Electromechanical Activation Time in the Prediction of Discharge Outcomes in Patients Hospitalized with Acute Heart Failure Syndrome

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Abstract

Objective Left ventricular systolic time intervals, including pre-ejection period (PEP), ejection time (ET), and their ratio (PEP/ET), is determined by systolic and diastolic function and ventriculo-arterial coupling. We investigated the usefulness of the electromechanical activation time [(EMAT) PEP minus isovolumic contraction time] in the prediction of cardiac mortality or re-hospitalization for heart failure in patients with the acute heart failure syndrome (AHFS).

Patients and Methods A total of 45 patients (71.9±16.1 years old) hospitalized for AHFS were enrolled. Systolic time intervals and EMAT normalized by cardiac cycle length (%) were measured separately by separate automated acoustic devices. All parameters were assessed within 24 hours of admission, before discharge, and 2 weeks after discharge.

Results During a mean follow-up of 242±156 days, 20 patients (44%) incurred adverse cardiovascular events including 18 re-hospitalizations for heart failure and 2 cardiovascular deaths. Using uni-variate Cox regression analysis, at admission %EMAT and %PEP, pre-discharge %EMAT, and post-discharge %EMAT significantly predicted post-discharge cardiovascular events with hazard ratios and 95% confidence intervals of 1.75(1.13-2.70), 1.67(1.02-2.70), 1.87 (1.10-3.17) and 2.50 (1.58-3.97) per 1-SD increment, respectively. The predictions remained significant after adjustment for age, sex, left ventricular ejection fraction, E/E' by Doppler echocardiography, and serum N-terminal pro-brain natriuretic peptide.

Conclusion EMAT measured during the hospitalization course is useful in the prediction of cardiovascular outcomes in patients with AHFS independent of left ventricular ejection fraction, E/E', and serum N-terminal pro-brain natriuretic peptide.

Key words: systolic time intervals, electromechanical activation time, acute decompensated heart failure, prognosis

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Introduction

Acute heart failure syndrome (AHFS) indicates gradual or rapid change in heart failure signs and symptoms resulting in a need for urgent therapy (1). The majority of patients appear to respond well to initial medical therapies (1). How-

ever, post-discharge mortality and re-hospitalization rates are high and may reach 10% to 20% and 20% to 30%, respectively, within 3 to 6 months (2). Thus, prognostic stratification of AHFS patients before or soon after discharge is desirable to optimize individual treatment and to reduce the overall health care burden related to heart failure.

In patients hospitalized due to AHFS, low systolic blood

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pressure on admission, renal insufficiency, hyponatremia, and use of positive inotropic therapy are associated with in-hospital and short term outcomes (3-5). In both chronic heart failure and patients hospitalized due to AHFS, plasma N-terminal pro-brain natriuretic peptide (NT-proBNP) is a powerful marker of short-term and long-term mortality and heart failure hospitalization, independent of conventional predictors (6).

Left ventricular (LV) systolic time intervals, including pre-ejection period (PEP), ejection time (ET), and their ratio (PEP/ET), is determined by the LV systolic and diastolic function and ventriculo-arterial coupling (7, 8). The electromechanical activation time (EMAT, the interval from beginning of electrical activation of LV to the onset of the first heart sound, encompassing both electromechanical delay and the portion of ventricular contraction from onset to mitral valve closure) constitutes the initial portion of PEP (9), and is useful in the detection of LV systolic dysfunction and resolving ambiguous values of B-type natriuretic peptide levels in patients with suspected heart failure (10, 11). However, the role of EMAT in the risk stratification of AHFS remains to be determined. Therefore, the goal of the present study was to evaluate the usefulness of EMAT in the prediction of post-discharge outcomes independent of common clinical predictors for patients hospitalized due to AHFS.

Methods

Participants and study design

AHFS was defined as either new-onset heart failure or decompensation of chronic, established heart failure with symptoms sufficient to warrant hospitalization. Hospitalized AHFS patients were assessed by an experienced cardiologist for ascertainment of the diagnosis and enrollment of the present study. Patients with atrial fibrillation, significant aortic valvular disease, or electrocardiographic left or right bundle branch block were not enrolled. The study protocol adhered to the principles of the Declaration of Helsinki and was approved by the Institutional Review Board at Taipei Veterans General Hospital. Informed consent was obtained from all patients.

Systolic time intervals and EMAT were performed within 24 hours after admission, before discharge, and two weeks after discharge. A comprehensive echocardiographic examination and measurement of serum NT-proBNP were also performed before discharge. NT-proBNP was measured by an enzyme-linked immunosorbent assay micro-titer plate (Roche Diagnostics, Basel, Switzerland) (7, 12).

Systolic time intervals were measured by an automated device (VP-2000, Colin Corporation, Komaki, Japan). Details of the measurement had been described in our previous works (7, 8). Briefly, the device performed electrocardiography, phonocardiography, and pulse volume recording on four extremities (ankles and arms). Pulse volume recording at cuff pressure of 60 mmHg was recorded for 10 seconds.

The beat-by-beat interval of the initial deflection of electrocardiographic Q wave to the first high frequency vibration of the aortic component of the second heart sound interval (QS2) and the interval of the beginning upstroke to the diastolic notch of the pulse volume trace of the right arm (ET) were determined. PEP was calculated by subtracting ET from QS2 (8). ET and PEP were the averages of around 10 beats.

After the measurement of systolic time intervals, a 10-second audio-electrocardiographic tracing was obtained and algorithmically analyzed using the Audicor device (Inovise Medical, Inc., Portland, OR, USA) (11). EMAT was determined by measuring the interval from the initial deflection of the electrocardiographic Q wave to the peak component of the first heart sound complex.

To correct for heart rate, PEP, ET, and EMAT were divided by the R-R interval to determine the percent of time in the cardiac cycle occupied by each interval and yield %PEP, %ET, and %EMAT, respectively (11). All measurements of the systolic time intervals and EMAT were obtained automatically from the two devices and the operators who performed the examinations were blinded to the other clinical data.

Doppler and M-mode echocardiographic examination was performed using a multifrequency transducer incorporated in a SONOS 5500 Echocardiograph (Hewlett Packard, Inc., Agilent Technologies, Andover, MA, USA) according to the American Society of Echocardiography criteria. LV ejection fraction (EF) was calculated using the M-mode measurements. Stroke volume (SV) was measured by pulse wave Doppler echocardiography. From the mitral inflow velocity tracings, peak velocity (E) and deceleration time (EDT) of the early inflow wave, and peak velocity (A) of late inflow wave at atrial contraction were measured. E/E' was calculated as the ratio of E and early peak (E') of mitral annulus velocity obtained from the apical 4-chamber view in the septal and lateral mitral valve annulus. The acquired values were averaged (13). The measurements were performed by an experienced investigator who was blinded to the other clinical data.

Ventriculo-arterial coupling was assessed using the framework of the ratio of effective arterial elastance (E_a) to end-systolic elastance (E_{es}) (8). E_{es} was estimated with a previously proposed single-beat method employing brachial systolic blood pressure (SBP) and diastolic blood pressure (DBP), SV, EF, and an estimated normalized ventricular elastance at arterial end-diastole [$E(N_d)$]: $E_{es} = [DBP - (E(N_d) * SBP * 0.9)] / [E(N_d) * SV]$, where $E(N_d)$ was estimated from a group-averaged value adjusted for individual contractile/loading effects (14). E_a was the ratio of LV end-systolic blood pressure (P_{es}), which is approximated to value of $SBP \times 2/3 + DBP \times 1/3$, to the value of SV (15).

After admission, all patients were stabilized by appropriate medical therapy and were discharged. All patients met the following discharge criteria: optimal volume status achieved, transition from intravenous to oral diuretic com-

pleted, free from oxygen support, and patient education completed. They were followed up 2 weeks after discharge and then monthly at outpatient clinics or by telephone consultations to check if there were any adverse cardiovascular events including re-hospitalization for heart failure, non-fatal myocardial infarction, non-fatal stroke, and cardiovascular death. These adverse cardiovascular events were confirmed by review of medical records. The period of event-free survival was defined as the interval between the pre-discharge hemodynamic survey and the date of adverse events or the end of follow-up.

Statistical analysis

Data are presented as mean values and standard deviations for normally distributed continuous variables, medians and interquartile ranges for skewed data, and proportions for categorical variables. Differences between continuous values were assessed using an unpaired 2-tailed t test for normally distributed continuous variables, the Mann-Whitney rank-sum test for skewed variables, and chi-square testing for nominal variables. The event-free survival curves were plotted via Kaplan-Meier method with statistical significance examined by the log-rank test. Cox regression analysis was used to identify the predictors for future cardiovascular events. All statistical significances were set at $p < 0.05$ and all statistical analyses were carried out by SPSS ver17.0 analytical software (SPSS Inc., Chicago, IL, USA).

Results

We enrolled 45 patients (89% male; mean age 71.9 years; range 24 to 92; 37.8% with LV EF $\geq 50\%$; 60% de novo heart failure hospitalization). During a follow-up of 242 ± 156 days, 20 patients incurred adverse cardiovascular events, including 18 re-hospitalizations for heart failure and 2 cardiovascular deaths. Their baseline characteristics and pre-discharge echocardiographic parameters were similar except that the patients with post-discharge cardiovascular events had significantly greater E/E' and higher levels of NT-proBNP as compared with those without events (Table 1).

Serial measurements of systolic time intervals and %EMAT at admission, before discharge, and 2 weeks after discharge are presented in Table 2. %PEP was significantly longer in patients with than without events at admission but not before or after discharge. In contrast, %EMAT was significantly longer in patients with than without events at admission, before and after discharge.

By Cox regression analysis, pre-discharge log-transformed value of NT-ProBNP levels significantly predicted post-discharge cardiovascular events with hazard ratios and 95% confidence intervals of 2.19 (1.24-3.84) per 1-SD increment. Similarly, at-admission %PEP, at-admission %EMAT, pre-discharge %EMAT, and post-discharge %EMAT significantly predicted post-discharge cardiovascular events with hazard ratios and 95% confidence intervals of 1.67 (1.02-2.70), 1.75 (1.13-2.70), 1.87 (1.10-3.17), and 2.50 (1.58-

3.97) per 1-SD increment, respectively. After adjustment for age, Sex, LV EF, E/E' and NT-proBNP, at-admission, pre-discharge and post-discharge %EMAT remained significant predictors for post-discharge cardiovascular events (Table 3). In contrast, NT-proBNP level was not a significant predictor in the multivariate analysis after adjustment for age, sex, LV EF, E/E' and at admission, pre-discharge and post-discharge %EMAT with hazard ratios and 95% confidence intervals of 1.86 (0.88-3.92), 1.97 (0.89-4.36), and 2.15 (0.97-4.76) per 1-SD increment, respectively. At a cut-point of 15 (16), Kaplan-Myer survival analysis showed that both high pre-discharge %EMAT (Fig. 1A) and high post-discharge %EMAT (Fig. 1B) significantly predicted cardiovascular events. The positive and negative predictive values of pre-discharge %EMAT at a cut-point of 15 for cardiovascular events were 66.67% and 63.64%, respectively. The positive and negative predictive values of post-discharge %EMAT at a cut-point of 15 for cardiovascular events were 75% and 72.4%, respectively. The specificities of the pre-discharge and post-discharge %EMAT were both 84%.

Correlation coefficients of %EMAT, %PEP, %ET, and PEP/ET with LV and arterial function parameters and log-transformed NT-proBNP levels are shown in Table 4. All 4 time-interval parameters were significantly correlated with LV EF. In addition, %EMAT significantly was correlated with Ea and Ea/Ees, whereas PEP/ET was significantly correlated with Ea/Ees. Furthermore, only %EMAT was significantly correlated with NT-proBNP levels.

Discussion

To our knowledge, this study was the first attempt to investigate the usefulness of time-interval related LV functional parameters, including the conventional systolic time intervals and EMAT in the prediction of discharge outcomes in patients hospitalized with AHFS. Our preliminary but encouraging results showed that none of the conventional systolic time intervals parameters independently predicted outcomes in AHFS patients. In contrast, values of at-admission, pre-discharge and post-discharge %EMAT were independently predictive of cardiovascular events in AHFS patients after discharge.

Systolic time intervals

Systolic time intervals are useful in the quantitative assessment of myocardial performance in patients with severe heart failure and ischemic heart disease (17), and after cardiac resynchronization therapy (18). It is well-established that PEP is prolonged and ET is shortened in patients with congestive heart failure, and PEP/ET correlates with LV EF (19). We further extended that PEP is prolonged and PEP/ET is increased in patients with diastolic heart failure (8). In addition, PEP/ET is useful in the identification of heart failure patients with abnormal ventriculo-arterial coupling (8). Despite the good correlation between systolic time intervals and LV dysfunction, there is considerable overlap

Table 1. In-hospital Characteristics of Patients with Acute Heart Failure according to Follow-up Status after Discharge

Characteristics	With events (n = 20)	No events (n = 25)	p value
Age, years	72.6 ± 15.3	71.3 ± 17.1	0.803
Male, %	90.0	88.0	0.608
Medical history			
Hypertension, %	80.0	84.0	0.513
Diabetes, %	50.0	32.0	0.221
Coronary artery disease, %	55.0	52.0	0.841
De novo heart failure, %	60.0	60.0	1
NYHA functional classification at admission	3.2 ± 0.7	3.2 ± 0.7	0.655
QRS duration on ECG, ms	111 ± 30	109 ± 28	0.878
Physical findings at admission			
Body mass index, kg/m ²	23.5 ± 4.8	26.8 ± 6.6	0.064
Systolic blood pressure, mmHg	130.0 ± 29.1	131.7 ± 19.1	0.855
Diastolic blood pressure, mmHg	71.9 ± 15.3	70.3 ± 9.2	0.661
Heart rate, beats/min	81.4 ± 12.5	76.1 ± 12.5	0.176
Use of intravenous medications			
Inotropic agents, %	35.0	36.0	0.944
Vasodilators, %	80.0	84.0	0.513
Predischarge NT-proBNP, pg/mL			
median	4464	1572	0.014*
Inter-quartile range	2494-12221	476-3808	
Predischarge echocardiographic findings			
LA, cm	4.2 ± 0.5	4.1 ± 0.7	0.646
LVIDD, cm	5.9 ± 1.0	6.0 ± 1.0	0.702
LVM, g	269 ± 87	263 ± 86	0.793
LVMI, g/m ²	163 ± 52	150 ± 51	0.419
LV EF, %	44.0 ± 13.5	46.7 ± 16.6	0.560
LV EF <50%	65.0%	60.0%	0.731
Peak E-wave velocity, cm/s	101.5 ± 39.0	81.8 ± 25.4	0.059
Peak A-wave velocity, cm/s	79.3 ± 19.6	79.5 ± 28.2	0.978
E/A ratio	1.36 ± 0.80	1.23 ± 0.90	0.711
EDT, ms	193.8 ± 54.1	203.8 ± 79.2	0.633
E/E'	15.3 ± 6.5	11.1 ± 2.4	0.011
Ea, mmHg/mL	2.27	2.22	0.827
Ees, mmHg/mL	1.84 ± 0.83	2.01 ± 1.12	0.595
Ea/Ees	1.52 ± 0.98	1.66 ± 1.57	0.723
NYHA functional classification at discharge	1.2 ± 0.4	1.3 ± 0.4	0.940
Medications at discharge			
Beta-blocker, %	45.0	36.0	0.540
ACEI or ARB, %	85.0	68.0	0.187
Nitrate, %	75.0	60.0	0.289
Spironolactone, %	56	50	0.687
Aspirin or clopidogrel, %	60	60	1
Statins, %	35.0	36.0	0.944

* statistical significance by Mann-Whitney test.

ECG = electrocardiogram; A = peak velocity of mitral inflow at atrial contraction; ACE = angiotensin-converting enzyme; ARB = angiotensin II-receptor blocker; E = peak velocity of early mitral inflow; EDT = E wave deceleration time; E/A = ratio of peak E over peak A; E'/E = peak velocity of early mitral annulus velocity over E; Ea = effective arterial elastance; Ea/Ees = ratio of Ea over Ees; Ees = left ventricular end-systolic elastance; eGFR = estimated glomerular filtration rate; LA = left atrium dimension; LV EF = left ventricular ejection fraction; LVIDD = left ventricular internal dimension at end-diastole; LVIDS = left ventricular internal dimension at end-systole; LVM = left ventricular mass; LVMI = left ventricular mass index; NT-proBNP = N-terminal pro-brain natriuretic peptide; NYHA = New York Heart Association.

in values between individual patients with and without LV dysfunction (9).

Although the systolic time intervals can be used to assess LV function and ventriculo-arterial coupling, the prognostic value in heart failure patients remains to be demonstrated (9, 20, 21). In 38 patients with acute transmural myocardial infarction, mean PEP values on the first and second days of myocardial infarction were significantly longer in patients who died than in the survivors (9). In another 51 patients with acute myocardial infarction, the mean PEP was

elevated on the first day of myocardial infarction but was within normal limits thereafter (21). PEP did not prove useful in predicting outcome because in the 8 patients who died, 3 had short PEP values and 2 patients had a normal PEP (21). The present study reconfirmed the significant correlation of %PEP, %ET and PEP/ET with LV EF, and between PEP/ET and Ea/Ees. %PEP at admission but not on pre- or post-discharge studies was significantly prolonged in patients with post-discharge events as compared with those without events (Table 2). Although %PEP at admission sig-

Table 2. Systolic Time Intervals and Electromechanical Activation Time Related Variables at Admission, PredischARGE, and 2-Week after Discharge, and the Univariate Hazard Ratios and 95% Confidence Intervals Per One-standard Deviation for Event Prediction

Variables	With events (n = 20)	No events (n = 25)	Hazard ratio (95% CI)	p values
At admission				
%EMAT	15.8 ± 4.1**	12.6 ± 3.1	1.75 (1.13-2.70)	0.012
%PEP	15.7 ± 4.0*	13.4 ± 4.2	1.67 (1.02-2.70)	0.04
%ET	33.7 ± 3.5	32.8 ± 5.2	0.62 (0.72-1.72)	0.623
PEP/ET	0.48 ± 0.14	0.42 ± 0.15	1.44 (0.87-2.34)	0.157
PredischARGE				
%EMAT	14.1 ± 4.1*	12.8 ± 2.8	1.87 (1.10-3.17)	0.021
%PEP	13.5 ± 3.6	13.2 ± 3.8	1.05 (0.70-1.60)	0.819
%ET	30.6 ± 5.0	32.6 ± 4.0	0.88 (0.59-1.31)	0.517
PEP/ET	0.45 ± 0.16	0.41 ± 0.13	1.13 (0.74-1.74)	0.570
After discharge				
%EMAT	15.4 ± 4.3**	12.6 ± 2.6	2.50 (1.58-3.97)	<0.001
%PEP	14.3 ± 4.0	13.3 ± 3.4	1.21 (0.78-1.87)	0.392
%ET	31.3 ± 4.9	33.5 ± 7.1	0.87 (0.50-1.49)	0.867
PEP/ET	0.46 ± 0.15	0.41 ± 0.12	1.16 (0.76-1.79)	0.497

*: p<0.05 as compared with patients without event.

**: p<0.01 as compared with patients without event.

%EMAT = normalized electromechanical activation time; %PEP = normalized pre-ejection period; %ET = normalized ejection time; PEP/ET = ratio of PEP over ET.

Table 3. Multi-variate Hazard Ratios and 95% Confidence Intervals Per One-standard Deviation for Systolic Time Intervals and EMAT in the Prediction of Cardiovascular Events

Variables	Hazard ratio (95% CI)	p value
At admission		
%EMAT	2.27 (1.21-4.28)	0.011
%PEP	2.07 (0.98-4.43)	1.10
Before discharge		
%EMAT	1.91 (1.06-3.64)	0.041
After discharge		
%EMAT	2.91 (1.70-5.01)	<0.001

Variables were adjusted for age, sex, LV EF, E/E' and NT-proBNP.

%EMAT = normalized electromechanical activation time; %PEP = normalized pre-ejection period; %ET = normalized ejection time; PEP/ET = ratio of PEP over ET.

nificantly predicted events, the significance disappeared after multivariate adjustment.

EMAT

EMAT (Q-S1 interval) and the subsequent isovolumic contraction time constitute the PEP. PEP measures the amount of time that LV requires to generate sufficient force to first close the mitral valve (EMAT) and then open the aortic valve (isovolumic contraction time) (22). In patients with myocardial infarction and heart failure with impaired myocardial function, both EMAT and isovolumic contraction time are prolonged (9, 20). However, PEP is a preload-dependent parameter (23). In subjects with normal heart function, reduction in preload and LV volume results in prolongation of PEP, which is mainly due to the prolonged isovolumic contraction time resulting from decreased LV filling pressure and increased pressure gradient across the aortic valve (24). Conversely, an increase in preload shortens PEP because of the decreased trans-aortic pressure gradient and

the increased contractility of the heart according to Starling's law. In contrast, patients with heart failure having raised LV filling pressures show a decrease in PEP and PEP/ET in response to preload reduction (23). On the other hand, recent studies demonstrated that %EMAT was not associated with LV end diastolic pressure (16, 25), indicating less preload sensitivity with %EMAT.

An abnormal %EMAT (≥ 15) had 44% sensitivity, 94% specificity, and a 7.0 likelihood ratio for the identification of patients with LV dysfunction (LV end-diastolic pressure >15 mmHg and LV EF $<50\%$) (16). In addition, in patients with a grey-zone brain natriuretic peptide levels (100-500 pg/mL), an abnormal %EMAT substantially improved the prediction for LV dysfunction (16). In the present study, %EMAT was significantly correlated with LV EF and Ea but not with E/E'. Ea is considered a lumped index of arterial load, including arterial stiffness (26). In 72 stable heart failure patients with an averaged LV EF of 53%, elevated arterial stiffness was a risk factor for re-hospitalization or car-

Figure 1. Survival curves for acute heart failure syndrome patients after discharge. Kaplan-Meier survival analysis showed a significantly reduced event-free survival for patients with prolonged pre-discharge (A) or post-discharge (B) %EMAT (>15). EMAT: normalized electromechanical activation time.

Table 4. Correlation Coefficients of Systolic Time Intervals EMAT with Pre-discharge Parameters of Left Ventricular and Arterial Function and NT-proBNP

	EF, %	E/E'	Ea, mmHg/L	Ea/Ees	NT-proBNP, pg/mL
%EMAT	-0.506***	0.124	0.331*	0.311*	0.291*
%PEP	-0.432***	-0.090	0.101	0.309	0.034
%ET	0.355*	-0.016	0.018	-0.296	-0.062
PEP/ET	-0.575***	0.032	0.168	0.410**	0.115

*: $p < 0.05$; **: $p < 0.01$; ***: $p < 0.005$

Ea = effective arterial elastance; Ea/Ees = ratio of Ea over Ees; Ees = left ventricular end-systolic elastance; EF = ejection fraction; E/E' = the ratio of early peak (E) of mitral inflow and early peak (E') of mitral annulus velocity; %EMAT = normalized electromechanical activation time; %ET = normalized ejection time; NT-proBNP = N-terminal pro-brain natriuretic peptide; PEP/ET = ratio of PEP over ET; %PEP = normalized pre-ejection period.

diac death (27). E/E' correlated well with simultaneously estimated pulmonary capillary wedge pressure (13) and LV filling pressure.28 E/E' >15 has been considered to be the best Doppler predictor of increased mean LV diastolic pressure (28). Furthermore, %EMAT but not systolic time intervals was significantly correlated with NT-proBNP levels (Table 4). Therefore, our results may support that %EMAT is sensitive to both LV systolic function and arterial stiffness while insensitive to change of preload, and may be a better predictor of outcome for the discharged AHFS patients than systolic time intervals.

Limitations of the present study

Although the results of the present study were statistically significant and clinically relevant, confirmation in future studies with a sufficiently large number of patients with

clearly defined systolic and diastolic heart failure is required.

Conclusions

Quick measurement of %EMAT by acoustic cardiography during the hospitalization or early after discharge may be useful in the prediction of future cardiovascular events in patients hospitalized for AHFS.

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