Dynamic Analysis of Cardiac Rhythms for Discriminating Atrial Fibrillation From Lethal Ventricular Arrhythmias

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Background—Implantable cardioverter-defibrillators (ICDs), the first line of therapy for preventing sudden cardiac death in high-risk patients, deliver appropriate shocks for termination of ventricular tachycardia (VT)/ventricular fibrillation. A common shortcoming of ICDs is imperfect rhythm discrimination, resulting in the delivery of inappropriate shocks for atrial fibrillation (AF). An underexplored area for rhythm discrimination is the difference in dynamic properties between AF and VT/ventricular fibrillation. We hypothesized that the higher entropy of rapid cardiac rhythms preceding ICD shocks distinguishes AF from VT/ventricular fibrillation.

Methods and Results—In a multicenter, prospective, observational study of patients with primary prevention ICDs, 119 patients received shocks from ICDs with stored, retrievable intracardiac electrograms. Blinded adjudication revealed shocks were delivered for VT/ventricular fibrillation (62%), AF (23%), and supraventricular tachycardia (15%). Entropy estimation of only 9 ventricular intervals before ICD shocks accurately distinguished AF (receiver operating characteristic curve area, 0.98; 95% confidence intervals, 0.93–1.0) and outperformed contemporary ICD rhythm discrimination algorithms.

Conclusions—This new strategy for AF discrimination based on entropy estimation expands on simpler concepts of variability, performs well at fast heart rates, and has potential for broad clinical application. (Circ Arrhythm Electrophysiol. 2013;6:555-561.)

Key Words: defibrillators, implantable □ tachycardia, ventricular □ ventricular fibrillation □ death, sudden, cardiac □ ECG □ nonlinear dynamics □ inappropriate shock □ entropy

Ventricular tachycardia (VT) and ventricular fibrillation (VF) are lethal cardiac arrhythmias, claiming a quarter million lives per year from sudden cardiac death (SCD).1 Implanted cardioverter-defibrillators (ICDs), the first line of therapy for preventing SCD, deliver appropriate shocks for termination of VT/VF.2,3 A common shortcoming of ICDs is inadequate rhythm discrimination, resulting in the delivery of inappropriate shocks for non–life-threatening arrhythmias, such as atrial fibrillation (AF).

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Even with optimal ICD programming and contemporary technological advances,4-15 about one third of ICD recipients receive inappropriate shocks for AF.16-24 Inappropriate shocks are painful, are associated with substantial psychological stress, decrease quality of life, can initiate more dangerous arrhythmias, and may increase mortality.15,22-25 Minimizing inappropriate shocks, while maintaining high sensitivity for detecting VT/VF, is an essential attribute of contemporary ICDs.

An underexplored opportunity for rhythm discrimination in patients with ICD is the difference in dynamic properties of AF and VT/VF. In AF, complexities of atrial activation and decremental impulse conduction through the atrioventricular node produce a highly irregular rhythm. As a result, the time series for ventricular activation approaches white noise. In most cases, this sharply differs from arrhythmias that arise from diseased ventricular myocardium.

One approach to characterize this distinctive difference is to measure the information entropy, a concept of uncertainty related to thermodynamic entropy.26 In this context, entropy is fundamentally different from conventional measures of heart rate variability (HRV) in that entropy exploits information on the ordering of the times between ventricular activation and quantifies the degree to which self-similar fluctuation patterns repeat. These self-similar fluctuations are indistinguishable in moment statistics and frequency domain measures of HRV.
We hypothesized that the entropy of rapid cardiac rhythms immediately preceding ICD shocks discriminates AF from VT/VF. We directly compared performances of entropy estimation with those of representative discrimination algorithms used in contemporary ICDs.

Materials and Methods

Adjudicated Rhythm Groups

The intracardiac electrogram data were drawn from a multicenter, prospective cohort of patients with dual- or single-chamber ICDs implanted for primary prevention of SCD. We studied patients with ischemic or nonischemic heart failure, ejection fraction ≤35%, New York Heart Association class I to III symptoms, and no history of VT/VF or SCD. Patients with secondary prevention indication, New York Heart Association class IV heart failure, permanent pacemaker, or pre-existing Class 1 indication for permanent pacemaker were not included in this cohort.

This study includes 119 consecutive patients, who received ICDs equipped with intracardiac electrogram storage that were retrieved for rhythm discrimination and analysis. The ICDs were manufactured by Medtronic (Minneapolis, MN), Boston Scientific (Natick, MA), and St. Jude Medical (St. Paul, MN). During the implant procedure, sensing, pacing, and defibrillation thresholds were tested as per standard protocol. ICDs were programmed at the discretion of the implanting physicians. High VT/VF cutoff zones were encouraged and supraventricular tachycardia (SVT) discriminators could be enabled. The ICDs were reprogrammed by the treating physician when considered clinically indicated (eg, hemodynamic well-tolerated VT and VT in monitor zone). The electrogram and interval data were downloaded from ICDs using proprietary software obtained from the manufacturers. The entropy calculations were performed offline as described below.

After each shock or after death, all available information, including electrograms before the shock, was reviewed by a committee of ≥3 board-certified clinical cardiac electrophysiologists. The committee blindly adjudicated the type of arrhythmia eliciting the shock (eg, VT, VF, SVT, and AF) and whether the shock was appropriate or inappropriate. An inappropriate shock was defined as an episode that started with a shock not delivered for VT or VF and ended when sinus rhythm was detected. If a patient received repetitive inappropriate shocks for the same rhythm, only the electrogram responsible for the first shock was analyzed. Causes of inappropriate shocks were categorized as SVT (including sinus tachycardia), AF (including atrial flutter), or artifact. Although the categorization of atrial flutter as AF diminished performance estimates, it reflects the common clinical situation in which these arrhythmias often coexist in the same patient populations and share underlying substrates, mechanisms, and management strategies.

The study was approved by the institutional review boards of the participating centers (Johns Hopkins University, University of Maryland, Washington Hospital Center, and Virginia Commonwealth University). All patients provided written informed consent.

Entropy Estimation

We optimized the sample entropy27,28 measure and developed the coefficient of sample entropy (COSEn) for the specific purpose of AF discrimination in electrograms at all heart rates using very short time series of ventricular activation.

An illustration of the COSEn calculation is provided in the Methods in the online-only Data Supplement. Briefly, sample entropy is the conditional probability that 2 short templates of length m that match within an arbitrary tolerance r will continue to match at the next point m+1. Mathematically expressed, SampEn=ln(A/B), where A denotes $\Sigma_{A}$ (total number of matches of length $m+1$) and B denotes $\Sigma_B$ (total number of matches of length $m+1$ and m), in a series of n consecutive intervals, $x_1$, $x_2$, ..., $x_n$, where the record may be as short as n=9. By allowing r to vary for sufficient matches and confident entropy estimation, conversion of the final probability to a density by dividing by the matching region volume, and correcting for the mean heart rate, the optimized sample entropy estimate was defined as COSEn. Unlike approximate entropy,26 frequency domain measures, or geometric measures, such as Poincaré plots,28 COSEn is accurate in very short time series.

AF Discrimination

For each patient, entropy analysis was performed only for the episode resulting in the first shock. The adjudicated ICD shock rhythms were considered the gold standard for rhythm diagnosis and compared with AF discrimination based on entropy estimation. Entropy values higher than a threshold (COSEn>−1.20) for 9 consecutive ventricular activation intervals preceding a shock were classified as AF. This threshold was preselected in a prior Holter database such that the proportion of AF misclassified as non-AF was equal to the proportion of non-AF misclassified as AF.31 Entropy estimation was also performed on all the electrograms, and intervals of the stored event and analysis of >9 consecutive intervals did not alter the accuracy of detection.

The diagnostic performance of entropy estimation was compared with that of standard metrics of heart rate, HRV, and stability calculated from the same 9 intervals. The heart rate was determined from the mean interval. The coefficient of variation (SD of the intervals divided by the mean) is a common measure of HRV. Stability, another measure of variability, is indexed as the trimmed range (ie, next-to-longest minus next-to-shortest intervals, and therefore, large values indicate less stable rhythms).

Statistical Analysis

Continuous variables were compared using t test and categorical variables were compared using $\chi^2$ test. The ability of entropy, stability, HRV, and heart rate to discriminate AF was evaluated using the receiver operating characteristic curve area. We also calculated the sensitivity, specificity, likelihood ratios, and predictive probabilities for detecting AF for standard cutoffs of each metric (COSEn=−1.20; stability=±20 ms; HRV=±10; heart rate<180 beats per minute). Logistic regression was used to evaluate whether stability, HRV, or heart rate provided any added discrimination with respect to entropy. Statistical analyses were performed using Stata 12 (StataCorp LP, College Station, TX). A P value <0.05 was considered statistically significant.

Results

Adjudicated Rhythm Groups

In a multicenter, prospective, observational study of patients with primary prevention ICDs, we identified 119 consecutive patients, who received shocks from ICDs with stored retrievable intracardiac electrograms. Blinded adjudication by expert clinical cardiac electrophysiologists revealed almost half of the shocks delivered were not for VT/VF and AF was responsible for two thirds of these inappropriate shocks (Table 1).

Interestingly, ICD rhythm discrimination algorithms were enabled in 50% of patients that received AF-induced inappropriate shocks, suggesting half of these AF rhythms had either eluded the discriminators or another algorithm superseded the discriminators to command delivery of a shock. The respective ICD program settings for the AF versus non-AF groups were as follows: VF zone cutoff 191±14 versus 197±14; lowest rate cutoff 167±23 versus 173±22; enabled morphology discriminator algorithms 26% versus 25%; enabled onset algorithms (17% versus 13%); enabled stability algorithms 15% versus 13%; ventricular sensitivity 0.279±0.0139 versus 0.273±0.0093; 1 zone programmed 41% versus 37%; and 2 zones 30% versus 37%; 3 zones 19% versus 9%. Although it is an appealing idea that sensed information from an atrial rhythm was detected. If a patient received repetitive inappropriate shocks for the same rhythm, only the electrogram responsible for the first shock was analyzed. Causes of inappropriate shocks were categorized as SVT (including sinus tachycardia), AF (including atrial flutter), or artifact. Although the categorization of atrial flutter as AF diminished performance estimates, it reflects the common clinical situation in which these arrhythmias often coexist in the same patient populations and share underlying substrates, mechanisms, and management strategies.

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lead can be used to reduce inappropriate shocks, the presence (63%) or absence of a right atrial lead did not affect the inappropriate shock rate, consistent with previous studies.17,32,33

**AF Discrimination**

We used a novel, conceptually simple strategy for AF discrimination on the basis of entropy estimation29 of electrograms.

**Table 1. Characteristics of Adjudicated Rhythm Groups**

<table>
<thead>
<tr>
<th></th>
<th>AF</th>
<th>SVT</th>
<th>VT</th>
<th>VF</th>
<th>Not AF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients, n</td>
<td>27</td>
<td>18</td>
<td>60</td>
<td>14</td>
<td>92</td>
</tr>
<tr>
<td>Age, y</td>
<td>66±11</td>
<td>58±15</td>
<td>62±11</td>
<td>58±14</td>
<td>61±13</td>
</tr>
<tr>
<td>Male, %</td>
<td>81</td>
<td>61</td>
<td>70</td>
<td>50</td>
<td>65</td>
</tr>
<tr>
<td>Black</td>
<td>26</td>
<td>50</td>
<td>20</td>
<td>7</td>
<td>24</td>
</tr>
<tr>
<td>Previous AF</td>
<td>22</td>
<td>17</td>
<td>12</td>
<td>21</td>
<td>14</td>
</tr>
<tr>
<td>Ischemic cardiomyopathy</td>
<td>52</td>
<td>44</td>
<td>62</td>
<td>43</td>
<td>55</td>
</tr>
<tr>
<td>Ejection fraction</td>
<td>24±11</td>
<td>18±7</td>
<td>23±8</td>
<td>18±10</td>
<td>21±8</td>
</tr>
<tr>
<td>NYHA</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Class I</td>
<td>7*</td>
<td>33</td>
<td>27</td>
<td>21</td>
<td>27</td>
</tr>
<tr>
<td>Class II</td>
<td>19</td>
<td>28</td>
<td>27</td>
<td>29</td>
<td>27</td>
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<td>Class III</td>
<td>74‡</td>
<td>39</td>
<td>47</td>
<td>50</td>
<td>46</td>
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<tr>
<td>Dual chamber ICD</td>
<td>63</td>
<td>44</td>
<td>38</td>
<td>64</td>
<td>43</td>
</tr>
<tr>
<td>Heart rate, beats per minute</td>
<td>185±26†</td>
<td>170±28</td>
<td>218±48</td>
<td>255±82</td>
<td>214±57</td>
</tr>
<tr>
<td>HRV (coefficient of variation)</td>
<td>0.15±0.060§</td>
<td>0.015±0.0085</td>
<td>0.067±0.10</td>
<td>0.086±0.13</td>
<td>0.060±0.099</td>
</tr>
<tr>
<td>Stability, ms</td>
<td>87±33§</td>
<td>11±8</td>
<td>27±60</td>
<td>28±52</td>
<td>24±53</td>
</tr>
<tr>
<td>Entropy (COSEn)</td>
<td>-0.82±0.53§</td>
<td>-3.2±0.71</td>
<td>-2.5±0.73</td>
<td>-2.5±0.88</td>
<td>-2.7±0.79</td>
</tr>
</tbody>
</table>

AF indicates atrial fibrillation; COSEn, coefficient of sample entropy; HRV, heart rate variability; ICD, implantable cardioverter-defibrillator; NYHA, New York Heart Association; SVT, supraventricular tachycardia; VF, ventricular fibrillation; and VT, ventricular tachycardia.

Continuous (mean±SD) and categorical (%) variables were compared between AF and non-AF groups: *P=0.03, †P=0.01, ‡P=0.009, §P<0.0001.

**Figure 1.** Representative preshock electrograms and corresponding entropy values. Bipolar electrograms from right atrial (RA) and right ventricular (RV) leads, unipolar far field (FF) electrograms, plots of entropy values, and an expanded view of the FF electrograms from 2 patients are shown. The bipolar electrograms were recorded from 2 poles in close proximity within the same lead. In contrast, FF electrograms were recorded using an active unipolar lead in the RV and an indifferent electrode outside the heart, and reflect electric activity from a larger portion of the ventricle, similar to surface ECG tracings. The dotted line represents the entropy threshold for atrial fibrillation (AF) detection. The arrows indicate the RV electrogram segment of 9 intervals immediately preceding the implantable cardioverter-defibrillator (ICD) shock that was used for the rhythm discrimination analyses. **A**, Data from a patient who received an appropriate shock for ventricular tachycardia (VT). The RV rate exceeded the RA rate and the FF electrogram demonstrated a similar morphology among beats. At all times, the entropy values accurately indicated VT/ventricular fibrillation. **B**, Data from a patient who received an inappropriate shock for AF. The RA electrogram exhibited AF. The ICD was programmed to deliver a shock for heart rates >190 beats per minute. The entropy values consistently indicated AF.
Entropy estimation of only 9 intervals of ventricular activation (within \( \pm 3 \) seconds) accurately distinguished AF from VT/VF. We directly compared performances of entropy estimation with those of representative rhythm discrimination algorithms routinely used in contemporary ICDs. Compared with VT/VF, the AF records had lower heart rate, higher HRV, reduced stability, and higher entropy (Table 1). Analysis of \( \geq 9 \) intervals of ventricular activation did not affect the results.

Figure 1 shows illustrative electrograms responsible for an appropriate shock for VT (Figure 1A) and an inappropriate shock for AF (Figure 1B). At all times, the entropy values accurately identified the adjudicated rhythms. Although these rhythms were also discernible on the basis of rate, stability, and morphology of the atrial and ventricular electrograms, other AF and VT/VF records were distinguishable only by entropy (Figure 2A). However, there were no examples of rhythms with comparable entropy and significantly different stabilities in the entire data set.

The high entropy of AF most clearly distinguished this rhythm from VT/VF with receiver operating characteristic curve area of 0.98 (Figure 2B). In a plot of ventricular rate and stability as a function of entropy, the only outlier in the AF group with lower entropy was atrial flutter with 2:1 conduction block to the ventricles (Figure 2C). Although this diminished performance estimates, AF and atrial flutter were grouped together to reflect the typical clinical setting more accurately in which their diagnosis and management often overlap.

Because missing even a single VT/VF episode is potentially fatal, programming a highly sensitive cutoff for AF without compromising VT/VF detection is a practical clinical challenge. On the basis of thresholds commonly used in clinical practice, heart rate, HRV, and stability correctly identified only \( \leq 85\% \) of the non-AF cases (Table 2). In contrast, entropy correctly identified 100\% of the non-AF cases using an objectively predetermined threshold. Entropy estimation was also the best AF detector in this data set. In logistic regression analyses, heart rate, HRV, and stability did not improve AF discrimination compared with entropy estimation alone (\( P > 0.3 \)).

Discussion

In this consecutive series of patients with primary prevention ICDs, almost half of the ICD shocks delivered were not for VT/VF and AF was responsible for two thirds of these inappropriate shocks. The ICD firing rates in this cohort are similar to those reported in randomized clinical trials, such as SC-D-Heart Failure Trial and lower than those reported in Multicenter Automatic Defibrillator Implantation Trial II.2,19 This novel strategy for discriminating AF from VT/VF based on entropy estimation of 9 ventricular beats from intracardiac electrograms was highly accurate, efficient, and performed well at fast heart rates. Entropy estimation exhibited better rhythm discrimination ability than representative algorithms used in contemporary ICDs.

Entropy estimation has potential for not only reducing inappropriate ICD shocks, but also other clinical applications. AF, the most common sustained arrhythmia and particularly frequent in patients with heart disease, is often asymptomatic and carries a substantially increased stroke risk.34 Diagnosis of asymptomatic AF remains a challenge\(^{34}\) (eg, in patients with single-chamber pacemakers and ICDs).\(^{35,36}\) About 50\% of patients with pacemakers have undiagnosed AF,\(^ {36}\) but no current single-chamber implantable device reports the amount of time in AF or the AF burden. In addition, knowing the amount of time a patient has AF can guide important clinical decisions (eg, anticoagulation management). Because AF detection based on entropy estimation is conceptually simple and computationally efficient, it may be applied to patients with implantable devices and for screening patients at high risk for development of AF and its complications.

There are some clinical situations, though, in which entropy estimation will be an imperfect AF discriminator. For example, entropy estimation will not distinguish AF from atrial flutter with variable atrioventricular block, but it can distinguish atrial flutter with fixed atrioventricular block, which has much lower entropy. In this study, all types of atrial flutter were categorized as AF. Despite the different dynamics, atrial flutter has a similar clinical profile as AF and is a limitation in entropy analysis for AF detection.

VF or polymorphic forms of VT with very fast ventricular rates may have higher entropy than monomorphic VT and overlap with the high entropy of AF. Because of a finite sampling rate or reconstitution of electrograms stored at lower resolution, the measurement precision of times between ventricular activations decreases at extremely high heart rates and measured intervals may be limited to a small range of values, resulting in more uniform entropy estimates and the possibility of mistaking very fast AF for VT/VF. However, ventricular arrhythmias at even the highest rates and variability had lower entropy than AF in this large data set (Figure 2C). Regardless, even if the discriminatory ability of entropy were to be reduced at extremely high heart rates, this would have little practical impact because the default for most ICDs is to deliver therapy to avoid undertreating potentially lethal arrhythmias.

We compared entropy estimation with representative metrics of stability and HRV used in SVT discriminators of contemporary ICDs. Although other variants of stability are used by different ICD manufacturers, they are mathematically similar and do not seem to affect the incidence of inappropriate shocks.\(^{15,17,18,21,32,33}\) Heart rate is the primary determinant for delivery of therapy by ICDs and thus is a surrogate for rhythm discrimination. Recent comparisons of sophisticated discrimination algorithms have demonstrated only a small reduction in inappropriate shocks that was attributed primarily to incorporation of a heart rate cutoff of at least 175 beats per minute.\(^ {16}\)

The relatively small number of AF cases in this study increased the risk of statistical overfitting of data. Although entropy estimation had a high predictive accuracy for AF detection in 24-hour Holter surface ECG recordings,\(^ {28}\) this study is restricted to shorter duration intracardiac electrograms retrieved for rhythm analysis after an ICD shock and as such cannot provide performance estimates for any episodes longer than the electrogram recordings. The performance estimates for entropy did not change over the duration of the electrogram recordings. Additional studies with larger sample sizes and longer electrogram recordings are necessary to validate these findings prospectively and to provide more reliable estimates of discrimination parameters for entropy compared with those used in contemporary ICDs. Because
the computational cost for entropy calculation is low, entropy can be continuously monitored by ICDs for the duration of the tachycardia. The ventricular activation intervals measured at the right ventricular lead are plotted >3 seconds preceding implantable cardioverter-defibrillators shocks in 2 patients. Shocks were delivered for AF (blue circles) and for VT (red squares). The stability of the 9 ventricular activation intervals preceding each shock was calculated as the trimmed range using the differences in the intervals indicated by the bold symbols. Although the AF and VT were indistinguishable on the basis of stability and heart rate, the entropy of AF (−0.999) was significantly higher than that of the VT (−1.89). B, The receiver operating characteristic (ROC) curves for discrimination of AF from supraventricular tachycardia/VT/ventricular fibrillation by heart rate, heart rate variability (HRV), stability, and entropy. The ROC area under curve (95% confidence interval) for entropy, stability, HRV, and heart rate were 0.98 (0.93–1.0), 0.91 (0.83–0.99; *P*<0.01 compared with entropy), 0.83 (0.74–0.92; *P*<0.001), and 0.75 (0.65–0.84; *P*<0.0001), respectively. C, Plots of ventricular rate (top) and stability (bottom, log_{10} scale), as a function of entropy for AF (blue circles) and other rhythms (red squares). Although the AF records had a larger stability value (87±33 ms) than other rhythms (24±53; *P*<0.0001), there was considerable overlap between groups. The HRV in AF was also higher (0.15±0.060 ms) than others (0.060±0.099; *P*<0.0001), but with even more overlap (data not shown). The ventricular rates in AF were lower (185±26 beats per minute) than others (214±57; *P*=0.01) but exhibited substantial overlap. The high entropy values of the AF records (−0.82±0.53) set them apart from other rhythms (−2.7±0.79; *P*<0.0001) more clearly than the range of distribution of stability, HRV, or heart rate.

How does entropy estimation differ from conventional measures of HRV? Although thermodynamic entropy relates to the distribution of a system among its substates, the information entropy of a time series is often characterized as uncertainty, complexity, disorder, or unpredictability. Entropy estimation is fundamentally different from measures of irregularity or
HRV in that it measures the degree to which self-similar heart rate fluctuation patterns repeat. In premature infants, entropy estimation has proven important in early detection of sepsis and reducing mortality.17 We now find that applying entropy estimation for discriminating nonlethal from lethal cardiac arrhythmias is efficient and highly accurate at fast heart rates, where rapid decisions about high voltage shocks must be made. The long-held and fundamental principle that measuring the dynamics of human rhythms can improve healthcare holds true in this life-saving cardiac therapy.

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Disclosures

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References

Atrial fibrillation (AF) is the most common sustained arrhythmia in man. The consequences of inadequate AF detection are a major public health concern and pose a significant societal burden. Despite recent advances in technology and rhythm discrimination strategies, about one third of patients with implantable cardioverter-defibrillators (ICDs) receive inappropriate shocks for AF; a nonlethal arrhythmia that does not require such aggressive therapy. Inappropriate shocks are painful, associated with substantial psychological stress, decrease quality of life, can initiate more dangerous arrhythmias, and may increase mortality. Minimizing inappropriate shocks while maintaining high sensitivity for detecting lethal ventricular arrhythmias is an essential attribute of contemporary ICDs. The authors introduce a novel nonlinear strategy for discriminating AF from very short intracardiac electrogram records from ICDs (ie, 9 heart beats). Entropy performs well at very fast heart rates and requires only 2 to 3 seconds for highly accurate AF discrimination. Entropy estimation fundamentally differs from conventional measures of heart rate variability in implanted ventricular devices.

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Dynamic Analysis of Cardiac Rhythms for Discriminating Atrial Fibrillation From Lethal Ventricular Arrhythmias

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SUPPLEMENTAL MATERIAL

Information entropy estimation using COSEn

Information entropy, a concept of uncertainty and complexity, is fundamentally different from conventional measures of heart rate variability (HRV) in that entropy exploits information in the ordering of the times between ventricular activation and quantifies the degree to which self-similar fluctuation patterns repeat themselves\(^1\). These self-similar fluctuations are indistinguishable in linear analytical methods, such as moment statistics and frequency domain measures of HRV\(^2\).

The coefficient of sample entropy (COSEn) was developed specifically for atrial fibrillation (AF) detection in very short RR interval series at all heart rates and builds on new concepts on entropy estimation\(^3\)\(^-\)\(^5\). The novel features of COSEn include converting probabilities to densities, ensuring confident probability estimation and interpreting quadratic entropy rate as a measure of Gaussian white noise\(^4\). These features are desirable for rhythm discrimination in implantable cardioverter-defibrillators (ICDs) where time for rhythm diagnosis is limited. When heart rate records are long and well-behaved, accurate entropy estimation can be achieved with a variety of traditional approaches\(^6\)\(^,\)\(^7\). However, more attention to the details of the estimation algorithm is needed for short records and complex signals. While COSEn is a single
measure of entropy rate, its full formulation (including the initial step of normalizing the signal by its mean) came out of an extensive multivariate analysis for detecting AF.

The gist of the COSEn method employed herein for entropy estimation is to quantify the extent to which short templates of ventricular activation intervals repeat themselves -- if repetition is frequent, we consider the process to be of low entropy and less likely to be AF. The COSEn algorithm determines if 2 intervals match within a certain tolerance $r$, and the degree of entropy is calculated as the adjusted conditional probability of subsequent matches exceeding a given threshold. This threshold was pre-determined by applying the method of equal proportion of misclassifications to a different patient dataset of 24 hour Holter surface ECG recordings with a prevalence of AF that is similar to this study.

For a segment length of $n$ beats, the entropy calculation starts with calculating the differences between the $[n \times (n - 1) \div 2]$ pairs of intervals (i.e., 36 pairs in a 9-beat segment), comparing each pair to the tolerance window $(2 \times r)$, and then deciding if a match has been made. The result is a conditional probability. If $A$ is equal to the number of pairs of intervals that match and $B$ is the subset of $A$ in which the next pairs also match, sample entropy is $[-\ln(A \div B)]$ where $\ln$ is the natural logarithm. COSEn is calculated by normalizing the sample entropy for the mean of the ventricular activation intervals and for the matching volume [i.e., for
tolerance \( r \) and template length \( m \), the matching volume is \((2 \times r)^m\). Normalizing for the matching volume allows comparison of entropy estimates made with different values of \( r \) \(^8\).

The value of \( r \) is an important factor for determining the underlying dynamics of a segment of intervals. If \( r \) is too small (i.e., smaller than the typical noise amplitude), then pairs of intervals that are similar shall fail to match. However, if \( r \) is too large, there will be a loss in discriminating power simply because pairs of intervals will look similar to one another given sufficiently lax matching conditions. The ideal condition would be to vary \( r \) with the scale of signal noise such that \( r \) is as small as possible for searching for order in the dynamics while ensuring the number of matches remains large enough to ensure precise statistics. This is analogous to varying the bin widths of a histogram to optimally describe its distribution.

To illustrate the COSEn calculation, consider the two 9-beat segments of ventricular activation intervals recorded during the AF and ventricular tachycardia (VT) in Figure 2-A. The rhythm diagnosis is made from inspection of the electrograms. The stability, a measure of variability and calculated as the trimmed range, is the same for both. The AF record, though, is more irregular, as reflected by the higher entropy value.

**Supplementary Table 1** lists the results for the first step (i.e., calculating the differences between all pairs of points) for the sequence of 9 ventricular activation intervals from the AF record in Figure 2-A. Each cell is the difference of the interval values appearing at the beginning
of the row and at the top of the column. Because the table is symmetric about its diagonal, only one set of results is shown.

Supplementary Table 1

<table>
<thead>
<tr>
<th>intervals</th>
<th>335</th>
<th>335</th>
<th>345</th>
<th>320</th>
<th>395</th>
<th>325</th>
<th>315</th>
<th>330</th>
<th>285</th>
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<td>-30</td>
<td>-45</td>
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</table>

Next, we seek matches within a certain tolerance $r$ for template lengths $m$ (a single interval) and $m + 1$ (two consecutive intervals). Previously, in a different dataset of 24 hour Holter surface ECG recordings, we established that $m = 1$ is suitable for AF detection. Because the resolution of the EGM data in this study is $\leq 5$ msec, we limited values for the tolerance $r$ to midpoint values of 2.5, 7.5, 12.5, and so on.
In the example of this AF record, we found 5 or more matches of length 2 when \( r = 22.5 \) msec.

The logical table below (Supplementary Table 2) was constructed by placing 1’s for differences less than 22.5 msec, and 0’s otherwise. For example, 1 appears in the cell in the third row, third column because the difference between 345 msec and 335 msec is less than 22.5 msec. The result is that there are 19 matches of length \( m = 1 \).

<table>
<thead>
<tr>
<th>intervals</th>
<th>335</th>
<th>335</th>
<th>345</th>
<th>320</th>
<th>395</th>
<th>325</th>
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In the next step, we determine whether a match for a template of length \( m = 2 \) occurs when a value of 1 has occurred for \( m = 1 \) (i.e., events in which matches follow sequentially both entries of a diagonal of length 2).
**Supplementary Table 3** lists the logical events for the AF record in which 2 matches follow sequentially. For example, 1 appears in the cell in the third row, second column because there were 1’s in the same two cells in Supplementary Table 2 [i.e., second row of second column (335 – 355 < 22.5) and third row of third column (345 – 335 < 22.5)].

<table>
<thead>
<tr>
<th>Intervals</th>
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<th>345</th>
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The conditional probability of matching at the \( m + 1 \) point having matched for \( m \) points, is

\[
A / B = 7 / 19 = 0.36842.
\]

The sample entropy (SampEn) is the negative natural logarithm of this probability:

\[
\text{SampEn} = - \ln \left( \frac{A}{B} \right) = - \ln \left( \frac{7}{19} \right) = 0.99853
\]
The quadratic sample entropy (QSE), which normalizes for $r$, is:

$$\text{QSE} = \text{SampEn} + \ln[(2 \times r)^m] = 0.99853 + \ln[2 \times 22.5]^1 = 4.8052$$

Then, COSEn, is calculated by further normalizing for the ventricular rate by subtracting the natural logarithm of the average ventricular activation interval. Here, the average ventricular activation interval is 331.67 milliseconds. The complete calculation of COSEn is:

$$\text{COSEn} = -\ln \left[ \frac{A}{B} \right] + \ln[(2 \times r)^m] - \ln[\text{average interval}]$$

$$= -\ln \left[ \frac{7}{19} \right] + \ln[2 \times 22.5]^1 - \ln[331.67] = -0.99895$$

The 9-beat VT record in Figure 2-A has the sequence of intervals (315, 330, 320, 350, 360, 330, 335, 345, 335). The minimum $r^*$ leading to a numerator count of 5 is $r = 17.5$ msec. The mean interval is 335.56 msec. The COSEn calculation for the VT record is:

$$\text{COSEn} = -\ln \left[ \frac{A}{B} \right] + \ln[(2 \times r)^m] - \ln[\text{average interval}]$$

$$= -\ln \left[ \frac{11}{16} \right] + \ln[2 \times 17.5]^1 - \ln[335.56] = -1.8858$$

We note that even though both the AF and VT records in Figure 2-A had identical values for the average heart rate (180 bpm) and stability (30 ms), the entropy of the VT record was significantly lower than that of the AF. However, there were no examples of rhythms with
comparable entropy and significantly different stabilities in the entire dataset (Figure 2-C).

There was no significant difference in the ROC curve areas for AF discrimination based on COSEn calculation of ≥8 intervals preceding ICD shock (Supplemental Figure 1). As demonstrated by the above calculations, COSEn builds on new concepts of entropy estimation and fundamentally differs from conventional measures of irregularity or HRV.

![Supplementary Figure 1](image)

**Supplementary Figure 1**

ROC curve area as a function of segment length (number of intervals before ICD shock).

**References**


