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Nocturnal thoracic volume overload and post-discharge outcomes in patients hospitalized for acute heart failure

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Abstract

Aims   Volume overload and perturbations of pulsatile haemodynamics may precipitate acute heart failure (AHF). Nocturnal thoracic volume overload due to rostral fluid shift during recumbency undetected by daytime measures may impact nighttime haemodynamics and post-discharge outcomes.

Methods and results   A total of 63 patients (median 60 years, 79.4% men, and left ventricular ejection fraction 29.4%) hospitalized for AHF were enrolled. Once clinical euvolaemia was achieved, noninvasive pulsatile haemodynamics were assessed during daytime followed by circadian monitoring (6 p.m. to 5 a.m.) of thoracic fluid content and thoracic fluid content index (TFCi) using impedance cardiography, normalized electromechanical activation time ratio (EMAT%) using acoustic cardiography, and mean blood pressure using ambulatory blood pressure monitoring before discharge. The primary endpoints were composited of the first hospitalization for heart failure and death from any cause. Patients were also followed for the repeated heart failure hospitalizations. During a median follow-up duration of 16 months, 33 patients encountered primary composite endpoints (52.4%), and there were 42 hospitalizations developed among 25 patients. An overnight increase in TFCi along with persistently prolonged EMAT% and low mean blood pressure was observed in the eventful group. Overnight increase in TFCi (ΔTFCi, the difference between the measures at 4 a.m. and 6 p.m.) was an independent predictor of primary composite events (hazard ratio and 95% confidence interval: 1.58, 1.07–2.33; P = 0.022) and recurrent composite events (2.22, 1.51–3.26; P < 0.001), after adjusting for potential confounding factors. A high ΔTFCi ($\geq$0.5/kΩ/m^2) significantly correlated with higher post-discharge events (hazard ratio 6.25; 95% confidence interval 2.30–16.96; P < 0.001) in comparison with a low ΔTFCi (<0.5/kΩ/m^2). ΔTFCi was significantly associated with EMAT%, estimated glomerular filtration rate, and left ventricular ejection fraction, but not with parameters of pulsatile haemodynamics.

Conclusions   Nocturnal thoracic volume overload in AHF before discharge, indicating the presence of residual volume overload unidentified by daytime measures, may predict post-discharge outcomes.

Keywords   Acute heart failure; Nighttime haemodynamics; Nocturnal thoracic volume overload; Post-discharge outcomes

Introduction

Hospitalization due to acute heart failure (AHF) has been associated with around 50% rehospitalization rate within 6 months and 20–30% post-discharge mortality at 1 year.[1] However, recent advances in pharmacological and device-based therapies for chronic heart failure have not demonstrated a parallel reduction in the morbidity and mortality due to AHF.[2–4] Volume overload is a well-recognized predisposing factor for AHF, and early identification and intervention of volume overload in patients with chronic heart failure are effective strategies to reduce hospitalization and mortality.[5–9] The high rates of rehospitalization and mortality may indicate that the current guidelines for discharge, typically based on clinical assessment of volume status, are insufficient for AHF patient stabilization.[10]

Daytime measures of haemodynamic parameters, such as blood pressure, left ventricular ejection fraction (LVEF), and cardiac output, are important determinants of prognosis in patients with heart failure.[11] We have previously demonstrated that daytime measures of pulsatile haemodynamics, such as carotid-femoral pulse wave velocity (CFPWV), backward (Pb) amplitude of the reflection wave, carotid pulse pressure,[12,13] and electromechanical activation time (EMAT),[9] a measure of the ventriculo-arterial coupling, were independently associated with post-discharge outcomes in patients with AHF. Recently, the importance of nighttime haemodynamics on cardiovascular events including heart failure has been emphasized.[14] We have also shown that pre-discharge nighttime EMAT may be a better predictor for post-discharge adverse events than the measures of the pulsatile haemodynamics in patients with AHF.[15]

Nighttime haemodynamics may be particularly relevant for patients with AHF. It is suggested that fluid return is facilitated in recumbent position at nighttime, which increases the preload and may deteriorate left ventricular performance in a failing heart, followed by lung congestion and neck swelling.[16,17] In fact, Ekundayo *et al.* have shown that paroxysmal nocturnal dyspnoea outperformed the other symptoms to specify patients with heart failure among 5771 community-dwelling elders,[18] supporting that the nocturnal fluid shift could be a sensitive challenge for a decompensating heart. However, the prognostic value of the nighttime haemodynamics in AHF patients remains to be explored thoroughly. In this study, we hypothesized that the rostral fluid shift during nighttime may adversely affect nocturnal haemodynamics and left ventricular performance, or alternatively, a significant rostral fluid shift may be a marker of residual volume overload, which may impact post-discharge outcomes. Therefore, the purpose of the present study was to investigate the association between pre-discharge nighttime haemodynamics and post-discharge outcomes in AHF patients.

Methods

Study participants

Consecutive patients hospitalized for AHF from May 2015 to May 2018 were eligible. Subjects with sinus rhythm and LVEF of <50% were prospectively enrolled. The diagnosis of heart failure was confirmed by both echocardiographic findings and an elevated N-terminal pro B-type natriuretic peptide (NT-proBNP). Subjects with significant valvular heart disease, end-stage renal disease, cardiogenic shock, or initial admission to an intensive care unit were excluded. The study protocol was approved by the Institutional Review Board of Taipei Veterans General Hospital, and a written informed consent was obtained from each patient before enrollment.

Study protocol

All patients were treated according to the heart failure guidelines and clinical symptoms and signs of excessive volume, including daily body weight measurements. A 15 mL blood sample was obtained from every participant for the measurement of haemograms and biochemistries on admission. When patients were stabilized and clinical euvolaemia as assessed by the attending physicians was achieved, the study subjects were arranged to receive comprehensive daytime pulsatile haemodynamic, and echocardiographic studies, followed by circadian haemodynamic studies, including impedance cardiography, 24 h acoustic cardiography, and ambulatory blood pressure monitoring (ABPM) on the same day before discharge. The on-admission and pre-discharge NT-proBNP were also obtained.

Daytime pulsatile haemodynamic study

Supine brachial systolic blood pressure (SBP), diastolic blood pressure (DBP), simultaneous right common carotid, and right femoral arterial waveforms were measured with a commercially available device (VP-2000; Colin, Komaki, Japan). The CFPWV was calculated from the foot-to-foot pulse transit time between right carotid and right femoral arteries, and the difference between the distance of carotid pulse recording site to suprasternal notch and suprasternal notch to femoral pulse recording site. Carotid arterial waveform was decomposed into forward and backward components using the triangulation method.[19] The amplitude of forward (Pf) and Pb pressure waves as well as the augmentation index (AI) was calculated.[19]

Daytime echocardiographic study

The echocardiographic study was conducted according to the recommendations from the American Society of Echocardiography. Left atrial dimension, left ventricular internal diameter at end-diastole, tricuspid annular plane systolic excursion,

and the largest dimension of inferior vena cava diameter were measured by M-mode. LVEF was obtained by biplane Simpson's method. Transmitral inflow parameters including the peak of early (E) and late (A) diastolic filling velocities were measured by pulsed wave Doppler, whereas early diastolic (e') mitral annulus velocity was derived by tissue Doppler. Every measure was the average of three measurements.

Circadian haemodynamic study

After completion of the daytime cardiovascular studies, patients received impedance cardiography (PhysioFlow; Manatec Biomedical, Poissy, France), 24 h acoustic cardiography (Audicor; Inovise Medical, Beaverton, OR, USA), and 24 h ABPM (Oscar 2; SunTech Medical, Morrisville, NC, USA), starting at around 6 p.m. Because of the battery limitation, impedance cardiography was applied from 6 p.m. to 5 a.m. for at most 11 h. In brief, six electrodes of the impedance cardiogram and three electrodes of the acoustic cardiogram were placed according to the manufacturers' instructions after skin preparation.[15] Data were then recorded at 30 s intervals for offline analysis. Stroke volume, stroke volume index, cardiac output, cardiac index, thoracic fluid content (TFC), and thoracic fluid content index (TFCi) were derived from the impedance cardiography, while EMAT and EMAT% (defined as the ratio of EMAT to RR interval) were derived from the acoustic cardiography. The ABPM was set to obtain blood pressure every 15 min during daytime and every 30 min from 10 p.m. to 5 a.m. The device displayed 'off' all the time to avoid any biofeedback; SBP, DBP, mean blood pressure (MBP), pulse pressure, and heart rate were calculated from the 24 h ABPM. The recorded data were retrieved and analysed, and the derived indices were presented as hourly averages using custom software developed within MATLAB 7.0 (MathWorks Inc., Natick, MA, USA). Nighttime measures were defined as the measurements averaged from 10 p.m. to 5 a.m. Daytime measures were the averages of the measurements before 10 p.m. Overnight change (Δ) was calculated as the difference between measures around 6 p.m. and 4 a.m. Early morning referred to the measures around 4 a.m. Throughout the study, all the haemodynamic measurements were blinded to the attending physicians.

Follow-up and clinical outcomes

All participants were followed 2 weeks after discharge and then monthly at outpatient clinics or by telephone contacts to monitor whether there was any adverse event, including rehospitalization for heart failure or mortality. Hospitalization for heart failure was based on clinical presentations of typical heart failure symptoms and signs, chest X-ray, and elevated NT-proBNP, if available. The primary endpoint was a composite of first hospitalization for heart failure or death from any cause. The event-free survival was defined as the interval between the date of discharge and either heart failure readmission, death, or the end of follow-up.

Statistical analysis

Continuous variables were reported as median with interquartile ranges and were compared by Mann–Whitney U test for non-normal distribution. Categorical variables were reported as absolute numbers and percentages and were compared by χ^2 test. We used Pearson's correlation coefficient to evaluate the associations between nighttime haemodynamics and daytime pulsatile haemodynamics. Kaplan–Meier survival curve analysis was used to assess the prognostic significance of the nighttime haemodynamics. Cox regression analysis was applied to examine the effects of potential predictors on the primary composite events. Recurrent composite events (hospitalizations for heart failure or death) were also analysed. A patient who died during a heart failure hospitalization was counted as one event. Considering each hospitalization may not be totally independent and multiple ordered events (e.g. heart failure hospitalization with or without following death event), the effect of each haemodynamic measurement on the composite of all hospitalizations and death was analysed using Wei–Lin–Weissfeld approach, which was an extension of the Cox proportional hazards model.[20] Hazard ratio (HR) and 95% confidence intervals (CIs) were calculated as estimates of relative risk. Because of the skewed distribution, NT-proBNP was logarithmic transformed for the statistical analysis. Cut-off values to dichotomize the independent continuous variables were determined by the receiver operating characteristic (ROC) curve analysis. All statistical significances were set at $P < 0.05$. All statistical analyses were carried out by SPSS 15.0 (SPSS, Chicago, IL, USA) and SAS 9.4 (IBM, Cary, NA, USA).

Results

Study participants

A total of 63 patients (median age 60 years; 79.4% men) were enrolled in this study. During a median follow-up duration of 16 months, 33 patients (52.4%) encountered heart failure rehospitalization ($n = 25$) or mortality ($n = 8$) as their first post-discharge event. There was a total of 42 heart failure hospitalizations developing among the 25 patients. The baseline characteristics of the study population are shown in *Table 1*. Comparing with the subjects without adverse events, the eventful patients were older, and had lower body surface area and body mass index. They were more likely to have diabetes and chronic obstructive pulmonary disease; lower LVEF, haemoglobin, and estimated glomerular filtration rate (eGFR), low density lipoprotein cholesterol; and higher

Table 1 Baseline characteristics of the study population with and without post-discharge adverse events

Variables	Event (+), n = 33	Event (−), n = 30	Total, n = 63	P
Age, years	65.5 (51.5–79.8)	46.0 (36.3–63.0)	60.0 (40.1–75.3)	**0.001**
Men, n (%)	25 (75.8)	25 (83.3)	50 (79.4)	0.458
Smoking, n (%)	7 (21.2)	9 (30.0)	16 (25.4)	0.424
BSA, m²	1.7 (1.6–1.9)	1.9 (1.7–2.1)	1.8 (1.6–2.0)	0.002
BW change during hospitalization, kg	−4.0 (−6.0 to −1.5)	−3.9 (−5.9 to −2.0)	−3.9 (−5.9 to −2.0)	0.994
BMI on discharge, kg/m²	23.2 (20.8–26.6)	28.0 (22.1–32.6)	24.3 (21.2–29.7)	0.011
Co-morbidities, n (%)				
Hypertension	16 (48.5)	17 (56.7)	33 (52.4)	0.516
Diabetes mellitus	15 (45.5)	6 (20.0)	21 (33.3)	0.032
Coronary artery disease	11 (33.3)	6 (20.0)	17 (27.0)	0.234
Stroke	3 (9.1)	2 (6.7)	5 (7.9)	0.722
COPD	4 (12.1)	0 (0)	4 (6.3)	0.049
Echocardiography				
LVEF, %	27.0 (19.2–35.0)	33.0 (27.9–40.7)	29.4 (24.2–36.5)	0.014
LVIDd, mm	62.9 (54.9–71.8)	65.7 (60.1–67.9)	65.4 (56.0–69.8)	0.853
LA dimension, mm	44.1 (39.1–47.5)	48.7 (38.7–51.1)	44.7 (39.1–49.1)	0.274
E/A, ratio	1.4 (0.8–2.3)	1.9 (1.1–2.6)	1.6 (0.9–2.3)	0.183
Medial E/e′, ratio	21.4 (15.4–27.3)	18.9 (15.6–26.4)	20.1 (16.0–26.6)	0.993
MR, n (%)				0.114
Mild	25 (75.8)	14 (46.7)	39 (61.9)	
Moderate	3 (9.1)	8 (26.7)	11 (17.5)	
Severe	3 (10.0)	2 (6.1)	5 (7.9)	
RVSP, mmHg	38.8 (32.1–52.7)	47.2 (29.1–57.3)	41.3 (32.1–55.9)	0.507
TAPSE, cm	1.6 (1.4–2.0)	1.7 (1.5–2.0)	1.7 (1.4–2.0)	0.522
IVC max diameter, cm	1.5 (1.2–1.7)	1.5 (1.0–2.3)	1.5 (1.1–1.9)	0.861
Haematological and biochemical variables				
Haemoglobin, gm/dL	12.4 (11.0–13.5)	14.5 (13.0–15.5)	13.3 (11.8–14.7)	0.004
LDLc, mg/dL	71.0 (66.0–110.0)	119.0 (86.0–146.0)	110.0 (76.3–140.3)	0.021
HDLc, mg/dL	39.5 (30.5–55.3)	37.5 (30.8–43.5)	37.5 (30.8–45.3)	0.616
Triglyceride, mg/dL	129.0 (87.3–150.0)	115.0 (85.0–125.0)	116.0 (85.5–144.0)	0.461
Albumin, mg/dL	3.7 (3.4–3.9)	3.6 (3.3–4.3)	3.7 (3.3–4.1)	0.724
BUN,[b] mg/dL	26.0 (17.8–54.0)	24.5 (18.8–29.8)	25.0 (18.3–36.0)	0.320
Creatinine,[b] mg/dL	1.2 (0.9–2.1)	1.1 (0.9–1.4)	1.2 (0.9–1.7)	0.375
eGFR,[a,b] mL/min/1.73 m²	40.1 (20.9–72.7)	80.4 (51.0–103.1)	58.8 (31.0–102.0)	0.007
NT-proBNP,[b] pg/mL	8428.5 (4386.0–20 380.0)	4564.5 (2080.3–10 431.5)	7219.0 (3160.8–14 607.8)	0.038
Daytime pulsatile haemodynamic parameters				
CFPWV, m/s	10.7 (7.5–12.2)	9.0 (7.2–12.5)	9.8 (7.3–12.3)	0.495
AI, %	5.6 (1.7–15.0)	4.6 (−4.4 to 8.6)	5.2 (−1.9 to 11.8)	0.146
Pf, mmHg	33.6 (22.2–45.8)	37.9 (28.7–43.4)	36.4 (27.7–44.0)	0.507
Pb, mmHg	17.5 (10.6–21.9)	17.7 (11.6–21.6)	17.6 (11.6–21.7)	0.915
Pb/Pf, %	45.2 (37.0–60.6)	37.0 (29.2–46.3)	42.7 (32.5–51.5)	0.019
Circadian haemodynamics[c]				
SVI, mL/m²	34.3 (26.6–42.6)	30.8 (26.1–37.1)	32.9 (26.3–40.3)	0.219
CI, L/min/m²	2.5 (2.2–3.1)	2.7 (2.6–3.1)	2.6 (2.3–3.0)	0.098
TFCi, 1/kΩ/m²	12.2 (10.2–15.3)	10.5 (8.0–12.2)	11.6 (8.6–12.7)	0.037
EMAT, %	15.9 (13.3–17.2)	14.2 (11.0–15.6)	15.0 (12.2–16.3)	0.016
SBP, mmHg	110.9 (88.1–122.2)	124.8 (108.9–142.5)	118.7 (101.3–127.0)	0.069
DBP, mmHg	61.6 (55.7–68.6)	77.5 (60.7–91.2)	65.9 (58.2–78.4)	0.048
MBP, mmHg	77.4 (64.4–80.5)	92.0 (78.1–107.3)	81.1 (73.3–93.2)	0.015
Heart rate, b.p.m.	72.3 (63.5–80.4)	80.3 (73.1–90.2)	77.5 (68.4–86.9)	0.118
Medications, n (%)				
RAS blocker	9 (27.3)	15 (50.0)	24 (38.1)	0.064
Beta-blocker	24 (72.7)	27 (90.0)	51 (81.0)	0.081
Spironolactone	24 (72.7)	23 (76.7)	47 (74.6)	0.720
Diuretics	30 (90.9)	25 (83.3)	55 (87.3)	0.367
Furosemide, mg	40 (20–60)	20 (20–40)	40 (20–40)	0.053
Spironolactone, mg	25 (12.5–25)	25 (12.5–25)	25 (12.5–25)	0.596
Statins	5 (15.2)	9 (30.0)	14 (22.2)	0.157

AI, augmentation index; BMI, body mass index; BSA, body surface area; BUN, blood urea nitrogen; BW, body weight; CI, cardiac index; CFPWV, carotid-femoral pulse wave velocity; COPD, chronic pulmonary obstructive disease; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; EMAT%, electromechanical activation time ratio; HDLc, high density lipoprotein cholesterol; IVC, inferior vena cava; LA, left atrium; LDLc, low density lipoprotein cholesterol; LVEF, left ventricular ejection fraction; LVIDd, left ventricular internal diameter at end-diastole; MBP, mean blood pressure; MR, mitral regurgitation; NT-proBNP, N-terminal pro B-type natriuretic peptide; Pb, amplitude of backward pulse wave component; Pf, amplitude of forward pulse wave component; RAS, renin-angiotensin system; RVSP, right ventricular systolic pressure; TAPSE, tricuspid annular plane systolic excursion; TFCi, thoracic fluid content index; SBP, systolic blood pressure; SVI, stroke volume index.
[a]The eGFR was calculated from the Modification of Diet in Renal Disease equation for Asians.
[b]Measurements before discharge.
[c]Circadian: measurements averaged from 6 p.m. to 5 a.m.

pre-discharge NT-proBNP. The Pb/Pf ratio was also higher in the eventful subjects than those without adverse events. Meanwhile, participants with post-discharge adverse events also had higher TFCi, longer EMAT%, and lower DBP and MBP during nighttime than their event-free counterparts. However, there was no significant difference in the prescribed medications on discharge (*Table 1*).

Circadian haemodynamic changes in acute heart failure

The circadian haemodynamic measures and changes over time were compared in *Table 2*. The eventful patients had a significant decrease in SBP (daytime, nighttime, and early morning), DBP (daytime and early morning), MBP (daytime,

nighttime, and early morning), and heart rate (early morning) and an increase in TFCi (nighttime, overnight Δ, and early morning) and EMAT% (daytime, nighttime, and early morning), comparing with those without post-discharge adverse events. However, there was no between-group difference in stroke volume index or cardiac index.

Figure 1 demonstrates the circadian changes of TFCi, EMAT %, and MBP from 6 p.m. to 4 a.m. A progressive increase in TFCi was observed in patients with events, whereas TFCi reached a plateau at midnight and then declined in patients without events (*Figure 1A*). The between-group difference was significant during the period from 10 p.m. to 4 a.m. (*Figure 1A*). In contrast, patients with events had significantly persistently prolonged EMAT% and low MBP from 6 p.m. to 4 a.m. in comparison with patients without events (*Figure 1B,C*).

Table 2 Comparisons of the circadian haemodynamic parameters between patients with and without post-discharge adverse events

Variables[a]	Event (+), n = 33	Event (−), n = 30	Total, n = 63	P
SVI, mL/m^2				
Daytime	36.1 (30.3–46.3)	32.2 (24.5–39.5)	35.8 (30.0–42.7)	0.947
Nighttime	33.8 (25.4–41.0)	30.9 (25.6–36.4)	31.8 (25.8–37.7)	0.301
Overnight Δ	−2.8 (−5.3 to −0.4)	−1.4 (−4.6 to 3.1)	−1.9 (−4.8 to 1.1)	0.161
Early morning	32.0 (25.0–39.7)	30.1 (23.5–37.7)	31.2 (25.8–38.6)	0.670
CI, L/min/m^2				
Daytime	2.9 (2.5–3.2)	3.0 (2.5–3.5)	2.9 (2.5–3.3)	0.350
Nighttime	2.4 (2.2–2.9)	2.6 (2.4–3.2)	2.5 (2.2–2.9)	0.103
Overnight Δ	−0.4 (−0.6 to −0.1)	−0.4 (−0.7 to 0.00)	−0.4 (−0.6 to −0.02)	0.779
Early morning	2.4 (2.1–3.0)	2.5 (2.3–3.1)	2.4 (2.3–3.0)	0.240
TFCi, 1/kΩ/m^2				
Daytime	10.9 (9.3–14.2)	10.0 (8.0–11.9)	10.3 (8.6–12.1)	0.248
Nighttime	12.3 (10.5–15.9)	10.3 (8.0–12.3)	11.6 (9.4–12.8)	**0.006**
Overnight Δ	1.3 (0.6–2.2)	0.4 (−0.3 to 0.8)	0.7 (0.3–1.6)	**<0.001**
Early morning	12.5 (10.5–16.4)	9.7 (7.8–12.5)	11.9 (8.8–13.1)	**0.005**
EMAT, %				
Daytime	16.4 (12.8–18.7)	13.9 (10.4–15.2)	14.5 (11.4–16.6)	**0.022**
Nighttime	13.9 (12.1–15.3)	12.8 (10.0–14.2)	13.3 (10.8–14.4)	**0.025**
Overnight Δ	−0.9 (−2.5 to −0.1)	−0.6 (−1.9 to 0.1)	−0.7 (−2.1 to −0.1)	0.434
Early morning	14.1 (12.7–16.5)	12.5 (10.3–14.5)	13.1 (11.3–14.6)	0.034
SBP, mmHg				
Daytime	101.8 (90.8–115.8)	129.5 (112.4–136.7)	116.0 (103.3–132.1)	0.002
Nighttime	102.0 (84.7–121.2)	123.3 (109.9–142.5)	117.0 (100.6–127.2)	0.023
Overnight Δ	2.7 (−6.1 to 7.4)	3.0 (−14.3 to 6.1)	2.8 (−8.4 to 6.8)	0.862
Early morning	104.5 (83.0–124.8)	124.8 (108.9–144.6)	119.5 (95.8–133.0)	0.041
DBP, mmHg				
Daytime	60.0 (55.4–67.5)	78.6 (67.2–88.8)	67.8 (58.8–82.7)	0.004
Nighttime	62.9 (56.4–70.4)	76.8 (59.8–89.9)	66.2 (58.1–78.2)	0.050
Overnight Δ	1.8 (−3.5 to 9.4)	1.0 (−7.3 to 12.7)	1.8 (−4.6 to 9.9)	0.972
Early morning	58.5 (55.5–71.8)	79.0 (65.1–93.8)	68.5 (57.5–86.0)	0.009
MBP, mmHg				
Daytime	74.8 (69.5–79.1)	94.2 (81.6–104.7)	80.4 (75.5–98.3)	**<0.001**
Nighttime	76.7 (64.2–81.7)	92.0 (83.4–107.3)	84.1 (75.8–93.3)	**0.004**
Overnight Δ	2.5 (−3.7 to 8.4)	2.4 (−8.6 to 9.6)	2.5 (−6.6 to 8.4)	1.000
Early morning	82.0 (65.0–85.5)	90.5 (81.5–112.1)	83.0 (71.5–100.0)	**0.018**
Heart rate, b.p.m.				
Daytime	77.0 (62.9–89.9)	83.8 (75.3–96.9)	80.8 (70.5–94.9)	0.201
Nighttime	71.8 (63.8–78.7)	78.4 (71.4–92.7)	76.6 (68.1–84.4)	0.111
Overnight Δ	−5.5 (−7.5 to 0.6)	−5.3 (−7.9 to 1.1)	−5.3 (−7.6 to 1.0)	0.776
Early morning	68.0 (62.3–75.8)	79.3 (73.8–91.1)	76.0 (66.0–82.8)	**0.033**

CI, cardiac index; DBP, diastolic blood pressure; EMAT%, electromechanical activation time ratio; MBP, mean blood pressure; SBP, systolic blood pressure; SVI, stroke volume index; TFCi, thoracic fluid content index.
[a]Daytime: measurements around 6 p.m.; Nighttime: measurements averaged from 10 p.m. to 5 a.m.; Overnight Δ: measurements around 4 a.m. minus measurements around 6 p.m.; Early morning: measurements around 4 a.m.

Associations between circadian thoracic fluid content index and parameters of daytime cardiac, pulsatile haemodynamic, and renal function parameters

Daytime TFCi (measurements around 6 p.m.) was only significantly associated with AI (*Table 3*). In contrast, nighttime TFCi (measurements averaged from 10 p.m. to 4 a.m.) was significantly associated with AI, Pb, LVEF, EMAT%, and eGFR. Moreover, overnight ΔTFCi (measurements around 4 a.m. minus the measurements around 6 p.m.) was significantly associated with LVEF, EMAT%, and eGFR (*Table 3*).

Predictors of adverse post-discharge events

In univariate Cox regression analyses, daytime measures of LVEF, eGFR, Pb/Pf, EMAT%, and MBP were crudely predictive of primary composite events, while cardiac index, EMAT%, and MBP were significantly predictive of recurrent hospitalizations (*Table 4*, unadjusted models). On the other hand, nighttime measures of TFCi (nighttime, overnight Δ, and early morning), EMAT% (nighttime and early morning), and nighttime MBP were significantly predictive of either primary composite events or recurrent hospitalizations. Nighttime measures of cardiac index (nighttime and early morning) were associated with recurrent hospitalizations. It is noteworthy that neither daytime body weight change during the hospitalization nor daytime TFCi was significantly associated with the outcomes. After adjusting for age, gender, and

Table 3 Correlation coefficients between circadian thoracic fluid content index with daytime cardiac, pulsatile haemodynamic, and renal function parameters

Variables	Daytime TFCi[a]	Nighttime TFCi[a]	Overnight ΔTFCi[a]
CFPWV, m/s	−0.007	0.137	−0.067
AI, %	0.382**	0.376**	0.189
Pf, mmHg	0.021	0.055	−0.005
Pb, mmHg	0.248	0.305*	0.293
Pb/Pf	0.151	0.183	0.206
LVEF, %	0.188	−0.452**	−0.328*
CI, L/min/m²	0.034	0.007	0.061
EMAT, %	−0.166	0.417**	0.405*
24 h MBP, mmHg	−0.034	−0.048	−0.185
eGFR	−0.188	−0.345*	−0.343*

AI, augmentation index; CFPWV, carotid-femoral pulse wave velocity; CI, cardiac index; eGFR, estimated glomerular filtration rate; EMAT%, electromechanical activation time ratio; LVEF, left ventricular ejection fraction; MBP, mean blood pressure; Pb, amplitude of backward pulse wave component; Pf, amplitude of forward pulse wave component; TFCi, thoracic fluid content index.
*$P < 0.05$.
**$P < 0.01$.
[a]Daytime TFCi: measurements around 6 p.m.; Nighttime TFCi: measurements averaged from 10 p.m. to 4 a.m.; Overnight ΔTFCi: measurements around 4 a.m. minus measurements around 6 p.m.

pre-discharge NT-proBNP, only nighttime measures of TFCi (HR and 95% CIs for nighttime TFCi: 1.040, 1.006–1.076; overnight ΔTFCi: 1.579, 1.068–2.334; and early morning TFCi: 1.042, 1.014–1.070) and EMAT% (nighttime EMAT%: 1.186, 1.020–1.377) remained the independent predictors of primary composite events (*Table 4*, Model 1). In the recurrent events analysis, overnight ΔTFCi was still an independent predictor of recurrent composite events by the Wei–Lin–

Figure 1 Comparison of circadian change of haemodynamic parameters by each hour derived from continuous recording of (A) impedance cardiography [thoracic fluid content index (TFCi)], (B) acoustic cardiography [electromechanical activation time ratio (EMAT%)], and (C) ambulatory blood pressure monitoring [mean blood pressure (MBP)] between patients with and without post-discharge adverse events. Error bars are standard errors. Asterisk (*) indicates significant difference ($P < 0.05$) between patients with and without events.
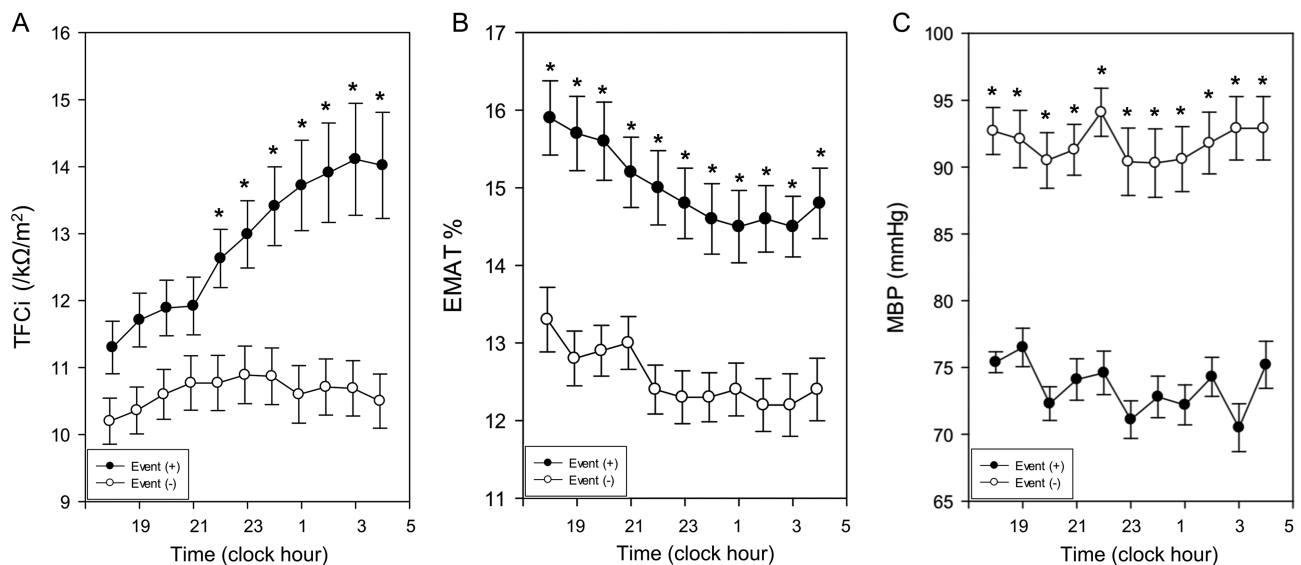
Table 4 Hazard ratios and 95% confidence intervals for the primary and recurrent composite events

| | Primary composite event | | | | Recurrent composite events | | | | | |
| | Unadjusted | | Model 1[a] | | Unadjusted | | Model 2[b] | | Model 3[c] | |
Variables	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P
Daytime measurements										
ΔBW	1.022 (0.952–1.096)	0.549			1.048 (0.988–1.112)	0.121				
LVEF	0.961 (0.931–0.990)	0.011	0.922 (0.846–1.004)	0.062	0.762 (0.568–1.022)	0.069				
eGFR	0.989 (0.980–0.999)	0.030	1.006 (0.988–1.025)	0.501	0.992 (0.982–1.001)	0.091				
CFPWV	1.000 (0.999–1.001)	0.432			1.000 (0.999–1.001)	0.717				
AI	1.023 (0.987–1.060)	0.209			1.017 (0.980–1.056)	0.377				
Pb	0.990 (0.941–1.043)	0.711			0.982 (0.919–1.050)	0.594				
Pb/Pf	1.036 (1.006–1.067)	0.018	1.008 (0.973–1.045)	0.641	1.027 (0.998–1.057)	0.064				
Cardiac index[d]	0.726 (0.386–1.366)	0.321			0.430 (0.235–0.785)	0.006	0.492 (0.317–0.966)	0.013	0.530 (0.338–1.333)	0.069
TFCi[d]	1.062 (0.944–1.195)	0.318			1.069 (0.949–1.204)	0.271				
EMAT%[d]	1.182 (1.042–1.340)	0.009	1.133 (0.988–1.299)	0.073	1.236 (1.125–1.357)	<0.001	1.195 (1.085–1.316)	<0.001	1.232 (0.958–1.473)	0.057
MBP[d]	0.910 (0.846–0.978)	0.010	0.890 (0.789–1.003)	0.056	0.902 (0.861–0.946)	<0.001	0.899 (0.823–0.982)	0.018	0.899 (0.802–1.007)	0.066
Nighttime measurements[e]										
Nighttime cardiac index	0.629 (0.347–1.143)	0.128			0.421 (0.222–0.799)	0.008	0.325 (0.169–0.626)	<0.001	0.264 (0.108–0.644)	0.003
Overnight Δcardiac index	0.931 (0.588–1.474)	0.760			0.917 (0.664–1.268)	0.601				
Early morning cardiac index	0.660 (0.371–1.173)	0.157			0.433 (0.23–0.809)	0.009	0.316 (0.165–0.606)	<0.001	0.255 (0.113–0.572)	<0.001
Nighttime TFCi	1.109 (1.035–1.189)	0.003	1.040 (1.006–1.076)	0.022	1.093 (1.043–1.145)	<0.001	1.081 (1.031–1.133)	0.001	1.081 (0.948–1.232)	0.246
Overnight ΔTFCi	1.545 (1.130–2.113)	0.006	1.579 (1.068–2.334)	0.006	1.692 (1.245–2.300)	<0.001	1.935 (1.360–2.753)	<0.001	2.220 (1.510–3.263)	<0.001
Early morning TFCi	1.082 (1.024–1.143)	0.005	1.042 (1.014–1.070)	0.005	1.067 (1.031–1.105)	<0.001	1.058 (1.023–1.094)	0.001	1.060 (0.911–1.234)	0.450
Nighttime EMAT%	1.200 (1.049–1.374)	0.008	1.186 (1.020–1.377)	0.008	1.218 (1.092–1.359)	<0.001	1.227 (1.114–1.350)	<0.001	1.267 (1.104–1.456)	<0.001
Overnight ΔEMAT%	1.045 (0.948–1.151)	0.380			1.021 (0.969–1.076)	0.455				
Early morning EMAT%	1.222 (1.042–1.433)	0.014	1.149 (0.978–1.351)	0.092	1.326 (1.156–1.522)	<0.001	1.263 (1.103–1.445)	<0.001	1.267 (0.942–1.709)	0.119
Nighttime MBP	0.941 (0.859–0.990)	0.019	0.942 (0.864–1.026)	0.172	0.949 (0.921–0.979)	0.001	0.968 (0.932–1.006)	0.097		
Overnight ΔMBP	1.002 (0.954–1.052)	0.929			0.999 (0.961–1.038)	0.950				
Early morning MBP	0.959 (0.920–1.000)	0.050			0.995 (0.980–1.010)	0.485				

AI, augmentation index; ΔBW, daytime body weight change during the hospitalization; CFPWV, carotid-femoral pulse wave velocity; CI, confidence interval; eGFR, estimated glomerular filtration rate; EMAT%, electromechanical activation time ratio; HR, hazard ratio; LVEF, left ventricular ejection fraction; MBP, mean blood pressure; Pb, amplitude of backward pulse wave component; Pf, amplitude of forward pulse wave component; TFCi, thoracic fluid content index.

[a]Model 1: Cox regression analysis for primary composite event, adjusted for age, gender, and pre-discharge N-terminal pro B-type natriuretic peptide levels.

[b]Model 2: Wei-Lin-Weissfeld model for recurrent composite events, adjusted for age, gender, and pre-discharge N-terminal pro B-type natriuretic peptide levels.

[c]Model 3: Wei-Lin-Weissfeld model for recurrent composite events, adjusted for age, gender, pre-discharge N-terminal pro B-type natriuretic peptide, estimated glomerular filtration rate, haemoglobin, and Pb/Pf.

[d]Daytime: measurements around 6 p.m.

[e]Nighttime: measurements averaged from 10 p.m. to 4 a.m.; Overnight Δ: measurements around 4 a.m. minus measurements around 6 p.m.; Early morning: measurements around 4 a.m.

Weissfeld model with an estimated HR of 2.20 (95% CI 1.510–3.263; $P < 0.001$), after accounting for age, gender, pre-discharge NT-proBNP, eGFR, haemoglobin, and Pb/Pf (*Table 4*, Model 3).

By ROC curve analysis, the area under curve of overnight ΔTFCi (0.784, 95% CI 0.648–0.886; $P < 0.001$) was larger than those of nighttime (0.721, 95% CI 0.584–0.857; $P < 0.001$) and early morning (0.721, 95% CI 0.584–0.858; $P < 0.001$) TFCi in the prediction of adverse post-discharge outcomes. A cut-off value of 0.5/kΩ/m^2 for overnight ΔTFCi was derived from the ROC analysis. Patients with an overnight ΔTFCi $\geq$ 0.5/kΩ/m^2 had a significantly higher risk of developing adverse post-discharge events (HR 6.25; 95% CI 2.30–16.96; $P < 0.001$) when compared with those with an overnight ΔTFCi $<$ 0.5/kΩ/m^2 (*Figure 2*).

Discussion

By combining impedance cardiography, acoustic cardiography, and ABPM, the present study provided a comprehensive evaluation of the circadian changes in volume status and haemodynamic parameters in AHF patients who were considered as near clinical euvolaemia and ready for discharge. We found a progressive increase in TFCi from 6 p.m. to 5 a.m. in patients with post-discharge events. Patients with post-discharge events were characterized by a lower LVEF, more prolonged EMAT%, and lower MBP when compared with those without events. The nocturnal increase in TFCi was not associated with significant changes in the concomitantly measured haemodynamic parameters. Patients with greater nighttime TFCi, overnight ΔTFCi, early morning TFCi,

and prolonged nighttime EMAT% had a significantly greater risk for worsening heart failure requiring hospitalization and mortality after discharge. It is noteworthy that daytime measures of cardiac index, TFCi, EMAT%, and pulsatile haemodynamics were not associated with the outcomes in the multivariate analyses. Therefore, our results suggest that the nocturnal increase in TFCi may indicate the presence of significant volume overload not uncovered by clinical assessment or daytime measures, which may impact the post-discharge prognosis if left untreated.

Assessment of volume overload in heart failure patients

Volume overload in patients with heart failure, indicating the presence of higher left ventricular filling pressures, is associated with higher risk for hospitalizations and mortality.[5,6] On the basis of the ambulatory monitoring of intracardiac pressures, filling pressures rise more than 2 weeks before rehospitalization. Early detection and targeted changes in diuretics and vasodilators to reduce filling pressures have resulted in significant reduction in heart failure rehospitalization in patients with heart failure.[6,21] On the other hand, non-invasive assessment of the volume status in heart failure patients using various bioimpedance devices has been present for decades.[10,22] In stable patients with heart failure with a recent episode of clinical decompensation, impedance cardiography (transthoracic impedance, providing three parameters: velocity index, TFCi, and left ventricular ejection time) performed every 2 weeks can identify patients at increased near-term risk of recurrent decompensation.[11] More recently, the lung impedance, more sensitive to lung

Figure 2 Kaplan–Meier curve of event-free survival in patients with high and low overnight ΔTFCi. TFCi, thoracic fluid content index.
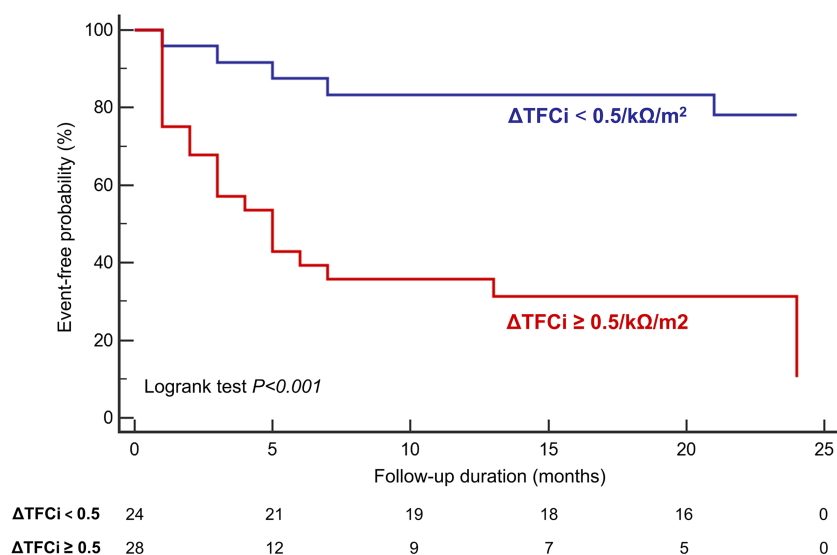
congestion than the transthoracic impedance, can be measured by subtracting the high impedance of the chest walls from the transthoracic impedance.[23] The lung impedance-guided pre-emptive treatment of chronic heart failure patients reduces hospitalizations for AHF and mortality, and the extent of pulmonary fluid content improvement based on the lung impedance measurement strongly predicted readmission and event-free survival time.[23,24] However, despite the advances in impedance cardiography, the accuracy and reproducibility of the parameters retrievable from the various bioimpedance devices continue to be challenged.[22]

In patients hospitalized due to AHF, the clinical utility of impedance cardiography is less clearly defined. In 163 hospitalized AHF patients, TFC measured by impedance cardiography at discharge was a predictor of post-discharge outcome in univariate but not in multivariate Cox regression analysis.[25] Similarly, we have shown in 120 AHF patients that TFC measured at discharge was higher in those with post-discharge events than those without, but TFC was not an independent predictor of outcomes in multivariate analysis.[26] The present study calculated TFCi from the measured transthoracic impedance. Although there is always a concern about the imprecision in the quantification of fluid contents by impedance cardiography, the observed increasing trend in TFCi during nighttime in patients with events is less affected by the measurement errors and is relatively robust. Moreover, we found that overnight ΔTFCi outperformed the daytime TFCi in the prediction of post-discharge events, suggesting that daytime measures of volume status may not be sufficient to define clinical euvolaemia for AHF patients.

Nocturnal rostral fluid shift

Rostral fluid displacement from the legs during sleep has been observed in men with and without heart failure.[27,28] Recumbency during sleep may increase renal arterial blood flow and cause nocturnal physiological diuresis, which may help remove the excess fluid from the legs accumulated during daytime.[29,30] It is conceivable that when the protective mechanism of nocturnal physiological diuresis is impaired due to renal function impairment, or overwhelmed by significant volume overload, the nocturnal rostral fluid shift may result in a progressive increase in TFCi, as observed in AHF patients with post-discharge outcomes in the present study. In patients with nocturnal hypertension, Kario et al. proposed that the left ventricular wall stress may be augmented by the nighttime increase in circulating volume by the shift of interstitial fluid from the soft tissue of the lower body, and the nighttime increase in left ventricular wall stress may constitute a risk for the nighttime onset of heart failure.[31] In the present study, both nighttime TFCi and overnight ΔTFCi were significantly associated with LVEF, EMAT%,

and eGFR (Table 3). Our results support that the nocturnal increase in TFCi may have detrimental effects on the failing heart.

Nighttime haemodynamics

In a longitudinal population-based cohort study of 11135 adults from Europe, Asia, and South America, nighttime blood pressure was more strongly associated with cardiovascular outcomes than the daytime measurement.[14] In 97 patients hospitalized due to AHF, nighttime EMAT, but not daytime EMAT, significantly predicted post-discharge events.[15] In the present study, nighttime measurements of TFCi, including nighttime TFCi, overnight ΔTFCi, and early morning TFCi were independently predictive of post-discharge events. In contrast, the diurnal congestion assessed by daytime TFCi was not related to the outcomes. Given all the patients were supposedly euvolaemic by physical examinations, diurnal impedance may not be incremental to predict post-discharge events in this study. Similarly, the present study also showed that nighttime EMAT%, but not daytime EMAT%, was associated with outcomes. In addition, the higher E/e′ measured during daytime indicated the persistently higher filling pressure before discharge in the study population. The study may suggest that the daytime echocardiographic filling pressure may be a less sensitive parameter than nighttime TFCi, reflecting the disease severity. Thus, the overall results of the present study may emphasize the importance of nighttime haemodynamics in the pathophysiology of AHF.

In the present study, nighttime TFCi was significantly associated with AI and Pb. However, none of the pulsatile haemodynamic parameters measured during daytime, including CFPWV, AI, Pf, Pb, and Pb/Pf, was significantly independently associated with post-discharge outcomes. Thus, it is likely that the nocturnal increase in TFCi may adversely impact outcomes independently of the daytime and nighttime haemodynamics.

Study limitations and clinical implications

The present study consisted of a relatively small population with considerable between-group differences in age and body size, which might confound both pulsatile and impedance haemodynamic measurements. Because the heterogeneous aetiologies underline heart failure with preserved ejection fraction and the measures of pulsatile haemodynamics in atrial fibrillation were not valid, we only enrolled patients with sinus rhythm and LVEF < 50% in this study. We also have adjusted for the available confounders to demonstrate the independence of circadian TFCi in the prediction of clinical outcomes. Although we did not evaluate the congestive symptoms/signs by either standard

questionnaires or an independent physician, all the study participants have been weaned from intravenous drugs and about to be discharged on the next day. This might be a true reflection of the real-world practice. However, we could only continuously record signals from 6 p.m. to around 5 a.m. rather than a true 24 h recording, due to the battery limit. In addition, we did not repeat the circadian measures of these haemodynamics after discharge to monitor the trajectory of certain congestion parameters. Further prospective studies were therefore needed.

Conclusions

Nocturnal thoracic volume overload in AHF patients before discharge may indicate the presence of residual volume overload unidentified by daytime measures, which is independently associated with post-discharge adverse outcomes. Whether nighttime haemodynamics-guided heart failure management improves patient outcomes may deserve future research and development.

Conflict of interest

None declared.

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