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# Characterization of cardiac acoustic biomarkers in patients with heart failure

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## Abstract

**Background:** The wearable cardioverter defibrillator (WCD) records electrocardiograms and cardiohemic vibrations that can be algorithmically combined to provide cardiac acoustic biomarkers (CABs). We characterized CAB variability, diurnal variations, and changes over time among heart failure patients.

**Methods:** Wearable cardioverter defibrillator heart failure patients who had CAB recordings from March 2015 to July 2017 were included. CAB parameters included: electromechanical activation time (EMAT), EMATc (EMAT/RR interval), left ventricular systolic time (LVST), LVSTc (LVST/RR interval), S3 and S4 strengths, and systolic dysfunction index (SDI). Descriptive statistics, correlation analysis, and analysis of variance were used to report temporal and clinical associations.

**Results:** One thousand and sixty-six WCD patients met the study criteria. Diastolic CAB parameters showed significantly greater intra-subject variability than systolic CAB parameters (>29% vs. <15%, $p < .01$). CAB parameters varied very little with age, gender, and ejection fraction ($R^2$ = 0.004 to 0.06) in this heart failure population. Similarly, all CABs except SDI ($R^2$ = 0.58) were independent of QRS duration, ($R^2$ = −0.01 to 0.58). Heart rate had a more of significant influence on the systolic CABs than the diastolic CABs ($p < .05$). CABs were significantly different when measured at daytime versus nighttime ($p < .01$) and were significantly lower at the end of WCD wear compared with the beginning of wear ($p < .05$).

**Conclusions:** Noninvasive CABs offer the possibility to assess parameters associated with LV function, clinical status, and other aspects of cardiovascular physiology that differ between normal and heart failure states. The present study provides critical information about typical values in heart failure patients, intra-subject variability, circadian rhythms, and changes over time of these parameters.

KEYWORDS

heart failure, systolic time interval, wearable cardiac defibrillator

## 1 | INTRODUCTION

Recent studies have shown that daily home monitoring of intracardiac or pulmonary artery pressures provides important insights into the physiological and clinical status of patients with heart failure (HF) across the spectrum of ejection fractions (EFs) (Abraham et al., 2011) (Adamson et al., 2016). While these approaches have been shown to be effective in anticipating HF exacerbation, facilitating preemptive intervention (e.g., altering medical therapies), and reducing HF hospitalizations, their adoption has been slower than anticipated, perhaps due to the invasive nature of the technology. Translating these successes to remote home monitoring with a noninvasive device could provide the same benefits to a much larger number of patients without necessitating invasive procedures. If equally effective, such an approach could provide large cost savings to healthcare systems by reducing the number of HF hospitalizations, particularly in the vulnerable period following hospital discharge due to a recent HF exacerbation.

Concurrently recorded vibrations of the cardiohemic system (cardiac cavities, valves, and blood) and electrocardiograms (ECG) can be algorithmically interpreted to provide information regarding systolic and diastolic time intervals and measures of abnormal cardiohemic vibrations (e.g., third and fourth heart sounds) (Erne, 2008). These systolic and diastolic parameters are collectively described as cardiac acoustic biomarkers (CABs). High fidelity acoustic and electrocardiographic recording systems combined with modern-day signal analysis algorithms overcome the limitations of standard auscultation which suffers from lack of diagnostic sensitivity, specificity, and reproducibility due to a variety of reason (Erne, 2008; Ishmail et al., 1987; Marcus et al., 2006; Wen, Lee, Lee, Fang, Jin, & Yu, 2014). In fact, recent studies have shown the ability of CABs to identify HF exacerbations and predict post-discharge outcomes. A randomized, single-blind trial of 194 patients using periodically assessed acoustic cardiographic parameters to guide outpatient management of HF found a 31% reduction in HF rehospitalization or cardiovascular mortality within 1 year (Sung, Yu, Yu, Cheng, Chang, & Chen, 2014). In the active intervention arm, medications were titrated using acoustic cardiographic parameters as a guide; the control group was medically managed based on symptoms alone without the benefit of acoustic cardiographic parameter data.

Given the potential broad application of CABs to help manage HF patients, the wearable cardioverter defibrillator (WCD; LifeVest™, ZOLL, Pittsburgh, USA) was modified to record cardiohemic vibrations while simultaneously recording ECG signals in order to monitor CABs.

The purposes of the present observational study were to determine: a) intra-subject variability of CABs; b) if CABs provide discriminative data independent to common clinical parameters such as age, ejection fraction, QRS duration, and heart rate; c) circadian variation of CABs; and d) temporal changes in CABs during the typical WCD wear period. This information is critical for the design of future studies aimed at testing the use of CABs to reduce heart failure hospitalizations.

## 2 | METHODS

### 2.1 | Wearable cardiac defibrillator description

Details of the WCD components and its functions have been described previously (Klein, Goldenberg, Goldenberg, & Moss, 2013). Briefly, the WCD-monitoring electrodes are held in place circumferentially around the chest by tension from an elastic belt to provide two non-standard, orthogonal surface ECG leads; electrodes are paired front-to-back and side-to-side. One defibrillation electrode is placed in a cardiac apical position while the remaining two defibrillation electrodes are placed posteriorly on the upper thorax. The apical defibrillation electrode incorporates a 3-axis accelerometer, located left of the xiphoid process over the 5th intercostal space, to measure the cardiohemic vibrations. CABs are calculated by combining the cardiohemic vibration signals and ECG signals. The typical relationships between electrical and cardiohemic vibrations recorded by the WCD are summarized in Figure 1. The automated algorithm of the WCD monitor calculates CABs using a hidden Markov model trained with input features derived both from a wavelet transform of the cardiohemic vibrations and timing information obtained from simultaneous ECG signal analysis (Nelson, 2007). The hidden Markov model is constructed from several Gaussian mixture models, each of which provides an estimate of the class-conditional likelihood for first heart sound (S1), second heart sound (S2), third heart sound (S3), and fourth heard sound (S4) and pauses following each of the heart sounds.

Once the cardiohemic vibrations are segmented into discrete heart sounds and time intervals, the following systolic and diastolic CABs can be calculated (Figure 1):

Systolic CABs

1. Electromechanical activation time (EMAT): measured from the Q wave onset to peak of the first heart sound (S1). EMAT reflects the time required by the ventricles to generate enough force to close the atrioventricular valves. Prolongation of EMAT reflects a decrease in systolic function. For the current analysis, an EMAT

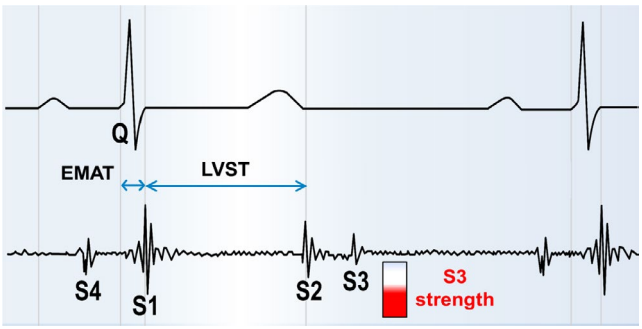


**FIGURE 1** ECG (top trace) and cardiohemic vibrations (bottom trace) recordings. Q represents the beginning of the Q wave with S1, S2, S3, and S4 representing the first, second, third, and fourth heart sound, respectively. EMAT, electromechanical activation time; LVST, left ventricular systolic time

**TABLE 1** Normal nighttime (12 a.m.-7 a.m.) and daytime (7 a.m.-12 a.m.) ranges for CABs, data from 25 normal volunteers

| CAB | Description | Nighttime normal range median [1st quartile–3rd quartile] mean (*SD*) | Daytime normal range median [1st quartile–3rd quartile] mean (*SD*) | *p* |
|---|---|---|---|---|
| Heart rate | | 61.9 [58.7–70.0]<br>62.7 (8.1) | 72.8 [66.6–77.6.1]<br>71.6 (8.6) | <.001 |
| Electromechanical activation time, EMAT (ms) | Time from Q wave to peak of first heart sound, S1 | 85.1 [78.5–90.0]<br>86.0 (10.1) | 80.2 [76.5–87.5]<br>83.2 (8.9) | <.05 |
| EMAT corrected for RR interval, EMATc | EMAT/RR interval | 8.8 [8.1–9.8]<br>9.0 (1.3) | 10.1 [8.7–10.9]<br>9.9 (1.6) | <.001 |
| Left ventricular systolic time, LVST | Time from peak of S1 to the peak S2 | 342.2 [332.7–355.2]<br>344.1 (17.1) | 318.4 [304.2–328.1]<br>317.1 (20.3) | <.001 |
| LVST corrected for RR interval, LVSTc | LVST/RR interval | 35.5 [32.9–38.6]<br>35.9 (4.1) | 36.9 [35.5–40.2]<br>37.5 (3.7) | <.001 |
| S3 strength | Based on third heart sounds timing, persistence, intensity, and frequency | 3.06 [2.67–3.31]<br>3.06 (0.55) | 2.98 [2.79–3.28]<br>3.1 (0.41) | .53 |
| S4 strength | Based on fourth heart sounds timing, persistence, intensity, and frequency | 3.88 [3.26–4.41]<br>3.77 (0.78) | 3.34 [2.95–3.74]<br>3.36 (0.64) | <.05 |
| Systolic dysfunction index, SDI | Multifactor index derived from S3, EMATc, QRS duration, and QR interval | 2.63 [2.46–3.04]<br>2.69 (0.54) | 2.89 [2.48–3.33]<br>2.95 (0.89) | .15 |

value >120 ms was considered abnormally prolonged based on a previous publication (Dillier, Zuber, Arand, Erne, & Erne, 2011) in which patients in chronic and acute heart failure had a mean EMAT value of 122.0 ± 29.4 ms and 118.0 ± 24.3 ms, respectively, and normal volunteers have a mean nighttime EMAT value of 89.7 ± 16.1 ms (Table 1; unpublished data collected as part of the study, "Heart Sounds Measurements Using the Wearable Cardioverter Defibrillator (HS_WCD) Study," with the www.clinicaltrials.gov identifier NCT02825966).

2. EMATc: ratio of EMAT to the RR interval. It indicates the proportion of the cardiac cycle occupied by the EMAT. Similar to EMAT, a prolonged EMATc reflects worsening systolic dysfunction. For the current analysis, an EMATc value >15% was considered abnormally prolonged based on a previous study where subjects in heart failure patients with reduced ejection fraction had a mean EMATc value of 15.1 ± 3.7% compared with normal nighttime EMAT value of 9.7 ± 2.5% (Wang et al., 2013).
3. Left ventricular systolic time (LVST): measured from S1 to the peak of second heart sound (S2).
4. LVSTc: ratio of LVST to the RR interval.

Diastolic CABs

5. S3 and S4 strengths: The overall S3 strength measurement is computed by extracting the log posterior probabilities of the S3 class from the Markov model output. Within each detected S3 segment, a S3 score is found as the maximum S3 log probability within the segment, normalized by the background probability (the median of the top several alternative posterior class probabilities) within the segment. In beats without an S3 segment, the median S3 segment relative to the QRS onset time is substituted. The largest S3 scores are added together and normalized to produce an overall S3 strength value from 0.0 to 10.0. A similar procedure is used to generate the S4 strength. In general, S3 and S4 strengths >5 indicate the presence of 3rd and4th heart sounds that can be auscultated with a standard stethoscope, respectively.

Combination of systolic and diastolic CABs

6. Systolic dysfunction index (SDI): The first step in the calculation of SDI is to multiplying S3 strength, EMATc, QRS duration, and QR interval and then performing a nonlinear transform of the product. Finally, SDI is obtained by expressing the output of this nonlinear transform on a continuous scale from 0 to 10.

Normal nighttime and daytime values, ranges, and standard deviations for CAB parameters obtained from 25 normal volunteers are summarized in Table 1. Each patient's median daytime and median nighttime CAB values were used for this analysis. With the exceptions of S3 and SDI, all other CABs showed significant daytime–nighttime variations. Thus, with the exception of those two CABs, differences between daytime and nighttime values will need to be considered in clinical studies.

### 2.1.1 | Patients

All patients prescribed a WCD at the time of hospital discharge for heart failure are entered into a database maintained by the manufacturer (ZOLL, Pittsburgh, PA, USA) for regulatory, reimbursement, and administrative purposes; patients hospitalized for acute MI were not included for this analysis. All patients signed consent to use their data for quality monitoring, healthcare operation activities, and/or research. The following criteria were used to identify subjects for

the study: (a) adult patients ≥18 years for age wearing a CAB-enabled device between March 2015 and July 2017; (b) only ischemic and non-ischemic HF patients were included; (c) the device was used for at least 30 days; and (d) device use was ≥250 min between 7 a.m. and 12 a.m. (daytime) and ≥100 min between 12 a.m. and 7 a.m. (nighttime) for at least one day during the first three calendar days of WCD wear and for at least one day during the last three calendar days of WCD wear.

### 2.1.2 | Data analysis

Beginning of WCD use (BOU) was defined as the first day during the first 3 days of WCD use where the device was worn ≥250 min between 7 a.m. and 12 a.m. and ≥100 min between 12 a.m. and 7 a.m. Similarly, end of WCD use (EOU) was defined as the first day during the last 3 days of WCD use, where the device was worn ≥250 min between 7 a.m. and 12 a.m. and ≥100 min between 12 a.m. and 7 a.m. Mean CAB and heart rate values were calculated every 5 min from a 10-s concurrent recording of ECG and cardiohemic vibrations. Data are presented as means ± *SD*, and for skewed distributions as medians and interquartile range (IQR). Data were analyzed using Student *t* tests or Mann–Whitney tests for continuous variables and chi-square tests for discrete variables. Coefficients of determination were used to assess relations between CABs and ejection fraction (EF), age, gender, and QRS duration. For the EF analysis, available ejection fraction at the time of WCD prescription was included. Analysis of variance examined the impact of heart rate changes on CABs. All analyses were conducted using RStudio version 1.1.44 (RStudio Inc, Boston, MA). $p < .05$ was considered significant.

## 3 | RESULTS

Between March 2015 and July 2017, 1,066 patients were identified for inclusion in the study. The mean age was 58 ± 13 years, and 77% of the patients were male. About 73.5% had an ischemic etiology reported as the etiology of their heart failure. The median wear time of the WCD was 79 days [IQR: 56–97 days]. Median left ventricular ejection fraction was 23% [IQR: 20%–28%] for patients in whom a value was available ($n = 75$).

### 3.1 | CAB values, intra-subject variability, and daytime–nighttime comparison

Daytime and nighttime BOU data were used to calculate mean (±*SD*) CAB values for each subject (Table 2). Overall, compared with normal healthy volunteers, HR, EMAT, EMATc, S3, and SDI were higher in heart failure patients, while LVST was lower and LVSTc was similar in the heart failure population.

Intra-subject variability was assessed by the ratio of the average standard deviation for all subjects to the average mean CAB values (expressed as a percentage) for all subjects. Focusing on nighttime values, S3 and S4 variabilities (33.3% and 29.7%, respectively; Table 2) were significantly higher than those of other CABs ($p < .01$). When comparing the different systolic time intervals, EMAT and EMATc had a significantly higher ($p < .01$) intra-subject variability than LVST and LVSTc (12.4% and 14.8% vs. 6.3% and 8.6%). SDI had a significantly higher intra-subject variability of 18.2% when compared to systolic time intervals (EMAT and LVST) and heart rate ($p < .01$). As further detailed in Table 2, intra-subject variability was similar between nighttime and daytime for each of the CABs.

Circadian changes in CABs are further explored in Table 3 which compares CAB values in patients having both daytime and nighttime measurements (i.e., paired comparisons). EMAT, LVST, S3 strength, and S4 strength values were significantly higher ($p < .01$) during nighttime compared with daytime (Table 3). Since heart rate values are lower at night, EMATc and LVSTc had significantly lower values at nighttime ($p < .01$), as they are corrected for heart rate.

### 3.2 | Correlation of CABs to age, gender, QRS duration, and ejection fraction

Age (available from all subjects) ranged from 22 years to 88 years with a median of 58 years [IQR: 49–67]. The coefficient of determination ($R^2$) between CABs and age ranged from 0.0009 to 0.06; the correlation for all CAB parameters was significant with $p < .05$ with

**TABLE 2** CAB value at beginning of use, intra-subject variation, and comparison of nighttime and daytime

| Variables | Average nighttime mean (*n*) | Average nighttime *SD* | Nighttime intra-subject variability (%) | Average daytime mean (*n*) | Average daytime *SD* | Daytime intra-subject variability (%) | *p* |
|---|---|---|---|---|---|---|---|
| Heart rate (BPM) | 70.1 (*n* = 1,042) | 6.7 | 9.6 | 77.0 (*n* = 1,065) | 8.6 | 11.2 | <.001 |
| EMAT (ms) | 110.4 (*n* = 1,041) | 13.7 | 12.4 | 107.1 (*n* = 1,065) | 15.1 | 14.1 | <.001 |
| EMATc (%) | 12.8 (*n* = 1,041) | 1.9 | 14.8 | 13.6 (*n* = 1,065) | 2.4 | 17.6 | <.001 |
| LVST (ms) | 325.6 (*n* = 1,041) | 20.6 | 6.3 | 305.0 (*n* = 1,065) | 26.2 | 8.6 | <.001 |
| LVSTc (%) | 37.4 (*n* = 1,041) | 3.2 | 8.6 | 38.4 (*n* = 1,065) | 3.9 | 10.2 | <.001 |
| S3 strength | 4.2 (*n* = 1,041) | 1.4 | 33.3 | 3.9 (*n* = 1,065) | 1.5 | 38.5 | <.001 |
| S4 strength | 3.7(*n* = 1,033) | 1.1 | 29.7 | 3.5 (*n* = 1,065) | 1.1 | 31.4 | <.001 |
| SDI | 5.5 (*n* = 1,034) | 1.0 | 18.2 | 5.4 (*n* = 1,063) | 1.0 | 18.5 | <.001 |

**TABLE 3** Comparison of cardiac acoustic biomarkers during BOU between daytime and nighttime

| CABs *n* = 1,066 | Daytime | Nighttime | *p*-value |
|---|---|---|---|
| Heart rate (BPM) | 76.0 ± 13.2 | 69.2 ± 12.8 | <.001 |
| EMAT (ms) | 105.9 ± 15.3 | 109.7 ± 17.1 | <.001 |
| EMATc (%) | 13.3 ± 2.8 | 12.6 ± 2.9 | <.001 |
| LVST (ms) | 305.3 ± 31.7 | 326.8 ± 35.1 | <.001 |
| LVSTc (%) | 38.0 ± 4.9 | 37.2 ± 5.0 | <.001 |
| S3 strength | 4.0 ± 1.2 | 4.2 ± 1.4 | <.001 |
| S4 strength | 3.4 ± 1.0 | 3.6 ± 1.3 | <.001 |
| SDI | 5.9 ± 1.8 | 5.4 ± 1.9 | <.01 |

the exception of daytime SDI and nighttime EMATc and SDI (Table A1 in Appendix).

WCD ECGs were retrievable from 510 subjects for calculation of QRS duration. The coefficient of determination between CABs and QRS duration ranged from 0.01 to 0.58 (Table A2 in Appendix). Among the CAB parameters, SDI had the strongest correlation with QRS duration ($R^2$ = 0.58, $p$ < .01). However, the SDI calculation includes QRS duration along with S3 strength, QR interval, and EMATc, which would bias a correlation of determination.

EF data were available for 75 of the 1,066 heart failure subjects. For these patients, EF ranged between 10% and 36%, with a median of 23% [IQR: 20%–28%]. The coefficient of determination ($R^2$) between BOU CABs (daytime and nighttime) and EF ranged from 0.0004 to 0.06 (Table A1 in Appendix) and all regressions were not statistically significant.

As with the other analyses, there were statistically significant gender differences in several CAB values (summarized in Table A3 in Appendix) but, for the most part, these were quantitatively small. Heart rate did not vary with gender, and other parameters varied by less than 10%.

Thus, many CABs were influenced by age, gender, QRS duration, and EF on a statistical basis. Despite this, the $R^2$ values were very small (indicating weak dependences). This is illustrated by the relatively small change of each parameter for 50-year changes of age, 80 ms increase in QRS duration, 25% (absolute) change of ejection fraction, and between males and females. We thus consider CABs to be essentially independent of age, gender, EF, and QRS duration.

### 3.3 | Impact of heart rate on CABs: comparison between beginning and end of use

Cardiac acoustic biomarker values were binned by heart rate in intervals of 10 bpm at BOU and EOU (Figure 2). At the BOU, EMAT did not significantly change with an increase in resting heart rate (Figure 2a), whereas LVST showed a significant decrease as heart rate increased (Figure 2c; $p$ < .01). Also at BOU, S3 strength showed a significant though modest increase with heart rate (Figure 2e; $p$ < .05), whereas S4 strength did not change significantly (Figure 2g).

At EOU, EMAT and S3 strength did not significantly change with heart rate (Figure 2b and f). In contrast, both LVST and S4 strength decreased significantly with increased heart rate (Figure 2d and H; $p$ < .01). Note that CAB parameters that included HR in their calculated value (EMATc, LVSTc, and SDI) were not separately compared with heart rate.

To further explore differences in parameters between BOU and EOU, analysis of covariance was applied to test for differences in slopes and intercepts between the BOU and EOU regressions lines for CABs and heart rate. For both EMAT and LVST, slopes of the BOU and EOU regression lines were not significantly different. However, the regression line intercepts showed small but significant difference in the BOU and EOU values for both EMAT (110.9 ms vs. 109.2 ms, $p$ < .05) and LVST (360 ms vs. 368 ms, $p$ < .001). For both S3 strength and S4 strength, slopes of the BOU and EOU regression lines were significantly different (S3 strength: 0.2 vs. 0.05, $p$ < .001; S4 strength: −0.01 vs. −0.11, $p$ < .001). Similarly, the intercepts of the BOU and EOU regression lines for S3 strength (3.6 vs. 3.0, $p$ < .001) and S4 strength (3.6 vs. 3.3, $p$ < .001) were significantly different.

### 3.4 | Temporal changes in CABs: beginning versus end of use

The median days of WCD wear between BOU and EOU were 79 days [IQR: 56–97 days]. Except for LVSTc, all CAB parameters and heart rate decreased significantly ($p$ < .005) at the EOU compared with their respective values at BOU (Table 4). For some parameters (e.g., EMAT, S4 strength and SDI), changes were statistically significant but clinically small; statistical significance is achieved due to the large number of observations contributing to the statistical analysis.

To gain further insights into clinical significance of changes over time, we plotted the percent of patients for which CAB values were above what are considered to be upper limits of normal values (Figure 3). There were decreases in the percent of patients with HR > 70 bpm (40% vs. 30%, $p$ < .05), patients with SDI > 5 (46.6% vs. 30.4%, $p$ < .05), patients with EMATc > 15% (23.6% vs. 17%, $p$ ≤ .05), the percent of patients with S3 strength >5 (16% vs. 2%, $p$ < .05), and patients with S4 strength >5 (10% vs. 4%, $p$=<0.05). Of the CABs examined, only EMAT did not change, with 21% of patients having a value >120 at both BOU and EOU. However, this may be due to the concomitant reduction in HR; as noted above once corrected for HR, EMATc did improve over time.

In yet another form of analysis, it is demonstrated that further insights may be attained by looking at concomitant changes in values of different combinations of parameters. For example, a comparison of EMAT and S3 strength between BOU and EOU is illustrated in Figure 4. As shown here, we can readily identify time-dependent shifts of sets of parameter values in the overall population.

## 4 | DISCUSSION

Cardiac acoustic biomarker parameters derived from acoustic and electrocardiographic measurements provide information related

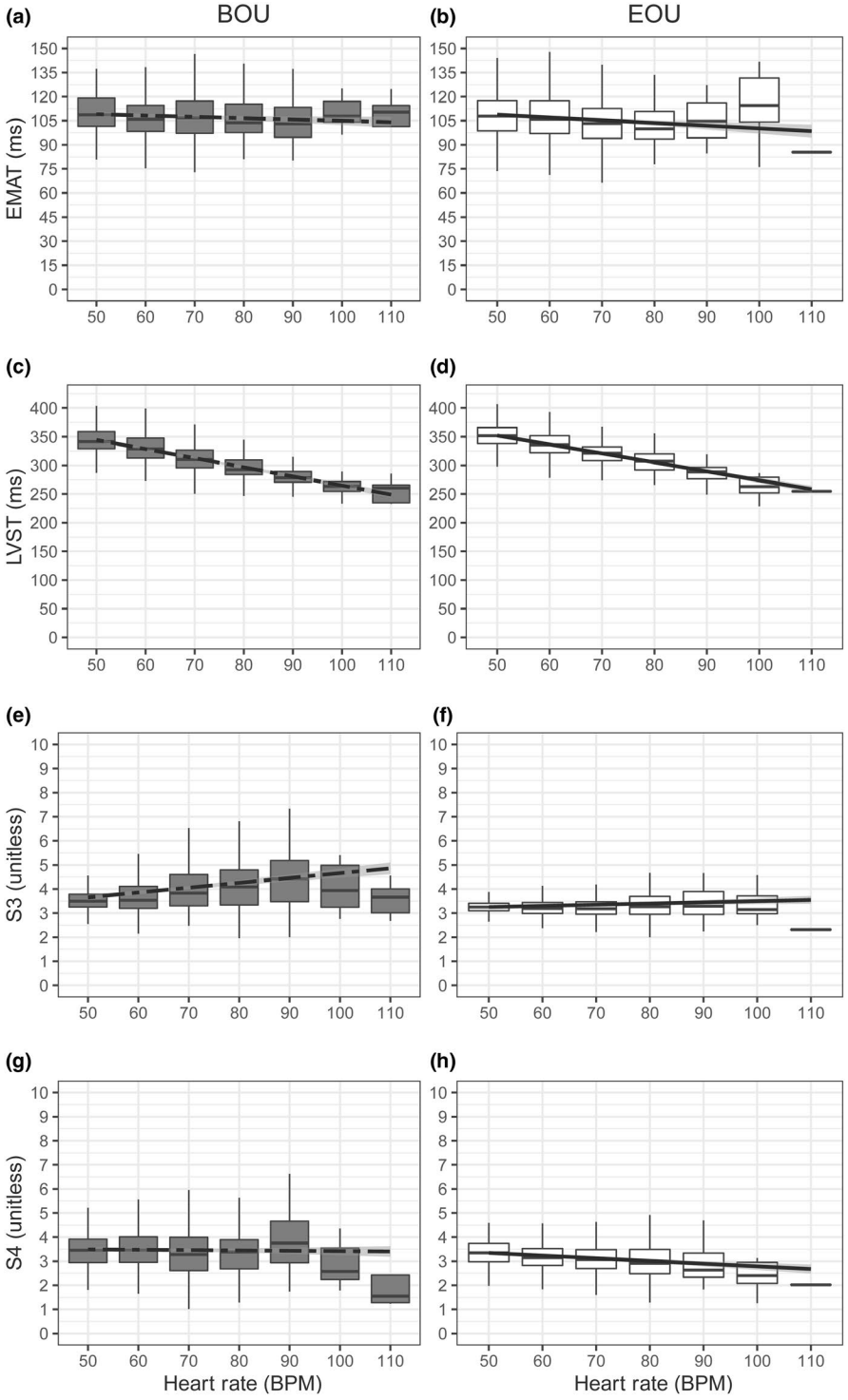


**FIGURE 2** Box plots showing the effect of resting heart rate on cardiac acoustic biomarkers at the beginning of WCD use (BOU) and end of WCD use (EOU). a and b. EMAT versus heart rate; c and d. LVST versus heart rate; e and f. S3 strength versus heart rate; g and h. S4 strength versus heart rate

to heart function and clinical status. They have been proposed to be useful to guide medical therapy in heart failure to beneficially impact clinical outcomes (Erne, 2008; Sung et al., 2014; Wang et al., 2013). However, relatively little is known about the normal values, typical values in heart failure patients, intra-subject variability, circadian rhythms, and how these values change over time. The data summarized in the present study provide values for all these aspects of CAB parameters that will be critical for designing and interpreting future clinical studies aimed at demonstrating the clinical utility of CABs in patients with heart failure. Specifically, this information is fundamental to the selection of the best CAB parameter (or groups of parameters) to be used for primary and secondary endpoints and for estimating study sample sizes.

Regarding specific new insights, it is clinically meaningful that average CAB values obtained from heart failure patients differed from those of normal healthy volunteers. In addition, it was demonstrated that interpretation of CAB values must account for changes in heart rate and daytime–nighttime variations. Normalization of EMAT and

**TABLE 4** Comparison of cardiac acoustic biomarkers during beginning of WCD use (BOU) and end of WCD use (EOU). Values recorded during daytime hours

| CABs *n* = 1,066 | Beginning of WCD use | End of WCD use | *p*-value |
|---|---|---|---|
| Heart rate (BPM) | 76.0 ± 13.2 | 72.5 ± 12.4 | <.001 |
| EMAT (ms) | 105.9 ± 15.3 | 104.8 ± 15.6 | <.01 |
| EMATc (%) | 13.3 ± 2.8 | 12.6 ± 2.7 | <.001 |
| LVST (ms) | 305.3 ± 31.7 | 319.8 ± 30.5 | <.001 |
| LVSTc (%) | 38.0 ± 4.9 | 37.8 ± 4.7 | .14 |
| S3 strength | 4.0 ± 1.2 | 3.3 ± 0.5 | <.001 |
| S4 strength | 3.4 ± 1.0 | 3.1 ± 0.6 | <.001 |
| SDI | 5.9 ± 1.8 | 5.3 ± 1.8 | <.001 |

LVST for changes in R-R intervals did not completely eliminate their daytime–nighttime differences, suggesting that there are true circadian variations in cardiovascular physiology. Comparison of intrasubject variability of the different CABs was particularly informative; given the high variabilities of S3 and S4 strengths, these parameters may have lower sensitivity and specificity for guiding medical therapies. Alternatively, the high variabilities of S3 and S4 strengths may mean these values are very sensitive to changes in patient physiology and represent the effects of medications, salt intake, or other factors.

Improvements in CAB parameters were identified over time following hospital discharge. While we could not study specific associations, it is presumed that, for the population as a whole, these improvements are linked with improvements in clinical status and LV function. The reduction of SDI is particularly interesting in this regard. However, exploration of associations between changes of CABs, clinical status, LV function, and heart failure hospitalizations is planned to be the focus of future studies.

In another form of analysis (Figure 4), plots of one CAB versus another can give insights into correlations between different parameters and population shifts over time. More generally, simultaneously combining information from multiple CABs sets the stage for a machine learning approach for feature identification and principle component analysis. Such an approach may yield the highest degree of discrimination (sensitivity and specificity) for guiding medical management in an unbiased manner.

Wearable cardioverter defibrillators are prescribed to patients in a number of clinical settings. The present study focused on patients discharged from the hospital for a heart failure exacerbation. In general, these are patients with LV ejection fraction <35% and are being evaluated for an ICD implantation. In addition to their risk for sudden cardiac death, these patients are at high risk for rehospitalization over the 90 days following hospital discharge. Approximately 25% of patients discharged from a heart failure hospitalization are readmitted within 30 days and about 67% are readmitted within 1 year (Abraham, 2017; Jencks, Williams, Williams, & Coleman, 2009; Kociol et al., 2010; Ross et al., 2010). The only strategy so far shown to reduce the rate of heart failure hospitalizations is with the use of invasive pulmonary artery pressure monitoring (Abraham et al., 2011). Adoption of

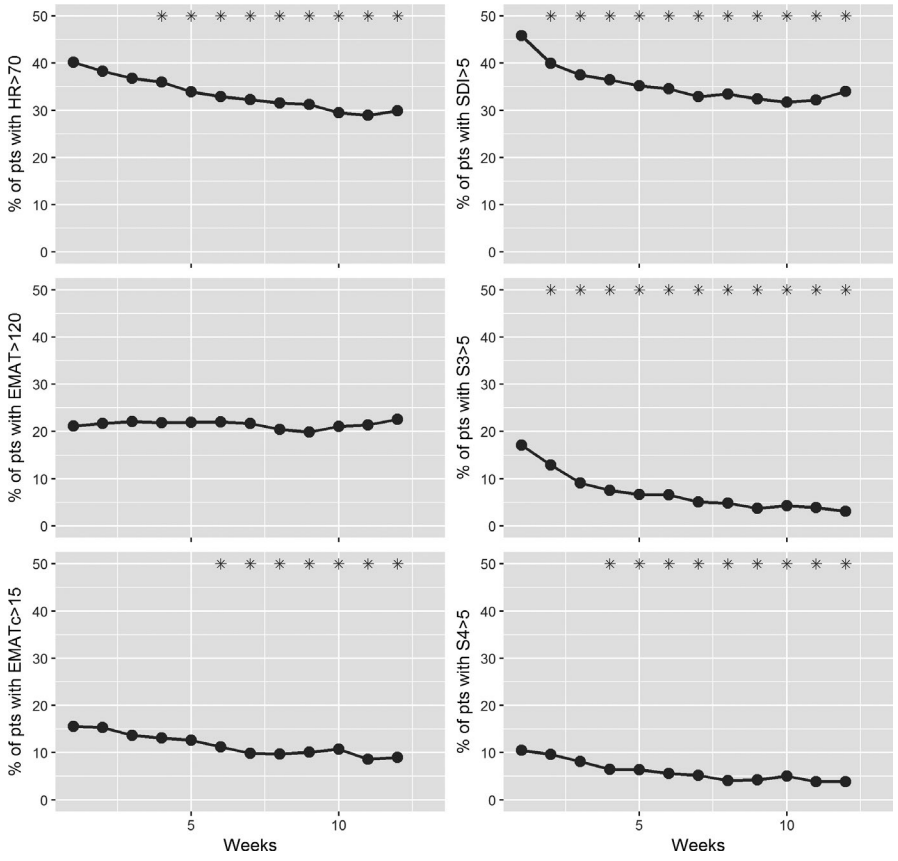


**FIGURE 3** Nighttime weekly trends of the percentage of WCD patient with HR > 70 (a), EMAT > 120 (b), EMATc > 15 (c), SDI > 5 (d), S3 strength > 5 (e), and S4 strength > 5 (f). *indicates significant difference in the weekly trend value when compared to the first week

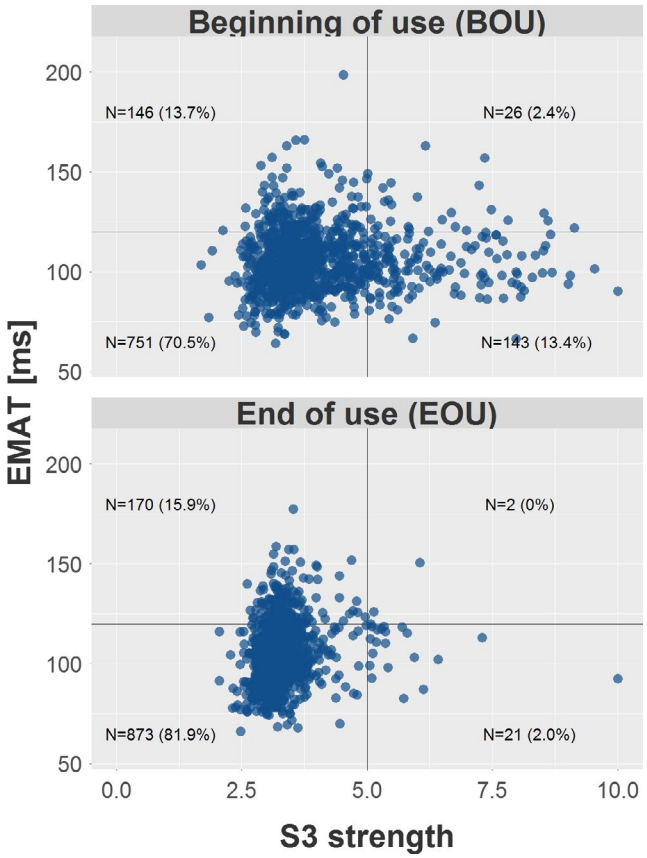


**FIGURE 4** EMAT and S3 strength at the beginning of WCD use (top) and end of WCD use(bottom). Each plot is divided in to 4 quadrants—EMAT > 120 and S3 strength > 5, EMAT > 120 and S3 strength < 5, EMAT < 120 and S3 strength < 5, EMAT < 120 and S3 strength > 5

this technology has been slower than expected, perhaps in part because of its invasive nature. A noninvasive monitoring strategy such as CABs that can be shown to guide medical therapies in such a manner that rehospitalizations are reduced would provide significant value to patients and to the healthcare system. In such a case, addition of CAB measurements to WCDs would provide additional incentives for patients to comply with WCD use; it comes as no surprise that compliance with WCD is key to its ability to prevent sudden cardiac death (Olgin et al., 2018; Reek et al., 2017) and limits the potential benefit for some patients.

### 4.1 | Study limitations

This was an observational study that included CAB data from a relatively large number of patients discharged following a heart failure hospitalization, but for whom very limited baseline demographic data were available. Beyond age and gender, only QRS duration and LV ejection fraction were available from a small subset of patients and no information was available concerning clinical outcomes over time. As such, the present study provides basic, though critical information about normal values and ranges, expected CAB values, ranges and variability in heart failure patients and general trends on how these parameters change over the typical 3-month wear time following discharge from a heart failure hospitalization. Specifically related to this last point, while it was demonstrated that CAB parameters change over time, there was no assessment of whether or how those changes correlated with changes in clinical status (e.g., NYHA functional class, quality of life, or rehospitalizations). Additionally, the present study did not include patients discharged from the hospital for an acute myocardial infarction. A separate study will be required to define the expected values, ranges, variability, and time course of change for those patients. Finally, the cohort of healthy volunteers was small, which precluded detailed analysis of demographic variability of CABs beyond comparison of daytime and nighttime values. For example, clarification of age and gender dependence would be of interest in healthy individuals. Also, CAB values that have been found to be independent of age and gender in the heart failure population may not be independent of such factors in normals.

## 5 | CONCLUSIONS

Cardiac acoustic biomarkers offer the possibility for noninvasive correlates of LV function, clinical status, and other aspects of cardiovascular physiology that differ between normal and heart failure states. The present study provides critical information about normal values, typical values in heart failure patients, intra-subject variability, circadian rhythms, and changes over time of these parameters. The data will form the basis of the design of future studies aimed at identifying which CABs yield the highest specificity and sensitivity for guiding modification of heart failure medications for the purpose of improving patient quality of life and reducing the rate of heart failure hospitalizations. In addition to use on their own (e.g., as point of care measurements), if proved to be effective in these aspects of patients care, inclusion of CABs may provide additional incentives for enhancing patient management with the use of WCDs.

## DISCLOSURES

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## APPENDIX 1

**TABLE A1** Coefficient of determination ($R^2$) for dependence of daytime and nighttime CABs on ejection fraction and age

| | Ejection fraction | | | | | | Age | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Regression between daytime EF and CABs ($n$ = 75) | | | Regression between nighttime EF and CABs ($n$ = 68) | | | Regression between daytime CABs and age ($N$ = 1,066) | | | Regression between nighttime CABs and Age ($N$ = 1,066) | | |
| CABs (BOU) | $R^2$ | Slope | ΔCAB for a 25% change of EF | $R^2$ | Slope | ΔCAB for a 25% change of EF | $R^2$ | Slope | Change in CABs for a 50 year change in age | $R^2$ | Slope | Change in CABs for a 50 year change in age |
| Heart rate (BPM) | 0.008 | −0.198 | −4.95 | 0.06 | −0.471 | −11.775 | 0.06* | −0.259 | −12.95 | 0.03* | −0.157 | −7.85 |
| EMAT (ms) | 0.004 | −0.141 | −3.525 | 0.004 | 0.172 | 4.3 | 0.02* | 0.154 | 7.7 | 0.01* | 0.136 | 6.8 |
| EMATc (%) | 0.01 | −0.057 | −1.425 | 0.03 | −0.075 | −1.875 | 0.01* | −0.025 | −1.25 | 0.003 | −0.012 | −0.6 |
| LVST (ms) | 0.0004 | 0 | 0 | 0.02 | 0.001 | 0.025 | 0.04* | 0 | 0 | 0.02* | 0 | 0 |
| LVSTc (%) | 0.008 | −0.073 | −1.825 | 0.03 | −0.134 | −3.35 | 0.03* | −0.067 | −3.35 | 0.01* | −0.043 | −2.15 |
| S3 strength | 0.04 | −0.05 | −1.25 | 0.04 | −0.068 | −1.7 | 0.04* | −0.021 | −1.05 | 0.04* | −0.023 | −1.15 |
| S4 strength | 0.05 | −0.032 | −0.8 | 0.04 | −0.039 | −0.975 | 0.02* | −0.011 | −0.55 | 0.01* | −0.011 | −0.55 |
| SDI | 0.03 | −0.048 | −1.2 | 0.03 | −0.044 | −1.1 | 0.0009 | 0.004 | 0.2 | 0.0016 | 0.005 | 0.25 |

*$p$ < .05

**TABLE A2** Coefficient of determination, slope of regression, and change for cardiac acoustic biomarkers for an 80 ms change of QRS duration. *$p < .05$

| CABs (first 3 days of WCD wear) | QRS duration versus CABs $n = 510$ | Slope of regression | Change in CABs for a 80-ms change in QRS duration (slope of regression*80) |
|---|---|---|---|
| Heart rate (BPM) | 0.03* | −0.071 | −5.68 |
| EMAT (ms) | 0.13* | 0.191 | 15.28 |
| EMATc (%) | 0.01* | 0.009 | 0.72 |
| LVST (ms) | 0.15* | 0.413 | 33.04 |
| LVSTc (%) | 0.01 | 0.013 | 1.04 |
| S3 strength | 0.01 | −0.003 | −0.24 |
| S4 strength | 0.01 | −0.001 | −0.08 |
| SDI | 0.58* | 0.047 | 3.76 |

**TABLE A3** Comparison of CAB values at beginning of use (BOU) between male and female patients during daytime and nighttime recordings. Comparisons of mean values were by unpaired *t* tests

| | Daytime | | | Nighttime | | |
|---|---|---|---|---|---|---|
| BOU | Male (822) | Female (244) | *p* | Male (822) | Female (244) | *p* |
| EMAT | 106.3 ± 15.5 | 104.6 ± 14.4 | .11 | 110.4 ± 16.9 | 107.2 ± 17.6 | .01 |
| EMATc | 13.4 ± 2.9 | 13.1 ± 2.5 | .14 | 12.8 ± 2.9 | 12.2 ± 2.6 | .003 |
| SDI | 5.4 ± 1.8 | 5.2 ± 1.9 | .13 | 5.4 ± 1.9 | 5.2 ± 1.9 | .04 |
| S3 | 4.1 ± 1.3 | 3.8 ± 0.9 | <.001 | 4.3 ± 1.5 | 4.0 ± 1.2 | .001 |
| S4 | 3.4 ± 1.0 | 3.4 ± 0.9 | .32 | 3.5 ± 1.3 | 3.7 ± 1.3 | .04 |
| LVST | 301.6 ± 30.3 | 318.0 ± 33.2 | <.001 | 322.5 ± 33.6 | 341.2 ± 36.6 | <.001 |
| LVSTc | 37.6 ± 4.9 | 39.4 ± 4.5 | <.001 | 36.8 ± 5.1 | 38.5 ± 4.7 | <.001 |
| HR | 76.1 ± 13.5 | 75.7 ± 12.2 | .63 | 69.4 ± 13.1 | 68.5 ± 11.6 | .33 |