Comparison of Left Ventricular Diastolic Function as Determined by Nuclear Cardiac Probe, Radionuclide Angiography, and Contrast Cineangiography

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In this investigation, determinations of peak diastolic filling rate (PDFR) and ejection fraction (EF) by two distinct nuclear techniques—gated radionuclide angiography (RNA) and nuclear cardiac probe (NCP)—were compared with contrast ventriculography in 44 patients with coronary artery disease (CAD). In addition, PDFR was tested as a potential index of the severity of disease. Good agreement in PDFR was found between NCP and contrast ventriculography ($r = 0.83$, $p < 0.001$), but there was poor correlation between RNA and contrast ventriculography. Ejection fraction measured by either RNA or NCP correlated well with contrast ventriculography ($r = 0.96$ and $r = 0.73$, respectively). A positive correlation was found between PDFR and the EF measured by the NCP ($r = 0.79$) and by contrast ventriculography ($r = 0.64$), but poor correlation was found between these parameters by RNA. Patients with multivessel CAD had lower PDFR than patients with single vessel disease when studied by the NCP (1.6 ± 0.4 versus 2.5 versus 0.6 EDV/sec [mean ± s.d.], $p < 0.0001$), but not by RNA. Thus, compared with contrast ventriculography, determination of PDFR is more accurate by NCP than by RNA. Furthermore, the PDFR measured by NCP, but not by RNA, may be a potentially useful index of the extent of CAD.

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Radionuclide angiography (RNA) is a well-established technique in the assessment of systolic cardiac function. In patients with coronary artery disease (CAD), hypertension, and cardiomyopathy, important alterations occur in left ventricular (LV) diastolic as well as systolic function (*1–6*). Recent clinical studies utilizing RNA have documented a reduction in LV diastolic filling parameters during acute episodes of infarction (*7–10*). We have previously reported that in the diagnostic evaluation of patients with chest pain, peak diastolic filling rate (PDFR) determined at rest angina, pacing induced ischemia, and acute myocardial and during exercise provides a potentially more sensitive index of CAD than global ejection fraction (EF) (*11*). In addition, successful percutaneous transluminal coronary angioplasty of critical coronary stenosis improves systolic and diastolic function during exercise (*12*). However, it has not been established whether systolic and diastolic parameters are independent from each other in patients with CAD. Furthermore, the relationship between PDFR and the extent of CAD has not been investigated.

Recently, the nuclear cardiac probe (NCP) has been introduced as an alternative noninvasive technique used to measure both left ventricular systolic and diastolic function. Although the assessment of systolic parameters by RNA or NCP have been validated by contrast ventriculography (CV), to date, measurements of diastolic indices by either RNA or the NCP have not been systematically validated by this standard independent technique.

Accordingly, this study was performed with the following objectives: (a) to compare measurements of

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PDFR and EF obtained with two distinct nuclear techniques (RNA and NCP) with the "gold standard" of CV; (b) to examine the relationships between PDFR and EF as determined by all three methods, and (c) to evaluate the usefulness of PDFR as assessed by both nuclear techniques as a potential noninvasive index of the extent of CAD.

METHODS

Patient Population

The study population consisted of 44 consecutive patients (38 male and six female) with a mean age of 59.5 ± 9.5 yr (mean ± s.d., range 29–77 yr), referred for evaluation of known or suspected CAD. Each patient underwent determination of left ventricular function by both RNA and the NCP. No selection criteria were applied for resting ventricular function, history of congestive heart failure, or history of prior myocardial infarction. Patients with frequent ventricular arrhythmia were excluded from RNA study due to difficulties with the gating technique (n = 4). Data from the remaining 40 RNA and all 44 NCP studies were analyzed. Contrast ventriculography was completed in 32 of 44 patients within 24 hr of the nuclear studies. Individual angiograms were excluded for the following reasons: (a) inadequate ventricular opacification (n = 7); (b) extra-systolic contractions interrupting normal cardiac rhythm (n = 3); (c) use of sublingual nitroglycerin during the procedure (n = 3); and (d) coronary arteriography preceding ventriculography (n = 5). Left ventriculograms were analyzed in the remaining 14 patients. Coronary arteriograms were available for interpretation in all 44 patients. Coronary artery disease was defined as luminal diameter stenosis of ≥ 70% in at least one major coronary artery. For purposes of subgroup analysis, patients were divided into two groups; those with single-vessel coronary artery disease (n = 21), and those with multi-vessel coronary artery disease (n = 23).

Radionuclide Angiography

After in vivo labeling of red blood cells with 30 mCi of technetium-99m (^{99m}Tc) sodium pertechnetate, blood-pool radionuclide angiography was performed at rest in the supine position in all patients. Images were obtained in the anterior as well as 30°, 40°, and 70° left anterior oblique projections, utilizing an Anger camera computer system.* Studies were carried out at a preset count density of 275 counts per pixel (64 × 64 matrix) over the left ventricle. Cardiac cycles with duration greater or smaller than 20% of the chosen R-R electrocardiographic interval were rejected by the computer. Data were acquired at 32 frames per cardiac cycle with average framing intervals of 28 ± 5 msec. The average acquisition time was 5 min. Separate regions of interest were defined for end-diastole and end-systole. Time-activity curves were constructed after spatial and temporal smoothing of the data with a commercial software program, using a nine-point-smoothing algorithm followed by temporal smoothing (seven-point).† Background subtraction, to bring background counts beyond the ventricular edge close to zero, was performed to create a sharp delineation of the ventricular boundary and optimize tracking of the region of interest by the software. EF was calculated as (end-diastolic counts − end-systolic counts)/end-diastolic counts. The ventricular boundary was then tracked with a semi-automated program with construction of the time-activity curve (*11*). The tracking of the ventricular edge was carefully observed for each patient to ensure its accuracy. The data were reformatted in some cases beginning at the termination of the cycle with the last frame from end-diastole to the onset of systole which allowed better tracking of the left ventricle to assess diastolic function (*11*). Peak diastolic filling rate was computer-calculated from the slope of the time-activity curve, after smoothing the curve with a three-point digital filter (*12*). The entire diastolic portion of the curve was scanned and the maximum slope obtained by a seven-point least square fit was normalized for end-diastolic counts and defined as the PDFR, in units of EDV/sec.

Nuclear Cardiac Probe

Immediately following acquisition of the gated equilibrium cardiac images, ventricular function was assessed by the NCP as described by Berger et al. (*13*). In the "position monitor mode," optimal LV position was determined by placement of the probe over a region with the maximal ratio of stroke counts (end-diastole − end-systole counts) to average counts. The chest position was marked and background activity counts, selected in a region just inferior and lateral to the LV region of interest, were collected for 15 sec. The probe was then repositioned over the LV area with a second verification of maximal periodicity. Counts were acquired for 2 min using the gated mode. A composite ventricular time-activity curve with 10 msec time-resolution was then computer-generated from the acquired cardiac cycles. Ejection fraction was computer-calculated with the use of three operator-adjusted time cursors to define appropriate end points of the averaged cardiac cycle. Ventricular filling rates were then determined in the diastolic portion of the curve with two time cursors spaced at 80 msec. Peak diastolic filling rate was defined as the maximum instantaneous slope of the time-activity curve between the two cursors.

Contrast Ventriculography

Left ventricular CV was performed in the fasting state without premedication, utilizing a No. 8 pigtail angiographic catheter or a No. 8 Sones catheter with injections of 35 to 50 ml of sodium-meglumine ditri-

zoate (Renographin 76) in the 30° right oblique position. Contrast angiograms were recorded at a frame rate of either 30 or 45 frames per sec. Left ventricular outlines were then manually traced for each frame for a single cardiac cycle not preceded by premature contractions. Volumes were calculated by a computer-interfaced graphic analyzer‡ utilizing the single plane modification of the area-length method and corrected for overestimation with the Kennedy regression equation. Volume data pertaining to each individual frame were then digitized to construct a ventricular volume curve which was smoothed by a custom designed software program utilizing a five-point least squares quadratic estimation. The computer calculated instantaneous derivative (dV/dt) was then determined and plotted against time. In a similar manner to the nuclear methods, PDFR was defined as the maximum dV/dt of the time volume curve and normalized for end-diastolic volume.

Statistical Analysis

All LV function studies and coronary arteriograms were interpreted by independent experienced observers blinded to the results of the other methods. Comparisons of paired data by all three techniques were analyzed by linear least squares regression analysis. Correlation coefficient (r), s.e.e., and significance level for each correlation were calculated. Comparison of group data was done by paired t-tests when appropriate, and categorical variables were analyzed by the chi-square test. The data were expressed as the mean ± s.d. Significance was assessed at the $p < 0.05$ level.

RESULTS

Comparison of Time-Activity Curves

Representative time-activity curves derived from NCP, RNA, and CV methods in a single patient are shown in Fig. 1. End-diastole and end-systole were defined for each curve at the labeled points. Diastole was divided into two equal time periods: early diastole and late diastole. In all cases PDFR was found to occur during early diastole.

Determination of Left Ventricular Function

Table 1 summarizes measurements of selected parameters of systolic and diastolic function. The group mean heart rate and mean diastolic time during the NCP study (68 ± 13 beats/min and 0.53 ± 0.12 sec) were similar during RNA study (69 ± 12 beats/min and 0.52 ± 0.10 sec). Correlation of individual diastolic time intervals measured by both nuclear methods revealed almost identical values (r = 0.99). Importantly, heart rate and diastolic time during both nuclear studies compared closely to CV (r = 0.95 for heart rate, r = 0.97 for diastolic time).

The group mean EF was similar whether determined by the NCP (52 ± 15%), RNA (54 ± 14%), or CV (53

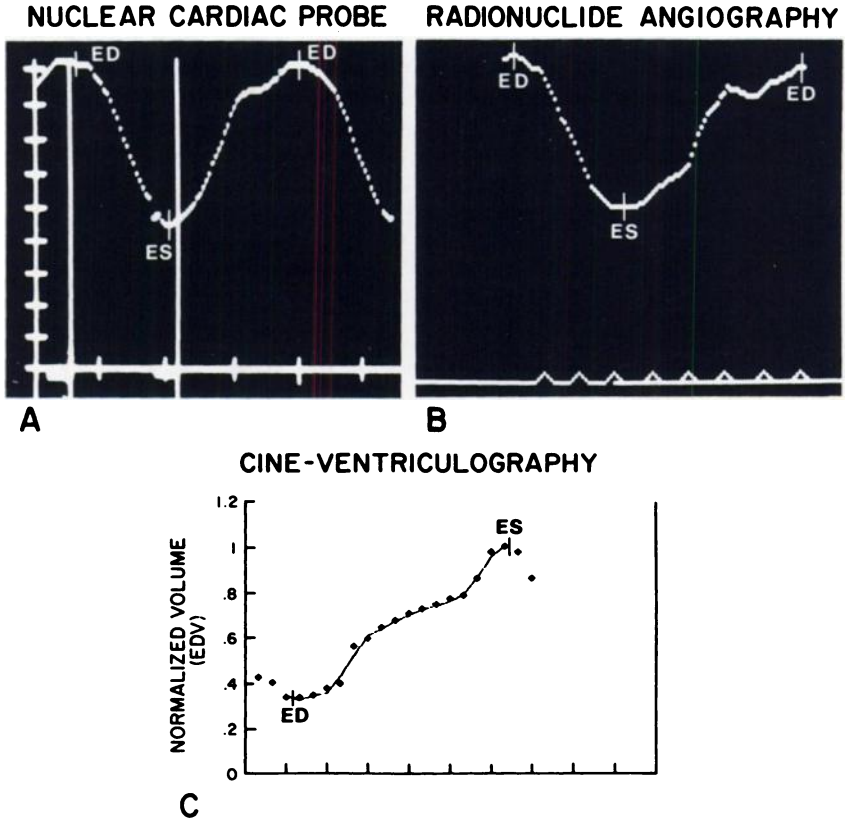

FIGURE 1
Representative time-activity curves of cardiac cycle in single patient determined by A: Nuclear cardiac probe, B: Radionuclide angiography, and C: Contrast ventriculography. Counts (nuclear methods) normalized to end-diastole are displayed in ordinate, and time (in msec) in the abciss. ED = End diastole; ES = End systole

TABLE 1
Determination of Left Ventricular Function: Comparison of Nuclear Cardiac Probe, Radionuclide Angiography, and Contrast Ventriculography

	N*	HR†	D-Time‡	EF§	PDFR¶	T-PDFR**
Nuclear cardiac probe	44	68 ± 13	0.53 ± 0.12	52 ± 15	2.0 ± 0.6	0.16 ± 0.04
Radionuclide angiography	40	69 ± 12	0.52 ± 0.10	54 ± 14	2.1 ± 0.9	0.17 ± 0.06
Contrast ventriculography	14	73 ± 10	0.50 ± 0.08	53 ± 13	2.2 ± 1.1	0.18 ± 0.04

* N = number of analyzed studies.
† HR = heart rate (beats/min).
‡ D-Time = total diastolic time (sec).
§ EF = Ejection fraction (%).
¶ PDFR = Peak diastolic filling rate (EDV/sec).
** T-PDFR = Time to peak diastolic filling rate (sec).
Data are expressed as mean ± s.d.

± 13%) (Table 1). Correlations of EF determinations, by either nuclear methods with CV (Fig. 2) were significant. Ejection fraction measured by RNA agreed closely with CV measured EF (r = 0.95) with a standard error of the estimate (s.e.e.) of only ± 3.4%. A moderate correlation for EF was found between RNA and NCP (r = 0.65, s.e.e. = 7%) as well as between NCP and CV (r = 0.73, s.e.e. 11%).

Although mean EF was >50% by all three methods, most patients in this study had a reduction in PDFR (<2.2 EDV/sec). The mean PDFR was similar whether determined by NCP (2.0 ± 0.6 EDV/sec), RNA (2.1 ± 0.9 EDV/sec), or CV (2.2 ± 1.1 EDV/sec) (Table 1). Comparison of individual values of PDFR by all three methods is shown in Fig. 3. Diastolic filling rates as determined by RNA studies were not in close agreement with paired data from either CV or NCP (r = 0.08 and r = 0.43, respectively). Conversely, PDFR derived from NCP studies was in good agreement with CV (r = 0.83) with a low error of the estimate (s.e.e. = 0.4 EDV/sec).

Comparison of Left Ventricular Systolic and Diastolic Function

To determine the relationship between systolic and diastolic function, by each method, individual EF and PDFR values were compared (Fig. 4). Although a positive correlation was observed between EF and PDFR by all three methods, the best correlation was found with the NCP studies (r = 0.79). In contrast, the correlation between EF and PDFR was only moderate by CV (r = 0.64) and poor by RNA (r = 0.46). In the latter two methods attempts of nonlinear analysis failed to improve the correlation coefficients.

Relationship of Diastolic and Systolic Function to Extent of Coronary Artery Disease

Peak diastolic filling rate, as determined by both nuclear methods, was compared in the 21 patients with single vessel and the 23 patients with multivessel coronary artery disease (Fig. 5). As determined by the NCP, mean PDFR was lower in the subset of multivessel disease patients compared with patients with single-vessel disease (1.6 ± 0.4 versus 2.5 ± 0.6 EDV/sec). This difference was highly significant ($p < 0.001$) (Fig. 5). Twenty-two of 23 (96%) patients with multivessel disease had a PDFR of <2.2 EDV/sec compared with 4/21 (19%) of patients with single vessel disease who had PDFR <2.2. Therefore, as a noninvasive predictive index of multivessel coronary artery disease, PDFR measured by the NCP had a sensitivity of 96%, speci-

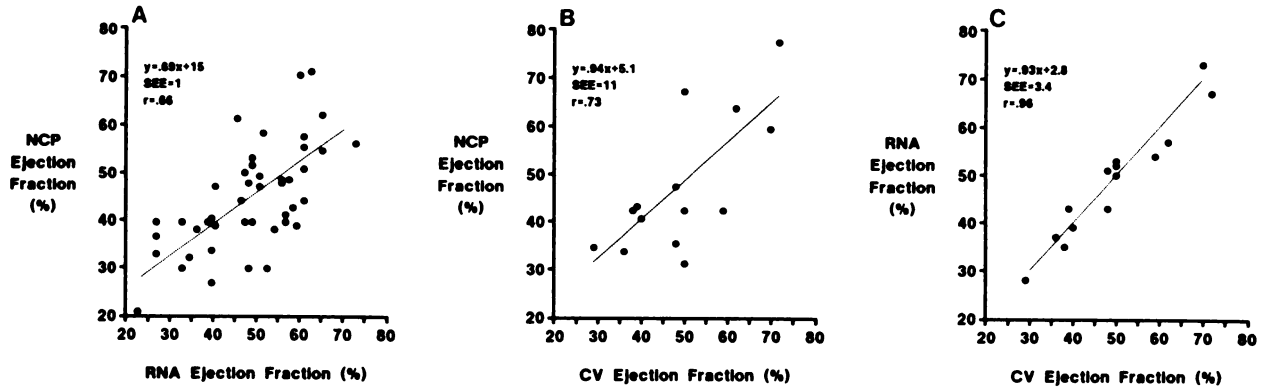

FIGURE 2
Comparison of left ventricular ejection fraction (%) measured at rest. A: Nuclear cardiac probe (NCP) versus radionuclide angiography (RNA); B: NCP versus contrast ventriculography (CV); C: RNA versus CV

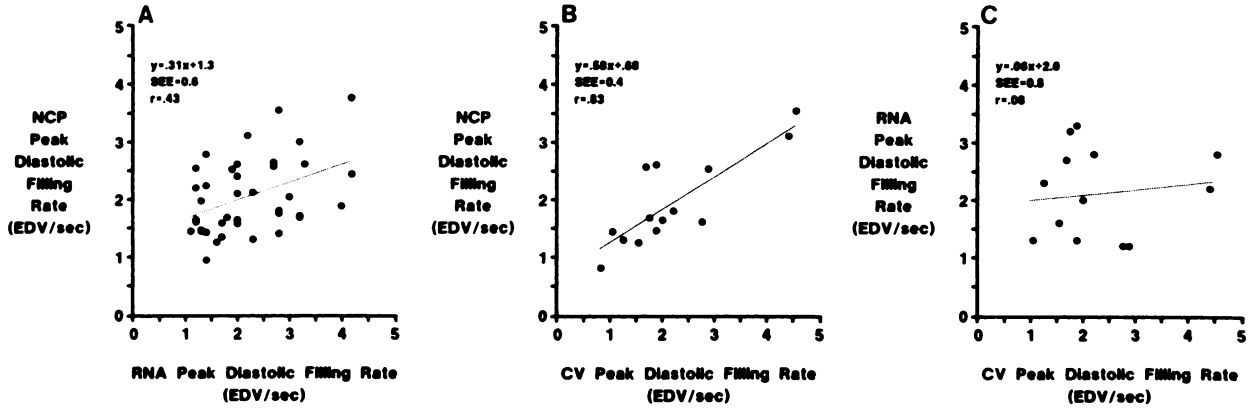

FIGURE 3
Comparison of left ventricular peak diastolic filling rate (EDV/sec) determined at rest. A: Nuclear cardiac probe (NCP) versus radionuclide angiography (RNA); B: NCP versus contrast ventriculography (CV); C: RNA versus CV

ficity of 81%, and a positive predictive accuracy of 85%. In contrast, mean PDFR determined by the RNA method was not significantly different in the two subgroups (2.1 ± 0.9 versus 2.3 ± 0.9, p = N.S.) of coronary disease patients. The sensitivity, specificity, and positive predictive accuracy using this technique were 57%, 63%, and 67%, respectively, for a PDFR discrimination threshold of <1.85.

DISCUSSION

This study provides the first validation of two independent radionuclide techniques with standard contrast angiographic methods for the assessment of ventricular diastolic function in patients with CAD. As expected, for determination of EF, RNA was in good agreement with CV (r = 0.95). However, in our patients with reduced compliance, the PDFR determined by RNA did not correlate with CV. In contrast, the NCP, although in less agreement with CV regarding EF measurements, did appear superior to RNA for determining diastolic filling rate (r = 0.83). Thus, important differences were observed when parameters of systolic and diastolic function were measured by these diagnostic techniques.

Contrast ventriculography provides good border definition (spacial resolution) and has a temporal resolution limited only by the cineangiographic frame rate. However, derivation of LV time-activity curves from frame by frame angiographic data requires certain geometric assumptions that may not be correct, especially in the presence of cardiac dilatation or ventricular dysynergy. In addition, inadequate opacification of the ventricular cavity and the provocation of extra-systolic beats are significant problems, as demonstrated by the large number of ventriculograms that had to be excluded in our investigation.

A unique advantage of RNA is the lack of geometric assumptions when measuring functional parameters. Thus, as previously reported by other investigators (*14*) and confirmed in this report, an excellent correlation can be expected between RNA and CV regarding EF measurement. More recently, the RNA method has been extended in selected patient populations to observations of diastolic filling (*6*). Although gated RNA can provide images of good spatial resolution, time resolution in this nuclear method is usually limited to 30 to 40 msec at heart rates between 60 to 100 bpm. In addition, the precision of the edge detection algorithm has a major influence on the accuracy of the PDFR determination. Due to low signal-to-noise characteristics of the radionuclide angiograms, edge detection by totally automatic algorithms is often unsatisfactory. Thus, we elected to use a semi-automatic edge detection algorithm based on gradient thresholds which allows the observer to correct for incongruencies in the ventricular edges. Furthermore, with this radionuclide method, the diastolic portion of the ventricular volume curve is affected by variations in heart rate and the presence of extrasystoles. This limitation of the multigated technique may be overcome by using list mode acquisition and backward processing or using more strict beat rejection algorithms, which are not universally available. Although absolute values of diastolic filling may be less reliable with RNA, this technique may still be useful to assess the relative changes in PDFR during interventions such as exercise, drug administration, or transluminal coronary angioplasty. However, if the decreased reliability of the PDFR by RNA is due to technical imperfections in the diastolic portion of the time-activity curve, great caution should be exercised when using RNA to assess this parameter of relaxation.

The introduction by Wagner in 1979 of the scintillation probe detector provided an alternative noninvasive radionuclide approach for assessing both systolic and diastolic LV function (*15*). The device has the

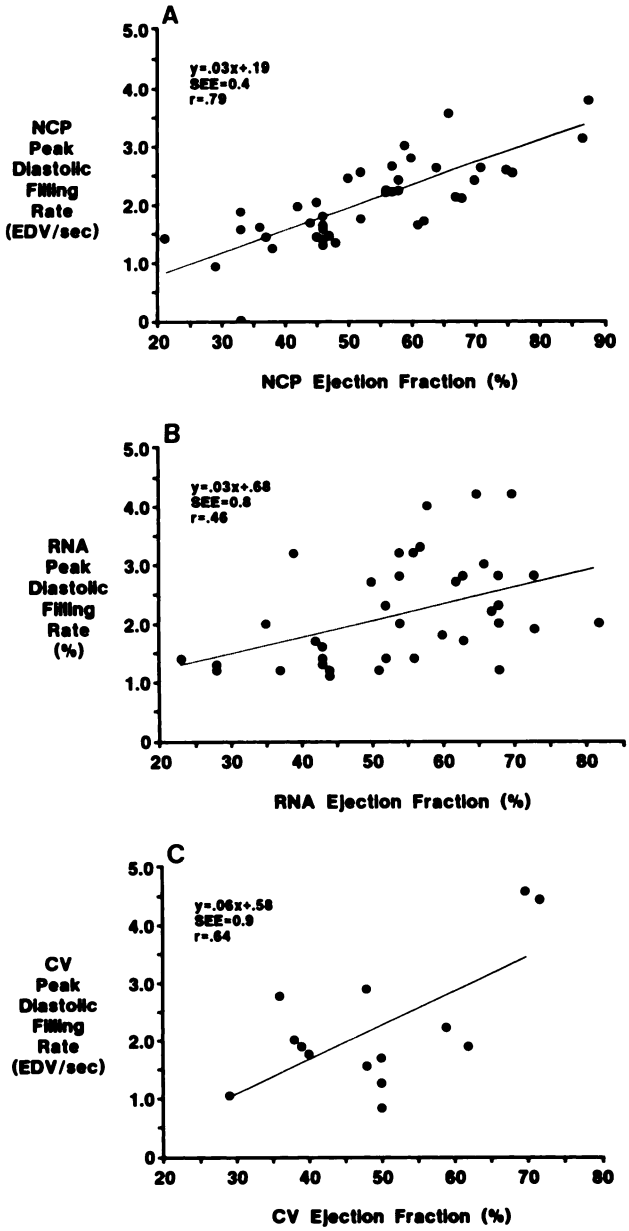

FIGURE 4
Relationship between left ventricular ejection fraction (%) and peak diastolic filling rate (EDV/sec) as determined by A: Nuclear cardiac probe (NCP); B: Radionuclide angiography (RNA); and C: Contrast ventriculography (CV)

advantage of compact size and increased portability, as well as the ability to do serial beat-to-beat analysis (*16*). In the initial report on this technique, investigators observed close agreement between EF obtained with the NCP and by gated RNA (*15*). Bruggemann et al. (*17*) also compared EF determined by NCP and RNA as well as bidimensional echocardiography with CV. The best correlation with CV was obtained using the RNA method (r = 0.78), followed by the NCP (r = 0.75). Poor correlation was found between echocardiography and CV (r = 0.56).

Other investigators have utilized this portable cardiac probe in the assessment of systolic function during cardiac arrhythmia, drug intervention, and after myocardial infarction (*16–18*). However, as a nonimaging device, the NCP may have some limitations in measuring EF, especially in patients with regional wall motion abnormalities (*19*). For example, if the NCP is positioned over an area of regional hypokinesis, the contribution of normal or hyperkinetic segments will be underrepresented and the study may underestimate the actual EF. Conversely, the deliberate positioning of the NCP on the region of maximal periodicity (maximal ratio of stroke counts to average counts), as routinely done, may overestimate the EF. Thus, it is not surprising that in our coronary artery disease patients with regional LV dysfunction, the EF measured by the NCP had only a modest correlation with CV.

Bonow et al. first reported the usefulness of radionuclide methods in determination of diastolic filling parameters in patients with CAD (*6*). Reduction in LV filling parameters has been documented by this method in patients with hypertension, hypertrophic cardiomyopathy, and valvular heart disease. Importantly, no published report is available validating radionuclide derived diastolic filling rates with other nuclear methods or standard contrast angiography. Strashun et al. first reported determinations of diastolic filling rates by the NCP, but no comparison was made with independent methods (*20*). In the present study, regarding measurement of PDFR, the NCP had a good correlation (r = 0.83) with CV, whereas RNA correlated poorly with CV. The NCP has the important advantage of a more rapid count acquisition and excellent time resolution (10 msec), enabling collection of more data points during the cardiac cycle. This important difference in the two methods results in potentially more accurate time-activity curves. Thus, the good correlation between the NCP and CV in measurements of PDFR in our patients may be attributed to the technically excellent ventricular volume curves obtained with the NCP. Differences in smoothing and count rates between the two nuclear techniques, however, in addition to a dependency on accurate edge recognition by RNA, but not by NCP, may have also affected our results. We acknowledge that the RNA technique may be further optimized by using beat rejection algorithms, higher temporal sampling rate, higher sensitivity collimator, and list mode acquisition. Many of these potential improvements are not widely available on existing commercial instruments.

The possible inter-relationship between systolic and diastolic function was also tested in our study. A positive correlation between EF and PDFR was observed with data derived from all three methods, with the best correlation achieved with the NCP. Bonow et al. also observed a similar positive relationship (r = 0.73) be-

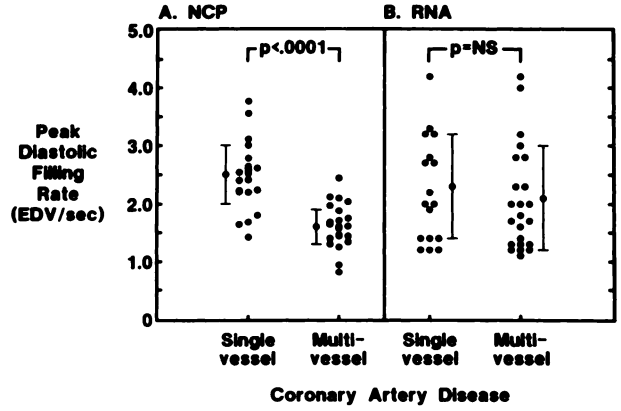

FIGURE 5
Peak diastolic filling rate (PDFR) as measured by A: Nuclear cardiac probe (NCP) or B: Radionuclide angiography (RNA) in patients with single vessel and multivessel CAD

tween EF and PDFR as determined by RNA (*6*). Of note, their higher correlation utilizing RNA was probably due to the use of list mode acquisition. In agreement with our results, these authors pointed out that coronary patients with normal systolic function (EF >50 %) often have a significant reduction in diastolic filling rate. This would further support the concept that in some patients with chronic stable CAD, diastolic function may be adversely affected earlier than systolic function.

The clinical significance of diastolic parameters is further enhanced by our observation that the degree of reduction in PDFR may reflect the severity of underlying CAD. In the present study, although EF did not correlate with the extent of disease, patients with multivessel disease had a significant reduction of PDFR compared with patients with single vessel disease, as determined by the NCP. Importantly, utilizing a PDFR cutoff value of 2.2 EDV/sec, we were able to separate these two subgroups of coronary patients. Such a distinction was not possibile utilizing the PDFR measured by RNA. The reason for this discrepancy between the two techniques is not clear. It may be due to preferential selection by the NCP of regions with intact function in patients with single vessel disease, as opposed to multivessel disease patients, in whom the dysfunction may be more global. Alternatively, the apparent technical superiority of curves obtained by the NCP may improve the ability to obtain the PDFR. Thus, when optimally measured, the PDFR may have a potential role in identifying patients more likely to have severe multivessel CAD and candidates for further invasive studies.

In summary, this study provides the first comparison of two distinct radionuclide methods of measuring LV diastolic function with standard CV. Our findings indicate that for measuring PDFR, the nonimaging radionuclide probe was in best agreement with CV. The superiority of the NCP to accurately measure PDFR was attributed to the high time resolution and consequent time-activity curves of excellent quality. A positive relationship between systolic and diastolic function was observed with all three techniques in our study. The noninvasive determination of PDFR with the NCP may have further clinical usefulness in defining a group of patients most likely to have severe multivessel coronary artery disease.

FOOTNOTES

* Technicare, Solon, OH (Technicare 420-560 system).
† Technicare, Solon, OH.
‡ Digisonics, Inc., Houston, TX (Digisonics EC-200).

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