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

Noriaki Iwahashi, MD, PhD, Kazuo Kimura, MD, PhD, Masami Kosuge, MD, PhD, Kengo Tsukahara, MD, PhD, Kiyoshi Hibi, MD, PhD, Toshiaki Ebina, MD, PhD, Mari Saito, PhD, and Satoshi Umemura, MD, PhD, *Yokohama, Japan*

Background: Early transmitral flow velocity (E) divided by early diastolic velocity of the mitral valve annulus (e′) is referred to as the E/e′ ratio, a variable that strongly correlates with mean left ventricular filling pressure. E/e′ obtained at acute phase has been reported as useful in predicting prognosis in patients with acute myocardial infarctions. The aim of this study was to evaluate the clinical utility of echocardiographic indices obtained 2 weeks after the onset of a first ST-segment elevation myocardial infarction as predictors of outcomes.

Methods: Echocardiography was performed and blood samples were obtained from 301 consecutive patients 2 weeks after the onset of a first ST-segment elevation myocardial infarction. All patients underwent primary percutaneous coronary intervention <12 hours after symptom onset and were followed for 51.7 ± 19.0 months. The primary end point was cardiac death or readmission for heart failure.

Results: During follow-up, cardiac death occurred in 10 patients, and heart failure developed in 35. On univariate analysis, age > 75 years, plasma brain natriuretic peptide > 180 pg/mL, early diastolic/late diastolic wave velocity of mitral inflow > 1.0, mitral inflow deceleration time < 140 msec, and E/e′ > 15 were associated with the primary end points. Multivariate analysis showed that E/e′ > 15 was the strongest predictor (hazard ratio, 3.702; 95% confidence interval, 1.895–7.391; $P = .0001$), followed by early diastolic/late diastolic wave velocity of mitral inflow > 1.0 (hazard ratio, 3.053; 95% confidence interval, 1.584–6.125; $P = .008$). Predictive accuracy was further enhanced by combing E/e′ > 15 and early diastolic/late diastolic wave velocity of mitral inflow > 1.0 (hazard ratio, 7.373; 95% confidence interval, 3.529–16.528; $P < .0001$).

Conclusions: E/e′ > 15 obtained 2 weeks after onset is the strongest predictor of cardiac death and readmission for heart failure after a reperfused first ST-segment elevation myocardial infarction. The predictive value of E/e′ at 2 weeks is further enhanced by combining this variable with mitral inflow filling pattern. (J Am Soc Echocardiogr 2012;25:1290-8.)

Keywords: Doppler tissue imaging, Acute myocardial infarction, Prognosis, Mitral inflow, Timing

A number of studies have suggested that left ventricular (LV) systolic dysfunction and a large infarction are predictors of poor survival after acute myocardial infarction (AMI).[1] Recently, high LV filling pressure after AMI has also been found to be a predictor of poor outcomes after AMI.[2] In particular, echocardiographic indices of elevated LV filling pressure are clearly associated with poor cardiac functional and clinical outcomes.[2-4] Mitral inflow velocities and mitral inflow deceleration time (TM-DT) strongly correlate with LV filling pressures in patients with impaired LV systolic function but are of limited value when LV systolic function is preserved.[4] Mitral annular velocity on Doppler tissue imaging (DTI) reflects the rate of change in the LV long-axis dimension. A recent study demonstrated that DTI can detect the time course of changes in regional myocardial deformation on a segmental basis during the first week after ST-segment elevation myocardial infarction (STEMI).[5] The ratio of early diastolic flow velocity of mitral inflow (E) to early diastolic mitral annular velocity (E/e′) has been shown to be the most accurate noninvasive marker of elevated LV filling pressure.[6-8] Furthermore, another study demonstrated that elevation of E/e′ suggests increased LV chamber stiffness.[9] Hillis *et al.*[10,11] reported that an E/e′ ratio > 15 several days after onset is superior to other features as a prognosticator and predictor of LV dilatation in patients with AMIs. Ideally, it is believed that echocardiography should be applied 2 weeks after onset to estimate prognosis, because eccentric hypertrophy of noninfarct-related segment becomes evident at 2 weeks after the onset of AMI.[12] However, to our knowledge, there has been no study of prognosis using echocardiographic indices 2 weeks after onset

From the Division of Cardiology, Yokohama City University Medical Center, Yokohama, Japan (N.I., K.K., M.K., K.T., K.H., T.E.); the Department of Biostatistics and Epidemiology, Yokohama City University Graduate School of Medicine and University Medical Center, Yokohama, Japan (M.S.); and the Department of Medical Science and Cardiorenal Medicine, Yokohama City University Graduate School of Medicine, Yokohama, Japan (S.U.).

Reprint requests: Noriaki Iwahashi, MD, PhD, Yokohama City University Medical Center, Division of Cardiology, 4-57 Urafune-chou, Minami-ku, Yokohama, Japan (E-mail: *iwahashi@ra2.so-net.ne.jp*).

0894-7317/$36.00

http://dx.doi.org/10.1016/j.echo.2012.09.010

Abbreviations

AMI = Acute myocardial infarction

BNP = Brain natriuretic peptide

DTI = Doppler tissue imaging

EF = Ejection fraction

HF = Heart failure

LA = Left atrial

LV = Left ventricular

MR = Mitral regurgitation

PCI = Percutaneous coronary intervention

PV-DT = Deceleration time of pulmonary venous flow

STEMI = ST-segment elevation myocardial infarction

TM-DT = Mitral inflow deceleration time

TM-E/A = Early diastolic/late diastolic wave velocity of mitral inflow

compared with other indices. Therefore, we assessed the clinical value of echocardiographic indices as predictors of outcomes in patients with STEMIs 2 weeks after onset.

METHODS

Patients and Protocols

The study group comprised 301 consecutive patients selected among 399 patients with STEMIs at Yokohama City University Medical Center (Yokohama, Japan). Patients with prior myocardial infarctions, chronic atrial fibrillation, unacceptable image quality, or chronic renal failure treated with dialysis were excluded. All subjects successfully underwent reperfusion therapy by percutaneous coronary intervention (PCI) <12 hours after symptom onset and were discharged from the hospital. Myocardial infarction was defined according to the European Society of Cardiology and American College of Cardiology guidelines.[13] Lesions with clinically significant residual stenosis underwent PCI during initial hospitalization. The presence of hypertension was defined as blood pressure >140/90 mm Hg.[14] Dyslipidemia was defined as plasma levels of fasting triglycerides ≥ 150 mg/dL and/or fasting total cholesterol ≥ 200 mg/dL and/or low-density lipoprotein cholesterol ≥ 130 mg/dL.[15] Patients without prior diagnoses of diabetes mellitus underwent a 75-g oral glucose tolerance test[16] while they were in stable condition, ≥4 days after admission. After an overnight fast, venous blood samples were taken for the measurement of plasma glucose levels at baseline, 60 min, and 120 min after the glucose load. Diabetes mellitus was defined as a fasting blood glucose level ≥ 126 mg/dL or blood glucose ≥ 200 mg/dL 120 min after glucose load. Hemodynamic status was defined using the Killip classification, and we defined patients with Killip class ≥ 2 as being in critical status. A large infarction was defined as a peak creatine phosphokinase level ≥ 3,000 IU/L. All patients were followed for 4 years (mean, 51.7 ± 19.0 months; follow-up rate, 98%) at regular visits to their attending physicians or by telephone interviews. The primary end point was the incidence of cardiac death or heart failure (HF) requiring readmission. HF was defined according to the Framingham criteria for congestive HF.[17] All patients provided written informed consent. The study protocol was approved by our institution's ethics committee.

Echocardiography

Echocardiography was performed about 2 weeks (mean, 13.6 ± 8.1 days; during convalescence) after symptom onset by an experienced observer blinded to all angiographic and clinical data in the convalescent stage. All patients were examined in the left lateral position using precordial two-dimensional and Doppler echocardiography. An Aplio ultrasound system (SSA-770A; Toshiba Corporation, Tokyo, Japan) with a 2.5-MHz phased-array transducer was used. The LV ejection fraction (EF) was calculated using the biplane modified Simpson's method. LV mass was calculated using Devereux's equation.[18] According to the recommendations of the American Society of Echocardiography, LV hypertrophy was defined as an increase in LV mass index to higher than the cutoff value of 131 g/m^2 for men and 113 g/m^2 for women.[19] Left atrial (LA) volume was calculated using the area-length method from apical four-chamber and two-chamber views and was indexed to body surface area. Severe LA enlargement was defined as LA volume index > 40 mL/m^2.[19] Mitral inflow was assessed in the apical four-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-wave and A-wave peak velocities, TM-DT, and A-wave duration were measured from the mitral inflow profile. Patients were categorized according to TM-DT. In these analyses, TM-DT < 140 msec was considered abnormally abbreviated.[2] DTI of the mitral annulus was performed from the apical four-chamber view, using a 1-mm to 2-mm sample volume placed at the septal side in 301 patients by careful use of the spectral pulse Doppler method averaged from three cardiac cycles. We rejected the e′ value when we were not able to measure three stable cycles. Therefore, we ultimately checked e′ in 301 patients. Septal e′ has excellent reproducibility, as previously reported by Hillis *et al.*[10,11] Lateral e′ values were obtained in 237 of 301 patients; therefore, the mean E/e′ values were also calculated in these 237 patients. Previous studies have confirmed the excellent reproducibility of this measurement and demonstrated that an E/e′ ratio > 15 is the best Doppler predictor of elevated mean LV diastolic pressure.[6] An elevated E/e′ ratio was therefore prospectively defined as E/e′ >15.[10,20] The guidelines of the American Society of Echocardiography and the European Association of Echocardiography recommend that mitral inflow pattern by itself can be used to estimate LV filling pressures with reasonable accuracy in patients with reduced EFs and that E/e′ should be calculated in patients with preserved EFs.[20] Peak velocities of systolic, early diastolic, and atrial contraction waves were obtained from pulmonary venous flow. To obtain the deceleration time of pulmonary venous flow (PV-DT), a line was drawn from the peak early diastolic velocity along the fall in initial velocity and extrapolated to the baseline. In this study, PV-DT < 150 msec was considered abnormally abbreviated.[21] By visually comparing the mitral regurgitation (MR) color flow jet area with the atrial area in multiple views, MR was graded as absent, slight, moderate, or severe. Color gain was adjusted just below the level of noise.

Biochemical Markers

Blood samples were obtained about 2 weeks after onset. Hemoglobin, creatinine, and plasma brain natriuretic peptide (BNP) were measured. Renal function was assessed on the basis of the estimated glomerular filtration rate, calculated using the abbreviated four-variable Modification of Diet in Renal Disease equation. BNP levels were measured directly using a specific fluoroenzyme-immunometric assay kit (TOSOH AIA-PACK BNP; TOSOH Corporation, Tokyo, Japan). Cutoff values for each marker were defined according to previous reports.[22-25]

Statistical Analyses

Statistical analyses were performed using JMP version 9.0 (SAS Institute Inc., Cary, NC). Results are expressed as mean ± SD for