

Abnormalities of Doppler Measures of Diastolic Function in the Healthy Elderly Are Not Related to Alterations of Left Atrial Pressure

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Background—Normal healthy aging results in changes in Doppler indexes of diastolic function. One widely accepted explanation for these alterations that is based on animal data is an age-associated impairment of myocardial relaxation resulting from abnormal myocyte calcium handling. However, an alternative theory based on altered left atrial compliance with aging has been proposed in which early left atrial pressure could be low in the aged heart but rise rapidly during atrial diastole, resulting in a higher late atrial pressure and thus a normal mean pressure. We sought to explore this issue directly by performing a detailed analysis of the pulmonary capillary wedge pressure waveform obtained by right-heart catheterization during 5 different loading conditions.

Methods and Results—Twelve healthy elderly sedentary subjects (mean age, 69.8 ± 3 years) were recruited for the seniors group. An additional 12 young sedentary subjects (mean age, 35 ± 8 years) made up the young group. All subjects were rigorously screened for comorbidities. All subjects underwent transthoracic echocardiography to determine Doppler variables of early and late transmitral filling (E and A velocities) and isovolumetric relaxation time. Each subject also underwent pulmonary artery catheterization with measurement of pulmonary capillary wedge pressure waveform during 5 different loading conditions: baseline, lower-body negative pressures of -15 and -30 mm Hg, and rapid saline infusions of 10 to 15 and 20 to 30 mL/kg. Pressure was measured at 6 points of the waveform: point 1, peak of the atrial contraction (a wave); point 2, the left atrial pressure during the start of ventricular systole; point 3, peak of atrial filling (v wave); point 4, earliest left atrial pressure during ventricular filling; and the line between points 5 and 6, pressure during diastasis. Aging resulted in a decrease in the E/A ratio ($P < 0.001$) and a prolongation of the isovolumetric relaxation time ($P < 0.001$) as assessed by echocardiography, but there was no effect of age on pulmonary capillary wedge pressure at any point throughout the cardiac cycle ($P = 0.290$). Specifically, at no measured point at any level of cardiac filling volume was the pulmonary capillary wedge pressure of the seniors lower than that of the young subjects.

Conclusions—We conclude that the age-related echocardiographic change of decreasing E/A ratio is not the result of a lowering of early diastolic left atrial pressure. (*Circulation*. 2005;111:1499-1503.)

Key Words: aging ■ diastole ■ heart diseases ■ heart failure ■ pulmonary wedge pressure

Normal healthy aging results in changes in Doppler indexes of diastolic function, including a prolongation of the isovolumetric relaxation time (IVRT), a reduction in the E-wave velocity of early mitral inflow compared with the late atrial wave (A), and a slower deceleration time of early mitral filling.¹⁻³ These parameters depend, in part, on the relationship between left atrial pressure (LAP) and the ventricular properties of relaxation and compliance.⁴

Although elevation of mean LAP can be seen in patients with congestive heart failure, normal healthy aging does not lead to an increase in mean LAP.⁵ Furthermore, mean LAP is normal in the elderly, despite marked alterations of mitral

inflow velocities. These findings suggest that the origin of abnormal Doppler indexes of diastolic function in the aged population lies in the ventricle, not the atrium. Recently, however, Hees et al,⁶ extrapolating from indirect, noninvasive Doppler measurements, suggested that early diastolic LAP might be lower in the elderly compared with young subjects and then rise rapidly during late diastole, resulting in a normal mean pressure. A low early diastolic LAP would result in a smaller driving force for early mitral filling, which would then manifest as abnormal Doppler filling indexes.

Our own studies have not demonstrated a significant difference in mean LAP in aged subjects compared with

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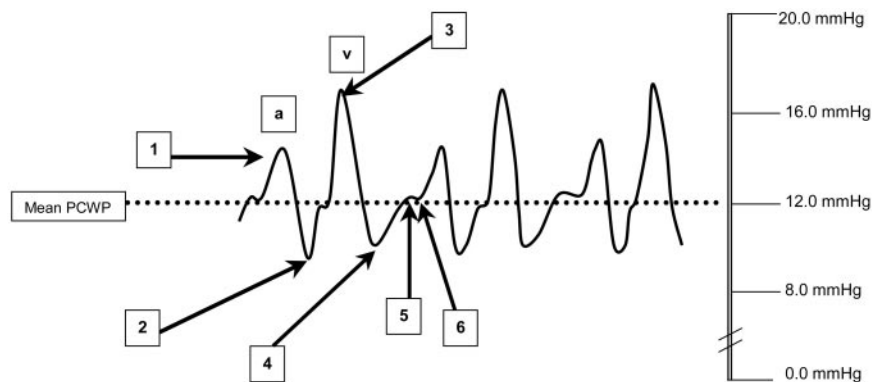


Figure 1. PCWP tracing from study subject. Six pressure points were taken from the tracing: point 1, peak of atrial contraction (a wave); point 2, LAP during start of ventricular systole; point 3, peak of atrial filling (v wave); point 4, earliest LAP during ventricular filling; line between points 5 and 6, pressure during diastasis.

young control subjects.⁷ In the present study, we sought to determine whether LAP is altered with aging, at any point in diastole, by performing a detailed, point-by-point analysis of the pulmonary capillary wedge pressure (PCWP) waveform obtained by right-heart catheterization in healthy young and senior subjects during 5 different loading conditions.

Methods

Subject Population

Twelve healthy seniors subjects (mean age, 69.8 ± 3 years; 6 men, 6 women) and 12 young subjects (mean age, 35 ± 8 years; 9 men, 3 women) were recruited as previously described.⁷ All participants were sedentary and were excluded if they engaged in endurance exercise for >30 minutes 3 times a week. Both groups had similar resting blood pressures (mean blood pressure, 123/73 mm Hg in the seniors, 114/74 mm Hg in the young) and heart rates (62 ± 9 bpm in the seniors, 66 ± 3 bpm in the young).

All subjects were screened for comorbidities, including systemic hypertension, obstructive coronary artery disease, and structural heart disease, through 24-hour ambulatory blood pressure measurements, exercise ECG testing, and transthoracic resting and postexercise echocardiograms. Exclusion criteria included mean daytime blood pressure $>140/90$ mm Hg, ECG changes suggestive of ischemic heart disease, left bundle-branch block, atrial flutter/fibrillation, AV block more than first degree, depressed systolic function, baseline or exercise-induced wall motion abnormalities, valvular heart disease other than mild valvular insufficiency, right or left ventricular hypertrophy, untreated thyroid disease, chronic lung disease, cigarette smoking within the past 10 years, body mass index >30 kg/m², cardiovascular medications, and anticoagulation with warfarin. All subjects signed an informed consent approved by the institutional review boards of the University of Texas Southwestern Medical Center and Presbyterian Hospital of Dallas.

Experimental Protocol

Catheterization

The subjects were studied in the resting, supine position. A 6F balloon-tipped fluid-filled catheter (Edwards Lifesciences) was placed under fluoroscopic guidance through an antecubital vein into the pulmonary artery. The catheter was connected to a physiological pressure transducer with the zero reference point set at 5.0 cm below the sternal angle. The wedge position of the catheter tip was confirmed by fluoroscopy and the presence of an appropriate PCWP waveform. The balloon was inflated briefly, and the baseline pressure waveform was recorded at end expiration.

Testing Protocol

Cardiac filling was decreased by applying lower-body negative pressure as has been previously described.⁷ The PCWP waveform was recorded after 5 minutes each of -15 and -30 mm Hg lower-body negative pressure. The negative pressure was then

released. After baseline measurements were repeated to confirm a return to a hemodynamic steady state, cardiac filling was increased by rapid infusion (100 mL/min) of warm (37°C) isotonic saline. The PCWP waveform was then recorded after 10 to 15 and 20 to 30 mL/kg had been infused.

A baseline PCWP waveform from 1 study subject is shown in Figure 1. Because the subjects were rigorously screened for potential pulmonary disease, PCWP was taken to represent LAP. Pressure waveforms from 9 cardiac cycles were averaged for each subject. The pressure was measured at 6 points of each waveform: point 1, peak of the atrial contraction (a wave); point 2, the LAP during the start of ventricular systole; point 3, peak of atrial filling (v wave); point 4, earliest LAP during ventricular filling; and the line between points 5 and 6, pressure during diastasis.

Frequency Response Determination of Catheter-Pressure Transducer System

A catheter-pressure transducer setup, which was identical to the one used in the testing protocol, was assembled with the tip of the catheter connected via a 3-way stopcock to a column of water that generated a pressure of 25 mm Hg. The stopcock was then rapidly switched from atmospheric pressure (0 mm Hg) to the column pressure to generate a step input of 25 mm Hg. The resulting output signal was recorded by a computer program (Acknowledge, Biopac) at a sampling rate of 1 kHz. A fast-Fourier transform was then applied to the first derivative of the output signal, assuming a step input, and the gain was calculated in decibels. The frequency at which the output gain fell by 3 dB was considered the maximum frequency response of the catheter system.⁸ This procedure was repeated 5 times, and the results were averaged. Figure 2 shows a typical frequency-response curve, with the 3-dB level evident at ≈ 8 Hz.

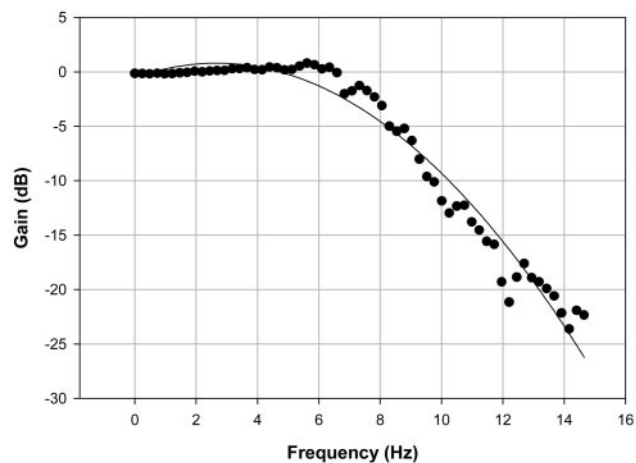


Figure 2. Frequency-response curve for catheter-pressure transducer system.

Echocardiographic Data

Subject Group	E, cm/s	A, cm/s	E/A	IVRT, ms
Young	72.2±11.6	43.6±9.5	1.71±0.36	107.7±14.1
Seniors	58.3±10.7	74.3±20.3	0.821±0.21	146.8±19.7
<i>P</i>	0.005	<0.001	<0.001	<0.001

In addition, we acquired true LAP recordings using a large (7.5F), stiff (Goodale-Lubin) catheter in a 60-year-old patient undergoing percutaneous closure of an atrial septal defect. In this same patient, we also measured PCWP using a Swan-Ganz catheter and assessed the frequency characteristics of both waveforms. First, we applied a fast-Fourier transform, followed by spectral analysis of the LAP signal (mean pressure, 8 mm Hg; minimum γ descent, 5 mm Hg), which showed that the peak power was present at 1.70 Hz, with smaller degrees of power (one-fifth magnitude) at 2.45 and 3.40 Hz. There was virtually no power contained in this signal at frequencies >4 Hz. For the PCWP waveform (mean pressure, 7 mm Hg; minimum γ descent, 6 mm Hg), the peak power was present at 1.68 Hz, with a smaller degree (one-fifth magnitude) of power at 2.46. As with the true LAP waveform, there was no substantive power in this signal >4 Hz.

Echocardiography

A resting and postexercise transthoracic echocardiogram (HDI 2000, ATL) was performed to screen for depressed ventricular function, structural abnormalities, and ischemic heart disease. At baseline, immediately after measurement of the PCWP, apical 4-chamber views were obtained for analysis of Doppler signals. If necessary for image quality, the subjects were turned 15° to 20° in the left lateral decubitus position via a motorized table that rotated the subject around the long axis of the body. Every effort was made to ensure that the images were not foreshortened and that there was optimal endocardial definition. Pulse-waved Doppler, with a sample volume of 2.0 mm placed at the tips of the mitral valve leaflets, was used to determine the peak velocities of mitral inflow (E, A velocities). The time interval between aortic outflow during systole and the opening of the mitral valve (IVRT) was also determined after the sample volume had been increased to 4.0 mm. All images were evaluated offline by a blinded sonographer.

Statistical Analysis

Data are presented as mean±SD. Results for the young and senior subjects were compared by use of 2-way repeated-measures ANOVA for the pressure points (SigmaStat, SPSS). Echocardiographic data were compared by use of an unpaired *t* test. A value of *P*<0.05 was considered statistically significant.

Results**Echocardiographic Data**

As expected, aging resulted in a decrement of the E/A ratio (0.821±0.21 in the senior versus 1.71±0.36 in the young; *P*<0.001). There was a prolongation of the IVRT with aging (146.8±19.7 in the seniors versus 107.7±14.1 in the young; *P*<0.001). The results are summarized in the Table.

Catheterization Data

The comparisons for each pressure point across filling conditions are shown in Figures 3 and 4. There was no significant effect of age on PCWP throughout the cardiac cycle at baseline (Figure 3) (*P*=0.290) or during any level of cardiac unloading (−15 mm Hg, *P*=0.137; −30 mm Hg, *P*=0.08) or loading (Figure 4) (10 to 15 mL/kg, *P*=0.726; 20 to 30 mL/kg, *P*=0.775). In particular, the pressure during early diastolic filling (point 4) was 10.8±1.9 mm Hg in the elderly

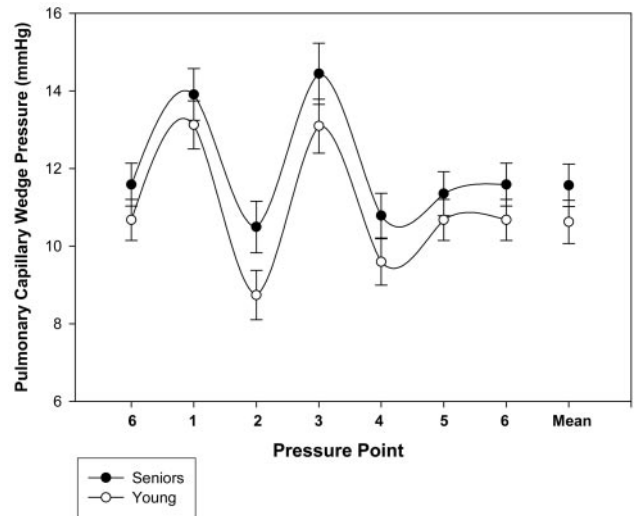


Figure 3. Elderly vs young baseline PCWP points. Mean data and SD are shown. PCWP was compared throughout cardiac cycle between 2 groups of subjects by use of 2-way repeated-measures ANOVA. For effect of age on PCWP, *P*=0.290.

versus 9.5±2.0 mm Hg in the young at baseline, and there was no difference in this point between the 2 groups during any cardiac filling condition.

Discussion

The primary new finding from this study is that there was no significant difference in LAP between healthy young adults and healthy elderly adults at any point in diastole. This relationship was maintained over a wide range of cardiac filling conditions. Therefore, the age-related echocardiographic change of decreasing E/A ratio is not the result of a low early diastolic LAP. Rather, this change may be the result of alterations of ventricular processes such as myocardial relaxation or ventricular compliance.

Technical Considerations

To use the PCWP waveform derived from a fluid-filled catheter to approximate LAP, the catheter-pressure transducer system must have an adequate frequency response to accurately detect the signal of interest. The PCWP waveform must not only provide an accurate representation of mean LAP but also should reflect the dynamic cyclical changes in the magnitude and contour of the LAP waveform.

Frequency Response Validation

As described in Methods, the 6F catheter system used in this experiment had a frequency response of 8.0 Hz. A resolution of 8.0 Hz allows the accurate sampling of signals occurring at a frequency of ≤4.0 Hz without an aliasing error. This frequency corresponds to a Nyquist limit of 250 ms. The baseline mean period of early diastolic filling in this study, as measured by the Doppler derived E-wave duration, was 285±29 ms; thus, it is unlikely that a pressure differential occurring during early diastolic filling that could alter the pattern of mitral inflow velocity would be missed by our catheter system.

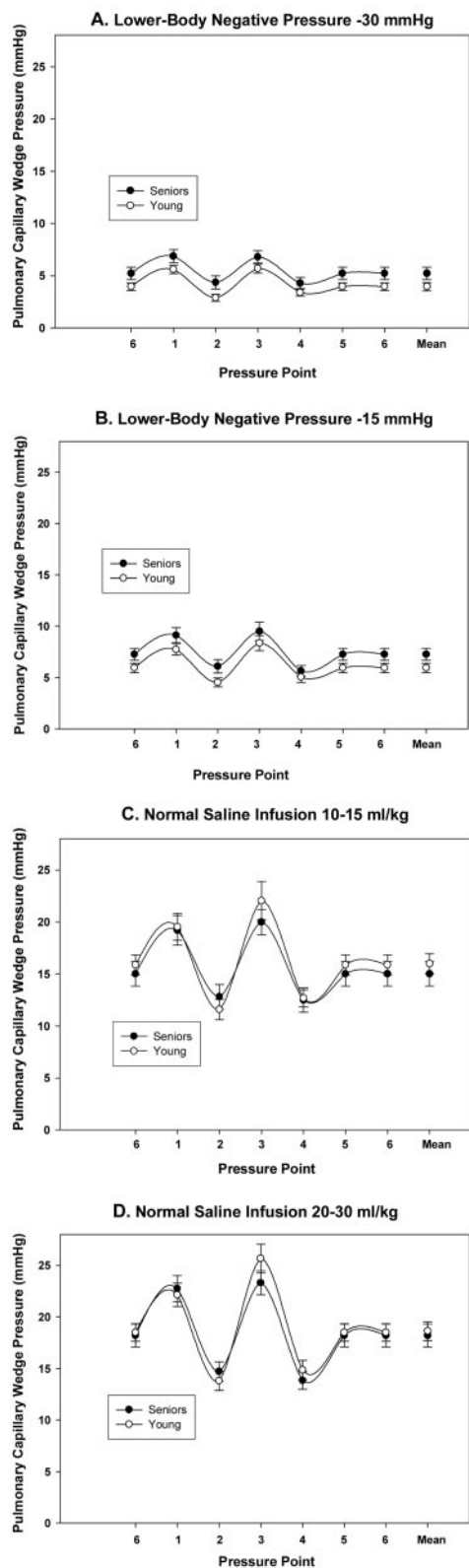


Figure 4. PCWP in response to loading conditions. PCWP was compared throughout cardiac cycle between 2 groups of subjects by use of 2-way repeated-measures ANOVA. A, Lower-body negative pressure -30 mm Hg, $P=0.08$. B, Lower-body negative pressure -15 mm Hg, $P=0.137$. C, Rapid saline loading 10 to 15 mL/kg, $P=0.726$. D, Rapid saline loading 20 to 30 mL/kg, $P=0.775$.

However, a waveform occurring during IVRT (100 to 200 ms) would not be measured accurately. Thus, we cannot exclude the possibility that LAP was lower in the elderly subjects at the very onset of relaxation. However, we can conclude with confidence that LAP was not lower at the point of mitral valve opening or throughout the early diastolic filling period. Therefore, a significant sustained drop in LAP during early diastole cannot explain the E/A reversal observed in elderly individuals.

Can the PCWP Waveform Be Used as a Representation of Dynamic Changes of LAP?

The use of PCWP to estimate mean LAP has been well validated and is commonplace in clinical practice.⁹ Given an adequate frequency response of the measurement system, the PCWP waveform can also be used to accurately determine both the magnitude and contour of the LAP waveform. Several studies involving patients with atrial septal defects or stenotic mitral valves have documented the close relationship between PCWP and directly measured LAP.^{10–12} Moreover, in the context of this study, direct recording of LA pressure with a large, stiff, fluid-filled catheter confirmed that there is little power in the LAP waveform at frequencies >4 Hz and that the mean, phasic, and power spectra of the pressure oscillations were very similar in the LAP and PCWP waveforms. Of course, to overlap the 2 pressure waveforms, a time delay representing transmission of the LAP through the pulmonary venous and capillary system must be considered.¹³ However, this issue does not apply to the present study because our interest was only in the absolute early diastolic pressure and not in the phasic delay.

Early Diastolic LAP Does Not Decrease With Aging

Our results counter the low early diastolic LAP theory proposed by Hees et al.⁶ In such a paradigm, a low early diastolic LAP would increase the amount of time required for the ventricular pressure to fall low enough for the mitral valve to open. This time delay would be reflected as a prolongation of IVRT. Furthermore, once the mitral valve opened, early filling would be reduced as a consequence of a smaller AV pressure gradient, resulting in a diminished E wave.

This theory is predominantly based on echocardiographic estimates of mean LAP such as the ratio of the peak E-wave velocity to the propagation velocity of early mitral inflow (E/Vp) and to myocardial motion velocities (E/Em). Although regression analysis has identified reasonable correlations between Doppler indexes and mean PCWP for groups of subjects, these measures have not been shown to precisely estimate mean LAP for individuals.¹⁴ Furthermore, they have never been shown to have the precision necessary to estimate LAP at multiple time points. Our detailed evaluation of the PCWP waveform did not demonstrate a difference in the early diastolic LAP, emphasizing the pitfalls in using Doppler measurements to estimate filling pressures.

Alternative Explanations for Abnormal Mitral Inflow Velocities With Aging

Myocardial relaxation and ventricular compliance likely both play important roles in the establishment of the AV pressure

gradient necessary for ventricular filling. A large amount of animal data suggests that as the heart ages, relaxation becomes impaired. The physiological explanation for this finding is likely multifactorial, involving, in part, alterations of key Ca^{2+} handling proteins, which regulate energy-dependent myocyte contraction and relaxation.^{15,16}

Unfortunately, few human data examine the effects of aging on myocardial relaxation. One of the few studies in this area by Yamakado et al¹⁷ did not show a change in ventricular isovolumetric pressure decay with aging. However, this study was clouded by the fact that it had few elderly participants. Only 9 of 55 patients in the study were >65 years of age. Furthermore, the experiment was not performed on normal healthy subjects but rather on patients referred for cardiac catheterization. Certainly, more human data are needed before this issue can be resolved.

Although myocardial relaxation likely plays an important role in early diastolic filling, the role of ventricular compliance remains unclear. Our laboratory has previously demonstrated that left ventricular compliance decreases with healthy sedentary aging.⁷ Whether this loss in compliance contributes to the Doppler abnormalities of mitral filling in the elderly remains to be examined. Overall ventricular stiffness may not, in fact, affect early diastolic filling because the ventricle is likely to be relatively compliant at the time of early mitral inflow. Chamber stiffness may become important predominantly at higher filling volumes later in the diastolic filling period or in instances of pericardial constraint.

Clinical Implications

We have demonstrated for the first time in normal healthy subjects, across a broad range of physiological filling conditions at rest, that neither early diastolic nor mean LAP is different in the elderly compared with the young, despite marked differences in Doppler measures of diastolic function. The abnormalities of Doppler indexes of early ventricular filling in the healthy aged are therefore likely not due to changes in LAP but rather the result of impairments in myocardial relaxation. The exact mechanisms have yet to be determined. A detailed analysis of diastolic function in the elderly, with particular attention to dynamic relaxation and myocardial compliance, is needed before this question can be fully answered.

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