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ORIGINAL ARTICLE
Imaging

Clinical Significance of Late Diastolic Tissue Doppler Velocity at 24 Hours or 14 Days After Onset of ST-Elevation Acute Myocardial Infarction

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Background: The significance of late diastolic velocity (a′) obtained by tissue Doppler imaging (TDI), which reveals atrial function, in ST-elevation myocardial infarction (STEMI) remains unclear. This study evaluated the association of TDI parameters determined either immediately or 2 weeks after percutaneous coronary intervention (PCI) with long-term outcomes.

Methods and Results: In all, 740 patients with first-time STEMI underwent immediate PCI (i.e., within 12 h of onset). Echocardiography was performed in 307 patients 2 weeks after onset (Group A; mean age 64 years, 249 males), in 277 patients immediately after PCI (Group B; mean age 65 years, 229 males), and in 156 patients twice (i.e., immediately and 2 weeks after PCI; Group C; mean age 65 years, 135 males). Patients were followed-up for up to 10 years (mean 81 months). The primary endpoints were cardiac death or heart failure hospitalization. Major adverse cardiovascular events (MACE) occurred in 143 patients (19%) during the follow-up period. Both univariate and multivariate Cox hazard analyses were used to determine predictors of MACE. At 24 h and 2 weeks after STEMI onset, a′ and E/e′ were the strongest predictors of MACE, respectively.

Conclusions: TDI parameters have different implications depending on the timing of echocardiography after a first-time STEMI. Based on the results of this study, atrial dysfunction measured by TDI 24 h after STEMI onset may indicate a poor prognosis.

Key Words: Atrial function; Prognosis; ST-elevation myocardial infarction; Tissue Doppler

In patients with STEMI, echocardiographic indices of elevated left ventricular (LV) filling pressure are clearly associated with poor functional and clinical outcomes. Mitral annulus velocity on tissue Doppler imaging (TDI) reflects the rate of change in the LV long axis dimension, and the ratio of early diastolic flow velocity of TMF (E) to early diastolic mitral annulus velocity (e′) has been shown to be the most accurate non-invasive marker of elevated LV filling pressure, and is suitable for ST-elevation myocardial infarction (STEMI).[1] Left atrial (LA) dilatation is a well-recognized strong predictor of adverse outcomes after STEMI. The LA is directly exposed to LV cavity pressure during diastole; thus, an enlarged LA is a robust marker of increased LV filling pressure in the absence of LA volume overload, which provides a causal link between LA dilatation and poor outcome.[2] Recently, atrial function was reported to be a predictor of STEMI[3] and heart failure (HF).[4,5] Furthermore, late diastolic velocity on TDI (a′) was reported as a useful marker for HF with preserved ejection fraction (EF).[6] Based on the Copenhagen City Heart Study, TDI echocardiography should not be limited to a focus on early diastolic function only.[7] However, to

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This study has been registered with the University Hospital Medical Information Network (UMIN) Clinical Trials Registry (ID: UMIN000041995).

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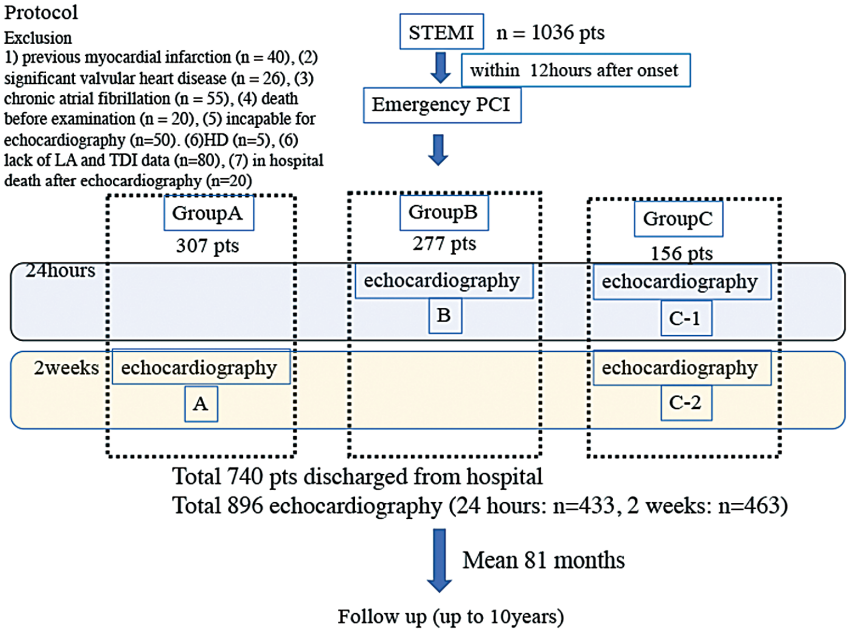

Figure 1. Study protocol. Patients in this study were divided into 3 study groups: Group A patients underwent echocardiography 2 weeks after onset; Group B patients underwent echocardiography 24 h after onset; and, to demonstrate the appropriateness of this study, Group C patients underwent echocardiography 24 h (Group C-1) and 2 weeks (Group C-2) after onset. Patients were followed up for a mean of 81 months. HD, hemodialysis; LA, left atrium; PCI, percutaneous coronary intervention; pts, patients; STEMI, ST-elevation myocardial infarction; TDI, tissue Doppler imaging.

the best of our knowledge, there have been no studies into the prognostic significance of a′ in patients with STEMI. Therefore, in this study we assessed the clinical value of TDI including a′ as a predictor of outcomes in patients with STEMI according to the time from onset of STEMI.

Methods

Patients and Protocols

The study protocol is shown in **Figure 1**. The observational study group comprised 1,036 consecutive patients with STEMI who were treated at Yokohama City University Medical Center (Yokohama, Japan) between April 2005 and August 2014. Patients were excluded from the study if they had previous myocardial infarction (MI; n=40), severe valvular heart disease (n=26), or atrial fibrillation (n=55), died before examination (n=20), could not undergo echocardiography, including TDI (n=50), were on hemodialysis (n=5), had missing LA function data (n=80), or died in hospital after echocardiography (n=20). This left 896 echocardiograms from 740 patients for analysis in the present study.

All patients successfully underwent reperfusion therapy by percutaneous coronary intervention (PCI) within 12 h after symptom onset and were discharged from hospital. STEMI was defined as typical chest pain lasting >30 min, ST-segment elevation >0.1 mV within 2 contiguous leads on the initial electrocardiogram (ECG), and an increase in creatinine phosphokinase (CPK) to twice the upper limit of the normal range. Hemodynamic status was defined using the Killip classification system.

Patients were divided into 3 study groups. Group A included the 307 patients treated between April 2005 and April 2008 who had undergone echocardiography 2 weeks after symptom onset. Group B included 277 patients treated between April 2008 and May 2012 who had undergone echocardiography 24 h after symptom onset (within 48 h). To demonstrate the appropriateness of our study, Group C included 156 patients treated between June 2012 and September 2014 who underwent echocardiography 24 h (C-1) and 2 weeks after (C-2) symptom onset (i.e., the C-1 and C-2 populations were identical, but the timing of echocardiography differed). Thus, a total of 896 echocardiograms were performed in this study.

Patients were followed-up for a long time (mean follow-up period 81 months) through regular visits to their attending physician or by telephone interviews. Major adverse cardiac events (MACE) was defined as cardiac death or HF hospitalization.

The Institutional Review Board of Yokohama City University waived the requirement for individual informed consent according to the "opt-out" principle in a retrospective study: patients could opt out of the database if they wished. Patients or the public were not involved in conducting this research. The study protocol was approved by the Yokohama City University Center for Novel and Exploratory Clinical Trials ethics committee (Reference no. B2101000026) and the study conformed to the provisions of the Declaration of Helsinki.

This study has been registered with the University Hospital Medical Information Network (UMIN) Clinical Trials Registry (ID: UMIN000041995).

Echocardiography

All patients were examined in the left lateral or supine position, depending on their condition, by precordial 2-dimensional and Doppler echocardiography. Echocardiography was performed by experienced cardiologists (N.I., M.G.) using an Aplio™ ultrasound system (SSA-770A; Toshiba), iE33 (Philips Medical System, Andover, MA, USA), Vivid q, or VividE9 (GE Vingmed Ultrasound, Horten, Norway). The LVEF was calculated with the biplane modified Simpson's method. LV mass and LA volume were calculated

Table 1. Patient Characteristics in Groups A, B, and C

	Group A (n=307)	Group B (n=277)	Group C (n=156)	P value
Age (years)	64±12	64±11	64±12	0.91
Male sex	243 (81)	222 (82)	135 (86)	0.29
BSA (m^2)	1.7±0.18	1.7±0.19	1.7±0.18	0.80
BMI (%)	24.1±3.1	24.3±3.7	24.8±3.6	0.11
Coronary risk factors				
Hypertension	165 (55)	167 (62)	85 (55)	0.17
Diabetes	110 (36)	76 (28)	44 (28)	0.11
Culprit vessel				0.81
LMT	5 (1)	7 (2)	4 (2)	
LAD	139 (47)	137 (51)	76 (48)	
LCx	39 (13)	26 (10)	16 (10)	
RCA	118 (39)	100 (37)	60 (38)	
Killip class ≥II	56 (18)	53 (17)	28 (15)	0.20
Multivessel disease	94 (32)	87 (34)	56 (35)	0.63
Reperfusion time (min)	175±121	189±214	181±130	0.60
Peak CPK (IU/L)	2,779±2,385	3,078±3,792	3,053±3,792	0.004
Peak CPK-MB (IU/L)	250±223	319±266	309±231	0.001
AUC-CPK (IU/L)	72,847±84,811	82,756±68,817	81,471±67,324	0.001
AUC-CPK-MB (IU/L)	6,129±7,712	7,360±5,908	7,251±5,691	0.001
Medication after AMI				
Aspirin	300 (99)	270 (100)	156 (100)	0.99
β-blocker	206 (70)	228 (84)	121 (78)	0.003
ACEI/ARB	238 (79)	259 (95)	144 (92)	<0.0001
Statin	265 (88)	267 (98)	150 (96)	<0.0001
2 weeks after onset				
BNP (pg/mL)	158±212	182±233	160±151	0.05
MACE (%)	54 (18)	58 (23)	31 (19)	0.15

Unless indicated otherwise, data are presented as the mean±SD or frequency (%). Patients were divided into 3 groups: Group A patients underwent echocardiography 2 weeks after onset; Group B patients underwent echocardiography 24 h after onset; and Group C patients underwent echocardiography 24 h and 2 weeks after onset. ACEI, angiotensin-converting enzyme inhibitor; AMI, acute myocardial infarction; ARB, angiotensin receptor blocker; AUC, area under the curve; BNP, plasma B-type natriuretic peptide; BSA, body surface area; CPK, creatine phosphokinase; LAD, left anterior descending coronary artery; LCx, left circumflex coronary artery; LMT, left main trunk; MACE, major adverse cardiovascular events; MB, myocardial band; RCA, right coronary artery.

by the area-length method from apical 4- and 2-chamber views and were indexed for body surface area; these measurements are based on guideline recommendations.[8] Transmitral flow (TMF) was assessed in the apical 4-chamber view using pulsed-wave Doppler echocardiography, with the Doppler beam aligned parallel to the direction of flow and the sample volume at the leaflet tips. E- and A-wave peak velocities, transmitral deceleration time (TM-DT), and the duration of the A-wave were measured from the mitral inflow profile. The TDI of the mitral annulus was obtained from the apical 4-chamber view, using a 1- to 2-mm sample volume placed at the septal side by careful use of the spectral pulsed Doppler method averaged from 3 cardiac cycles. Systolic velocity (s′), early diastolic velocity (e′), and late diastolic velocity (a′) of the mitral annulus at both septal and lateral sites were measured and E/e′ was calculated.

Mitral regurgitation (MR) was graded as absent, slight, mild, moderate, or severe, and jet area or the jet area/LA area ratio and vena contracta were measured. MR was quantified by an integrated approach comprising mitral valve morphology, the proximal isovelocity surface area method including the effective regurgitant orifice area, and the regurgitant volume.

LA total emptying fraction (TEF), LA passive emptying fraction (PEF), and LA active emptying fraction (AEF) were calculated.[9] LA volumes were measured: (1) just before mitral valve opening, at end-systole (maximum LA volume [Vmax]); (2) at the onset of the P wave on the ECG (pre-atrial contraction volume [VpreA]); and (3) at mitral valve closure, at end-diastole (minimum LA volume [Vmin]).[10] From these measurements, the following parameters were calculated:

$$\text{LA (PEV)} = \text{Vmax} - \text{VpreA}$$

where PEV is passive emptying volume;

$$\text{LA (PEF)} = \text{PEV/Vmax} \times 100$$
$$\text{LA AEV} = \text{VpreA} - \text{Vmin}$$

where AEV is active emptying volume;

$$\text{LA AEF} = \text{AEV/VpreA} \times 100$$
$$\text{LA TEV} = \text{Vmax} - \text{Vmin}$$

where TEV is total emptying volume;

$$\text{LA TEF} = \text{TEV/Vmax} \times 100.$$

Table 2. Echocardiographic Characteristics

	Echocardiography at 24 h			Echocardiography at 2 weeks		
	Group B	Group C-1	P value	Group A	Group C-2	P value
No. patients	277	156		307	156	
SBP (mmHg)	123±20	125±22	0.409	112±22	110±12	0.21
DBP (mmHg)	69±13	70±10	0.621	65±10	64±10	0.621
Heart rate (beats/min)	68±11	71±12	0.165	61±12	61±12	0.165
LVDd (mm)	46.5±6.0	47.1±7.4	0.1	48.8±6.4	48.9±7.4	0.72
LVDs (mm)	32.2±6.7	32.5±8.4	0.1	33.0±7.2	33.8±7.7	0.26
LVEDVI (mL/m^2)	56.5±20.3	55.5±14.5	0.05	61.2±20.2	61.6±17.3	0.91
LVESVI (mL/m^2)	27.2±16.4	27.5±12.7	0.12	28.4±13.9	28.5±12.7	0.22
LVEF (%)	51.1±9.7	51.6±11.3	0.77	55.3±10.1	54.1±10.4	0.1
LVMI (g/m^2)	129±30	124±27	0.06	137±37	131±26	0.05
MR>moderate	25 (9)	12 (8)	0.81	24 (8)	11 (7)	0.7
Transmitral flow						
Peak E-wave velocity (cm/s)	74.2±21.5	71.9±16.7	0.32	72±19	70±19	0.97
Peak A-wave velocity (cm/s)	80.9±18.4	78.6±21.1	0.13	78±22	78±23	0.94
E/A ratio	1.00±0.57	0.99±0.45	0.96	1.0±0.4	1.0±0.5	0.16
TM-DT (ms)	212.7±51.6	215.0±55.8	0.93	219±52	228±66	0.06
Mitral annulus velocity (m/s)						
s′ velocity	7.2±1.8	7.2±1.5	0.9	7.2±1.8	7.2±1.5	0.91
e′ velocity	5.8±1.7	5.7±2.1	0.67	6.3±1.7	6.3±2.1	0.67
a′ velocity	9.5±1.7	9.0±2.1	0.67	9.3±2.3	9.1±2.2	0.26
E/e′ ratio	13.6±4.0	13.4±4.4	0.26	12.3±4.9	12.0±4.5	0.56
A/a′	9.1±4.1	9.2±3.6	0.81	8.6±3.1	8.9±3.4	0.53
LA-related indices						
Maximum LAVI (mL/m^2)	30.3±12.4	29.1±11.0	0.41	32.9±11.5	32.9±11.4	0.78
LAV PreA index (mL/m^2)	21.0±6.7	20.4±6.9	0.29	24.3±8.7	22.3±8.5	0.12
Minimum LAVI (mL/m^2)	14.9±6.7	13.7±6.7	0.21	18.1±8.4	18.2±8.1	0.06
LA total emptying fraction (%)	53.4±13.0	54.3±11.4	0.62	48.4±8.1	48.3±13.3	0.7
LA passive emptying fraction (%)	28.1±12.9	29.2±13.5	0.09	25.9±11.2	25.9±11.2	0.78
LA active emptying fraction (%)	32.1±12.8	33.9±10.8	0.07	30.5±11.0	31.8±10.1	0.07

Unless indicated otherwise, data are presented as the mean±SD or n (%). Patients were divided into three groups: Group A patients underwent echocardiography 2 weeks after onset; Group B patients underwent echocardiography 24 h after onset; and Group C patients underwent echocardiography 24 h (C-1) and 2 weeks (C-2) after onset. A, late diastolic velocity; a′, late diastolic velocity of mitral annulus velocity; DBP, diastolic blood pressure; E, early diastolic velocity; e′, early diastolic velocity of mitral annulus velocity; LA, left atrium; LAVI, left atrial volume index; LV, left ventricular; LVDd, LV end-diastolic dimension; LVDs, LV end-systolic dimension; LVEDVI, LV end-diastolic volume index; LVEF, LV ejection fraction; LVESVI, LV end-systolic volume index; LVMI, LV mass index; MR, mitral regurgitation; PreA, pre-atrial contraction volume; s′, systolic velocity of mitral annulus velocity; SBP, systolic blood pressure; TM-DT, deceleration time of transmitral flow.

Biochemical Markers

Blood samples were obtained 2 weeks after symptom onset. Creatinine and plasma B-type natriuretic peptide (BNP) concentrations were determined. Renal function was assessed on the basis of the estimated glomerular filtration rate (eGFR). CPK and myocardial band (MB) were obtained on admission then at 3-h intervals during the first 24 h, at 6-h intervals for the next 2 days, and then daily until discharge. Furthermore, the area under the curve (AUC) for CPK/MB was calculated by the linear trapezoidal method to identify the extent of myocardial injury.

Coronary Angiography

Coronary angiography was performed according to standard criteria. Epicardial blood flow in the infarct-related artery and myocardial perfusion grade were graded according to the Thrombolysis in Myocardial Infarction (TIMI) group definitions.[11] The reperfusion time was defined as the time from onset until TIMI Grade 2 was achieved.

Statistical Analyses

Results are expressed as the mean±SD for continuous variables and as frequencies and percentages for categorical variables. Group comparisons were made using Student's t-test or the Mann-Whitney U-test and χ^2 test, as appropriate. Survival curves were estimated by thee Kaplan-Meier method, and log-rank tests were used for group comparisons. Potential independent predictors were identified by Cox proportional hazard analysis. Variables that were significant on univariate analysis were then entered into Cox proportional hazard models with entry and retention set at a significance level of $P<0.05$. When multicollinearity was observed, a variable was removed from the model. Model 1 included all indices except E/e′. Model 2 included all indices except a′. Hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated.

In addition, the incremental effect of TDI indices (a′, E/e′) on the variables identified as significant predictors of future MACE was evaluated using net reclassification improvement (NRI), as described previously.[12] To determine the

Table 3. Echocardiographic Characteristics in Patients With and Without MACE

	Echocardiography at 24 h			Echocardiography at 2 weeks		
	MACE(–) (n=277)	MACE(+) (n=156)	P value	MACE(–) (n=307)	MACE(+) (n=156)	P value
LVDd (mm)	46.8±5.7	47.8±7.1	0.16	48.7±5.8	49.6±8.3	0.75
LVDs (mm)	33.2±6.7	35.1±7.1	0.002	32.7±6.5	9.4±7.7	0.01
LVEDVI (mL/m^2)	56.0±20.1	62.1±22.3	0.007	58.1±17.6	67.4±24.3	0.001
LVESVI (mL/m^2)	28.8±13.7	35.9±16.9	<0.0001	27.2±11.3	35.1±19.0	0.0004
LVEF (%)	52.1±11.8	48.9±11.8	0.02	55.5±9.6	50.7±12.0	0.0006
LVMI (g/m^2)	123.5±32.7	137.8±41.3	0.001	120.0±28.6	133.7±41.6	0.07
MR>moderate	17 (5)	21 (24)	<0.0001	18 (5)	19 (22)	<0.0001
MR jet area/LA area (%)	16±10	25±15	<0.0001	12.7±9.7	19.8±13.8	<0.0001
Vena contracta (mm)	1.7±1.0	2.7±1.6	<0.0001	1.5±1.1	2.1±1.5	0.0008
EROA (cm^2)	0.16±0.10	0.28±0.17	<0.0001	0.15±0.12	0.23±0.11	0.0003
RegVol (mL/beat)	8.0±6.4	15.1±12.4	<0.0001	7.9±8.6	14.4±13.7	0.0004
Transmitral flow						
Peak E-wave velocity (cm/s)	70.9±17.6	81.5±24.9	<0.0001	72±19	70±19	0.97
Peak A-wave velocity (cm/s)	80.9±20.7	79.6±29.4	0.58	78±22	78±23	0.94
E/A ratio	0.94±0.42	1.23±0.79	0.01	1.0±0.4	1.0±0.5	0.16
TM-DT (ms)	216.3±65.7	202.2±79.7	0.01	219±52	228±66	0.06
Mitral annulus velocity (m/s)						
s′ – septal velocity	7.2±2.3	6.1±2.1	<0.0001	7.5±1.8	6.3±1.4	<0.0001
e′ – septal velocity	6.0±1.8	5.0±2.6	<0.0001	6.5±1.8	5.1±1.3	<0.0001
a′ – septal velocity	9.9±2.2	7.2±2.2	<0.0001	9.6±2.4	7.8±2.4	<0.0001
E/e′ ratio – septal	12.6±4.3	17.2±7.0	<0.0001	11.0±3.9	16.4±5.5	<0.0001
LA-related indices						
Maximum LAVI (mL/m^2)	28.9±11.2	33.2±14.2	0.01	31.1±10.0	39.8±14.3	<0.0001
LAV PreA index (mL/m^2)	20.2±7.9	24.4±11.0	0.002	23.3±5.5	23.9±6.5	0.27
Minimum LAVI (mL/m^2)	13.3±5.9	17.8±9.9	<0.0001	16.3±4.9	17.2±6.0	0.2
LA total fraction (%)	54.6±8.7	48.6±11.7	<0.0001	50.1±9.7	40.9±11.7	<0.0001
LA passive emptying fraction (%)	29.1±10.9	26.4±10.8	0.07	32.1±14.4	28.6±12.5	0.11
LA active emptying fraction (%)	34.0±9.2	29.7±10.4	0.0001	31.4±9.1	29.5±8.7	0.16

Unless indicated otherwise, data are presented as the mean±SD or frequency (%). EROA, effective regurgitant orifice area; MACE, major adverse cardiac events; RegVol, regurgitant volume. Other abbreviations as in Table 2.

optimal threshold of a′, E/e′, LA volume index (LAVI), and LA TEF for the prediction of the endpoints, receiver operating characteristic (ROC) curve analysis was used. AUCs were compared between a′, E/e′, LAVI, and LA TEF using the DeLong method.[13] Furthermore, to determine the ability of a′, E/e′, LAVI, and LA TEF to predict the endpoints, we used time-dependent ROC curve analysis.[14] Then, the time until MACE, AUC, and 95% CIs for a′, E/e′, LAVI, and LA TEF were obtained.

For all analyses, 2-sided P<0.05 was considered to indicate statistical significance. Statistical analyses were performed using JMP Pro 15.0 (SAS Institute, Cary, NC, USA) and the 'nricens' and 'timeROC' packages in R (R Foundation for Statistical Computing, Vienna, Austria).

Results

Patient Characteristics

Table 1 shows the characteristics of the patients in Groups A (n=307), B (n=277), and C (n=156).

Echocardiographic characteristics are presented in **Table 2**, including LA-related indices. LA volumes increased and LA function decreased from 24 h to 2 weeks. Differences between Groups B and C-1 and between Groups A and C-2 were evaluated. Most patients did not have significant MR. **Supplementary Table 1** presents patient characteristics according to the time of examination (24 h or 2 weeks).

Significant relationships were found between a′ and LA-related indices (**Supplementary Figure**).

Predictors of Outcome

During the follow-up period (mean 81 months), 143 of 740 patients (19%) experienced MACE (40 cardiac deaths, 103 HF hospitalizations). **Table 3** shows the echocardiographic indices (obtained at 24 h and 2 weeks) among patients with and without MACE. We selected TDI parameters at the septal side because they are easiest to obtain (the other TDI parameters are provided in **Supplementary Table 2**).

Associations with MACE among the indices determined at 24 h are presented in **Table 4**. Taking multicollinearity into consideration, we performed multivariate analyses separately. Univariate analysis revealed that age, peak CPK, Killip class >I, E-wave, LVEF, LVMI, LAVI, E/A, a′, and E/e′ are significant predictors of MACE. Model 1 showed that a′ is the strongest prognosticator and Model 2 showed E/e′ as the strongest predictor. Associations with MACE among the indices at 2 weeks are also presented in **Table 4**. In the univariate analysis, age, peak CPK, anterior MI, Killip class >I, E-wave, LVEF, LVMI, LAVI, E-wave, E/A,

Table 4. Associations of Variables With MACE According to Time of Examination (24 h or 2 Weeks)

	Univariate analysis		Model 1		Model 2	
	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value
24-h indices (n=433)						
Age	1.06 (1.04–1.08)	<0.0001	1.04 (1.02–1.06)	<0.0001	1.05 (1.03–1.07)	<0.0001
Female sex	1.58 (0.84–2.90)	0.159				
Peak CPK/1,000	1.09 (1.02–1.17)	0.008	1.00 (0.97–1.00)	0.843	0.99 (0.99–1.01)	0.952
Killip class >I	3.11 (1.97–4.89)	<0.0001	1.59 (1.01–2.52)	0.045	1.76 (1.10–2.28)	0.017
Anterior MI	1.58 (1.02–2.43)	0.04	1.63 (1.03–2.58)	0.037	1.45 (0.91–2.31)	0.121
EF	0.98 (0.96–0.99)	0.02	0.99 (0.97–1.01)	0.448	0.99 (0.98–1.02)	0.723
LVMI	1.01 (1.00–1.02)	0.0008	1.00 (0.99–1.01)	0.418	1.01 (1.00–1.01)	0.019
LAVI	1.03 (1.01–1.05)	0.003	1.00 (0.99–1.02)	0.723	1.01 (0.99–1.03)	0.272
E/A	2.45 (1.57–3.81)	<0.0001	1.21 (0.88–1.59)	0.202	1.11 (0.84–1.50)	0.437
a′	0.76 (0.68–0.85)	<0.0001	0.70 (0.63–0.78)	<0.0001		
E/e′	1.08 (1.05–1.11)	<0.0001			1.05 (1.01–1.09)	0.009
2-week indices (n=463)						
Age	1.06 (1.04–1.09)	<0.0001	1.04 (1.02–1.06)	<0.0001	1.03 (1.01–1.06)	0.006
Female sex	1.02 (0.57–1.83)	0.95				
Peak CPK/1,000	1.12 (1.06–1.18)	<0.0001	1.01 (0.92–1.09)	0.835	1.01 (0.930–1.10)	0.813
Killip class >I	2.42 (1.57–3.73)	<0.0001	2.17 (1.32–3.58)	0.002	1.99 (1.19–3.34)	0.008
Anterior MI	1.61 (1.15–2.25)	0.005	1.41 (0.88–2.23)	0.156	1.35 (0.86–2.15)	0.402
EF	0.96 (0.94–0.98)	<0.0001	0.99 (0.97–1.01)	0.586	1.01 (0.99–1.03)	0.634
LVMI	1.01 (1.00–1.02)	0.027	1.00 (0.99–1.00)	0.065	1.00 (0.99–1.03)	0.237
LAVI	1.05 (1.03–1.06)	<0.0001	1.02 (0.99–1.07)	0.08	1.00 (0.99–1.01)	0.41
E/A	2.40 (1.84–3.05)	<0.0001	1.31 (0.95–1.77)	0.08	1.31 (0.96–1.75)	0.08
a′	0.71 (0.64–0.78)	<0.0001	0.81 (0.73–0.91)	0.0002		
E/e′	1.16 (1.12–1.99)	<0.0001			1.10 (1.05–1.15)	<0.0001

Model 1 included all indices except E/e′. Model 2 included all indices except a′. CI, confidence interval; EF, ejection fraction; HR, hazard ratio; MI, myocardial infarction. Other abbreviations as in Tables 1,2.

e′, a′, and E/e′ were significant predictors of MACE; Model 1 showed that age and a′ are independent predictors of MACE, whereas Model 2 showed that age, Killip class >I, and E/e′ were independent predictors of MACE. Results of analyses of s′ and e′ are presented in **Supplementary Tables 3,4**.

We next examined the incremental effect of a′ and E/e′ on strong predictors of MACE (age, CPK, anterior MI, Killip class >I, EF, LAVI, E/A) using the NRI (**Table 5**). As indicated in **Table 5**, the inclusion of a′ at 24 h was associated with an NRI of 0.39 (95% CI 0.11, 0.41); conversely, E/e′ at 24 h was not significant (NRI 0.08; 95% CI −0.02, 0.19). A′ at 24 h was associated with an NRI of 0.04 (95% CI −0.03, 0.12) and E/e′ was associated with an NRI of 0.14 (95% CI 0.03, 0.23). Thus, **Table 5** suggests an effective reclassification of a′ at 24 h and E/e′ at 2 weeks. Accordingly, a′ at 24 h and E/e′ at 2 weeks had significant incremental effects on the conventional significant predictors of MACE.

Table 5. Incremental Effect of Adding a′ and E/e′ to the Base Model

	NRI (95% CI)
Indices at 24 h	
Base model+a′	0.39 (0.11, 0.41)
Base model+E/e′	0.08 (−0.02, 0.19)
Indices at 2 weeks	
Base model+a′	0.04 (−0.03, 0.12)
Base model+E/e′	0.14 (0.03, 0.23)

Variables included in the base model were age, peak CPK/1,000, Killip class >I, anterior MI, EF, LAVI, and E/A. NRI, net reclassification index. Other abbreviations as in Tables 2,4.

Figure 2A shows ROC curves for predicting MACE for different indices at 24 h (i.e., a′, E/e′, LAVI, and LA TEF), along with their AUCs and 95% CIs. There was a significant difference among the 4 curves for values obtained at 24 h (P<0.0001). Furthermore, a′ was a stronger predictor of MACE than LAVI (P<0.0001) and LATEF (P=0.0001). **Figure 2B** shows ROC curves for predicting MACE for the indices obtained at 2 weeks, along with their AUCs and 95% CIs. There were no significant differences among the 3 LA-related indices (a′, LAVI, LATEF). Finally, we examined Kaplan-Meier curves in patients dichotomized according to median values of a′, E/e′, and LATEF (**Figure 3**); all the indices were found to be significant predictors of MACE.

Based on time-dependent ROCs for the prediction of MACE among the indices at 24 h, the time in days for a′, E/e′, LAVI, and LATEF was 13 (AUC 60.5; 95% CI 47.9–73.1), 84 (AUC 53.4; 95% CI 47.0–59.7), 108 (AUC 50.5; 95% CI 43.5–57.5), and 84 (AUC 52.3; 95% CI 46.1–58.5), respectively. For indices at 2 weeks, the time in days for a′, E/e′, LAVI, and LATEF was 21 (AUC 64.2; 95% CI 49.5–79.0), 60 (AUC 50.3; 95% CI 38.2–62.5), 21 (AUC 50.6; 95% CI 36.2–65.0), and 69 (AUC 51.7; 95% CI 45.0–58.5), respectively.

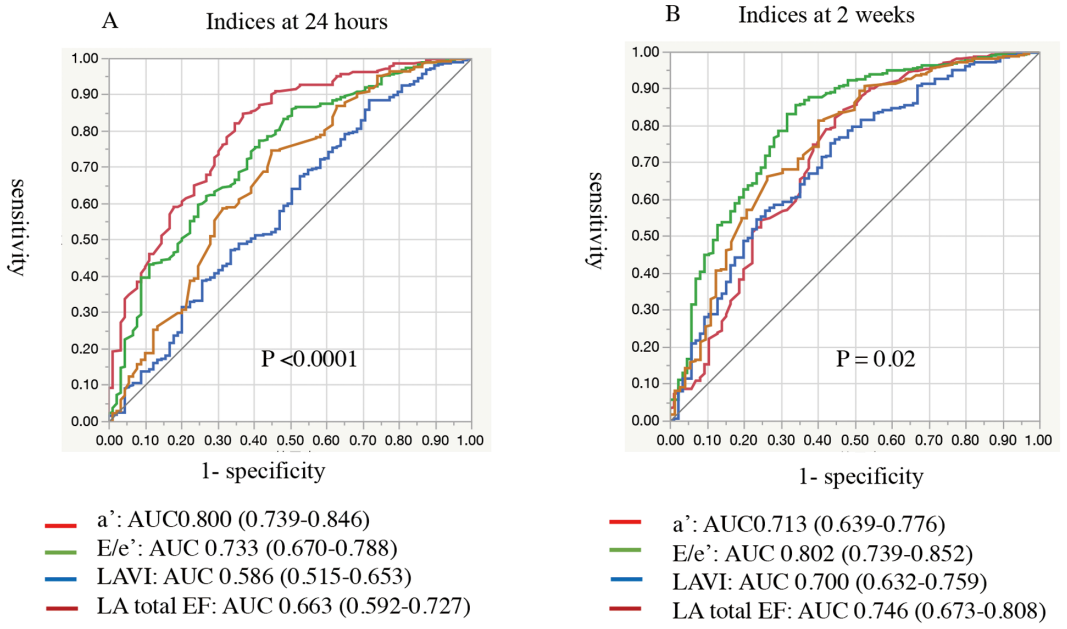

Figure 2. Comparison of receiver operating characteristic (ROC) curves between (**A**) Groups B and C-1 and (**B**) Groups A and C-2 for different parameters. Values for areas under the curve (AUC) and 95% confidence intervals (CIs) are also provided. For measurements at 2 weeks (**B**), there were no significant differences among the 3 left atrium (LA)-related indices (a′, LA volume index [LAVI], LA total emptying fraction [TEF]; all NS).

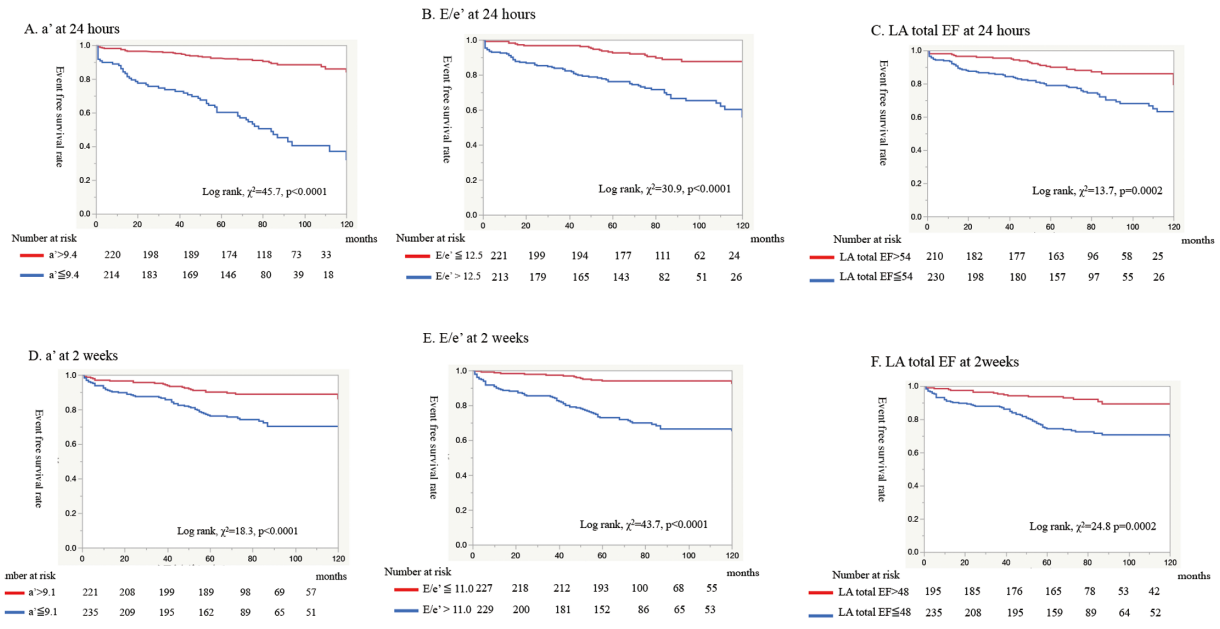

Figure 3. Kaplan-Meier curves according to median values of (**A**) a′ (9.4) at 24 h (log rank, X^2=45.7, P<0.0001), (**B**) E/e′ (12.5) at 24 h (log rank, X^2=30.9, P<0.0001), (**C**) left atrial total emptying fraction (LA TEF; 54%) at 24 h (log rank, X^2=13.7, P=0.0002), (**D**) a′ (9.1) at 2 weeks (log rank, X^2=18.3, P<0.0001), (**E**) E/e′ (11.0) at 2 weeks (log rank, X^2=43.7, P<0.0001), and (**F**) LA TEF (48%) at 2 weeks (log rank, X^2=24.8, P<0.0001).

Discussion

The main findings of this study were that: (1) a′ obtained immediately after the onset of first-time STEMI was the strongest predictor of MACE among the TDI and LA-related parameters; and (2) E/e′ obtained 2 weeks after onset of the first STEMI was the strongest predictor of MACE, as reported previously.[1] Of the LA-related indices, a′ at 24 h was the strongest of MACE, and a′ remained a significant predictor of MACE even at 2 weeks. The clinical implications of TDI parameters can change according to the time after onset of STEMI.

Measurement of a′

Although e′ and E/e′ can be measured in patients with an atrial fibrillation rhythm, a′ was the most useful parameter to predict MACE in patients with HF with preserved EF (HFpEF) in sinus rhythm.[15] We think that a′ may have some merit worth consideration. LA dysfunction measured by speckle tracking echocardiography in patients with HFpEF is associated with adverse events.[4,16] Recently, peak atrial longitudinal strain has been suggested as a reliable method for the evaluation of LA dysfunction, and it is applicable for acute MI.[17,18] However, strain analysis requires special equipment, as well as standardization and validation, and there are inter-vendor variability in strain imaging.[19] Therefore, we believe that the greatest merit of a′ is that it is a simple and easily repeatedly measured index that could be a useful and reliable marker of LA function. Among these relationships, the strongest relationships were observed in those with LA TEF, followed by LA AEF (**Supplementary Figure**). LA TEF is considered to be a useful marker of reservoir function. LA reservoir function was reported to be a prognostic marker in patients with various heart diseases, and LA AEF is thought to be a marker of prognosis in patients with HFpEF.[20] A previous studies reported that a′ represented LA pump function and that decreased a′ was associated with progressive LA remodeling.[21] Another study suggested that TDI can demonstrate LA function as strain imaging.[22] Therefore, a′ was an approximate but significant prognosticator in patients with STEMI.

Deterioration of a′ After Onset of STEMI

In the present study, a′ was a stronger prognosticator at 24 h after onset than E/e′. This may be mainly because atrial function plays an important role in protecting against immediate stress. LA function provides estimates of structural and functional adaptive changes that may help to characterize LV diastolic function, especially during exercise, when the LA may contribute considerably (up to one-third) to total cardiac output.[23] Adaptive LA functional changes could be evident with LV deterioration.[24] Acute MI causes a sudden increase in LV filling pressure, leading to higher atrial pressure. In the present study, the size of the LA increased 2 weeks after STEMI onset; this may be an adaptation to the deterioration in LV function as a result of the damage caused by STEMI. LA pump function is enhanced in response to elevated LV filling pressure as long as the Frank-Starling mechanism is working properly. The LA is directly exposed to LV cavity pressure during diastole; thus, an enlarged LA is a robust marker of increased LV filling pressure in the absence of LA volume overload, which provides a causal link between LA dilatation and poor outcome.[2,17] Thus, a′ is useful for detecting damage to the LV and the effect of LV deterioration,[7] and a′ at 24 h could be a strong prognosticator.

Clinical Implications

This study has proposed the clinical usefulness of a′ and the importance of considering the timing of examinations after the onset of STEMI. TDI can accurately predict the long-term prognosis after STEMI. Immediately after STEMI, prognosis can be predicted using a′, whereas E/e′ can be used to predict prognosis 2 weeks after STEMI. TDI is convenient, repeatable, and free from any limitations, such as requirements for a large space or special equipment.

Study Limitations

First, this was a small retrospective study conducted at a single center. Second, the underlying variables may change with time or over the course of the disease, and a single measurement may not convey accurate prognostic information. However, measurement of a′ at a single time point is simple. Third, cases of atrial fibrillation were excluded from the present study because these were high-risk patients. Fourth, as described in the Discussion, peak atrial longitudinal strain is thought to be the most reliable marker for LA assessment,[5] but it was not analyzed in this study. Two-dimensional measurements of LA size and function are not always precise, like 3-dimensional analysis. Fifth, infarct size was estimated by CPK, not by troponin. Finally, comparisons of the time course should have been done in the same patients. However, there were 156 patients in Group C, in which patients underwent echocardiography repeatedly. Nevertheless, we have revealed the clinical usefulness of TDI including a′ for first-time STEMI depending on the timing of examination; furthermore, a′ is easy to measure.

Conclusions

We conclude that a′ obtained immediately after onset of STEMI was the strongest prognosticator among the TDI indices for patients with first-time STEMI. However, E/e′ at 2 weeks after onset is also a powerful predictor. The meaning of each index is differs depending on the timing of the examination. We conclude that a′ at 24 h can be a more useful index because of its ease of determination. Further studies are needed to confirm the role of TDI in STEMI.

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None.

Disclosures

M.K. is a member of *Circulation Reports*' Editorial Team. The remaining authors have no conflicts of interest to declare.

IRB Information

This study was approved by the Institutional Review Board of Yokohama City University, Center for Novel and Exploratory Clinical Trials (Reference no. B2101000026).

Data Availability

Individual deidentified participant data and all analyzable data related to the study will be shared. The study protocol and statistical analysis plan will be available. The data will be available immediately following publication, ending 10 years after publication. The data will be shared as Excel files via E-mail.

References

1. Iwahashi N, Kimura K, Kosuge M, Tsukahara K, Hibi K, Ebina T, et al. E/e′ two weeks after onset is a powerful predictor of cardiac death and heart failure in patients with a first-time ST elevation acute myocardial infarction. *J Am Soc Echocardiogr* 2012; **25:** 1290–1298.
2. Moller JE, Hillis GS, Oh JK, Seward JB, Reeder GS, Wright RS, et al. Left atrial volume: A powerful predictor of survival after acute myocardial infarction. *Circulation* 2003; **107:** 2207–2212.
3. Modin D, Pedersen S, Fritz-Hansen T, Gislason G, Biering-Sorensen T. Left atrial function determined by echocardiography predicts incident heart failure in patients with STEMI treated by primary percutaneous coronary intervention. *J Card Fail* 2020; **26:** 35–42.
4. Thomas L, Marwick TH, Popescu BA, Donal E, Badano LP. Left atrial structure and function, and left ventricular diastolic dysfunction: JACC state-of-the-art review. *J Am Coll Cardiol* 2019; **73:** 1961–1977.
5. Deferm S, Martens P, Verbrugge FH, Bertrand PB, Dauw J, Verhaert D, et al. LA mechanics in decompensated heart failure: Insights from strain echocardiography with invasive hemodynamics. *JACC Cardiovasc Imaging* 2020; **13:** 1107–1115.
6. Oike F, Yamamoto E, Sueta D, Tokitsu T, Usuku H, Nishihara T, et al. Clinical significance of diastolic late mitral annular velocity in heart failure with preserved ejection fraction. *Int J Cardiol* 2020; **316:** 145–151.
7. Mogelvang R, Biering-Sørensen T, Jensen JS. Tissue Doppler echocardiography predicts acute myocardial infarction, heart failure, and cardiovascular death in the general population. *Eur Heart J Cardiovasc Imaging* 2015; **16:** 1331–1337.
8. Lang RM, Badano LP, Mor-Avi V, Afilalo J, Armstrong A, Ernande L, et al. Recommendations for cardiac chamber quantification by echocardiography in adults: An update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *Eur Heart J Cardiovasc Imaging* 2015; **16:** 233–270.
9. Leung DY, Boyd A, Ng AA, Chi C, Thomas L. Echocardiographic evaluation of left atrial size and function: Current understanding, pathophysiologic correlates, and prognostic implications. *Am Heart J* 2008; **156:** 1056–1064.
10. Blume GG, McLeod CJ, Barnes ME, Seward JB, Pellikka PA, Bastiansen PM, et al. Left atrial function: Physiology, assessment, and clinical implications. *Eur J Echocardiogr* 2011; **12:** 421–430.
11. The TIMI study group. The Thrombolysis in Myocardial Infarction (TIMI) trial: Phase I findings. *N Engl J Med* 1984; **33:** 523–530.
12. Pencina MJ, D'Agostino RB Sr, D'Agostino RB Jr, Vasan RS. Evaluating the added predictive ability of a new marker: From area under the ROC curve to reclassification and beyond. *Stat Med* 2008; **27:** 157–172.
13. DeLong ER, DeLong DM, Clarke-Pearson DL. Comparing the areas under two or more correlated receiver operating characteristic curves: A nonparametric approach. *Biometrics* 1988; **44:** 837–845.
14. Blanche P, Dartigues JF, Jacqmin-Gadda H. Estimating and comparing time-dependent areas under receiver operating characteristic curves for censored event times with competing risks. *Stat Med* 2013; **32:** 5381–5397.
15. Oike F, Yamamoto E, Sueta D, Tokitsu T, Usuku H, Nishihara T, et al. Clinical significance of diastolic late mitral annular velocity in heart failure with preserved ejection fraction. *Int J Cardiol* 2020; **316:** 145–151.
16. Santos AB, Roca GQ, Claggett B, Sweitzer NK, Shah SJ, Anand IS, et al. Prognostic relevance of left atrial dysfunction in heart failure with preserved ejection fraction. *Circ Heart Fail* 2016; **9:** e002763.
17. Ersbøll M, Andersen MJ, Valeur N, Mogensen UM, Waziri H, Møller JE, et al. The prognostic value of left atrial peak reservoir strain in acute myocardial infarction is dependent on left ventricular longitudinal function and left atrial size. *Circ Cardiovasc Imaging* 2013; **6:** 26–33.
18. Fernandes RM, Le Bihan D, Vilela AA, Barretto RBM, Santos ES, Assef JE, et al. Association between left atrial strain and left ventricular diastolic function in patients with acute coronary syndrome. *J Echocardiogr* 2019; **17:** 138–146.
19. Tschöpe C, Kasner M. Can speckle-tracking imaging improve the reliability of echocardiographic parameters for outcome evaluation in clinical trials? *Eur Heart J* 2014; **35:** 605–607.
20. Khan MS, Memon MM, Murad MH, Vaduganathan M, Greene SJ, Hall M, et al. Left atrial function in heart failure with preserved ejection fraction: A systematic review and meta-analysis. *Eur J Heart Fail* 2020; **22:** 472–485.
21. Nagueh SF, Sun H, Kopelen HA, Middleton KJ, Khoury DS. Hemodynamic determinants of the mitral annulus diastolic velocities by tissue Doppler. *J Am Coll Cardiol* 2001; **37:** 278–285.
22. Park CS, Kim YK, Song HC, Choi EJ, Ihm SH, Kim HY, et al. Effect of preload on left atrial function: Evaluated by tissue Doppler and strain imaging. *Eur Heart J Cardiovasc Imaging* 2012; **13:** 938–947.
23. Hoit BD. Left atrial size and function: Role in prognosis. *J Am Coll Cardiol* 2014; **63:** 493–505.
24. Matsuda Y, Toma Y, Ogawa H, Matsuzaki M, Katayama K, Fujii T, et al. Importance of left atrial function in patients with myocardial infarction. *Circulation* 1983; **67:** 566–571.

Supplementary Files

Please find supplementary file(s);
http://dx.doi.org/10.1253/circrep.CR-21-0056