ORIGINAL ARTICLE

Novel frequency analysis of signal-averaged electrocardiograms is predictive of adverse outcomes in implantable cardioverter defibrillator patients

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Abstract

Background: Current noninvasive risk stratification methods offer limited prediction of arrhythmic events when selecting patients for ICD implantation. Our laboratory has recently developed a signal processing metric called Layered Symbolic Decomposition frequency (LSDf) that quantifies the percentage of hidden QRS wave frequency components in signal-averaged ECG (SAECG) recordings. The purpose of this pilot study was to determine whether LSDf can be predictive of ventricular arrhythmia or death in an ICD patient cohort.

Methods and Results: Fifty-two ICD patients were recruited from 2008 to 2009. These were followed for a mean of 8.5 ± 0.4 years for the primary outcome of first appropriately treated ventricular arrhythmia (VT/VF) or death. Thirty-four subjects met the primary outcome. LSDf was significantly lower, and 12-lead QRS duration was significantly greater in patients meeting the primary outcome ($12.14 \pm 3.97\%$ vs. $16.45 \pm 3.73\%$; $p = 0.001$) and (111.59 ± 14.96 ms vs. 97.69 ± 13.51 ms; $p = 0.012$) respectively. A 13.25% LSDf threshold (0.74 sensitivity and 0.85 specificity) was selected based on an ROC curve. Kaplan–Meier survival analysis was conducted; patients above the 13.25% threshold demonstrated significantly better survival outcomes (log-rank $p < 0.001$). In Cox multivariate regression analysis, the LSDf threshold (13.25%) was compared to LVEF (28.5%), 12-lead QRSd (100 ms), age, % male sex, NYHA classification, and antiarrhythmic usage. LSDf was a predictor of the primary outcome ($p = 0.005$) and an independent predictor for solely ventricular arrhythmia ($p = 0.002$).

Conclusion: Layered Symbolic Decomposition frequency analysis in SAECG recordings may be a viable predictor of negative ICD survival outcomes.

1 | INTRODUCTION

Sudden cardiac death (SCD) is the leading global cause of natural death, causing an estimated 450,000 deaths a year in the United States alone (Deo & Albert, 2012). Ventricular arrhythmias, such

as ventricular tachycardia (VT) and ventricular fibrillation (VF), are a common cause of SCD that might be prevented with appropriate Implantable Cardioverter Defibrillator therapy (ICD; Deo & Albert, 2012; Mozaffarian et al., 2015). Both primary and secondary ICD implantation have demonstrated significant

long-term survival benefit (Goldenberg et al., 2010; Saxon et al., 2010). Cardiomyopathy patients are at greater risk of SCD and are stratified using a series of clinical markers which identify high-risk patients that may be prescribed an ICD. However, current clinical markers for arrhythmia risk assessment are suboptimal. Left ventricular ejection fraction (LVEF) in heart failure patients is currently the only clinically relevant marker employed for primary prevention, but does not provide sufficient sensitivity and specificity when predicting arrhythmic events (Dagres & Hindricks, 2013; Yap et al., 2007).

Layered Symbolic Decomposition (LSD) is a novel signal analysis method that analyses signals based on fluctuations in positive/negative/neutral slope changes. Like traditional frequency decomposition analysis, LSD decomposes signals in multiple layers based on signal features. However, unlike traditional frequency analysis, LSD does not require the selection of a basis function. Following signal decomposition with LSD, a time–frequency representation of signals can be used to determine the proportion of a specific frequency–energy band which we call “LSD-frequency” (LSDf). Our laboratory has recently demonstrated LSD can decompose both test signals and high-resolution electrocardiograms (ECGs) with high accuracy and reproducibility, and can effectively stratify ICD patients based on prior ventricular arrhythmia (Torbey, Akl, & Redfearn, 2015). This study explores the possibility of LSDf as a novel arrhythmia risk stratification metric.

Herein, we describe the initial clinical application of LSDf to stratify patients at risk of ventricular arrhythmia and/or death in a long-term follow-up of a prospective cohort of ICD recipients. We hypothesized LSDf could be used to predict adverse outcomes in the ICD recipient population, such as ventricular arrhythmia or mortality.

2 | METHODS

2.1 | Patient population

The study protocol of this pilot study was approved by the Queen's University Health Sciences and Affiliated Teaching Hospitals Research Ethics Board. Ischemic and nonischemic cardiomyopathy patients undergoing routine ICD follow-up at a high-volume regional center were prospectively recruited to this study between November 10, 2008, and June 4, 2009. Patients on continuous cardiac pacing or patients diagnosed with bundle branch block were excluded. Following informed written consent, a standard orthogonal high-resolution ECG was performed (as below). Demographic data were recorded at time of inclusion to the study. Data were collected on left ventricular ejection fraction (LVEF) by transthoracic echo no more than 12 months old, New York Heart Association (NYHA) classification, history of ischemic heart disease, and medical therapy. An additional normal control population was selected to provide comparison to the at-risk population. This cohort consisted of subjects with no family history of cardiomyopathy, had no current indication of ischemic or nonischemic heart disease, and were hemodynamically stable.

2.2 | High-resolution electrocardiogram and signal averaging

An orthogonal high-resolution (1,000 Hz, 12-bit) ECG was recorded for 10 min for ICD patients in native rhythm. Following careful skin preparation with alcohol, a modified orthogonal lead system was applied comprising of three bipolar leads referenced to an isolated ground placed on the right shoulder (X: Manubrium sternum [positive] to Xiphisternum. Y: V4 [positive] to V4R. Z: V2[positive] to a position directly opposite on the posterior chest wall). Patients were instructed to remain in a supine position to minimize any noise that would be picked up from muscle movement. The digitized data were stored for subsequent processing blinded to the patient outcome. Approximately 600 beats were stored for subsequent analysis. All high-resolution recordings were performed by a trained ECG technologist.

One lead exhibiting the most obvious QRS complex was used as a trigger to align subsequent QRS complexes for signal averaging. The signal averaging resulted in three averaged orthogonal QRS complexes ($X(t)_{avr}$, $Y(t)_{avr}$, $Z(t)_{avr}$) in a 3D Cartesian coordinate system. The vector magnitude of these complexes is a representative of ventricular activity and was used to extract time and frequency domain parameters.

2.3 | Time–frequency analysis with layered symbolic decomposition

Following signal averaging, the resultant vector magnitude was analyzed for duration and frequency analysis. Layered Symbolic Decomposition has been described previously (Torbey et al., 2015). Briefly, the algorithm was designed for biologic signals and does not depend on a basis function to decompose a signal. Rather, the LSD algorithm analyses a biological signal in several layers by generating a tree data structure. The root represents a view of the lowest frequency components, and the leaves represent the highest frequency components in the signal. Our pilot study during algorithm development suggested that the LSD metric corresponding to signal features in the 40–300 Hz frequency band calculated by:

$$\text{LSD}_{(40-300)\text{Hz}} (\%) = 100 * \frac{\sum_{f_i=40}^{150} \text{energy of LSD at } f_i}{\sum_{f_i=1}^{300} \text{energy of LSD at } f_i}, \quad (1)$$

can be effectively used for discriminating different QRS patterns. Thus, in this work we used LSD to quantify the morphology and power of QRS for each SAECD (Figure 1).

2.4 | Follow-up and outcomes

The primary outcome of this study was defined as an appropriate ICD therapy for ventricular arrhythmic events or mortality. Ventricular arrhythmia events were defined as VT or VF, sustained for over 30 s and receiving appropriate treatment from the ICD. Appropriately, treated events were identified by an experienced

FIGURE 1 Comparison of signal-averaged electrocardiograms (top) and spectrograms derived from LSD analysis (bottom) between patients with and without adverse outcomes (ventricular arrhythmia, death). Both patients have similar QRS duration (≈ 90 ms), but the outcome patient (left) has an LSDf of 13.0% while the no outcome patient has an LSDf of 19.6%

cardiologist as either appropriate anti-tachycardia pacing (ATP) or appropriate shock for either VT or VF. Inappropriate therapies for events such as atrial fibrillation or nonsustained VT were excluded.

Patients were monitored for treated arrhythmic events or death using electronic records on the Patient Care System (PCS) at Kingston General Hospital. Device files containing physician diagnosis and ICD recordings were examined to determine the first occurrence of a treated ventricular arrhythmic event since study inclusion. Follow-up was conducted from inclusion until the study completion date of October 1, 2017. Time from inclusion to primary outcome or end of study, whichever was sooner, was recorded.

2.5 | Statistical analysis

Mean differences in clinical characteristics (age at consent, LVEF, QRSd, LSDf) were compared using independent sample students *t* tests. Categorical clinical characteristics (male sex %, ICD indication, NYHA, drug therapy) were compared using 2×2 chi-square tests for proportions with continuity correction.

Receiver operating characteristic (ROC) curves were created for LSDf, LVEF, and QRSd stratification methods. The area under the

curve (AUC) was calculated to assess the overall predictive value of each metric. For each metric, a point on the curve with optimal specificity and sensitivity was selected to be used as a threshold for further survival analysis. Kaplan–Meier analysis was conducted to compare survival rates between patients above and below the selected LSDf threshold. Kaplan–Meier analysis was also conducted to compare survival rates between patients stratified as high-risk/low-risk by QRSd and LVEF thresholds from ROC data. Cox multivariate regression analysis was finally used to evaluate the predictive value of LSDf, QRSd, LVEF, age at screening, sex, NYHA classification, and Class III antiarrhythmic usage. A two-sided *p*-value < 0.05 was considered statistically significant. IBM SPSS Statistics software (IBM) was used for all analyses mentioned.

3 | RESULTS

3.1 | Patient characteristics

Fifty-two ICD patients were enrolled between November 10, 2008, and June 24, 2009. The mean age of these patients was 66.14 ± 10.16 years at baseline. The patient cohort was followed

	No outcome (n = 18)	Outcome (n = 34)	All patients (n = 52)	p-Value
Age at consent (years)	60.8 (11.9)	66.6 (9.4)	65.16 (10.3)	0.076
Male sex	9 (69.2%)	36 (92.3%)	45 (86.5%)	0.101
Primary prevention	7 (53.8%)	26 (66.7%)	33 (63.5%)	0.618
Ischemic disease	8 (61.5%)	28 (71.8%)	36 (69.2%)	0.729
NYHA score				
I	8 (61.5%)	18 (46.2%)	26 (50%)	0.622
II	4 (30.8%)	16 (41.0%)	20 (38.5%)	
III	1 (7.7%)	5 (12.8%)	6 (11.5%)	
Mean LVEF (%)	35.46 (12.46)	28.38 (13.07)	30.15 (13.17)	0.094
Mean QRSd (ms)	97.69 (13.51)	111.59 (14.96)	108.12 (15.71)	0.005 [*]
Mean LSDf (%)	16.45 (3.73)	12.14 (3.97)	13.22 (4.31)	0.001 [*]
Pharmacological treatment				
Class III antiarrhythmics	1 (7.7%)	11 (28.2%)	12 (23.1%)	0.254
Beta blockers	10 (76.9%)	24 (61.5%)	34 (65.4%)	0.501
ACE inhibitor	7 (53.8%)	26 (66.7%)	33 (63.5%)	0.618
Statins	9 (69.2%)	29 (74.4%)	38 (73.1%)	1.0
Blood thinners	4 (30.8%)	14 (35.9%)	18 (34.6%)	1.0
Anti-platelets	7 (53.8%)	16 (41.0%)	23 (44.2%)	0.629

Mean Age, LVEF, QRSd, and LSDf are reported with standard deviation in ().

ACE: Angiotensin converting enzyme; LSDf: Layered Symbolic Decomposition Frequency; LVEF: Left Ventricular Ejection Fraction; NYHA: New York Heart Association; QRSd: QRS duration.

^{*}Indicates a significant $p < 0.05$ value.

TABLE 1 Clinical characteristics of the ICD cohort

for a period of 9.55 ± 0.18 years. Patients were predominantly male ($n = 45$, 86.5%) and were diagnosed with ischemic cardiomyopathy ($n = 36$, 69.2%). During follow-up, 34 patients exhibited the primary outcome (28 with ventricular arrhythmia, six expired). The mean time to primary outcome was 4.58 ± 3.17 years from baseline recordings. ICD indication, percentage of ischemic disease, medication, NYHA classification, and LVEF were not significantly different among outcome and outcome-free patients (Table 1). LSDf was significantly lower, and QRSd was significantly greater in patients meeting the primary outcome ($12.14 \pm 3.97\%$ vs. $16.45 \pm 3.73\%$; $p = 0.001$) and (111.59 ± 14.96 ms vs. 97.69 ± 13.51 ms; $p = 0.012$), respectively.

The normal control cohort consisted of 46 healthy individuals. Mean age and proportion of male patients did not significantly differ between the ICD and control cohorts. Mean LSDf in the controls was significantly greater than the overall ICD patient cohort ($16.79 \pm 3.09\%$ vs. $13.22 \pm 4.31\%$; $p < 0.001$). Upon further inspection, mean LSDf in controls was also significantly greater than primary outcome patients ($16.79 \pm 3.09\%$ vs. $12.14 \pm 3.97\%$; $p < 0.001$) but not different from patients without a primary outcome ($16.79 \pm 3.09\%$ vs. $16.45 \pm 3.73\%$; $p = 0.745$).

3.2 | Receiver operating characteristic analysis

Receiver Operating Characteristic (ROC) analysis was conducted to assess the ability of LSDf, LVEF, and QRSd to predict arrhythmic

events (i.e., Shocks or ATP) or mortality in the ICD patient cohort following screening (Figure 2). The area under curve (AUC) was 0.815 for LSDf ($p = 0.001$), 0.707 for LVEF ($p = 0.027$), and 0.747 for QRSd ($p = 0.080$). For further survival analysis, a value of 13.25% for LSDf was selected as threshold based on suitable sensitivity of 0.74 and specificity of 0.85. An LVEF of 28.5% was selected based on 0.64 sensitivity and 0.77 specificity, and a QRSd of 100 ms was selected based on 0.8 sensitivity and 0.62 specificity (Table 2).

3.3 | Survival analysis

Kaplan–Meier survival analysis was conducted to assess the ability of LSDf to predict the occurrence the primary outcome (treated ventricular arrhythmia, death; Figure 3). ICD patients were stratified into two groups using the previously calculated LSDf threshold (i.e., $>13.25\%$ threshold, $\leq 13.25\%$ threshold). Patients above the LSDf threshold demonstrated significantly better survival (i.e., longer time till outcome) than those below the LSDf threshold, as determined by Log-Rank (Mantel–Cox) equality test in survival distributions ($p < 0.001$). QRSd and LVEF were also evaluated through Kaplan–Meier survival analysis using the previously calculated thresholds (QRSd > 100 ms, LVEF $\leq 28.5\%$). Patients with a QRSd < 100 ms had significantly longer time to the primary outcome than patients with QRSd ≥ 100 ms ($p = 0.004$). Kaplan–Meier analysis of LVEF did not demonstrate a significant difference in survival among patients above/below 28.5% ($p = 0.05$).

FIGURE 2 Receiver operating characteristic (ROC) curve assessing LSDf (a), LVEF (b), and QRSd (c) ability to predict adverse outcomes (ventricular arrhythmia, mortality). An LSDf threshold of 13.25%, an LVEF of 28.5%, and a QRSd of 100 ms was selected based on optimal sensitivity and specificity. Diagonal segments are produced by ties

Cox survival analysis was performed to assess univariate and multivariate survival models of the following metrics: LSDf $\leq 13.25\%$, LVEF $\leq 28.5\%$, QRSd ≥ 100 ms, Screening Age, Sex, NYHA, and Class III antiarrhythmic usage (Table 3). In univariate analysis, the LSDf threshold, the QRSd threshold, and Age at Screening were significant predictors of the primary outcomes (ventricular arrhythmia, death). The 13.25% LSDf threshold was found to be the most significant ($p < 0.001$), with a hazard ratio of 3.71 if below the threshold.

In a multivariate model comparing all metrics (Multivariate Analysis 1), only LSDf and Age at Screening were significant predictors. The LSDf threshold was a more significant predictor ($p = 0.007$)

with a hazard ratio of 3.63 if below the threshold. A second multivariate model was created using only ventricular arrhythmic events as the outcome (Multivariate Analysis 2). LSDf threshold proved to be a significant independent predictor of ventricular arrhythmia ($p = 0.006$), with a hazard ratio of 4.99 if below the threshold.

4 | DISCUSSION

We hypothesized the LSDf marker derived from SAECG recordings can independently identify patients at risk for VT/VF and mortality.

LSDf was significantly lower in patients with adverse outcomes (arrhythmia, mortality). A single LSDf threshold of 13.25% was selected based on 0.74 sensitivity and 0.85 specificity from ROC analysis. Patients stratified above the LSDf threshold demonstrated significantly better survival from adverse outcomes than their lower LSDf

TABLE 2 Receiver Operating Characteristic results for adverse outcomes (arrhythmia, death)

	Area under curve (AUC)	<i>p</i> -Value	95.0% CI for AUC	
			Lower	Upper
LSDf (%)	0.815	0.001	0.695	0.934
LVEF (%)	0.706	0.027	0.556	0.856
QRSd (ms)	0.747	0.080	0.590	0.903

Note. CI: Confidence Interval; LSDf: Layered Symbolic Decomposition Frequency; LVEF: Left Ventricular Ejection Fraction; QRSd: QRS duration.

**p* < 0.05

counterparts over 9.55 ± 0.18 years of follow-up. Further multivariate survival analysis revealed the 13.25% LSDf threshold and age as predictors of adverse outcomes, and only the 13.25% LSDf threshold as an independent predictor of ventricular arrhythmia.

4.1 | Physiological implications of layered symbolic decomposition frequency analysis

Our study indicates LSDf analysis of SAEKG recordings may be a viable identifier of ICD patients at risk for arrhythmic events and mortality based on univariate and multivariate survival models. While this is an optimistic finding, it is currently unclear how LSDf frequency decomposition measures the physiological risk of ventricular arrhythmia. We believe the most likely explanation is related to ventricular conduction abnormalities such as myocardial tissue scarring. Other noninvasive methods assessing QRS waveform abnormalities, like fragmented QRS, have demonstrated significant correlation to the presence of myocardial scarring assessed by echocardiography

FIGURE 3 Kaplan-Meier survival curves of patients stratified by 13.25% LSDf (a), 28.5% LVEF (b), and 100 ms QRSd (c) thresholds. All thresholds were determined through receiver operating characteristic analysis (Figure 1; *Statistically significant *p* < 0.05)

TABLE 3 Cox Regression Analysis for prediction of adverse outcomes (arrhythmia, death)

	Univariate analysis (primary outcome)		Multivariate analysis 1 (primary outcome)		Multivariate analysis 2 (ventricular arrhythmia)	
	HR (95% CI)	p-Value	HR (95% CI)	p-Value	HR (95% CI)	p-Value
LSDf (13.25%)	3.71 (1.82–7.56)	<0.001*	3.63 (1.43–9.22)	0.007*	4.99 (1.59–15.66)	0.006*
LVEF (28.5%)	2.12 (1.07–4.20)	0.304	1.36 (0.63–2.95)	0.438	1.45 (0.62–3.40)	0.397
QRSd (100 ms)	2.82 (1.29–6.16)	0.013*	1.08 (0.37–3.12)	0.889	1.84 (0.44–7.78)	0.406
Age at screening	1.03 (1.00–1.06)	0.048*	1.03 (1.00–1.07)	0.043*	1.03 (1.00–1.07)	0.094
Male sex	2.73 (0.84–8.85)	0.096	1.18 (0.27–5.12)	0.822	2.96 (0.53–16.45)	0.216
NYHA score	1.11 (0.72–1.70)	0.638	0.90 (0.55–1.46)	0.655	0.84 (0.51–1.41)	0.515
Class III antiarrhythmics	1.65 (0.82–3.33)	0.161	1.03 (0.46–2.28)	0.948	1.17 (0.52–2.63)	0.711

Note. CI: Confidence Interval; HR: Hazard Ratio; LSDf: Layered Symbolic Decomposition Frequency; NYHA: New York Heart Association; QRSd: QRS duration.

* $p < 0.05$.

(Das et al., 2008). A study by Strauss et al. (2008) determined that the Selvester QRS score was positively associated with the identification and quantity of scar tissue in ischemic and nonischemic patients receiving ICDs.

While much research has investigated the clinical utility of ventricular late potentials (VLPs) in the terminal region of the QRS complex, little research has been conducted assessing the abnormal frequencies of the entire complex using frequency-domain analysis of SAECGs. Comparable to this study, research by Tsutsumi et al. (2011) found that a metric quantifying frequency powers within the QRS complex improved the sensitivity and specificity for predicting ventricular arrhythmia when combined with VLPs. A follow-up study later revealed that their measured frequency power metric abnormalities were related to increased local fibroblast density, which would explain an increased propensity for arrhythmia (Tsutsumi et al., 2014).

4.2 | Advantages of LSD over previous time-frequency analysis methods

Novel risk stratification methods in the time domain have also shown promise as ventricular arrhythmia risk stratification tools. A study by Das et al. (2017) recently validated a metric of low-amplitude QRS peaks in ischemic and nonischemic patients eligible for prophylactic ICD implant. The study determined that the metric was predictive of ventricular arrhythmia events in a multivariate survival model. While time-domain methods may provide an intuitive form of visualization and analysis, we believe frequency decomposition methods provide additional diagnostic data about the QRS complex that is otherwise not visible and presents an excellent opportunity for future research.

A major advantage of LSD over prior methods of frequency analysis is the nonreliance on a basis function for frequency decomposition. A basis function is a mathematical function that is used to decompose and model signal data (Ghaffari, Golbayani, & Ghasemi,

2008; Gothwal, Kedawat, & Kumar, 2011). However, the dynamic nature of biological signals makes decomposing them with basis functions challenging and potentially inaccurate (Kotsas, Pappas, Strintzis, & Maglaveras, 1993). Classic studies that attempted frequency decomposition of SAECG recordings using Fourier transform did not significantly impact clinical arrhythmia risk stratification (Pierce, Easley, Windle, & Engel, 1989). Wavelet decomposition of SAECG in the frequency domain electrocardiogram signals has recently shown some promise in identifying and predicting arrhythmia in post-MI patients, but has not shown consistency across the literature (Keshtkar et al., 2013; Tsutsumi et al., 2011). We propose that these studies' reliance on basis function selection have precluded their effectiveness in analyzing biological signals, which may explain why LSDf appears to be a potent arrhythmia risk stratification marker.

4.3 | Clinical relevance and future directions

Improved diagnostic tools in prediction of SCD are needed both in patients known to be at risk and in less well understood clinical scenarios such as postmyocardial infarction, nonprodromal syncope, and preserved ejection fraction heart failure. In addition, inherited cardiomyopathies such as channelopathies and hypertrophic cardiomyopathy might benefit from addition risk markers. Imaging techniques are of increasing value but are both expensive and time consuming (Priori et al., 2015). Surface ECG based technologies are comparatively inexpensive and accessible, affording a potential for screening of large groups of at-risk patients.

Our data support an SAECG-based approach to risk stratification. The results were promising in a population selected to be at risk of major cardiovascular adverse events. We were able to use the LSDf metric to derive a dichotomous variable to identify patients that were at greatest risk. These preliminary data require validation in a larger cohort but suggests a role for the application of signal processing techniques designed for biologic signals in patient populations.

4.4 | Limitations

The limited number of patients in our ICD cohort was highly selected by both LVEF and surface QRSd using Canadian guidelines for primary prevention and cardiac resynchronization. SAEKG is currently not a routine diagnostic procedure in most clinical settings, and performing SAEKG testing is not always practical. Accordingly, a future project of our laboratory is to test LSD analysis in standard 12-lead ECG data. Additionally, we were unable to determine the cause of death during patient follow-up. We would have ideally liked to only incorporate cardiac-related causes of death in our analyses, but perhaps this can be assessed by future studies.

5 | CONCLUSIONS

Layered Symbolic Decomposition (LSD) is a novel method to perform spectral analysis without basis function selection. Our pilot data support the notion of LSDf as a viable arrhythmia risk stratification marker in ICD recipients and identifies those at high risk of arrhythmic events following implant.

CONFLICT OF INTEREST

The authors have no conflicts of interest to disclose.

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