PULSED DOPPLER ECHOCARDIOGRAPHIC ASSESSMENT OF TRANSMITRAL FLOW IN PACING-INDUCED ANGINA PECTORIS

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We analyzed transmitral flow using pulsed Doppler echocardiography during anginal attack provoked by atrial pacing in 11 patients with coronary artery disease (CAD). Left ventricular (LV) filling period was divided into 4 time intervals (Tr1: the time interval to peak velocity of rapid filling (peak R), Tr2: the time interval from peak R to the end of rapid filling, Ts: the time interval of slow filling, Ta: the time interval of atrial contraction). The velocity in each interval was integrated by planimeter as IR1, IR2, IS or IA which indicates relative filling volume in each interval. During angina, IR1 was unchanged due to prolongation of Tr1 (82 ± 21 to 102 ± 23 msec, $p < 0.02$), despite a decrease in peak R (54 ± 11 to 43 ± 11 cm/sec, $p < 0.005$), while IR2 decreased (5.8 ± 1.9 to 4.3 ± 1.4 cm, $p < 0.005$) and IA increased (6.7 ± 1.4 to 7.3 ± 1.3 cm, $p < 0.005$). In conclusion, these results suggested that in acute myocardial ischemia in CAD a decrease in transmitral flow from the time of peak R to the end of rapid filling (IR2) reflected the impairment of the LV rapid filling, which was incompletely compensated by an increase in atrial contraction.

SINCE Hammermeister et al¹ reported that left ventricular filling rates derived by cineangiography were equal to transmitral flow, many investigators have reported impaired left ventricular filling at rest and during anginal attack in patients with coronary artery disease using cineangiography²⁻⁵ or radionuclide angiography⁶⁻⁹. However, these methods cannot evaluate the detailed phase analysis of left ventricular filling, because the time interval from one sampling point to the next sampling point in a single diastole is much too long to assess the phase analysis.

Recent technological developments^{10-16,21} have made possible the application of pulsed

Doppler echocardiography to the direct measurement of the velocity of transmitral flow at sampling rate of 250 points/sec. Therefore, this study was designed to examine the changes in transmitral flow during anginal attack induced by atrial pacing using pulsed Doppler echocardiography with accurate phase analysis for assessing the impaired left ventricular filling during the attack.

METHODS

Patients

Sixteen subjects studied were divided into 2 groups. One group consisted of 5 control subjects (3 men and 2 women, age range 26 to 59 years old, mean age 42 years old). Three of them underwent cardiac catheterization for evaluation of atypical chest pain and had normal left ventriculogram (mean left ventricular ejection frac-

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Measurements of Transmitral Flow by Pulsed Doppler

Fig.1. Doppler frequency shifts (fd) are expressed graphically as flow velocity (V) by solving the Doppler equation: $V = (C/2\cos\theta)(fd/fo)$, where C = the speed of sound in the medium (1540 m/sec), fo = emitting frequency of the transducer, θ = the angle of incidence between sound waves and flow. Then left ventricular filling period is divided into 4 time intervals, namely Tr_1 , Tr_2 , T_s and T_a , and the velocity of each time interval is integrated by planimeter and is shown as IR_1 , IR_2 , IS or IA . peak R = peak velocity of rapid filling, peak A = peak velocity in atrial contraction.

tion $75 \pm 3\%$) and coronary angiogram; the remaining 2 were young volunteers who were diagnosed as healthy by check-up examinations, including interviews, physical findings, chest roentgenogram, electrocardiography and echocardiography. Another group consisted of 11 patients with angina pectoris (9 men and 2 women, age range 45 to 71 years old, mean age 57 years old). They had angiographically documented stenosis (more than 50% reduction in luminal diameter) in at least one major coronary artery. Mean left ventricular ejection fraction derived by cineangiography was $62 \pm 11\%$. In addition, each patient had exertional angina which was proved by thallium-201 stress myocardial scintigraphy and/or exercise electrocardiography. Six patients had had a previous myocardial infarction more than 8 weeks previously. Patients with valvular, congenital or

hypertensive heart disease or cardiomyopathy were excluded from this study. This study was performed within 7 days before or after cardiac catheterization. In all patients, treatment with calcium antagonists or β -blockers had been discontinued for at least 72 hours and treatment with nitrates for at least 12 hours before this study. None of them had any treatment with digitalis or diuretics.

Pulsed Doppler technique

A commercially available pulsed Doppler flowmeter combined with an electronic sector-scanning echocardiography (Toshiba SSH 40A/SDS 21A) was used to measure the transmitral flow velocity. The ultrasonic frequency used was 2.4 MHz and the pulse repetition rate was 4 KHz. The sampling interval from one point to the next point was 4 msec. The system has a movable

TABLE 1 CHANGES IN FILLING INDICES AFTER ATRIAL PACING

		Control subjects		Coronary artery disease	
		at rest	post-pacing	at rest	post-pacing
R-R interval	(msec)	833 ± 80	858 ± 108	950 ± 74	934 ± 95
Tr1	(msec)	92 ± 10	83 ± 14	82 ± 21	102 ± 23*
Tr2	(msec)	159 ± 45	154 ± 35	172 ± 44	143 ± 44*
Tr1 + Tr2	(msec)	251 ± 18	237 ± 28	255 ± 41	245 ± 49
Ts	(msec)	70 ± 33	98 ± 67	85 ± 52	70 ± 71
Ta	(msec)	137 ± 12	140 ± 12	153 ± 15	155 ± 17
Filling time	(msec)	459 ± 59	475 ± 95	492 ± 83	472 ± 94
Peak R	(cm/sec)	59 ± 14	59 ± 13	54 ± 11	43 ± 11**
Peak A	(cm/sec)	51 ± 8	53 ± 6	62 ± 15	69 ± 14*
IR1	(cm)	3.8 ± 1.0	3.1 ± 0.9	3.1 ± 0.7	3.0 ± 0.9
IR2	(cm)	5.9 ± 0.5	5.9 ± 0.5	5.8 ± 1.9	4.3 ± 1.4**
IS	(cm)	1.1 ± 0.8	1.3 ± 1.0	1.1 ± 0.8	0.8 ± 0.8
IA	(cm)	5.2 ± 1.2	5.4 ± 0.9	6.7 ± 1.4	7.3 ± 1.3**

Data are expressed as mean ± SD. * = $p < 0.05$; ** = $p < 0.005$ vs at rest in each group; Filling time = Tr1 + Tr2 + Ts + Ta; IR1 = the integration of velocity in Tr1; IR2 = the integration of velocity in Tr2; IS = the integration of velocity in Ts; IA = the integration in Ta; Other abbreviations are as in Fig. 1.

cursor that allows Doppler searching anywhere on simultaneous 2-dimensional echo image. When the Doppler mode is selected, the sector sector scanning is stopped and 2-dimensional echo image is frozen on the CRT screen. The detected Doppler signals are analyzed by means of fast Fourier transform method and are recorded on a strip-chart recorder. The paper speed was 100 mm/sec in this study. The incident angle of the ultrasonic beam to the blood stream (θ) was measured as the angle between the direction of the ultrasonic beam and the direction perpendicular to the mitral annulus on the plane of the echo image (apical long-axis view) as shown in Fig. 1¹⁰. Flow velocity (V) was calculated from the Doppler frequency by using the following equation: $V = (C/2\cos\theta)(fd/fo)$, where C = the speed of sound in the medium (1540 m/sec), fo = emitting frequency of the transducer (2.4 MHz), and fd = Doppler shift frequency.

Pulsed Doppler echocardiograms were taken during breath holding at mid expiration phase in all patients. The transducer was placed nearly at the apical impulse in all patients who were in lateral recumbent position, and was manually rotated to obtain an apical long-axis view of the heart that provided good visualization of the left ventricular cavity with maximal excursion of the mitral leaflets. As shown in Fig. 1, the sampling volume was placed at the left ventricular inflow

tract just below the tips of the mitral leaflets, where we attempted to maximize Doppler shift by small changes in the position of the sampling volume so as to be close to parallel to the stream of mitral inflow. Once this position was obtained, we attempted to keep the same position throughout this study.

Study protocol

A no. 7 Fr bipolar pacing catheter was introduced percutaneously into the femoral vein and advanced to the high position of right atrium in 2 of the control subjects and in 10 of the patients with coronary artery disease. On the other hand, a flexible silicone rubber-coated bipolar pacing catheter was used transesophageally in the 4 remaining subjects, in whom the same rapid atrial pacing as the invasive right atrial pacing could be obtained. After these procedures, all patients had a resting period of at least 30 min. Pulsed Doppler echocardiograms were initially taken at rest and then the heart rates were incrementally increased with atrial pacing by 20 beats every 3 min until anginal attack was induced, when all patients were maintaining 1 : 1 A-V conduction, and a mean value of maximum pacing rate was 138 ± 15 beats/min (bpm) in control subjects and 126 ± 9 bpm in patients with coronary artery disease. In both groups R-R intervals were more than 750 msec in all subjects before and after atrial pacing and

Fig. 2. Changes in transmitral flow demonstrated by pulsed Doppler echocardiography (PDE) between at rest (left panel) and at the 5th diastole after cessation of rapid pacing (right panel) in a patient with angina pectoris. After pacing peak velocity of rapid filling decreased and the time interval to peak velocity of rapid filling was prolonged. EP = ear plethysmogram, SV = sampling volume, PCG = phonocardiogram, II = lead II in electrocardiogram.

there were no significant changes in R-R intervals after pacing (Table I). Pulsed Doppler echocardiograms during anginal attack were recorded immediately after cessation of this rapid atrial pacing.

Data analysis

In the control group, transmitral flow detected by pulsed Doppler echocardiogram was compared between a mean value of 3 beats at rest and a value at the 5th diastole after cessation of the pacing and an effect of rapid atrial pacing on the transmitral flow disappeared at the 5th diastole after pacing (Table I, Fig. 3). Transmitral flow in patients with coronary artery disease was analyzed between a mean value of 3 beats at rest and that of the 5th-7th diastolic phase immediately after cessation of the pacing stress, when peak velocity of rapid filling was typically most decreased (Fig. 2).

We divided left ventricular filling period of transmitral flow into 4 time intervals, especially regarding the timing of peak velocity of rapid filling. Each interval was shown as Tr1, Tr2, Ts or Ta. Tr1 indicates the time interval to peak velocity of rapid filling, Tr2 indicates the time interval from peak velocity of rapid filling to the end of rapid filling, Ts indicates the time interval of slow filling and Ta indicates the time interval of atrial contraction. The velocity in each time

interval was integrated by planimeter system (SANYO MBC-200, KANTOH DENSEI MYPADS-A3) and shown as IR1, IR2, IS or IA, respectively. These parameters were represented in Fig. 1.

Statistics

Averaged data are presented as mean $\pm$ SD. Statistical analysis was performed by Student's *t* test for paired data in each group. Results were regarded as significant if the *p* values were less than 0.05.

RESULTS

Figure 2 shows an example of transmitral flow at rest and during anginal attack provoked by atrial pacing in a patient with coronary artery disease. Peak velocity of rapid filling decreased and the time interval to peak velocity of rapid filling was prolonged in the diastole after cessation of the pacing stress.

Figure 3 summarizes the integrated transmitral flow both in control subjects and in patients with coronary artery disease. In control subjects, the following parameters were not significantly different between at rest and after pacing: the integrated total transmitral flow (IR1 + IR2 + IS + IA) 15.9 ± 1.2 vs 15.6 ± 1.8 cm (Fig. 3-A); the integrated transmitral flow

Fig.3. Changes in integrated total transmitral flow (IR1 + IR2 + IS + IA) (A), integrated transmitral flow during rapid filling phase (IR1 + IR2) (B), integrated transmitral flow to the time of peak velocity of rapid filling (IR1) (C) and integrated transmitral flow from the time of peak velocity of rapid filling to the end of rapid filling phase (IR2) (D) between at rest (open bar) and after pacing (closed bar) in control subjects (Control) and patients with coronary artery disease (CAD). * = $p < 0.05$, ** = $p < 0.005$.

during rapid filling phase (IR1 + IR2) 9.7 ± 0.7 vs 9.1 ± 0.9 cm (Fig. 3-B); the integrated transmitral flow to time of peak velocity of rapid filling (IR1) 3.8 ± 1.0 vs 3.1 ± 0.9 cm (Fig. 3-C); and the integrated transmitral flow from the time of peak velocity of rapid filling to the end of rapid filling (IR2) 5.9 ± 0.5 vs 5.9 ± 0.5 cm (Fig. 3-D). In patients with coronary artery disease, however, the integrated total transmitral flow (IR1 + IR2 + IS + IA) decreased from 16.7 ± 3.4 to 15.4 ± 2.9 cm ($p < 0.05$) (Fig. 3-A). The integrated transmitral flow during rapid filling phase (IR1 + IR2) decreased from 8.8 ± 2.2 to 7.3 ± 2.0 cm ($p < 0.001$) (Fig. 3-B). The integrated transmitral flow to the time of peak velocity of rapid filling (IR1) was unchanged (3.1 ± 0.7 vs 3.0 ± 0.9 cm) (Fig. 3-C), while the

integrated transmitral flow from the time of peak velocity of rapid filling to the end of rapid filling (IR2) decreased from 5.8 ± 1.9 to 4.3 ± 1.4 cm ($p < 0.005$) (Fig. 3-D).

Table I summarizes other indices of transmitral flow derived from the pulsed Doppler echocardiogram. After pacing in patients with coronary artery disease the time interval to peak velocity of rapid filling (Tr1) was prolonged from 82 ± 21 to 102 ± 23 msec ($p < 0.02$) and the time interval from peak velocity of rapid filling to the end of rapid filling phase (Tr2) decreased from 172 ± 44 to 143 ± 44 msec ($p < 0.05$), although R-R interval was unchanged (950 ± 74 vs 934 ± 95 msec). Peak velocity of rapid filling (peak R) decreased from 54 ± 11 to 43 ± 11 cm/sec ($p < 0.005$). The integrated transmitral flow during atrial contraction (IA) increased from 6.7 ± 1.4 to 7.3 ± 1.3 cm ($p < 0.005$) and peak velocity in atrial contraction (peak A) also increased from 62 ± 15 to 69 ± 14 cm/sec ($p < 0.05$). In control subjects the same indices were not significantly changed after atrial pacing.

DISCUSSION

Recently, some investigators¹⁰⁻¹² have assessed left ventricular filling at rest in coronary artery disease using indices of filling velocity and time calculated by pulsed Doppler techniques. However, there are few reports that assess left ventricular filling during anginal attack when the heart rate is less than 80 bpm. This study was designed to evaluate not only changes in filling velocity or time but changes in filling volume during acute myocardial ischemia when the heart rate was less than 80 bpm using atrial pacing and pulsed Doppler echocardiography.

In this study we attempted to assess left ventricular filling in patients with angina pectoris using pulsed Doppler echocardiography. The integrated transmitral flow during the rapid filling phase was reduced in the 5th-7th diastole immediately after rapid atrial pacing. Despite a decrease in peak velocity of rapid filling, the integrated transmitral flow to peak velocity of rapid filling was unchanged due to an extended time interval to peak velocity of rapid filling. The integrated transmitral flow from peak velocity of rapid filling to the end of rapid filling decreased due to its shortened duration in addition to a decrease in peak velocity of rapid filling. Furthermore, we documented that the integrated total transmitral flow decreased im-

mediately after pacing, although the integrated transmitral flow during atrial contraction and peak velocity in atrial contraction increased.

In this study it is impossible to detect the mitral orifice simultaneously with recording the velocity of transmitral flow. Therefore, we do not study the area of mitral orifice when calculating our volume index of transmitral flow which is shown as IR1, IR2, or IA in this text. However, there is evidence that the leaflet motion follows the pattern of blood flow through the mitral orifice.¹⁷⁻²¹ Rasmussen et al calculated stroke volume from the mitral valve echogram and showed a good correlation ($r = 0.90$) with stroke volume determined by the Fick or thermodilution techniques.²⁰ On the other hand, Stewart et al reported that changes in the integrated velocity of transmitral flow were closely correlated with changes in cardiac output controlled by roller pump in the same subject.²¹ These results suggest that changes in the volume of transmitral flow parallel those in the integrated velocity of transmitral flow or the area of mitral orifice in the same subject. When changes in the integration of the velocity of transmitral flow parallels changes in the volume of transmitral flow, we can use the integration of velocity as relative indices of the volume of transmitral flow. Accordingly, our results suggested that in acute myocardial ischemia in patients with coronary artery disease, a reduction in the filling volume of the left ventricle in the latter phase of rapid filling mainly caused a decrease in the total volume in the rapid filling phase, which was incompletely compensated by the augmentation of atrial contraction.

We analyzed transmitral flow under the condition of heart rate of less than 80 bpm and could separate a rapid filling flow from the filling flow in the atrial contraction in all patients using pulsed Doppler echocardiography. The ventricular filling pattern is characterized by a biphasic pattern, when rapid filling is separated from the late atrial contribution by a slow filling.²² Hammermeister et al¹ also showed, with the use of cineangiography, that one can detect the effect of atrial contraction on diastolic ventricular volume in most patients with sinus rhythm with a heart rate of less than 80 bpm. The monophasic filling pattern by the fusion of early rapid filling and filling by atrial contraction^{3,6} makes the analysis of left ventricular filling difficult.

During ischemia, why is the integrated trans-

mitral flow unchanged in the former phase of rapid filling and decreased in the latter phase of rapid filling? Our data showed that this difference after rapid pacing was due to the difference between changes in each duration. Left ventricular filling is proportional to the magnitude of atrioventricular pressure gradient, as previously proposed by Yellin et al²³ and the pressure gradient may be maximized at the left ventricular minimum pressure. Therefore, at this point maximum pressure gradient is expected to induce peak velocity of rapid filling. Accordingly, an extended time interval to peak velocity of rapid filling induced by acute ischemia is believed to mean that of the time interval from mitral valve opening to left ventricular minimum pressure, which may be caused by impaired ventricular relaxation in acute ischemia^{25,26} if the relaxation extends up to left ventricular minimum pressure.² It is reasonable to suggest that in the former phase of rapid filling, the filling volume was unchanged in acute ischemia, since the delay in left ventricular pressure fall to minimum pressure associated with the impaired relaxation may cause prolonged filling time as well as reduction in filling velocity. It should be noticed that the reduction in flow velocity or rate does not necessarily mean a reduced filling volume when the filling time is prolonged. On the other hand, when the duration from peak velocity of rapid filling velocity to the end of rapid filling was shortened in acute ischemia induced by atrial pacing, its filling volume was reduced. If the atrioventricular pressure gradient is a major factor in reducing the ventricular filling in the rapid filling phase,²³ it is suggested that the duration of the latter phase of rapid filling may be shortened in acute myocardial ischemia, since elevation of left ventricular diastolic pressure induced by ischemia⁸ can rapidly minimize the atrioventricular pressure gradient after reaching left ventricular minimum pressure. Increased myocardial stiffness,²⁴ incomplete relaxation^{25,26} or a combination of both in acute ischemia are expected to contribute to elevating left ventricular pressure after reaching the minimum pressure. As mentioned above, our data suggest that in acute ischemia, the filling volume in the former phase of rapid filling was maintained due to the prolonged duration, while the filling volume in the latter phase of rapid filling was reduced by not only the decreased filling velocity but also its shortened duration. This reduction mainly caused a decrease in the total volume of rapid

filling. In this study we can not clarify whether the shortened duration in the latter phase of rapid filling follows the prolonged duration in the former phase of rapid filling.

With regard to the augmented atrial contraction, Sharma et al⁴ recently showed, using cineangiography, that the left atrial stroke work index increased by 35% during spontaneous angina and the volume contribution to the left ventricle by the left atrial contraction was not significantly changed but increased (15 ml to 18 ml). Our data also showed that the integrated transmitral flow during atrial contraction increased after pacing. This result suggested that the augmentation of atrial contribution incompletely compensated for a decrease in the volume of rapid filling in acute ischemia. This augmentation of left atrial contraction may be attributable to the Frank-Starling mechanism in the left atrium as previously suggested in myocardial infarction²⁷⁻²⁹

There remain a few minor problems with the pulsed Doppler method. A problem in this study is the positional change between the sampling volume at rest and that after pacing, since blood flow measurement by the Doppler technique is dependent upon the angle ($\cos\theta$) between the direction of blood flow and the direction of the ultrasonic signal. Although this angle cannot be accurately measured, the error due to this angle is very small when compared at the same position of the sampling volume in each subject between different states with a short time interval. In this study the error is nearly zero when the direction of blood flow is expected on a 2-dimensional echocardiogram, as reported by Kitabatake et al¹⁰. And this error becomes less by apical approach for Doppler beam to be close to parallel to transmitral blood flow as reported by Lewis et al¹⁵. Therefore, we attempted to keep the same position of the sampling volume in each patient throughout this study by apical approach of echocardiography as shown in the M mode echocardiogram of Fig. 2. It confirms reliability of our data that in normal subjects, our mean values of peak velocity of rapid filling (59 cm/sec) nearly equal the mean values of peak velocity of rapid filling (61 cm/sec), reported by Kitabatake et al¹⁰. Even though the axis of blood flow changed in each phase of transmitral flow which was expressed by rapid filling or atrial contraction, the error was marginal in the same subject as shown by an excellent correlation ($r = 0.99$) between changes in the integration of ve-

locity of transmitral flow and changes in cardiac output controlled by roller pump²¹. Thus, these errors are believed to be minimal in our study. Another problem in this study is the detection of an initial or end point of rapid filling. However, many investigators could detect an initial point of rapid filling and calculate cardiac output using Doppler techniques^{13,15,21}. The detection of an initial point of transmitral flow by Doppler techniques may not be less accurate than that by RI angiography or cineangiography, because RI angiography can not detect mitral opening, and mitral opening is difficult to detect by frame-by-frame analysis of cineangiography and causes an error of 16.7 msec if we mistake mitral opening by one frame on a cineangiography of 60 frames/min. An end point of rapid filling is also detectable on pulsed Doppler echocardiograms when the heart rate is less than 80 bpm as reported using cineangiography¹ and a magnetic flowmeter²².

In summary, the present study demonstrated that, using pulsed Doppler echocardiography in angina pectoris in circumstances where the heart rate was less than 80 bpm : 1) the integration of velocity of total transmitral flow decreased at the 5th-7th diastole after rapid atrial pacing; and 2) this reduction was caused by a decrease in the integration of velocity of transmitral flow during rapid filling phase, which was incompletely compensated for by an increase in the integration of velocity of transmitral flow during atrial contraction. In a detailed phase analysis of the transmitral flow we also showed that the reduction of the integration of velocity of transmitral flow during the rapid filling phase with pacing stress was mainly caused by that from peak velocity of rapid filling to the end of rapid filling. These results suggested that rapid filling was restricted with acute myocardial ischemia and its restriction was mainly caused by impairment of the latter phase of rapid filling, while atrial contribution was augmented as a possible mechanism of compensation.

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