DIAGNOSTIC NUCLEAR MEDICINE

Analysis of Cardiac Diastolic Function: Application in Coronary Artery Disease

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Separation of systolic and diastolic parameters in gated cardiac blood-pool imaging (RVG) was achieved with the retention of two harmonics in the Fourier-series representation of the time-activity curve. Regional and global analysis of left-ventricular peak filling rate (PFR) and time to peak filling (TPF) was performed in 18 control subjects, 20 patients with coronary artery disease (CAD) but with normal RVG (normal regional wall motion and ejection fraction), and 16 CAD patients with abnormal RVG. In regional analysis of CAD patients, the standard deviation of the TPF histogram identified 13/20 (65%) of normal RVG patients and 12/16 (75%) of abnormal RVG patients as abnormal. In global analysis of CAD patients, PFR values identified 10/20 (50%) of normal RVG patients and 11/16 (69%) of abnormal RVG patients as abnormal. Thus, left-ventricular systolic and diastolic parameters can be separately measured with retention of higher-order harmonics in the Fourier transform, and regional inhomogeneity of diastolic filling can be detected in CAD patients with normal resting ejection fraction and wall motion.

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Improved analysis of cardiac dynamic function has been achieved with the use of frequency-domain, or Fourier transform, techniques applied to data derived from gated cardiac blood-pool imaging (*1–3*). In so-called "phase analysis", the time-activity curve of each pixel within the cardiac image is fitted by a Fourier series including only the first harmonic. This approach, although useful, suffers from the limitation that abnormalities related to systolic as opposed to diastolic phases of the cardiac cycle cannot be distinguished.

From a clinical point of view, optimal scintigraphic analysis of dynamic cardiac function should discriminate between systolic and diastolic behavior. Abnormalities of left-ventricular diastolic function may be important in disease entities such as hypertrophic cardiomyopathy and may account for impaired ventricular performance in this condition (*4,5*). Furthermore, alterations in diastolic function, particularly subtle regional abnormalities, may provide a sensitive index of early ischemic heart disease in which they may antedate abnormalities of systolic function (*6*).

The present work was undertaken to develop a quantitative, noninvasive method for characterization of both regional and global left-ventricular diastolic function. Diastolic abnormalities were detected and distinguished from systolic changes by performing frequency-domain analysis with retention of higher-order terms in the Fourier-series representation of the time-activity curve, thus providing the needed temporal structure for the analysis. To determine their sensitivity in detecting ischemic heart disease, diastolic filling rates and time intervals were determined globally and regionally in studies of normal subjects and patients with coronary artery disease.

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MATERIALS AND METHODS

Frequency-domain analysis. The general principles underlying application of frequency-domain analysis to cardiac nuclear medicine have been reviewed recently in detail (*7*). Briefly, a periodic function of time, such as the volume or time-activity curve (TAC) of a gated

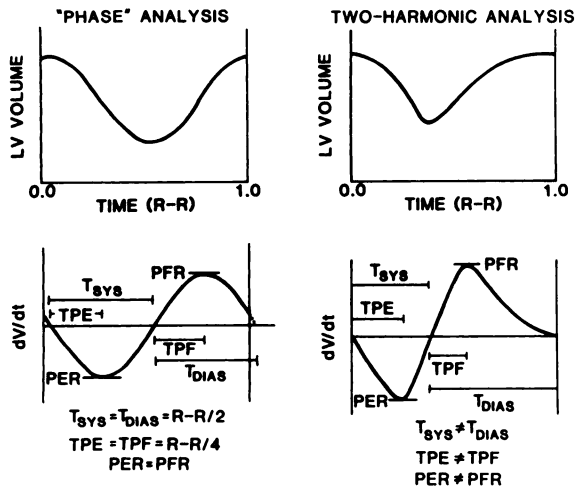

FIG. 1. Left panel: Left-ventricular time-activity curve and first derivative retaining only one harmonic in the Fourier transform. First derivative (dV/dt) is used to compute peak emptying rate (PER), peak filling rate (PFR), time to peak emptying (TPE), time to peak filling (TPF), and total systolic and diastolic time intervals. With only one harmonic important systolic and diastolic parameters are necessarily equal. Right panel: Time-activity curve and first derivative retaining two harmonics in the Fourier transform. In this case, systolic and diastolic parameters are independent.

cardiac study, may be represented exactly by the sum of a series of sinusoidal waves of different frequencies and amplitudes—the Fourier series. Expressed mathematically,

$$TAC(t) = a_0 + a_1 \cos(\omega t - \phi_1) + a_2 \cos(2\omega t - \phi_2) + a_3 \cos(3\omega t - \phi_3) + \ldots \quad (1)$$

where the a's are the amplitudes and the ϕ's the phases of the Fourier series terms. ω, the fundamental frequency, equals $2\pi/T$ where T is the period of the function, i.e. the R-R interval. In the conventional phase analysis, terms above the first harmonic are ignored. That is,

$$TAC(t) \approx a_0 + a_1 \cos(\omega t - \phi_1). \quad (2)$$

When the time-activity curve of each pixel is fitted by this first-harmonic function, the systolic and diastolic components of the cardiac cycle will be averaged together, giving results that are mathematically identical in systole and diastole. This can be demonstrated mathematically or illustrated graphically, as in the left-hand panel of Fig. 1, where the peak ejection rate, PER, (maximum negative dV/dt) must equal the peak filling rate, PFR, (maximum positive dV/dt), the total systolic and diastolic time intervals are each one-half the R-R interval, and the time to peak emptying, TPE, and time to peak filling, TPF, are each one fourth the R-R interval.

Separation of systolic from diastolic events can be achieved by retaining higher-order terms in the Fourier series of Eq. 1. For example, retaining even the second harmonic, i.e.

$$TAC(t) \approx a_0 + a_1 \cos(\omega t - \phi_1) + a_2 \cos(2\omega t - \phi_2), \quad (3)$$

gives additional structure to the fitted TAC curves, as shown in the right-hand panel of Fig. 1. In this case the ejection and filling rates and time intervals need not be equal, thus permitting separate quantitation of systolic and diastolic events.

Representative gated cardiac studies were analyzed with this approach to determine the number of statistically significant terms in Eq. 1 (*8*). Briefly, the fast Fourier transform (FFT) was used to determine the amplitudes in Eq. 1 (the power spectrum) for a single pixel in the center of the left ventricle in 20 typical gated cardiac studies, and for the left ventricle taken as a whole (the global time-activity curve) in eight patients. This analysis demonstrated that two harmonics could be retained in the Fourier series fitted to the single-pixel data and four harmonics could be retained in analysis of global left-ventricular time-activity curves without appreciable addition of noise, which is represented primarily by the higher-order harmonics.

Study population. A control group was studied consisting of 18 subjects without coronary artery disease (mean age 38 ± 13; 14 male, 4 female). Twelve were volunteers with normal electrocardiograms and gated cardiac blood-pool studies at rest and during maximal supine bicycle exercise (Table 1). The other six were patients with normal coronary arteriograms at cardiac catheterization. A second group, patients with coronary artery disease (CAD), consisted of 36 patients with significant lesions (≥75% stenosis) in one or more coronary vessels documented at catheterization (22 with 3-vessel disease, 6 with 2-vessel, 3 with disease in right coronary only, 4 in LAD, 1 in circumflex). This group was subdivided into (a) those with normal resting left-ventricular ejection fraction (≥55%) and regional wall

TABLE 1. STUDY POPULATION*

Control group (N = 18)	Coronary artery disease Group A (N = 20)	Coronary artery disease Group B (N = 16)
12 "normal" volunteers —Nl ECG at rest —Nl exercise ECG —Nl exercise RVG 6 patients with Nl coronary arteriograms	Nl ejection fraction Nl wall motion by RVG	Abn† wall motion

* Nl = Normal.
† Abn = Abnormal.

motion as assessed by a three-view gated cardiac blood-pool study (20 patients, mean age 59 ± 10, 15 male, 5 female); and (b) those with abnormal regional wall motion (16 patients, mean age 59 ± 7, 14 male, 2 female), 13 of whom had depressed left-ventricular ejection fractions (range 14–54%). In the control group, 11% were taking beta blockers, 6% were taking digoxin, and none were taking calcium antagonists. Among the CAD patients, 50% in group A and 73% in group B were on beta-blocker therapy, 17% in group A and 18% in group B were on digoxin, and 8% of both groups were receiving calcium-channel blockers.

Data acquisition and analysis. Imaging was performed with a standard-field-of-view scintillation camera with a crystal 0.635 cm thick and low-energy all-purpose parallel-hole collimator. Following in vivo labeling of red blood cells with 25 mCi technetium-99m, gated cardiac studies, 5–8 million counts each, were collected in frame mode using 32 frames per R-R interval and a 64 × 64-pixel image matrix. The computer rejected the two subsequent beats after the occurrence of any premature contraction.

A series of FORTRAN IV computer programs was written for analysis of the data. For the pixel-by-pixel regional analysis, each 64 × 64-pixel frame of the 32 frame study was compressed to 32 × 32 pixels and then processed with an 11 × 11 FIR low-pass filter (*9*) with properties carefully designed to achieve optimal noise reduction without loss of spatial resolution. Next, the data were sorted on the disc into 32 frames (Y dimension), each of size 32 (X dimension) by 32 (T dimension). This sorting, making time a primary coordinate of the arrays processed in computer memory, greatly simplified the subsequent calculation of temporal parameters. The terms of the Fourier series for each pixel were then computed using the FFT applied to each single-pixel time-activity curve. The first two harmonics were then used to reconstruct the time-activity curve of each pixel. This computation represents, in effect, temporal low-pass filtering. To avoid introducing spurious terms into the FFT due to "leakage" arising from fall-off of counts late in diastole (*7*,*10*), all frames were scaled to the same total counts. The first derivative of each single-pixel time-activity curve was determined by analytically differentiating Eq. 3:

$$\frac{d}{dt}[TAC(t)] = -a_1\omega \sin(\omega t - \phi_1) - 2a_2\omega \sin(2\omega t - \phi_2). \quad (4)$$

The peak filling rate, PFR, and time to peak filling, TPF, shown in the right-hand panel of Fig. 1, were then automatically determined for each pixel from the time-activity curve and first-derivative curve. Rates were expressed in units of end-diastolic-volumes/sec (EDV/sec) and time intervals in msec. For each of these parameters, functional images were generated in which the color assigned to each pixel was determined by the value of the functional variable at that point. Pixels in regions of negligible temporal variation, including the lungs and great vessels, were not suppressed in the quantitative analysis, although in the images displayed below they are set to black to clarify the presentation.

Histograms were generated to facilitate interpretation of the regional variations in time and rate parameters within the left ventricle. For the TPF parameter, the histograms showing temporal distribution represented time on the abscissa versus number of pixels on the ordinate (see Fig. 4). For histograms showing the peak filling rate, the rate was plotted on the abscissa. The spread of each of these factors was measured by the standard deviation of the histogram. Other measures, including skew, were computed and yielded essentially the same results as the standard deviation.

The rate and time parameters were computed for the left ventricle taken as a whole as well as regionally. The global left-ventricular time-activity curve was obtained with an ejection-fraction program validated previously (*11*). Four terms were retained in the Fourier series for analysis of the global data.

Standard deviations of the mean values were reported only for data sets with a normal distribution, determined on the basis of mean and median. If the mean and the median differed significantly, the set was judged not to be normal and standard deviations were not reported (*12*). The statistical significance of differences between groups was evaluated by the chi-square test or the Wilcoxon-Mann-Whitney test (*13*).

RESULTS

In Table 2 the results are tabulated for the control group and the two groups with coronary artery disease. The mean values are shown for the standard deviations of the peak filling rate (PFR) and time to peak filling (TPF) histograms generated in the regional analysis, and for the global PFR and TPF. The standard deviations of these mean values are shown for data with a normal distribution.

Figure 2 shows the standard deviation of the TPF histogram for each patient in each of the groups. The dashed line represents the upper 95% confidence limit for the control group. In the first CAD group (those with normal ejection fraction and wall motion) 13/20 (65%) have a TPF histogram with an abnormally large standard deviation, indicating significant regional inhomogeneity of filling. In the second CAD group (those with abnormal gated cardiac studies) 12/16 (75%) also have an abnormal TPF histogram. The analysis of regional peak filling rate did not effectively separate the three groups.

The results of the global analysis of peak filling rate

TABLE 2. SUMMARY OF REGIONAL AND GLOBAL ANALYSIS IN CONTROL GROUP AND PATIENTS WITH CORONARY ARTERY DISEASE

	Control N = 18	Coronary artery disease	
		Normal EF Normal RWM N = 20	Abn RWM N = 16
Regional analysis†:			
s.d. of PFR histogram (msec)	0.97 ± 0.66	0.85	2.20
s.d. of TPF histogram (msec)	11.2 ± 3.4	70.2*	71.7*
Global analysis:			
peak filling rate (EDV/sec)	3.04 ± 1.06	2.16*	1.60*
time to peak filling (msec)	159 ± 65	199	171

Data are mean ± s.d. with s.d. computed only for groups with normal distribution.
* $p < 0.005$ (relative to control group).
† PFR = peak filling rate, TPF = time to peak filling, s.d. = standard deviation.

are shown in Fig. 3 for each patient in each of the groups. None of the patients in the control group have a PFR less than 2.00 EDV/sec, although 10/20 (50%) of the first CAD group have filling rates below this level and 11/16 (69%) of the second coronary-disease group have subnormal PFRs. The global time to peak filling did not effectively separate the control and CAD groups.

Table 3 summarizes the sensitivity of the regional analysis of time to peak filling and the global analysis of peak filling rate in detecting coronary artery disease. The regional analysis appears more sensitive than the global analysis in both CAD groups, but the differences are not statistically significant.

The functional images and histograms are shown in Fig. 4 for representative studies from the control group and the two CAD groups. In the normal study, note the uniform time to peak filling in the left ventricle and the corresponding narrow histogram with small standard deviation (9 msec in this case). The middle panel shows an abnormal study from the CAD group with normal ejection fraction and regional wall motion. Significant diastolic regional dysfunction is observed, manifested by the markedly inhomogeneous TPF image and histogram. In the right-hand panel, a study from the CAD group with abnormal regional wall motion is shown. Again, diastolic inhomogeneity is seen in the TPF image and histogram.

The effect of lesions in individual vessels could not be determined, since most patients had double- or triple-vessel disease. There was no statistically significant difference between patients receiving cardiac medica-

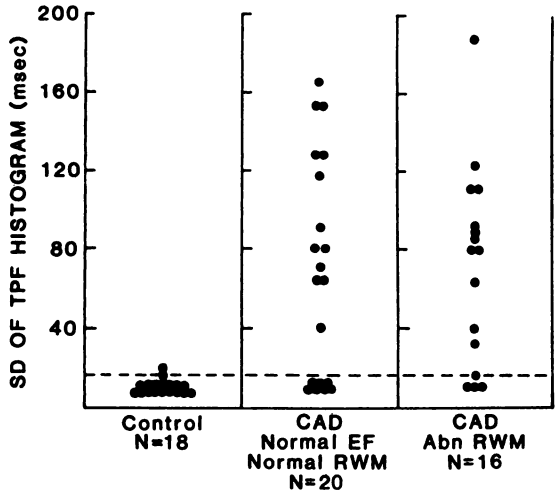

FIG. 2. Standard deviation of TPF histogram for 18 control patients and 36 CAD patients. Dashed line at 17.9 msec represents the 95% confidence limit for normal range. In CAD groups, 13/20 (65%) of subjects with normal regional wall motion and 12/16 (75%) of patients with abnormal regional wall motion had standard deviations outside of normal range.

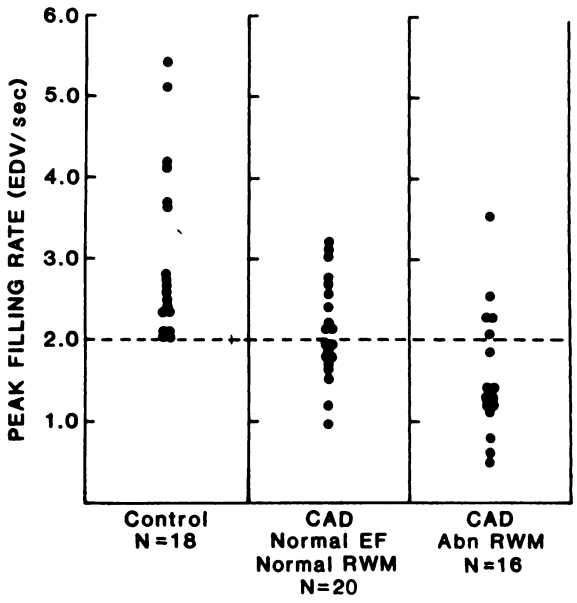

FIG. 3. Peak filling rate for 18 control subjects and 36 CAD patients. Dashed line at 2.0 EDV/sec was chosen as lower boundary of normal range such that all control subjects fall within normal range. In CAD groups, 10/20 (50%) of patients with normal regional wall motion and 11/16 (69%) of patients with abnormal regional wall motion had peak filling rates below normal range.

TABLE 3. SENSITIVITY OF PEAK FILLING RATE AND TIME TO PEAK FILLING IN PATIENTS WITH CORONARY ARTERY DISEASE

	Coronary artery disease	
	Normal EF Normal RWM† N = 20	Abnormal RWM† N = 16
Regional analysis*:		
Abnormal s.d. of TPF histogram	65%	75%
Global analysis:		
Depressed PFR	50%	69%
P (regional vs. global)	N.S.	N.S.

* s.d. = standard deviation, TPF = time to peak filling, PFR = peak filling rate, N.S. = not significant ($p > 0.05$).

† RWM = regional wall motion.

tions and those not receiving them.

DISCUSSION

Important mathematical considerations make the "frequency domain" approach well suited to analysis of the dynamic behavior of the heart. Trigonometric functions comprise a unique set of functions (eigenfunctions) that form a mathematical basis for the analysis of periodic variables, such as the cardiac time-activity curve (*14*). Thus, Fourier-series analysis provides valuable mathematical insights into the nature of the data leading to simple computational algorithms. With these trigonometric functions, temporal characterization of cardiac data can be better achieved than when other approaches, such as fitting with polynomials, are used.

Phase-analysis methods based on determination of only the fundamental frequency, or first harmonic (*1–3*), do not differentiate abnormalities occurring in systole from those seen in diastole, although this method is often incorrectly assumed to reflect purely systolic behavior. The approach developed in the present work retains higher-order harmonics to provide the structure required to fit time-activity curves better, thereby separating systolic from diastolic components.

In the present study, emphasis was placed on analysis of regional as well as global left-ventricular diastolic dysfunction. Manifestations of coronary artery disease in diastole are, of course, regional in character, just as are systolic manifestations (*15*). Regional alterations in systolic function provide sensitive measures of disease. Analogously, the earliest manifestations of abnormal diastolic performance may be regional. Thus, by providing quantitative criteria of regional cardiac diastolic performance, the approach developed in this study may yield enhanced diagnostic sensitivity for detection of early disease.

To assess the value of this method in the characterization of ischemic heart disease, two groups of patients with coronary artery disease were studied: those with normal resting ejection fraction and regional wall motion, and those with obvious abnormalities in the resting gated cardiac blood-pool study. In the former group, 65% had grossly inhomogeneous regional diastolic filling times, as shown in Fig. 2 and Table 3. Thus, regional analysis can detect coronary artery disease, manifested by left-ventricular diastolic abnormalities, in patients with normal resting gated cardiac studies.

In Fig. 2 the tight clustering of values for the control group indicates the high specificity of the method (i.e., normal results are consistently obtained in patients without disease). In the group with abnormal gated cardiac studies, diastolic inhomogeneity was detected in 75% (Fig. 2 and Table 3). Of the four negative cases, two had wall-motion abnormalities seen only on the 70° LAO view and not evident on the 35° view used for computer analysis. Regional analysis of peak filling rate did not separate the control and CAD groups. The explanation of this finding is uncertain.

The global left-ventricular peak filling rate was abnormally depressed in 50% of patients in the CAD group with normal ejection fraction and wall motion, and in 69% of patients in the group with abnormal wall motion (Fig. 3 and Table 3). Similar global analyses have been performed by Bonow et al. (*16*), Polak et al. (*17*), and Reduto et al. (*18*). In a study of 46 normal subjects, Bonow et al. found a mean peak filling rate of 3.3 ± 0.6 EDV/sec and a mean time to peak filling rate of 136 ± 22 msec, while Polak et al. reported means of 2.14 ± 0.63 EDV/sec and 151 ± 38 msec in 12 normal subjects, and Reduto et al. obtained a mean peak filling rate of 3.13 ± 0.85 in 32 normal subjects. Our results, shown in Table

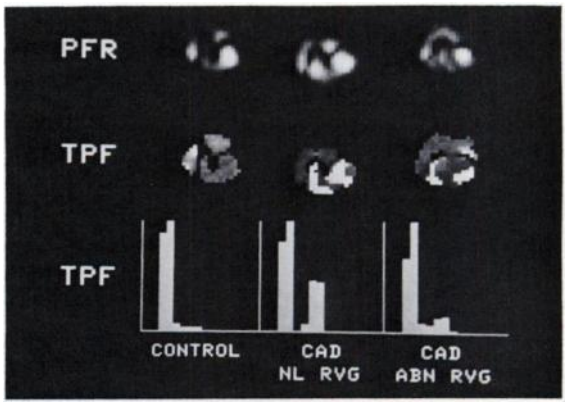

FIG. 4. Regional peak filling rate (PFR), time to peak filling (TPF), and TPF histogram for left ventricle are shown for representative patients in the control group, the CAD group with normal gated cardiac blood-pool study (RVG), and the CAD group with abnormal RVG. Left-ventricular TPF is homogeneous in control patient and markedly inhomogeneous in the two CAD patients.

2, resemble those reported in these studies. Bonow et al. found a reduced peak filling rate in 72% of CAD patients with normal ejection fraction and wall motion, in 76% of those with normal ejection fraction, and in 85% of all patients. Polak et al. reported a depressed peak filling rate in 52% of patients with coronary disease without myocardial infarction, and in 85% of those with prior myocardial infarction. Our findings generally agree with both studies but more closely approximate the results of Polak et al. Reduto et al. analyzed the first-third filling fraction but did not report individual peak filling rates.

Comparing the regional and global analyses in the present study, six patients were correctly identified as abnormal only by the regional method while two were abnormal based only on results of global analysis. This slightly greater overall sensitivity of the regional analysis in both disease groups (65% vs. 50% and 75% vs. 69%, Figs. 2 and 3 and Table 3), tends to support the view that regional abnormalities are a more sensitive indicator of ischemic disease than is global dysfunction, although the difference is not statistically significant and further study in a larger group of patients is required to substantiate this impression.

In summary, the results reported here indicate that regional as well as global left-ventricular diastolic behavior can be characterized quantitatively by noninvasive analysis of diastolic cardiac function, providing a sensitive, practical means for early detection of ischemic heart disease.

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ERRATUM

The footnote to the title of the 1982 Author Index (page 1155) and Subject Index (page 1161) should read:

P preceding a page number indicates an abstract of the Annual Meeting, appearing in the May 1982 issue.