Dynamic Determinants of Left Ventricular Early Diastolic Filling in Old Myocardial Infarction

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The determinants of left ventricular early diastolic filling were assessed in 15 patients with old myocardial infarction. The left atrial pressure (LAP) and left ventricular pressure (LVP) were simultaneously measured by a Millar's multisensor micromanometer with the pulsed Doppler mitral inflow velocity at baseline and during angiotensin infusion (20 ng/kg/min). Cardiac output was measured by a thermodilution method. LV peak systolic pressure and end-diastolic pressure were significantly ($p < 0.001$) increased during angiotensin infusion from 137 ± 19 to 170 ± 21 mmHg and from 13.3 ± 5.9 to 20.4 ± 6.2 mmHg, respectively. Cardiac index was significantly decreased during angiotensin infusion. Heart rate, diastolic time, and peak positive dP/dt were unchanged. Although the LA-LV peak pressure gradient[(LAP-LVP) max]was unchanged (from 2.8 ± 1.0 to 3.0 ± 1.4 mmHg), the pressure gradient interval (the interval between the first and second points of transmitral pressure crossover) was significantly ($p < 0.001$) decreased from 154 ± 38 to 117 ± 26 msec during angiotensin infusion. Peak early diastolic mitral inflow velocity (peak E) and the time-velocity integral of E wave (Ei) were significantly decreased during angiotensin infusion from 51 ± 10 to 45 ± 11 cm/sec ($p < 0.002$) and from 7.47 ± 1.96 to 5.70 ± 1.66 cm ($p < 0.001$), respectively. Peak E had a significant linear correlation with[(LAP-LVP) max]($r = 0.660$, $p < 0.0001$), while Ei had a significant linear correlation with pressure gradient interval ($r = 0.751$, $p < 0.0001$). Thus, LV early diastolic filling is determined not only by the LA-LV peak pressure gradient, but also by the pressure gradient interval in the diseased human LV.

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DOPPLER echocardiography is now widely accepted for the noninvasive evaluation of left ventricular (LV) function, and the early diastolic mitral inflow velocity has been used for detecting LV diastolic dysfunction. It is well known that clinically the early diastolic mitral inflow velocity decreases

in patients with hypertension, hypertrophic cardiomyopathy, dilated cardiomyopathy, and myocardial infarction¹⁻³ Recent clinical and experimental studies have demonstrated that LV relaxation and left atrial pressure (LAP) were the most important determinant factors of LV early diastolic filling in normal hearts⁴⁻⁷ However, the precise mechanisms which determine the early diastolic mitral inflow velocity in the diseased heart remain obscure. Therefore, the present study was

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Fig.1. Simultaneous recordings of pulsed Doppler echogram of mitral inflow (MVF), left ventricular pressure (LVP), left atrial pressure (LAP), electrocardiogram (ECG), and phonocardiogram (PCG) at control state and during angiotensin infusion. P=pressure, E=early filling wave, A=atrial filling wave.

Fig.2. Schematic diagram illustrating the method used to measure several diastolic parameters. ECG=electrocardiogram, dP/dt = the first derivative of left ventricular pressure, LVP=left ventricular pressure, LAP=left atrial pressure, MVF=mitral inflow velocity, E=early filling wave, A=atrial filling wave, Ei=time-velocity integral of E wave, Ai=time-velocity integral of A wave, MVO=mitral valve opening, pPgrad=LA-LV peak pressure gradient, PGI=pressure gradient interval.

designed to further elucidate the relations between the early diastolic mitral inflow velocity and hemodynamics in 15 patients with old myocardial infarction by simul-

taneous recordings of LAP, LV pressure (LVP) and pulsed Doppler mitral inflow velocity at baseline and during angiotensin infusion.

METHODS

Fifteen patients with old myocardial infarction (MI) were studied. All subjects were in sinus rhythm and their ages ranged from 38 to 71 years (mean 57 ± 12). MI was diagnosed according to the history, enzyme elevation (SGOT, LDH, CK-MB), ECG changes, and coronary angiography. Nine patients had antero-septal, 4 had inferior, 1 had postero-lateral, and 1 had non-Q wave MI. Coronary angiography showed one-vessel disease in thirteen, two-vessel disease in one, and three-vessel disease in 1 patient. None had the symptoms of post-infarction angina.

After obtaining informed consent, right- and left-heart catheterization was performed in the postabsorptive state, approximately 30 min after premedication with diazepam (Horizon®) 10 mg by intramuscular injection. All other medications had been discontinued 24 h before the study. The LAP and LVP were simultaneously measured by a multisensor micromanometer (8F, model SSD-374, pigtail, Millar Instruments Inc.,

TABLE I HEMODYNAMIC AND RELATED PARAMETERS

	BASILINE	ANGIOTENSIN	p
HR (bpm)	66±7	66±8	ns
LVPSP (mmHg)	137±19	170±21	0.001
LVPDP (mmHg)	13.3±5.9	20.4±6.2	0.001
(+) dP/dt (mmHg/sec)	1451±267	1471±254	ns
(-) dP/dt (mmHg/sec)	1832±400	1761±328	ns
Pmvo (mmHg)	9.9±3.9	15.2±5.4	0.001
Pmin (mmHg)	4.2±2.3	8.3±3.5	0.001
(LAP-LVP) max (mmHg)	2.8±1.0	3.0±1.4	ns
PGI (msec)	154±38	117±26	0.001
DT (msec)	542±87	526±105	ns
T (msec)	43±8	52±10	0.001
LAPv (mmHg/sec)	56±35	94±62	0.02
CI (ml/min m ²)	3.02±0.94	2.66±0.75	0.01

HR=heart rate; bpm=beat per minute; LVPSP=left ventricular peak systolic pressure; LVEDP=left ventricular end-diastolic pressure; (+) dP/dt=peak positive dP/dt; (-) dP/dt=peak negative dP/dt; Pmvo=mitral valve opening pressure; Pmin=left ventricular minimum pressure; (LAP-LVP) max=left atrial-left ventricular peak pressure gradient; PGI=pressure gradient interval; DT=diastolic time; T=time constant; LAPv=mean velocity of left atrial pressure decline after the mitral valve opening; CI=cardiac index. Values are mean ± SD.

Houston, Texas). The catheter has 2 pressure sensors with one end-opening lumen. Both pressure sensors were calibrated against the same mercury column before insertion, and then during measurement, the output from the micromanometer was adjusted to the pressure measured through the fluid channel of this catheter by means of a Statham P23ID transducer (Gould Inc., Oxnard, California). The first derivative of the LVP (dP/dt) was obtained from the R-C differentiating circuit (Analog data processor model V4202, Electronics for Medicine Inc., Pleasantville, New York) and was calibrated by a known slope. The catheter was introduced through the brachial artery, and the distal pressure sensor was placed in the LA and the proximal sensor in the LV⁸. Mitral inflow velocity was obtained by a range-gated pulsed Doppler echocardiography (model SSD-730, Aloka Inc., Tokyo). From the apical 4 chamber view, the Doppler cursor line was carefully placed in the mitral valve at an angle as parallel to flow as possible, and the sample volume was carefully placed at the center of the mitral ring during diastole⁹. Electrocardiogram (ECG), phonocardiogram (PCG), LVP, LAP, magnified LVP and LAP, and LV dP/dt were recorded on the Electronics for Medicine VR-12 recorder at a paper speed of 150 mm/sec. As

shown in Fig. 1, MVF, ECG, PCG, magnified LVP and LAP were also recorded on the thermal recorder at a paper speed of 100 mm/sec separately, and the markers on the ECG signal in each chart enabled us to match those two tracings. After recording the baseline condition at end-expiration, angiotensin was infused 20 ng/kg/min intravenously. When LVP had increased by 40 mmHg, the same measurements were repeated. Cardiac output was measured by a thermodilution method before and during angiotensin infusion. After achieving these procedures, biplanar left ventriculography and coronary arteriography by Sones' method were carried out. The LV volumes at end-diastole and end-systole were derived using standard area-length method by SICOR cathlab computer system (Siemens-Elcoma Inc. Solna, Sweden). Mean circumferential fiber shortening (meanVcf) was calculated as follows:¹⁰ meanVcf=(Ced-Ces)/(Ced·ET), where Ced=end-diastolic equatorial circumference, Ces=end-systolic equatorial circumference, and ET=ejection time.

According to the method of Weiss et al, LVP during isovolumic relaxation period was fitted by the least squares method to the function $P=Ae^{-t/T}$ (P: LVP, A: constant) and the time constant (T) was derived!^{1,12}

Fig.3. Bar graph illustrating changes in Pmvo (mitral valve opening pressure), LAPv (mean velocity of left atrial pressure decay), peak Pgrad (peak LA-LV pressure gradient), and PGI (pressure gradient interval) before and during angiotensin infusion. Pmvo and LAPv increased significantly with angiotensin. Although peak LA-LV pressure gradient was unchanged, pressure gradient interval showed a significant decrease during angiotensin infusion. C=control, A=angiotensin.

TABLE II DOPPLER ECHOCARDIOGRAPHIC PARAMETERS

	BASELINE	ANGIOTENSIN	p
peak E (cm/sec)	51±10	45±11	0.002
peak A (cm/sec)	59±13	55±14	0.03
Ei (cm)	7.47±1.96	5.70±1.66	0.001
Ai (cm)	4.98±1.43	4.10±1.33	0.001
peak E/A	0.89±0.27	0.85±0.24	ns
Ei/Ai	1.56±0.40	1.50±0.50	ns
DR _E (cm/sec ²)	233±80	259±95	ns
DR _A (cm/sec ²)	779±166	771±172	ns

peak E=peak E wave velocity; peak A=peak A wave velocity; Ei=time-velocity integral of E wave; Ai=time-velocity integral of A wave; peak E/A=the ratio of peak E to peak A; Ei/Ai=the ratio of Ei to Ai; DR_E=mean deceleration rate of E wave; DR_A=mean deceleration rate of A wave. Values are mean±SD.

From the simultaneous recording of LVP and LAP, the following parameters were derived (see Fig. 2). Mitral valve opening

pressure (Pmvo): pressure at the first crossover of LAP and LVP after the peak negative dP/dt; pressure gradient interval

Fig. 4. Upper panel: Scatterplots showing relations between peak E (peak E wave velocity) and peak Pgrad (LA-LV peak pressure gradient) at baseline ($\circ$) and during angiotensin infusion ($\bullet$). There is a significant linear correlation between the two variables. Lower panel: Scatterplots showing relations between Ei (time-velocity integral of E wave) and PGI (pressure gradient interval) at baseline and during angiotensin infusion. There is also a significant linear correlation between the two variables.

(PGI): the time interval between the first and second points of transmitral pressure crossover; (LAP-LVP) max: the LA-LV maximum difference between the first and second points of transmitral pressure crossover; LAPv: mean velocity of LAP decline after the mitral valve opening; and Pmin: minimum LVP. With the aid of a computer-interfaced digitizer, we also measured the following variables: peak early diastolic mitral inflow velocity (peak E) and peak flow velocity at atrial contraction (peak A), time-velocity integral of E and A waves (Ei and Ai, respectively), ratio of peak E to

peak A and Ei to Ai (peak E/A and Ei/Ai, respectively).

Baseline and intervention data are presented as mean $\pm$ SD. For statistical comparisons of the variables, the Student's paired t-test was employed. Changes in data and correlation coefficients were considered as significant at values of p less than 0.05.

RESULTS

The mean values of angiographic data at resting state in all 15 patients studied were as follows. LV end-diastolic volume index was 97 ± 21 ml/m², ejection fraction was ranged from 42 to 75% (mean $56 \pm 10\%$), and mean Vcf was 0.95 ± 0.29 1/sec.

Table I presents the hemodynamic and related parameters obtained at baseline state and during angiotensin infusion. LV peak systolic and end-diastolic pressure were significantly increased during angiotensin infusion from 137 ± 19 to 170 ± 21 mmHg ($p<0.001$) and from 13.3 ± 5.9 to 20.4 ± 6.2 mmHg ($p<0.001$), respectively. During afterload manipulation, heart rate (from 66 ± 7 to 66 ± 8 bpm), diastolic time (from 542 ± 87 to 526 ± 105 msec) and peak positive dP/dt (from 1451 ± 267 to 1471 ± 254 mmHg/sec) were unchanged. The time constant of LVP decay during isovolumic relaxation period was significantly prolonged during angiotensin infusion from 43 ± 8 to 52 ± 10 msec ($p<0.001$), while peak negative dP/dt was unchanged (1832 ± 400 vs 1761 ± 328 mmHg/sec). LV minimum pressure significantly increased during angiotensin administration from 4.2 ± 2.3 to 8.3 ± 3.5 mmHg ($p<0.001$). As shown in Fig. 3, mitral valve opening pressure (Pmvo) and mean velocity of LAP decay after mitral valve opening (LAPv) were significantly increased during angiotensin infusion from 9.9 ± 3.9 to 15.2 ± 5.4 mmHg ($p<0.001$) and from 56 ± 35 to 94 ± 62 mmHg/sec ($p<0.02$), respectively. Although the LA-LV peak pressure gradient [(LAP-LVP) max] was unchanged (2.8 ± 1.0 vs 3.0 ± 1.4 mmHg, ns) with angiotensin, pressure gradient interval (PGI) was significantly decreased from 154 ± 38 to 117 ± 26 msec ($p<0.001$). Cardiac index was significantly decreased during angiotensin administration from 3.02 ± 0.94 to 2.66 ± 0.75 ml/min·m² ($p<0.01$).

The representative pulsed Doppler echocardiogram recordings of mitral inflow, magnified LAP and LVP at baseline and during angiotensin infusion are shown in Fig. 1. During angiotensin infusion, peak E wave velocity and the time-velocity integral of E wave were markedly decreased, associated with the shortened LA-LV pressure gradient interval and unchanged LA-LV peak pressure gradient.

Table II summarizes the Doppler echocardiographic results obtained at baseline and during angiotensin infusion. Peak E and peak A both decreased during angiotensin infusion from 51 ± 10 to 45 ± 11 cm/sec ($p < 0.002$) and from 59 ± 13 to 55 ± 14 cm/sec ($p < 0.03$), respectively. Ei and Ai were also decreased during angiotensin infusion from 7.47 ± 1.96 to 5.70 ± 1.66 cm ($p < 0.001$) and from 4.98 ± 1.43 to 4.10 ± 1.33 cm ($p < 0.001$), respectively, accompanied by unchanged ratios of peak E to peak A and Ei to Ai. Deceleration rate of E and A wave was unchanged during angiotensin infusion from 233 ± 80 to 259 ± 95 cm/sec² and from 779 ± 166 to 771 ± 172 cm/sec², respectively.

Fig. 4 shows the relationships between LA-LV peak pressure gradient and peak E wave velocity, and between pressure gradient interval and Ei. Peak E wave velocity had a significant linear correlation with peak pressure gradient ($r = 0.660$, $p < 0.0001$). Ei had also a significant linear correlation with pressure gradient interval ($r = 0.751$, $p < 0.0001$). The weak relations were demonstrated between peak E and pressure gradient interval ($r = 0.400$, $p < 0.05$) and between Ei and peak pressure gradient ($r = 0.390$, $p < 0.05$). There was no significant correlation between time constant and peak E ($r = -0.066$, $p = 0.186$) or Ei ($r = -0.248$, $P = 0.730$).

DISCUSSION

Numerous investigations have documented the afterload dependence of LV relaxation¹³⁻¹⁵. However, few investigations have described the effect of afterload on LV early diastolic filling, especially in the diseased heart. The present data, obtained from 15 patients with old myocardial infarction demonstrated that peak E wave veloc-

ity, as well as time-velocity integral of E wave, were significantly decreased during angiotensin infusion (Table II). Experimental studies have been conducted to elucidate the effect of afterload on LV early diastolic filling in normal hearts. Ishida et al⁴ demonstrated, using conscious dogs, that peak filling rate was decreased with a large increase in peak LVP (change in peak LVP of greater than 35%), but not with moderate increase in peak LVP (change in peak LVP less than 35%). Using an open-chest right heart bypass preparation, Choong et al⁵ found the Doppler peak E wave velocity was decreased with increasing LV systolic pressure at constant LAP. Nishimura et al¹⁶ have shown that peak E velocity in anesthetized dogs is independent afterload. Meanwhile, in human studies, Colan et al¹⁷ demonstrated in 18 normal subjects that the peak rate of LV dimension change (dd/dt_{max}) and peak rate of LV wall thinning ($-dh/dt_{max}$) were both unchanged during increase in afterload with methoxamine. Likewise, Takenaka et al¹⁸ described that after methoxamine and atropine injection the Doppler peak E wave velocities were unchanged in 10 normal subjects without mitral regurgitation. Discrepancy between the afterload dependence^{4,5} and independence¹⁶⁻¹⁸ of LV early diastolic filling may be attributed to the magnitude of increase in afterload and the methods used to increase afterload. As shown in the report by Ishida et al⁴, moderate pressure rise could not influence the LV filling. Nishimura et al¹⁶ increased afterload by aortic balloon inflation, and moderate increase in afterload (98 ± 12 to 121 ± 18 mmHg) failed to produce a reduction in peak E wave velocity. In human studies, the above authors^{17,18} used methoxamine to manipulate afterload in normal subjects. Afterload independence of LV early diastolic filling in human studies might be due to the inotropic action of this drug, which had masked the decrease in the LV early diastolic filling, and also due to different patient characteristics. In the present study using patients with old myocardial infarction, cardiac index significantly decreased by 12% from the baseline value with a corresponding 24% increase in LVP associated with the marked elevation of LV end-diastolic pressure by 53%. These re-

sults suggest that afterload mismatch might be induced by angiotensin infusion accompanied by considerable impairment of LV preload reserve.¹⁹ This failure of LV preload reserve might play an important role for the reduction of early diastolic mitral inflow velocity.

As shown in Table I and Fig. 3, it was revealed that the pressure gradient interval shortened during angiotensin infusion, however, LA-LV peak pressure gradient remained unchanged when the LV early diastolic filling was reduced. Furthermore, peak E wave velocity had a close correlation with LA-LV peak pressure gradient, while time-velocity integral of E wave had a close correlation with pressure gradient interval (Fig. 4). Our findings suggest that pressure gradient interval is one of the determining factors of ventricular filling, besides LA-LV peak pressure gradient. A recent experimental study demonstrated that LAP (or LA-LV pressure difference at the time of peak flow) and relaxation were two important determinants in LV filling.⁴ Che-Ping Cheng et al⁶ also described that relaxation filling (amount of LV filling that occurred while LVP is falling) was influenced by LAP and relaxation. The discrepancy between our results and Ishida's concerning the effect of afterload on LA-LV pressure gradient may originate from differences in methodology and subjects. The model used in their study has no pericardium, and the mitral annular motion could be disturbed by the electromagnetic flow probe which was sutured to the mitral annulus. This restriction of annular motion might have caused the decrease in LA-LV pressure gradient at the time of peak flow during angiotensin infusion in their study.

What kind of factors underlie the mechanisms for changing LA-LV peak pressure gradient or pressure gradient interval? Several factors which determine the ventricular filling can be considered, as was pointed out by Yellin et al²⁰ We would propose the factors to be as follows: LV relaxation, LV compliance, LV elastic recoil, and LA compliance. In our present study, after an increase in afterload, the time constant of LVP decay was significantly prolonged, and a weak inverse correlation between the time-velocity integral of E wave

and time constant was observed, but it was not significant. The experimental study⁴ demonstrated that there was a weak correlation between rapid filling rate and time constant ($r = -0.369$). The clinical study by Magorien et al²¹ also showed a weak correlation between time constant and peak filling rate. ($r = -0.499$). Incomplete LV relaxation imposed by augmented afterload could cause the elevation of LV minimum pressure, hence LA-LV peak pressure gradient and pressure gradient interval were reduced. LV compliance is the second important determining factor of LV early diastolic filling. Although we have not considered the LV compliance in the present study, it is suggested that the elevated LV end-diastolic pressure was due to the increase in compliance by angiotensin infusion.²² The report by Alderman et al²³ demonstrated clinically that angiotensin shifted the entire pressure volume curve up, and nitroprusside shifted the curve down. Their study had been confirmed by experiment²⁴ which had shown that shifts of the curve were caused by shifting blood between the systemic venous bed and the heart, and thereby changing the heart size and pericardial pressure. The decreased operational compliance in early diastole, which impede the filling from LA to LV, could reduce the LA-LV peak pressure gradient and pressure gradient interval. The LV elastic recoil is the third important factor in LV early diastolic filling. This force is difficult to quantify, but the LV minimum pressure might be influenced by the elastic recoil of the LV.²⁵ The LV minimum pressure increased during angiotensin infusion in our present study (Table I). Caillet et al²⁶ reported that there was a significant correlation between peak velocity of fiber lengthening and the extent of systolic shortening. Zile et al²⁷ described that myocardial segment lengthening rate had an inverse correlation with end-systolic dimension in anesthetized dogs. These authors support the existence of elastic recoil, which produces the energy of restoring forces. Therefore, reduced restoring force during angiotensin infusion might produce the decrease in LA-LV peak pressure gradient. Finally, we should consider the LA compliance during the LV early diastolic filling. As shown in this study (Fig. 3), LAP at the

mitral valve opening increased and the mean velocity of LAP decay was accelerated during angiotensin infusion. With angiotensin infusion, the LA pressure-volume relation must be operating on the steeper part of LA compliance curve, which might accelerate the rate of LAP decline after the beginning of mitral inflow, and hence reduce LA-LV peak pressure gradient and pressure gradient interval.

In conclusion, the pressure gradient interval, as well as LA-LV peak pressure gradient, were the important determining factors of LV early diastolic filling in the diseased heart. Factors such as LV relaxation, LA and LV compliance could influence the LV early diastolic hemodynamics, and modulate the LV diastolic filling.

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