when the end-diastolic count rate is 2,000 per 40 msec (typical of a multicrystal camera), a first-third ejection fraction of 25% is associated with a relative error of 10% or 3 EF units. The relative error increases as either end-diastolic count rate or ejection fraction decreases. Thus, at an end-diastolic count rate of 100/40 msec, a 25% first-third ejection fraction is associated with a relative error of 46% or 11 EF units. These calculated statistical uncertainties are obtained without consideration of the necessary background corrections; therefore, actual errors may be significantly higher.

The raw data (Fig. 2, top) of a typical 40 msec

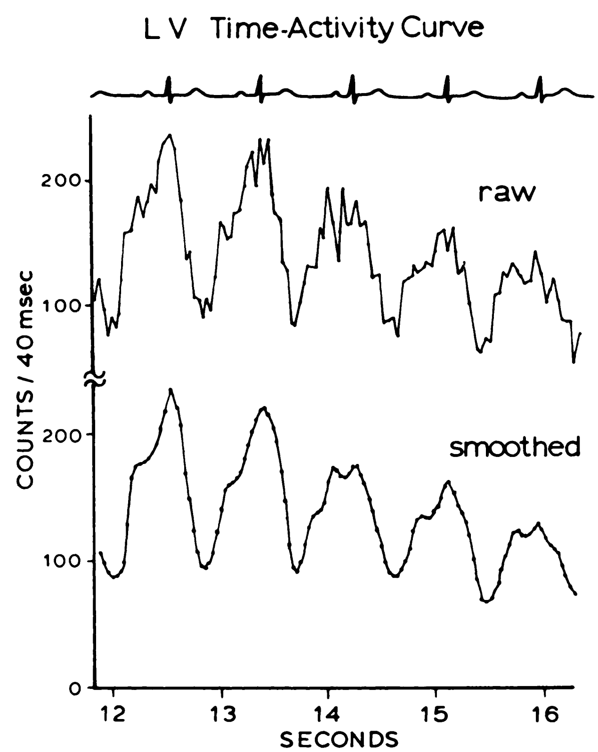

FIGURE 2
Left ventricular time-activity curve without statistical smoothing or filtering (top) and with Fourier filtering (bottom)

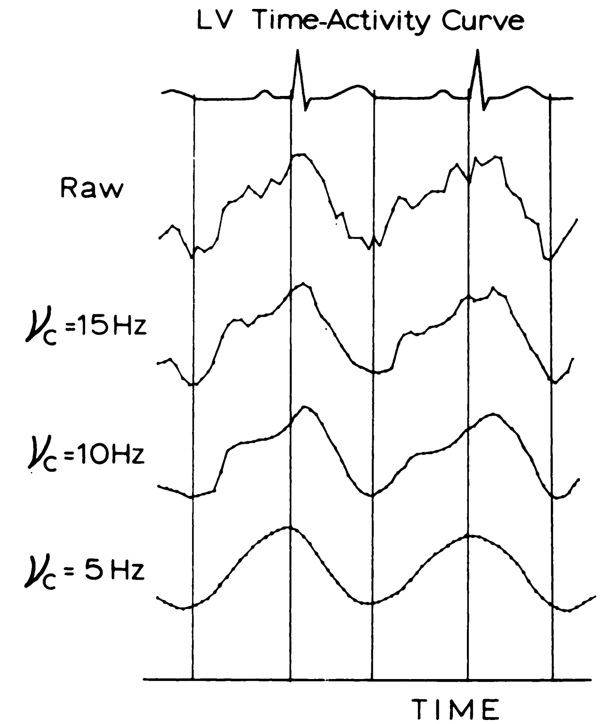

FIGURE 3
Left ventricular time-activity curve without filtering and with different Fourier filtering (at cutoff frequency of 15 Hz, 10 Hz, and 5 Hz). Slightly different filtering frequency results in varying end-interval time points. ν_c is cutoff frequency

framing of the left ventricular time-activity curve with no statistical smoothing or filtering, obtained from a normal subject, shows that the exact time points for diastole and systole cannot be consistently defined due to high statistical noise. The uncertainty in the actual count rate at each frame may be reduced by the application of a digital filter as seen at the bottom of Fig. 2. For example, the application of least-squares five-point quadratic smoothing will reduce the coefficient of variation of the count rate at each frame by $\sim\sqrt{2}$. However, another problem becomes apparent with the introduction of filtering, namely, the lack of precision with which times of maxima and minima may be defined. This is demonstrated in Fig. 3, in which the application of the same Fourier filtering technique with different roll off frequencies causes an apparent variation of end-diastolic and end-systolic time points. Such subtle changes of end-interval time points may cause significant errors in the calculation of the first-third ejection fraction. This error depends upon the slope of the volume curve at the time of first-third ejection, and is greater with increasing first-third ejection fraction. Figure 4 demonstrates such a significant change in the calculated first-third ejection fraction with a slight change only in the choice of the end-diastolic time point.

Another problem arises from the framing rate. At a heart rate of 75/min, systole is typically composed of eight to ten 40 msec frames, while first-third ejection time is composed of only two to four frames. For this reason, the approximation of either a neighboring or interpolated data point is required at the first-third ejection time. Obviously this problem is more severe at higher heart rates. However, significantly faster framing rates cannot be accomodated with an Anger camera because of the attendant increase of relative Poisson counting errors. Even when several consecutive beats are averaged for this calculation, the statistical errors are reduced only by the square root of the number of beats.

Indeed, these limitations of low count rate led Schelbert to create the root-mean-square method to determine the holosystolic ejection fraction, utilizing count data available throughout the cardiac cycle, rather than simply at the beginning and end of the ejection intervals (*8*).

Given these theoretical considerations, we questioned the precision with which first-pass radionuclide data, at count rates available using an Anger camera with standard collimation, could indicate the times of volume inflections, and whether this precision is sufficient to determine the first-third ejection fraction. Accordingly,

1. In 15 patients, we analyzed the first-third ejection

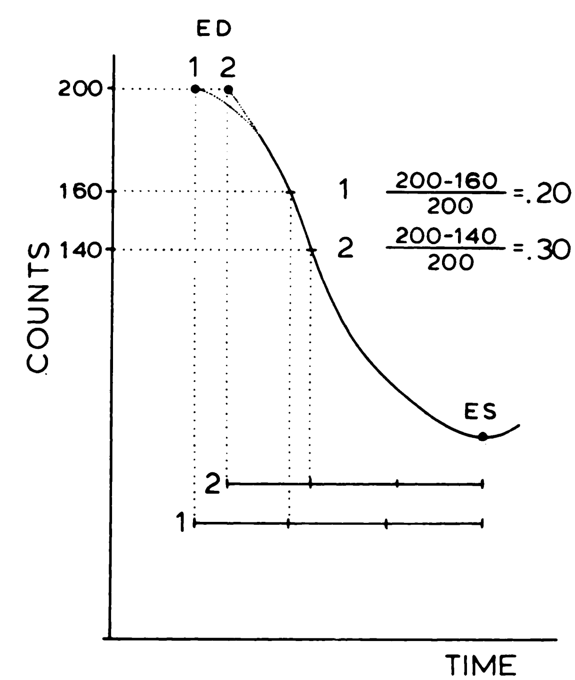

FIGURE 4
Graphic demonstration of significant difference in calculated first-third ejection fraction induced by slightly different choice of end-diastolic (ED) time points (from 0.20 to 0.30)

fraction using a radionuclide technique similar to that of Slutsky (*4*), but with the addition of simultaneous digital recording of the electrocardiogram for precise timing.

2. We developed a computer simulation to study the statistical errors introduced by the laws of radionuclide decay.

MATERIALS AND METHODS

Radionuclide angiography

Fifteen patients with ejection fraction greater than 50% (range 50 to 81%), with sinus rhythm and normal intraventricular conduction were selected retrospectively from our routine clinical data. These patients consisted of eight men and seven women with a mean age of 60 ± 12 yr (range 32–76 yr); eight patients had ischemic heart disease, two had valvular heart disease, one was hypertensive, and four were normal.

First-pass radionuclide angiography was accomplished with the patient supine in the 30° right anterior oblique position under a mobile single crystal scintillation camera equipped with a low-energy, general purpose, parallel-hole collimator. Fifteen to 25 mCi of technetium-99m human serum albumin, dissolved in less than 1 ml of normal saline, was injected into an external jugular vein and flushed with 10 ml of normal saline. Data was collected in list mode (reaching a typical maximal average count rate of 35,000 cps) on a dedicated computer as the bolus of radionuclide traversed the central circulation. In our method, the complete electrocardiogram is acquired at 10 msec intervals together with the isotopic data.

Time-activity curves, at 25 frames per sec, were derived from manually defined regions of interest, one for the left ventricle, and one for a horseshoe shaped background surrounding the left ventricle (typical maximum net LV counts was of the order of 200 counts per 40 msec, and ranged from 70 to 340 counts per 40 msec). The left ventricular time-activity curve was Fourier filtered (*9*) to exclude frequencies higher than a roll off frequency beginning at 10 Hz (Fig. 2). Holosystolic ejection fraction was calculated from the first two or three beats following the left ventricular peak using Schelbert's root-mean-square method (*8*). First-third ejection fraction was calculated on a beat-by-beat basis. To avoid beats when the time-activity curve did not sufficiently represent volume variation, owing to inadequate mixing or crosstalk contamination, the four consecutive beats following the left ventricular peak were used. As proposed by Slutsky, the end-diastolic time point was chosen at the count peak just before ejection, and the end-systolic time point was chosen at the subsequent nadir. Ejection time, defined as the intervening interval, was divided into thirds, and first-third ejection fraction was evaluated from counts at end-diastole and at the end of the first third of the ejection interval:

$$\text{First-third EF} = \frac{\text{EDC} - 1/3\ \text{ETC}}{\text{EDC}}$$

where EDC is the background corrected end-diastolic count rate, and 1/3 ETC is the background corrected count rate at the first third of ejection time (Fig. 5). The interval from the onset of the R-wave of the electrocardiogram to the apparent end-diastolic time point was measured from the time-activity curve and the simultaneously recorded electrocardiogram (Fig. 5).

Computer simulation study

To evaluate the first-third ejection fraction using radionuclide first-pass time-activity curve data, and to study in detail the effect of frame time on the evaluation of first-third ejection volume, a computer simulation was developed to introduce Poisson counting errors. A typical analog left ventricular volume curve, having a total ejection fraction of 64% and a first-third ejection fraction of 24% at heart rate of 75/min was obtained from angiographic data of a normal subject. This analog data was sampled cumulatively by the computer over 40 msec intervals and normalized to various count

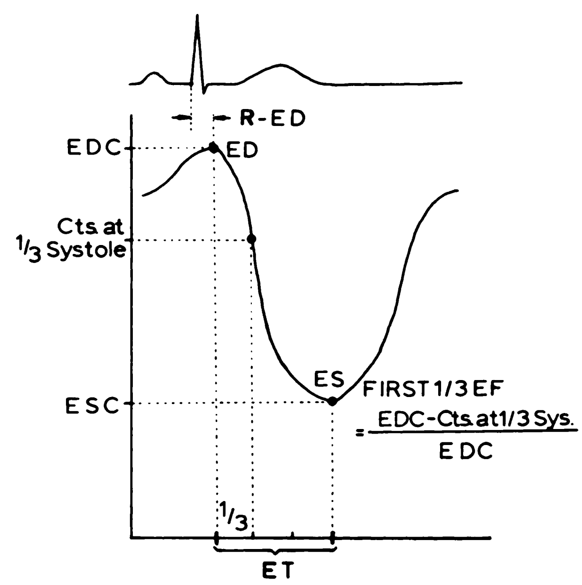

FIGURE 5
Schematic demonstration of measurement of first-third ejection fraction. Representative time-activity curve of left ventricle is shown with reference of electrocardiogram. Peak before ejection is chosen as end-diastole (ED) and nadir is chosen as end-systole (ES). Intervening interval of these two points is defined as ejection time (ET) and is divided into thirds. First-third ejection fraction is derived from counts at ED and at first third of systole. Interval between onset of R-wave and time of the apparent ED is measured as R-ED time (cts = counts)

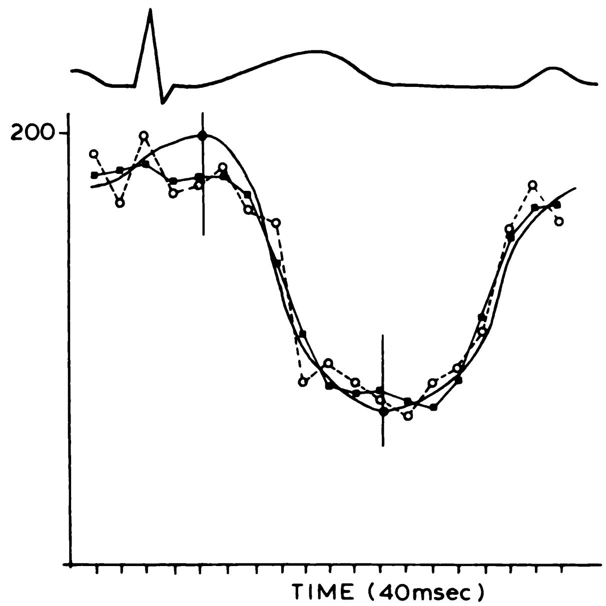

FIGURE 6
Overlay of curves of simulated analog volume curve from angiographic data (—), Poisson randomized curve after quantization (- O -), and Fourier filtered curve of randomized data (- ■ -). Two vertical lines indicate end-diastolic and end-systolic time points derived from angiographic analog volume curve. These points are used as ED and ES times

rates. Random Poisson counting errors were applied to each interval count using random numbers selected from a normal distribution centered about zero and having a standard deviation (s.d.) equal to the square root of that count, i.e.,

$$C_p = C_o + R \cdot C_o^{1/2}$$

where C_p is the Poisson-distorted count, C_o is the initial interval count, and R is a normally distributed random number with a mean of zero and s.d. of unity (*10*). This Poisson-altered left ventricular time-activity curve was Fourier filtered (*9*) as in usual processing of first-pass data by our technique as discussed above. From this filtered curve, end-interval time points were chosen at maximum and minimum data values in the cycle (max/min criterion). Additionally, end-interval time points were chosen at the end-diastole (ED) and end-systole (ES) indicated by the analog data of the original curve (fixed ED/ES criterion) (Fig. 6). First-third ejection fraction was calculated from counts at these end-diastolic time points and at the derived ends of the first third of systole. The mean, s.d., and coefficient of variation of first-third ejection fractions, and the distribution of end-interval time points, were obtained from 1,000 such single beat randomizations at different assumed end-diastolic counts of 200, 400, 1,000, 2,000, 4,000, and 8,000.

RESULTS

Radionuclide angiography

The results in the 15 patients are listed in Table 1. Heart rate averaged 72/min and total ejection fraction averaged 70%.

The interval from the onset of the R-wave to apparent end-diastole was very variable in consecutive beats, and ranged from minus 60 to plus 140 msec in all patients; the apparent end-diastolic time point preceded the R-wave in 11 of 60 beats, and coincided in 16. Further, there was no consistent trend for consecutive beats in individual patients. Lacking a definitive reference in the electrocardiogram, end systole was not examined. Apparent ejection time, the interval between end-diastolic and end-systolic time points, also varied widely from beat to beat in individual patients. The largest interbeat variation in the R to end-diastole interval in each patient averaged over 100 msec. Given the 10 msec framing rate of the EKG and the 40 msec framing rate of radionuclide data, a maximum variation of 40 msec would be expected on the basis of sampling error.

Calculated first-third ejection fraction showed very significant interbeat variation for the fifteen patients studied. As shown above, the variance of first-third ejection fraction is inversely proportional to the end-diastolic count. The four-beat weighted s.d. derived from each of the 15 patients averaged 7.5 EF units, while first-third ejection fraction averaged 22.9 EF units. The relative error averaged 32%. Note that this refers to the interbeat precision achievable from such a first-pass analysis and not to the estimate of first-third ejection fraction as the average result of four beats for an individual patient. This precision is expressed as the standard error of the mean (s.e.m.), in this example averaging 3.8 EF units. Since no "gold standard" was available for these patients, no comparisons of these estimates were possible. The computer simulation discussed below was thus used to assess the accuracy of these determinations.

Further, as a practical problem, 15 of 60, or 25% of end-diastolic time points, and six of 60, or 10% of end-systolic time points were difficult to determine due to double peaks or double nadirs as typified in Fig. 7.

Computer simulation study

Figure 8 shows the relative errors associated with first-third ejection fraction calculated from a single beat at varying end-diastolic count rates for the two different end-interval time point selection criteria.

When end-interval time points were selected by the fixed ED/ES criterion, where only Poisson counting errors are encountered, first-third ejection fraction was associated with high statistical error at typical Anger

TABLE 1
Heart Rate, Holosystolic Ejection Fraction, R-Wave to End-Diastolic Time, Ejection Time, and First-Third Ejection Fraction in Individual Subjects, in Four Consecutive Cardiac Cycles

Patient no.	HR*/min	EF%	R-ED† (msec) 1	2	3	4	ET‡ (msec) 1	2	3	4	1/3 EF%¶§ 1	2	3	4
1	57	81	0	60	70	80	380	330	340	400	21	14	35	32
2	81	66	50	100	0	40	270	270	300	350	23	25	22	25
3	52	71	0	20	−60	110	400	400	500	280	22	21	13	28
4	69	71	80	40	60	120	350	350	280	230	43	31	14	10
5	57	79	−60	110	20	20	430	370	350	460	21	50	18	31
6	58	61	0	0	90	−60	400	350	330	460	20	9	16	13
7	107	81	0	0	0	0	290	230	260	290	28	39	35	45
8	72	77	0	140	−30	120	370	290	340	180	16	26	20	15
9	79	62	40	0	0	−20	300	340	340	400	22	9	23	33
10	58	50	40	40	30	60	390	310	340	310	14	26	28	25
11	93	65	70	−30	60	110	170	250	170	340	11	9	17	29
12	76	79	0	−40	40	0	290	350	230	230	11	26	13	22
13	81	69	−10	30	−50	0	340	360	310	280	19	51	7	28
14	94	66	−20	50	−30	0	350	180	310	300	36	10	23	14
15	46	72	50	40	30	70	340	310	400	340	30	16	22	27

* HR = heart rate.
† R-ED= Onset of R-wave to end-diastolic time.
‡ ET = Ejection time.
¶ EF = holosystolic ejection fraction.
§ 1/3 EF = first-third ejection fraction.

camera count rates. For example, an s.d. of 7 EF units and a relative error of 30%, were associated with a first-third ejection fraction at an end-diastolic count rate of 200/frame. However, the errors were significantly reduced at higher count rates when this fixed ED/ES criterion was applied. For example, the calculated first-third ejection fraction was associated with a s.d. of only 2 EF units, or a 9% relative error, at an end-diastolic count rate of 2,000/frame.

When end-interval time points were selected by the more customary max/min criterion, standard deviations and relative errors increased because of the attendant errors in the choice of end-interval time points. For example, at the same end-diastolic count rate of 200, the first-third s.d. was 11 EF units, a relative error of 47%. Even at an end-diastolic count rate of 2,000/frame, the relative error exceeded 20%.

The end-interval time points demonstrated signifi-

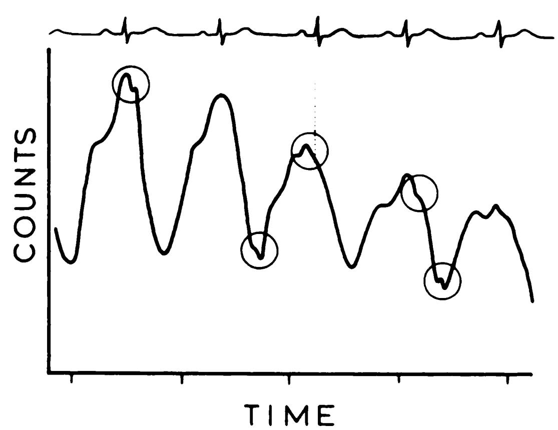

FIGURE 7
Typical difficulties in definition of end-interval time points from time-activity curve. Encircled points demonstrate double peaks, double nadirs, or peaks unphysiologically preceeding R-wave

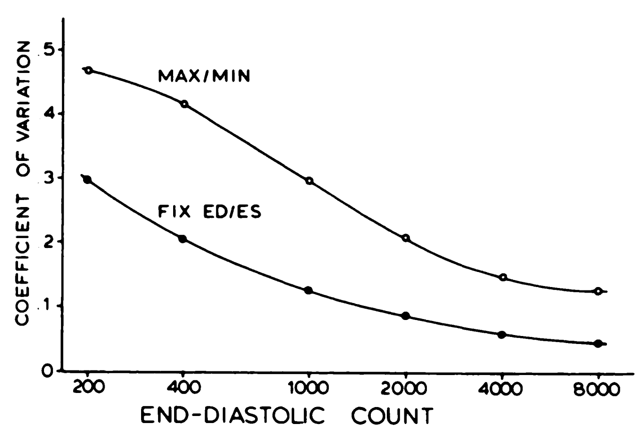

FIGURE 8
Coefficient of variation of calculated first-third ejection fraction at various end-diastolic counts for two different time point selection criteria from computer simulation study

TABLE 2
Deviation of Apparent End-Interval Time Points from Original Points for Different End-Diastolic Count Rates from Computer Randomized Simulation Study*

EDC†	ED‡ (msec)	ES§ (msec)
200	44	44
400	33	40
1,000	18	29
2,000	8	25
4,000	2	20
8,000	1	15

* Deviation is expressed as their 1 s.d. in msec.
† EDC is end-diastolic count.
‡ ED is end-diastole.
§ ES is end-systole.

cant variations from the original end-interval time points indicated by the analog curve, especially at lower end-diastolic count rates. At an end-diastolic count rate of 200, the distribution of both end-diastolic and end-systolic time points had an s.d. of 44 msec. At an end-diastolic count rate of 2,000, the distribution of these end-interval time points was reasonably small with an s.d. of 8 msec for end-diastole and 25 msec for end-systole (Table 2). However, the relative error associated with first-third ejection fraction was still high and exceeded 20%.

DISCUSSION

At present, a variety of parameters of left ventricular function can be measured by radionuclide techniques. For these measurements, the left ventricular time-activity curve is frequently used, and may be obtained by several different methods, utilizing either imaging or nonimaging devices with either first-pass or equilibrium techniques (*4,11–15*). However, the left ventricular time-activity curve is not a precise reflection of true left ventricular volume variations. Various factors affect the accuracy of the left ventricular time-activity curve, as presented earlier. It is significantly distorted at low count rates, at slower framing rates, by high crosstalk, and by background contamination. Poisson counting errors are not truly corrected by the application of filtering algorithms. When the left ventricular time-activity curve thus lacks constant identification with true left ventricular volume variations, derived functional parameters may no longer be accurate. The calculation of first-third ejection fraction is particularly fragile, and, under such circumstances, will often be erroneous.

As demonstrated by computer simulation in which only Poisson counting errors were incorporated, the left ventricular time-activity curve is significantly different from the original analog curve at count rates achievable with an Anger camera. Neither filtering nor smoothing can totally correct these distortions. Variation of apparent end-diastolic and end-systolic time points and Poisson errors in measured count rates result in high statistical uncertainties in the measurement of the first-third ejection fraction. Even at the higher count rates achievable with a multicrystal camera, the derived curve constructed with Poisson distributed errors is still distorted. Calculated first-third ejection fractions are still associated with a predicted high relative error in excess of 20%.

In the computer simulation, first-third ejection fraction was determined with reasonably small errors only when the end-interval time points were selected by a fixed ED/ES criterion at high end-diastolic count rates. However, in clinical studies, additional systematic errors, such as background and/or crosstalk contamination, errors in the selection of regions of interest, long framing rate, and accuracies in the determination of end-interval time points result in significantly higher errors than estimated by the computer simulation study. In fact, in the radionuclide studies reported here, in comparing individual patients, calculated first-third ejection fraction varied considerably among the four beats analyzed, with no apparent trend (either increasing or decreasing). The time parameters obtained from left ventricular time-activity curves also demonstrated wide interbeat variation when referenced to the simultaneously recorded ECG, with no apparent trend.

Although pre-ejection period and systolic time interval are affected by various factors, e.g., age, sex, heart rate, intraventricular conduction, myocardial contractility, preload, and afterload, these time intervals are quite stable in consecutive beats at basal condition with regular rhythm. However, data obtained in this study demonstrate very wide variation, far beyond the physiological range.

We have examined first-third ejection fraction at Anger camera count rates of 200/40 msec in both clinical and simulation studies, and at count rates up to 2,000 counts per time interval in simulation studies alone. Although the digital filter utilized was not "optimal," it is typical of those used in the literature for first-pass curve analysis. We thus conclude that first pass radionuclide angiography with presently available equipment does not result in a sufficiently accurate description of left ventricular volume variations to be utilized in calculation of first-third ejection fraction.

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