Mechanical Alternans Is Associated With Mortality in Acute Hospitalized Heart Failure
Prospective Mechanical Alternans Study (MAS)

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Background—Acute hospitalized heart failure (AHHF) is associated with 40% to 50% risk of death or rehospitalization within 6 months after discharge. Timely (before hospital discharge) risk stratification of patients with AHHF is crucial. We hypothesized that mechanical alternans (MA) and T-wave alternans (TWA) are associated with postdischarge outcomes in patients with AHHF.

Methods and Results—A prospective cohort study was conducted in the intensive cardiac care unit and enrolled 133 patients (59.6±15.7 years; 65% men) admitted with AHHF. Surface ECG and peripheral arterial blood pressure waveform via arterial line were recorded continuously during the intensive cardiac care unit stay. MA and TWA were measured by enhanced modified moving average method. All-cause death or heart transplant served as a combined primary end point. MA was observed in 28 patients (25%), whereas TWA was detected in 33 patients (33%). If present, MA was tightly coupled with TWA. Mean TWA amplitude was larger in patients with both TWA and MA when compared with patients with lone TWA (median, 37 [interquartile range, 26–61] versus 22 [21–23] μV; P=0.045). After a median of 10-month postdischarge, 42 (38%) patients died and 2 had heart transplants. MA was associated with the primary end point in univariable Cox model (hazard ratio, 1.84; 95% confidence interval, 1.00–3.40; P=0.05) and after adjustment for left ventricular ejection fraction, New York Heart Association HF class, and implanted implantable cardioverter defibrillator/cardiac resynchronization therapy defibrillator (hazard ratio, 2.12 95% confidence interval, 1.13–3.98; P=0.020). TWA without consideration of simultaneous MA was not significantly associated with primary end point (hazard ratio, 1.42; 95% confidence interval, 0.77–2.64; P=0.260).

Conclusions—MA is independently associated with outcomes in AHHF.

Clinical Trial Registration—URL: http://www.clinicaltrials.gov. Unique identifier: NCT01557465. (Circ Arrhythm Electrophysiol. 2014;7:259-266.)

Key Words: alternans ■ heart failure ■ mortality

Heart failure (HF) is one of the most frequent reasons for hospital admissions in the United States. There are ≈1 million admissions per year with the primary diagnosis of HF and an additional 2 million admissions per year with the secondary diagnosis of HF. Although mortality in chronic HF has substantially decreased during the past 15 years, postdischarge mortality in acute hospitalized HF (AHHF) has not changed. To facilitate the development of novel prognostic and therapeutic approaches, and to improve outcomes, AHHF was recognized as a distinct entity.

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Sudden cardiac death is the second (after pump failure) most frequent cause of death in AHIF, responsible for about a third of all deaths. There is an unmet need for timely (before hospital discharge) risk stratification of patients with AHHF. T-wave alternans (TWA) on the surface ECG, as a manifestation of action potential duration alternans and action potential voltage alternans, is directly linked to ventricular arrhythmia. However, results of clinical studies are controversial. Mechanical alternans (MA; aka pressure alternans and pulsus alternans) is a phenomenon of alternating strong and weak beats, as measured by pulse or blood pressure. The first observation of pulsus alternans in a patient with HF was published in 1872 by Traube (1818–1876). MA is prevalent in HF and is associated with cardiovascular death and HF hospitalizations. Coupling between MA and TWA has been previously shown. Mechanistically,
abnormal intracellular Ca2+ cycling could be responsible for both TWA and MA.16,17 However, the mechanisms of TWA and MA may be different,18 and beat-to-beat alternations in stroke volume could be because of variations in preload and contractility. Few studies have simultaneously measured both MA and TWA. We conducted a prospective observational cohort study of MA and TWA to compare the association of these 2 types of alternans with AHHF outcomes. We hypothesized that MA and TWA is associated with postdischarge outcomes in patients with AHHF.

Methods

Study Population

We conducted a single-center prospective observational cohort Mechanical Alternans Study (MAS; NCT01557465) at the Johns Hopkins Hospital intensive cardiac care unit (ICCU) between December 1, 2009, and November 30, 2011, and enrolled 133 participants. The study protocol was approved by the Johns Hopkins University Institutional Review Board, and all patients gave written informed consent before enrolling in the study.

Patients were eligible for the study if they were admitted to the ICU with either acute decompensated HF or new onset acute HF because of one of the following conditions: (1) decompensated ischemic or nonischemic cardiomyopathy; (2) acute coronary syndrome; (3) electrical storm in patients with implantable cardioverter defibrillator (ICD) or resuscitated out-of-hospital sudden cardiac arrest. Study participants had to have clinical indications for, and undergo, continuous invasive monitoring of peripheral arterial blood pressure via arterial line. Patients with (1) pericardial effusion, (2) congenital heart disease, (3) hemodynamically significant (moderate or severe) valvular heart disease, (4) children, and (5) pregnant women were excluded.

All study participants underwent clinical echocardiographic examinations during the ICU stay. Left ventricular ejection fraction (LVEF) was measured by biplane Simpson method.

Continuous Recording and Analysis of ECG and Blood Pressure

Simultaneous recording of ECG (leads V1 and II) and peripheral arterial blood pressure waveform via arterial line was performed continuously during the ICU stay (as long as invasive blood pressure monitoring continued). The initiation and discontinuation of intra-aortic balloon pump or percutaneous cardiopulmonary support were carefully documented.

Recordings were excluded from this analysis if ≥1 of the following was present: (1) the use of intra-aortic balloon pump or percutaneous cardiopulmonary support system; (2) atrial fibrillation; (3) frequent premature ventricular contractions as bigeminy, trigeminy, or quadrigeminy; Heart rate, QT interval, systolic and diastolic arterial pressure were averaged for each 15-s period.

Alternans Detection and Analysis

Customized MATLAB (MathWorks, Inc, Natick, MA) software was developed to detect MA and microvolt TWA. Details of alternans method are provided in the Methods in the Data Supplement. The correlation method was applied first to determine the presence of alternans.19 Then a modified moving average method was applied to quantify alternans.20 Rapid update factor of 1/8 was used in our study to provide high sensitivity.3 A subset of data (n=12) was reanalyzed using an incremental updating factor of 1 in 32. A sustained TWA event was detected when TWA lasted for ≥20 beats (Figure 1A). Similarly, a sustained MA event was defined as arterial pressure alternans that lasted for ≥20 beats (Figure 1B). Actual duration (number of beats) of each alternans events was measured as the number of consecutive beats whose alternans correlation index values alternated around the value of one. No amplitude threshold was defined a priori to detect sustained alternans. The resolution of MA evaluation was 1 mmHg, and the resolution of TWA evaluation was 10 μV.

Follow-Up and Study Primary End Point

After ICU discharge, patients were followed up prospectively via the electronic medical record review and via a phone call once a year. A combined end point, defined as all-cause death or heart transplant, served as the primary end point in this study.

Statistical Analysis

Statistical analysis was performed using STATA version 13.0 software (StataCorp LP, College Station, TX). All normally distributed continuous variables are presented as mean±SD, whereas median and interquartile range is reported if distribution was not normal. Two-group mean comparison t test was used to compare normally distributed characteristics of patients with and without MA. Wilcoxon rank-sum test was used for 2-group comparison of skewed continuous

Figure 1. Illustration of the method of (A) T-wave alternans and (B) mechanical alternans (MA) measurements by modified moving average. Bottom, Averaged odd and even beats. Alternans are marked by arrows. CM indicates correlation method; MMA, modified moving average method; and STT=ST–T ECG segment.
variables in patients with lone TWA versus those with both MA and TWA. Categorical variables were compared by Pearson χ² test. A P value <0.05 was considered statistically significant. Kaplan–Meier survival curves were constructed for subjects with and without MA and TWA. The log-rank (Mantel-Cox) statistic was computed to test the equality of survival distributions. Univariable and multivariable Cox proportional hazards regression analyses were performed. MA and TWA were entered in the models as categorical variables (yes/no). First, the association of each variable (MA, TWA, demographics, and potential confounders [New York Heart Association [NYHA] class III–IV, LVEF ≥35%, implanted ICD/CRT-D, mean heart rate >90 beats per minute, type of cardiomyopathy]) with outcome was tested in univariable Cox models. Then, variables that were associated with outcome at P value <0.1 were included in the multivariable model. To evaluate proportionality of hazards, we performed tests of nonzero slope in a generalized linear regression of the scaled Schoenfeld residuals.

### Results

#### Study Population

Of the 133 ICCU patients enrolled in the MAS study, 22 patients were excluded because of the use of the intra-aortic balloon pump or percutaneous cardiopulmonary support system, atrial fibrillation, or frequent premature ventricular contractions. Data from the remaining 111 patients were analyzed. Clinical characteristics of the study population are presented in Table 1. The mean age of participants was 58.9±15.9 years, and most were white (60%) men (71%). Most of the patients (82.3%) had NYHA HF class III to IV. Mean EF was 29.0±18.1%. About half of the study population had ischemic cardiomyopathy and had an ICD or cardiac resynchronization therapy defibrillator (CRT-D) implanted.

#### MA and TWA

Mean heart rate of analyzed ECG and blood pressure epochs in all study participants exceeded 80 beats per minute. Sustained MA events were observed in 28 patients (25.2%). Sustained TWA events were observed in ≥30% (33 patients). TWA was observed in all 28 patients with MA, and thus isolated TWA without accompanying MA was observed in 5 patients. A representative example of an observed sustained MA event is presented in Figure 2A. Clusters of sustained MA and TWA events frequently occurred at the same time (Figure 2B). Simultaneous MA and TWA events were observed in 22 of 28 patients who had both MA and TWA events. The number of simultaneous MA and TWA events in a patient ranged 0 to 11 per hour, and the average duration of the overlapping periods was 25.2±29.0 sec. Movie 1 in the Data Supplement shows relationships and coupling between TWA and MA in 10 study participants. The use of incremental updating factor of 1 in 32 resulted in a negligible decrease in the number of detected alternans (0.5% MA and 3% TWA events).

To explore temporal association of TWA and MA, we computed amplitude and duration of sustained TWA events that occurred within 1 hour before and after each sustained MA event. There were 624 sustained TWA events (31.4±7.0 beats) that occurred within 1 hour before sustained MA events and 1402 sustained TWA events (65.2±17.7 beats) that occurred within 1 hour after MA events. The durations of TWA events that followed MA events were significantly longer than those of TWA events that occurred before MA events (P<0.0001). Thus, the number of TWA beats was significantly larger within 1 hour after each MA event than within 1 hour before.
each MA event (Figure 1). In other words, on average, longer TWAs were detected within 1 hour after each MA event. However, the average duration of MAs detected within 1 hour before each TWA event (32.7±7.5 beats) was almost identical to the average duration within 1 hour after each TWA event (32.5±7.5 beats). This suggests that MA events were more likely to precede TWA events and that far more TWA events than MA events were detected. MA event did not affect TWA amplitude (27.0±7.5 μV before MA versus 24.1±5.6 μV after MA; nonsignificant). Similarly, TWA event did not affect MA amplitude (14.5±1.7 before TWA versus 12.0±3.2 mm Hg after TWA event). However, MA amplitude within 1 hour of a TWA event was higher than average MA amplitude (13.3±2.5 versus 5.0±4.7 mm Hg; \( P = 0.046 \)).

No significant difference in LVEF, medications, and indications for ICCU admission between patients with and without MA was observed (Table 1). Remarkably, patients with lone TWA had less impaired systolic function. All 5 patients with lone TWA were admitted to the ICCU because of either resuscitated out-of-hospital sudden cardiac arrest or electrical storm in patients with ICD. Mean TWA amplitude and TWA amplitude at maximum heart rate were significantly larger in patients with both TWA and MA when compared with patients with lone TWA (Table 2). Alternans was measured during ventricular pacing in 18 (16%) patients (Table 1). Amplitude of alternans in patients with ventricular pacing did not differ from the amplitude of alternans, measured in patients in sinus rhythm.

**Prospective Follow-Up**

During a median 10 months of follow-up, 44 patients (39.6%) died or had successful heart transplantation. Of these 44 patients, 38 patients (86.4%) were hospitalized in the ICCU with decompensated end-stage HF, 24 patients (59%) had NYHA class IV symptoms, and 27 patients (61.4%) had ICD or CRT-D.
implanted. Review of the medical records showed that heart transplantation (n=2), progressive pump failure with pulseless electric activity, or asystole was an underlying cause of the primary end point in 35 patients (80%). In the remaining 9 patients (20%), the immediate cause of death was not determined. Patients with the primary end point were likely to have ischemic cardiomyopathy with advanced systolic dysfunction (Table 3).

There was no difference in the percentage of patients with ICD/CRT-D implanted among alternans groups (Table 1). Importantly, study participants died regardless of having ICD/CRT-D implanted. Moreover, a significantly larger percentage of patients with the primary end point had an implanted ICD/CRT-D (Table 3) when compared with end point–free group.

### Association Between Alternans and Mortality

There were no statistically significant differences in the presence and characteristics of MA and TWA in patients with and without the primary end point (Tables 4 and 5). In univariable Kaplan–Meier survival analysis, MA (Figure 3A) was associated with the primary outcome. Global test (P=0.484), as well as the test for MA (P=0.141), confirmed that proportional hazards assumption has been met. In univariable Cox regression, association of MA with primary outcome was borderline (hazard ratio [HR], 1.84; 95% confidence interval [CI], 1.00–3.41; P=0.050). An interaction between MA and TWA was observed. A univariable Kaplan–Meier survival analysis showed differences in cumulative survival in patients with and without alternans (Figure 3). The worst survival was observed in patients with both MA and TWA at baseline, whereas patients without alternans had an intermediate probability of survival. Surprisingly, all patients with lone TWA remained free from primary end point at the end of the follow-up period (Figure 3C) although because of the small group size (N=5) observed differences cannot be considered conclusive and should be validated in another prospective study.

In the Cox regression analysis after adjustment for LVEF and NYHA class, the presence of MA was associated with a nearly tripled risk of death or transplantation (HR, 2.81; 95% CI, 1.43–5.50; P=0.003). In the Cox model that included MA and LVEF, dichotomized at 35%, low EF was a stronger predictor than MA—MA: HR, 2.00 (95% CI, 1.07–3.71), P=0.029 and LVEF≤35%: HR, 2.69 (95% CI, 1.28–5.63), P=0.009. In the final multivariable Cox model (Table 6), MA remained a significant predictor of the primary outcome (HR, 2.12; 95% CI, 1.13–3.98; P=0.020).

### Discussion

This prospective cohort study of patients with acute HF admitted to the ICCU showed that MA was independently

### Table 2. Comparison of TWA Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>TWA Without MA (N=5)</th>
<th>TWA With MA (N=28)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean amplitude of TWA, median (IQR), μV</td>
<td>22 (21–23)</td>
<td>37 (26–61)</td>
<td>0.045</td>
</tr>
<tr>
<td>TWA amplitude at max HR, median (IQR), μV</td>
<td>36 (23–42)</td>
<td>58 (44–137)</td>
<td>0.021</td>
</tr>
<tr>
<td>Number of TWA beats, median (IQR), n</td>
<td>22 (22–26)</td>
<td>24 (22–30)</td>
<td>0.480</td>
</tr>
<tr>
<td>Mean heart rate at TWA, median (IQR), beats per minute</td>
<td>79.8 (70.6–92.6)</td>
<td>72.4 (57.8–86.2)</td>
<td>0.292</td>
</tr>
<tr>
<td>Mean QTc at TWA, median (IQR), ms</td>
<td>431 (385–441)</td>
<td>410 (359–481)</td>
<td>0.920</td>
</tr>
</tbody>
</table>

HR indicates hazard ratio; IQR, interquartile range; MA, mechanical alternans; and TWA, T-wave alternans.

### Table 3. Comparison of Patients With and Without Primary End Point

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Free From Primary End Point (N=67)</th>
<th>With Primary End Point (N=44)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (SD), y</td>
<td>59.8 (16.1)</td>
<td>59.0 (15.0)</td>
<td>0.795</td>
</tr>
<tr>
<td>Male sex, n (%)</td>
<td>44 (65.2)</td>
<td>35 (79.6)</td>
<td>0.103</td>
</tr>
<tr>
<td>Whites, n (%)</td>
<td>42 (62.1)</td>
<td>25 (56.8)</td>
<td>0.578</td>
</tr>
<tr>
<td>History of ischemic CM, n (%)</td>
<td>22 (32.3)*</td>
<td>28 (59.1)*</td>
<td>0.005*</td>
</tr>
<tr>
<td>Acute HF hospitalization, n (%)</td>
<td>41 (60.6)*</td>
<td>38 (86.4)*</td>
<td>0.004*</td>
</tr>
<tr>
<td>ACS hospitalization, n (%)</td>
<td>18 (25.8)</td>
<td>9 (20.5)</td>
<td>0.521</td>
</tr>
<tr>
<td>NYHA class III–IV, n (%)</td>
<td>35 (51.5)*</td>
<td>33 (75.0)*</td>
<td>0.013*</td>
</tr>
<tr>
<td>ICD/CRT-D, n (%)</td>
<td>26 (37.9)*</td>
<td>27 (61.4)*</td>
<td>0.016*</td>
</tr>
<tr>
<td>β-blockers, n (%)</td>
<td>45 (71.0)</td>
<td>26 (65.0)</td>
<td>0.526</td>
</tr>
<tr>
<td>Amiodarone, n (%)</td>
<td>15 (22.6)</td>
<td>15 (37.5)</td>
<td>0.103</td>
</tr>
<tr>
<td>Mechanical ventilation, n (%)</td>
<td>2 (3.0)</td>
<td>2 (4.6)</td>
<td>0.677</td>
</tr>
<tr>
<td>Inotropic medications, n (%)</td>
<td>21 (31.8)</td>
<td>20 (45.5)</td>
<td>0.147</td>
</tr>
<tr>
<td>Baseline LVEF (SD), %</td>
<td>33.4 (18.7)*</td>
<td>22.7 (15.2)*</td>
<td>0.0027*</td>
</tr>
<tr>
<td>Heart rate±SD, beats per minute</td>
<td>90.3 (22.9)</td>
<td>89.0 (20.4)</td>
<td>0.750</td>
</tr>
<tr>
<td>QTc (SD), ms</td>
<td>451.3 (33.5)</td>
<td>442.0 (52.2)</td>
<td>0.665</td>
</tr>
<tr>
<td>Mechanical alternans, n (%)</td>
<td>12 (18.2)*</td>
<td>16 (36.4)*</td>
<td>0.032*</td>
</tr>
<tr>
<td>TWA, n (%)</td>
<td>17 (25.8)</td>
<td>16 (36.4)</td>
<td>0.234</td>
</tr>
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ACS indicates acute coronary syndrome; CM, cardiomyopathy; CRT-D, cardiac resynchronization therapy defibrillator; HF, heart failure; ICD, implantable cardioverter defibrillator; LVEF, left ventricular ejection fraction; MA, mechanical alternans; NYHA, New York Heart Association; SCA, sudden cardiac arrest; and TWA, T-wave alternans.

*P<0.05.

predictor than MA—MA: HR, 2.00 (95% CI, 1.07–3.71), P=0.029 and LVEF≤35%: HR, 2.69 (95% CI, 1.28–5.63), P=0.009. In the final multivariable Cox model (Table 6), MA remained a significant predictor of the primary outcome (HR, 2.12; 95% CI, 1.13–3.98; P=0.020).

### Table 4. Comparison of MA in Patients With and Without Primary End Point

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<tr>
<td>Amplitude of MA, median (IQR), mm Hg</td>
<td>4.1 (2.7–9.3)</td>
<td>4.7 (1.5–21.1)</td>
<td>0.816</td>
</tr>
<tr>
<td>Number of MA beats, median (IQR), n</td>
<td>31 (25–64)</td>
<td>39 (29–56)</td>
<td>0.546</td>
</tr>
<tr>
<td>Mean heart rate at MA (SD), beats per minute</td>
<td>85.7 (21.4)</td>
<td>83.3 (17.7)</td>
<td>0.757</td>
</tr>
<tr>
<td>MA at max HR, median (IQR), mm Hg</td>
<td>17.3 (9.6–32.9)</td>
<td>15.7 (7.8–49.2)</td>
<td>0.963</td>
</tr>
</tbody>
</table>

HR indicates hazard ratio; IQR, interquartile range; and MA, mechanical alternans.

Importantly, study participants died regardless of having ICD/CRT-D implanted. Moreover, a significantly larger percentage of patients with the primary end point had an implanted ICD/CRT-D (Table 3) when compared with end point–free group.

### Table 2. Comparison of TWA Characteristics

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HR indicates hazard ratio; IQR, interquartile range; MA, mechanical alternans; and TWA, T-wave alternans.
associated with a 2- to 3-fold increased risk of all-cause death or heart transplant short-term postdischarge. Importantly, MA was associated with the primary outcome after adjustment for LVEF, NYHA class, and implanted ICD/CRT-D. If validated in another prospective study, MA could become a valuable tool for risk stratification in patients with AHHF.

Importantly, study showed that during ≥12 hours of recording, sustained MA was periodically accompanied by sustained TWA, but an opposite statement does not hold true. TWA may be present as lone TWA, without MA. More studies of coupled and uncoupled TWA and MA are needed to improve accuracy of the prediction of outcomes.

**Postdischarge Outcomes in ICCU Patients**

AHHF is characterized by extremely high short-term postdischarge mortality. In our study, all-cause mortality (39.6%) during 10-month postdischarge (4.0% per month) was comparable with high-risk subgroup of patients as reported in Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients with Heart Failure (OPTIMIZE-HF). Our finding of the independent association between MA and postdischarge mortality suggests that after validation MA could become an important prognostic tool and help to identify a population of patients that more likely benefit from advanced HF support (ventricular assist devices), rather than from ICDs. Importantly, even if LVEF was a stronger predictor of outcomes in this study, all-cause mortality (39.6%) during 10-month postdischarge (4.0% per month) was comparable with high-risk subgroup of patients as reported in Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients with Heart Failure (OPTIMIZE-HF). Our finding of the independent association between MA and postdischarge mortality suggests that after validation MA could become an important prognostic tool and help to identify a population of patients that more likely benefit from advanced HF support (ventricular assist devices), rather than from ICDs. Importantly, even if LVEF was a stronger predictor of outcomes in this study, MA remained predictive after adjustment for LVEF, NYHA class, and implanted ICD/CRT-D. The high frequency of large MA amplitude (>10 mmHg) observed represents another advantage of MA assessment and provides an opportunity to recognize MA phenomenon without any special equipment.

**Mechanical Alternans**

Our study is the first relatively large prospective observational cohort study of MA in patients with AHHF admitted to the ICCU. It was shown that MA is associated with adverse prognosis in patients with idiopathic dilated cardiomyopathy. Development of MA was linked to deteriorating pump function in patients with HF. Correlation has been demonstrated between TWA and systolic pressure alternans detected noninvasively (via finger photoplethysmography), and cases of ventricular fibrillation in patients with MA have been described.

Yet, the mechanism of MA is complex and is not completely understood. Beat-to-beat alternations in stroke volume can result from the variations in preload and ventricular compliance. Reduced stroke volume results in elevated end-diastolic volume for the next contraction, which, in turn, results in increased stroke volume and, therefore, increased systolic pressure with the next beat. The strong beat suggests prolonged systole, a shortened diastolic filling time and reduced end-diastolic volume of the subsequent weak beat, and alternans persists.

The second mechanism could be explained by the existence of the groups of myocytes that are electrically activated in an alternating fashion (eg, because of differences in refractory period in action potential duration alternans). Therefore, these cells are synchronized and mechanically activated in the same alternating pattern. Alternations in action potential morphology can lead to alternation in the contractile strength of each cell. Theoretically, this mechanism could be responsible for the manifestation of both MA and TWA in this study.

The predictive value of TWA remains controversial. The results of our study suggest that a simultaneous assessment of both MA and TWA may be needed to improve the predictive value of alternans. The small subgroup of lone TWA (N=5) observed in our study does not allow any conclusive statement. However, possible interaction between TWA and MA indicates that lone TWA versus TWA coupled with MA can carry different risks. We speculate that when coupled with MA, TWA carries a high risk of pump failure progression, whereas lone TWA is associated with ventricular arrhythmias. We further speculate that patients with AHHF and lone TWA would likely benefit from ICD/CRT-D, whereas patients with AHHF and MA would likely benefit from advanced HF support (eg, ventricular assist device). More studies of simultaneously measured TWA and MA are needed to test these hypotheses.

### Table 5. Comparison of TWA in Patients With and Without Primary End Point

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Alive (N=17)</th>
<th>Dead (N=16)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amplitude at Baseline</td>
<td>22 (20–49)</td>
<td>37 (26–64)</td>
<td>0.235</td>
</tr>
<tr>
<td>Number of TWA beats, median (IQR), n</td>
<td>25 (22–29)</td>
<td>24 (21–29)</td>
<td>0.515</td>
</tr>
<tr>
<td>Mean Heart rate at TWA (SD), beats per minute</td>
<td>76.9 (15.3)</td>
<td>68.6 (19.2)</td>
<td>0.184</td>
</tr>
<tr>
<td>Mean QTc at TWA (SD), ms</td>
<td>395 (142)</td>
<td>443 (154)</td>
<td>0.362</td>
</tr>
</tbody>
</table>

**Figure 3.** Kaplan–Meier curves for the probabilities of the primary end point (all-cause death or heart transplant) in patients with and without (A) mechanical alternans (MA), (B) T-wave alternans (TWA), and (C) MA and TWA.
Limitations
Several limitations of this study need to be acknowledged. First, the study population was heterogeneous, and even though this study is the largest prospective study of MA, statistical power was not sufficient for subgroup analysis. However, this study provided important prognostic information for the heterogeneous critical care patients studied. Additional prospective evaluation of ambulatory patients with HF is warranted. Importantly, small subgroup of lone TWA patients (N=5) warrants further evaluation. It is possible that our methodology of MA detection was not sensitive enough and, therefore, we missed MA in 5 patients with lone TWA. It is equally possible that our methodology for TWA detection was overly sensitive, and we detected subthreshold TWA. It is equally possible that our methodology of MA detection was not sensitive enough and, therefore, we missed MA in 5 patients with lone TWA. Several limitations of this study need to be acknowledged. Additional prospective evaluation of ambulatory patients with HF is warranted. Importantly, small subgroup of lone TWA patients (N=5) warrants further evaluation. It is possible that our methodology of MA detection was not sensitive enough and, therefore, we missed MA in 5 patients with lone TWA. It is equally possible that our methodology for TWA detection was overly sensitive, and we detected subthreshold TWA. It is equally possible that our methodology of MA detection was not sensitive enough and, therefore, we missed MA in 5 patients with lone TWA.

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We thank D. Das and E.S. Choi for helping with the data analysis.

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Disclosures
None.

References
16. Kim et al. Alternans in Heart Failure. 265

Table 6. Univariable and Multivariable Cox Regression Hazard Ratios

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Univariable Hazard Ratio (95% CI)</th>
<th>P Value</th>
<th>Multivariable Hazard Ratio (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>MA presence</td>
<td>1.84 (1.00–3.41)</td>
<td>0.050</td>
<td>2.12 (1.13–3.98)</td>
<td>0.020</td>
</tr>
<tr>
<td>Age, y</td>
<td>1.00 (0.98–1.02)</td>
<td>0.868</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female sex</td>
<td>0.63 (0.34–1.17)</td>
<td>0.146</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Black race</td>
<td>0.97 (0.57–1.65)</td>
<td>0.912</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NYHA III–IV class</td>
<td>2.12 (1.14–3.97)</td>
<td>0.018</td>
<td>1.91 (0.87–4.15)</td>
<td>0.104</td>
</tr>
<tr>
<td>LVEF≤35%</td>
<td>2.36 (1.24–4.51)</td>
<td>0.009</td>
<td>1.72 (0.73–4.04)</td>
<td>0.217</td>
</tr>
<tr>
<td>ICD/CRT-D implanted</td>
<td>1.68 (0.98–2.87)</td>
<td>0.058</td>
<td>1.40 (0.72–2.74)</td>
<td>0.322</td>
</tr>
<tr>
<td>Nonischemic cardiomyopathy</td>
<td>0.66 (0.35–1.25)</td>
<td>0.207</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heart rate≥90 beats per minute</td>
<td>1.54 (0.90–2.61)</td>
<td>0.114</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

CI indicates confidence interval; CRT-D, cardiac resynchronization therapy defibrillator; ICD, implantable cardioverter defibrillator; LVEF, left ventricular ejection fraction; and NYHA, New York Heart Association.

CLINICAL PERSPECTIVE

Acute hospitalized heart failure is a global pandemic with high postdischarge mortality and readmission rates. Competing risk of sudden cardiac death because of ventricular arrhythmias versus pump failure death brings difficult management choices. We conducted a prospective observational cohort study of acute hospitalized heart failure patients admitted to the intensive cardiac care unit. Study showed that the risk of death or heart transplant during 10-month postdischarge is twice higher in patients with mechanical pulsus alternans than in patients with acute hospitalized heart failure and without alternans, even after adjustment for left ventricular ejection fraction, New York Heart Association class, and implanted implantable cardioverter defibrillator/CRT-D. Large amplitude (>10 mm Hg) mechanical alternans could be easily recognized without any special equipment. At the same time, T-wave alternans (TWA) did not predict the outcome in this study. In addition, this study showed that mechanical alternans was often accompanied by TWA, with lone TWA events observed in a small group of patients. When coupled with mechanical alternans, TWA carried a high risk of pump failure progression, whereas lone TWA was associated with ventricular arrhythmias. Further studies of simultaneously measured TWA and mechanical alternans are needed. If validated in another prospective study, mechanical alternans could become a valuable tool for risk stratification in acute hospitalized heart failure.
Mechanical Alternans Is Associated With Mortality in Acute Hospitalized Heart Failure: Prospective Mechanical Alternans Study (MAS)

Robert Kim, Oscar Cingolani, Ilan Wittstein, Rhondalyn McLean, Lichy Han, Kailun Cheng, Elizabeth Robinson, Jeffrey Brinker, Steven S. Schulman, Ronald D. Berger, Charles A. Henrikson and Larisa G. Tereshchenko

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SUPPLEMENTAL MATERIAL

Supplemental Methods

Recording of ECG and blood pressure signal

After obtaining informed consent, a research laptop equipped with a customized Labview (National Instruments, Austin, TX) software application was connected to the analog output of the ICCU bedside monitor via the NI USB-9215A portable data acquisition system, and signal waveforms were digitized at 200 Hz.

Analysis of ECG and blood pressure signal

Before the beginning of an automated analysis, all recordings were manually reviewed by 3 operators [RK, KC, DD]; epochs with visible noise were manually marked and subsequently excluded from alternans analysis. Noise level on included epochs was continuously measured. Beats with >5 μV of noise, and regions with >25% of noisy beats were excluded. A third-order lowpass Bessel filter was applied to subdue noises. A bandpass filter (0.14 – 0.35 Hz) was applied to remove respiration effect.

Alternans analysis

First, the correlation method was applied to determine presence of alternans. Given n beats in a time interval (15 sec), the median beat was used as a template for beat alignment. Each beat was cross-correlated with the median beat, and the optimal alignment was achieved with the maximum correlation. Alternans correlation index was then computed for each beat as described...
by Burattini et al\textsuperscript{1}. An alternans event was detected when alternans correlation index values alternated around the value of one for at least 7 consecutive beats.

Then, if the correlation method determined the presence of alternans, a modified moving average (MMA) method was applied to quantify alternans\textsuperscript{2}. Signal beats (ECG or arterial blood pressure) were first separated into even and odd beats. Then, weighted moving average values for even and odd beats were computed recursively as suggested by Nearing et al\textsuperscript{2}. Alternans amplitude was computed as the absolute difference between the peak amplitudes of even and odd modified moving average computed beats. In order to avoid inaccurate measurement from misaligned waves, continuous dynamic time warping method was used to align even, and odd beats accurately\textsuperscript{3}.

References


Supplemental Figure 1. A. Comparison of the duration of TWA events, detected during 1 hour before and 1 hour after MA events. B. Comparison of the duration of MA events detected 1 hour before and 1 hour after TWA events. Data are presented as group means and standard deviations. **p < 0.01.

Supplemental Movie 1. Relationships between MA (green) and TWA (red) events in 10 study participants during 48 hours of observation. Each asterisk mark represents one beat in an alternans event.