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Atrial Kinetics and Left Ventricular Diastolic Filling in the Healthy Elderly

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A delay of left ventricular isovolumic relaxation and decrease in myocardial compliance may result in a decline of measured early filling rates in elderly subjects. Previous studies of diastolic function, however, have not excluded coronary artery disease or addressed the contribution of atrial contraction to diastole. The present study evaluated radionuclide-derived diastolic variables in 13 healthy elderly volunteers aged 75 ± 6 years without symptoms or risk factors for coronary disease who had normal findings on the stress electrocardiogram, stress gated blood pool imaging and two-dimensional echocardiogram. Results were compared with those of a group of 10 healthy young volunteers aged 26 ± 5 years. High count, 32 frame, double-buffered gated blood pool acquisitions were obtained at rest in the left anterior oblique view with an RR interval variation <5%. Left ventricular time-activity curves were analyzed and flow-volume loops for each group were constructed.

In the healthy elderly: 1) peak early diastolic filling rate is decreased, 2) time of peak early filling and time to first third of diastolic filling are delayed, and 3) peak late left ventricular filling rate and percent of atrial filling volume are augmented, suggesting an adaptive response of the atria to diminished left ventricular compliance.

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Left ventricular diastolic function is altered in a spectrum of disease states including coronary artery disease (1–4), hypertrophic cardiomyopathy (5,6), hypertension (7,8) and congestive heart failure (9,10). Additionally, atrial contraction augments ventricular filling to a variable degree in different conditions (6,11–13). Although age-related alteration in diastolic function in elderly subjects has been noted (11–14), it has not been previously studied in a group of asymptomatic volunteers in whom silent coronary artery disease has been effectively excluded. Accordingly, the present study was undertaken to evaluate the kinetics of early and late diastolic filling with high temporal resolution gated blood pool scintigraphy after careful noninvasive exclusion of coronary artery disease and other myocardial and valvular diseases that may alter diastolic function.

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Methods

Study subjects. The present prospective study evaluated 13 healthy elderly volunteers (Group I) aged 68 to 86 years (mean 75); there were 11 women and 2 men. All volunteers were asymptomatic, had no risk factors for coronary artery disease and were not receiving cardiotonic medications. Physical examination, rest and maximal or fatigue-limited exercise electrocardiogram, M-mode, two-dimensional and Doppler echocardiograms and exercise radionuclide ventriculograms were normal in all subjects. Criteria for exclusion included valvular, myocardial or pericardial disease, a positive stress electrocardiogram, exercise-induced asynergy or abnormal left ventricular functional response to exercise. A total of 14 elderly volunteers were excluded because of murmurs (n = 6), previous myocardial infarction (n = 2), abnormal two-dimensional or Doppler echocardiogram (n = 4) and technically inadequate radionuclide imaging (n = 2). In addition, 10 healthy young volunteers (Group II) with a normal two-dimensional echocardiogram and no cardiac risk factors, aged 20 to 33 years (mean 26), were studied; there were 9 men and 1 woman.

All 13 elderly subjects had visually normal rest and exercise left ventricular function; 11 of them had an increased left ventricular ejection fraction ≥5% with exercise and 2 an increase of 2 and 3%, respectively (no change). Ten of

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the 13 subjects achieved at least 85% of the maximal predicted heart rate; the remaining 3 achieved 70 to 85% of the expected rate. Although two patient studies were interpreted as showing rest hypokinesia of the right ventricular apex which was not seen on the two-dimensional echocardiogram, this did not worsen with exercise as seen by gated blood pool imaging and was not associated with exercise electrocardiographic ST segment abnormalities. Informed written consent was obtained from all volunteers. This protocol was approved by the Human Research Committee at our institution.

Radionuclide imaging. The patient's red blood cells were labeled with 25 mCi of technetium-99 using the in vivitro method (15). Gated blood pool images were acquired with a small field of view single crystal gamma camera (Technicare 550) using a low energy all-purpose parallel hole collimator. Rest supine multigated images were obtained in the best septal left anterior oblique view using 32 frames/cycle in a 64 × 64 pixel matrix for an average count density of 300 counts/pixel within a left ventricular region of interest. The framing rate and count total were double that of the usual clinical study acquisition. The acquisition was performed using a double buffered method to achieve an RR interval variation of <5%. Images were digitally recorded on a microprocessor equipped with a hard disc (Technicare 560). This technique stores the information acquired during each cardiac cycle in a temporary buffer before accepting or rejecting each beat. The mean time of acquisition was 30 to 40 minutes. In addition, anterior and extreme left anterior oblique views were obtained in a routine manner with 16 frames/cycle and a count density of 300 counts/pixel (without double buffering). All subjects then performed graded supine bicycle exercise in 3 minute stages of 25 W increments until extreme fatigue, maximal predicted heart rate or dyspnea were reached (none stopped because of chest pain or significant ST segment depression). The patients were monitored with a full 12 lead electrocardiogram (EMCI Medtronics), and routine gated images were acquired at each stage for 2½ minutes.

Radionuclide image analysis. The rest left anterior oblique and peak exercise images underwent routine analysis for ejection fraction by an experienced nuclear cardiology technologist after background subtraction and temporal and spatial smoothing. All diastolic functional variables were separately obtained from the high count double-buffered rest left anterior oblique 32 frame images. These images were initially smoothed spatially with a routine 3 × 3 point filter and temporally with a 3 point filter. Left ventricular regions of interest were obtained using the interactive quadrant threshold method (Technicare QMICA). These regions were saved and superimposed on the original unsmoothed images to obtain unsmoothed left ventricular time-activity curves. The curves then underwent a discrete Fourier transformation and were filtered temporally in the frequency domain using a Hanning filter with a cutoff of five cycles/period. This filter was chosen to optimize the tradeoff between resolution and noise for diastolic variables of global left ventricular time-activity curves, consistent with the work of Bacharach et al. (16,17). A filtered, continuous curve was reconstructed in the time domain as well as its first and second derivatives. Points of maximal and minimal counts and maximal and minimal slopes were obtained and calculated to a millisecond time precision by the reiterative method of Newton previously used in our work (18,19). The following variables were calculated: peak early filling rate, peak late filling rate, time of peak early filling rate and time of first third filling. The time of peak early filling rate was calculated as the time differences between the R wave of the electrocardiogram signal and the timing of peak early filling rate. The time of first third filling was the interval between end-systole and the time when the volume of filling equaled one-third of the stroke volume. The peak filling and ejection rates were divided by the end-diastolic counts.

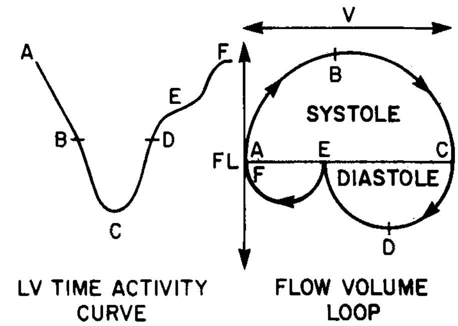


Figure 1. Schematic diagram of the relation between left ventricular (LV) time-activity curve (**left**) and flow-volume loops (**right**). A = beginning of ejection; B = peak ejection rate; C = end-systole; D = peak filling rate; E = commencement of atrial filling; F = end-diastole; FL = flow; V = volume.

In addition to the variables calculated directly from the time-activity curve (Fig. 1, left), the relation of early and late filling phases was studied in the following manner. The relative volume (counts) was plotted against the first derivative of the continuous filtered curve (Fig. 1, right) similar to the technique of Green et al. (20). However, in contrast to that technique, the systolic ejection rate was normalized to the maximal ejection rate and the diastolic filling rate was normalized to the maximal filling rate so that maximal deflections were constant. Thus, the shape of the curve rather than the absolute ejection or filling rates are displayed. This was done because these rates tend to be dependent on the ejection fraction.

All subjects showed discrete separation of the diastolic portion of the curve into early and late (atrial) filling phases, although only some showed the rate of filling dip to zero (diastasis). This enabled us to separately measure the maximal early and delayed (atrial) filling rates and to measure the relative contribution of early filling and atrial filling to

Table 1. Summary of Findings

	PEFR*	PLFR*	TPEFR (ms)	TFT (ms)	AF%
Group I	2.3 ± 0.5	1.9 ± 0.8	543 ± 52	169 ± 30	31 ± 10
Group II	3.5 ± 0.5	0.8 ± 0.3	471 ± 33	125 ± 21	16 ± 4
p Value	<0.002	<0.005	<0.005	<0.005	<0.005

*Measured as end-diastolic volumes. AF% = percent of atrial filling volume; PEFR = peak early filling rate; PLFR = peak late filling rate; TFT = time of first third filling; TPEFR = time to early filling rate.

the total filling volume (% atrial filling). The latter was expressed as a percent of total diastolic filling and was measured by calipers directly from the flow-volume loops.

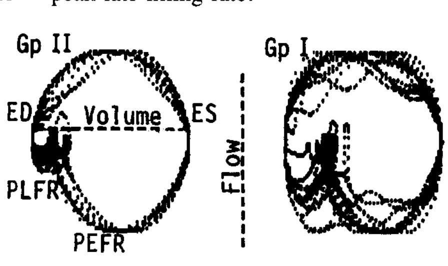
Statistical analysis. The following variables were examined and plotted for the two groups: rest heart rate, left ventricular rest ejection fraction, time of peak early filling rate, time of first third filling, peak early (fast) filling rate, late (atrial) filling rate and the percent of diastole due to atrial contraction. The means of the individual variables for the two groups were tested by Student's *t* test (21). The Bonferroni correction was applied to compensate for the multiple tests used (22); a corrected probability (p) value of <0.05 of two means belonging to the same population was considered significant enough to reject the null hypothesis.

Results

Table 1 shows the mean and standard deviations for Group I (elderly) and Group II (young) volunteers. Figure 2 displays the superimposed flow-volume loops of each subject in Groups I and II containing many of the measured variables, demonstrating in Group I augmented peak late filling rate relative to the peak early filling rate and augmented percent filling volume due to atrial systole.

Figures 3 to 6 compare these variables between the elderly (Group I) and young (Group II) subjects. The mean heart rate and ejection fractions did not differ significantly in the two groups (Fig. 3). In the healthy elderly, the peak early filling rate was decreased ($p < 0.002$), and both the time to peak early filling rate and the time to first third filling were delayed compared with values in the younger subjects ($p < 0.005$ and $p < 0.005$, respectively). The peak late filling rate was augmented ($p < 0.005$) and the percent atrial filling volume was also augmented in the elderly when compared with that in the young volunteers.

Figure 2. Superimposed flow-volume loops of younger subjects (**left**, Group II [Gp II]) and the elderly (**right**, Group I [Gp I]) showing differences in shape, particularly during diastole. In diastole the initial negative deflection represents the early filling phase and the later second deflection the atrial contribution. ED = end-diastole; ES = end-systole; PEFR = peak early filling rate; PLFR = peak late filling rate.

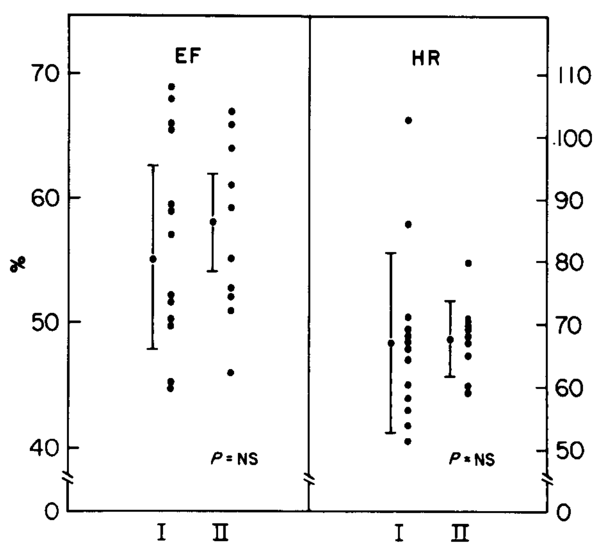


Discussion

Previous studies on effect of aging in cardiac function. Although abnormalities in systolic ventricular function in the elderly can be induced with stress, several variables of cardiovascular function also demonstrate changes at rest. Strandell (23) found that the interval between the first and second heart sounds was longer in a group of men 61 to 83 years of age than in a group of 21 to 25 year olds.

In addition to changes in the contractile properties of the aging cardiac muscle, there is considerable evidence to suggest that there are alterations in the compliance or stiffness properties of the ventricle (24,25). Noninvasive and invasive estimation of diastolic function in both aging humans

Figure 3. Comparison of the mean heart rate (HR) and ejection fraction (EF) in the elderly (Group I) and younger subjects (Group II), showing no significant differences.



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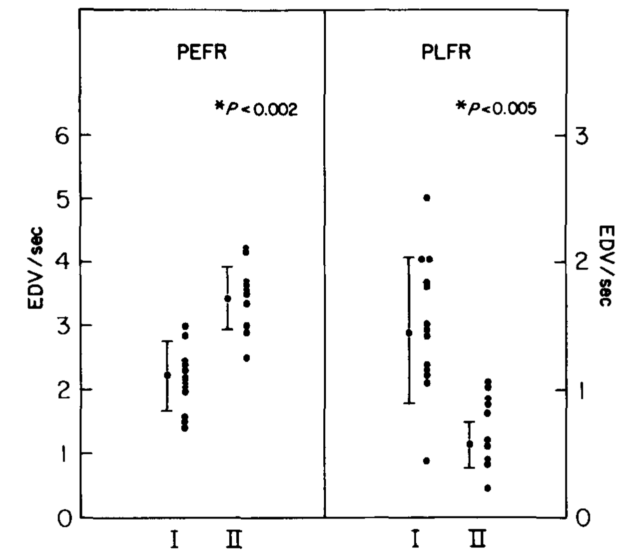


Figure 4. Comparison of peak early filling rate (PEFR) and peak late filling rate (PLFR) in the elderly (Group I) and the younger subjects (Group II), showing statistically significant differences in both variables. EDV = end-diastolic volume.

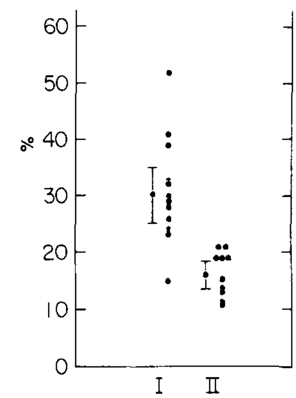


Figure 6. Comparison of the percent volume of atrial filling in the elderly (Group I) and the younger subjects (Group II), showing a statistically significant difference.* $p < 0.005$.

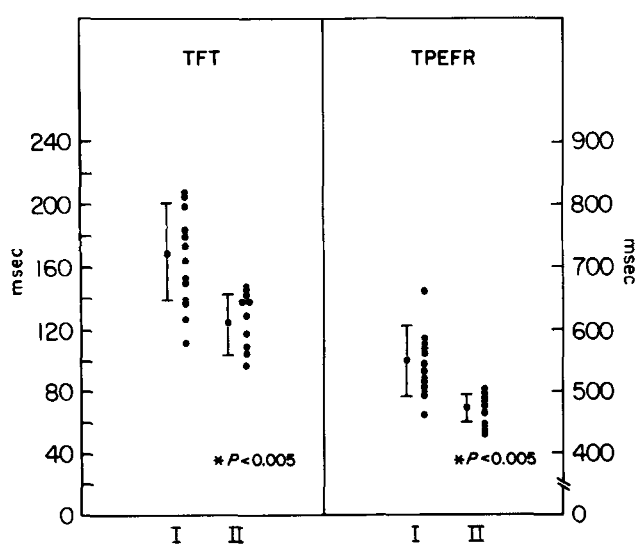
and animals suggest a progressive decline in diastolic function with increasing age (11–14). Studies of isolated hearts and cardiac muscle from aging animals (26,27) suggest that functionally significant decreases in overall cardiac function may follow prolonged contraction duration as a result of a prolongation of the active state, decreased inotropic response to catecholamines and increased chamber stiffness.

Changes in myocardial collagen may lead to increased passive stiffness of the myocardium and a decrease in compliance. Furthermore, the contractile proteins themselves may develop an increased resistance to separation. Echocardiograms of clinically normal patients have also demonstrated an increase in left ventricular wall thickness with age, with increases in both systolic and diastolic posterior wall thickness (13,28). These changes may become hemodynamically important as the result of any process that produces an increase in diastolic left ventricular volume, creating a disproportionate increase in diastolic pressure in a noncompliant ventricle.

Role of coronary artery disease. Most previous studies of diastolic dysfunction in the elderly have failed to adequately screen for asymptomatic coronary artery disease. Therefore, their observed altered diastolic filling may be due to the aging process alone or to occult coronary artery disease. Epidemiologic studies (29–34) report that the prevalence of coronary artery disease increases markedly with age to at least 50% in men by the end of the sixth decade with at least 50% of the disease being occult. The highest prevalence of coronary artery disease found by clinical and laboratory methods in the community-dwelling elderly population over age 75 years is >30% (29–34). Therefore, careful screening of the study population must be performed before assessing the effect of aging alone on diastolic function.

Previous studies of myocardial function in older age groups have not excluded occult coronary artery disease. The elderly population in the present study had no risk factors for coronary artery disease, a normal echocardiogram at rest and normal baseline and exercise electrocardiograms and no exercise-induced asynergy. Thus, the probability of occult coronary artery disease in our group would be small. This estimate is confirmed by the Baltimore Longitudinal Study on Aging (35,36), in which the prevalence of occult coronary artery disease by history and rest electrocardiogram was doubled when stress criteria (electrocardiographic ST shifts and abnormal thallium scan) were added.

Figure 5. Comparison of time to peak early filling rate (TPEFR) and time of first third filling (TFT) in the elderly (Group I) and the younger subjects (Group II), showing statistically significant differences in both parameters.



Noninvasively measured changes with aging. Radionuclide scintigraphy has been previously utilized as a tool for measuring diastolic function, but only rarely in elderly subjects (1–6,8,10,11,37,38). Echocardiographic studies (28,29) have shown that the diastolic descent of the mitral valve tends to decrease and the ratio of the height of the presystolic peak to that of the early diastolic peak tends to increase with aging. These changes are believed to be related to diminished left ventricular compliance. However, mitral valve apparatus stiffness may also be contributory. Smith et al. (39) demonstrated that atrial function, reflected in the radionuclide time-activity curve as augmented left ventricular end-diastolic volume, appears to distinguish physiologic (athletes) from pathologic (hypertensive) left ventricular hypertrophy and left atrial enlargement. Echocardiography, however, showed an increased left atrial index in both groups and did not separate out the two groups. Miyatake et al. (40) have demonstrated by Doppler echocardiography that the ratio of peak flow during the atrial contraction phase to the rapid filling phase showed a significant increase with age. However, again, no stress study was undertaken to exclude occult coronary artery disease.

The Doppler technique may be limited by several factors. Tachycardia may cause the atrial and rapid filling waves to overlap (this is a limitation of the radionuclide method as well). The geometry of left ventricular inflow may not permit a satisfactory Doppler study, and if angulation between the sampling Doppler beam and the blood flow direction at the mitral inflow is >10°, the error may be >3%.

Contribution of atrial contraction to ventricular filling. Although William Harvey (41) first suggested that atrial contraction contributes to ventricular filling, it was Gessel (42) who quantified the contribution of the atria. He demonstrated that in heart-lung preparations, atrial contraction could augment ventricular filling by about 50% at any operative filling pressure and that ventricular output was augmented most effectively when atrial contraction was completed 0.008 to 0.02 second before the onset of ventricular contraction. Wiggers and Katz (43) showed that atrial systole contributed from 18 to 60% of the total volume of blood that filled the left ventricle. The factors that determine atrial contraction appear to be length of the atrial fibers and reflex control through the vagal and sympathetic nerves.

Braunwald and Frahm (44) demonstrated that in normal subjects aged 5 to 49 years, left ventricular end-diastolic pressure is not raised above the mean left atrial pressure, although atrial systole may augment ventricular filling. However, in left ventricular disease states, the left ventricular end-diastolic pressure is increased, but mean left atrial pressure is maintained at a much lower level. Both the force and duration of atrial contraction may contribute to this phenomenon. The force of contraction was found to be greater in patients with left ventricular disease than in normal subjects and the duration of atrial contraction was increased. These hemodynamic observations, however, did not involve healthy elderly subjects.

Radionuclide angiographic changes with aging. Gated blood pool imaging has been used to demonstrate an age-related decline in maximal filling rate at rest (11,37) although atrial kinetics were not addressed previously. Green et al. (38) showed that the flow-volume loops of a group of seven elderly patients in whom coronary artery disease had been excluded mimicked those of a group with coronary artery disease, suggesting that aging may produce similar results. This flow-volume method, similar to the one used in the present study, offers a graphic representation of the multiple changes in global systolic and diastolic left ventricular function.

The present study demonstrates that atrial contribution to left ventricular filling increases with aging, as seen by the augmentation of peak late (atrial) filling velocity and a doubling of the (percent) atrial volumes. The reduced early filling velocities suggest abnormal isovolumetric relaxation or reduced compliance of the ventricle, or both. Wall thickness measured by ultrasound was normal, and thus did not explain these findings. Possibly, the atrial changes are an adaptive mechanism in response to early reduced left ventricular filling and greater atrial systolic pressures.

Limitations. The methodologic limitations of radionuclide angiography, however, should not be underestimated. Unlike the routine determination of left ventricular ejection fraction, the determination of global left ventricular filling rates appears to require high temporal resolution. Both decreased framing rate and low count acquisition can result in significant errors. In addition, the time-activity curve shape is sensitive to the region of interest determination. Errors may also occur with cycle length variations that can distort the shape of the curve. To overcome the last problem, we used a high framing rate and high count density study with minimal RR interval variation. Fluctuation in heart rate and loading conditions limit the potential usefulness of the diastolic measurements to rest studies alone, although these conditions influence the reference standard evaluation of left ventricular diastolic filling by invasive methods also. In our study both the normal and the elderly subjects had insignificant differences in mean rest heart rates and mean rest ejection fractions. Thus, the results in diastolic variables found here are unlikely to be artifacts secondary to these variables (Fig. 3).

Conclusions. There is augmentation of both atrial filling velocities and atrial volume, associated with declining early peak filling velocities of the left ventricle in the healthy elderly.

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