Lack of Inertia Force of Late Systolic Aortic Flow Is a Cause of Left Ventricular Isolated Diastolic Dysfunction in Patients With Coronary Artery Disease

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OBJECTIVES
We investigated whether a lack of inertia force of late systolic aortic flow and/or apical asynergy provoke early diastolic dysfunction in patients with coronary artery disease (CAD).

BACKGROUND
Left ventricular (LV) isolated diastolic dysfunction is a well-recognized cause of heart failure.

METHODS
We evaluated LV apical wall motion and obtained left ventricular ejection fraction (LVEF) (1–3). An elevated left atrial pressure with left ventricular diastolic dysfunction causes symptoms of heart failure at rest and during exercise (4–7). Several pathophysiological conditions, such as myocardial hypertrophy, myocardial ischemia, interstitial fibrosis of the LV wall, and abnormal Ca\(^{2+}\) handling in myocytes, are seen in patients with diastolic dysfunction (8–12). The role of hypertension as a cause of diastolic heart failure has been well recognized (13,14). In contrast, coronary artery disease (CAD), especially with prior myocardial infarction (MI), is acknowledged as the most common cause of systolic heart failure (13). Although patients suffering from diastolic heart failure have a high incidence of CAD, including MI (1,14,15), CAD’s role as a cause of diastolic heart failure has not been fully elucidated. Accordingly, in patients with CAD, we hypothesized that mild LV systolic dysfunction and/or LV apical asynergy may be associated with LV abnormal relaxation and impaired early diastolic filling.

RESULTS
An absence of inertia force in patients with PSF is one of the causes of isolated diastolic dysfunction in patients with CAD. Normal LV apical wall motion is substantial enough to give inertia to late systolic aortic flow. (J Am Coll Cardiol 2006;48:983–91) © 2006 by the American College of Cardiology Foundation

CONCLUSIONS
The Tp was significantly longer in patients with SDF (85.7 ± 21.0 ms) and with PSF without inertia force (81.1 ± 23.6 ms) than in those with PSF with inertia force (66.3 ± 12.8 ms) (p < 0.001). The Vp was significantly less in the former 2 groups than in the last group. In patients with PSF, LV apical wall motion abnormality was less frequently observed in those with inertia force than in those without (p < 0.0001).

METHODS
Study subjects. Study subjects consisted of 101 consecutive patients with suspected CAD who underwent cardiac catheterization. Patients with an acute coronary syndrome, primary valvular heart disease, atrial fibrillation, or intraventricular conduction disturbance were excluded from the study. According to the findings of cardiac catheterization, 91 patients had CAD, 36 without prior MI and 55 with prior MI. Coronary artery disease was defined as a narrowing of at least 50% in luminal diameter of 1 or more of the major coronary arteries as determined by selective coronary angiography. Prior MI was diagnosed on the finding of localized LV wall motion abnormality using biplane contrast left ventriculography with related electrocardiographic changes. Of the 55 MI patients, 37 had anterior-wall MI, 11 had inferior-wall MI, and 7 had combined anterior- and inferior-wall MI. The remaining 10 patients (those not identified as having CAD) had neither significant coronary stenosis nor LV wall motion abnormality, but had atypical chest pain. On the basis of the LVEF obtained by biplane left ventriculography, patients were divided into 2 groups: the preserved LV systolic function (PSF) group, which had LVEFs ≥50% (n =
Doppler echocardiography. All patients were examined at rest lying in the left semilateral decubitus position. Doppler measurements were made using a Power Vision-6000 or -8000 (Toshiba Medical Co., Tokyo, Japan) echocardiographic system with a 2.5-MHz transducer. The acquisition of Doppler data was performed by 1 observer throughout the study. The transmitral flow velocity waveform at the mitral orifice was obtained by pulsed Doppler echocardiography, and the ratio of peak flow velocity during early diastole to that during atrial contraction (E/A) was calculated. As Doppler parameters of LV systolic and early diastolic function, which are relatively independent of preload to the LV, peak mitral annular velocity during systole (Sm) and that during early diastole (Em) were also measured at the septal and lateral corners of the mitral annulus using pulsed tissue Doppler imaging. The mean value of velocities at both sides was used in statistical analysis. The propagation of the peak of the early diastolic flow velocity wave in the LV (Vp) was imaged by appropriately changing the first aliasing limit of the color M-mode Doppler signals. The time-distance slope of the peak velocity tracing was measured as Vp; the reproducibility of these measurements in our hospital was as reported elsewhere (17).

Cardiac catheterization. Diagnostic cardiac catheterization was performed within 2 h after echocardiography. Before contrast material was injected into the LV or coronary artery, LV pressure was obtained using a catheter-tipped micromanometer (SPC-454D, Millar Instrument Co., Houston, Texas) and recorded on a polygraph system (RMC-2000, Nihon Kohden Inc., Tokyo, Japan) and also on a digital data recorder (NR-2000, Keyence, Osaka, Japan). The offset of pressure waves obtained using a catheter-tipped micromanometer was adjusted to that obtained using a fluid-filled system. From the recorded pressure waves, the peak negative first derivative of left ventricular pressure (dP/dt) was determined, and then Tw was calculated using the method proposed by Weiss et al. (18). In the calculation of Tw, the following assumption is applied: a monoexponential curve fitting with LV pressure decay after the phase of peak negative dP/dt has a zero asymptote. This assumption may bring a possibility that Tw is dependent on LV contraction phase and less sensitive to the deterioration of LV relaxation. Another LV relaxation time constant (Tp), which is relatively independent of LV systolic function; SDF = systolic dysfunction; Sm = peak mitral annular velocity during systole; Tp = LV relaxation time constant obtained from LV pressure—dP/dt relation; Tw = LV relaxation time constant obtained by the method proposed by Weiss et al. (18); Vp = propagation velocity of early diastolic filling flow.
contractile phase and has a floating asymptote, was calculated from the LV pressure (P)–dP/dt relation (phase loop) according to the method proposed by Sugawara et al. (19). From the phase loops, we also computed the inertia force of late systolic aortic flow (19). Details of the calculations are indicated in Figure 2. Little fluctuation was observed on the obtained phase loops, so that small amount of inertia force may be erroneously calculated in some patients without having an apparently observed bump (red area in Fig. 2A) in those loops around the phase of peak negative dP/dt. The consensus we reached by reviewing the phase loops in all patients was that we could confirm the existence of the

![Figure 1](image1.png)

**Figure 1.** A flow diagram of patients’ classification. (A) Patients' classification from the viewpoint of baseline disease. (B) Patients' classification from the standpoint of left ventricular function. CAD = coronary artery disease; Combined MI = anterior myocardial infarction plus inferior MI; LVEF = left ventricular ejection fraction.

![Figure 2](image2.png)

**Figure 2.** Left ventricular pressure (LVP)–first derivative of left ventricular pressure (dP/dt) relationship (phase loop). (A) A loop obtained from a patient with inertia force. (B) A loop obtained from a patient without inertia force. The negative inverse slope of the best linear-fitting line between the points a and b is equal to the time constant of exponential pressure decay during isovolumic relaxation (Tp). The Tp was 56.3 ms in A and 83.1 ms in B. The area in red divided by the vertical distance between P_{0,0} and point d is equal to the amount of pressure decay augmented by the effect of the inertia of blood flowing out of the LV, and is defined as the inertia force. The inertia force in A was 3.6 mm Hg, and 0.12 mm Hg in B.
bump of phase loops in patients with computed inertia force $\geq 0.5$ mm Hg. Thus, we defined the patients with computed inertia force $\geq 0.5$ mm Hg as those with inertia force, and the patients with calculated inertia force $< 0.5$ mm Hg as those without inertia force. We then divided the patients with PSF into 2 subgroups: patients with inertia force ($n = 53$) and those without inertia force ($n = 30$). No patient with SDF had inertia force (Fig. 1). Immediately after the pressure measurements, biplane contrast left ventriculography was performed. Left ventricular end-systolic and end-diastolic volumes were calculated using the method of Chapman et al. (20), using a cardiac image analyzer. The LVEF was then determined. The LV end-systolic volume was divided by the body surface area of each patient and expressed as an LV end-systolic volume index to normalize body size. Regional LV wall motion was evaluated using the centerline method (21), which is a reliable method to assess LV regional wall motion from contrast left ventriculography. As we reported previously (22), LV apical wall motion abnormality was confirmed when wall motion deteriorated by more than 2 standard deviations from the normal wall-motion amplitude on at least 20 lines that formed the apex of the 200 equidistant lines, which were drawn perpendicular to the centerline extending from the end-diastolic to the end-systolic counter in each 30° right anterior oblique (100 lines) and 60° left anterior oblique (100 lines) projection.

Data related to LV pressure waves were analyzed by 1 observer, and data concerned with left ventriculography were independently analyzed by another observer through the study. Both observers were blinded to the Doppler data.

**Statistical analysis.** Normally distributed continuous data are expressed as mean ± SD. The inertia force is presented as the median with interquartile range (IQR) (25th to 75th percentiles). Relationships between 2 parameters were evaluated using Spearman’s correlation coefficients by ranks. Differences in parameters between 2 groups were compared using the unpaired Student $t$ test. Differences between 3 groups were evaluated using 1-way analysis of variance with a Bonferroni adjustment. The $p$ values shown in Table 2 are those after Bonferroni adjustment among 3 comparisons. A difference in incidence was compared using the chi-square test. Differences with $p$ values $< 0.05$ were considered significant.

**Results**

The median of calculated inertia force was 1.19 (IQR 0.19 to 3.98) mm Hg and ranged from 0.002 to 12.0 mm Hg. The inertia force significantly correlated with the LV systolic function parameters, such as LVEF and LV end-systolic volume index ($r = 0.72, p < 0.0001$ and $r = -0.68, p < 0.0001$, respectively) (Fig. 3). It also significantly correlated with the parameters of LV relaxation, $T_p$, and of LV early diastolic filling, $V_p$ ($r = -0.31, p < 0.005$ and $r = 0.73, p < 0.0001$, respectively) (Fig. 4). The correlation coefficient was greater in the relation between the inertia force and $V_p$ than in that between the inertia force and $T_p$.

No significant differences were found in age, heart rate, or mean blood pressure between the patients with PSF with or without inertia force and those with SDF (Table 1). Time constants of LV relaxation were significantly greater in patients with SDF and with PSF without inertia force than in those with PSF with inertia force. The peak negative $dP/dt$ was significantly less in patients with SDF and with PSF without inertia force than in those with PSF with inertia force. Propagation velocity of early diastolic filling flow was also significantly less in the first 2 groups than in the last group. There were no significant differences in $T_w$, $T_p$, peak negative $dP/dt$, or $V_p$ between patients with SDF and those with PSF without inertia force (Figs. 5 and 6). The $E/A$ ratio of the transmitral flow velocity waveform also was not significantly different between the groups. In contrast, $E_m$ was significantly less in patients with SDF and with PSF without inertia force than in those with PSF with inertia force. No significant difference was found in $E_m$ between patients with SDF and those with PSF without inertia force (Fig. 6).

Left ventricular ejection fraction was greater in patients with PSF with inertia force than in those with PSF without inertia force. Similarly, $S_m$ was also significantly greater in the former than in the latter. Left ventricular end-systolic volume index was significantly lower in the former than in the latter (Fig. 7). These data are summarized in Table 2.

In 53 patients with PSF with inertia force, 5 had LV apical asynergy and 48 did not. On the other hand, in 30 patients with PSF without inertia force, 26 had apical asynergy and 4 did not. The incidence of LV apical asynergy was significantly higher in patients without inertia force than in those with inertia force (chi square = 48.8, $p < 0.0001$).

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**Table 2. Summary of Hemodynamic Variables of the Subjects in Each Group**

<table>
<thead>
<tr>
<th></th>
<th>PSF With Inertia Force</th>
<th>PSF Without Inertia Force</th>
<th>SDF</th>
</tr>
</thead>
<tbody>
<tr>
<td>LVEF (%)</td>
<td>70.8 ± 7.7</td>
<td>59.5 ± 5.0*</td>
<td>44.6 ± 5.6*</td>
</tr>
<tr>
<td>LV ESVI (ml/m²)</td>
<td>23.2 ± 8.0</td>
<td>35.5 ± 9.2*</td>
<td>55.0 ± 15.2*</td>
</tr>
<tr>
<td>$S_m$ (cm/s)</td>
<td>11.6 ± 1.8</td>
<td>10.6 ± 1.2‡</td>
<td>10.1 ± 1.8†</td>
</tr>
<tr>
<td>$T_p$ (ms)</td>
<td>66.3 ± 12.8</td>
<td>81.1 ± 23.6*</td>
<td>85.7 ± 21.0*</td>
</tr>
<tr>
<td>$T_w$ (ms)</td>
<td>37.9 ± 6.0</td>
<td>44.9 ± 7.5*</td>
<td>44.1 ± 5.1*</td>
</tr>
<tr>
<td>Peak negative $dP/dt$ (mm Hg/s)</td>
<td>$-1,700 ± 370$</td>
<td>$-1,510 ± 260$</td>
<td>$-1,370 ± 310$ *</td>
</tr>
<tr>
<td>$E/A$</td>
<td>0.79 ± 0.34</td>
<td>0.97 ± 0.70</td>
<td>0.73 ± 0.29</td>
</tr>
<tr>
<td>$E_m$</td>
<td>12.2 ± 2.4</td>
<td>10.6 ± 2.4‡</td>
<td>9.7 ± 1.7*</td>
</tr>
<tr>
<td>$V_p$ (cm/s)</td>
<td>47.9 ± 9.3</td>
<td>33.2 ± 9.1*</td>
<td>27.9 ± 4.4*</td>
</tr>
</tbody>
</table>

$*$ $p$ values are those after Bonferroni adjustment among 3 comparisons. $†p < 0.001; ‡p < 0.01; §p < 0.05$ (vs. PSF with inertia force).

$dP/dt$ = first derivative of left ventricular pressure; $E/A$ = the ratio of transmitial flow velocity during early diastole to that during atrial contraction; $E_m$ = peak mitral annular velocity during early diastole; LVEF = left ventricular ejection fraction; LV ESVI = left ventricular end-systolic volume index; $S_m$ = peak mitral annular velocity during systole; $T_p$ = left ventricular relaxation time constant calculated from phase loop; $T_w$ = left ventricular relaxation time constant calculated by Weiss’ method (18); $V_p$ = propagation velocity of left ventricular early diastolic filling flow; other abbreviations as in Table 1.
In 22 patients with PSF and a time constant $T_w \geq 48$ ms, who met the definite criteria for isolated diastolic dysfunction, 1 had inertia force and 21 did not. In contrast, in 61 patients with PSF and a time constant $T_w < 48$ ms, 52 had inertia force and 9 did not. The rate at which patients did not have inertia force was significantly greater in those who satisfied the definite criteria for isolated diastolic dysfunction ($\chi^2 = 45.6$, $p < 0.0001$).

**DISCUSSION**

The present study indicates that patients with PSF without inertia force have similar levels of deterioration in LV relaxation and $V_p$ compared with those in patients with SDF. The lack of inertia force in patients with PSF impairs LV relaxation and early diastolic filling and it may be one of the causes of isolated diastolic dysfunction in CAD patients. Normal LV apical wall motion appears to be substantial enough to give inertia to late systolic aortic flow.

**Coupling of LV systolic and diastolic function mediated by inertia force.** From the viewpoint of cardiac mechanics, Gilbert and Glantz (23) reported that LVs with good systolic function have relatively smaller LV end-systolic volumes, producing a greater magnitude of LV rearrangement at the isovolumic relaxation phase by releasing elastic energy stored during systole. This phenomenon, called LV elastic recoil, speeds LV relaxation independently of the $Ca^{2+}$ reuptake process by the sarcoplasmic reticulum (19, 23).

**Figure 3.** Relationships between inertia force and left ventricular (LV) systolic function parameters. (A) Relation of inertia force to LV ejection fraction (LVEF). A significant positive correlation is observed. (B) Relation of inertia force to LV end-systolic volume index (ESVI). A significant inverse correlation is found. Circles = patients with preserved systolic function with inertia force; squares = patients with preserved systolic function without inertia force; $X$ = patients with systolic dysfunction.

**Figure 4.** Relationships between inertia force and parameters of left ventricular relaxation ($T_p$) and left ventricular early diastolic filling ($V_p$). A Relation of inertia force to $T_p$. A significant inverse correlation is observed. B Relation of inertia force to $V_p$. A significant positive correlation is found. Symbols are as in Figure 3; other abbreviations as in Figure 1.
Eichhorn et al. (24) demonstrated that a hyperbolic rather than a linear relationship was observed between LV contractile function as shown by end-systolic elastance and LV relaxation as shown by the slope of the time constant to the LV end-systolic pressure relation. The concept that LV myocardial contraction and ejection dynamics are intimately linked to LV relaxation has been established (25–27). In addition, Sugawara et al. (19) reported that late systolic aortic flow ejected from a LV with good contraction has inertia force. The blood, once set in motion, will continue in motion because of its inertia until the heart stops it (28). In late systole, when LV muscle shortening has reached a limit but its tension-bearing ability is still maintained, the inertia of the blood flowing out of the LV causes swift end-systolic unloading of the LV, producing a much smaller LV end-systolic volume and much greater elastic recoil force (19,22,29). The schematic diagram that demonstrates the idea that inertia force of late systolic aortic flow enhances LV elastic recoil is shown in Figure 8. Thus, the enhanced LV elastic recoil brought by the inertia force of late systolic aortic flow in patients with good LV contraction may produce faster LV relaxation (30). Furthermore, we demonstrated that the direct effect of LV end-systolic volume index on Vp was much greater than that of LV relaxation time constant on Vp (17). Smaller LV end-systolic volume, which is usually accompanied by a marked ellipsoidal LV cavity shape during the isovolumic relaxation phase, produces a greater intraventricular pressure gradient between the LV base and apex during the early diastolic filling phase and increases Vp (31). Thus, in addition to LV relaxation, LV elastic recoil itself also has a striking effect on Vp. As we demonstrated in this study, the magnitude of inertia force significantly and positively correlated with LV ejection fraction and inversely with LV end-systolic volume index, supporting the hypothesis shown in Figure 8. The finding that the inertia force showed a much closer relationship with Vp than with Tp may indicate that enhanced LV elastic recoil directly speeds Vp in addition to the effect through accelerated LV relaxation, similar to our previous report (17). Thus, the concept of hemodynamically induced inertia force may contribute further to the understanding of LV contraction-relaxation coupling, which has been mainly considered from the viewpoint of LV mechanics (25–27).

If the LV does not have inertia force even though LVEF is more than 50%, it would not have enough elastic recoil to speed LV relaxation and Vp. One of the main messages of the present study—that the lack of inertia force deteriorates LV relaxation—was also confirmed by the finding that the patients with PSF without inertia force had a decreased Em (32,33).

We found more significant decreases in LVEF and Sm in patients with PSF without inertia force than in those with PSF with inertia force, and we also found a more significant increase

![Figure 5. Comparisons of parameters regarding left ventricular relaxation between patients with preserved systolic function (PSF) with or without inertia force and those with systolic dysfunction (SDF). (A, B) The time constant Tp from phase loops and the time constant Tw obtained by the method of Weiss et al. (18) were significantly greater in patients with SDF and with PSF without inertia force than in those with PSF with inertia force. (C) The peak negative dP/dt was significantly less in the first 2 groups than in the last group. *p < 0.001; †p < 0.01; ‡p < 0.05. Other abbreviations as in Figure 4.](image-url)
in LV end-systolic volume index in the former patients than in the latter. These findings suggest that patients with PSF without inertia force have mild LV systolic dysfunction.

**Calculation of inertia force.** Inertia force can be calculated from the LV P-dP/dt relation (phase loop) (19). Left ventricular pressure decay during the isovolumic relaxation phase can be assumed to be exponential if this process only depends on Ca\(^{2+}\) reuptake by the sarcoplasmic reticulum in myocytes (23). In the LV P-dP/dt plane, the exponential relationship is shown as a straight line. However, enhanced elastic recoil produced by inertia force observed in a LV with good contraction may shift such an exponential decay

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**Figure 6.** Comparisons of the mitral annular velocity during early diastole (Em) and the propagation velocity of left ventricular early diastolic flow (Vp) between the patient groups. (A) Em was significantly lower both in patients with SDF and those with PSF without inertia force than in those with PSF with inertia force. (B) Vp was also significantly less in the first 2 groups than in the last group. *p < 0.001; ‡p < 0.05. Other abbreviations as in Figure 5.

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**Figure 7.** Comparisons of left ventricular systolic function parameters between patients with PSF with inertia force and those with PSF without inertia force. (A) Left ventricular ESVI was significantly smaller in patients with PSF with inertia force than in those with PSF without inertia force. (B) Left ventricular ejection fraction (LVEF) was significantly greater in the former than in the latter. (C) Peak mitral annular velocity during systole (Sm) was also significantly greater in the former than in the latter. *p < 0.001; ‡p < 0.05. Other abbreviations as Figures 3 and 5.
Inconsistent with the study by Baicu et al. (35). Our results dysfunction in addition to diastolic dysfunction, which is failure with preserved LVEF is associated with mild systolic dysfunction in patients with LV apical asynergy (22,34). Normal LV aortic flow has a significant relation with LV apical asyn-

downward at the beginning of relaxation, as shown in Figure 2. In accord with the method proposed by Sugawara et al. (19), we calculated the inertia force as a deviation of the LV P-dP/dt relation during the isovolumic relaxation phase from the expected straight line, which would be observed in a LV without significant elastic recoil.

LV apical asynnergy and inertia force. In the present study, we demonstrated that the lack of inertia force of late systolic aortic flow has a significant relation with LV apical asyn-

Comparison to previous studies. Baicu et al. (35) have recently indicated that no significant differences are found in LVEF, pre-load recruitable stroke work, or peak dP/dt between normal control subjects and patients with diastolic heart failure (LVEF ≥50%). They concluded that the pathophysiology of diastolic heart failure does not appear to be due to significant abnormalities in LV systolic properties. In contrast, using tissue Doppler imaging of the mitral annulus, Brucks et al. (14) have demonstrated that heart failure with preserved LVEF is associated with mild systolic dysfunction in addition to diastolic dysfunction, which is inconsistent with the study by Baicu et al. (35). Our results regarding LVEF, LV end-systolic volume index, and Sm support the finding reported by Brucks et al. (14). They also reported that 60% to 70% of their subjects had CAD. Furthermore, Tsutsui et al. (15) reported 34% of their patients suffering from heart failure with preserved LV systolic function had MI. Thus, in the pathophysiology of isolated diastolic heart failure in CAD patients, LV apical wall motion abnormality due to prior MI may be important.

From the viewpoint of the definite criteria for isolated diastolic dysfunction, we reanalyzed the data of our patients with PSF. We then demonstrated that most patients who satisfied the criteria did not have inertia force, whereas a majority of patients who did not meet the criteria had inertia force. These findings suggest that a lack of inertia force of late systolic aortic flow is one of the aspects of isolated diastolic dysfunction.

Clinical implications. An absence of inertia force of late systolic aortic flow causes both LV relaxation and early diastolic filling to be impaired in patients with PSF. Thus, an evaluation to determine whether such patients have inertia force should be important for the assessment of their LV early diastolic function. However, an invasive examination is needed for this issue. Our present study indicates that LV apical asynergy observed in CAD patients frequently accompanies the lack of inertia force. One could noninvasively evaluate whether patients with CAD have isolated diastolic dysfunction by observing their LV apical wall motion using echocardiography.

CONCLUSIONS

The lack of inertia force of late systolic aortic flow plays a substantial role in provoking isolated diastolic dysfunction in patients with CAD. Mild LV systolic dysfunction and LV apical asynergy may be related to this pathophysiology.

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