Association between amount of biventricular pacing and heart failure status measured by a multisensor implantable defibrillator algorithm

Luca Santini, MD,* Leonardo Calò, MD,† Antonio D'Onofrio, MD,‡ Michele Manzo, MD,§ Antonio Dello Russo, MD,‖ Gianluca Savarese, MD,¶ Domenico Pecora, MD,# Claudia Amellone, MD,** Vincenzo Ezio Santobuono, MD, PhD,†† Raimondo Calvanese, MD,‡‡ Miguel Viscusi, MD,§§ Ennio Pisanò, MD,‖‖ Antonio Pangallo, MD,¶¶ Antonio Rapacciuolo, MD,## Matteo Bertini, MD, PhD,*** Carlo Lavalle, MD,††† Amato Santoro, MD,‡‡‡ Monica Campari, MS,§§§ Sergio Valsecchi, PhD,§§§ Giuseppe Boriani, MD, PhD‖‖‖

*From the *Giovan Battista Grassi Hospital, Rome, Italy, †Policlinico Casilino, Rome, Italy, ‡Unità Operativa di Elettrofisiologia, Studio e Terapia delle Aritmie, Monaldi Hospital, Naples, Italy, §OO.RR. San Giovanni di Dio Ruggi d'Aragona, Salerno, Italy, ‖Università Politecnica delle Marche, Ospedali Riuniti, Ancona, Italy, ¶S. Giovanni Battista Hospital, Foligno, Italy, #Fondazione Poliambulanza, Brescia, Italy, **Maria Vittoria Hospital, Turin, Italy, ††University Cardiology Unit, Interdisciplinary Department of Medicine, University of Bari Aldo Moro, Policlinico di Bari, Bari, Italy, ‡‡Ospedale del Mare, ASL NA1, Naples, Italy, §§S. Anna e S. Sebastiano Hospital, Caserta, Italy, ‖‖Vito Fazzi Hospital, Lecce, Italy, ¶¶Grande Ospedale Metropolitano Bianchi-Melacrino, Reggio Calabria, Italy, ##Department of Advanced Biomedical Sciences, Federico II University of Naples, Naples, Italy, ***Cardiology Unit, University of Ferrara, S. Anna University Hospital, Ferrara, Italy, †††Policlinico Umberto I, Rome, Italy, ‡‡‡AOU Senese, Siena, Italy, §§§Boston Scientific Italia, Milan, Italy, and ‖‖‖Cardiology Division, Department of Biomedical, Metabolic and Neural Sciences, University of Modena and Reggio Emilia, Policlinico di Modena, Modena, Italy.*

BACKGROUND Achieving a high biventricular pacing percentage (BiV%) is crucial for optimizing outcomes in cardiac resynchronization therapy (CRT). The HeartLogic index, a multiparametric heart failure (HF) risk score, incorporates implantable cardioverter-defibrillator (ICD)-measured variables and has demonstrated its predictive ability for impending HF decompensation.

OBJECTIVE This study aimed to investigate the relationship between daily BiV% in CRT ICD patients and their HF status, assessed using the HeartLogic algorithm.

METHODS The HeartLogic algorithm was activated in 306 patients across 26 centers, with a median follow-up of 26 months (25th–75th percentile: 15–37).

RESULTS During the follow-up period, 619 HeartLogic alerts were recorded in 186 patients. Overall, daily values associated with the best clinical status (highest first heart sound, intrathoracic impedance, patient activity; lowest combined index, third heart sound, respiration rate, night heart rate) were associated with a BiV% exceeding 99%. We identified 455 instances of BiV% dropping below 98% after consistent pacing periods. Longer episodes of reduced BiV% (hazard ratio: 2.68; 95% CI: 1.02–9.72; $P = .045$) and lower BiV% (hazard ratio: 3.97; 95% CI: 1.74–9.06; $P=.001$) were linked to a higher risk of HeartLogic alerts. BiV% drops exceeding 7 days predicted alerts with 90% sensitivity (95% CI [74%–98%]) and 55% specificity (95% CI [51%–60%]), while BiV% $\leq$96% predicted alerts with 74% sensitivity (95% CI [55%–88%]) and 81% specificity (95% CI [77%–85%]).

CONCLUSION A clear correlation was observed between reduced daily BiV% and worsening clinical conditions, as indicated by the HeartLogic index. Importantly, even minor reductions in pacing percentage and duration were associated with an increased risk of HF alerts.

KEYWORDS Heart failure; ICD; CRT; Biventricular pacing; Remote monitoring; Multisensor

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Address reprint requests and correspondence: Dr Luca Santini, Cardiology Division, Giovan Battista Grassi Hospital, Via Gian Carlo Passeroni 28 - 00122 Rome, Italy. E-mail address: lsantini@alice.it.

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KEY FINDINGS

- In patients who received a CRT-D device, a clear association exists between lower daily BiV pacing percentages and deteriorating clinical condition, as detected by the combined HeartLogic index and the individual ICD-based sensors.
- A decline in BiV pacing explains only a fraction of heart failure events (i.e., from 10% to 19% in cases of concurrent atrial fibrillation).
- Nonetheless, even minor reductions in BiV pacing percentage and duration were found to elevate the risk of heart failure.

Introduction

The utilization of defibrillators for resynchronization therapy (cardiac resynchronization therapy defibrillator; CRT-D) has demonstrated significant efficacy in enhancing outcomes for a carefully selected cohort of heart failure (HF) patients. This therapeutic approach is now a recommended component of contemporary guidelines for managing chronic HF.[1,2] To achieve optimal results, continuous delivery of CRT is imperative. Several extensive investigations have been conducted to determine the ideal level of biventricular (BiV) pacing percentage.[3–5] Notably, in the MADIT-CRT trial, patients who received less than 90% BiV pacing exhibited HF event rates comparable to those who did not receive CRT.[6] Conversely, individuals with BiV pacing levels of ≥97% experienced a further reduction in HF events, with each 1% increment in BiV pacing percentage translating to a 6% reduction in HF risk. However, the effective delivery of BiV pacing may be hindered by factors such as atrial fibrillation or spontaneous atrioventricular conduction patterns resulting from suboptimal device programming. Consequently, expert consensus statements advocate for the meticulous adjustment of CRT-D therapy to achieve the highest attainable percentage of BiV pacing, ideally surpassing the 98% threshold.[7] In a contemporary context, certain modern defibrillators are equipped with automated algorithms that furnish comprehensive insights into a patient's HF condition on a daily basis.[8] Notably, the Multisensor Chronic Evaluation in Ambulatory Heart Failure Patients (MultiSENSE) study[9] introduced an innovative algorithm for HF monitoring known as the HeartLogic index (Boston Scientific, St. Paul, MN). This index combines physiological data obtained from multiple implantable cardioverter-defibrillator (ICD)-based sensors, demonstrating its sensitivity and timeliness in predicting impending HF decompensation,[10,11] as well as in identifying patients at higher risk for all-cause mortality.[12] In the current study, we endeavor to explore the association between daily BiV pacing percentages in patients who have received a CRT-D device and their HF status, as evaluated by the HeartLogic algorithm.

Methods

Patient selection

The study was a prospective, nonrandomized, multicenter evaluation of patients who had received a CRT ICD (CRT-D) endowed with the HeartLogic™ diagnostic algorithm. Consecutive HF patients with reduced left ventricular ejection fraction (≤35% at the time of implantation) who had received a device in accordance with standard indications[1,2] and were enrolled in the LATITUDE (Boston Scientific) remote monitoring platform were included at 26 study centers (full list of participating centers in Supplemental Material) and followed up in accordance with the standard practice of the participating centers.[13] Data on the clinical events that occurred during follow-up were collected at the study centers within the framework of a prospective registry (ClinicalTrials.gov identifier: NCT02275637). The Institutional Review Boards approved the study, and all patients provided written informed consent for data storage and analysis.

Device characteristics

Commercially available CRT-Ds equipped with the HeartLogic diagnostic feature and standard transvenous leads were used in this study. The details of the HeartLogic algorithm have been reported previously.[9] Briefly, the algorithm combines data from multiple sensors: accelerometer-based first and third heart sounds, intrathoracic impedance, respiration rate, the ratio of respiration rate to tidal volume, night heart rate, and patient activity. Each day, the device

Table 1 Demographics and baseline clinical parameters of the study population

Parameter	Total (N = 306)
Male sex, n (%)	234 (77%)
Age, years	70 ± 10
Ischemic etiology, n (%)	139 (46%)
NYHA class, n (%)	
Class I	11 (4%)
Class II	177 (58%)
Class III	112 (36%)
Class IV	6 (2%)
LV ejection fraction, %	30 ± 7
Left bundle branch block, n (%)	210 (69%)
QRS duration, ms	156 ± 20
AF history, n (%)	118 (39%)
AF on implantation, n (%)	62 (20%)
Diabetes, n (%)	87 (29%)
COPD, n (%)	57 (19%)
Chronic kidney disease, n (%)	90 (30%)
Hypertension, n (%)	180 (59%)
β-Blocker use, n (%)	282 (92%)
ACE-I, ARB, or ARNI use, n (%)	290 (95%)
Diuretic use, n (%)	278 (91%)
Antiarrhythmic use, n (%)	135 (44%)
Primary prevention, n (%)	276 (90%)

ACE = angiotensin-converting enzyme; AF = atrial fibrillation; ARB = angiotensin II receptor blockers; ARNI = angiotensin receptor-neprilysin inhibitor; COPD = chronic obstructive pulmonary disease; LV = left ventricular; NYHA = New York Heart Association.

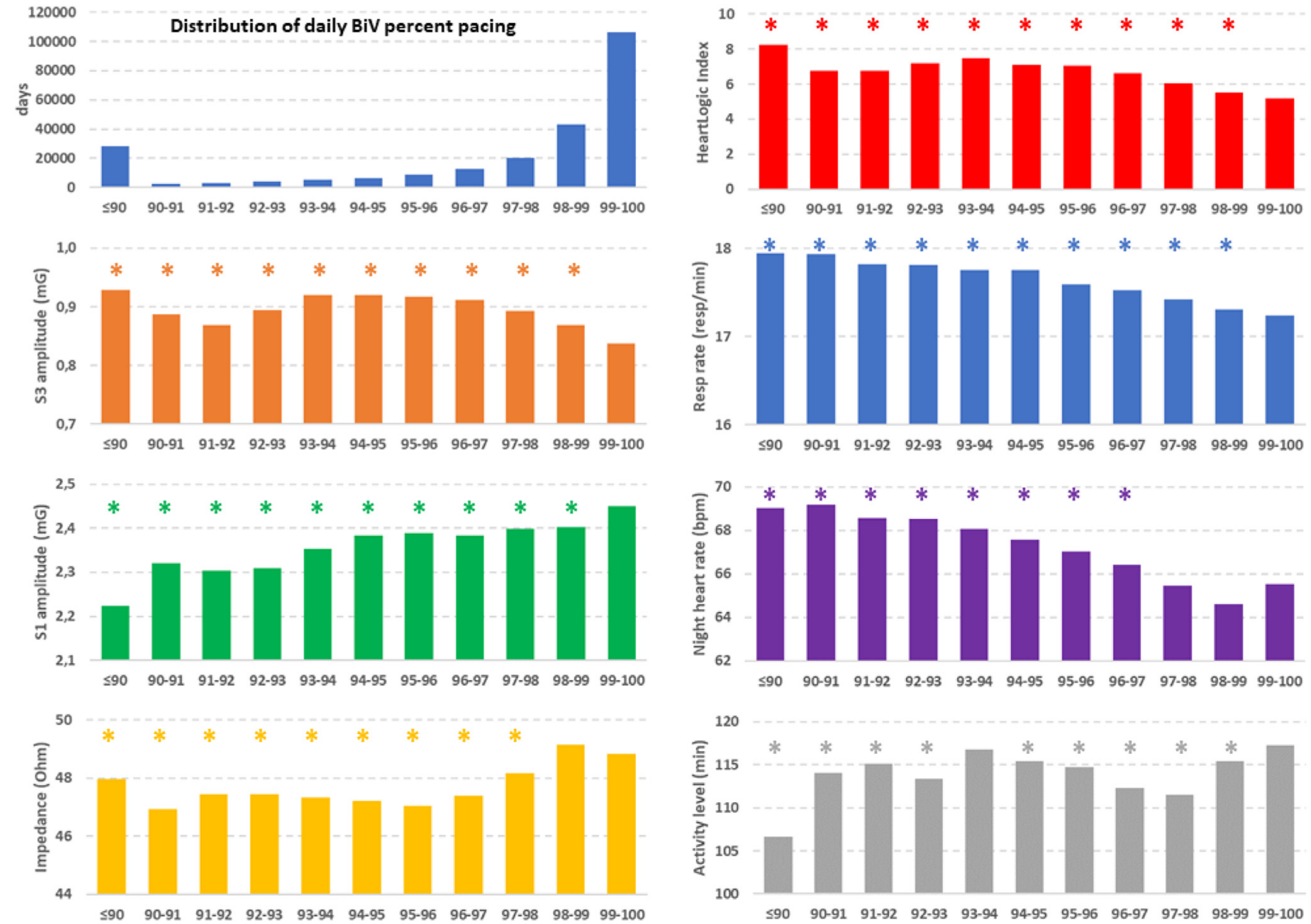

Figure 1 Distribution of daily biventricular (BiV) percent pacing during the observation period and average combined index and sensor values at different BiV pacing percentages. $^*P < .05$ vs values observed with BiV percent pacing >99%.

calculates the degree of worsening in sensors from their moving baseline and computes a composite index. An alert is issued when the index crosses a programmable threshold (nominal value, 16). When the index enters an alert state, the "exit-alert" threshold is automatically dropped to a recovery value (nominal value, 6).

Analysis design

The primary objective of this analysis was to explore the correlation between the percentage of BiV pacing in patients who received a CRT-D device and their HF status, as determined by the HeartLogic algorithm. This algorithm integrates data from multiple ICD-based sensors.

We initially examined the average values of both the composite index and the individual HF sensors in relation to the level of BiV pacing for each follow-up day throughout the observation period encompassing the entire cohort. Subsequently, we excluded patients with an average BiV pacing <90% over the entire observation period, considering BiV pacing as optimal when it equaled or exceeded 98%.[7] In our secondary analysis, we aimed to identify instances of pacing percentages falling below 98% after a sustained period of consistently optimal BiV pacing lasting for 30 days or more. Consequently, we scrutinized the device-stored data, commencing from the initial day of pacing percentage decline until 30 days after restoration of continuous pacing, with the aim of assessing the impact of reduced optimal BiV pacing on physiological indicators of the HF condition. As a third analysis, we delved into the temporal evolution of daily BiV pacing percentages, combined index values, and sensor data changes preceding any HeartLogic alerts. Specifically, we compared a patient's 30-day baseline (averages calculated from 30 days prior to the alert, ie, spanning from -60 to -30 days) with a 7-day average state immediately preceding the alert.[14]

Statistical analysis

Descriptive statistics are reported as means ± SD for normally distributed continuous variables, or medians with 25th to 75th percentiles in the case of skewed distribution. Normality of distribution was tested by means of the nonparametric Kolmogorov–Smirnov test. Categorical data are expressed as percentages. Differences between mean data were compared by a *t* test for Gaussian variables, and by Mann–Whitney nonparametric test for non-Gaussian variables. Differences in proportions were compared by a χ^2

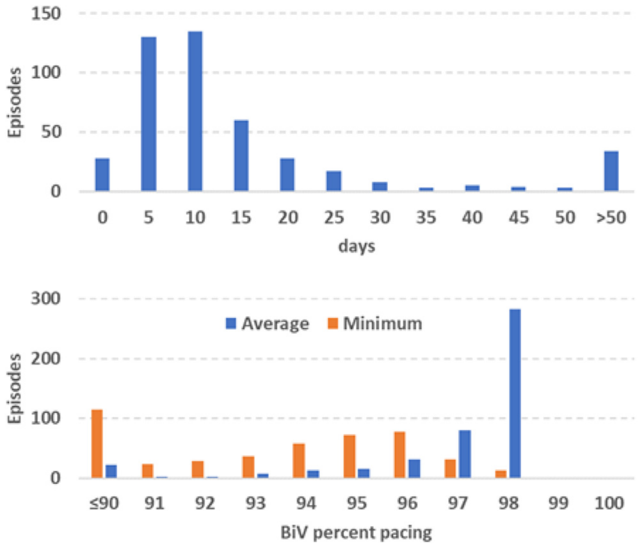

Figure 2 Distribution of the durations and the average/minimum biventricular (BiV) percent pacing for the episodes (n = 455) of BiV percent pacing reduction to <98% following at least 30 days of consistent pacing ≥98%.

analysis. Analysis of the time to the first episode was made by means of the Kaplan–Meier method, and the distributions of the groups were compared by a log-rank test. Cox proportional hazards models were used to determine the association between the occurrence of HeartLogic alerts and the characteristics of the episodes of BiV percent pacing reduction, and to estimate the hazard ratios (HRs) and the 95% confidence intervals (CIs). A receiver operating characteristic curve analysis was conducted to assess the performance of the amplitude and duration of the BiV pacing decrease as predictors for a HeartLogic alert, and we regarded the value resulting in the maximum product of sensitivity and specificity on the curve as the optimal cutoff. A P value <.05 was considered significant for all tests. All statistical analyses were performed by means of R: a language and environment for statistical computing (R Foundation for Statistical Computing, Vienna, Austria).

Results

Study population

From December 2017 to June 2021, HeartLogic was activated in 306 patients who had received a CRT-D. The index threshold was programmed to the nominal value of 16 in all patients and was not modified during follow-up. Table 1 shows the baseline clinical variables of all patients in the present analysis.

Follow-up

The median follow-up duration was 26 months [25th–75th percentile: 15–37]. The distribution of daily BiV percent pacing during the observation period is shown in Figure 1. The median BiV percent pacing was 98% [25th–75th percentile: 95%–100%] on a patient basis, and 277 (91%) patients showed an average BiV percent pacing >90% during the follow-up. Among these patients, the HeartLogic index crossed the threshold value 619 times in 186 (67%) patients. An atrial high rate episode (AHRE) burden of ≥5 min/day was documented in 51 (18%) patients. Higher average values of the combined index and worse individual HF sensors were found with progressively lower pacing percentages (Figure 1). Values associated with the best clinical status (highest first heart sound, intrathoracic impedance, patient activity; lowest combined index, third heart sound, respiration rate, night heart rate) were observed with BiV percent pacing >99%.

Physiological measures of the HF condition after pacing reduction

In the study cohort, we identified 455 episodes of BiV percent pacing reduction to <98% following at least 30 days of consistent pacing ≥98%. The median duration of these episodes was 7 days [25th–75th percentile: 4–14] and the BiV percent pacing during the episodes was 97% [25th–75th percentile: 96%–98%]. The distribution of the episode durations and the average and minimum BiV percent pacing are shown in Figure 2. The HeartLogic index crossed the threshold value 31 times after episodes of BiV percent pacing reduction. The risk of HeartLogic alert was higher after longer episodes (HR: 2.68; 95% CI: 1.02–9.72; P = .045) and in case of lower percent pacing (HR: 3.97; 95% CI: 1.74–9.06; P = .001). Based on the receiver operating characteristic curve analysis, the value of BiV% reduction duration that maximized the product of sensitivity and specificity for the prediction of HeartLogic alert was >7 days—area under the curve 0.81 (95% CI [0.77–0.85], P < .001); sensitivity 90% (95% CI [74%–98%]); specificity 55% (95% CI [51%–60%]; and the value of BiV percent pacing was ≤96%—area under the curve 0.83 (95% CI [0.80–0.87], P < .001); sensitivity 74% (95% CI [55%–88%]); specificity 81% (95% CI [77%–85%]). Figure 3 shows the Kaplan–Meier analysis of time to HeartLogic alert. Patients are stratified according to the BiV% reduction duration (hazard ratio: 2.14, 95% CI: 1.08–5.07, P = .042) and the value of BiV percent pacing (hazard ratio: 3.14, 95% CI: 1.55–6.39, P < .001).

Daily percent pacing and sensor data before HeartLogic alerts

In 384 out of 619 episodes of alert (62%), the daily BiV percent pacing was ≥98% during the 30-day baseline calculated 30 days prior to the alert. In 50 (13%) of these episodes, the BiV percent pacing decreased below 98% during the 7-day average prealert state. Analyzing separately patients with or without AHRE during follow-up, we observed that the BiV percent pacing decreased below 98% before the alert in 25 out of 130 alert episodes (19%) occurring in patients with AHRE burden of ≥5 min/day, and in 25 out of 254 alert episodes (10%) occurring in patients with AHRE burden <5 min/day (P = .010).

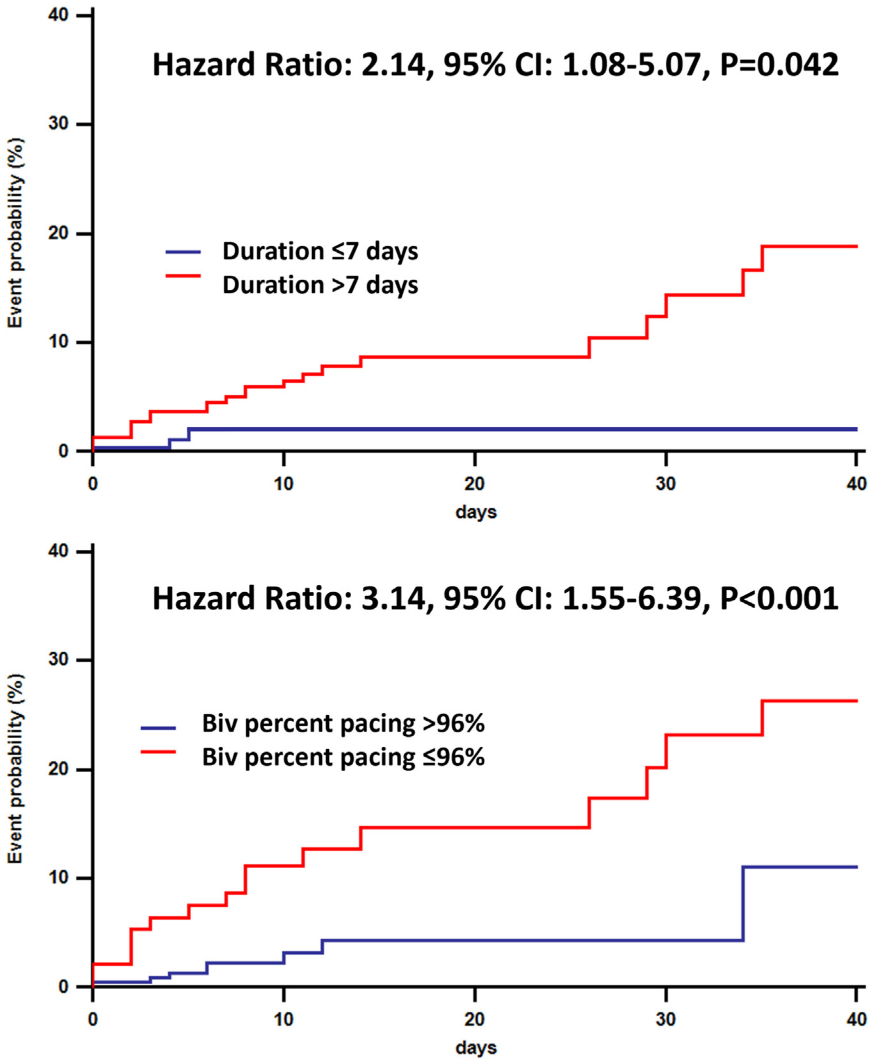

Figure 3 Kaplan–Meier analysis of time to HeartLogic alert. Day 0 is the first day of biventricular (BiV) percent pacing below 98%. Patients are stratified according to the BiV% reduction duration (hazard ratio: 2.14, 95% CI: 1.08–5.07, $P = .042$) and the value of BiV percent pacing (hazard ratio: 3.14, 95% CI: 1.55–6.39, $P < .001$).

The trends in the average index and the relative changes of the individual sensors preceding the HeartLogic alert are reported in Figures 4 and 5 for patients with AHRE burden <5 min/day and ≥5 min/day, respectively. The increase in the combined index was accompanied by a reduction of BiV percent pacing ($P < .05$ for all changes from the 30-day baseline average to the 7-day average immediately preceding the alert). The reduction of percent pacing appeared to be larger for events from patients with AHRE, who also experienced an increase in daily AHRE burden before the HeartLogic alert. In patients with AHRE the average HeartLogic index was higher more than 30 days prior to the alert ($P < .05$ vs patients with AHRE burden <5 min/day) and showed a steeper increase in the days immediately preceding the alert. Among the HF sensors, heart sounds amplitude (increase in the third sound and decrease in the first sound) showed the largest changes ($P < .05$ vs other sensors) and, as for the combined index, seemed to change closer to the alert in the case of AHRE patients.

Discussion

In our study involving patients who received a CRT-D device, we established a clear association between lower daily BiV pacing percentages and deteriorating clinical condition, as detected by the combined HeartLogic index and the individual ICD-based sensors. Furthermore, we identified an elevated risk of HF alerts following relatively minor and short episodes of reduction in BiV pacing.

An analysis of pacing distribution during the observation period revealed that the vast majority of patients who received a CRT-D device in clinical practice achieved a high level of BiV pacing. Specifically, the median percent pacing was 98%, which aligns with the cutoff value

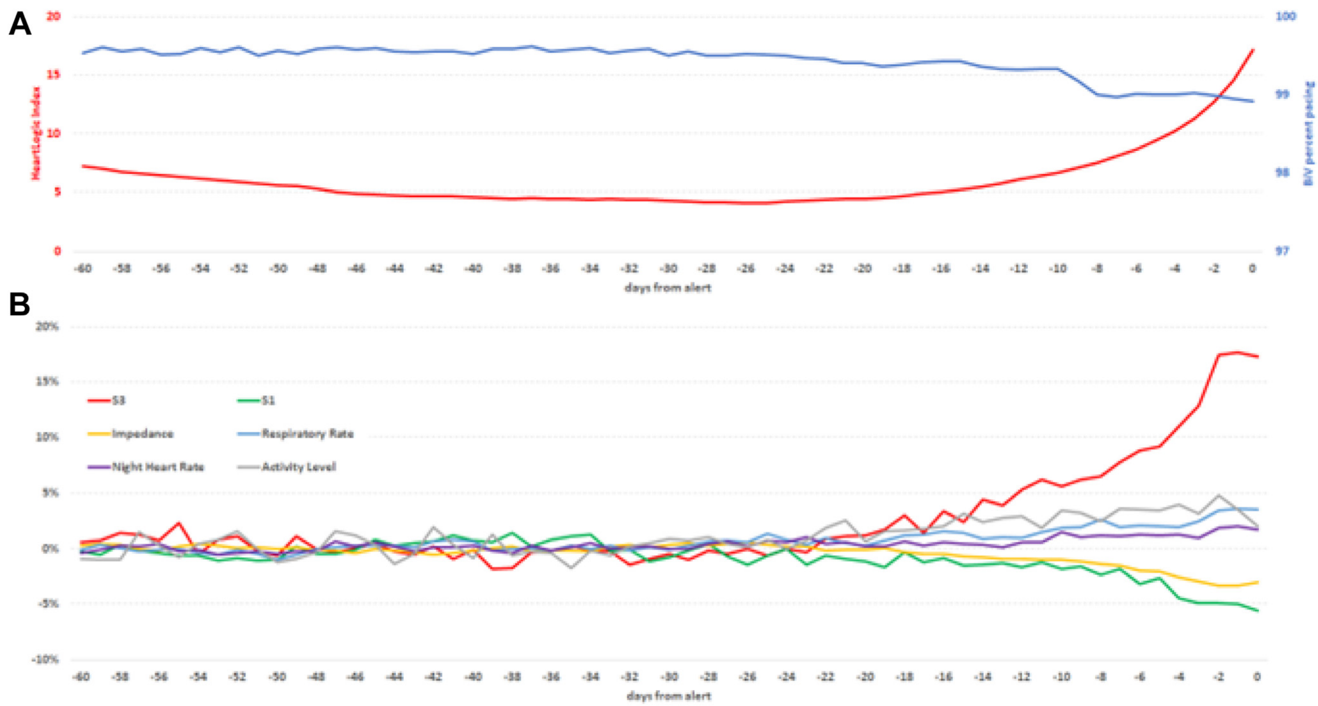

Figure 4 Trends in the average index and the average biventricular (BiV) percent pacing (**A**) and relative changes of the individual sensors (**B**) preceding the HeartLogic alert for patients with atrial high rate episode burden <5 min/day.

associated with the most significant reduction in mortality observed with CRT.[4] Only 9% of patients exhibited less than 90% BiV pacing, a level of stimulation that exposes patients to not deriving therapeutic benefits from CRT.[6]

Previous studies investigated the performance of the HeartLogic index, a multiparametric HF risk score obtained by combining ICD-measured variables, and proved its ability to timely predict impending HF decompensation and to identify time intervals when patients were at significantly increased risk of worsening HF.[9–12,15–17] Recorded parameters are objective measurements of the underlying pathophysiology associated with signs and symptoms of worsening HF.[18–22] Specifically, the third heart sound is detected in order to provide an objective measure of elevated filling pressure, while the first heart sound is taken as a surrogate for left ventricular contractility. Intrathoracic impedance is monitored to detect fluid accumulation, higher respiratory rate is associated with shortness of breath, and higher nocturnal heart rate is a marker of abnormal autonomics. Device-measured activity is a measure of global patient status and fatigue. When evaluating ICD-detected physiological metrics in relation to pacing percentages, our findings consistently indicated a more adverse HF status with progressively lower pacing percentages, while the best clinical condition corresponded to the highest percentage of BiV stimulation. It is worth noting that while some sensors might be directly influenced by changes in pacing percentage (eg, heart sounds, heart rate), other parameters (eg, intrathoracic impedance, patient activity, respiration rate) are independent indicators of clinical deterioration, unaffected by heart rate or native conduction. Expert consensus statements have advocated maintaining BiV pacing percentages above 98%.[7] Thus, we conducted an analysis of device-stored data, commencing from the first day of BiV pacing falling below 98%. This allowed us to assess the impact of reduced optimal BiV pacing on physiological HF measures. Despite a relatively modest degree (median BiV percent pacing was 97%) and duration (median of 7 days) of the observed pacing reductions, these episodes were associated with a significantly increased risk of HF events diagnosed by the ICD. Specifically, pacing reductions exceeding 4% or lasting more than 1 week were linked with HeartLogic alerts. The proportion of HeartLogic-detected episodes involving a reduction in pacing percentage preceding the alerts was approximately 13%. Notably, this occurrence was more frequent in patients who reported episodes of AHRE during follow-up, with rates of 19%, compared to 10% in those without AHRE. Atrial arrhythmias are recognized triggers for ventricular pacing reduction and can exacerbate HF,[23] and they have also been shown to correlate with subsequent HeartLogic alerts.[24] However, despite the steeper changes in the combined index and pacing percentage in the presence of AHRE, our study demonstrated that the association between BiV pacing reduction and worsening HF persisted even in the absence of atrial arrhythmias, suggesting that atrial arrhythmias are not the sole link between these 2 factors. However, upon analyzing the average trend of ICD-based sensors before HeartLogic alerts, we observed that the HeartLogic index appeared to rise before the decline in BiV pacing. This raises questions about a direct causal link between reduced BiV pacing and exacerbation of HF. This observation aligns with the findings of a prior study[25] that explored pacing

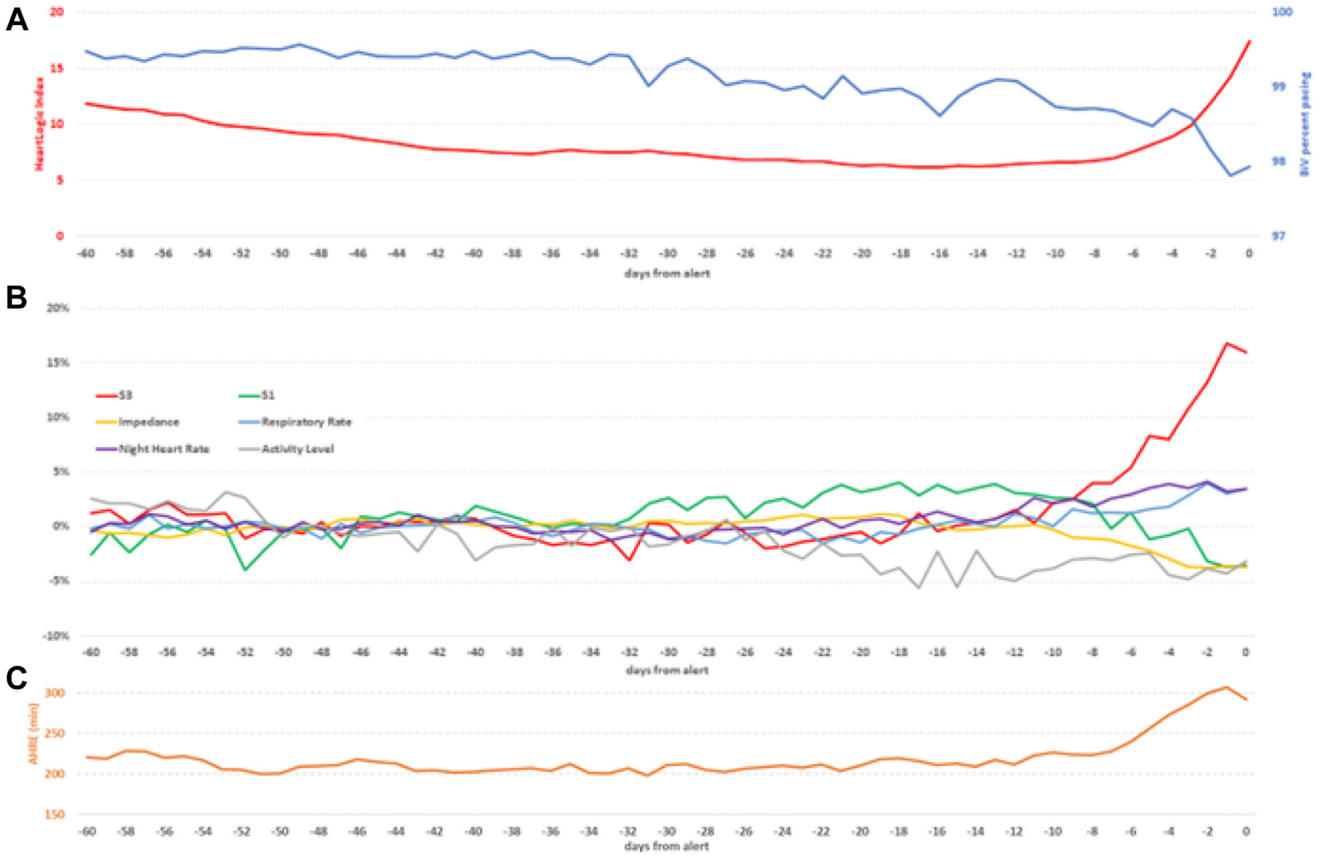

Figure 5 Trends in the average index and the average biventricular percent pacing (**A**), relative changes of the individual sensors (**B**), and daily atrial high rate episode (AHRE) burden (**C**) preceding the HeartLogic alert for patients with AHRE burden ≥5 min/day.

percentage and ICD sensor trends before clinical HF events. Among the sensed parameters contributing to the calculation of the HeartLogic index, accelerometer-based heart sounds emerged as the most sensitive, consistent with previous research.[26] For patients with AHRE, the onset of atrial fibrillation episodes or an increased burden of atrial fibrillation could account for the decline in BiV pacing percentage and changes in heart sounds, in line with previously described mechanisms.[27] However, in the absence of AHRE, the link between early changes in heart sounds and reduced BiV pacing is less evident. The mechanism may involve an increased burden of premature ventricular contractions, which could induce a decline in cardiac function detectable through heart sound assessment.[28] Indeed, previous research has demonstrated that relatively low frequencies of ectopic beats significantly increase the likelihood of low BiV pacing, leading to reduced CRT efficacy characterized by diminished reverse remodeling and an elevated risk of HF and mortality.[29] Unfortunately, our ability to specifically investigate the role of ectopic beat frequency was constrained, as the device only provided summary information over the entire follow-up period, lacking daily measurements of recorded beats. A prior study on the same subject,[25] which analyzed sensor values averaged over periods, revealed a significantly lower average BiV percentage during periods with a higher ectopic beat burden. However, a high burden alone was not associated with an elevation of the HeartLogic index. In a recent investigation into HF risk stratification, an alternative multiparametric HF risk score incorporating the daily number of premature ventricular complexes was assessed.[30] The study indicated that the relative contribution of a higher ectopic beat burden over the last 7 days preceding HF events did not exceed 8%. Nevertheless, further investigations are warranted to elucidate this mechanism and identify specific interventions to prevent clinical deterioration. Our findings underscore the significance of even a minor reduction in BiV pacing, which can elevate the risk of worsening HF. This emphasizes the importance of promptly addressing and restoring continuous pacing in response to automatic ICD alerts indicating pacing reduction. While we did not establish a direct causal link between reduced BiV pacing and HF decompensation, and while a decline in BiV pacing explained only a fraction of HF events (ie, from 10% to 19% in cases of concurrent atrial fibrillation), in CRT patients it seems prudent to investigate the consistency of BiV pacing immediately upon receiving a HeartLogic alert. In contrast to a preceding study,[25] where average trends were described, we opted to scrutinize individual episodes of pacing percentage decline. This approach enabled us to precisely quantify the risk of HF diagnosed by the ICD in the event of BiV%

reduction. These findings hold significance for the management of patient follow-up in clinical practice.

Limitations

The primary limitation of this study pertains to its observational retrospective design. Additionally, in our analysis, we regarded HeartLogic alerts as a proxy for HF events. Although the algorithm has demonstrated sensitivity and timely prediction of impending HF decompensation,[9] further research is warranted to specifically address the risk of HF progression and determine the optimal threshold for BiV pacing percentage, thereby validating our findings and evaluating their clinical implications. Furthermore, it is important to note that the level of BiV pacing percentage may directly impact certain contributing sensors (eg, increased heart rate), potentially leading to an index change unrelated to worsening HF. However, it is essential to consider that for an alert to be generated, the algorithm necessitates the occurrence of several conditions, which also rely on other sensors that are less sensitive to immediate changes induced by alterations in pacing parameters. Moreover, in this analysis we employed a predefined threshold of 98% and required a minimum of 30 days to define periods of optimal BiV pacing. It should be acknowledged that these choices were somewhat arbitrary and may have influenced the results to some extent.

Conclusion

In summary, this study establishes a clear association between reduced daily BiV pacing percentages and deteriorating clinical conditions, as indicated by the combined HeartLogic index. Notably, even minor reductions in pacing percentage and duration were found to elevate the risk of HF alerts. These findings underscore the critical importance of maintaining optimal BiV pacing to prevent HF exacerbation.

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Disclosures

M. Campari and S. Valsecchi are employees of Boston Scientific, Inc. No other conflicts of interest exist.

Authorship

All authors attest they meet the current ICMJE criteria for authorship.

Patient Consent

All patients provided written informed consent.

Ethics Statement

The authors designed the study, gathered and analyzed the data according to the Helsinki Declaration guidelines on human research. The research protocol used in this study was reviewed and approved by the institutional review board.

Data Availability

The experimental data used to support the findings of this study are available from the corresponding author upon request.

Appendix

Supplementary data

Supplementary data associated with this article can be found in the online version at https://doi.org/10.1016/j.cvdhj.2024.02.005.

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