Detection of Coronary Artery Disease by Analysis of Ventricular Filling

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Rapid left-ventricular (LV) diastolic filling assessed by radionuclide ventriculography is re-evaluated in patients with coronary artery disease and normal LV systolic function considering the effects of age and heart rate. Thirty normal subjects were studied along with 44 patients with coronary artery disease and normal LV ejection fractions. The peak filling rate was not quite significantly different between the controls and patients (2.67 ± 0.95 EDV/sec versus 2.25 ± 0.65 EDV/sec, p = 0.08), and the time to peak filling rate was not different. When an inappropriate young control group was compared with coronary disease patients aged 40–65 yr, large differences in peak filling rate were seen. Sensitivity for detection of disease was very low (0%–9%) except when the inappropriate young control group was used. Thus, analysis of rapid diastolic filling cannot detect individual patients with coronary disease who have normal LV ejection fractions. Previous reports to the contrary may have suffered from failure to include the effects of age and heart rate.

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Rapid diastolic filling of the left ventricle (LV) has been evaluated by radionuclide ventriculography in coronary artery disease (*1–6*), and a wide variety of other diseases (*7–10*). There are several reports that the peak filling rate can be used to identify patients with coronary artery disease who have normal LV ejection fractions (*1–5*). More recently these data have been disputed, with the apparent success of the method attributed to failure to exclude patients with coexisting hypertension (*11*) or to other factors (*12*). None of these reports has considered possible age or heart rate dependence of rapid diastolic filling. It has only recently been discovered (*13*) that the peak filling rate is, in fact, strongly dependent on age and heart rate. Therefore, the present study was undertaken to re-evaluate the use of radionuclide measurements of rapid diastolic filling in detecting coronary artery disease in patients with normal ejection fractions.

METHODS

Study Population

Two groups of subjects were studied: normal controls without evidence of heart disease (Group 1) and patients with coronary artery disease and normal LV ejection fractions (Group 2). The coronary disease group was subdivided into patients with normal regional wall motion (Group 2A) and patients with abnormal wall motion (Group 2B). The characteristics of the groups are summarized in Table 1.

There were 30 normal subjects in Group 1 (21 men). Sixteen were normal volunteers and 14 were found to be normal at cardiac catheterization. The normal volunteers (age range 24–64 yr, mean 42) were all asymptomatic and had no risk factors for coronary artery disease and no evidence of cardiovascular or pulmonary disease by history or physical examination. They all had normal rest and exercise electrocardiograms and radionuclide ventriculograms. The 14 normal subjects who underwent cardiac catheterization for evaluation of chest pain (age range 22–80 yr, mean 56) had no significant coronary lesions (≥75% luminal diameter narrowing), no significant valvular disease, and normal LV end-diastolic pressures (<12 mmHg). None of the normal subjects had electrocardiographic evidence of infarction or conduction abnormalities and none had evidence of systemic hypertension or LV hypertrophy as assessed by electrocardiography, contrast ventriculography, or radionuclide ventriculography. The resting radionuclide ventriculograms were normal in all 30 subjects, demonstrating normal regional wall motion and ejection fractions ≥50%.

Group 2 consisted of 44 patients (30 men) with catheterization-proven coronary artery disease and normal radionuclide ejection fractions. None had evidence of significant valvular lesions. No patient had hypertension or evidence of LV hypertrophy by electrocardiography, contrast ventriculography, or radionuclide ventriculography. This group was sub-

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TABLE 1
Ages and Heart Rates of the Normal and Coronary Artery Disease Groups

	Group			
	1	2	2A	2B
Number of subjects	30	44	21	23
Age (yr)	48 ± 18	57 ± 11*	64 ± 8†	52 ± 11‡
Age-range	22–80	32–76	45–76	32–69
Heart rate (bpm)	67 ± 9	68 ± 13	65 ± 11	72 ± 13

* $p < 0.05$ versus Group 1.
† $p < 0.001$ versus Group 1.
‡ $p < 0.05$ versus Group 2A.
All other differences are not significant.

divided into those with normal LV regional wall motion (Group 2A, 21 patients), and those with abnormal regional wall motion (Group 2B, 23 patients). Regional wall motion was assessed from the radionuclide ventriculograms following digital filtering as described below. Electrocardiographic Q waves were present in eight patients in Group 2A and 13 patients in Group 2B. Eight patients had single vessel disease, ten double vessel disease, and 26 triple vessel disease.

To further explore the age dependence of diastolic filling, age-matched subsets of subjects with ages between 40 and 65 yr were also evaluated. Six of the age-matched normals were volunteers, whereas, six were normal at catheterization. To assess the posssible effect of ignoring age, an additional subgroup of normals was analyzed consisting of the ten young normal volunteers, a group frequently recruited for research studies. The characteristics of these groups are shown in Table 2. Eight of the normals were not included in either control group: they were all catheterization normals with ages <40 yr or >65 yr.

Cardiac Imaging and Analysis

Following in vivo labeling of the patient's red blood cells with 25 mCi ^{99m}Tc, 7 million count images were obtained in the best-septal projection [typically 35°–45° left anterior oblique (LAO) with 10°–20° caudal tilt], and in anterior and 70° LAO projections. Images were acquired on a standard field-of-view scintillation camera equipped with a low-energy, all-purpose collimator. Data were stored in a computer in frame mode with 32 frames, each 64 × 64 pixels.

TABLE 2
Ages and Heart Rates of the Age-Matched Groups and Young Normal Volunteers

	Young normal volunteers	Age 40–65			
		Group			
		1	2	2A	2B
Number of subjects	10	12	26	10	16
Age (yr)	29 ± 4*	59 ± 6†	54 ± 7	57 ± 5	53 ± 7
Age-range	24–38	48–65	41–65	45–64	41–65
Heart rate (bpm)	74 ± 9‡	62 ± 7	65 ± 9	63 ± 10	67 ± 9

* $p < 0.001$ versus all groups.
† $p < 0.05$ versus Group 2B.
‡ $p < 0.05$ versus Group 1.
All other differences are not significant.

Analysis of the image data has been described in detail previously (*13*). Briefly, all analysis was performed on images obtained in the best septal projection. The LV ejection fraction was determined from the counts in manually drawn end-diastolic and end-systolic regions of interest. To evaluate the diastolic parameters, a LV time-activity curve was first generated from the background-corrected raw counts in the fixed end-diastolic region of interest. The time-activity curve was then smoothed by fitting with a five-harmonic Fourier series. The first derivative was computed by analytic differentiation of the fitted curve. The peak filling rate was then determined as the maximum slope of the time-activity curve in diastole, indicated by the maximum value of the first derivative. The time to peak filling rate is the time from end-systole, defined as the zero crossing of the first derivative, to the time of the peak filling rate. The peak filling rate is expressed in units of end-diastolic volumes per second (EDV/sec), and the time to peak filling rate is in milliseconds. To ensure analysis of only the rapid filling period, studies were excluded that failed to show a clear separation between rapid filling and atrial contraction.

Regional wall motion was determined by independent visual assessment of the three-view radionuclide ventriculograms by two experienced observers following processing with a digital filter that has both edge-sharpening and smoothing properties (*14*). This filter has been shown in quantitative studies to yield more accurate analysis of regional wall motion than conventional methods.

Age and Heart Rate Dependence

A recent paper from this laboratory (*13*) reports an investigation of the age and heart rate (HR) dependence of rapid filling in the same group of 30 normal control subjects employed in the present study. Peak filling rate (PFR) was found to correlate significantly with age ($r = -0.82$, $p < 0.0001$) and with heart rate ($r = 0.61$, $p < 0.001$). Multiple regression analysis yielded the following equation incorporating these two effects:

$$\text{PFR (EDV/sec)} = 2.24 - 0.036\ \text{AGE} + 0.032\ \text{HR}, \quad (1)$$

where age is in years and HR is in bpm.

To account for this age and heart rate dependence, Eq. (1) is used to determine the predicted normal peak filling rate, PFR (predicted, age, HR), for each control and coronary disease patient based on that patient's age and heart rate. This predicted peak filling rate will have an associated error SD (age, HR), the standard deviation of PFR (predicted, age, HR) associated with the regression equation [Eq. (1)]. The difference, ΔPFR, is then computed as

$$\Delta\text{PFR} = \text{PFR (measured)} - \text{PFR (predicted, age, HR)}, \quad (2)$$

where PFR (measured) is the actual peak filling rate for the particular patient. To determine if this difference from the expected normal value is statistically significant, Eq. (2) is divided by the s.d. of the predicted value determined in Eq. (1), giving the relative deviation from the expected value, called the normalized PFR difference, as

$$\text{normalized PFR difference} = \Delta\text{PFR/s.d. (age, HR)}. \quad (3)$$

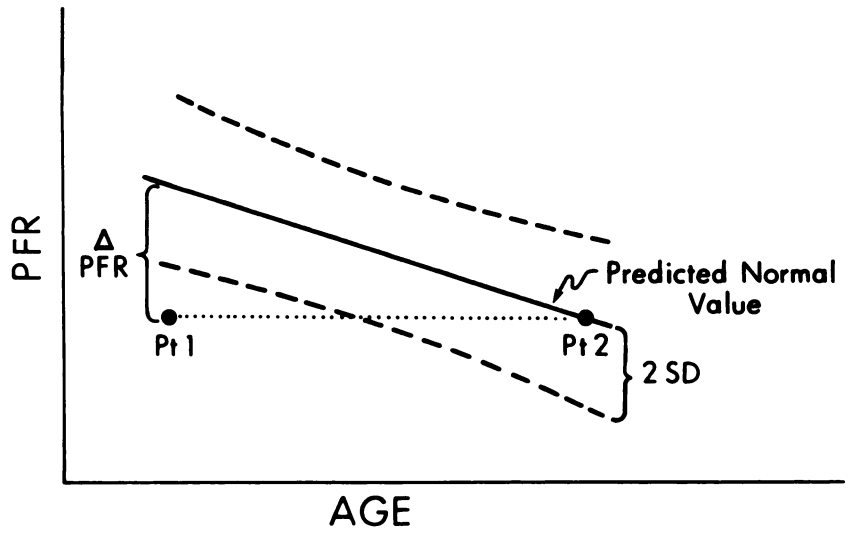

FIGURE 1
The measured PFR is shown in this idealized drawing for two subjects with the same PFR and HR who differ only in age. Patient 1 is young and Patient 2 is old. The solid line is the predicted normal filling rate as a function of age [Eq. (1)], whereas, the broken lines are the two S.D. limits for the predicted normal values. Note that the measured PFR for the young Patient 1 is abnormally low ($|\Delta PFR/S.D.| > 2$), whereas, the identical filling rate for the old Patient 2 is normal (Δ PFR/S.D. = 0). PFR = peak filling rate; Pt 1 = Patient 1; Pt 2 = Patient 2; S.D. = standard deviation.

This normalized peak filling rate difference is analogous to the *t*-test widely used in statistics (*15*): A value greater in magnitude than ~ 2 indicates there is at least a 95% chance that the difference between the measured and predicted filling rates is real and not simply due to a statistical fluctuation. These considerations are illustrated graphically in Figure 1 for two patients with the same peak filling rates and heart rates but different ages.

Statistical Methods

All values are expressed as the mean ± 1 s.d. The statistical significance of differences between group means was determined by analysis of variance and the Scheffe test for multiple comparisons (*15*). Differences are considered significant if $p < 0.05$. To determine the sensitivity for detection of coronary artery disease, the lower limit of normal for the peak filling rate was chosen as the lower 95% confidence limit for the normal controls (two-tailed t-test). The significance of differences between sensitivities was assessed by the chi-square test (*15*).

RESULTS

The group mean values for peak filling rate, time to peak filling rate, age, and heart rate corrected peak filling rate (the normalized peak filling rate difference), and LV ejection fraction are shown in Table 3. Time to peak filling rate was not analyzed further because the group mean values did not discriminate between groups (p = N.S.), and because this parameter is not significantly dependent on age (*13*). Figure 2 shows the peak filling rates for all patient studies. Figure 3 shows the normalized peak filling rate differences reflecting the age and heart rate adjustments given by Eqs. (1)–(3) and illustrated in Figure 1.

When the effects of age and heart rate are ignored (Table 3, Fig. 2) the mean peak filling rate of all coronary disease patients (Group 2) is not quite significantly different than controls (Group 1); 2.25 versus

TABLE 3
Diastolic Parameters and Ejection Fractions for the Normal Subjects and the Coronary Artery Disease Groups

	Group			
	1	2	2A	2B
Peak filling rate (EDV/sec)	2.67 ± 0.95	2.25 ± 0.65*	2.28 ± 0.57	2.22 ± 0.73
Time to peak filling rate (msec)	180 ± 40	176 ± 62	185 ± 63	169 ± 61
Normalized peak filling rate difference**	0.00 ± 0.83	−0.26 ± 1.15†	0.39 ± 1.02‡	−0.85 ± 0.94§
Ejection fraction (%)	64 ± 6	63 ± 8	66 ± 8	60 ± 6¶

EDV/sec = end-diastolic volumes per second.
*p = 0.08 versus Group 1.
†p > 0.25 versus Group 1.
‡p < 0.001 versus Group 2B.
§p < 0.01 versus Group 1.
¶p < 0.05 versus Group 2A.
All other differences are not significant ($p > 0.05$).
**Defined in Eqs. (1)–(3) and Figure 1.

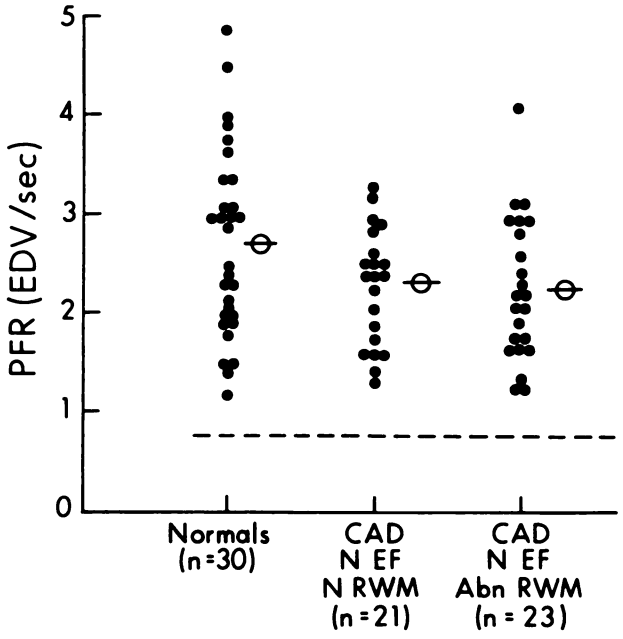

FIGURE 2
The PFR is shown for the normal controls (Group 1) and the patients with coronary artery disease and normal ejection fraction who have normal regional wall motion (Group 2A) and abnormal regional wall motion (Group 2B). The large circles indicate the group mean values. The dashed line is the lower 95% confidence limit. Abn RWM = abnormal regional wall motion; CAD = coronary artery disease; EDV/sec = end-diastolic volumes per second; n = number of subjects; NEF = normal ejection fraction; NRWM = normal regional wall motion; PFR = peak filling rate.

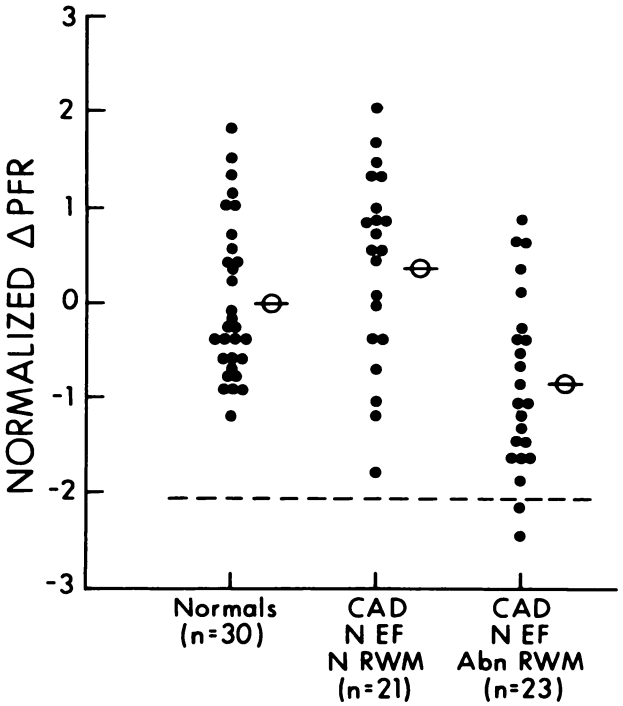

FIGURE 3
The normalized PFR difference is shown for the normal controls (Group 1) and the patients with coronary artery disease and normal ejection fraction who have normal regional wall motion (Group 2A) and abnormal regional wall motion (Group 2B). The large circles indicate the group mean values. The dashed line is the lower 95% confidence limit. Normalized ΔPFR = normalized peak filling rate difference; other abbreviations are defined in Figure 2.

2.67, $p = 0.08$). No effect is detected when patients with normal and abnormal wall motion (Groups 2A and 2B) are considered separately. Note that one patient in Group 2B has a much higher peak filling rate than the others. This is because he is the youngest coronary patient studied (age 32); this apparent outlier falls well within the range of the other patients when age is considered (compare Figs. 2 and 3).

The age and heart rate effects are explicitly taken into account with the normalized peak filling rate differences shown in Table 3 and Figure 3. Again, the mean value for all patients (Group 2) is not different than the controls (−0.26 versus 0.00, $p > 0.25$). However, the subgroup with abnormal regional wall motion (Group 2B) now has a lower mean value than both the controls (Group 1) and the subgroup with normal regional wall motion (Group 2A).

To further evaluate the age dependence of the peak filling rate, subsets of normal subjects and patients with coronary artery disease between ages 40 and 65 yr were analyzed. Figure 4 shows those patients matched with normals in the same age-range and to the group of young normal volunteers. Table 4 presents the diastolic data and the ejection fractions for the 40- to 65-yr-old patients, compared with the two control groups. Note the lack of separation between the age-matched controls and coronary patients and the great difference when the inappropriate young control group is used. Here, in this smaller patient group, no differences were detected in the data for the normalized peak filling rate differences.

Table 5 gives the sensitivity for detection of coronary artery disease using the 95% confidence intervals shown by the dashed lines in Figures 2–4. Note the apparent good sensitivity only when the inappropriate young control group is used.

To assess the effect of disease severity on the findings described above, the data were reanalyzed excluding the eight patients with single-vessel coronary artery disease, leaving 36 patients with double or triple vessel disease. The mean ages, heart rates, and ejection fractions were not significantly different in this subgroup than in the full groups. The peak filling rate for Group 2 was now significantly different than for the controls (2.19 ± 0.60 versus 2.67 ± 0.95 for Group 1, $p < 0.05$). Peak filling rate was not significantly different for Group 2A, but it was lower in Group 2B (2.07 ± 0.63, $p < 0.05$ versus Group 1). No significant changes were found in the normalized peak filling rate differences

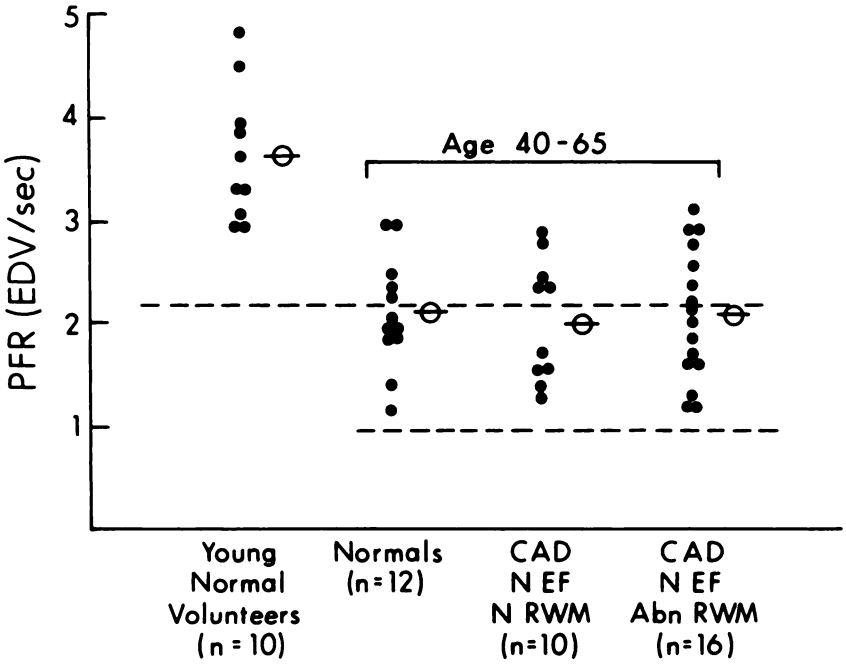

FIGURE 4
The PFR is shown for the young normal volunteers and subjects aged 40–65 in Group 1 (normal controls), Group 2A (coronary disease with normal regional wall motion), and Group 2B (coronary disease with abnormal regional wall motion). The large circles indicate the group mean values. The upper dashed line is the lower 95% confidence limit derived from the young normals and the lower dashed line is the confidence limit from the age-matched normals. Abbreviations are defined in Figure 2.

between the two- and three-vessel subgroup and the complete coronary disease groups. The conclusions drawn from the age-matched groups (Tables 2 and 4) and the sensitivity results (Table 5) were not substantially affected by exclusion of the single-vessel patients.

DISCUSSION

Early reports of measurement of LV diastolic filling by radionuclide angiography (*1–5*) indicated that patients with coronary artery disease and normal resting LV ejection fractions frequently had depressed rapid ventricular filling. Thus, it appeared that radionuclide angiography could identify patients with coronary disease who had previously gone undetected by noninvasive evaluation because they had normal ejection fractions. More recently, it has been suggested that this distinction between normal and diseased hearts with good contractile function cannot, in fact, be made by scintigraphic analysis of diastole (*11,12*). One report (*11*) postulated that LV hypertrophy due to hypertension could be a possible explanation for the apparent success of the method in earlier studies because hypertrophy alone is known to depress the peak filling rate (*8,9*). To avoid this potential confounding factor, no patients with evidence of hypertension or LV hypertrophy were included in the present study. Disease in the left anterior descending coronary artery has also been proposed as a cause for depressed rapid filling (*11*). There were too few patients in our study who did not have left anterior descending disease to permit a distinction on this basis.

No previous studies have explicitly included the effects of age and heart rate on diastolic filling. Recently, both these factors have been shown to be important determinants of rapid filling in normal subjects (*13*). Thus, the present study was undertaken to reassess the value of scintigraphic measurements of rapid filling in the detection of coronary artery disease when age and heart rate are explicitly taken into account.

The most diagnostically challenging group are those

TABLE 4
Diastolic Parameters and Ejection Fractions for Age Matched Groups and Young Normal Volunteers

	Young normal volunteers	Age 40–65			
		Group			
		1	2	2A	2B
Peak filling rate (EDV/sec)	3.64 ± 0.65	2.12 ± 0.53*	2.07 ± 0.62*	2.02 ± 0.61*	2.09 ± 0.64*
Time to peak filling rate (msec)	170 ± 41	194 ± 39	187 ± 60	192 ± 74	187 ± 51
Normalized peak filling rate difference†	0.12 ± 1.02	−0.02 ± 0.78	−0.61 ± 0.95	−0.36 ± 0.85	−0.76 ± 1.00
Ejection fraction (%)	64 ± 5	64 ± 8	62 ± 7	65 ± 8	60 ± 6

The abbreviations are listed in Table 3.
* $p < 0.001$ versus normal volunteers; all other differences are not significant.
† Defined in Eqs. (1)–(3) and Figure 1.

TABLE 5
Sensitivity of the Peak Filling Rate for Detection of Coronary Artery Disease

	All ages		Age 40–65‡	
Group	No correction*	With correction†	Versus 40–65 normals	Versus young normals
2	0/44 (0%)	2/44 (5%)	0/26 (0%)	14/26 (54%)¶
2A	0/21 (0%)	0/21 (0%)	0/10 (0%)	5/10 (50%)¶
2B	0/23 (0%)	2/23 (9%)	0/16 (0%)	9/16 (56%)¶

*These data are obtained from Figure 2.
†These data are obtained from Figure 3 using Eqs. (1)–(3).
‡These data are obtained from Figure 4.
¶$p < 0.001$ versus all other columns; all other differences are not significant.

patients with completely normal radionuclide studies by conventional criteria: They have both normal ejection fractions and normal regional wall motion. Those patients (Group 2A) were separated from a group with normal ejection fractions but abnormal regional wall motion (Group 2B).

The first analysis ignored the age and heart rate effects (Table 3, Fig. 2). The mean value for peak filling rate was lower in the patients with coronary artery disease (Group 2), but the difference did not achieve statistical significance ($p = 0.08$). When the regression equation relating peak filling rate to age and heart rate was employed to give the normalized peak filling rate difference (Table 3, Fig. 3), the mean value for all patients with coronary disease (Group 2) was not different from controls ($p > 0.25$), whereas, in the subgroup with abnormal regional wall motion, the normalized peak filling rate difference was significantly lower than the value in controls and in the subgroup with normal regional wall motion. Thus, when proper correction for the large age and heart rate effects are made, there may, in fact, be depressed rapid filling in patients with coronary artery disease with normal ejection fractions and abnormal regional wall motion.

When the patients with milder, single-vessel disease were excluded, the peak filling rate for all patients (Group 2) and for the subgroup with abnormal regional wall motion (Group 2B) became significantly lower than in the normal controls.

It is uncertain if the failure to find a difference in the group mean values for peak filling rate is due to a true identity of these parameters or if the almost significant difference (2.25 versus 2.67, $p = 0.08$, Table 3) would have become significant if larger samples were available. As discussed above, the difference was significant when the patients with single-vessel disease were excluded. The clearly more similar results with age and heart rate correction (−0.26 versus 0.00, $p > 0.25$, Table 3) may arise from the correction for the difference in mean ages between Groups 1 and 2.

To illustrate the error caused by using young normal controls to evaluate the generally older patients with coronary artery disease, the peak filling rate was reanalyzed using patients with ages between 40 and 65 yr and two control groups, one comprised of age-matched controls and the other a group of young normal volunteers (Table 3, Fig. 4). When the correct, age-matched controls are used, no group differences are identified. Note, however, the strikingly different findings with the inappropriate young control group. These data further emphasize the great importance of age in studies of diastolic function. In this analysis the failure to observe a difference between controls and Group 2B, observed in Figure 3, may be a result of the small number of patients evaluated in the age-matched groups.

When the radionuclide ventriculogram is used to identify individual patients who may have coronary artery disease, the sensitivity and specificity are the key parameters, not the group means discussed above. Although the specificity of the test is high (all control subjects fall within the 95% confidence limits), the sensitivities, shown in Table 5 and derived from Figures 2–4, demonstrate that peak filling rate cannot detect coronary disease in individual patients (even those with two- or three-vessel disease) who have normal LV ejection fractions (sensitivity = 0%–9%) when age is taken into account. The previously reported high sensitivities (*1–5*) are now obtained only when the inappropriate young control group is used.

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