Journal of Interventional Cardiac Electrophysiology
https://doi.org/10.1007/s10840-019-00668-y

ICD-measured heart sounds and their correlation with echocardiographic indexes of systolic and diastolic function

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Received: 2 October 2019 / Accepted: 11 November 2019

Abstract
Background Novel implantable defibrillators (ICDs) allow first (S1) and third (S3) heart sounds to be measured by means of an embedded accelerometer. ICD-measured S1 and S3 have been shown to significantly correlate with hemodynamic changes in acute animal models. The HeartLogic algorithm (Boston Scientific) measures and combines multiple parameters, including S3 and S1, into a single index to predict impending heart failure decompensation. We evaluated the echocardiographic correlates of ICD-measured S1 and S3 in patients with ICD and cardiac resynchronization therapy ICD.
Methods The HeartLogic feature was activated in 104 patients. During in-office visits, patients underwent echocardiographic evaluation, and parameters of systolic and diastolic function were correlated with S3 and S1 amplitude measured on the same day as the visit.
Results S3 amplitude inversely correlated with deceleration time of the E-wave (r = −0.32; 95% CI -0.46 – -0.17; $P < 0.001$), and S1 amplitude significantly correlated with left ventricular ejection fraction (r = 0.17; 95% CI 0.03–0.30; $P = 0.021$). S3 > 0.9 mG detected a restrictive filling pattern with 85% (95% CI 72%–93%) sensitivity and 82% (95% CI 75%–88%) specificity, while S1 < 1.5 mG detected ejection fraction < 35% with 28% (95% CI 19%–40%) sensitivity and 88% (95% CI 80%–93%) specificity.
Conclusion ICD-measured heart sound parameters are significantly correlated with echocardiographic indexes of systolic and diastolic function. This confirms their utility for remote patient monitoring when used as single sensors and their potential relevance when considered in combination with other physiological ICD sensors that evaluate various aspects of heart failure physiology.

Keywords ICD · Heart sounds · Heart failure · Systole · Diastole

1 Introduction

Implantable defibrillators (ICD) and defibrillators for resynchronization therapy (CRT-D) are the only therapeutic technologies with a class I recommendation in current guidelines for the management of chronic heart failure (HF) in patients with reduced left ventricular ejection fraction (LVEF) [1]. Moreover, patients with ICD and CRT-D can benefit from the ability of modern devices to measure multiple clinical variables, which can be used for the continuous monitoring of changes in clinical status. Indeed, European Society of Cardiology HF guidelines specify that ICD-based multiparameter monitoring may be considered in order to improve clinical outcomes [1].

The novel HeartLogic (Boston Scientific, St. Paul, Minnesota) algorithm combines data from multiple ICD and CRT-D-based sensors and has proved to be a sensitive and

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timely predictor of impending HF decompensation [2]. As part of this suite of sensors, the implanted device measures heart sounds by using an embedded accelerometer. Specifically, the third heart sound (S3) is detected to provide an objective measure of elevated filling pressure, while the first heart sound (S1) is taken as a surrogate for left ventricular contractility, since it has been shown to correlate with the maximum pressure derivative [3].

However, that these implanted device-based sensors can serve as surrogates for conventional measures of cardiac function in clinical practice remains to be proven. Thus, the aim of this study was to evaluate the echocardiographic correlates of ICD-measured heart sound in patients with ICD and CRT-D.

2 Methods

At the study centers, HeartLogic was activated in all heart failure patients with reduced LVEF (≤ 35% at the time of implantation) who had received a HeartLogic-enabled ICD or CRT-D device (RESONATE family, Boston Scientific) in accordance with standard indications [1] and were enrolled in the LATITUDE (Boston Scientific) remote monitoring platform. During the first in-office visit after activation, patients underwent an evaluation consisting of demographics and medical history, 12-lead electrocardiogram, echocardiographic evaluation and clinical examination. Auscultation was performed to detect possible gallop rhythm, and congestion was assessed and graded according to Gheorghiade et al. [4]. Remote data reviews and patient phone contacts were undertaken monthly. In-office visits were scheduled after 6 months, in case of clinical decompensation, and at the time of HeartLogic alerts, to assess the patient's decompensation status through clinical examination and to repeat echocardiographic evaluation. The alerts were issued when the combined index crossed the programmable threshold, that in this series was set at 16 (nominal value). With this threshold the algorithm effectively detected 70% of worsening heart failure events a median of 34 days before the event, with a low rate of unexplained detections of < 1.5 per patient-year in the validation study [2]. Echocardiographic evaluation was performed by operators blinded to the ICD diagnostics and included assessment of left ventricular end-diastolic and end-systolic volume and LVEF by means of Simpson's equation in the apical four-chamber view. The pulsed-wave Doppler echocardiography sample volume was positioned between the tips of the mitral leaflets to derive the following variables: peak early transmitral filling velocity (E) and late transmitral filling velocity (A), their ratio (E/A), and the deceleration time of E. A restrictive filling pattern (RFP) was defined as E/A ≥ 2 or the combination of E/A between 1 and 2 and deceleration time ≤ 140 ms. A non-RFP was defined as E/A ≤ 1 or E/A between 1 and 2 with deceleration time > 140 ms [5, 6]. Data were collected at the study centers in the framework of a prospective registry. The Institutional Review Boards approved the study, and all patients provided written informed consent to data storage and analysis.

2.1 HeartLogic algorithm and sensor data

The HeartLogic algorithm combines data from multiple sensors. Each day the device calculates the shift of sensor-detected values from the baseline and computes a composite index [2]. A full report of automatic diagnostics is available for remote data review. This includes the composite HeartLogic index and sensor data collected since device implantation. An alert is issued when the index crosses a programmable threshold. The sensor-detected values included in the calculation are: accelerometer-based S1 amplitude, S3/S1 amplitude ratio, intrathoracic impedance, respiration rate, the ratio of respiration rate to tidal volume, night heart rate, and patient activity. To measure heart sounds, the implanted CRT-D device uses its embedded accelerometer. Measurements are taken on heart sound waveforms, according to previously described methods [3, 7]. Specifically, the waveforms are parsed into individual beats by means of device electrograms and averaged to obtain ensemble averages to mitigate the impact of non-cardiac variability on the data, i.e., respiration or other spurious external noise. Then, after detecting the timings of heart sound parameters, the algorithm measures S1 and S3 amplitudes.

2.2 Objectives

The objective of the study was to evaluate the correlation between ICD-measured S3 and S1 and echocardiographic indexes of diastolic and systolic function in patients with ICD and CRT-D. Moreover, we evaluated the performance of device-measured S3 and S1 values as binary discriminators of RFP and reduced LVEF, respectively.

2.3 Statistical analysis

Descriptive statistics are reported as means ± SD for normally distributed continuous variables or medians with range in the case of skewed distribution. Normality of distribution was tested by means of the nonparametric Kolmogorov-Smirnov test. Differences between mean data were compared by means of a paired or unpaired t-test for Gaussian variables, using the F-test to check the hypothesis of equality of variance. The Mann-Whitney or Wilcoxon non-parametric test was used to compare non-Gaussian variables. Differences in proportions were compared by applying $\chi 2$ analysis or Fisher's exact test, as appropriate. Statistical correlations between variables were tested by means of linear regression analysis. Receiveroperating characteristic (ROC) curve analysis was conducted to assess the performance of S3 and S1 as predictors of RFP and reduced LVEF (< 35%). In our analysis, we optimized sensitivity and specificity simultaneously; that is, we regarded the value resulting in the maximum product of sensitivity and specificity on the curve as the optimal cutoff. A p value < 0.05 was considered significant for all tests. All statistical analyses were performed by means of STATISTICA software, version 7.1 (StatSoft, Inc., Tulsa, OK).

3 Results

From December 2017 to November 2018, HeartLogic was activated in 104 patients who had received an ICD or CRT-D. Table 1 shows the baseline clinical variables of all patients in analysis. Overall, 230 in-office visits with HeartLogic index < 16 and 22 alert visits (with HeartLogic index > 16, occurred in 16 patients) were performed. Among the sensed parameters that contribute to the calculation of the HeartLogic index, increase in the S3 was detected in 15 (68%) cases and decrease in the S1 in 18 (82%) cases; worsening of respiratory rate or rapid shallow breathing was measured for 9 (41%) alerts, decreased thoracic impedance for 14 (64%) alerts, and increased night heart rate for 15 (68%) alerts. Table 2 summarizes the results of the echocardiographic evaluation and the clinical examination at the time of in-office visits (in and out of alert state). The table also reports values collected at the time of scheduled visits (with HeartLogic index < 16) in patients who had alerts to allow paired comparisons. Lower values of LVEF and higher indexes of impaired left ventricular filling were more frequently measured during alert visits than during non-alert visits at paired and unpaired comparison. Moderate/severe functional limitation and congestion were more frequently detected at the time of alert. The HeartLogic index was higher at both paired and unpaired comparisons, while S3 amplitude was significantly higher and S1 amplitude was lower only at unpaired comparison.

Table 1 Demographics and baseline clinical parameters of the study population

Parameter	Total $N = 104$
Male gender, n (%)	76 (73)
Age, years	71 ± 10
Ischemic etiology, n (%)	42 (40)
QRS duration, ms	152 ± 26
NYHA class	
Class I, n (%)	2 (2)
Class II, n (%)	46 (44)
Class III, n (%)	53 (51)
– Class IV, n (%)	3 (3)
LV ejection fraction, %	29 ± 7
AF history, n (%)	44 (42)
AF at implantation, n (%)	23 (22)
Valvular disease, n (%)	24 (23)
Diabetes, n (%)	32 (31)
COPD, n (%)	21 (19)
Chronic kidney disease, n (%)	38 (36)
Hypertension, n (%)	79 (76)
β-Blocker use, n (%)	97 (93)
ACE-inhibitor use, n (%)	54 (52)
Diuretic use, n (%)	97 (93)
Antiarrhythmic use, n (%)	27 (26)
Ivabradine use, n (%)	12 (11)
CRT device, n (%)	96 (92)
Primary prevention, n (%)	101 (97)

NYHA: New York Heart Association; LV: left ventricular; AF: atrial fibrillation; COPD: chronic obstructive pulmonary disease; ACE: angiotensin converting enzyme

3.1 Echocardiographic results and correlation with ICD-measured heart sounds

S3 amplitude inversely correlated with deceleration time (r = –0.32; 95% CI –0.46 – -0.17; $P < 0.001$) and S1 amplitude significantly correlated with LVEF (r = 0.17; 95% CI 0.03–0.30; $P = 0.021$) (Fig. 1).

On the basis of the ROC curve analysis of S3 values for the prediction of RFP, the AUC was 0.91 (95% CI 0.86–0.94; $P < 0.001$). The cutoff that best identified RFP and maximized sensitivity and specificity was 0.9 mG. This enabled RFP to be detected with 85% (95% CI 72%–93%) sensitivity and 82% (95% CI 75%–88%) specificity. The results of the echocardiographic evaluation stratified by the S3 value are reported in Fig. 2. On ROC curve analysis of S1 values for the prediction of LVEF < 35%, the AUC was 0.59 (95% CI 0.52–0.66; $P = 0.030$). The cutoff that best identified LVEF < 35% and maximized sensitivity and specificity was 1.5 mG. This enabled LVEF < 35% to be detected with 28% (95% CI 19%–40%) sensitivity and 88% (95% CI 80%–93%) specificity. Echocardiographic variables according to the S1 value are reported in Fig. 2. Gallop rhythm was detected on auscultation only during 14 visits; on these occasions, the diastolic function was not different from that observed during the remaining visits [E/A: 1.0 ± 0.7 versus 0.9 ± 0.7, $P = 0.742$; deceleration time: 212 ± 75 ms versus 220 ± 74, $P = 0.764$; RFP: 3 (21%) versus 49 (21%), $P = 1.000$].

4 Discussion

In the present analysis, we demonstrated the correlation between ICD-measured heart sounds and echocardiographic

Table 2 Results of echocardiographic evaluation and clinical examination at the time of non-alert visits (with HeartLogic index < 16) and at alert visits (22 visits with HeartLogic index > 16). The last column reports values collected at the time of scheduled visits (with HeartLogic index < 16) in patients who had alerts

Parameter	HeartLogic < 16 (*n* = 230)	HeartLogic > 16 (*n* = 22)	HeartLogic < 16 paired (*n* = 22)
LV ejection fraction, %	37 ± 8*	31 ± 9	35 ± 9#
LV end-systolic volume, ml	99 ± 45	130 ± 65	114 ± 60
LV end-diastolic volume, ml	153 ± 56	185 ± 72	162 ± 67
Early-to-late transmitral filling velocity ratio (E/A)	0.9 ± 0.6	1.8 ± 1.7	1.2 ± 1.2
Deceleration time of E, ms	222 ± 76*	178 ± 36	194 ± 51#
Restrictive filling pattern, %	20*	73	41#
NYHA Class III or IV, %	21	38	23
Congestion grade			
None, %	78*	59	64
Mild, %	17	32	27
Moderate, %	5	9	9
HeartLogic Index	3 ± 3*	27 ± 9	5 ± 4#
S3 amplitude, mG	0.9 ± 0.3*	1.3 ± 0.3	1.1 ± 0.4
S1 amplitude, mG	2.4 ± 0.9*	1.9 ± 0.9	1.8 ± 0.7

LV: Left ventricular; NYHA: New York Heart Association. *$p < 0.05$ (unpaired comparison), # $p < 0.05$ (paired comparison) versus HeartLogic > 16

indexes of diastolic and systolic function. This suggests that heart sounds may serve as surrogates for standard measures of left ventricular function. Heart sounds are automatically collected by the ICD on a daily basis, and, since they seemed accurate in detecting systolic and diastolic dysfunction, they may be useful for remote HF patient monitoring, either as single sensors or in combination with other physiological ICD sensors that evaluate various aspects of HF physiology.

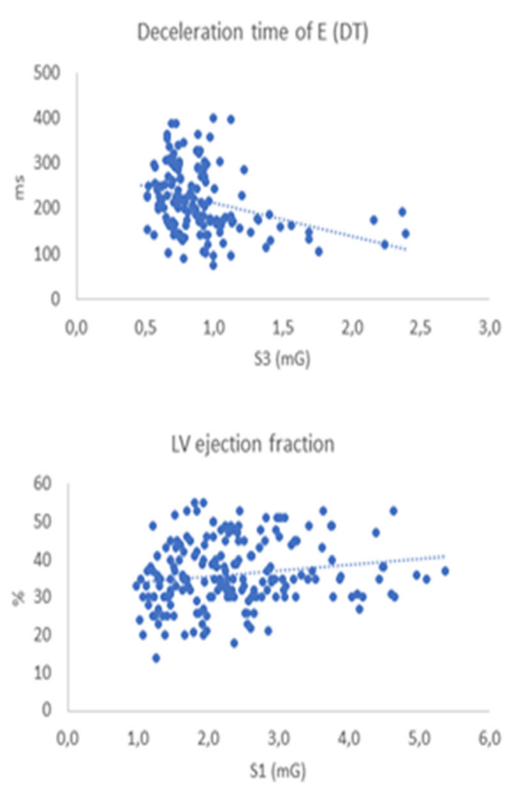

Fig. 1 ***Upper panel.*** Correlation between deceleration time of early transmitral filling velocity and amplitude of device-measured S3 (r = −0.32; 95% CI -0.46 – -0.17; *P* < 0.001). ***Lower panel.*** Correlation between left ventricular ejection fraction and amplitude of device-measured S1 (r = 0.17; 95% CI 0.03–0.30; *P* = 0.021)

Several sensors, in association with remote patient-monitoring platforms, have been proposed for monitoring clinical changes in HF status, with a view to preventing hospitalization without the need for regular and frequent in-clinic interaction. Previously proposed diagnostics for the clinical management of HF have mainly been based on monitoring intra-thoracic impedance to detect fluid accumulation [8]. However, it has been shown that, instead of improving the management of HF, these diagnostics are associated with a relatively high rate of false-positive detections and a consequent increase in hospital admissions [9, 10]. Implantable pressure sensors have also been developed to monitor elevated filling pressures associated with HF [11–13]. Although studies showed rare complications with these monitoring systems, pressure sensor monitoring requires the implantation of dedicated devices, which exposes patients to added risks.

S1 amplitude is known to be related to contractility [14, 15]. Moreover, S3, which is caused by a sudden deceleration of blood flow into the left ventricle during early diastole, correlates with left ventricular filling pressures [16, 17] and is an important clinical and prognostic sign in HF [18, 19]. However, heart sounds are often difficult to hear, as their intensity and frequency are near to the lowest level that can be perceived. In agreement with this, in the present study we observed that gallop rhythm detected on auscultation did not

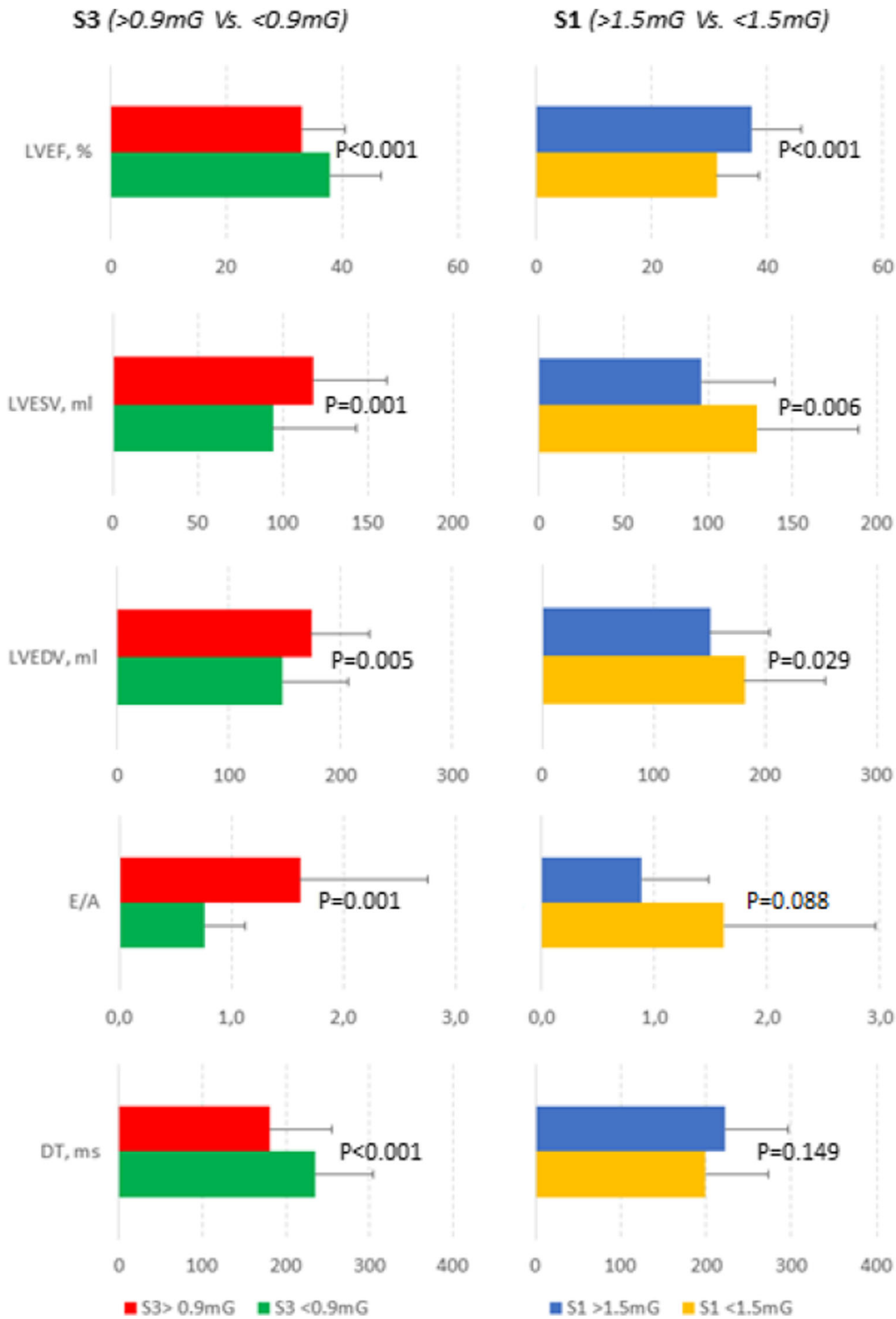

Fig. 2 Results of the echocardiographic evaluation stratified by the S3 value (> 0.9 mG versus < 0.9 mG) and by the S1 value (> 1.5 mG versus < 1.5 mG)

allow us to detect diastolic dysfunction. The existence of subaudible S3 components has previously been demonstrated [20], and it has been shown that the ability to distinguish HF patients from normal subjects is augmented by including these components in the assessment [7]. A previous study, using an animal model of pulmonary edema, demonstrated that the S3 amplitude measured by means of an accelerometer embedded within the ICD was able to detect elevated left atrial pressure with 58% sensitivity and 90% specificity [3]. Our results confirmed that, in clinical practice, the ICD-measured S3 detected RFP with 85% sensitivity and 82% specificity.

It has become increasingly clear that abnormalities of diastolic function have a major role in producing signs and symptoms in patients presenting HF [21, 22]. Even in patients with systolic HF, it is the increase in left ventricular filling pressure that correlates most closely with the degree of exercise limitation, independently of the severity of systolic dysfunction [21, 23]. Previous studies have demonstrated that, in dilated cardiomyopathy, an RFP is associated with a more severe hemodynamic status and with increased mortality and heart transplantation rates [24, 25]. In advanced HF, different filling patterns appear to represent a dynamic continuum, with the potential to change from one to another as a result of disease progression, medical therapy, or sudden changes in hemodynamics [26]. RFP, and particularly its persistence after therapy, is associated with a more severe clinical status and increased mortality [21, 22, 27]. It has previously been demonstrated that CRT is able to cause a significant improvement in diastolic function that is already evident on early follow-up examination, inducing a reversal of filling pattern in a considerable number of RFP patients [28]. Thus, the ability of the implanted device to automatically monitor changes in diastolic function provides an opportunity to continuously monitor the efficacy of the therapy delivered. Moreover, it could also constitute a measure of outcome, given that RFP reversal is associated with improved survival and reduced morbidity compared with persistence of RFP, after maximization of medical therapy [27] and after CRT [28].

In patients with HF, the depressed cardiac function is a consequence of impaired myocardial contractility, coupled with abnormal pre-load and after-load conditions [29]. Prior studies have demonstrated the acute relationship between the maximum left ventricular pressure derivative, i.e., a surrogate for left ventricular contractility, and S1 amplitude [14]. Thakur and colleagues [3] have confirmed that this association also exists when S1 is measured by means of the ICD accelerometer. In the present analysis, we found that S1 correlated with LVEF and that it could detect LVEF < 35% with high specificity but relatively low sensitivity.

The complexity of HF manifestations requires that multiple signs and symptoms be assessed and interpreted in clinical practice. Accordingly, recent European HF guidelines suggest a multiparametric approach to ICD-based monitoring, too, in order to improve the clinical outcome [1]. The HeartLogic algorithm combines data from multiple ICD-based sensors and proved to be a sensitive and timely predictor of impending HF decompensation in the validation study [2]. According to preliminary experience in clinical practice [30], heart sounds correlate well with HF status, and a strong association between HeartLogic alerts and HF-related clinical events seems to have been confirmed. In the present analysis, that observation was complemented by our finding of more impairment of systolic and diastolic function during alert visits, which was associated with more frequent signs of functional limitation and congestion.

4.1 Limitations

Although the present results agree with those from previous animal models [3], the main limitations of this study remain the small sample size and the limited number of visits included in analysis. Although we showed a significant correlation between ICD-measured heart sounds and echocardiographic indexes, we must recognize a rather large amount of scatter around the regression line that may limit the clinical value of this correlation. Nonetheless, on the basis of the ROC curve analysis we demonstrated a good performance of device-measured S3 and S1 values as binary discriminators of RFP and reduced LVEF, respectively. Further studies are therefore needed to confirm our findings and, more importantly, to establish whether this HF alert, when associated to an appropriate intervention strategy, may improve patient outcomes.

4.2 Conclusions

ICD-measured heart sounds correlate with echocardiographic indexes of cardiac function and are able to accurately detect systolic and diastolic impairment. Thus, since heart sounds are automatically collected by the ICD on a daily basis, they may be useful for remote HF patient monitoring, either as single sensors or in combination with other physiological ICD sensors that evaluate various aspects of HF physiology.

Compliance with ethical standards

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

Ethical approval The study was approved by the Local Ethics Committee.

Informed consent Informed consent was obtained from all individual participants included in the study.

Disclosures M. Campari and S. Valsecchi are employees of Boston Scientific. The other authors report no conflicts.

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