CLINICAL SIGNIFICANCE OF EARLY DIASTOLIC TIME INTERVALS FOR THE EVALUATION OF LEFT VENTRICULAR FUNCTION IN PATIENTS WITH CORONARY ARTERY DISEASE

MICHIHITO SEKIYA, M.D., MAREOMI HAMADA, M.D. AND TATSUO KOKUBU, M.D.

To investigate non-invasively the diagnostic significance of diastolic properties in coronary artery disease (CAD), the following early diastolic time intervals (EDTs): IIA-O time (from the aortic component of the second heart sound to the O-point on the apexcardiogram), IIA-MVO time (from IIA to the mitral valve opening) and MVO-O time (from MVO to the O-point), were estimated in 18 patients with angina pectoris (AP) and 29 with old myocardial infarction (OMI) who were subdivided into two groups according to ejection fraction (EF): group I (OMI-I): more than 50% and group II (OMI-II): less than 50%. Seventeen patients without evidence of CAD were used as controls (N).

Left ventricular pressure (LVP) and pulmonary capillary wedge pressure (PCWP) were measured simultaneously to clarify the relationship between EDTs and early diastolic hemodynamics.

IIA-O time and IIA-MVO time in AP, OMI-I and OMI-II were significantly longer than in N. This prolongation accorded with the reduction of left ventricular function. MVO-O time in AP and OMI-I also was significantly longer compared with that in N. In OMI-II, however, it was significantly shorter than in N.

The prolongation of IIA-MVO time reflected impaired LV relaxation accompanied by LV dysfunction. The maintenance of low minimal LVP was the main contributor to the lengthening of MVO-O time in AP and OMI-I. Conversely, elevated minimal LVP and impaired LV relaxation resulted in the shortening of MVO-O time in OMI-II.

These results indicate that EDTs are useful and reliable non-invasive parameters for the evaluation of LV function and the prediction of early diastolic hemodynamic properties in patients with CAD.

It is well known that systolic as well as diastolic functions are affected by coronary artery disease (CAD). Recent attention has focussed on the diastolic properties of left ventricular function. Radionuclide cineangiography has provided evidence that the diastolic phase is more sensitive than the systolic phase for detection of left ventricular (LV) dysfunction in CAD.

In this study, in order to evaluate the usefulness and reliability of diastolic properties, early diastolic time intervals (EDTs) were investigated in patients with CAD. The relationship between changes in EDTs and early diastolic hemodynamics derived from LV pressure and pulmonary

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The 2nd Department of Internal Medicine, Ehime University School of Medicine, Ehime, Japan
Mailing address: Michihito Sekiya, M.D., The 2nd Department of Internal Medicine, Ehime University School of Medicine, Sigenobu, Onsen-gun, Ehime 791-02, Japan

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TABLE I  EARLY DIASTOLIC TIME INTERVALS OF ALL PATIENT GROUPS

<table>
<thead>
<tr>
<th></th>
<th>Age</th>
<th>HR</th>
<th>IIA-O</th>
<th>IIA-MVO</th>
<th>MVO-O</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(years)</td>
<td>(beats/min)</td>
<td>(msec)</td>
<td>(msec)</td>
<td>(msec)</td>
</tr>
<tr>
<td>Normal Subjects</td>
<td>49 ± 10</td>
<td>67 ± 8</td>
<td>126 ± 11</td>
<td>70 ± 8</td>
<td>54 ± 7</td>
</tr>
<tr>
<td>(n = 17)</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Angina Pectoris</td>
<td>54 ± 7</td>
<td>59 ± 6**</td>
<td>163 ± 14**</td>
<td>89 ± 8**</td>
<td>74 ± 12**</td>
</tr>
<tr>
<td>(n = 18)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Old Myocardial Infarction</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group I*</td>
<td>53 ± 9</td>
<td>59 ± 6**</td>
<td>179 ± 26**</td>
<td>106 ± 20**</td>
<td>75 ± 12**</td>
</tr>
<tr>
<td>(n = 18)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group II**</td>
<td>56 ± 7</td>
<td>68 ± 10</td>
<td>162 ± 26**</td>
<td>124 ± 9**</td>
<td>37 ± 25**</td>
</tr>
<tr>
<td>(n = 11)</td>
<td></td>
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</tbody>
</table>

Values are shown as mean ± SD
Abbreviations:  HR = heart rate; IIA = aortic component of second heart sound; O = O point of apexcardiogram; MVO = point of mitral valve opening; Group I* = old myocardial infarction with an ejection fraction of over 50%; Group II** = old myocardial infarction with an ejection fraction of under 50%
* = p < 0.05; ** = p < 0.01; as compared to normal subjects

capillary wedge pressure (PCWP) also were investigated.

METHODS

Subjects
Sixty-four patients admitted to our hospital were divided into the following 4 groups for this study.

Normal subjects (N): This group consisted of 17 subjects (males 11, females 6). All had no abnormalities in physical examination, chest roentgenogram, electrocardiogram and echocardiogram. Nine patients underwent cardiac catheterization and coronary arteriography due to chest pain of unknown etiology. Their coronary arteriograms and left ventriculograms were normal. Mean age in this group was 49 ± 10 years (range 32–65).

Angina pectoris (AP): This group consisted of 18 patients (males 16, females 2) with no history of myocardial infarction. All had significant angiographically documented stenosis (more than 75% reduction in luminal diameter) of at least one major coronary artery. Twelve had one-vessel disease, 5 had two-vessel disease and 1 had three-vessel disease. The mean age was 54 ± 7 years (range 45–67).

Patients with old myocardial infarction (OMI) were subdivided into the following 2 groups according to the ejection fraction (EF) established by left ventriculography. We defined "old" myocardial infarction as that which had occurred at least 3 months before the study. All patients in this group were males.

Group I (OMI-I): This group consisted of 18 patients. They showed an EF of over 50%. Eleven had one-vessel disease, 5 had two-vessel disease and 2 had three-vessel disease. The group’s mean age was 53 ± 9 years (range 36–65).

Group II (OMI-II): This group consisted of 11 patients showing an EF of under 50%. Two had one-vessel disease, 6 had two-vessel disease and 3 had three-vessel disease. The mean age in this group was 56 ± 7 years (range 46–65).

Patients whose echocardiograms and apexcardiograms could not be recorded clearly and who had systemic hypertension and valvular heart disease were excluded from this study. All patients had regular sinus rhythm with normal A-V conduction and no bundle branch block.

Procedure
Early diastolic time intervals (EDTIs): Simultaneous recordings of electrocardiogram, phonocardiogram, echocardiogram and apexcardiogram were made using an Aloka SSD-810 with a 2.5 MHz transducer. Apexcardiogram was recorded using a TY-303 transducer (Fukuda Denshi Co., Ltd) with a time constant of 4 sec, and phonocardiogram was recorded using a MA-250 (Fukuda Denshi Co., Ltd). All patients were placed in the left lateral decubitus position for recording of the apexcardiogram and the echocardiogram.

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Early Diastolic Time Intervals in Coronary Artery Disease

<table>
<thead>
<tr>
<th>TABLE II CATHETER DATA OF ALL PATIENT GROUPS</th>
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<tbody>
<tr>
<td>ACP (mmHg)</td>
</tr>
<tr>
<td>Normal Subjects (n = 9)</td>
</tr>
<tr>
<td>Angina Pectoris (n = 18)</td>
</tr>
<tr>
<td>Old Myocardial Infarction</td>
</tr>
<tr>
<td>Group I (n = 18)</td>
</tr>
<tr>
<td>Group II (n = 11)</td>
</tr>
</tbody>
</table>

Values are shown as mean ± SD
Abbreviations: ACP = aortic closing pressure; LVVmin = minimal left ventricular pressure; LVEDP = left ventricular end diastolic pressure; PCWP = pulmonary capillary wedge pressure; SVI = stroke volume index; LVEDVI = left ventricular end diastolic volume index; EF = ejection fraction
* = p < 0.05; ** = p < 0.01; as compared to normal subjects

The output was recorded using a Honeywell strip chart recorder at a paper speed of 100 mm per sec. The following EDTIs were measured, as reported previously3: 1) IIA-O time (the interval from the onset of the aortic component of the second heart sound to the O point on the apexcardiogram), 2) IIA-MVO time (the interval from IIA to the mitral valve opening (MVO)); this time corresponds to the isovolumic relaxation time (IRT), and 3) MVO-O time (the interval from MVO to the O point on the apexcardiogram).

Cardiac catheterization and selective cineangiography
Informed consent was obtained from all patients. Premedication consisting of 25 mg of hydroxyzine hydrochloride was given 30 min before catheterization. Routine cardiac catheterization, including left ventriculography and selective coronary arteriography, was performed using the Judkins’ technique. Left ventriculography at both the right and left anterior oblique positions was recorded on 35 mm cine film exposed at 60 frames per second. Selective coronary cineangiography was carried out at several positions before and after the administration of nitroglycerin. EF and end-diastolic volume were measured by the area-length method.6 Segmental disease of the left ventricle, expressed as a percentage of abnormally contracting segment (% ACS), was determined from left ventriculograms at the right and left anterior oblique positions by the modified method of Feild et al.5 Cardiac output was measured by the dye-dilution method using a cuvette densitometer. Stroke volume and stroke volume index (SVI) also were calculated. Aortic closing pressure (ACP), minimal LV pressure (LVVmin) and LV end-diastolic pressure (LVEDP) were measured using a fluid-filled catheter (8F Cordis pigtail catheter), a P-23ID pressure transducer (Gould Co., Ltd) and a LB-812 amplifier (Fukuda Denshi Co., Ltd). PCWP was measured using a Swan-Ganz catheter (American Edwards Laboratories Co., Ltd), a P-23ID pressure transducer and a LB-812 amplifier. The recordings were made with a Mingograph 804 (Seamens Co., Ltd) at a paper speed of 100 mm/sec.

Statistical analysis
All data are expressed as mean ± SD. Comparison of group’s data was made using the Wilcoxon signed-ranks test. Statistical significance was defined as p < 0.05.

RESULTS
The EDTI and catheter data results are summarized in Table I and Table II, respectively.
Early diastolic time intervals: The IIA-O time and IIA-MVO time in AP, OMI-I and OMI-II were significantly longer than in N. The IIA-MVO time in OMI-I and OMI-II was significantly longer than in AP and that in OMI-II tended to be longer, compared to OMI-I. The MVO-O time was significantly longer in AP and OMI-I than in

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In contrast, the MVO-O time in OMI-II was significantly shorter than in N.

Hemodynamic data: SVI was the same in N and AP. It was significantly lower in OMI-I and extremely reduced in OMI-II compared with N and AP. There was no difference in LVEDVI between N and AP. LVEDVI in OMI-I and OMI-II was significantly larger than in N. LVEDP was significantly higher in AP, OMI-I and OMI-II than in N. There was no difference in ACP among 4 groups. LVMax in N, AP and OMI-I was similar but LVMax in OMI-II was significantly higher than in the other 3 groups. PCWP in AP, OMI-I and OMI-II was significantly higher than in N and OMI-II had the highest value. Although EF in AP showed no significant difference compared to that in N, those in the OMI groups were significantly lower than in N.

The relationship between EDTIs and %ACS: The IIAMVO time was prolonged as %ACS increased. The relationship between the MVO-O time and %ACS is shown in Fig. 1. The MVO-O time in patients whose %ACS was less than 30% was longer than that in N. However, in patients whose %ACS was more than 30% it was markedly shorter than even N.

DISCUSSION

The abnormalities in both the systolic and diastolic function of the left ventricle in patients with CAD have been studied previously, and one of the recent studies focussed on the importance of the early diastolic properties. These works, however, have employed parameters such as time constant and negative dp/dt which are derived from invasive techniques. Non-invasive and repeatable methods are desirable.

Recent progress in echocardiography and radionuclear medicine has made it practicable to investigate the impaired LV function non-invasively. Nevertheless, these methods have been of questionable value in assessing early diastolic properties. Echocardiography does not necessarily provide reliable and adequate information since CAD patients often have regional LV dysfunction. Radionuclear medicine has difficulty separating the isovolumic relaxation period and the rapid filling phase because it is impossible to detect the mitral valve opening point.

With regard to these issues, EDTIs measured from simultaneous phonocardiogram, echocardiogram, apaxoeadiogram and electocardiogram records provides the most reliable way to study events during the diastolic phase.

Significant lengthening of the IIAMVO and IIAMVO times were observed in AP, OMI-I and OMI-II. The prolongation of IIAMVO time accorded with the progression of LV dysfunction. The most striking phenomenon was the shortening of MVO-O time in OMI-II.

These changes in EDTIs, representing impaired
LV function, were in good agreement with those derived from invasive parameters used to assess LV function (Table I, Table II).

IIA-MVO time depends on the aortic closing pressure, the rate of LV pressure fall and the level of left atrial pressure, represented by PCWP.13 The O point on the apexcardiogram corresponds approximately to the nadir of LV pressure, so the MVO-O time was affected by LV relaxation and the pressure gradient between left atrial pressure and LV minimal pressure. These facts help to elucidate the relationship between intracardiac events during early diastole and EDTIs.

Figure 2 shows schematically the relationships between LV pressure, PCWP and EDTIs. Panels A, B and C correspond to AP, OMI-I and OMI-II, respectively.

The decreased rate of LV pressure decay was the main cause of the prolongation of IIA-MVO time observed in AP. Furthermore, because the pressure gradient between LVPmin and PCWP was not significantly different between AP and N, the progression of MVO-O time in AP was due to impaired LV relaxation during the energy-dependent active suction phase (Panel A).

The rate of LV pressure decay in OMI-I was much more decreased than those in N and AP. This may have been responsible for the significant prolongation of IIA-MVO time in OMI-I compared with N and AP. On the other hand, MVO-O time in OMI-I, which was significantly longer compared with N, showed no significant difference from that in AP. The minimal LV pressure was not elevated in OMI-I, as shown in panel B. This may have contributed to keeping the pressure gradient between LV minimal pressure and PCWP in OMI-I.

Unlike those in AP and OMI-I, the early diastolic hemodynamics were clearly distinguishable in OMI-II. The fall rate of LV pressure decay in OMI-II showed further reduction compared with those in AP and OMI-I. Moreover, of interest was the elevation of LVPmin, which resulted in almost no pressure gradient between LVPmin and PCWP. These changes explain the marked prolongation of IIA-MVO time, and the converse shortening of MVO-O time in OMI-II (Panel C).

As mentioned above, analysis of the relationship between LV pressure, PCWP and EDTIs provides evidence for the usefulness and reliance of EDTIs in assessing LV diastolic function.

CAD often causes regional dysfunction of left ventricle. The percent of abnormally contracting segment (%ACS) presented an interesting finding in relation to MVO-O time. The shortening of MVO-O time, characteristically observed in OMI-II, was associated with the increment of %ACS. The shortening of MVO-O time was likely to begin when the %ACS became more than 30% (Fig. 1). If the increment of %ACS indicates the extension of myocardial necrosis or
fibrosis, the shortening of MVO-O time is of great value for assessing the possibility of marked reduction of LV function in CAD.

In conclusion, our results indicated that the EDTIs are useful and reliable non-invasive parameters in assessing LV dysfunction and in predicting impaired early diastolic hemodynamics in patients with CAD.

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