Left Atrial Contribution to Ventricular Filling During the Course of Evolving Heart Failure

Tatsui Kono, MD; Hani N. Sabbah, PhD; Howard Rosman, MD; Mohsin Alam, MD; Paul D. Stein, MD; and Sidney Goldstein, MD

Background. Abnormal left ventricular (LV) filling has been observed in patients with heart failure and is characterized by marked heterogeneity of mitral inflow velocity. In the present study, the contribution of the left atrium to LV filling was examined in eight dogs during the course of evolving heart failure.

Methods and Results. Heart failure was produced by multiple sequential intracoronary embolizations with microspheres. Pulsed Doppler echocardiography was used to measure mitral inflow velocity at baseline, before embolization, and at 3, 8, 15, 23, and 33 weeks after initiation of microembolization. The early rapid LV filling (Ei) and late left atrial filling (Ai) components were quantitated based on the time-velocity integral of the early and late mitral inflow velocity waveforms, respectively. Ei decreased progressively from 7.6±1.5 cm at baseline to 4.0±0.4 cm at 33 weeks (p<0.01). In contrast, Ai initially increased from 1.8±0.9 cm at baseline to 2.7±0.4 cm at 3 weeks (p<0.01) and subsequently decreased gradually to below baseline values reaching 0.8±0.4 cm at 33 weeks (p<0.01). These temporal changes of Ei and Ai were accompanied by a gradual reduction of LV ejection fraction (56±5% versus 22±2%) (p<0.01) (baseline versus 33 weeks) and by a gradual increase of LV end-diastolic wall stress (24±7 versus 92±8 g/cm²) (p<0.01), left atrial dimension (2.4±0.2 cm to 3.3±0.3 cm) (p<0.01), and left atrial fractional shortening (22±3% versus 15±2%) (p<0.01).

Conclusions. The initial rise in left atrium contribution to LV filling may represent a compensatory response to the diminution of the rapid early component of LV filling. With further progression of LV dysfunction, the left atrium contribution to LV filling gradually decreased. This reduction may be mediated by increased workload imposed on the left atrial myocardium due to increased LV diastolic wall stress, which, over time, may have lead to intrinsic left atrium dysfunction. (Circulation 1992;86:1317-1322)

Key Words • left atrium • heart failure • echocardiography, Doppler

Under both normal and abnormal physiological conditions, left ventricular (LV) filling is determined primarily by the instantaneous pressure difference between the left atrium (LA) and the LV.1,5 This pressure gradient is influenced by the interaction of multiple factors, including LV preload and afterload, rate of LV isovolumic relaxation, extent of LV chamber stiffness, and intrinsic contractility of the LA: all undergo considerable alteration in the heart failure state.6,7

Abnormal LV diastolic filling has been observed in patients with heart failure and is characterized by marked heterogeneity of mitral inflow velocity patterns.8-10 In some patients with heart failure, LA contribution to LV filling was reportedly enhanced compared with normal subjects, whereas in other patients, early rapid filling remained the primary contributor to overall ventricular filling during diastole with only limited contribution by LA contraction.8-10 We hypothesize that this disparity in mitral inflow velocity patterns in patients with heart failure is the result of observations obtained at different time points of a dynamically evolving disease process. In this report, we present data that describe the temporal changes of LV filling during the course of evolving heart failure in dogs. The temporal changes in the patterns of mitral inflow velocity observed during the course of heart failure are explained on the basis of concurrent alterations in LA size and function and LV chamber size, stiffness, wall stress, and rate of isovolumic relaxation.

Methods

The canine model of chronic heart failure used in the present study has been previously described in detail.11 In this experimental preparation, heart failure is produced by multiple sequential intracoronary embolizations with polystyrene latex microspheres (70–102-um diameter), which lead to the loss of viable myocardium. The model manifests many of the sequelae of heart failure observed in patients, including marked and sustained depression of LV systolic and diastolic function, LV hypertrophy and dilation, reduced cardiac output, increased systemic vascular resistance, and enhanced activity of the sympathetic nervous system as demonstrated by marked elevation of plasma norepinephrine concentration.11

In the present study, eight healthy mongrel dogs, weighing between 23 and 35 kg, underwent a series of
TABLE 1. Number of Coronary Embolizations, Last Week of Embolization, and Left Ventricular Ejection Fraction at the Time of the Last Embolization

<table>
<thead>
<tr>
<th>Dog</th>
<th>No. of embolizations</th>
<th>Week of last embolization</th>
<th>LVEF at last embolization (%)</th>
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<tr>
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LVEF, left ventricular ejection fraction.

cardiac catheterizations and coronary embolizations to produce heart failure. The protocol was approved by the Henry Ford Hospital Care of Experimental Animals Committee. All cardiac catheterizations were performed with the chest closed, the animal under general anesthesia, and under sterile conditions. Dogs were anesthetized with an intravenous injection of 0.1 mg/kg Innovar-Vet (droperidol 2.0 mg/kg and fentanyl citrate 0.04 mg/kg) followed by an intravenous injection of 7.5 mg/kg sodium pentobarbital. Embolizations were performed 1–3 weeks apart and were discontinued when the LV ejection fraction, determined angiographically, was ≤35%. The number of embolizations, week of the last embolization, and LV ejection fraction at the time of the last embolization are shown in Table 1 for each of the dogs studied.

Hemodynamic and Angiographic Assessments

Aortic and LV pressures were measured with a 5F catheter-tip micromanometer (Millar Instruments, Houston, Tex.). Mean LV filling pressure was estimated by integration of the area under the diastolic LV pressure waveform starting at the level of end-diastolic pressure and extending to the same level on the relaxation downstroke. Changes of LV relaxation were quantitated using the time constant τ calculated as described by Weiss and associates. Because instantaneous LV pressure–volume relations were not obtained in this study, LV end-diastolic chamber stiffness was estimated as the ratio of end-diastolic pressure to end-diastolic volume.

Left ventriculograms were performed with the dog placed on its right side and were recorded on 35-mm cine during the injection of 20 ml of contrast material (RENO-M-60, Squibb Diagnostics). Correction for image magnification was made with a radiopaque calibrated grid placed at the level of the LV. LV chamber volumes at end systole and end diastole were calculated using the area–length method and were used to determine LV ejection fraction. Premature beats and postextrasystolic beats were excluded from the analysis.

Echocardiographic and Doppler Measurements

Echocardiographic studies were performed using a Hewlett-Packard model 77020A ultrasound system with a 2.5-MHz transducer. Measurements were made during cardiac catheterization with the dog placed in the right lateral decubitus position. Echocardiograms were recorded on a Panasonic 6300 VHS recorder. Selected records were recorded on a Hewlett-Packard model 77000A strip-chart recorder at a paper speed of 50 mm/sec for M-mode echocardiograms and at 100 m/sec for pulsed wave Doppler echocardiograms. The maximum LA dimension, thickness of the intraventricular septum, and thickness of the LV posterior wall were determined using M-mode echocardiography according to the recommendation of the American Society of Echocardiography. The thicknesses of the intraventricular septum and the LV posterior wall were summed and averaged to obtain a single representative measure of LV wall thickness. Minimum LA dimension was measured from the same M-mode echocardiograms at the time of onset of the QRS complex of the ECG. The fractional shortening of the LA was estimated as the difference between the maximal and minimal LA dimensions divided by the maximal dimension and multiplied by 100. The end-diastolic LV major and minor semiaxes at the midwall were measured from two-dimensional echocardiograms using the apical four-chamber view. LV end-diastolic circumferential wall stress was calculated according to the following equation:

\[ \text{Stress} = \frac{P}{h} \left(1 - \frac{h}{2b}\right) \left(1 - \frac{h^2}{2a^2}\right) \]

where P is LV end-diastolic pressure, a is LV major semiaxis, b is LV minor semiaxis, and h is LV wall thickness (average of septum and posterior wall).

The presence or absence of functional mitral regurgitation was determined with color Doppler imaging the apical two- and four-chamber views. The severity of the regurgitation was quantitated based on the ratio of the regurgitant jet area to the area of the left atrium. Regurgitant fractions, assessed from both echocardiographic views, were averaged to obtain a single representative measure of severity of mitral regurgitation.

Mitral inflow velocity was measured by pulsed wave Doppler echocardiography performed from the cardiac apex with the Doppler beam aligned parallel to the assumed transmitral flow. The sample volume was placed between the tips of the mitral leaflets to obtain maximal inflow velocity in early diastole. The angle between the Doppler flow direction and the assumed mitral flow direction was approximately 20°. The characteristics of mitral inflow velocities that were measured are 1) peak mitral flow velocity in early diastole (PE), 2) peak mitral flow velocity during atrial contraction (PA), 3) ratio of PE to PA, 4) time-velocity integral of the velocity waveform representing rapid early LV filling (Ei), 5) time-velocity integral of the velocity waveform representing LA contraction (Ai), 6) ratio of Ei to Ai, and 7) deceleration time of mitral inflow velocity during rapid early LV filling (DT). DT was defined as the time interval between the peak velocity and the zero intercept of the deceleration slope. When atrial contraction occurred before early diastolic inflow had decelerated to zero baseline, the slope was linearly extrapolated to the baseline to obtain the deceleration time as previously described. For each transmitral flow measurement, five consecutive spectral tracings were evaluated and averaged to obtain a single representative value.

Statistical Analysis

Hemodynamic, angiographic, and pulsed wave Doppler echocardiographic measurements were obtained at
Results

Temporal Change of Hemodynamic and Angiographic Indices

Heart rate increased from 86±13 beats per minute at baseline to 95±34 beats per minute at 33 weeks. This increase, however, was not statistically significant by ANOVA. Aortic systolic pressure decreased gradually from 130±13 mm Hg at baseline to 112±11 mm Hg (p<0.05). LV ejection fraction decreased gradually from 56±5% at baseline to 22±2% at 33 weeks (p<0.01). LV end-diastolic pressure increased from 8±2 mm Hg to 19±2 mm Hg (p<0.01), LV end-diastolic volume increased gradually from 59±7 ml to 90±14 ml (p<0.01), and the time constant of LV relaxation increased gradually from 34±6 msec to 50±9 msec (p<0.01). The temporal changes of these parameters over the course of the study are depicted in Figure 1. Mean LV filling pressure increased gradually from 6±2 mm Hg at baseline to 18±4 mm Hg at 33 weeks (p<0.01) and subsequently declined slightly to 14±4 mm Hg at 33 weeks once overt LV dilation developed.

LA size increased progressively during the study period (Figure 2). The maximum LA dimension was 2.4±0.2 cm at baseline and increased to 3.3±0.3 cm at 33 weeks (p<0.01). The increase of LA size was accompanied by a progressive reduction of LA function. The fractional shortening of the LA was 22±3% at baseline and decreased to 15±2% at 33 weeks (p<0.01) (Figure 2). Estimated LV end-diastolic chamber stiffness increased gradually from 0.13±0.04 mm Hg/ml at baseline to 0.39±0.09 mm Hg/ml at 15 weeks (p<0.05) and subsequently declined to 0.21±0.04 mm Hg/ml at 33 weeks as LV dilation developed (Figure 2). LV end-diastolic wall stress progressively increased from 24±7 g/cm² at baseline to 92±8 g/cm² (p<0.01) and remained elevated thereafter (Figure 2). Among the eight dogs studied, seven developed mild-to-moderate functional mitral regurgitation at 15 weeks, which persisted thereafter. The severity of regurgitation in these dogs was 8±4% at 15 weeks and increased to 15±6% at 33 weeks (p<0.01).

Temporal Changes of LV Diastolic Filling

PE was essentially unchanged between baseline and 23 weeks but declined sharply at 33 weeks (Figure 3). In contrast, PA increased significantly between baseline and 3 weeks (32±13 versus 49±9 cm/sec) (p<0.01). This early increase of PA was followed by a gradual reduction to near-baseline values at 33 weeks (Figure 3). These temporal changes of PE and PA resulted in a

FIGURE 1. Temporal changes (mean±SD) of left ventricular (LV) ejection fraction (EF) (top left), LV end-diastolic volume (EDV) (top right), LV end-diastolic pressure (EDP) (bottom left), and time constant of LV relaxation (τ) (bottom right) during the course of evolving heart failure. Measurements at week zero represent baseline values obtained before any coronary embolizations. *p<0.05, **p<0.01 relative to baseline.

FIGURE 2. Temporal changes (mean±SD) of maximum (Max) left atrial (LA) dimension (top left); LA fractional shortening (FS) (top right); ratio of left ventricular (LV) end-diastolic pressure (EDP) to end-diastolic volume (EDV), a measure of end-diastolic chamber stiffness (bottom left); and LV circumferential wall stress (bottom right) during the course of evolving heart failure. *p<0.05, **p<0.01 relative to baseline.

FIGURE 3. Temporal changes (mean±SD) of peak E (PE) inflow velocity (top left), peak A (PA) inflow velocity (top right), ratio of peak E to peak A velocity (PE/PA) (bottom left), and deceleration time of the early rapid left ventricular filling component (DT) (bottom right) during the course of evolving heart failure. **p<0.01 relative to baseline.
reduction of the PE/PA ratio at 3 weeks relative to baseline followed by a gradual increase of this ratio to near-baseline levels by 33 weeks (Figure 3). The DT of the rapid filling velocity waveform progressively shortened from 124±19 msec at baseline to 66±15 msec at 15 weeks \((p<0.01)\) and remained unchanged thereafter (Figure 3).

Ei decreased sharply between baseline \((7.6±1.5 \text{ cm})\) and 3 weeks \((5.8±1.0 \text{ cm})\) \((p<0.01)\) and continued to decline thereafter, reaching a value of 4.0±0.4 cm at 33 weeks \((p<0.01)\) (Figure 4). The rapid early decline of Ei was accompanied by an early marked increase in Ai. At baseline, Ai was 1.8±0.9 cm; it increased to 2.7±0.4 cm at 3 weeks \((p<0.01)\) and subsequently fell gradually to below-baseline values at 33 weeks \((0.8±0.4)\) \((p<0.01)\) (Figure 4). These temporal changes of Ei and Ai resulted in an early reduction of the Ei/Ai ratio at 3 weeks followed by a gradual increase to near-baseline values at 33 weeks (Figure 4). Figure 5 shows a diagrammatic representation of the temporal changes of transmitral inflow patterns seen at baseline and at 3, 15, and 33 weeks.

**Discussion**

Observations made in this study of mitral inflow velocity during the course of evolving heart failure demonstrate unique but well-defined patterns of LV diastolic filling that appear to be dictated by the functional state of the LV and LA chambers. The observed changes in the patterns of LV filling are characterized by a reduction in the rapid filling component during the early stages of LV dysfunction associated with a compensatory increase in the LA component of LV filling. Further progression of LV dysfunction elicits a greater reduction of the rapid filling component and an eventual loss of compensation by the LA component. In the end, the development of profound LV dysfunction and failure leads to a marked reduction in both the early rapid and the late LA components of LV filling.

The patterns of LV filling observed in the present study during the course of evolving heart failure can be explained based on the interactions of multiple factors, including temporal changes of LV isovolumic relaxation, LV chamber stiffness and wall stress, and functional performance of the LA chamber. In the present study, moderate LV dysfunction was accompanied by a significant reduction of the rapid early component of LV filling and by a rise in the LA component. The decrease in Ei can be explained on the basis of a concomitant decrease in DT of the rapid inflow velocity waveform. This reduction in DT may be the consequence of a concurrent increase in LV chamber stiffness and wall stress. Increased LV chamber stiffness has been shown to be associated with diminution of DT.\(^1\)\(^2\)\(^3\) The increased contribution of Ai, on the other hand, may represent a compensatory action aimed at maintaining stroke volume in response to a reduction in the early component of ventricular filling.

With increasing severity of LV dysfunction, different patterns of LV diastolic filling emerged. At this stage, Ei continued to decline, and LA compensation was lost as evident by a decrease in Ai to near-baseline levels. The loss of LA compensation was associated with atrial dilatation and marked reduction of LA systolic performance, both of which can be explained on the basis of a longstanding increase in LA afterload as a result of an elevated LV chamber stiffness and wall stress.

In the present study, the development of profound LV dysfunction and failure was accompanied by another change in the pattern of LV diastolic filling. This advanced stage was associated with a marked reduction of both components of LV filling. Further reduction of Ei can be explained on the basis of a concomitant
reduction of PE resulting from prolonged isovolumic relaxation. The reduction in the LA component of LV filling at this time was associated with a further increase of LA size and overt LV dilation. This reduction of the LA component of filling may be explained on the basis of a decrease in the contractility of the LA. The fact that LA systolic function remained depressed in the face of a reduction in LV chamber stiffness and end-diastolic pressure supports the notion of failure of the LA in the mechanical sense. The reduction in LV chamber stiffness and LV end-diastolic pressure at this time may be reflections of the development of overt LV dilation.

A compensatory increase of LA contribution to LV filling has been described in patients with remote myocardial infarction as well as in patients with dilated cardiomyopathy who were either asymptomatic or mildly symptomatic. In patients with myocardial infarction, this compensatory response was attributed to the Frank-Starling mechanism in the LA. A reduction in LA contribution to LV filling has been demonstrated in patients with heart failure and was attributed to elevated LV filling pressure. Patients with high pulmonary artery wedge pressure were shown to have a lower LA filling fraction compared with patients with lower pulmonary capillary wedge pressure. This relation, however, need not imply a cause-and-effect relation but rather a confirmation that patients with more advanced heart failure—those with higher LV filling pressure—manifest a greater reduction of the LA filling fraction. This interpretation is supported by the observations made by Greenberg and colleagues. In their study, the LA filling fraction was examined in two groups of patients with equally elevated pulmonary artery wedge pressure (≥20 mm Hg). Their results showed that patients with a history of heart failure had significantly lower LA filling fraction compared with patients without a history of heart failure despite the fact that both groups had similar elevations of pulmonary artery wedge pressure. As a result of these observations, these investigators raised the question of abnormal LA function as a potential mechanism of reduced LA filling in patients with heart failure and impaired ventricular function.

In the present study, seven of the eight dogs developed mild-to-moderate mitral regurgitation. The regurgitation was first observed at an average of 15 weeks after the first embolization and persisted thereafter. The regurgitant fraction was 8% at 15 weeks and increased significantly to 15% at 33 weeks. Studies by Lavine and Arends in patients with dilated cardiomyopathy showed that the presence of mitral regurgitation does not influence the distribution of diastolic LV filling. Mitral regurgitation, however, caused a significant increase of PE. Other studies in patients, however, reported a lack of correlation between the severity of mitral regurgitation and peak rapid inflow velocity. In the present study, the onset of mitral regurgitation was accompanied by a mild but significant increase of peak velocity during the phase of early rapid filling. Despite a significant increase in the severity of mitral regurgitation once profound failure developed, peak rapid filling velocity decreased. The reduction of peak rapid filling velocity in the present study is most likely due to the development of impaired LV isovolumic relaxation.

The canine model of chronic heart failure used in this study shares many similarities with human heart failure resulting from loss of viable myocardium. The present results, therefore, may be more safely extrapolated to patients with heart failure due to myocardial infarction and subsequent myocardial remodeling than to patients with dilated cardiomyopathy. Furthermore, because the model is produced by multiple coronary embolizations with microspheres, it is possible that some of the observed early changes in the diastolic properties of the LV may be the result of the global nature of myocardial injury and, as such, may be independent of the heart failure that ensues. Other limitations of the study include a lack of simultaneous LA and LV pressure measurements and the possible effects of anesthesia on the observed results.

In conclusion, the results of this study indicate that the pattern of mitral inflow velocity undergoes considerable changes during the course of evolving heart failure. In this canine model of heart failure, these changes are characterized by a progressive decline in the early rapid component of left ventricular filling. In contrast, the LA component of filling initially increases but eventually declines with onset of profound pump failure. The early increase in LA contribution to filling may represent a compensatory response to the decline in the rapid filling component. The loss of this compensatory action and the subsequent decline in the LA contribution to ventricular filling may reflect increased work load imposed on the LA myocardium, which, over time, can lead to LA dilation and intrinsic LA dysfunction.

References

Left atrial contribution to ventricular filling during the course of evolving heart failure.
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