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ORIGINAL RESEARCH ARTICLE

Night-time electromechanical activation time, pulsatile hemodynamics, and discharge outcomes in patients with acute heart failure

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Abstract

Aims Both electromechanical activation time (EMAT) and pulsatile hemodynamics measured during the hospitalization course are useful in the prediction of cardiovascular outcomes in patients with acute heart failure syndrome (AHFS). We investigated whether night-time monitoring of EMAT with the ambulatory acoustic cardiography is superior to the measures of pulsatile hemodynamics for prediction of AHFS post-discharge outcomes.

Methods and results A total of 97 patients (71.1 ± 15.4 years old, 81% male, and 73.8% systolic heart failure) hospitalized for AHFS were included. Before discharge, 24 h ambulatory acoustic cardiography and a comprehensive echocardiographic and pulsatile hemodynamic study were performed to assess the mean 24 h, daytime, and night-time EMAT, carotid systolic blood pressure (SBP) and pulse pressure (PP), amplitude of the reflected pressure wave from a decomposed carotid pressure wave (Pb), and carotid–femoral pulse wave velocity (cfPWV), in addition to measurement of N-terminal pro-brain natriuretic peptide (NT-proBNP) levels. During a mean follow-up of 389 ± 281 days, 49 patients (50.5%) experienced events including re-hospitalization for heart failure, myocardial infarction, stroke, or death. Pulsatile hemodynamics, including carotid SBP and PP and Pb, but not cfPWV, and night-time EMAT, but not daytime EMAT, significantly predicted post-discharge events when age and NT-proBNP were accounted for (all $P < 0.05$). In a final model with adjustment for age and NT-proBNP, night-time EMAT, but not Pb, significantly predicted post-discharge events [hazard ratio per 1 SD and 95% confidence intervals: 1.33 (1.05–1.69), $P < 0.05$].

Conclusion Pre-discharge night-time EMAT may be a better predictor for post-discharge adverse events than the measures of the pulsatile hemodynamics in patients with AHFS.

Keywords Night-time EMAT; Acute heart failure

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Introduction

Despite advances in the management of acute heart failure syndrome (AHFS), early post-discharge re-hospitalization and mortality rates remain high.[1] The prognostic value of natriuretic peptides in heart failure is well established, and the pre-discharge N-terminal pro-brain natriuretic peptide (NT-proBNP) levels can be used to predict death or hospital readmission in patients hospitalized because of AHFS.[2] Because pulsatile hemodynamics resulting mainly from arterial stiffening and wave reflection phenomenon are involved in the development and progression of AHFS,[3] measures of the pre-discharge pulsatile hemodynamics may predict the short-term post-discharge cardiovascular outcomes in AHFS patients independently of the pre-discharge NT-proBNP levels.[4]

Acoustic cardiography is a new technology for the automated quantitative assessment of heart sounds and systolic time intervals, such as the electromechanical activation time

(EMAT, defined as the time from Q-wave onset to the peak first heart sound).[5] EMAT is associated with preload, afterload, left ventricular contractility, and the ratio of effective arterial elastance (Ea) to ventricular end-systolic elastance (Ees)[6] and is therefore considered as a composite index of cardiac performance and ventriculo-arterial coupling.[6] We have shown that a prolonged EMAT measured during daytime along the hospitalization course (at admission, pre-discharge, and 2 weeks post-discharge) was useful in the prediction of cardiovascular outcomes in patients with AHFS independent of NT-proBNP.[6] Another study suggested that the acoustic cardiography may be useful in identifying the high-risk heart failure patients with reduced ejection fraction.[7]

Acoustic cardiography is now available in an ambulatory device, which can record continuous electrocardiogram (ECG) and heart sound for up to 24 h.[5] In asymptomatic subjects[8] and patients with acute and chronic heart failure,[9] little nocturnal variation of EMAT was observed with the ambulatory acoustic cardiography, except in the subgroup of AHFS patients aged 50–60 years where apparent prolongation of EMAT during sleep was observed.[9] The clinical significance of the nocturnal prolongation of EMAT in patients with AHFS remains to be determined. Therefore, the purpose of this study was to investigate the prognostic value of the night-time EMAT and compare it with measures of pulsatile hemodynamics in patients with AHFS.

Methods

Participants and study design

Acute heart failure syndrome was defined as new onset or gradually or rapidly worsening heart failure symptoms and signs requiring urgent therapy.[1] A total of 102 hospitalized AHFS patients with sinus rhythm and the New York Heart Association functional class III or IV symptoms were enrolled in the present study. Patients with atrial fibrillation, significant valvular disease, electrocardiographic left or right bundle branch block, or cardiogenic shock, or those who were admitted to an intensive care unit were not included . The final study population consisted of 97 patients, after exclusion of five patients who were lost to follow-up after discharge. The investigation conformed to the principles outlined in the Declaration of Helsinki. A written informed consent approved by our Institutional Review Board was obtained from each patient before enrolment.

Patients received anti-heart failure treatments at the physicians' discretion. When patients were stabilized and expected to be discharged in a few days, an ambulatory acoustic cardiography monitor (AUDICOR® AM, Inovise Medical, Inc., Portland, OR, USA) was employed for 24 h. After completion of the ambulatory acoustic cardiography on the following day, a comprehensive hemodynamic study involving echocardiography and arterial tonometry was performed, and a blood sample was drawn for test of NT-proBNP. Patients' baseline demographics, functional status, and medications during the hospitalization were recorded.

Ambulatory acoustic cardiographic recordings

The ambulatory acoustic cardiography recorder unit incorporates three ECG channels and two heart sound channels (AUDICOR® AM, Inovise Medical, Inc., OR, USA).[9] Standard ECG electrodes were placed on the right arm, left arm, and left leg locations. Combined ECG/sound sensors were placed in the pre-cordial V3 and V4 positions. Cardiac acoustic and ECG data were recorded simultaneously for 24 h including the sleeping time. The data were analysed for the presence of third and fourth heart sounds (S3 and S4), and for the systolic time intervals including EMAT and left ventricular systolic time (LVST). The measurements were calculated for each 10 s interval within the ambulatory monitoring session. These interval measurements were then averaged to produce a value for each hour. Intervals with poor sound or ECG quality were not included in the average.

Pulsatile hemodynamics

Carotid systolic blood pressure (SBP) and pulse pressure (PP) were measured from a tonometry-derived, ensemble-averaged, carotid pressure waveform calibrated to the non-invasive brachial diastolic blood pressure (DBP) and mean arterial pressure (MAP).[10] MAP was calculated as brachial DBP + 1/3 brachial PP.

Carotid augmentation index (cAI) and augmented pressure (cAP) were calculated by identifying the inflexion point resulting from the wave reflection on the upstroke or downstroke of the carotid pressure waveform.[10] The carotid pressure waveform was further separated into its forward and backward components using the validated triangulation method.[10,11] Pf and Pb were the pressure amplitudes of the forward and backward components of the carotid pressure wave, respectively.[10]

Carotid–femoral pulse wave velocity (cfPWV) was calculated from the travelling distance and the foot-to-foot pressure wave transit time between the right carotid and right femoral arteries.[12]

Echocardiography

The 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. Left ventricular ejection fraction (LVEF) was measured by M-mode echocardiography and left ventricular diastolic volume (LVEDV) was calculated from LVEF and stroke volume (SV) measured by the Doppler echocardiography. Ventriculo-arterial coupling was assessed using the framework of the ratio of effective arterial elastance (Ea) to end-systolic elastance (Ees).[13] Ees was estimated with a previously proposed single-beat method employing brachial SBP and DBP, SV, LVEF, and an estimated normalized ventricular elastance at arterial end-diastole [E(Nd)]: $Ees = [DBP - (E(Nd) * SBP * 0.9)]/[E(Nd) * SV]$, where E(Nd) was estimated from a group-averaged value adjusted for individual contractile/loading effects.[14] Ea was the ratio of LV end-systolic blood pressure, which is approximated to the value of $SBP \times 2/3 + DBP \times 1/3$, to the value of SV.[14]

Follow-up

Patients were followed up 2 weeks after discharge and then monthly at outpatient clinics or by telephone consultations to check whether there were any adverse cardiovascular events including re-hospitalization for heart failure, non-fatal myocardial infarction, non-fatal stroke, and death for up to 2 years. Elevations in biomarkers were fundamental to the diagnosis of acute myocardial infarction according to the criteria issued by a Joint Committee of the European Society of Cardiology and the American College of Cardiology.[15] A neurologist made a clinical diagnosis of acute stroke and documented the presence of an acute, focal neurological deficit. These adverse cardiovascular events were confirmed by review of medical records by an independent investigator, who was blinded to the ambulatory acoustic cardiography measurements.

Data analysis

The probability of the presence of an S3 or S4 was indicated by a score ranging from 0 to 10, respectively.[5] Values of 5 or more were considered detections.[5] EMAT was measured as the time from the onset of the Q wave to the mitral component of the first heart sound (milliseconds).[5] The percentage of EMAT (%EMAT) was calculated by dividing EMAT by the RR interval.[5] LVST was measured as the time from the first heart sound to the second heart sound (milliseconds).[5] The percentage of LVST (%LVST) was the ratio of LVST to RR interval. Hourly, mean 24 h, daytime (7 a.m.–9 p.m.), and night-time (9 p.m.–7 a.m.) EMAT were analysed.

Statistical analysis

Means, SD, and percentages were used to describe the characteristics of participants in the study. Student's *t*-test and χ^2 test were used for between-group comparisons where appropriate. The correlations between systolic time intervals, cardiac function, and pulsatile hemodynamic measures were analysed by linear regression model. Cox regression analysis was used to identify the predictors for future cardiovascular events. Significant predictors identified from the univariate analysis were further examined in the multivariate models by adjusting for age and NT-proBNP levels. The number of independent variables was limited to a maximum of 4 in the multivariate models because of the limited sample size and event rate in the present study. Collinearity in the multivariate Cox regression models was examined by calculating the variance inflation factor. No significant collinearity was found in any of the multivariate Cox regression models. Because of the skewed distribution, log transformation was performed for NT-proBNP before Cox regression analysis. The Kaplan–Meier method was used to estimate survival curves of adverse events. All statistical significances were set at $P < 0.05$, and all statistical analyses were carried out by SPSS 15.0 (SPSS Inc., Chicago, IL, USA).

Results

The 97 eligible patients with validated outcome status were characterized with a mean age of 71.1 ± 15.4 years (range: 28–94 years), 81% of male sex, and 73.8% of systolic heart failure defined by LVEF < 45%.[16] During a mean follow-up of 389 ± 281 days, 49 patients (50.5%) experienced adverse events, including 31 re-hospitalizations for heart failure, five non-fatal myocardial infarctions, one fatal myocardial infarction, two non-fatal strokes, and 10 deaths. Their baseline characteristics are displayed in *Table 1*. Patients with events had significantly older age, higher percentage of hypertension, and higher plasma NT-proBNP levels than those without. The two groups had similar LVEF, LVEDV, Ea, Ees, Ea/Ees ratio, and pre-discharge medications (*Table 1*). In contrast, patients with events had significantly greater perturbation of the pulsatile hemodynamics, including higher brachial and carotid SBP and PP, cAI, cAP, Pb, and cfPWV (*Table 1*).

Table 2 shows the 24 h, daytime, and night-time ambulatory acoustic cardiographic findings. Patients with events had significantly lesser 24 h and night-time S3 strength and night-time S4 strength, and less frequent night-time S3 detection. On the other hand, patients with events had more prolonged 24 h, daytime, and night-time EMAT. In patients with events, night-time EMAT was significantly greater than daytime EMAT, and the night-time–daytime EMAT difference was significantly greater than that in those without events (*Table 2*). The hourly EMAT analysis showed a trend of progressive lengthening during night-time in patients with events, so the hourly EMAT was significantly longer

Table 1 Baseline characteristics of the study patients

	Patients without events, *n* = 48	Patients with events, *n* = 49	*P* value
Age, years	67.0 ± 17.1	74.8 ± 12.7	0.018
Male gender, *n* (%)	41 (85.4)	38 (77.6)	0.435
Hypertension, *n* (%)	28 (58.3)	40 (81.6)	0.015
Diabetes, *n* (%)	24 (50.0)	27 (55.1)	0.686
CAD, *n* (%)	33 (68.8)	32 (65.3)	0.830
eGFR, mL/min/1.73 m^2	66.4 ± 28.4	50.7 ± 22.1	0.080
NT-proBNP, pg/mL	3420 ± 6859	4980 ± 6411	0.017
Echocardiography			
LVEF, %	38.3 ± 15.1	38.5 ± 13.1	0.953
LVEF < 45%, *n* (%)	34 (70.8)	31 (62)	0.518
LVEDV, mL	168.5 ± 75	170.8 ± 60	0.876
Ea, mmHg/mL	2.5 ± 0.9	2.4 ± 0.8	0.937
Ees, mmHg/mL	2.0 ± 0.8	2.1 ± 0.9	0.522
Ea/Ees ratio	1.3 ± 0.7	1.6 ± 1.5	0.354
Pulsatile hemodynamics			
Heart rate, beats/min	75.9 ± 13.0	75.1 ± 14.8	0.781
Brachial SBP, mmHg	114.5 ± 19.6	123.5 ± 19.3	0.044
Brachial PP, mmHg	48.5 ± 11.8	57.2 ± 14.6	0.009
Carotid SBP, mmHg	109.0 ± 15.3	119.1 ± 20.9	0.047
Carotid PP, mmHg	40.0 ± 12.2	48.3 ± 14.8	0.011
cAI, %	15.5 ± 17.8	24.2 ± 11.5	0.006
cAP, mmHg	6.8 ± 7.5	12.1 ± 7.0	0.001
Pb, mmHg	14.9 ± 5.8	18.1 ± 5.8	0.015
cfPWV, m/s	11.4 ± 3.8	13.7 ± 4.6	0.018
Post-discharge medications			
ACEI, *n* (%)	15 (31.3)	15 (30.6)	1.000
ARB, *n* (%)	22 (45.8)	18 (36.7)	0.413
ACEI or ARB, *n* (%)	35 (72.9)	32 (64)	0.511
Beta-blockers, *n* (%)	40 (83.3)	42 (85.7)	0.830
Spironolactone, *n* (%)	24 (50.0)	25 (51.0)	1.000
Nitrate, *n* (%)	32 (66.7)	34 (69.4)	0.830

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CAD, coronary artery disease; cAI, augmentation index; cAP, augmented pressure; cfPWV, carotid–femoral pulse wave velocity; DBP, diastolic blood pressure; Ea, effective arterial elastance; Ees, ventricular end-systolic elastance; eGFR, estimated glomerular filtration rate; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro-brain natriuretic peptide; Pb, amplitude of the decomposed backward pressure wave; PP, pulse pressure; SBP, systolic blood pressure.

during most of the night-time hours than those without (*Figure 1*). In contrast, the hourly %EMAT (*Figure 2*) and heart rate (*Figure 3*) showed little diurnal variation in both groups.

Predictors of events within 2 years after discharge

By univariate analysis, age, estimated glomerular filtration rate, NT-proBNP, brachial PP, carotid SBP, carotid PP, cAI, cAP, Pb, cfPWV, 24 h EMAT, and night-time EMAT were significantly predictive of the adverse post-discharge outcomes (*Table 3*). With adjustment for age and NT-proBNP levels, only estimated glomerular filtration rate, brachial PP, carotid SBP, carotid PP, Pb, and night-time EMAT remained significantly predictive of the events (*Table 3*). In final multivariate Cox models including age, NT-proBNP, night-time EMAT, and one of the significant pulsatile hemodynamics parameters, NT-proBNP and night-time EMAT, but not hemodynamics parameters, were significant independent predictors for post-discharge events (*Table 4*).

Night-time electromechanical activation time and N-terminal pro-brain natriuretic peptide

The Kaplan–Meier survival curves for the four groups stratified by high and low NT-proBNP (cut-off value 3803 pg/mL determined by the ROC curve analysis) and night-time EMAT (cut-off value 112 ms) are shown in *Figure 4*. Patients with high NT-proBNP levels and high night-time EMAT had more post-discharge adverse events than patients with low NT-proBNP and low night-time EMAT with a hazard ratios of 4.33 and 95% confidence intervals of 1.77–10.5 ($P = 0.001$).

Correlations between electromechanical activation time, pulsatile hemodynamics, and ventriculo-arterial coupling

Table 5 provides the correlation coefficients between systolic time intervals, pulsatile hemodynamics, and ventriculo-arterial coupling parameters. Night-time EMAT significantly

Table 2 Characteristics of ambulatory acoustic cardiographic recordings

	Patients without events, $n = 48$	Patients with events, $n = 49$	P value
EMAT, 24 h, ms	102.9 ± 13.8	110.8 ± 18.4	0.035
Daytime, ms	101.4 ± 12.8	108.5 ± 17.6	0.047
Night-time, ms	103.0 ± 13.8	114.3 ± 20.5	0.007
Night-time–daytime, ms	1.6 ± 5.01	5.0 ± 8.4	0.035
Per cent EMAT, 24 h, %	12.9 ± 2.7	13.8 ± 3.0	0.192
%EMAT > 15%, 24 h, *n* (%)	9 (18.0)	18 (36.7)	0.098
Daytime, %	13.1 ± 2.7	13.6 ± 2.8	0.422
Daytime %EMAT > 15%, *n* (%)	10 (20.8)	16 (32.6)	0.362
Night-time, %	12.9 ± 2.7	14.0 ± 3.1	0.118
Night-time %EMAT > 15%, *n* (%)	8 (16.6)	14 (28.5)	0.148
LVST, 24 h, ms	310.6 ± 30.1	310.1 ± 29.7	0.951
Daytime, ms	305.3 ± 29.4	307.7 ± 31.0	0.737
Night-time, ms	314.5 ± 31.5	304.4 ± 59.3	0.361
Per cent LVST, 24 h, %	38.8 ± 4.0	38.2 ± 5.3	0.583
Daytime, %	38.7 ± 4.0	38.1 ± 5.5	0.579
Night-time, %	38.8 ± 3.9	37.4 ± 8.0	0.344
Heart rate, 24 h, beats/min	75.3 ± 12.6	74.8 ± 14.9	0.866
Daytime, beats/min	77.1 ± 12.3	75.6 ± 15.0	0.617
Night-time, beats/min	75.0 ± 12.6	74.1 ± 12.6	0.735
QRS duration, 24 h, ms	112.2 ± 30.7	116.0 ± 33.1	0.595
Daytime, ms	111.4 ± 30.5	115.2 ± 32.9	0.605
Night-time, ms	112.3 ± 31.6	116.9 ± 34.1	0.544
S3 strength, 24 h	4.0 ± 1.8	3.3 ± 1.1	0.042
Daytime	3.9 ± 1.7	3.3 ± 1.0	0.057
Daytime S3 detection, %	18.9	7.9	0.191
Night-time	4.1 ± 1.9	3.4 ± 1.2	0.043
Night-time S3 detection, %	29.7	10.5	0.047
S4 strength, 24 h	4.5 ± 1.4	4.0 ± 1.3	0.069
Daytime	4.4 ± 1.4	4.0 ± 1.2	0.145
Daytime S4 detection, %	27.0	18.4	0.419
Night-time	4.9 ± 1.6	4.1 ± 1.4	0.017
Night-time S4 detection, %	43.2	23.7	0.09

Daytime: 7 a.m.–9 p.m.; night-time: 9 p.m.–7 a.m.
S3 strength: a 0–10 score indicating the probability that an S3 exists. Values of 5 or more are considered detections.
S4 strength: a 0–10 score indicating the probability that an S4 exists. Values of 5 or more are considered detections.
Electromechanical activation time (EMAT) = time from Q onset to S1 (milliseconds).
Per cent EMAT (%EMAT) = fraction of the RR interval between Q onset and S1.
Left ventricular systolic time (LVST) = time from S1 to S2 (milliseconds).
Per cent LVST (%LVST) = fraction of the RR interval between S1 and S2.

correlated with LVEDV, LVEF, Ea, Ees, and Ea/Ees. In contrast, night-time EMAT did not correlate with NT-proBNP or any of the pulsatile hemodynamics parameters.

Discussion

To the best of our knowledge, the present study is the first to demonstrate that in AHFS patients with post-discharge events, night-time EMAT is significantly prolonged as compared with daytime EMAT and is significantly longer than that in those without events. Moreover, a pre-discharge measure of night-time EMAT by ambulatory acoustic cardiography is a strong predictor of post-discharge outcomes in patients with AHFS. The prognostic value of night-time EMAT is independent of NT-proBNP and may be superior to that of pulsatile hemodynamics. The superiority of night-time EMAT may partly be due to its association with ventriculo-arterial coupling and its independency of NT-proBNP levels and pulsatile hemodynamics. These novel findings may advance our understanding of the clinical relevance of ventriculo-arterial coupling in AHFS outcomes.

Electromechanical activation time and heart failure outcomes

It has well been demonstrated that a prolonged EMAT is associated with reduced LVEF,[7,17] but its prognostic role in patients with heart failure remains to be explored.[5] We have firstly shown that a pre-discharge 10 s snap-shot %EMAT recorded during daytime correlated significantly with LVEF, Ea, Ea/Ees, and NT-proBNP, and could predict post-discharge events independently of LVEF, E/E′, and NT-proBNP levels in 45 patients (89% male; mean age, 71.9 years; and range, 24 to 92; 37.8% with LVEF ≥ 50%) hospitalized for AHFS.[6] However, in the present study, the 24 h, daytime, and night-time %EMAT were not significantly different between patients with and without events (*Table 2*). Because %EMAT is the

Figure 1 The 24 h electromechanical activation time (EMAT) profiles from ambulatory acoustic cardiography in patients with acute heart failure syndrome with and without post-discharge events. Black symbols indicate hourly EMAT during night-time and white symbols indicate daytime EMAT. Asterisk (*) indicates the significant difference ($P < 0.05$) between the hourly EMAT from the two groups.

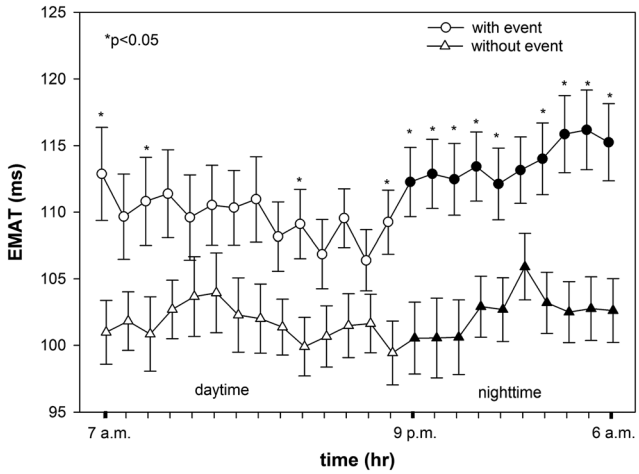


Figure 2 The 24 h per cent electromechanical activation time (%EMAT) profiles from ambulatory acoustic cardiography in patients with acute heart failure syndrome with and without post-discharge events. Black symbols indicate hourly %EMAT during night-time and white symbols indicate daytime %EMAT. Asterisk (*) indicates the significant difference ($P < 0.05$) between the hourly %EMAT from the two groups.

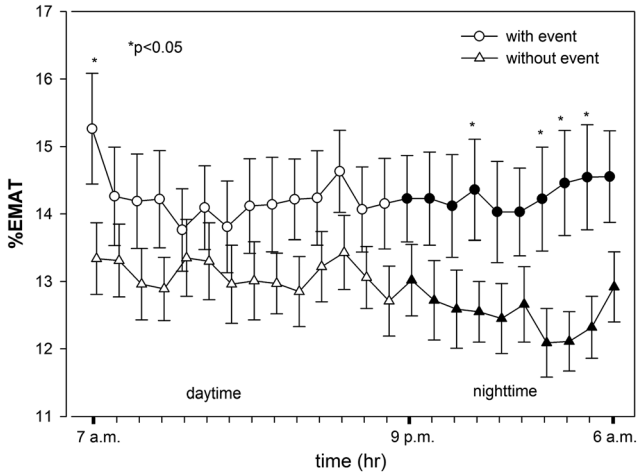
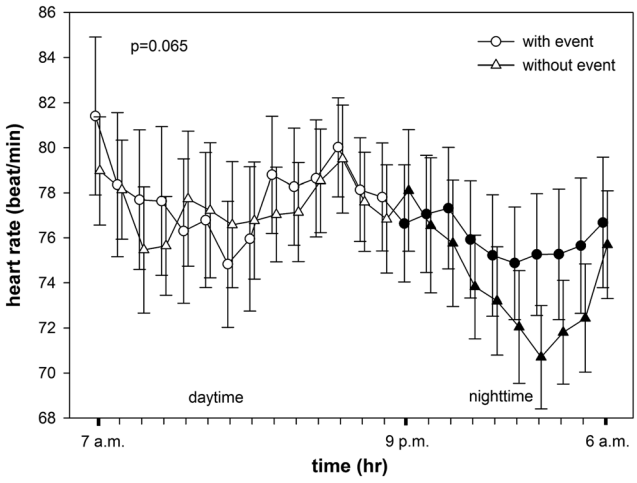


Figure 3 The 24 h heart rate profiles from ambulatory acoustic cardiography in patients with acute heart failure syndrome with and without post-discharge events. Black symbols indicate hourly heart rate during night-time and white symbols indicate daytime heart rate. Asterisk (*) indicates the significant difference ($P < 0.05$) between the hourly heart rate from the two groups.



ratio of EMAT to RR interval, averages of %EMAT over 24 h, daytime, and night-time periods would likely be affected by the variation of heart rate over the same period. Because there was little variation of heart rate over 24 h, daytime, and night-time in both groups (*Table 2* and *Figure 3*), the significant between-group differences of EMAT over 24 h, daytime, and night-time might thus be diminished with %EMAT.

In AHFS patients with events, daytime EMAT was significantly longer than that in those without events (*Table 2*). Because a significant nocturnal prolongation of EMAT was only observed in patients with events, the between-group difference in EMAT over daytime was further widened over night-time (*Table 2* and *Figure 1*). The cause of nocturnal prolongation of EMAT remains obscure. It has been recognized that some symptoms of AHFS, such as paroxysmal nocturnal dyspnoea[18] and sleep apnoea,[19] occur during sleep, very likely because of overnight worsening of hemodynamics.[20] A postural change to the recumbent position during sleep in patients with heart failure may increase venous return from the legs and lead to a further increase in right atrial pressure and pulmonary capillary pressure.[21,22] Therefore, AHFS patients with low LVEF and paroxysmal nocturnal dyspnoea had increased plasma atrial natriuretic peptide levels at baseline and overnight increases in atrial natriuretic peptide.[20] Moreover, progressive overnight rostral fluid displacement contributes to the pathogenesis of obstructive and central sleep apnoea.[19] However, in the present study, night-time S3 strength was significantly smaller and night-time S3 detection rate was significantly less frequent in patients with events than without (*Table 2*). Because S3 is a recognized marker of left ventricular decompensation and increased filling pressure,[5] our results do not support the nocturnal volume overload as a major pathophysiology for the nocturnal prolongation of EMAT.

The present study reconfirmed our previous observation that EMAT is associated with left ventricular systolic function (LVEF and Ees), left ventricular afterload (Ees), and ventriculo-arterial coupling (Ea/Ees) (*Table 5*).[6] Because

Table 3 Hazard ratios and 95% confidence intervals of each variable per 1 SD increment for events within 2 years of discharge

Variable	Hazard ratio (95% CI)	*P* value	Adjusted[a] hazard ratio (95% CI)	*P* value
Age, 1 SD = 14.6 years	1.71 (1.03–2.83)	0.036		
Log NT-proBNP, 1 SD = 0.64 pg/mL	1.97 (1.15–3.38)	0.013		
eGFR, 1 SD = 26.0 mL/min/1.73 m^2	0.47 (0.28–0.78)	0.004	0.51 (0.28–0.92)	0.025
Heart rate, 1 SD = 12.8 beat/min	0.99 (0.97-1.02)	0.905	1.01 (0.98–1.03)	0.502
Echocardiography				
LVEDV, 1 SD = 67.2 mL	1.00 (0.99–1.00)	0.954	1.00 (0.99–1.00)	0.511
LVEF, 1 SD = 13.9%	1.64 (0.23–11.7)	0.623	1.75 (0.14–22.5)	0.667
Ea, 1 SD = 0.87 mmHg/mL	0.97 (0.67–1.39)	0.865	0.94 (0.63–1.39)	0.742
Ees, 1 SD = 0.84 mmHg/mL	1.22 (0.85–1.75)	0.281	1.08 (0.74–1.57)	0.699
Ea/Ees, 1 SD = 1.21	1.02 (0.81–1.27)	0.900	1.04 (0.84–1.28)	0.753
Pre-discharge pulsatile hemodynamic measures				
Brachial SBP, 1 SD = 18.4 mmHg	1.60 (0.96–2.67)	0.071	1.67 (0.95–2.94)	0.072
Brachial PP, 1 SD = 13.7 mmHg	1.99 (1.15–3.41)	0.013	2.08 (1.13–3.85)	0.019
Carotid SBP, 1 SD = 19.0 mmHg	1.78 (1.08–2.95)	0.023	1.73 (1.10–2.97)	0.045
Carotid PP, 1 SD = 14.2 mmHg	1.89 (1.13–3.18)	0.015	1.83 (1.03–3.25)	0.038
cAI, %, 1 SD = 16.1%	2.15 (1.09–4.26)	0.027	1.76 (0.84–3.64)	0.129
cAP, 1 SD = 6.7 mmHg	1.36 (1.06–1.74)	0.016	1.26 (0.95–1.66)	0.106
Pb, 1 SD = 6.0 mmHg	1.85 (1.09–3.13)	0.021	1.83 (1.02–3.26)	0.041
cfPWV, 1 SD = 4.4 m/s	1.78 (1.08–2.92)	0.023	1.41 (0.78–2.54)	0.244
Pre-discharge systolic time intervals				
EMAT, 1 SD = 16.8 ms	1.69 (1.01–2.81)	0.042	1.72 (0.96–3.09)	0.067
Daytime EMAT, 1 SD = 16.5 ms	1.67 (0.99–2.82)	0.054	1.81 (0.96–3.39)	0.063
Night-time EMAT, 1 SD = 18.0 ms	2.09 (1.17–3.75)	0.012	2.34 (1.16–4.71)	0.017
% EMAT, 1 SD = 2.9%	1.06 (0.95–1.17)	0.319	1.11 (0.99–1.24)	0.062
LVST, 1 SD = 31.9 ms	1.00 (0.99–1.01)	0.516	1.00 (0.99–1.01)	0.431
EMAT/LVST ratio, 1 SD = 6.6%	1.35 (0.98–1.85)	0.068	1.39 (1.00–1.04)	0.050

cAI, augmentation index; cAP, augmented pressure; cfPWV, carotid–femoral pulse wave velocity; CI, confidence interval; Ea, effective arterial elastance; Ees, ventricular end-systolic elastance; eGFR, estimated glomerular filtration rate; EMAT, electromechanical activation time; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; LVST, left ventricular systolic time; NT-proBNP, N-terminal pro-brain natriuretic peptide; Pb, amplitude of the decomposed backward pressure wave; PP, pulse pressure; SBP, systolic blood pressure.
[a]Adjusted for age and log NT-proBNP.

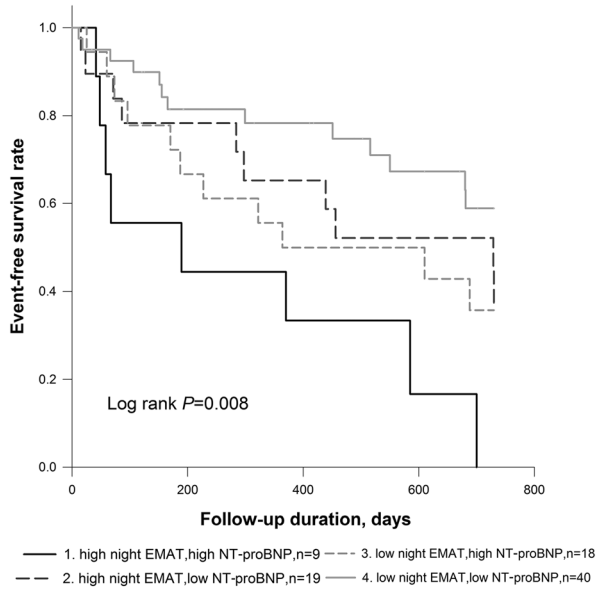
Table 4 Hazard ratios and 95% confidence intervals of each variable per 1 SD increment for events within 2 years of discharge by multivariate Cox regression analysis

	Hazard ratio (95% CI)			
Variable	Model 1	Model 2	Model 3	Model 4
Age, 1 SD = 14.6 years	1.30 (0.87–1.95)	1.37 (0.93–2.01)	1.35 (0.91–1.98)	1.35 (0.90–2.01)
Log NT-proBNP, 1 SD = 0.64 pg/mL	1.59 (1.08–2.34)*	1.58 (1.07–2.33)*	1.60 (1.08–2.36)*	1.62 (1.08–2.39)*
Night-time EMAT, 1 SD = 15.8 ms	1.31 (1.03–1.66)*	1.36 (1.08–1.71)*	1.33 (1.04–1.69)*	1.33 (1.05–1.69)*
Brachial PP, 1 SD–14.9 mmHg	1.01 (0.99–1.03)	—	—	—
Carotid SBP, 1 SD = 19 mmHg	—	1.01 (0.99–1.02)	—	—
Carotid PP, 1 SD = 14.2 mmHg	—	—	1.02 (0.99–1.03)	—
Pb, 1 SD = 6.0 mmHg	—	—	—	1.03 (0.98–1.08)

CI, confidence interval; EMAT, electromechanical activation time; NT-proBNP, N-terminal pro-brain natriuretic peptide; Pb, amplitude of the decomposed backward pressure wave; PP, pulse pressure; SBP, systolic blood pressure.
*P value < 0.05.

patients with events had significantly more perturbed pulsatile hemodynamics and higher NT-proBNP levels but similar LVEF, Ees, and Ea/Ees in comparison with patients without events, one potential reason for the prolonged EMAT in AHFS patients with events is the adverse coupling of left ventricle with the perturbed pulsatile hemodynamics, an important component of late-systolic afterload that is not fully accounted for by Ea.[23] The late-systolic afterload is mediated predominantly by systolic wave reflections and arterial stiffness and is relevant for patients with hypertension and heart failure.[23] Likewise, Ea/Ees may not adequately address the coupling between left ventricle and the pulsatile hemodynamics. We have shown that acute perturbation of the pulsatile hemodynamics may exacerbate the ventriculo-arterial coupling in patients with AHFS.[3] We therefore hypothesize that more prolonged 24 h, daytime, and night-time EMAT in patients with events may imply more worsening of the ventriculo-arterial coupling resulting from the more perturbed pulsatile hemodynamics than those patients without events.

Figure 4 Post-discharge clinical outcomes in subgroups of patients with acute heart failure syndrome. Kaplan–Meier survival analysis for patients with high or low pre-discharge night-time electromechanical activation time (EMAT) and high or low N-terminal pro-brain natriuretic peptide levels (NT-proBNP).



Diurnal variation of electromechanical activation time

Ambulatory acoustic cardiography has been performed in asymptomatic subjects and heart failure patients.[8,9] In the 128 asymptomatic subjects, EMAT slightly increased with age (80 ± 8 ~ 89 ± 12 ms) with little circadian variation.[8] In the 37 chronic and 28 acute heart failure patients, EMAT (122.0 ± 29.4 and 118.0 ± 24.3 ms, respectively) were significantly longer than that in the 63 asymptomatic controls (89.2 ± 9.4 ms).[9] Little circadian variation of EMAT was observed, except the subgroup of acute heart failure patients within the age range of 50–60 years.[9] Our AHFS patients had a 24 h EMAT of 102.9 ± 13.8 and 110.8 ± 18.4 ms, for those without and with events, respectively (*Table 2*). Consistent with previous findings, little circadian variation of EMAT was observed in patients without events (*Figure 1*). In contrast, a small but significant nocturnal prolongation of EMAT was observed in patients with events. We therefore further hypothesize that the nocturnal prolongation of EMAT may partly be due to the worsening of central pulsatile hemodynamics from the progressive overnight rostral fluid shift.[19] Therefore, night-time EMAT may be better than daytime EMAT in identifying the high-risk AHFS patients who have adverse ventriculo-arterial coupling due to a prominent perturbation of the pulsatile hemodynamics.

Limitations of the present study

There are several limitations to the present study. First, the independent predictive values of the night-time EMAT in specific subgroups (such as patients with preserved ejection fraction) need further confirmation in future studies with sufficient sample size and event rate. Second, we did not measure nocturnal NT-proBNP levels or pulsatile hemodynamics. Future studies are required to prove the concept of nocturnal deterioration of ventriculo-arterial coupling resulting from worsening of pulsatile hemodynamics during night-time. Third,

Table 5 Correlation coefficients between systolic time intervals, pulsatile hemodynamics, and ventriculo-arterial coupling

	EMAT	Night-time EMAT	%EMAT	LVST	EMAT/LVST	LVEF	Ea	Ees	Ea/Ees
Age	−0.104	−0.076	−0.324**	0.145	−0.178	0.349**	−0.238*	0.196	−0.119
NT-proBNP	−0.088	−0.149	−0.160	0.298*	−0.182	−0.022	0.097	0.358*	−0.169
eGFR	−0.305	0.006	0.180	−0.228*	0.118	−0.097	0.074	−0.084	0.060
Heart rate	−0.148	−0.088	0.712**	−0.704**	0.291**	−0.249*	0.056	−0.121	0.073
LVEDV	0.412**	0.329**	0.327**	−0.013	0.333**	−0.467**	0.185	−0.292**	0.323**
LVEF	−0.353**	−0.311**	−0.481**	0.286*	−0.445**	1.000	−0.594**	0.252*	−0.406**
Ea	0.428**	0.385**	0.354**	−0.039	0.342**	−0.594**	1.000	0.226*	0.268*
Ees	−0.178	−0.247*	−0.235*	0.129	−0.222	0.239*	0.187	1.000	−0.572**
Ea/Ees	0.278*	0.350**	0.269*	−0.180	0.314**	−0.406**	0.268*	−0.616**	1.000
Brachial SBP	−0.045	−0.067	−0.251*	0.332**	−0.107	0.371**	−0.076	0.515**	−0.331**
Brachial PP	0.113	0.071	−0.240*	0.337**	−0.087	0.387**	−0.163	0.369**	−0.234*
Carotid SBP	0.123	0.050	−0.115	0.250*	−0.047	0.317**	0.027	0.461**	−0.280*
Carotid PP	0.193	0.087	−0.199	0.314**	−0.020	0.297**	−0.059	0.358**	−0.203
cAI	0.122	0.159	−0.063	0.101	0.053	−0.180	−0.036	0.269*	−0.051
cAP	0.247*	0.226	−0.080	0.278*	0.054	0.150	0.126	0.353**	0.013
Pb	0.190	0.112	−0.195	0.354**	−0.044	0.269*	−0.060	0.298**	−0.130
cfPWV	−0.160	−0.060	−0.139	−0.123	−0.046	0.165	−0.139	0.204	-0.125

cAI, augmentation index; cAP, augmented pressure; cfPWV, carotid–femoral pulse wave velocity; Ea, effective arterial elastance; Ees, ventricular end-systolic elastance; eGFR, estimated glomerular filtration rate; EMAT, electromechanical activation time; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; LVST, left ventricular systolic time; NT-proBNP, N-terminal pro-brain natriuretic peptide; Pb, amplitude of the decomposed backward pressure wave; PP, pulse pressure; SBP = systolic blood pressure.
*Correlation is significant at the 0.05 level.
**Correlation is significant at the 0.001 level.

our study populations had sinus rhythm and relatively stable conditions. The study findings should be confirmed in patients with atrial fibrillation or more critical conditions.

In conclusion, pre-discharge night-time EMAT may be a better predictor for post-discharge adverse events than measures of the pulsatile hemodynamics in patients with AHFS. Ambulatory acoustic cardiography may be useful in identifying the high-risk patients hospitalized for AHFS.

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Conflict of Interest

Dr C-H.C. has received honoraria for lectures during scientific meetings sponsored or arranged by Boehringer Ingelheim, Sanofi-Aventis, Novartis, Astra Zeneca, and Pfizer. The other authors report no conflicts.

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