Assessment of Left Ventricular Diastolic Function: Comparison of Contrast Ventriculography and Equilibrium Radionuclide Angiography

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Twenty-two patients with coronary artery disease were studied first by radionuclide angiography (RNA) and then by contrast ventriculography. Cardiac medications were discontinued at least 72 hr before study. The patients were studied during atrial pacing at heart rates close to their spontaneous sinus rhythm. Contrast ventriculography was performed at 50 frames/sec in the 30° right anterior oblique projection using 40 ml of a nonionic contrast medium (iopamidol) at a flow rate of 10–12 ml/sec. The contours of the left ventricular silhouette at contrast ventriculography were traced, frame by frame, on a graphic table with a digitizing penlight. Equilibrium ^{99m}Tc RNA was performed in the best septal 45° left anterior oblique projection, acquiring 150,000 cts/frame, at 50 frames/sec and with a 5% gate tolerance. Time-activity curves from both end-diastolic and end-systolic ROIs were built and interpolated. Both RNA and contrast ventriculography volume curves were filtered with Fourier five harmonics. A close relationship was found between RNA and contrast ventriculography measurements of peak filling rate normalized to end-diastolic cps ($r = 0.87$, $p < 0.001$) and stroke count ($r = 0.87$, $p < 0.001$), ejection fraction ($r = 0.94$, $p < 0.001$). Thus, in patients with coronary artery disease, LV filling can be accurately assessed using RNA.

J Nucl Med 1991; 32:1849–1853

Left ventricular (LV) diastolic dysfunction has been observed in patients with coronary artery disease (CAD), even in the absence of previous myocardial infarction (*1*), and seems to be related to the extent of CAD (*2*). Left ventricular diastolic dysfunction can be associated with normal systolic function in patients with CAD and may even cause symptoms of congestive heart failure (*3,4*).

Radionuclide angiography (RNA) has proved useful in the noninvasive evaluation of diastolic filling properties in patients with various heart diseases (*5–7*), as well as in the assessment of the effects of treatments on diastolic dysfunction (*8–10*). Moreover, reproducibility of rate estimates of diastolic filling with RNA proved to be quite good (*9,11–13*). Despite this widespread use of RNA in the evaluation of LV diastolic properties, its accuracy (in terms of comparison with other techniques) has not been thoroughly examined. In particular, Seals and coworkers (*2*) have found poor correlation between RNA and invasive contrast left ventriculography in the assessment of peak filling rate (PFR), a clinically useful estimate of the LV filling properties. Because contrast ventriculography still represents the gold standard in studies of LV mechanics in man, it would be important to verify or disprove Seals' conclusion on the lack of reliability of RNA-derived PFR.

The aim of the present study compares the indices of systolic and diastolic function measured by RNA and contrast ventriculography in a controlled setting where the two studies were performed in close temporal sequence and analyzed with similar algorithms.

METHODS

Patients Selection

Twenty-four patients without prior information referred for hemodynamic and angiographic evaluation of CAD were enrolled in the study. Cardiac medications were discontinued at least 72 hr before the study. Patients with associated cardiac or pulmonary diseases or diabetes mellitus were excluded. Furthermore, patients with supraventricular or ventricular arrhythmias were not included due to difficulties with the gating in the RNA technique. Of the study group, two patients were eventually excluded because contrast ventriculography could not be analyzed due to: inadequate ventricular opacification in one patient and frequent premature ventricular contractions in another patient. The study population therefore consisted of 22 patients (20 men, 2 women) with a mean age of 55 ± 10 yr (mean ± s.d., range 37–74) (Table 1). All patients were studied by RNA followed immediately by

Received Feb. 15, 1991; revision accepted May 9, 1991.

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TABLE 1
Clinical Characteristics of the Patients

Patient no.	Age	Sex	Coronary angiography			Contrast ventriculography		Radionuclide angiography	
			LAD	CX	RCA	PFR (EDV/sec)	EF (%)	PFR (EDV/sec)	EF (%)
1	56	M	100%			3.4	70	3.5	71
2	55	F	70%			2.1	50	2.2	40
3	70	M	90%		50%	3.2	34	3.3	34
4	65	M	60%	60%		2.3	56	2.1	52
5	56	M	90%		70%	3.5	72	3.5	75
6	53	M		80%	100%	2.2	60	2.2	55
7	48	M			90%	2.3	41	1.9	42
8	46	M	100%	50%	60%	5.0	61	4.8	58
9	42	M	90%	70%		3.9	72	4.0	73
10	49	M			90%	2.9	41	2.0	40
11	57	M	70%	70%		4.1	70	3.4	70
12	37	F	70%	70%	90%	3.7	50	3.7	52
13	59	M	80%	80%		3.6	78	4.0	76
14	57	M	60%		90%	3.5	75	3.2	72
15	54	M	60%	60%		3.5	91	3.1	82
16	42	M			70%	3.2	69	3.0	74
17	37	M	70%			3.1	70	3.5	71
18	74	M			80%	2.6	75	2.9	63
19	63	M		70%		3.7	65	3.2	62
20	64	M	70%			2.0	54	2.3	62
21	72	M	90%	80%		4.6	78	3.6	77
22	64	M		90%	70%	2.7	60	2.2	52

LAD = Left anterior descending coronary artery; CX = circumflex coronary artery; and RCA = right coronary artery.

contrast ventriculography. Both studies were performed during atrial pacing at the same heart rate, close to the spontaneous sinus rhythm (atrial pacing = 84 ± 16 bpm, normal sinus rhythm = 76 ± 14 bpm).

Coronary arteriography was performed after contrast ventriculography in multiple views for diagnostic purposes. All patients had CAD, defined as 50% or greater luminal diameter narrowing in at least one of the major coronary arteries (Table 1).

Contrast Ventriculography

Single plane (30° right anterior oblique) contrast ventricular cineangiograms were performed at held mid-inspiration with a 35-mm Siemens-Elema Angioskop at a filming rate of 50 frames/sec. Approximatively 40 ml of nonionic contrast media (iopamidol) were injected at 10–12 ml/sec through an 8 French pigtail LV catheter. In six patients, contrast left ventriculography had to be repeated due to inadequate opacification or frequent arrhythmias in the first injection. A 1-cm grid was filmed at mid-chest level to correct for magnification. Frame-by-frame LV silhouettes were manually traced on the first well opacified cardiac cycle that was not preceded by premature contractions. The first silhouette was drawn three frames before end-systole (i.e., smallest ventricular size) and the last one three frames after the end-diastolic image (largest ventricular size) of the following cycle on a graphic tablet with the aid of a digitizing lightpen. All contours were drawn by an operator unaware of the RNA results and coded and stored using a PDP 11/34 computer onto a hard disk. Left ventricular volumes were calculated with the area-length method (*14*) and corrected for overestimation with the Kennedy regression equation (*15*). Intraobserver variability of the method was assessed in a previous study from our laboratory (*16*).

A time-volume curve was computer-generated from the individual data points; ejection fraction was computed on the "raw" curve, whereas PFR was calculated after filtering with a Fourier expansion with five harmonics as the maximum of the first derivative of the time-volume curve and normalized by end-diastolic as well as stroke volumes.

Radionuclide Angiography

Radionuclide angiography was performed with the patient at rest in the supine position. Red blood cells were labeled *in vivo* with 25 mCi of ^{99m}Tc. Imaging was performed with a small field of view Anger camera equipped with a low-energy, general-purpose, parallel-hole collimator, oriented in the 45° left anterior oblique position with a 15° caudal tilt. Data were acquired in frame-mode by computer-based electrocardiographic gating with a 2× digital zoom. The imaging rate was 50 frames/sec (or 20 msec/frame) with a gate tolerance of ±5% to minimize distortion in the diastolic part of the curve, although in this particular study, this was of little relevance, since patients were paced and the heart rate was constant.

Left ventricular and background regions of interest (ROIs) were automatically drawn on both end-diastolic and end-systolic frames and from such areas where time-activity curves were obtained. Left ventricular time-activity curves computed from the end-diastolic and end-systolic ROIs were subtracted point-by-point by the corresponding background time-activity curves. The final curve was obtained by weighted interpolation of end-diastolic and end-systolic curves according to the following algorithm:

$$C_i(t) = [C_d(t)\cdot(1 - k)] + [C_s(t)\cdot K],$$

where C_i, C_d, and C_s are, respectively, the interpolated, end-

diastolic, and end-systolic time-activity curves at time t, and K is the weighting factor calculated as:

$$k = \frac{C_d(D) - C_d(t)}{C_d(D) - C_d(S)},$$

where $C_d(D)$ and $C_d(S)$ are the end-diastolic and end-systolic counts measured on the background-subtracted end-diastolic time-activity curve, respectively. Such a weighting factor is equal to 1 at end-systole and to 0 at end-diastole; hence the interpolated curve coincides with the end-diastolic curve at the beginning and at the end of the cycle, because there k is equal to 0. The value of k increases progressively when approaching end-systole, where it is equal to 1; hence the interpolated curve is equal to the end-systolic curve at end-systole. Anywhere else, the relative contribution of the end-diastolic and end-systolic curves to the interpolated curve is determined by k.

Ejection fraction was measured on the raw time-activity curve by standard technique. All other variables were measured, as in the contrast ventriculographyc study, on time-activity curve filtered by using a Fourier expansion with five harmonics. Further details on accuracy and reproducibility of this technique in our laboratory have been reported previously (*9*). Our method of analysis requires little intervention from the operator; nonetheless, studies were analyzed by an operator unaware of the contrast ventriculography results.

Statistical Methods

The mean value and standard deviation of the differences between the same parameter evaluated by both the methods were calculated for all the variables. Correlations between contrast ventriculographic and scintigraphic measurements were made by linear regression analysis. The mean value ± 1 s.d. for each variable was calculated separately for cineventriculographic and scintigraphic images. Paired t-test was used to compare the cineventriculographic and scintigraphic measurements. A probability value of less than 0.05 was considered significant.

Because it is known that even nonionic contrast media for left ventriculography can affect cardiac mechanics, we analyzed separately the six patients in whom contrast ventriculography had to be repeated for technical reasons and found a similar correlation between the two techniques as in the group as a whole.

RESULTS

Clinical characteristics of each patient included in the study are reported in Table 1.

Table 2 summarizes the mean value of the considered parameters of systolic and diastolic function assessed by contrast ventriculography and RNA.

Measurements of ejection fraction by RNA and contrast ventriculography were similar and closely correlated ($r = 0.94$ with a s.e.e. of 4.94%; $p < 0.001$) (Fig. 1). The range for this variable by contrast ventriculography was 34–91, while for RNA it was 34–82; the mean difference between studies was 4.2 ± 3.9 (range −5 ±12). A trend toward higher ejection fraction values was evident in contrast ventriculography.

The mean values of PFR, determined by both methods, were similar and highly related ($r = 0.87$ with a s.e.e. of 0.39 end-diastolic volumes/sec; $p < 0.001$) (Fig. 2). The range of PFR normalized to end-diastolic volumes/sec was 2.0–5.0 with contrast ventriculography and 1.9–4.8 with RNA. The mean variation was 0.27 ± 0.48 end-diastolic volumes/sec (range = 1.3±1.0). A close relationship was also found when PFR was normalized to stroke cps ($r = 0.87$, $p < 0.001$, with a s.e.e. of 0.86 stroke cps) (Fig. 3). The mean difference between the two methods was 0.05 ± 0.8 with a range of −1.8 ± 1.2).

TABLE 2
Mean Values ± s.d. of the Parameters Evaluated by Both Techniques

	Contrast ventriculography	Radionuclide angiography	p
Ejection fraction (%)	63.2 ± 14	61.5 ± 14	ns
PFR (EDV/sec)	3.23 ± 0.79	3.07 ± 0.77	ns
PFR (SV/sec)	5.78 ± 1.69	5.73 ± 1.72	ns

DISCUSSION

Diastolic dysfunction is a commonly encountered feature in many clinical situations, and it may affect per se symptoms of congestive heart failure in some patients with normal systolic performance. Thus, noninvasive evaluation of diastolic function has drawn the attention of many investigators. Several techniques have been employed, but RNA and Doppler echocardiography have become widely used.

Doppler echocardiographic assessment of diastolic function has proven reliable when compared to either contrast ventriculography (*17*) or to RNA (*18,19*). Contrast ventriculographic assessment of diastolic function has some important limitations, mainly due to the potential hemodynamic effects of the contrast medium injection on diastolic parameters and the influence that regional wall motion abnormalities and changes in ventricular shape

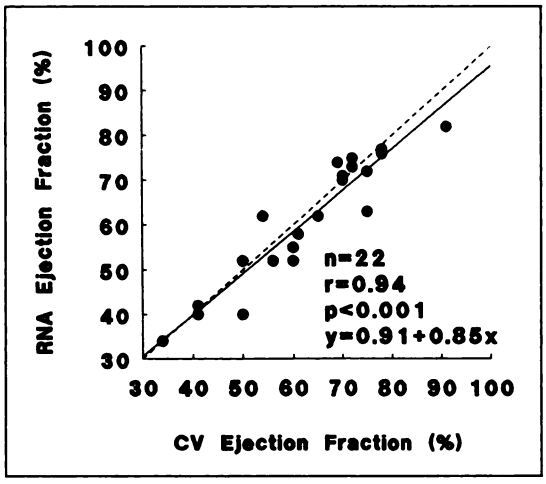

FIGURE 1. Correlation between EF by radionuclide angiography and contrast ventriculography (CV). The solid line represents the line of regression; the dashed line represents the line of identity.

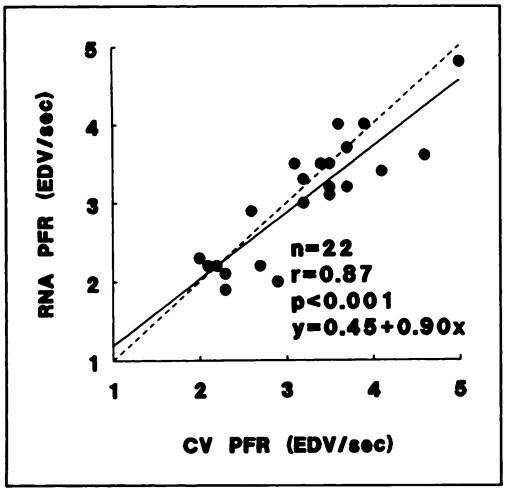

FIGURE 2. Correlation between peak filling rate normalized for end-diastolic volume (PFR) by radionuclide angiography (RNA) and that by contrast ventriculography (CV). The solid line represents the line of regression; the dashed line represents the line of identity.

can have on the reliability of geometric assumptions used in calculations of diastolic parameters.

RNA-derived parameters of LV function have also been compared to similar measures obtained by invasive contrast ventriculography. Magorien and coworkers (20) showed no differences in PFR measured by either contrast ventriculography or RNA with a short time interval between each study, although a nonsignificant trend toward higher values was seen for contrast ventriculography. They did not, however, supply correlation coefficients. McKay et al. (*21*) also performed RNA and contrast ventriculography 30 min apart. They did not measure PFR, however, the time-volume curves obtained by both methods were compared point-by-point and were closely correlated (value of correlation coefficients ranging from 0.85 to 0.95). It can be inferred that had they measured PFR this parameter would have been similar for the two methods. In contrast, a later study by Seals and coworkers (*2*) demonstrated a satisfactory correlation between PFR measured by contrast angiography and a non-imaging nuclear cardiac probe, whereas no correlation was found with PFR measured by RNA.

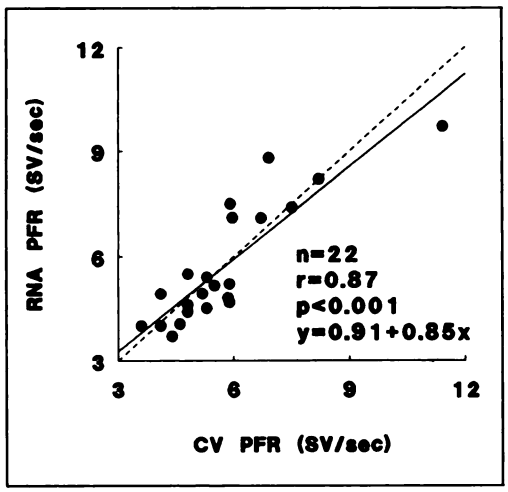

FIGURE 3. Correlation between peak filling rate normalized for stroke counts (PFR) by radionuclide angiography (RNA) and that by contrast ventriculography (CV). The solid line represents the line of regression; the dashed line represents the line of identity.

In the present study, RNA proved reliable when compared to contrast ventriculography in assessing PFR; the parameter measured by either method was very similar and the difference between them was not significant. Furthermore, the mean difference between the two measurements was small in this study group. In addition, PFR measured with the two methods were closely correlated (Fig. 2) with a low s.e.e. (0.39 end-diastolic volumes/sec). In our study population, PFR spanned over a relatively wide range (about a 2.5 ratio between the highest and the lowest values), but the correlation between the two methods was constant throughout the range.

Ejection fraction measured by RNA is undisputedly considered reliable. In our study, it showed a somewhat better correlation than PFR (0.94 versus 0.87, $p < 0.001$ for both), whereas the mean difference between the two methods was similar (approximately 6% for ejection fraction and 8% for PFR of their mean values). Likewise, the s.e.e. (expressed as a percentage of the mean value) was similar for ejection fraction and PFR (approximately 8% and 10%).

Thus our data show that RNA determination of PFR is almost as reliable as the determination of ejection fraction. Moreover, errors in the measurement of PFR are to be considered quite acceptable for clinical use, since they do not exceed 10%.

The striking difference between our findings and those of Seals needs to be addressed. An obvious cause of differences is that in Seals' paper, contrast and radionuclide ventriculographies were performed as far as 24 hr apart in 73% of the patients and longer in the remaining patients, whereas we performed contrast ventriculography within 5 min from the end of the RNA data collection. Moreover, we performed both studies with the patients lying on the cardiac catheterization cradle. The emotional stress associated with cardiac catheterization is capable of affecting cardiac mechanics and thus may account for differences between studies performed in a different environment. This is confirmed by the good correlation found between time-volume curves obtained by contrast and radionuclide angiography in the studies of Magorien and McKay and their coworkers, who used a protocol similar to ours (*20, 21*).

Probably the most relevant difference between the Seals' study and this study is the gate tolerance allowed in RNA collection parameters: ±20% in their protocol as opposed to ±5% in ours. It has to be pointed out that our ±5%

standard by far overestimates the spread in cardiac cycle lengths in our study. In fact, RNA data were collected during atrial pacing when cycle length variation is negligible. This may appear as a limitation of our protocol, introducing a degree of precision which can not possibly be achieved in a standard clinical setting. However, we have demonstrated the intrinsic accuracy of RNA in the assessment of PFR when compared to PFR measured by a single beat on contrast ventriculography. By allowing heart rate to fluctuate as much as ±20%, one blunts measurements of PFR in individuals with greater variability in cycle length. Furthermore, one potential factor that improved the reliability of our measurements is that we used the same filtering algorithm for RNA and contrast ventriculography and, once the final time-volume curve was obtained, the same program for calculating derivative curves and PFR. We have not sought, however, to assess the impact of different filtering techniques on data accuracy and we do not know whether this played a role in explaining the differences between our study and Seals'.

Finally, our results may have been enhanced by the lack of previous myocardial infarction in our patient population. It is possible that the presence of akinetic or dyskinetic areas would affect precision in the measurement of ejection fraction and PFR. Furthermore, our study group did not include patients with severely depressed LV systolic function (lowest ejection fraction value 35%). Sugrue and co-workers (*12*) have shown that reproducibility of RNA evaluation of PFR is poor in patients with dilated cardiomyopathy and impaired LV performance. It is conceivable that this is due to an intrinsic weakness of RNA in drawing time-volume curves in such patients and, hence, it is possible that our correlation with contrast ventriculography would have been poorer if our patient population was comprised of patients with poor LV systolic function.

In conclusion, intrinsic reliability of RNA in assessing PFR seems to be quite good and is comparable to that in the measurement of ejection fraction. A narrow gate tolerance in RNA data collection seems to play a pivotal role in determining the accuracy of PFR determinations. In patients with areas of severe LV wall motion abnormalities, as well as in those with poor LV performance, reliability of RNA in the assessment of diastolic filling properties is yet to be proved.

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