ATRIAL CONTRIBUTION TO VENTRICULAR FILLING IN PATIENTS WITH CORONARY ARTERY DISEASE AS ASSESSED BY CARDIAC PACING

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Analysis of beat to beat changes in left ventricular (LV) ejection time during cardiac pacing was utilized to assess the atrial contribution to ventricular filling in coronary artery disease. The recordings of aortic pressure were made during atrial and ventricular pacing at a rate of 5 to 10 beats/min above sinus rhythm. During ventricular pacing, LV ejection time became maximum when an atrial contraction preceded a ventricular contraction by a physiologic interval and was similar to that obtained during atrial pacing (max ET). When the atrial systole occurred with or followed the paced ventricular contraction, LV ejection time became minimum (min ET). The atrial contribution was calculated as $(\text{max ET} - \text{min ET})/\text{max ET} \times 100(\%)$. Patients with coronary artery disease had a significantly large atrial contribution. In patients without myocardial infarction, the atrial contribution was increased to compensate for impaired early diastolic filling. In patients with myocardial infarction, the atrial contribution was reduced when LV end-diastolic pressure was markedly high. The atrial contribution generally plays an important role in increasing stroke volume, but it had less effect despite the forceful atrial contraction as LV filling pressure became more elevated.

MANY patients with coronary artery disease have abnormal left ventricular (LV) diastolic function during pacing-induced ischemia. Several mechanisms of altered diastolic function during angina have been demonstrated, including incomplete or impaired relaxation and asynchronous wall motion in the left ventricle.¹⁻⁷ Diminished ventricular compliance has also been reported at rest in patients with coronary artery disease who had no evidence of either acute ischemia or previous myocardial infarction.^{8,9} This abnormal diastolic function may reduce the contribution of rapid diastolic filling to total LV filling volume and the contribution of atrial

systole to LV filling might then be increased. In the current study, analysis of beat to beat changes in LV ejection time during cardiac pacing was utilized to assess the atrial contribution to ventricular filling and to investigate some factors influencing this atrial contribution in patients with coronary artery disease.¹⁰

METHODS

Study patients:

Sixty-seven consecutive patients, aged 24 to 68 years, undergoing right and left heart catheterization and coronary angiography were included in this study. Eleven were women and 56 were men. All patients had typical or atypical angina pectoris and the hemodynamic study was performed for diagnostic purposes. Significant coronary artery disease, defined as stenosis of

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TABLE I HEMODYNAMIC AND ANGIOGRAPHIC DATA

Group	No. of case	Age (year)		H.R. (beats/min)	Left ventricular				
		Range	Mean		EDV (ml/m ²)	ESV (ml/m ²)	SI (ml/m ²)	EF (%)	EDP (mmHg)
Control	22	24-67	50 ± 10	65 ± 8	80 ± 10	23 ± 5	57 ± 9	72 ± 6	9.4 ± 2.0
CAD	45	29-68	52 ± 8	67 ± 8	89 ± 16*	39 ± 16***	51 ± 11*	58 ± 13***	15.6 ± 7.0***
with MI	25	29-64	50 ± 8	70 ± 8	95 ± 17**	49 ± 14***	46 ± 9***	49 ± 8***	18.7 ± 7.8***
without MI	20	39-68	55 ± 7	64 ± 8	83 ± 11	26 ± 10	57 ± 9	69 ± 9	11.7 ± 2.6**

CAD = coronary artery disease; EDP = end-diastolic pressure; EDV = end-diastolic volume index; EF = ejection fraction;
 EFV = end-systolic volume index; H.R. = heart rate; MI = myocardial infarction; SI = stroke index;
 * = $p < 0.05$; ** = $p < 0.01$; *** = $p < 0.001$

75% or greater in at least one major coronary artery, was shown in 45 patients, all of whom had typical angina. Twenty-five of the 45 patients with coronary artery disease had evidence of previous myocardial infarction, based on a previous history of ischemic cardiac pain, appropriate changes in cardiac enzyme levels and characteristic changes of the electrocardiogram. Fifteen patients had anteroseptal infarction and 10 had inferior infarction. Twenty-two patients with completely normal coronary arteries and left ventriculography served as controls. All patients were in sinus rhythm and none had mitral regurgitation seen on the left ventriculograms. Cardiac medications were discontinued at least 24 hours before the procedure, except for sublingual nitroglycerine which was allowed for anginal attack. Hemodynamic and angiographic data are presented in Table I.

Hemodynamic studies:

All the patients were investigated in the fasting state in the cardiac catheterization laboratory. For premedication, 10 mg of diazepam was subcutaneously administered 30 minutes prior to starting the procedure. Before left heart catheterization, a micromanometer tipped angiographic catheter (PC-471, Millar) or a pig tail catheter was positioned in the ascending aorta using the femoral approach. The micromanometer system was calibrated electronically against a mercury manometer before insertion and again after withdrawal. The recordings of aortic pressure were made on a multichannel recording system (Mingograf 82, Siemens-Elema) at a paper speed of 100 mm/sec. A bipolar electrode catheter inserted percutaneously to the femoral vein was first introduced in the high atrium for atrial pacing and then transferred to the right ventricular apex for ventricular pacing. Stimulation was performed with a programmable stimulator and an isolated constant current source. The stimuli were rectangular pulses 1.5 msec in duration at twice diastolic threshold (0.3 to 2.0 mA). If excessive energies were required, the site of the electrode catheter was changed.

LV ejection time:

LV ejection time was measured from the beginning of the upstroke of the aortic pressure to the incisura. During atrial pacing at a rate 5 to 10 beats/min above each individual's sinus rhythm, LV ejection time varied slightly de-

Fig.1. Effect of atrial systole on LV ejection time. A(top). During atrial pacing, LV ejection time is constant and approximately similar to the longest LV ejection time observed during ventricular pacing. B(bottom). During ventricular pacing, LV ejection time varies from beat to beat because of the changing relation of atrial to ventricular systole. A = atrial activation; AO = aorta; ECG = electrocardiogram; ET = ejection time; RA = right atrial cardiogram; S = pacing spike; V = ventricular activation

pending on the phase of respiration. During ventricular pacing at the same rate as atrial pacing, LV ejection time varied greatly depending on the temporal relationship of the dissociated atrial systole to the paced ventricular contraction. LV ejection time was maximum when an atrial contraction preceded a paced ventricular contraction by a physiologic interval and was approximately similar to that obtained during atrial pacing (Fig. 1). Consequently, the

average of 10 consecutive LV ejection times measured during atrial pacing was defined as the maximum ejection time (max ET). When the atrial contraction occurred with or followed the ventricular contraction, LV ejection time was decreased. The average of the 10 smallest LV ejection times measured during ventricular pacing, although not consecutive, was defined as the minimum ejection time (min ET). In 8 patients with coronary artery disease and in 3

Fig.2. Ventriculo-atrial conduction during ventricular pacing. A = atrial activation; AO = aorta; ECG = electrocardiogram; ET = ejection time; RA = right atrial cardiogram; S = pacing spike; V = ventricular activation

control subjects, ventriculo-atrial (V-A) conduction was recognized during ventricular pacing (Fig. 2). In these patients, the average of 10 consecutive LV ejection times measured during ventricular pacing was defined as min ET because of the constant V-A interval. Since max ET occurred in the presence of an atrial contraction that maximally enhanced diastolic filling and min ET occurred in the loss of such a contraction, the atrial contribution to diastolic ventricular filling as assessed by cardiac pacing was calculated as $(\text{max ET} - \text{min ET})/\text{max ET} \times 100(\%)$.

LV volume analysis:

LV volume analysis was made in 22 patients with coronary artery disease and 10 control subjects, whose left ventriculography was performed with a micromanometer tipped angiographic catheter. After both atrial and ventricular pacing were completed, the micromanometer tipped angiographic catheter was transferred to the left ventricle. High fidelity LV pressures were recorded at low and high gains. LV cine-angiography was performed after the recording of the pressures in a 30 degree right anterior oblique projection. Thirty to 40 ml of contrast material (Urografin 76) were injected over 3

Fig.3. Atrial contribution measured from LV volume. ECG = electrocardiogram; V1 = LV volume at end-systole; V2 = LV volume before atrial contraction (LV volume at pre A wave); V3 = LV volume at end-diastole

Fig. 4. Relation of A-S interval to LV ejection time during ventricular pacing. When the A-S interval is similar to the intrinsic PQ interval observed during sinus rhythm, LV ejection time is maximum and the pattern of the QRS complex shows a fusion beat. The LV ejection time becomes minimum when the pacing spike occurs with or precedes the atrial activation. A = atrial activation; max ET = maximum LV ejection time; min ET = minimum LV ejection time; S = pacing spike

seconds by a power injector (Mark 4, Medrad). Film was exposed at a rate of 50 frames/sec with a 35 mm cine camera (Arritechno 35, Arritechno) mounted on a 25 cm image intensifier (Angioskop, Siemens-Elema). Simultaneous electrocardiogram, LV diastolic pressure, cine-frame event and contrast injection were recorded at a paper speed of 100 mm/sec for the identification of diastolic frames at end-systole, before atrial contraction and at end-diastole. LV volumes were obtained by the area-length method of Sandler and Dodge¹¹ by tracing the silhouette with a sonic pen using a computer system (PDP 11/34, DEC). The atrial contribution to diastolic ventricular filling was determined from the LV volume curve. The effect of atrial systole was usually easily detectable from this volume curve, since the rate of the change in LV volume was little in the slow filling period and was abruptly increased at the beginning upstroke of A wave of the LV pressure curve. The difference between LV volume at end-diastole (V3) and before atrial contraction (V2 = LV volume at pre A wave) was considered

Fig. 5. Relationship between atrial contributions calculated from LV ejection time and those measured from LV volume. CAD = coronary artery disease; MI = myocardial infarction

to be the filling volume during atrial systole. Angiographic stroke volume or all filling volume was taken as the difference between end-diastolic volume (V3) and end-systolic volume (V1). Consequently, the atrial contribution to diastolic ventricular filling was calculated as $(V3-V2)/(V3-V1) \times 100(\%)$ (Fig. 3).

After left ventriculography, coronary angiography was performed in multiple projections by the Judkins technique, using a 17 cm image intensifier of the same system.

Statistical analysis:

Data were analyzed by either the unpaired Student's t test or the Mann-Whitney's U test where appropriate, for parametric and non-parametric distributions. Linear regression analysis was performed by the least squares fit method. Differences were considered significant if the p value was less than 0.05. All data are presented as the mean $\pm$ standard deviation.

RESULTS

Relation of A-S interval to LV ejection time:

During atrial pacing, LV ejection time was almost constant because of the presence of a constant PQ interval and it was approximately similar to the largest LV ejection time measured during ventricular pacing. During ventricular pacing, LV ejection time varied from beat to beat

because of the changing relation of atrial to ventricular contraction. Since the rate of ventricular pacing was 5 to 10 beats/min faster

Fig. 6. Atrial contribution calculated from LV ejection time. CAD = coronary artery disease; MI = myocardial infarction

than the sinus rhythm, the interval between atrial deflection (A on atrial electrogram) and ventricular pacing spike (S) changed cyclically (Fig. 1). When the A-S interval corresponded closely to the intrinsic PQ interval observed during sinus rhythm, LV ejection time became the longest and the pattern of the QRS complex showed a fusion beat resulting from simultaneous ventricular activation by sinus rhythm and ventricular pacing. As the A-S interval was decreased, LV ejection time grew shorter. Finally, the LV ejection time became minimum when the ventricular pacing spike occurred with or preceded the atrial deflection which, at that point, could not activate the ventricle because of the ventricular refractory period. An atrial deflection appearing during an A-S interval that was a little longer than the intrinsic PQ interval and thus escaping the ventricular refractory period could activate the ventricle and interfere with ventricular pacing. After ventricular pacing was interrupted, the A-S interval again corresponded to the PQ interval and the same cycle as described above was repeated (Fig. 4).

Atrial contribution to ventricular filling:

There was a good correlation ($r = 0.85$, $p < 0.01$) between the atrial contributions calculated from the changes in LV ejection time and those

Fig. 7. Ejection fraction, stroke index and atrial contribution in control subjects and patients with coronary artery disease without myocardial infarction. CAD = coronary artery disease; MI = myocardial infarction; NS = not significant

Fig.8. Ejection fraction and left ventricular end-diastolic pressure in patients with coronary artery disease and previous myocardial infarction, subdivided into patients with an atrial contribution of 20% or less or patients with an atrial contribution of 21% or greater. CAD = coronary artery disease; MI = myocardial infarction; NS = not significant

measured from LV volumes, in spite of a difference of 5 to 10 beats/min in heart rate between the two methods (Fig. 5). In patients with coronary artery disease, the atrial contribution measured from LV ejection time was significantly greater ($p < 0.001$) than that in the control subjects ($21.0 \pm 3.8\%$ versus $15.5 \pm 2.6\%$) (Fig. 6). Because the majority of patients with evidence of previous myocardial infarction had subnormal ejection fraction and elevated LV end-diastolic pressure, analysis of the atrial contribution to ventricular filling was repeated after subgrouping patients with coronary artery disease on the basis of previous history of myocardial infarction. The 20 patients without evidence of myocardial infarction had an atrial contribution to ventricular filling of $22.0 \pm 2.5\%$, significantly larger than the control subjects ($p < 0.001$). However, their ejection fraction, end-diastolic volume, end-systolic volume and stroke index were approximately similar to those of the control subjects (Fig. 7). In the 25 patients with previous myocardial infarction, the atrial contribution to ventricular filling was also significantly greater ($p < 0.001$) than that

Fig.9. Influence of LV end-diastolic pressure on atrial contribution in patients with coronary artery disease. CAD = coronary artery disease; MI = myocardial infarction

in the control subjects ($20.4 \pm 3.8\%$ versus $15.5 \pm 2.6\%$). However, their atrial contributions were widely dispersed. In 14 of the 25 patients with myocardial infarction, the atrial contribution to ventricular filling exceeded the normal

95% confidence limit (atrial contribution greater than or equal to 21%). The remaining 11 patients with myocardial infarction had an atrial contribution of 20% or less and fell within the normal range defined by the 95% confidence limit. In patients with myocardial infarction and an atrial contribution of 20% or less, the end-diastolic pressure was significantly higher ($p < 0.01$) than that in patients with myocardial infarction and an atrial contribution of 21% or greater (25.2 ± 6.6 mmHg versus 13.5 ± 3.8 mmHg) (Fig. 8). However, there were no significant differences in the ejection fraction, heart rate and stroke index between these two groups. The atrial contribution was plotted against the LV end-diastolic pressure in patients with coronary artery disease. As the LV end-diastolic pressure was elevated, the atrial contribution was decreased ($r = -0.60$, $p < 0.01$) (Fig. 9).

DISCUSSION

Atrial contribution calculated from LV ejection time:

In this study the atrial contribution to ventricular filling was calculated from the changes in LV ejection time during right atrial and ventricular pacing. Because of the methodological uncertainties in determining the atrial contribution by the pacing method, the pacing data were compared with the atrial contributions measured from LV volumes. Although one of the most important hemodynamic effects of radiographic contrast medium into the left ventricle is elevation of the LV end-diastolic pressure, this change does not occur during the immediate opacification phase but rather requires some minutes to appear.¹² Magorien and associates¹³ reported that the LV pressure-volume data derived from contrast angiography were similar to those obtained using combined radionuclide angiography and micromanometer pressure recordings. There was a good correlation between the atrial contributions of the two methods. Weissler and colleagues¹⁴ reported that LV ejection time was influenced by the following three major factors: heart rate, LV stroke volume and the condition of the cardiac valves. Other factors of some importance are ventricular contractility and total systemic vascular resistance. Since heart rate was kept constant in each individual by right atrial and ventricular pacing, the changes in LV ejection time should reflect only variations in LV stroke

volume. Furthermore, both ventricular contractility and total systemic vascular resistance should remain relatively constant because of the pacing method.¹⁵ It seems reasonable to assume that alterations in ventricular filling account for most of the changes in LV ejection time observed during ventricular pacing. Harley and associates¹⁶ studied the relationship of stroke volume to LV ejection time and stated that it appeared to be linear at a constant heart rate.

The effects of the abnormal pattern of ventricular activation caused by right ventricular pacing on LV performance are incompletely defined and remain controversial. Several reports¹⁷⁻¹⁹ indicated that the pathway of ventricular activation did not affect ventricular function and LV ejection time. On the other hand, Lister et al²⁰ and Askenazi et al²¹ demonstrated that the deterioration in LV function noted during ventricular pacing must be due in part to the asynchronous pattern of ventricular activation. In the present study, stimulation of the outflow tract, apex and inflow tract of the right ventricle at an identical rate did not show any significant changes in max ET and min ET. These observations clearly demonstrate that the absence of synchronized atrioventricular activity rather than aberrant ventricular activation is primarily responsible for the changes in LV ejection time during atrial and ventricular pacing.

It is possible that a decrease in LV ejection time observed during ventricular pacing is due to mitral regurgitation.²² Walston and associates²³ reported that LV angiograms obtained during ventricular pacing revealed minimal mitral regurgitation in only 4 of 16 dogs. Naito and colleagues²⁴ also stated that in 20 open-chest dogs with experimental A-V heart block, LV angiography failed to reveal mitral regurgitation during fixed rate pacing at any A-V interval. Although the degree and frequency of pacing-induced mitral regurgitation remain controversial, it is likely that a decrease in LV ejection time due to mitral regurgitation occurs infrequently and is recognized in only a few patients.

Atrial contribution in coronary artery disease:

In patients with coronary artery disease, the atrial contribution to ventricular filling was greater than that in the control subjects. Previous studies have shown that in patients with impaired LV function, a synchronized atrial contraction is important for adequate diastolic filling of the ventricle.^{25,26} It has been suggested

that LV relaxation and compliance may be the major determinants of diastolic ventricular filling in patients with coronary artery disease^{27,28}. Because myocardial fibrosis reduces LV diastolic distensibility,²⁹⁻³¹ the patients with coronary artery disease were subdivided into two groups with or without previous myocardial infarction.

The patients without myocardial infarction had a larger atrial contribution than the normal subjects. However, there were no significant differences in the ejection fraction and stroke index between the patients without myocardial infarction and the control subjects. It seems reasonable to assume that the atrial contribution to LV filling is increased to compensate for impaired early diastolic filling in patients with coronary artery disease and no previous myocardial infarction, since LV systolic function assessed by ejection fraction is normal and the stroke index or total filling volume is similar to that of the control subjects. Bonow and associates³² reported that the abnormalities in LV diastolic filling were present under resting conditions in a large number of patients with coronary artery disease without previous myocardial infarction who had normal LV systolic function. The present data also indicate that the augmented atrial contribution to LV diastolic filling at rest is common in patients with coronary artery disease, even in the subgroup without previous myocardial infarction and with normal LV systolic function. In patients without previous myocardial infarction, the LV end-diastolic pressure was slightly, but significantly, higher than that in the control subjects. However, the atrial kick was not prominent in these patients. This finding suggests that a small rise in LV diastolic pressure during atrial contraction is related to a large atrial contribution to LV filling.

The atrial contribution to LV filling also was significantly greater in patients with coronary artery disease and previous myocardial infarction, compared with the control subjects. However, their atrial contributions were scattered in a wide range. In 11 of the 25 patients with previous myocardial infarction, the atrial contribution to LV filling was less than or equal to 20% and fell within the normal range defined by the 95% confidence limit. It is interesting to note that in patients with myocardial infarction who had a reduced atrial contribution, the LV end-diastolic pressure was extremely high. The reason why the atrial contribution tends to

decrease as LV filling pressure is increased has been explained by Greenberg and associates.³³ The curvilinear relationship between LV pressure and LV volume is assumed to be exponential. When the steep portion of the curve is reached, further increments in LV volume result in large increments in LV pressure. This sharp rise in pressure prevents ventricular filling despite the powerful atrial contraction. When the LV filling pressure is elevated, a further increase in LV pressure resulting from the atrial contribution would be expected to have less effect in increasing stroke volume than it would when LV pressure is lower. Consequently, in patients with previous myocardial infarction, the atrial contribution to ventricular filling generally plays a greater role in increasing stroke volume, but it has less effect despite the forceful atrial contraction as LV filling pressure becomes more elevated. In patients with an elevated LV filling pressure, the reduced atrial contribution may reflect diminished LV distensibility or compliance produced by myocardial fibrosis.²⁹⁻³¹ There were no significant differences in the ejection fraction and stroke index between patients with myocardial infarction and an atrial contribution of 20% or less and patients with myocardial infarction and an atrial contribution of 21% or greater. Patients with a marked increase in LV end-diastolic pressure might have an increased LV filling in early diastole and a reduced LV compliance, since their stroke index or total filling volume was similar to that in patients without an increase in LV end-diastolic pressure. In patients with myocardial infarction, LV diastolic filling seemed to be influenced by a greater driving pressure across the mitral valve due to elevated LV filling pressure rather than to impaired early filling observed in patients with coronary artery disease without previous myocardial infarction.

LV end-diastolic pressure increases characteristically during attacks of angina in patients with coronary artery disease.¹⁻⁷ Sharma and associates³⁴ studied the LV pressure-volume and filling characteristics in patients with severe coronary artery disease who developed spontaneous angina pectoris in the cardiac catheterization laboratory. They found a significant increase in the rate of filling during mid-diastole and an increased left atrial stroke work index during anginal attack. It is important to clarify whether the elevation of LV end-diastolic pressure during anginal pain reflects a large atrial contribution to LV filling in

compensation for reduced early diastolic filling due to impaired relaxation or, conversely, a reduced atrial contribution to LV filling because of reduced LV distensibility or including both mechanisms. Further studies are required to elucidate the behavior of the atrial contribution to ventricular filling during angina pectoris.

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