ESC HEART FAILURE
ESC Heart Failure 2021; **8**: 4037–4047
Published online 28 June 2021 in Wiley Online Library (wileyonlinelibrary.com) **DOI:** 10.1002/ehf2.13492

ORIGINAL RESEARCH ARTICLE

Temporal changes of cardiac acoustic biomarkers and cardiac function in acute decompensated heart failure

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Abstract

Aims Relationships between cardiac acoustic biomarkers (CABs) measured by acoustic cardiography and clinical outcomes have been reported in heart failure (HF) patients. However, no studies have investigated the temporal change of CABs and the corresponding changes in HF status. The purpose of this study was to assess whether the temporal changes of CABs in patients with acute decompensated heart failure (ADHF) reflect changes in cardiac function and status.

Methods and results Sixty ADHF patients were enrolled prospectively. CABs and echocardiography data were collected at admission, before discharge, and at the first clinic visit. CABs included electromechanical activation time (EMAT); the time interval from Q wave onset on electrocardiography to the first heart sound (S1), QoS2; the time interval from Q wave onset on electrocardiography to the second heart sound (S2); and third heart sound (S3) and fourth heart sound (S4) intensities, defined as the peak-to-peak amplitudes of S3 and S4. EMATc (EMAT/RR) ($P = 0.001$), S3 intensity ($P < 0.001$), and S4 intensity ($P < 0.001$) were significantly decreased, and QoS2 ($P = 0.005$) was significantly increased from admission to discharge. The change in S3 intensity was significantly correlated with that of E/A ($\rho = 0.571$, $P < 0.001$), and the extended QoS2 was also significantly correlated with the increase in the stroke volume index ($\rho = 0.383$, $P = 0.004$).

Conclusions Some CABs in ADHF patients changed significantly in the normal direction throughout the treatment course and could be useful biomarkers in ADHF management.

Keywords Acoustic cardiography; Cardiac acoustic biomarkers; Heart failure; Heart sound

Received: 11 February 2021; Revised: 26 May 2021; Accepted: 15 June 2021
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Introduction

Heart failure (HF) has a global prevalence and causes high morbidity and mortality.[1] Although the prognosis of patients with HF has improved because of recent advances in medical management, these patients' mortality and readmission rates remain a global public health concern.[2] There is a need for a method to assess a patient's HF promptly, easily, and accurately, but the existing comprehensive assessment performed in HF patients is labour intensive, time-consuming, and generally requires expertise and skills to obtain or interpret the data.

Recently, a new technology, acoustic cardiography, which consists of a simultaneously recorded electrocardiogram and phonocardiogram, that could assist in HF assessment has been reported.[3] Acoustic cardiography, which can be measured by an ambulatory device[4] or by a wearable cardioverter defibrillator,[5] provides quantitative information regarding the combination of systolic and diastolic time intervals and extra cardiohemic vibrations (e.g. third and fourth heart sounds) as cardiac acoustic biomarkers (CABs). Previous studies in which CABs were investigated in HF patients have shown their associations with left ventricular (LV) dysfunction and an increased risk of rehospitalization.[3] In addition, some other reports suggested that third heart sounds measured by cardiac implantable electronic devices and the indices from multiple parameters, including the invasive first and third

heart sounds, may be useful for early detection of worsening HF.[6–8] Therefore, the third heart sound measured non-invasively rather than by implantable devices may also be a useful biomarker reflecting HF status.

Although CABs have been suggested as useful for the assessment of cardiac function in HF patients at the diagnostic stage or for predicting their prognosis,[3] no reports have examined the temporal changes of CABs and the corresponding changes in cardiac function and status in HF patients through the treatment course following hospitalization due to acute decompensated heart failure (ADHF). The purpose of the present study was to assess whether the temporal changes of CABs in patients hospitalized due to ADHF reflect changes in cardiac function and status as assessed by echocardiographic parameters.

Methods

Subjects

The Audicor Clinical Trial for Observation of Response to treatment in HF (ACTOR-HF study) was a single-centre, observational study. Sixty patients hospitalized for ADHF between June 2017 and February 2018 at Juntendo University Hospital (Tokyo, Japan) were prospectively enrolled. In this study, ADHF patients were assessed for changes in CABs and the corresponding changes in echocardiographic parameters, because it was expected that dynamic changes would be seen in parameters indicating cardiac function and status in response to their treatment throughout the hospital course. The inclusion criteria were men and women $\geq$ 20 years of age hospitalized due to ADHF with a New York Heart Association functional class $\geq$ II. ADHF was defined according to the modified Framingham criteria. Patients were excluded from this study if they met the following criteria: shock, acute coronary syndrome, severe ventricular arrhythmia, severe stenotic valvular diseases or organic severe mitral regurgitation, apparent chronic lung disease, severe liver dysfunction, cerebrovascular disease with neurological deficit, end-stage renal disease requiring dialysis, and LV assist device or pacemaker implantation, including an implantable cardioverter defibrillator or cardiac resynchronization therapy-defibrillator. The reason for excluding pacemaker implantation was that the controlled R–R interval would make it difficult to interpret the changes of interval-based CABs. Baseline data including vital signs and blood sampling data were obtained within the initial few days after admission. The ACTOR-HF study was approved by the Juntendo University Hospital Institutional Review Board and complied with the ethical principles of the Declaration of Helsinki. Written, informed consent was obtained from all participants prior to enrolment. This study was registered with the UMIN Clinical Trials Registry (identifier: UMIN000027945).

To obtain reference CAB values in Japanese subjects, CABs were collected from 11 healthy volunteers from Asahi Kasei Corp. (Tokyo, Japan) in October 2016. The protocol for healthy volunteers was approved by the ethics committee of Asahi Kasei Corp., and written, informed consent was obtained from all healthy volunteers before participation.

Data collection

Measurement of cardiac acoustic biomarkers

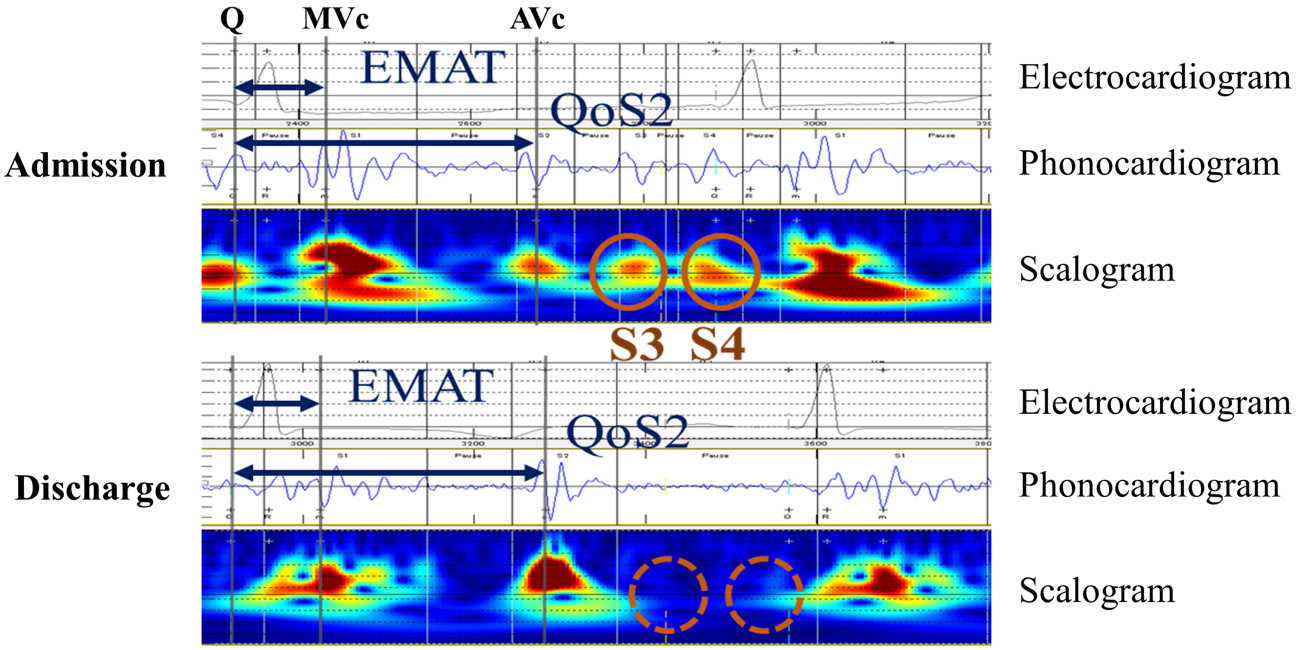
Cardiac acoustic biomarkers were recorded by an approved medical device, AUDICOR AM-RT (Inovise Medical Inc., Portland, OR, USA), with three electrodes for electrocardiography placed at the right upper, left upper, and left lower chest areas, and the other two electrodes with an accelerometer attached at the V3 and V4 positions of the chest wall. In patients with ADHF, CABs were measured while the patient was supine at rest on the following three occasions: at admission, before discharge, and at the first clinic visit after discharge. In healthy volunteers, CABs were measured on one occasion. All CAB measurements were done while the volunteers were supine at rest for 5 min.

The AUDICOR algorithm automatically segmented cardiohemic vibrations into heart sounds and pauses with the aid of machine learning technology based on acoustic models consisting of the synchronously recorded heart sounds and electrocardiography, and it provided the scalogram for heart sounds and quantitatively calculated the CABs every 10 s, as in previous reports.[3,4] CABs in this study were taken as the median values over 5 min. Electromechanical activation time (EMAT) was defined as the time interval from Q wave onset on electrocardiography to the first heart sound (S1) (*Figure 1*). Prolongation of EMAT, especially more than 120 ms, has been reported to reflect impaired LV performance.[3] EMATc was defined as the ratio of EMAT to the R–R interval. Similar to EMAT, a higher EMATc, especially more than 15%, has been reported to reflect impaired systolic performance.[9] The total electromechanical systolic interval (QoS2) was defined as the time interval from Q wave onset on electrocardiography to the second heart sound (S2) (*Figure 1*). The QoS2 consists of EMAT, and the time interval from S1 to S2 is equal to the total LV systolic time.[10] S3 and S4 intensities were defined as the peak-to-peak amplitudes of the third heart sound (S3) and the fourth heart sound (S4), respectively. The amplitude of S3 measured by an implanted device has been reported to be a parameter correlated with the auscultated S3.[8]

Echocardiography

Echocardiography was performed in patients with ADHF just before collecting CABs on each occasion. The changes of both

Figure 1 Definitions of CABs. AVc, aortic valve closure; EMAT, time interval from Q on electrocardiogram to the first heart sound; MVc, mitral valve closure; Q, Q wave onset; QoS2, time interval from Q on electrocardiogram to the second heart sound; S3, third heart sound; S4, fourth heart sound. The vertical axis of the scalogram means the frequency band and the shades of colour on the blue background express the intensities of each sound.



from admission to discharge and from admission to the first clinic visit after discharge were evaluated. Standard two-dimensional echocardiography and Doppler ultrasound examinations were performed.[11] The left ventricular ejection fraction (LVEF), stroke volume index (SVI), and left atrial volume index (LAVI) were calculated using Simpson's biplane method. Mitral inflow velocities (E and A) were obtained in the apical four-chamber view using pulse-wave Doppler, with the sample volume placed between the mitral leaflet tips. Mitral E-wave deceleration time (DcT) was measured from the peak of the E-wave velocity. SVI and LAVI were divided by the body surface area and are expressed as the SVI and LAVI indices, respectively.

Other data

Subjects had their systolic blood pressure (BP) and diastolic BP measured by a sphygmomanometer while seated after 5 min of rest at the time of echocardiography. Heart rate (HR) and weight were also measured at the same time. Serum N-terminal pro-B-type natriuretic peptide (NT-proBNP) and creatinine levels were measured on each occasion.

Statistical analysis

Continuous variables are reported as means ± standard deviation or medians and interquartile range (IQR), and categorical variables are reported as numbers and proportions. After confirming the normality of individual parameter distributions on each occasion, the differences in CABs between HF patients and healthy subjects were compared by the Wilcoxon rank-sum test. Variations of these parameters across the treatment course were assessed by the Friedman test, and then post hoc pairwise tests were performed between admission and discharge and between admission and the first clinic visit by the Wilcoxon signed-rank test with the Bonferroni correction. Correlations of the changes between CABs and echocardiographic and other parameters were evaluated by Spearman's rank correlation coefficient. The differences in changes of CABs in association with HF medications were assessed by the Wilcoxon rank-sum test. Statistical analysis was performed by RStudio ver. 1.2.5033 (RStudio Inc., Boston, MA, USA).

Results

Of the 60 ADHF patients enrolled, 54 who completed data collection both at admission and before discharge were assessed as an analysis dataset, and their baseline demographic and clinical characteristics are shown in *Table 1*. The patients' mean age was 69.7 ± 13.0 years, 75.9% were male, the mean body mass index (BMI) was 24.3 ± 4.5 kg/m^2, and 53.7% had atrial fibrillation (AF). The mean hospital length of stay was 12.7 ± 7.1 days, and these patients had

Table 1 Demographic and clinical characteristics of acute decompensated heart failure patients

Parameter	$N = 54$
Age, years	69.7 ± 13.0
Men, *n* (%)	41 (75.9)
BMI, kg/m^2	24.3 ± 4.5
Systolic BP, mmHg	131.5 [112.2, 147.8]
Diastolic BP, mmHg	73.5 [63.5, 90.0]
Atrial fibrillation, *n* (%)	29 (53.7)
Ischaemic aetiology, *n* (%)	15 (27.8)
Previous hospitalization due to HF, *n* (%)	12 (22.2)
NYHA class, *n* (%)	
II	10 (18.5)
III	37 (68.5)
IV	7 (13.0)
LVEF, %	43.5 [30.3, 54.8]
Classification of HF, *n* (%)	
HFpEF	20 (37.0)
HFmrEF	9 (16.7)
HFrEF	25 (46.3)
Serum NT-proBNP, pg/mL	3779 [2164, 6825]
Serum creatinine, mg/dL	0.97 [0.80, 1.31]
Medications, *n* (%)	
Beta-blockers	51 (94.4)
ACEIs/ARBs	34 (63.0)
MRAs	33 (61.1)
Diuretics	49 (90.7)

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; BMI, body mass index; BP, blood pressure; HFmrEF, heart failure with mid-range ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association.
HFmrEF was defined as LVEF 40–49%.

CABs, echocardiography, and other data measured within 3 days after admission and within 5 days before discharge. Correlation analyses for the changes of CABs during hospitalization with echocardiographic parameters were performed in these patients. Of these 54 patients, seven discontinued by the first clinic visit after discharge. Analyses of the temporal changes of CABs and other test values were performed in the remaining 47 patients. *Figure 2* shows the study flow chart and the reasons for discontinuation for each patient. As for the demographic characteristics of the 11 healthy reference subjects, all were male, and their mean age was 42.4 ± 11.1 years.

Comparison of cardiac acoustic biomarkers between patients at baseline and healthy subjects

The CABs at the first clinical visit after discharge were regarded as the patients' baseline values and compared with those of healthy subjects (*Table 2*). HR was not significantly different but tended to be higher in patients, and, accordingly, EMAT and QoS2 were also longer in the patients. In addition, EMATc was significantly higher in patients (10.6%, IQR = 9.1–13.0%) than in healthy subjects (7.7%, IQR = 7.1–9.6%; $P < 0.001$). Regarding CABs related to extra cardiohemic vibrations such as S3 intensity and S4 intensity,

Figure 2 Study flow chart.

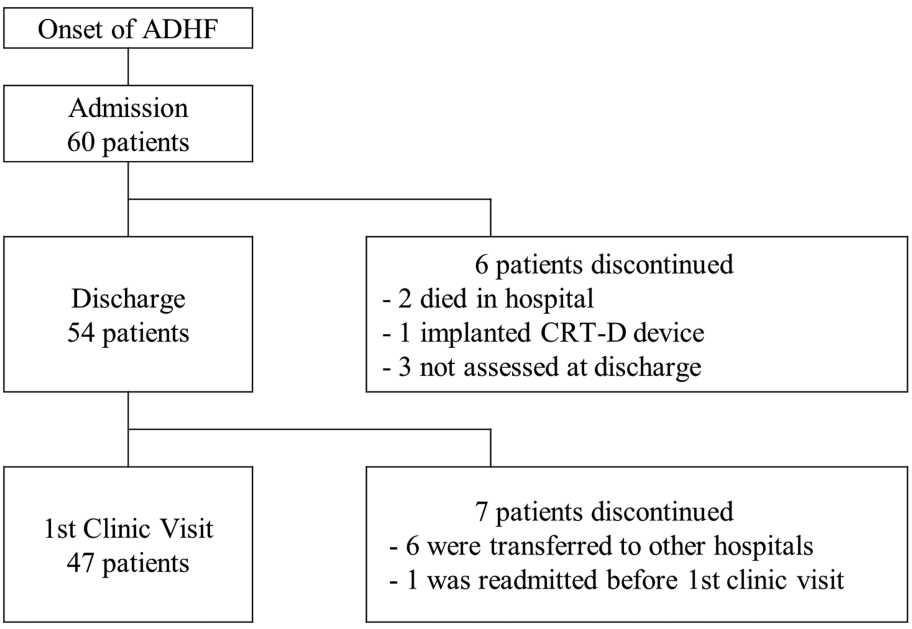


Table 2 Comparison of CABs between ADHF patients at the first clinic visit after discharge and healthy subjects

CABs	ADHF patients at the first clinic visit after discharge $N = 47$	Healthy subjects $N = 11$	P
HR, b.p.m.	65.5 [57.2, 75.5]	57.3 [55.6, 60.5]	0.054
EMAT, ms	101.8 [90.0, 121.6]	79.7 [72.9, 96.2]	0.002*
EMATc, %	10.6 [9.1, 13.0]	7.7 [7.1, 9.6]	<0.001*
QoS2, ms	440.9 [425.2, 458.0]	423.3 [416.1, 437.4]	0.036*
S3 intensity, mV	0.92 [0.84, 1.01]	0.92 [0.88, 1.04]	0.513
S4 intensity, mV	0.83 [0.73, 0.94]	0.87 [0.73, 1.10]	0.519

ADHF, acute decompensated heart failure; CAB, cardiac acoustic biomarker; EMAT, electromechanical activation time; HR, heart rate; QoS2, the total electromechanical systolic interval; S3, third heart sound; S4, fourth heart sound.
One millivolt of the accelerometer signal for S3 and S4 intensities of AUDICOR is physically equivalent to 2.0 mG of gravitational acceleration.
*Wilcoxon rank-sum test: $P < 0.05$.

significant differences were not observed between the patients and healthy subjects.

Temporal changes of cardiac acoustic biomarkers, echocardiographic parameters, and other data

Temporal changes of CABs in ADHF patients during the treatment course are shown in *Figures 3* and *4*, and the descriptive statistics of echocardiographic parameters and other data at each point are presented in *Table 3*. HR decreased, and, accordingly, QoS2 increased over time. These changes from admission to discharge and from admission to the first clinic visit were significant (all $P < 0.01$) (*Figure 3A,B*). Whereas EMATc also decreased significantly from 14.0% (IQR = 12.1–17.5%) at admission to 10.6% (IQR = 9.1–13.0%) at the first clinical visit ($P < 0.001$), EMAT did not change throughout the treatment course (*Figure 3C, D*). Furthermore, S3 intensity and S4 intensity decreased significantly from admission to discharge and from admission to the first clinic visit (all $P < 0.01$) (*Figure 4A,B*). On the other hand, LVEF, LAVI, inferior vena cava diameter (IVCD), E, E/A, E/e′, DcT, and tricuspid regurgitation (TR) velocity of the echocardiographic parameters and weight, systolic BP, diastolic BP, creatinine, and NT-proBNP were significantly changed in the normal direction during the treatment course (*Table 3*).

Correlations between changes in cardiac acoustic biomarkers and changes in other parameters

Correlation coefficients between changes in CABs and changes in other parameters are summarized in *Table 4*. There was a significant but weak inverse correlation between changes in EMATc and SVI ($\rho = -0.274$, $P = 0.047$) and a significant direct correlation between changes in EMATc and serum NT-proBNP levels ($\rho = 0.406$, $P = 0.006$). There were significant positive correlations between changes in QoS2 and SVI ($\rho = 0.383$, $P = 0.004$), S3 intensity and E ($\rho = 0.475$, $P < 0.001$), and S4 intensity and E ($\rho = 0.421$, $P = 0.005$). Moreover, there was a significant negative correlation between changes in S3 intensity and A ($\rho = -0.417$, $P = 0.022$) and a positive correlation between changes in S3 intensity and E/A in patients without AF ($\rho = 0.571$, $P = 0.001$). Some significant but weak direct or inverse correlations between changes in BP and changes in EMAT, EMATc, QoS2, and S3 intensity were also observed.

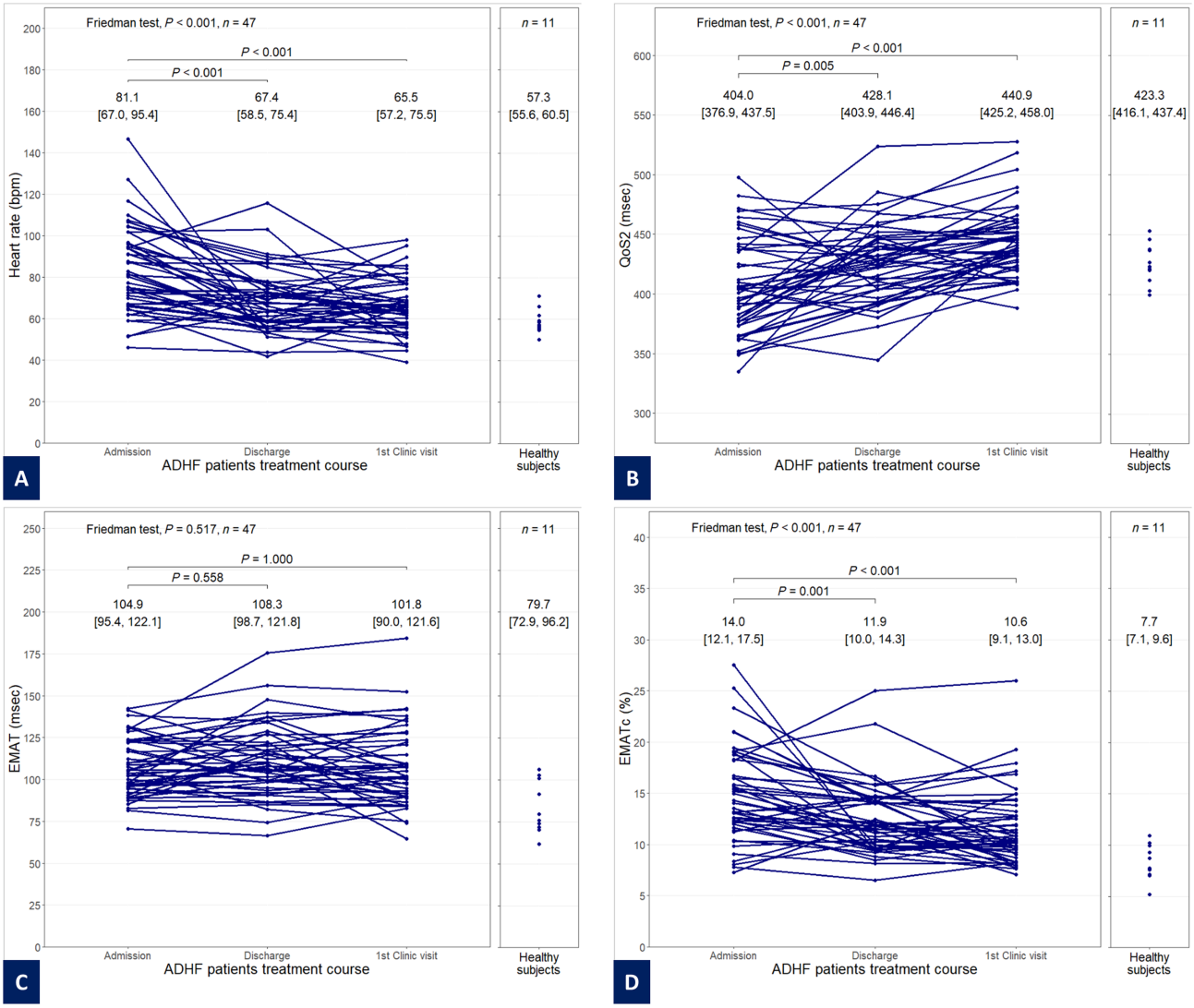
Heart failure medications and changes of cardiac acoustic biomarkers

Associations between HF medications and changes of CABs from admission to discharge are summarized in Supporting Information, *Table S1*. HR and EMATc decreased significantly more in patients treated with beta-blockers than in those without beta-blockers ($P = 0.034$, $P = 0.024$, respectively). In patients treated with angiotensin-converting enzyme inhibitors/angiotensin II receptor blockers, S3 intensity decreased significantly more than in those without angiotensin-converting enzyme inhibitors/angiotensin II receptor blockers ($P = 0.034$). In addition, in patients treated with mineralocorticoid receptor antagonists, EMATc decreased significantly more than in those without mineralocorticoid receptor antagonists ($P = 0.033$). However, there were no differences in the changes of CABs between patients with and without diuretics.

Discussion

The present study showed that ADHF patients had significantly decreased HR, EMATc, and S3 intensity and significantly increased QoS2 during the treatment course. The decrease in S3 intensity from admission to discharge was significantly correlated with that of E/A. The extended QoS2 was also significantly correlated with the increase of

Figure 3 Changes of CABs in time intervals during the treatment course. Summary statistics are presented as medians [interquartile range]. *P* values in the graphs of ADHF patients were calculated by the post hoc Wilcoxon signed-rank test with the Bonferroni correction.

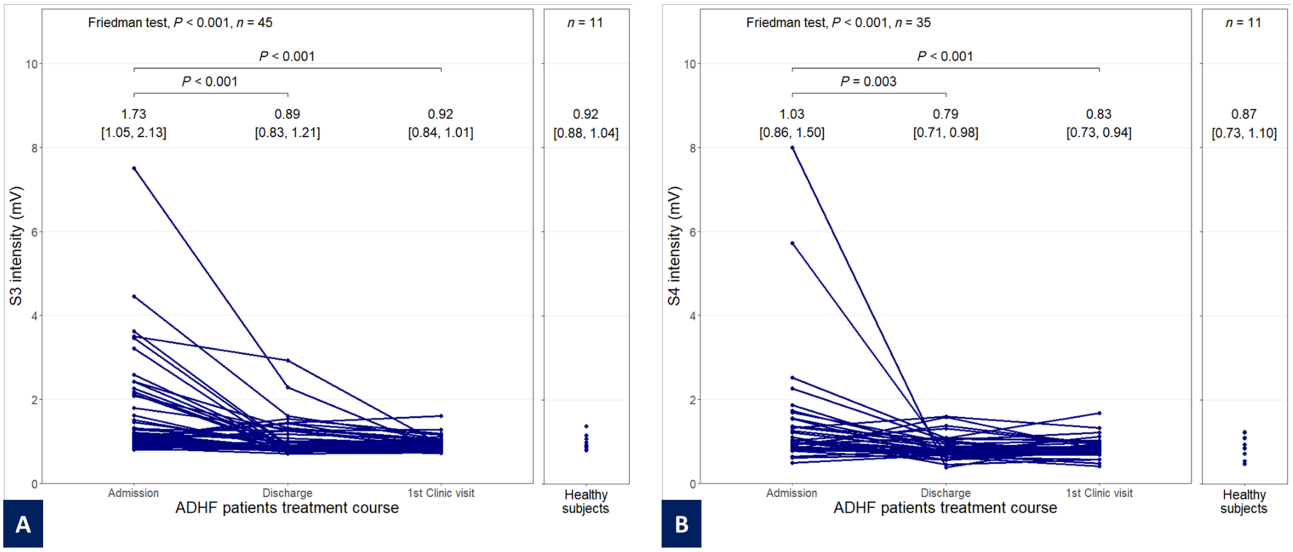


SVI. To the best of our knowledge, this study is the first to assess the changes of CABs and their correlations with echocardiography during hospitalization for treatment in ADHF patients. The results demonstrated that CABs can reflect the changes in the HF patient's cardiac status and could assist in the development of a treatment strategy for patients with ADHF.

S3, which occurs in early diastole during the rapid LV filling phase, reflects increased LV filling pressures and decreased compliance.[12] A registry of Japanese ADHF patients (i.e. ATTEND registry) reported that the presence of the auscultated S3 on admission was independently associated with increased in-hospital cardiac death.[13] On the other hand, this conventional diagnostic approach by auscultation relies on a physician's experience, which sometimes makes consistent evaluation difficult.[14] The S3 in the present study was quantified as S3 intensity using acoustic cardiography, and the parameter showed changes according to the patients' status. Recently, Cao *et al*. reported that S3 amplitude measured by implantable cardiac devices was correlated with auscultated S3 and appears to be a strong prognostic factor in patients with ADHF.[8] Non-invasive S3 was also reported to have possible practical application and prognostic value,[3] but the change in S3 intensity over time, which is measured as peak-to-peak amplitude of the heart sound as an ambulatory evaluation, has not been reported. The present study showed the non-invasively assessed intra-individual change of S3 intensity during the treatment course of ADHF patients

DOI: 10.1002/ehf2.13492

Figure 4 Changes of CABs for extra cardiohemic vibrations during the treatment course. (A) S3 intensity. (B) S4 intensity. Two subjects for S3 intensity and 12 subjects for S4 intensity had points for which AUDICOR could not calculate the values. The numerical characters in the graphs are defined as in *Figure 3*.



and suggested that S3 intensity can be a useful biomarker reflecting patients' HF status, such as pulmonary congestion. Although the presence of an auscultated S3 has been used for diagnosing HF, S3 intensity could be compared quantitatively among several time points in individual patients, so that it may help formulate the treatment strategy in patients with ADHF.

In the present study, correlations between S3 intensity and echocardiographic parameters were also evaluated, and a significant correlation between S3 intensity and transmitral flow velocity measured by echocardiography was found. Van de Werf *et al*. reported that an increased amount of inflow and a steeper rapid early filling wave due to altered diastolic properties of the LV generate a more rapid than normal deceleration of the E wave, which is likely to generate a third heart sound.[15] They showed that the heart sound occurred during the rapid deceleration of the early mitral inflow, which was caused by reversing the transmitral gradient. The present findings are in line with these previous studies that showed the associations of S3 detected by phonocardiography and parameters of diastolic dysfunction measured by echocardiography.

The systolic time interval (STI), which was originally assessed by simultaneous measurement of electrocardiogram, phonocardiogram, and carotid arterial pulse tracings, has been established as a non-invasive technique for the assessment of cardiovascular performance.[10,16] Although the commonly understood STI includes the pre-ejection period and LV ejection time (LVET), EMAT and QoS2 have also been reported to be useful for the assessment of cardiovascular performance.[17] EMAT has been shown to be prolonged in patients with impaired LV systolic function.[18] Moyers and colleagues reported that an abnormal EMATc ($\geq$ 15%) identified patients with LV dysfunction (LV end-diastolic pressure $>$ 15 mmHg and LVEF $<$ 50%).[9] Wang and colleagues also suggested that EMATc measured by acoustic cardiography at the bedside might be helpful for identifying the phenotype, such as HF with reduced ejection fraction (HFrEF) or HF with preserved ejection fraction (HFpEF), especially when echocardiography was not available.[17] Recently, Sung and colleagues also showed that optimization of post-discharge HF therapy guided by acoustic cardiography targeting an EMATc $<$ 15% might improve the clinical outcomes of all-cause mortality and readmission for HF within a year in an ADHF study population.[19] Although the present study showed that EMATc was significantly shortened during the course of treatment for ADHF patients, there was a significant but only weak inverse correlation between EMATc and SVI (ρ = $-$0.274, P = 0.047). Furthermore, LVEF increased significantly from admission to discharge, but EMATc was not correlated with LVEF (ρ = $-$0.160, P = 0.248). These suggested that the change of EMATc was not directly indicative of change of LVEF in ADHF patients.

The QoS2 consists of the pre-ejection period, including EMAT, plus the LVET. It may be considered that change of QoS2 is more affected by LVET than the pre-ejection period because of the time distribution. It is commonly known that the pre-ejection time is prolonged and LVET is shortened in patients with HF.[16] Furthermore, LVET has been considered to shorten when LVEF increases, whereas it has been

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Table 3 Changes in echocardiographic parameters and other test values in acute decompensated heart failure patients

Value	Admission (1)	Discharge (2)	1st clinic visit (3)	Repeated measures, P^a	Change			
					(2)–(1)	P^b	(3)–(1)	P^b
Echo								
LVEF, %	41.5 [30.0, 52.6]	48.0 [32.8, 55.8]	50.0 [35.0, 62.5]	<0.001	3.0 [−0.8, 8.2]	<0.001	6.0 [0.2, 12.5]	<0.001
Peak dP/dt, mmHg/s	969.0 [727.0, 1454.0]	842.0 [653.0, 969.0]	831.0 [653.0, 1185.0]	0.097	−129.0 [−382.0, 57.5]	0.296	−135.5 [−484.0, 0.0]	0.089
LAVI, mL/m^2	93.0 [76.0, 113.0]	76.7 [63.2, 96.0]	73.0 [61.6, 100.1]	<0.001	−14.6 [−28.5, 2.5]	0.001	−13.6 [−37.0, 2.0]	<0.001
IVCD, mm	18.0 [15.0, 21.8]	12.0 [9.5, 14.5]	10.0 [8.3, 13.0]	<0.001	−5.5 [−8.0, −2.8]	<0.001	−7.0 [−9.5, −4.4]	<0.001
SVI, mL/m^2	26.5 [20.5, 36.2]	28.8 [22.0, 36.8]	31.3 [24.4, 38.3]	0.256	1.3 [−4.7, 8.9]	1.000	3.5 [−3.0, 8.7]	0.213
E, cm/s	97.0 [84.0, 107.5]	80.0 [65.5, 92.0]	74.0 [60.5, 100.0]	<0.001	−15.0 [−30.3, −0.8]	<0.001	−17.0 [−33.0, 0.0]	<0.001
A, cm/s	48.0 [30.0–76.8]	59.0 [39.0, 77.3]	68.0 [42.5, 81.3]	0.102	4.5 [−8.3, 26.5]	0.136	11.0 [−6.5, 35.3]	0.089
E/A	1.99 [1.37, 3.15]	1.30 [0.91, 2.15]	1.03 [0.83, 1.65]	0.001	−0.44 [−1.13, −0.16]	0.010	−0.39 [−1.21, −0.04]	0.007
s′, cm/s	4.00 [3.00, 4.88]	4.00 [3.00, 5.00]	4.00 [3.00, 5.00]	0.728	0.00 [−0.25, 1.00]	0.756	0.00 [−0.75, 1.00]	1.000
E/e′	16.7 [13.5, 19.6]	14.0 [10.5, 17.0]	12.6 [10.4, 16.8]	<0.001	−3.8 [−6.5, 0.9]	0.001	−2.3 [−6.5, −0.2]	<0.001
DcT, ms	161.0 [137.5, 190.0]	204.0 [161.0, 232.0]	197.0 [159.0, 224.0]	<0.001	32.5 [9.8, 66.0]	<0.001	20.0 [0.0, 52.0]	<0.001
TR velocity, m/s	2.68 [2.15, 3.03]	2.28 [1.60, 2.54]	2.20 [1.74, 2.52]	<0.001	−0.50 [−0.91, −0.05]	<0.001	−0.61 [−1.04, −0.11]	<0.001
Other test values								
Weight, kg	64.6 [53.0, 73.7]	57.3 [48.3, 69.3]	58.2 [48.5, 69.8]	<0.001	−5.5 [−7.5, −2.6]	<0.001	−5.4 [−7.5, −3.2]	<0.001
Systolic BP, mmHg	132.0 [111.0, 148.5]	112.0 [98.0, 119.5]	111.0 [101.5, 125.0]	<0.001	−12.0 [−30.1, −1.0]	<0.001	−15.0 [−26.0, 0.0]	<0.001
Diastolic BP, mmHg	74.0 [63.0, 94.0]	60.0 [58.0, 68.0]	64.0 [58.0, 72.5]	<0.001	−13.5 [−26.5, −3.8]	<0.001	−14.0 [−26.0, 0.0]	<0.001
NT-proBNP, pg/mL	3601.0 [2218.2, 6430.0]	1098.0 [527.0, 2252.0]	1522.5 [690.6, 2310.7]	<0.001	−2229.7 [−3993.0, −917.6]	<0.001	−1693.0 [−2612.4, −836.0]	<0.001
Creatinine, mg/mL	0.97 [0.78, 1.24]	1.03 [0.89, 1.62]	1.04 [0.88, 1.53]	<0.001	0.10 [−0.02, 0.22]	0.001	0.10 [0.00, 0.28]	0.004

BP, blood pressure; DcT, deceleration time; IVCD, inferior vena cava diameter; LAVI, left atrial volume index; SVI, stroke volume index; TR, tricuspid regurgitation; other abbreviations as in *Table 1*.

[a]Friedman test for 47 acute decompensated heart failure patients who completed data collection on three occasions.

[b]*P* values calculated by the post hoc Wilcoxon signed-rank test with the Bonferroni correction.

Table 4 Correlations of changes of CABs with echocardiographic parameters and other test values

	CABs (Δ = Admission − Discharge)											
	ΔHR, b.p.m.		ΔEMAT, ms		ΔEMATc, %		ΔQoS2, ms		ΔS3 intensity, mV		ΔS4 intensity, mV	
Parameter	*n*	ρ	*n*	ρ	*n*	ρ	*n*	ρ	*n*	ρ	*n*	ρ
Echo												
ΔLVEF, %	54	−0.059	54	−0.183	53	−0.160	54	0.145	52	−0.103	42	−0.103
ΔPeak dP/dt, mmHg/s	33	0.136	33	−0.179	33	0.090	33	0.076	33	0.143	29	0.057
ΔSVI, mL/m^2	54	−0.349†	54	0.093	53	−0.274*	54	0.383†	52	−0.129	42	0.216
ΔE, cm/s	54	−0.035	54	0.017	53	−0.022	54	0.154	52	0.475†	42	0.421†
ΔA, cm/s	31	0.007	31	−0.028	30	0.169	31	0.025	30	−0.417*	28	−0.045
ΔE/A	31	−0.017	31	−0.061	30	−0.052	31	0.003	30	0.571†	28	0.360
Other test values												
ΔWeight, kg	54	−0.026	54	−0.016	53	0.066	54	0.072	52	0.147	42	0.218
ΔSystolic BP, mmHg	54	0.282*	54	−0.323*	53	0.149	54	−0.100	52	0.286*	42	0.169
ΔDiastolic BP, mmHg	54	0.364†	54	−0.175	53	0.312*	54	−0.301*	52	0.365†	42	0.122
Δlog$_{10}$ NTpro-BNP	47	0.377†	47	0.113	46	0.406†	47	−0.226	45	0.329*	35	0.038
ΔCreatinine, mg/mL	54	−0.126	54	−0.169	53	−0.169	54	0.070	52	0.137	42	0.047

Abbreviations as in *Tables 1–3*.
*Spearman's rank correlation: $P < 0.05$.
†Spearman's rank correlation: $P < 0.01$.

considered to prolong when stroke volume increases.[20] It has been reported that, among various factors, the factors that more strongly affect LVET are HR and SVI.[21] The present study showed that QoS2 was significantly increased during the treatment course in patients with ADHF, and the change was significantly correlated with the SVI measured by echocardiography. Collectively, it was considered that changes in SVI affected changes in QoS2, including LVET, more than improvement of LVEF, consistent with the previous reports. The result of the present study suggested that increasing QoS2 may be a marker of improvement of SVI in patients with ADHF. This study excluded ADHF patients with severe valvular disease, even though outflow obstruction, atrioventricular valvular incompetence, and myocardial insufficiency have also been reported to cause abnormalities in LVET.[21] For this reason, there is a need for further studies to elucidate how QoS2 changes in various cardiovascular diseases.

Associations between HF medications and changes in CABs from admission to discharge in this study suggested that greater improvements of CABs were observed in patients with optimal HF medications. However, another well-controlled study focused on such effects of medications on CABs is needed to prove specific relationships between HF medications and changes in CABs.

Taken together, these results suggest that CABs could be indicators of cardiac status in ADHF patients. Although several CABs were significantly correlated with echocardiographic parameters, most such correlations were not strong. The CABs may be somewhat specific indicators of the status of ADHF patients that are different from echocardiographic assessment. Acoustic cardiography can be used easily and non-invasively without specialized techniques and knowledge, and CABs can be evaluated objectively. Therefore, CABs could be useful for various medical staff other than cardiologists to easily determine a patient's HF status. However, the benefit of assessing changes in CABs in the actual clinical setting remains to be established. Considering the association between CABs and haemodynamic parameters, a comparison study with minimally invasive cardiac devices such as a pulse contour cardiac output monitor may confirm the clinical value of CABs. In addition, a prospective trial with a larger population is needed to confirm the clinical benefits of a CAB-guided strategy in the care of patients with HF.

There are several limitations in this study. First, this was a single-centre study, and the sample size was relatively small. Second, the sound intensity may vary among patients due to differences in the physique of each patient; thus, such parameters should be used to assess intra-individual changes. Last, HF patients with severe valvular disease, severe chronic lung disease, and LV hypertrophy, which affect heart sounds, were not included or evaluated in this study; therefore, further investigation is required to clarify the utility of this technology for HF patients with such diseases.

In conclusion, the CABs in ADHF patients were found to change significantly towards normal, reflecting improvement in the patients' status throughout the treatment course. Thus, the present results suggest that CABs could be easily obtainable biomarkers whose changes are associated with changes in echocardiographic parameters suggestive of the ADHF status and may be another useful tool for managing patients with ADHF.

Acknowledgements

A2 Healthcare Corporation performed data management for this study. Asahi Kasei Corporation provided the reference data of healthy subjects.

Conflict of interest

Dr. Kasai is affiliated with a department endowed by Philips Respironics, ResMed, Teijin Home Healthcare, and Fukuda Denshi. Dr. Daida received manuscript fees, research funds, and scholarship funds from Kirin Co. Ltd., Kaken Pharmaceutical Co. Ltd., Abbott Japan Co. Ltd., Astellas Pharma Inc., Astrazeneca K.K., Bayer Yakuhin Ltd., Boston Scientific Japan K.K., Bristol-Myers Squibb, Daiichi Sankyo Company, MSD K. K., Pfizer Inc., Philips Respironics, Sanofi K.K., and Takeda Pharmaceutical Co. Ltd. Other authors report no financial involvement in connection with this study that represents any conflicts of interest.

Data availability statement

The data that support the findings of this study are available from the corresponding author, T.K., upon reasonable request.

Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1. Association between HF medications and changes in CABs from admission to discharge.

Funding

This study was sponsored by Asahi Kasei Corporation.

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