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AN EARLY ECHOCARDIOGRAPHIC PREDICTION FOR FUNCTIONAL MYOCARDIAL RECOVERY AFTER ST ELEVATION MYOCARDIAL INFARCTION

Goal	Discrimination of the time course of functional recovery in early period following ST elevation myocardial infarction (STEMI) has prognostic importance. This study aims to establish the ability of the combined systolic-diastolic index (E/(Ea x Sa), for differentiating recoverable myocardium or persistent non-viability in subjects with STEMI.
Material and methods	77 patients with first acute STEMI were enrolled to the study. Serial transthoracic echocardiography (TTE) examinations were performed at the time of the admission (immediately after reperfusion), hospital discharge (5±1 days) and control examination (30±2 days). To assess the association between E/(Ea×Sa) index and myocardial recovery, two categories (Transient stunning and persistent non-viability) were defined on basis of improvement of left ventricle ejection fraction (LV EF) (Improvement was defined as an increase more than 10% in LV EF at day 30 compared to baseline).
Results	55 patients (71.4%) had improvement of LV EF and 24 patients (28.6%) had no recovery of systolic function (30 days LV EF 48.78±6.1 vs. 39.31±8.1%, p=0.01). The E/(Ea×Sa) index were significantly higher in the "non-viability" than in stunning group on predischarge and 1 month (1.61±0.64 vs 1.25±0.43, p=0.01 and 1.33±0.25 vs 1.14±0.21, p=0.01, respectively). The change in the E/(Ea×Sa) index in early period (within 5±1 days) was higher in the stunning group (26%) compared to non-viability group (15%) (p=0.033). E/(Ea×Sa) index was found to be a significant predictor of myocardial recovery in multivariable logistic regression (OR 0.91, 95% CI 0.83–0.98, p=0.001). Roc curve showed that the cutoff value of E/(Ea×Sa) index is 1.29 with 73% of sensitivity and 61% of specificity (AUC: 0.71, p=0.01, CI: 0.54–0.89).
Conclusions	Our findings suggest that E/(Ea×Sa) index is a strong predictor of functional recovery; the odds of recovery decreases as E/(Ea×Sa) index value increases.
Keywords	Diastolic dysfunction; echocardiography; functional recovery; myocardial stunning; non-viability; ST elevation myocardial infarction
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Introduction

ST segment elevation myocardial infarction (STEMI) is the foremost cause of cardiovascular mortality and morbidity [1]. Primary percutaneous coronary intervention (PPCI) is the standard mechanical re-vascularization technique for patients with STEMI and aims to limit myocardial necrosis. Even if after a successful PPCI, re-perfused myocardium by the infarct-related coronary artery may remain akinetic due to transient myocardial stunning or persistent non-viability [2].

Stunning is a delayed response in myocardial recovery [3]. But the persistent non-viability is associated with adverse clinical outcomes and poor contractile function [4]. Over and above, patients who will not have a functional recovery will also be patients who are more likely to develop heart failure. So, predicting myocardium with potential for improvement in contractility and myocardium with irreversible damage can be useful to detect this group of patients at the early period of STEMI following PPCI.

The striking point, the initial studies limited the notion of myocardial stunning to systolic dysfunction. But the current studies support the presence of diastolic dysfunction (evidenced both by regional diastolic index [impaired left ventricular (LV) untwisting rate) and global diastolic index (increased E/e' ratio)] [5, 6].

A wide range of diagnostic techniques (Including dobutamine stress echocardiography, positron emulsion tomography scanning, radionuclide myocardial perfusion imaging, and cardiovascular magnetic resonance imaging) can determine the presence or absence of metabolic activity in that dysfunctional myocardial segment. However, these modalities are relatively costly and limited in availability.

The combined systolic-diastolic index, which is calculated as E/(Ea×Sa), is a reliable estimate parameter of increased LV

filling pressure and decreased systolic functions, particularly in patients with regional wall motion abnormalities (E is the early diastolic mitral velocity, Ea is the early diastolic mitral annular velocity, and Sa is the systolic mitral annular velocity) [7–11].

We believe that myocardial recovery may be reflected to improvement of diastolic filling and systolic functions at early days after PPCI. So, in the present study we tested the ability of this combined systolic-diastolic index for differentiating recoverable myocardium or persistent non-viability.

Material and methods

Study Protocol and Population

The study was conducted in Bursa City Hospital (Turkey) between July 2020 and August 2020 and collaborated with Adıyaman Besni State Hospital (Turkey) for study design and data analysis. Eighty-nine patients with acute STEMI were enrolled to this cross-sectional study. Ethics Committee approved the study protocol (Registration number: 2020–5/4) and subjects who met study criteria consented informed.

The study inclusion criteria
- First acute STEMI based on the 2018 European Society of Cardiology (ESC) guideline on Fourth Universal Definition of Myocardial Infarction Guidelines [12].
- The onset of symptoms <12 hours.

The study exclusion criteria
- Patients with unsuccessful reperfusion (Thrombolysis in myocardial infarction (TIMI) score < III).
- Any complication during PPCI or requiring re-PCI during follow-up.
- Presence of pathological q/Q wave in admission electrocardiogram.
- History of previous coronary intervention.
- Use of loop diuretics during follow-up.
- Presence of previous MI, heart failure, cardiomyopathy, dysrhythmia (included atrial fibrillation) or any valvulopathy, which is more than mild.

Angiographic Procedure

The femoral or radial approach was used for coronary angiography and PPCI. The patients who needed thrombus aspiration or glycoprotein IIb-IIIa inhibitors infusion excluded from study. All patients received drug-eluting stents. TIMI III flow was achieved in all patients. All patients received medical treatment, including acetylsalicylic acid, P2Y12 inhibitor, beta-blockers, statins, aldosterone antagonists as appropriate, and angiotensin converting enzyme inhibitors or angiotensin receptors blockers according to 2017 ESC guideline on Acute Myocardial Infarction in Patients Presenting with ST-Segment Elevation (Management) Guidelines [13].

Echocardiographic Evaluation

Serial transthoracic echocardiography (TTE) examinations were performed by using GE Vivid S60 system with 2.5 MHz transducer (GE Vingmed Ultrasound AS, Horten, Norway).
- The admission TTE was done immediately after reperfusion (with seen more than 50% resolution in ST segment elevation on ECG in 1 hour after PPCI).
- The second TTE was done at the time of hospital discharge (5±1 days).
- The Third TTE was done at the time of the control examination (30±2 days).

The LV ejection fraction (EF) was calculated by modified Simpson (biplane) method. LV myocardial recovery was defined as an increase more than 10% in LV EF between after PPCI and day 30.

Peak early (E) and late (A) mitral entry velocities were recorded from the apical four-chamber view by pulsed-wave Doppler with the 5-mm sample volume. Tissue Doppler imaging recordings, Sa, Ea, and Aa values were recorded from the medial and lateral annulus in an apical four-chamber view and taken average of at least 3 cardiac cycles. $E/(Ea \times Sa)$ index value was calculated and presented as the arithmetic mean of the lateral and medial Ea and Sa velocities.

Statistical Analysis

The normality was analyzed by The Kolmogorov–Smirnov test. According to the normality pattern, continuous variables were presented as mean±standard deviation, or median and interquartile range. Student's T test was used when the assumption of normal distribution was met, and Mann–Whitney U test was used when normal distribution was not obtained. Categorical variables were compared by using the Chi-square test and the results were presented as percentages. One-way repeated ANOVA was used in terms of echocardiographic parameters for each group. Additionally, post-hoc test was applied to determine the groups that are significant. To assess the association between $E/(Ea \times Sa)$ index and myocardial recovery, two categories were defined according to whether there was a 10% improvement in EF. The effects of NT pro-BNP, creatinine, $E/(Ea \times Sa)$ index, high sensitive C reactive protein (Hs-CRP), door to balloon time, and age on myocardial recovery were determined with logistic regression analysis. The significant P-value was <0.05. SPSS 26.0 Statistical Package Software was used to perform all data analyses.

Results

Eighty-nine patients were evaluated for the study. Twelve patients with STEMI were excluded from initial study population (One patient dead, 5 patient had history of previous MI, 3 patients had history of previous PCI, 1 patient had missing data, 2 patients were not reached for follow up). The data of the remaining 77 patients were analyzed.

Table 1. Baseline characteristics and laboratory findings of the study patients

Variables	Patients with myocardial stunning (Group 1, n=55, 71.4%)	Patients with non viability (Group 2, n=22, 28.6%)	p value
Age (years)	56.8±9.5	60±13.1	0.24
Sex (n, %) females	10 (18.1)	5 (22.7)	0.53
Hypertension, n (%)	21 (38.1)	7 (31.8)	0.66
Dyslipidemia, n (%)	5 (9)	3 (13.6)	0.57
DM, n (%)	20 (36.3)	5 (22.7)	0.22
Smoker, n (%)	27 (49)	13 (59.1)	0.47
Body mass index (kg/m²)	23.9±2.4	24.7±3.5	0.88
Glucose (mg/dl)	174±43	153±44	0.10
Creatinine (mg/dl) Admission Control	0.83±0.2 0.93±0.2	0.98±0.3 1.08±0.3	0.034 0.018
Triglyceride (mg/dl)	171±92	143±87	0.23
LDL (mg/dl)	118±36	126±33	0.36
HDL (mg/dl)	37.9±18	37.2±8	0.87
TSH (µIU/mL)	1.73±1.3	1.89±1.3	0.64
Na (mmol/L)	137±3.6	138±3	0.37
K (mmol/L)	4.1±0.4	4.0±0.5	0.49
AST (U/L)	27±11	31±6	0.62
ALT (U/L)	24±7	26±9	0.42
Hs-CRP (nmol/L) Admission Control	7.7±1.9 3.45±0.9	7.1±1.6 5.2±0.6	0.75 0.15
NTproBNP (µmol/L) Admission Control	677±95 610±87	678±67 2235±564	0.99 0.026
Leukocyte (10⁹/L)	10.9±2.5	11.6±3.8	0.37
Hemoglobin (g/dl)	13.6±1.7	12.9±1.6	0.51
Platelet (10⁹/L)	276±77	259±72	0.38

DM: Diabetes mellitus, LDL: Light density lipoprotein, HDL: High density lipoprotein, TSH: Thyroid-stimulating hormone, Na: Sodium, K: Potassium, AST: aspartate aminotransferase, ALT: alanine aminotransferase, HsCRP: High sensitive C reactive protein, Admission: 1 hour after primary percutaneous intervention, Control: 30±2 days after admission.

Table 2. The angiographic characteristics of study groups

Variables	Patients with myocardial stunning (Group 1, N=55, 71.4%)	Patients with Non viability (Group 2, N=22, 28.6%)	p value
Stent length (mm)	28.5±11.8	27.1±9.9	0.63
Stent diameter (mm)	2.93±0.3	2.82±0.2	0.13
MI territory Anterior MI, n (%) Non-anterior MI, n (%)	23 (41.8) 32 (58.2)	9 (41) 13 (59)	0.12 0.94
Door-to-balloon time (min)	38.5±17	41.5±16	0.86
IRA LAD, n (%) Non-LAD, n (%)	23 (41.8) 32 (58.2)	9 (41) 13 (59)	0.12 0.94

MI: Myocardial Infarction, IRA: Infarct related artery, LAD: Left anterior descending, Min: Minute.

Study patients were categorized into two groups according to LV EF improvement compared to EF, which detected at first or second TTE examination at 1-month follow up. Patients with improvement in EF >10% during follow-up compared to the basal echocardiographic study who considered to have stunning (Group I or transient stunning group) were 55 (71.4%) while the other patients without improvement of EF were 22 (28.6%) (Group II or permanent non-viability group).

Baseline and Follow-Up Characteristics

Baseline demographic and clinical characteristics of study populations are presented in table 1. In brief, there was no found significant difference between both groups regarding the risk factors of coronary artery disease (including diabetes mellitus, hypertension, hyperlipidemia and smoking). Creatinine level was significantly higher in non-viability group than stunning group at baseline (0.98±0.3 vs 0.83±0.2 mg/dl, p=0.034) and at 1 month (1.08±0.3 vs 0.93±0.2 mg/dl, p=0.018). NT pro-BNP was significantly higher in non-viability group compared to stunning group at follow up.

Angiographic Characteristics

No significant difference was observed between the groups regarding stent length and diameter, myocardial infarction territory and door to balloon time. The angiographic features were summarized in table 2.

Echocardiographic Characteristics

Regarding the baseline echocardiographic characteristics, peak E (Admission), E/A ratio (Admission), and E/Ea ratio (Admission and 1 month) were significantly higher in the non-viability group. The results are shown in table 3.

The Combined Systolic-Diastolic Index

The E/(Ea×Sa) index value in both groups is presented in table 3. The E/(Ea×Sa) index (Predischarge and 1-month values) were significantly higher in the non-viability than in stunning group. On the other hand, in the stunning group, the index before discharge from the hospital decreased by 26% compared to the early period index after PPCI (Admission), while this decrease was observed by 15% in the non-viability group. The percentage of change of E/(Ea×Sa) index at hospitalization period (5±1 days) was compared between both groups and found statistically significant (p=0.033).
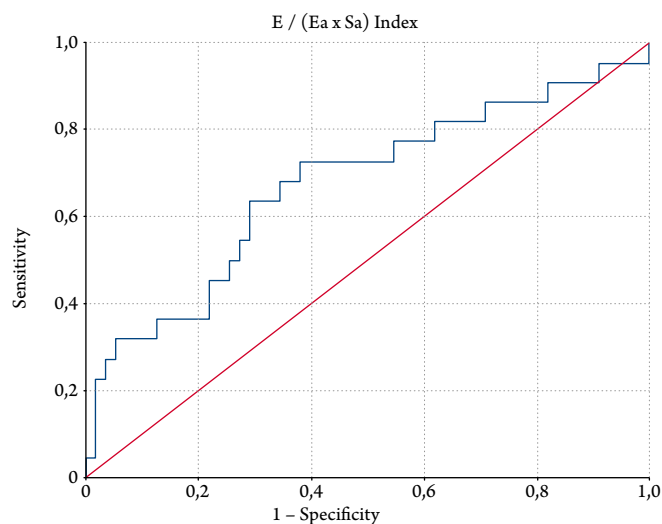
Identification of the Predictors for Myocardial Recovery

Multivariable logistic regression analysis to assess factors predictive of myocardial recovery included NT-proBNP, creatinine, baseline E/(Ea×Sa) index, Hs-CRP, door to balloon

Table 3. Comparison of echocardiographic parameters of the study patients

Variables	Patients with myocardial stunning (Group 1, n=55, 71.4%)	Patients with non viability (Group 2, n=22, 28.6%)	p* value
LV EF (%)			
Admission	44.50±6.6	43.1±0.4	0.45
Predischarge	44.58±6.8	42.95±9.3	0.40
Control	48.78±6.1	39.31±8.1	0.01
p** value	0.02[a,b]	0.03[a]	-
Mitral E velocity#			
Admission	72.39±21.32	85.86±13.76	0.01
Predischarge	87.58±17.84	90.14±18.55	0.33
Control	76.30±16.38	80.04±11.83	0.27
p** value	0.01[b,c]	0.02[b]	-
Mitral A velocity#			
Admission	82.80±15.62	84.54±21.66	0.69
Predischarge	83.53±16.50	80.86±20.70	0.55
Control	82.60±16.41	82.36±20.33	0.95
p** value	0.75	0.30	-
Mitral E/A			
Admission	0.90±0.35	1.07±0.27	0.04
Predischarge	1.03±0.37	1.08±0.35	0.56
Control	0.97±0.34	1.04±0.41	0.43
p** value	0.04[c]	0.28	-
Mitral Eᵃ velocity#			
Admission	9.20±2.1	9.07±1.5	0.79
Predischarge	9.76±2.3	9.76±2.3	0.31
Control	10.7±1.9	10.7±1.9	0.64
p** value	0.01[a,b]	0.02[a,b]	-
Mitral Aᵃ velocity#			
Admission	11.1±1.7	11.5±2.1	0.34
Predischarge	11.5±2.1	10.6±2.1	0.11
Control	12.0±1.7	11.5±2.1	0.24
p** value	0.13	0.29	-
Mitral Sᵃ velocity#			
Admission	10.2±1.8	10.5±2.1	0.48
Predischarge	10.4±2.0	10.2±2.2	0.72
Control	10.9±1.7	11.0±1.9	0.98
p** value	0.04[a]	0.03[b]	-
LV E/Ea			
Admission	7.9±1.8	9.8±2.6	0.01
Predischarge	8.8±1.7	9.2±2.3	0.46
Control	8.1±1.8	9.1±2.5	0.04
p** value	0.03[b,c]	0.10	-
E/(Ea×Sa) index			
Admission	1.83±0.63	2.02±0.92	0.30
Predischarge	1.25±0.43	1.61±0.64	0.01
Control	1.14±0.21	1.33±0.25	0.01
p** value	0.01[a,c]	0.01[a,c]	-

LV; Left ventricle, EF; ejection fraction, Admission: 1 hour after primary percutaneous intervention, Predischarge: 5±1 days after admission. Control: 30±2 days after admission. #; (cm/s), *; p values; Independent Samples-T Test, ***; p values; repeated measures ANOVA. a: p<0.05: Admission vs. Control; b: p<0.05: Predischarge vs. Control; c: p<0.05: Admission vs. Predischarge.

Figure 1. Roc curve showed that the cutoff value of E/(Ea×Sa) index is 1.29 with 73% of sensitivity and 61% of specificity

AUC: 0.71, p=0.01, CI: 0.54-0.89

time, and age showed that E/(Ea × Sa) index was the only predictive factor for myocardial recovery (OR: 0.91, 95% CI (0.83–0.98), P=0.001) (tab. 4). Roc curve showed that the cutoff value of E/(Ea x Sa) index is 1.29 with 73% of sensitivity and 61% of specificity (AUC: 0.71, p=0.01, CI: 0.54–0.89) (fig. 1).

Discussion

Our findings suggest that persistent LV dysfunction and transient myocardial stunning can be distinguished in the early period after STEMI. Furthermore, E/(Ea×Sa) index value to be a strong predictor of functional recovery; the odds of full recovery decreases as E/(Ea×Sa) index value increases.

Myocardial stunning is typically defined as transient myocardial dysfunction in areas of restored coronary perfusion after STEMI [3]. Acute occlusion of a coronary artery rapidly impairs contractile function and may result in myocardial necrosis depending on the occlusion duration [14–16]. Previous research demonstrated the diastolic dysfunction of LV during myocardial stunning.

Table 4. Identification of the predictors for myocardial recovery with multiple regression analysis

Variables	OR (CI, 95%)	p value
Age	1.03 (0.99–1.08)	0.08
E/(Ea x Sa) index	0.91 (0.83–0.98)	0.001
Creatinine	1.14 (1.06–1.23)	0.32
NT-proBNP	1.01 (0.94–1.07)	0.70
Hs-CRP	1.11 (0.97–1.19)	0.09
Door to balloon time	1.05 (0.97–1.11)	0.65

Hs-CRP: High sensitive C reactive protein, NT-proBNP: N-terminal pro-b-type natriuretic peptide.

Besides, Mornos C. et al. demonstrated that E/(Ea×Sa) index is useful and reliable parameter to assess the LV filling pressure, particularly in patients with regional wall motion abnormalities [7]. And also, it is more logical to evaluate diastolic (relaxation) and systolic (contraction) functions together as part of the ongoing cycle. So, in this present study, we assessed the early predictive value of E/(Ea×Sa) index for improvements in LV functions after STEMI.

The substantial recovery of systolic function that occurred within 30 days after MI was the endpoint of our study; 71.4% of patients had improvement of LV EF and 28.6% had no recovery of systolic function (48.78±6.1 vs. 39.31±8.1%, p=0.01). And, there was no statistically significant difference in term of LV EF in both groups before discharge from the hospital (44.58±6.8 vs. 42.95±9.3%, p=0.40). This extent of systolic recovery in our study population appears to be consistent with that reported in most previous studies [17, 18].

Patients who did not have myocardial recovery had significantly higher E/(Ea×Sa) index value pattern during entire follow up compared to patients who had improvement of LV EF. The one of the most striking findings of our study is that there was, on average, decrease of 26% in the E/(E×Sa) index value compared to the initial TTE measurement in transient stunning group (within 5 days). This dramatic change was seen, on average, of 15% in non-viability group. Likewise, we did observe that E/(Ea×Sa) index was higher level in non-viability group (1.33±0.25 vs. 1.14±0.21, p=0.01), similar to the predischarge measures. The literature suggests that most systolic myocardial recovery occurs within the first 2 weeks after MI, but the available data do not allow further discrimination of the time course of recovery [19–21]. So, our findings may have important implications about the prognostic value of clinical assessment of LV function early in the course of STEMI.

At 1 month, we found that patients in the stunning group had a significantly better LV diastolic function, reflecting in a lower ratio of E/Ea. We found that other conventional echocardiographic measurements including mitral E velocity, mitral E/A ratio had shown differences between groups. But they were less linked to improvement in ventricular function. Our analysis demonstrated that the diagnostic accuracy of the E/(Ea×Sa) index in predicting functional myocardial recovery after PPCI is more sensitive and specific than that of traditional diastolic parameters including E/Ea ratio and Sa wave (the E/(Ea×Sa) index = 73% of sensitivity and 61% of specificity (AUC: 0.71, p=0.01, CI: 0.54–0.89), the E/Ea ratio = 64% of sensitivity and 41% of specificity (AUC=0.67, p=0.03, CI: 0.61–0.74), Sa wave = 53% of sensitivity and 56% of specificity (AUC=0.65, p=0.03,

CI: 0.57–0.73)). Similar results were demonstrated by Lam W. which evaluating LV suction functions in the dobutamine stress echocardiography -based study [5]. In contrast, Faustino M. et al. reported that E/Ea ratio was an independent predictor of myocardial recovery in patients with MI [6]. Consequently, our findings suggest that the severity of the E/(Ea × Sa) index and its ratio of change in early period was superior to other echocardiographic parameters in predicting recovery of LV function at 1 month after STEMI and PPCI. The patient with lower decrease of initial E/(Ea×Sa) index (within 5 days) and the patients with predischarge E/(Ea×Sa) index >1.29 presented with poor functional recovery after 1 month following STEMI.

Additionally, we did not find differences in the initial examination of any inflammatory response (increased white blood cell counts and high level of Hs-CRP and plasma glucose) related to functional recovery in both groups. It is not surprising that control NT-proBNP level compared to admission was higher in non-viability group. The increased NT-proBNP may play a role in why improvement of EF was lesser in this group. Likewise, creatinine level was higher in non-viability group than transient stunning group. But it may be arguable that creatinine level at admission was also significantly higher in this group. Nevertheless, creatinine levels were not found to be associated with E/(Ea×Sa) index and improvement of LV EF. So, we believe that these data did not reflect any selection bias against functional recovery.

This study has some strengths and limitations that are worth noting. One of strengths is that contrary to other imaging modalities, no contrast agent or inotropic agent was used. Another one is that predicting functional recovery occurs relatively early. And also, we believe that our results can be used for the risk stratification of the patient following STEMI and PPCI. First limitation, the all differences between stunning and non-viability groups were assessed by echocardiography and were limited by 30 days. Thus, no other imaging modality was used to reveal the ultimate extent of functional recovery. Second, PPCI based successful reperfusion therapy was mandated by the study protocol. Therefore, the data can only be interpreted for this patient group. Third, the power of study is under limitation of relatively small sample size. On the other hand, our results could be pioneer for larger studies.

In conclusion, our findings suggest that the combined systolic-diastolic ([E/(Ea×Sa)]) index, is related to recovery of ventricular function after STEMI and could be a more important predictor of functional recovery than other early echocardiographic measures. And, using this index in early period for prognostic assessment may be the ideal.

Informed consent

The study protocol was approved with registration number of 2020–5/4 by the Bursa City Hospital ethics committee.

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