Mitral A Velocity Wave Transit Time to the Outflow Tract as a Measure of Left Ventricular Diastolic Stiffness

Hemodynamic Correlations in Patients With Coronary Artery Disease

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**Background** Subjects in sinus rhythm have two distinct diastolic flow velocities in the left ventricular (LV) outflow tract directed toward the aortic valve. These follow E and A waves of the transmitral flow and are referred to as Er and Ar waves, respectively. The A wave transit time from the mitral valve to the LV outflow tract is shorter than that of the E wave and is shorter in those with LV hypertrophy and the aged, suggesting its possible dependence on LV late diastolic stiffness.

**Methods and Results** We measured the peak-to-peak and onset-to-onset A wave transit times from the mitral valve to the LV outflow tract (AAr, and AAr intervals, respectively) using Doppler echocardiography in 20 patients undergoing left heart catheterization for evaluation of coronary artery disease. These intervals were correlated with indices of LV late diastolic stiffness obtained from high-fidelity LV pressure tracings and angiographic volume assessments. The AAr and AAr intervals correlated significantly with LV Dp/DV (conventionally Dp/DV) (r = -.68 and -.65, respectively), volume stiffness, V · Dp/DV (r = -.74 and -.80, respectively) and LV (V/P) (Dp/DV) (r = -.69 and -.74, respectively). The AAr interval correlated better with the square roots of LV Dp/DV and volume stiffness (r = -.86 and -.87, respectively).

**Conclusions** We conclude that AAr and AAr intervals are easily obtainable Doppler parameters that reflect LV late diastolic stiffness in patients with coronary artery disease and possibly in other patient groups. *(Circulation, 1994;89:553–557.)*

**Key Words** ⋅ waves ⋅ diastole ⋅ stiffness ⋅ intervals

Color flow imaging and pulsed Doppler examination of the left ventricular (LV) outflow tract show two distinct diastolic flow velocities directed toward the aortic valve. These represent the transmitted transmirtal E and A waves and are referred to as Er and Ar waves, respectively. The A wave transit time from the mitral valve to the LV outflow tract is generally shorter than that of the E wave. In a previous clinical study, we have demonstrated that the peak-to-peak A wave transit time referred to as the AA interval is shorter in those with LV hypertrophy and the aged, suggesting its possible dependence on some LV late diastolic event such as stiffness. This study was undertaken to correlate the peak-to-peak and onset-to-onset A wave transit time to the LV outflow tract (AAr, and AAr, intervals) with direct invasive measures of LV late diastolic stiffness.

**Methods**

**Study Subjects**

Twenty-four patients with technically adequate echocardiograms undergoing cardiac catheterization for clinical indications were screened for the study. Subjects with significant mitral stenosis and a prosthetic mitral valve in which the direction of transmitral flow may be altered, patients with significant aortic regurgitation that may mask the Ar wave, and patients with unstable angina or recent myocardial infarction were excluded from the study. Only patients in sinus rhythm and normal PR interval were studied. Four patients were excluded for the above reasons, and 20 patients were included in the study after obtaining informed consent. The study protocol was approved by the Institutional Review Board and the Human Studies Subcommittee of Jerry L. Pettis Veterans Hospital, where the study was conducted. All were men with a mean age of 59 years (range, 41 to 72). Eleven patients had stable angina pectoris and nine had prior myocardial infarctions. Six patients had a history of systemic hypertension.

**Echocardiography**

The echocardiograms were obtained using Toshiba SSH-65A echograph equipped with 2.5-MHz phased-array transducer, with the patients turned slightly to their left side on the cardiac catheterization table. Transmitral Doppler signals were recorded with the sample volume placed at the tips of the mitral leaflets from the apical four-chamber view. The Ar waves were recorded from the apical five-chamber view (with aortic root in view) with the Doppler sample placed in the LV outflow tract about 1 cm below the aortic valve. In the majority of the patients, both the A wave and the Ar wave could be recorded on the same tracing by placing the Doppler sample volume slightly toward the mitral valve. All recordings were obtained on paper at a speed of 100 mm/s. Echocardiographic data were obtained immediately after LV pressure recordings (as described later) but before left ventriculography.
Measurement of A Wave Transit Times

The peak-to-peak and onset-to-onset A wave transit times (AAr and AAo intervals, respectively) were measured from the peak or onset of the A wave to the nadir or onset of the Ar wave, respectively. These measurements were made directly from the same recording when the two waves were clearly seen together (n=14), otherwise indirectly from two different recordings using the R wave of the ECG as a reference point (Fig 1). The measurements were made off-line by an investigator blinded to the hemodynamic data. Three to five consecutive beats were measured, and the mean was taken. These values have been used for analysis. In patients in whom direct measurements were possible, these intervals also were measured by the indirect method. The correlations between direct and indirect methods were good for the measurements of both the AAr interval (r=.97, SEE=1.0 millisecond, Y=4.2+0.93x) and the AAo interval (r=.96, SEE=1.1 millisecond, Y=6.6+0.87x) interval. The excellent reproducibility of these measurements has been reported previously.3

Cardiac Catheterization

Patients were premedicated with 5 mg of diazepam given orally, and left heart catheterization was performed from the right femoral approach. The LV pressures were obtained with Millar micromanometer catheters and recorded at 50 and 200 mm Hg scales at a paper speed of 100 mm/s. The Millar catheter was calibrated against mean aortic and LV diastolic pressures obtained by fluid channel (which was calibrated against a mercury manometer) of the Millar catheter. After this, Doppler data were obtained as detailed above. This was followed by left ventriculography at 30° right anterior oblique and 60° left anterior oblique projections with 60 frames per second film speed using iopamidol, a nonionic contrast agent. The coronary angiograms were performed after obtaining the above data.

As shown in Fig 2, the LV pressures were measured before and after the atrial contraction (pre-A and post-A LV diastolic pressures, P1 and P2, respectively). The LV volumes were computed using biplane Simpson's method at corresponding points in diastole with frame-by-frame replay of the left ventriculogram from the mitral valve opening to its closure. The pre-A LV volume (V1) was obtained immediately preceding the mitral valve excursion with atrial contraction, and the

![Figure 1](http://circ.ahajournals.org/)

**Fig 1.** Method of measurement of AAr and AAo intervals (int): From the apical view, the Doppler sample volume is placed in the left ventricular outflow tract about 1 cm below the aortic valve to record the Ar wave. The flow above the baseline represents the transmitral flow and the one below represents the flow velocities in the left ventricular outflow tract. The Ar wave occurs soon after the A wave of the transmitral flow but before left ventricular systolic ejection (Syst). The AAr interval is measured from the peak of the A wave to the nadir of the Ar wave. The AAo interval is the interval between the onsets of A and Ar waves. When both A and Ar waves are not seen together in the same tracing, these intervals can be measured using the R wave of the ECG as the reference point. The figure also illustrates the temporal relation between E and Er waves.

![Figure 2](http://circ.ahajournals.org/)

**Fig 2.** Left ventricular (LV) pressure tracing with fluid channel and micromanometer sensor of the Millar catheter. The LV pressure immediately before and after left atrial contraction, P1 and P2, respectively, were measured and used for the calculation of LV Dp/DV (conventionally dP/dV).
LV end-diastolic volume or the post-A volume (V₂) was recorded after mitral valve closure and before LV ejection.

Indices of Left Ventricular Chamber Stiffness

The LV chamber stiffnesses and various derivatives were obtained as follows: (1) LV late diastolic stiffness \(\frac{Dp}{Dv}\) as \(\frac{Dp}{Dv} = (P₂ - P₁)/(V₂ - V₁)\) mm Hg/mL; this measure of LV late diastolic stiffness is expressed as \(\frac{Dp}{Dv}\) to differentiate from the first derivative of LV late diastolic pressure with respect to simultaneously obtained LV volume, which is conventionally referred to as LV dP/dV; (2) LV volume stiffness \((V \cdot \frac{Dv}{Dp})\) as \(V \cdot \frac{Dv}{Dp} = (\frac{Dv}{Dp}) \cdot \frac{(V₂ + V₁)}{2}\) mm Hg, where \((V₂ + V₁)/2\) is the average LV volume during atrial systole; and (3) LV \(\frac{Dp}{Dv}\) as \(\frac{Dp}{Dv} = (\frac{Dp}{Dv}) \cdot \{V₂ + V₁\}/(P₂ + P₁)\); this is a dimensionless index of LV stiffness.

Analysis

The continuous variables were correlated by linear regression using the method of least squares. Stepwise multiple regression was used to find the independent determinants of
The AAr$_t$ interval had a better correlation with measures of LV late diastolic stiffness, as shown in the Table. It correlated significantly with LV Dp/DV ($r=-.83$, $P=.0001$), volume stiffness ($r=-.80$, $P=.0001$), and (V/P) (Dp/DV) ($r=-.74$, $P=.0002$). It also had a weak negative correlation with LV end-diastolic pressure ($r=-.46$, $P=.0438$) and the difference between LV end-diastolic and pre-A pressures ($r=-.55$, $P=.0126$). There was no correlation with LV end-diastolic volume, pre-A LV diastolic pressure, A wave amplitude, or A/E velocity ratio. Stepwise multiple regression incorporating the above variables showed LV Dp/DV to be the only independent determinant of AAr$_t$ interval ($r=.83$). There was a significant correlation between AAr$_p$ and AAr$_o$ intervals ($r=.71$, $P=.0005$). The relation between AAr$_p$ and AAr$_o$ intervals and LV Dp/DV and volume stiffness is shown in Fig 3. The AAr$_t$ interval correlated better with the square roots of LV Dp/DV ($r=-.86$, $P=.0001$) and volume stiffness ($r=-.87$, $P=.0001$), as shown in Fig 4.

**Discussion**

The results of this study support the hypothesis that A wave transmission inside the left ventricle depends on operative LV stiffness in late diastole, during which A wave transmission occurs. It was not influenced by A wave velocity or LV end-diastolic volume, and in the multivariate analysis, its transmission was independent of any influence by LV end-diastolic pressure. The negative correlation between AAr$_t$ interval and LV end-diastolic pressure in the univariate analysis may indirectly be due to a change in LV Dp/DV. Although geometrically dissimilar, it is possible that A wave transmission inside the left ventricle may share some of the principles of pressure or flow wave transmission inside the arterial system, where the propagation of these waves is strongly correlated with arterial wall stiffness, its wall thickness to radius (h/r) ratio, and Young’s modulus (E). This relation is mathematically expressed in terms of the Moens-Korteweg equation, which states that C equals the square root of (Eh/2dr), where C is the velocity of wave transmission and d is the density of blood ($\approx 1.06$), or the Bramwell-Hill equation, which states that C equals the square root of volume stiffness. The improved correlation of the AAr$_t$ interval with the square root of the measures of LV stiffness is consistent with the principles of these equations. However, there are geometric and functional differences between the left ventricle and the arterial system. First, in the left ventricle, the direction of flow wave transmission changes as it approaches the apex. Second, the left ventricle is not a tube, and its h/r ratio is higher than that of the arteries. Third, the diastolic flow wave propagation occurs at a lower pressure than does the arterial system. However, the results of this study indicate that the principles of flow wave propagation in a tube may apply to the left ventricle, at least in a qualitative manner.

We measured both the peak-to-peak and the onset-to-onset A wave transit times, the latter showing a better correlation with the measures of LV late diastolic stiffness. Both were easy to measure but were numerically slightly different. This may be due to the morphological changes that the A wave undergoes as it is transmitted to the LV outflow tract with a reduction in
its duration. It is possible that the transmission of the peak is affected by the reflected waves affecting its transit time. As can be seen from Fig 3, an AArp interval of ≤45 milliseconds and AArs interval of ≤50 milliseconds predicted an LV Dp/DV of >0.45 mm Hg/mL with a fair degree of accuracy.

Some of the limitations of this study include a small sample size limited to patients with coronary artery disease, the inability to calculate the actual velocity of A wave transmission, and the inability to obtain AArs and AArp intervals in rhythms other than sinus rhythm because of the absence of A waves. The LV late diastolic stiffness measured in this study, unlike the modulus of chamber stiffness, is a function of LV filling pressure and volume and does not necessarily reflect intrinsic myocardial properties. Also, LV Dp/DV calculated in this study is an approximate of dP/dV, which is obtained as the first derivative of the simultaneous pressure-volume relation. However, it is fair to conclude that AArs and AArp intervals may give useful insight into LV diastolic function noninvasively, at least in patients with coronary artery disease. These preliminary data must be confirmed by larger studies encompassing a wider range of patient populations.

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