Circulation
Arrhythmia and Electrophysiology
JOURNAL OF THE AMERICAN HEART ASSOCIATION

American Heart Association
Learn and Live

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

Deeptankar DeMazumder, Douglas E. Lake, Alan Cheng, Travis J. Moss, Eliseo Guallar, Robert G. Weiss, Steven Jones, Gordon F. Tomaselli and J. Randall Moorman

Circ Arrhythm Electrophysiol published online May 16, 2013;
DOI: 10.1161/CIRCEP.113.000034
Circulation: Arrhythmia and Electrophysiology is published by the American Heart Association. 7272 Greenville Avenue, Dallas, TX 72514
 Print ISSN: 1941-3149. Online ISSN: 1941-3084

DOI: 10.1161/CIRCEP.113.000034

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

Running title: *DeMazumder et al.; Dynamic analysis for discriminating AF from VT/VF*

Deeptankar DeMazumder, MD, PhD[1]; Douglas E. Lake, PhD[2,3]; Alan Cheng, MD[1]; Travis J. Moss, MD[2]; Eliseo Guallar, MD, PhD[4]; Robert G. Weiss, MD[1]; Steven Jones, MD[1]; Gordon F. Tomaselli, MD[1]; J. Randall Moorman, MD[2]

[1]Division of Cardiology, Johns Hopkins University School of Medicine, Baltimore, MD;[2]Division of Cardiology, [3]Dept of Statistics, University of Virginia, Charlottesville, VA;[4]Dept of Epidemiology & Welch Center for Prevention, Epidemiology, and Clinical Research, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD

Corresponding Authors:

Deeptankar DeMazumder, MD, PhD
Division of Cardiology
Johns Hopkins Univ School of Medicine
720 North Rutland Ave., Ross 844
Baltimore, MD 21205
Tel: 410-955-2774
Fax: 410-502-2096
E-mail: Deep@jhmi.edu

Gordon F. Tomaselli, MD
Division of Cardiology
Johns Hopkins Univ School of Medicine
720 North Rutland Ave., Ross 844
Baltimore, MD 21205
Tel: 410-955-2774
Fax: 410-502-2096
E-mail: gtomasel@jhmi.edu

Journal Subject Codes: [22] Ablation/ICD/surgery, [121] Primary prevention, [110] Congestive, [171] Electrocardiology, [5] Arrhythmias, clinical electrophysiology, drugs

DOI: 10.1161/CIRCEP.113.000034

Abstract

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/fibrillation (VT/VF). 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/VF. We hypothesized that the higher entropy of rapid cardiac rhythms preceding ICD shocks distinguishes AF from VT/VF.

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/VF (62%), AF (23%), and supraventricular tachycardia (15%). Entropy estimation of only 9 ventricular intervals prior to ICD shocks accurately distinguished AF (ROC curve area 0.98; 95% CI 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.

Key words: implantable cardioverter-defibrillator, ventricular tachycardia, ventricular fibrillation, sudden cardiac death, ECG, nonlinear, inappropriate shock, entropy

DOI: 10.1161/CIRCEP.113.000034

Introduction

Ventricular tachycardia (VT) and fibrillation (VF) are lethal cardiac arrhythmias, claiming a quarter million lives per year from sudden cardiac death (SCD)[1]. Implantable 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).

Even with optimal ICD programming and contemporary technological advances[4-15], about a third of ICD recipients receive inappropriate shocks for AF[15-24]. 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 ICD patients 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 in the ordering of the times between ventricular activation and quantifies the degree to which self-similar fluctuation patterns repeat themselves. 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 (EGM) 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 non-ischemic heart failure, ejection fraction≤35%, New York Heart Association (NYHA) class I-III symptoms, and no history of VT/VF or SCD. Patients with secondary prevention indication, NYHA class IV heart failure, permanent pacemaker or pre-existing Class 1 indication for permanent pacemaker were not included in this cohort.

The present study includes 119 consecutive patients who received ICDs equipped with intracardiac EGM storage that were retrieved for rhythm discrimination and analysis. The ICDs were manufactured by Medtronic (Minneapolis, Minnesota), Boston Scientific (Natick, Massachusetts), and St. Jude Medical (St. Paul, Minnesota). During the implant procedure, sensing, pacing and defibrillation thresholds were tested as per standard protocol. ICDs were programmed at the discretion of implanting physicians. High VT/VF cutoff zones were encouraged and supraventricular tachycardia (SVT) discriminator algorithms could be enabled. The ICDs were reprogrammed by the treating physician when deemed clinically indicated (e.g., hemodynamic well-tolerated VT, VT in monitor zone). The EGM 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 EGMs prior to the

shock was reviewed by a committee of 3 or more board-certified clinical cardiac electrophysiologists. The committee blindly adjudicated the type of arrhythmia eliciting the shock (e.g., VT, VF, SVT, 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 EGM 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 entropy (SampEn)[27,28] measure and developed the coefficient of sample entropy (COSEn)[29] for the specific purpose of AF discrimination in EGMs at all heart rates using very short time series of ventricular activation.

An illustration of the COSEn calculation is provided in the **Supplementary Methods**. Briefly, SampEn is the conditional probability that two short templates of length $\boldsymbol{m}$ that match within an arbitrary tolerance $\boldsymbol{r}$ will continue to match at the next point $\boldsymbol{m+1}$. Mathematically expressed, $\text{SampEn} = -\ln(\boldsymbol{A/B})$, where $\boldsymbol{A}$ denotes $\sum \boldsymbol{A_i}$ (total number of matches of length $\boldsymbol{m+1}$) and $\boldsymbol{B}$ denotes $\sum \boldsymbol{B_i}$ (total number of matches of length $\boldsymbol{m+1}$ and $\boldsymbol{m}$), in a series of $\boldsymbol{n}$ consecutive intervals, $\boldsymbol{x_1, x_2, \ldots, x_n}$ where the record may be as short as $\boldsymbol{n=9}$. By allowing $\boldsymbol{r}$

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 SampEn estimate was defined as COSEn. Unlike approximate entropy[26], frequency domain measures or geometric measures such as Poincaré plots[30], 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[29] 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 of the EGMs and intervals of the stored event and analysis of more than 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 (standard deviation of the intervals divided by the mean) is a common measure of HRV. Stability, another measure of variability, is indexed as the trimmed range (i.e., next-to-longest minus next-to-shortest intervals, so large values indicate less stable rhythms).

Statistical Analysis

Continuous variables were compared using t-test and categorical variables were compared using chi-squared test. The ability of entropy, stability, HRV, and heart rate to discriminate AF was

evaluated using the ROC 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≥30 ms; HRV≥0.10; heart rate<180 bpm). 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, Texas). 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 EGMs. 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 vs. non-AF groups were: VF zone cutoff 191±14 vs. 197±14; lowest rate cutoff 167±23 vs. 173±22; enabled morphology discriminator algorithms 26% vs. 25%; enabled onset algorithms (17% vs. 13%), enabled stability algorithms 15% vs. 13%; ventricular sensitivity 0.279±0.0139 vs. 0.273±0.00932; one zone programmed 41% vs. 37%; two zones 30% vs. 37%; three zones 19% vs. 9%. Although it is an appealing idea that sensed information from an atrial 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 employed a novel, conceptually simple strategy for AF discrimination based on entropy estimation[29] of EGMs. Entropy estimation of only 9 intervals of ventricular activation (within about 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 to VT/VF, the AF records had lower heart rate, higher HRV, reduced stability, and higher entropy **(Table 1)**. Analysis of more than 9 intervals of ventricular activation did not affect the results.

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

The high entropy of AF most clearly distinguished this rhythm from VT/VF with ROC curve area of 0.98 **(Figure 2-B)**. 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 2-C)**. Although this diminished performance estimates, AF and atrial flutter were grouped together to more accurately reflect the typical clinical setting 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.

Based on thresholds commonly used in clinical practice, heart rate, HRV and stability correctly identified up to only 85% of the non-AF cases **(Table 2)**. In contrast, entropy correctly identified 100% of the non-AF cases using an objectively pre-determined threshold. Entropy estimation was also the best AF detector in this dataset. In logistic regression analyses, heart rate, HRV and stability did not improve AF discrimination compared to 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 SCD-HeFT[3] and lower than those reported in MADIT II[2,19]. This novel strategy for discriminating AF from VT/VF based on entropy estimation of 9 ventricular beats from intracardiac EGMs 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 not only for reducing inappropriate ICD shocks but also for other clinical applications. AF, the most common sustained arrhythmia in man 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], for example, 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 (e.g., 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 EGMs 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 dataset (Figure 2-C). 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 in order to avoid under treating 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 employed by different ICD manufacturers, they are mathematically similar and do not seem to affect the incidence of inappropriate shocks[11,15-17,19-21,32,33]. Heart rate is the primary determinant for delivery of therapy by ICDs and thus is a surrogate for rhythm discrimination. Recent comparisons of the

most sophisticated discrimination algorithms have demonstrated only a small reduction in inappropriate shocks (i.e., 19% vs. 25%) that was attributed primarily to incorporation of a heart rate cutoff of 175 bpm[16].

The relatively small number of AF cases in the present study increased the risk of statistical overfitting of data. While entropy estimation had a high predictive accuracy for AF detection in 24-hour Holter surface ECG recordings[29], the present study is restricted to shorter duration intracardiac EGMs retrieved for rhythm analysis after an ICD shock and as such, cannot provide performance estimates for any episodes longer than the EGM recordings. The performance estimates for entropy did not change over the duration of the EGM recordings. Additional studies with larger sample sizes and longer EGM recordings are necessary to prospectively validate these findings and to provide more reliable estimates of discrimination parameters for entropy compared to those employed 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. Like all such measures, entropy estimation is not intended to function alone, and implementation with other rhythm detection features or criteria (e.g., rate, sustained high rate) should maximize discrimination accuracy.

How does entropy estimation differ from conventional measures of HRV? While 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 themselves. In premature infants, entropy estimation has proven important in early detection of sepsis and reducing mortality[37]. We now find that applying entropy estimation for discriminating

non-lethal 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 health care holds true in this life-saving cardiac therapy.

Acknowledgments: This work was supported by the Donald W. Reynolds Cardiovascular Clinical Center at the Johns Hopkins University, NIH HL R01 091062 (G.F. Tomaselli), and in part by an American Heart Association Mid-Atlantic grant-in-aid at the University of Virginia (J.R. Moorman). We gratefully acknowledge Daniel Hecker (St. Jude Medical), Ward Stephenson, Jr. (Medtronic), and Allen Wish (Boston Scientific) for providing software for retrieval of intracardiac EGMs. We gratefully acknowledge Barbara Butcher, Sanaz Norgard, Deborah Disilvestre and Solmaz Masoudi for managing PROSe-ICD.

Conflict of Interest Disclosures: Drs. DeMazumder, Lake, Moss, Guallar, Weiss, Jones, Tomaselli and Moorman have no disclosures. Dr. Cheng has received significant consulting fees/honoraria from Biotronik, EP Technologies, St. Jude Medical, and modest consulting fees/honoraria from Medtronic.

References:

1. Chugh SS, Reinier K, Teodorescu C, Evanado A, Kehr E, Al Samara M, Mariani R, Gunson K, Jui J. Epidemiology of sudden cardiac death: Clinical and research implications. *Prog Cardiovasc Dis*. 2008;51:213-228.

2. Moss AJ, Zareba W, Hall WJ, Klein H, Wilber DJ, Cannom DS, Daubert JP, Higgins SL, Brown MW, Andrews ML. Prophylactic implantation of a defibrillator in patients with myocardial infarction and reduced ejection fraction. *N Engl J Med*. 2002;346:877-883.

3. Bardy GH, Lee KL, Mark DB, Poole JE, Packer DL, Boineau R, Domanski M, Troutman C, Anderson J, Johnson G, McNulty SE, Clapp-Channing N, Davidson-Ray LD, Fraulo ES, Fishbein DP, Luceri RM, Ip JH. Amiodarone or an implantable cardioverter-defibrillator for congestive heart failure. *N Engl J Med*. 2005;352:225-237.

4. Saeed M, Razavi M, Neason CG, Petrutiu S. Rationale and design for programming implantable cardioverter-defibrillators in patients with primary prevention indication to prolong time to first shock (PROVIDE) study. *Europace*. 2011;13:1648-1652.

5. Lo R, Al-Ahmad A, Hsia H, Zei PC, Wang PJ. Optimal programming of ICDs for prevention of appropriate and inappropriate shocks. Curr Treat Options Cardiovasc Med. 2008;10:408-416.

6. Klein GJ, Gillberg JM, Tang A, Inbar S, Sharma A, Unterberg-Buchwald C, Dorian P, Moore H,

Duru F, Rooney E, Becker D, Schaaf K, Benditt D. Improving SVT discrimination in single-chamber icds: A new electrogram morphology-based algorithm. *J Cardiovasc Electrophysiol*. 2006;17:1310-1319.

7. Singh SN, Poole J, Anderson J, Hellkamp AS, Karasik P, Mark DB, Lee KL, Bardy GH. Role of amiodarone or implantable cardioverter/defibrillator in patients with atrial fibrillation and heart failure. *Am Heart J.* 2006;152:974 e977-911.

8. Williams JL, Shusterman V, Saba S. A pilot study examining the performance of polynomial-modeled ventricular shock electrograms for rhythm discrimination in implantable devices. *Pacing Clin Electrophysiol*. 2006;29:930-939.

9. Dash S, Chon KH, Lu S, Raeder EA. Automatic real time detection of atrial fibrillation. *Ann Biomed Eng*. 2009;37:1701-1709.

10. Higgins SL, Lee RS, Kramer RL. Stability: An icd detection criterion for discriminating atrial fibrillation from ventricular tachycardia. *J Cardiovasc Electrophysiol.* 1995;6:1081-1088.

11. Kuhlkamp V, Dornberger V, Mewis C, Suchalla R, Bosch RF, Seipel L. Clinical experience with the new detection algorithms for atrial fibrillation of a defibrillator with dual chamber sensing and pacing. *J Cardiovasc Electrophysiol*. 1999;10:905-915.

12. Fukunami M, Yamada T, Ohmori M, Kumagai K, Umemoto K, Sakai A, Kondoh N, Minamino T, Hoki N. Detection of patients at risk for paroxysmal atrial fibrillation during sinus rhythm by P wave-triggered signal-averaged electrocardiogram. *Circulation*. 1991;83:162-169.

13. Tateno K, Glass L. Automatic detection of atrial fibrillation using the coefficient of variation and density histograms of rr and deltarr intervals. *Med Biol Eng Comput*. 2001;39:664-671.

14. Huang C, Ye S, Chen H, Li D, He F, Tu Y. A novel method for detection of the transition between atrial fibrillation and sinus rhythm. *IEEE Trans Biomed Eng*. 2011;58:1113-1119.

15. van Rees JB, Borleffs CJ, de Bie MK, Stijnen T, van Erven L, Bax JJ, Schalij MJ. Inappropriate implantable cardioverter-defibrillator shocks: Incidence, predictors, and impact on mortality. *J Am Coll Cardiol*. 2011;57:556-562.

16. Gold MR, Ahmad S, Browne K, Berg KC, Thackeray L, Berger RD. Prospective comparison of discrimination algorithms to prevent inappropriate icd therapy: Primary results of the RHYTHM ID going head to head trial. *Heart Rhythm*. 2012;9:370-377.

17. Sweeney MO. Overcoming the defects of a virtue: Dual-chamber versus single-chamber detection enhancements for implantable defibrillator rhythm diagnosis: The detect supraventricular tachycardia study. *Circulation*. 2006;113:2862-2864.

18. Koneru JN, Swerdlow CD, Wood MA, Ellenbogen KA. Minimizing inappropriate or "unnecessary" implantable cardioverter-defibrillator shocks. *Circ Arrhythm Electrophysiol.*

2011;4:778-790.

19. Daubert JP, Zareba W, Cannom DS, McNitt S, Rosero SZ, Wang P, Schuger C, Steinberg JS, Higgins SL, Wilber DJ, Klein H, Andrews ML, Hall WJ, Moss AJ. Inappropriate implantable cardioverter-defibrillator shocks in madit ii: Frequency, mechanisms, predictors, and survival impact. *J Am Coll Cardiol*. 2008;51:1357-1365.

20. Friedman PA, McClelland RL, Bamlet WR, Acosta H, Kessler D, Munger TM, Kavesh NG, Wood M, Daoud E, Massumi A, Schuger C, Shorofsky S, Wilkoff B, Glikson M. Dual-chamber versus single-chamber detection enhancements for implantable defibrillator rhythm diagnosis: The detect supraventricular tachycardia study. *Circulation*. 2006;113:2871-2879.

21. Saeed M, Neason CG, Razavi M, Chandiramani S, Alonso J, Natarajan S, Ip JH, Peress DF, Ramadas S, Massumi A. Programming antitachycardia pacing for primary prevention in patients with implantable cardioverter defibrillators: Results from the PROVE trial. *J Cardiovasc Electrophysiol.* 2010;21:1349-1354.

22. Germano JJ, Reynolds M, Essebag V, Josephson ME. Frequency and causes of implantable cardioverter-defibrillator therapies: Is device therapy proarrhythmic? *Am J Cardiol.* 2006;97:1255-1261.

23. Stempniewicz P, Cheng A, Connolly A, Wang XY, Calkins H, Tomaselli GF, Berger RD, Tereshchenko LG. Appropriate and inappropriate electrical therapies delivered by an implantable cardioverter-defibrillator: Effect on intracardiac electrogram. *J Cardiovasc Electrophysiol*. 2011;22:554-560.

24. Poole JE, Johnson GW, Hellkamp AS, Anderson J, Callans DJ, Raitt MH, Reddy RK, Marchlinski FE, Yee R, Guarnieri T, Talajic M, Wilber DJ, Fishbein DP, Packer DL, Mark DB, Lee KL, Bardy GH. Prognostic importance of defibrillator shocks in patients with heart failure. *N Engl J Med*. 2008;359:1009-1017.

25. Sears SF, Lewis TS, Kuhl EA, Conti JB. Predictors of quality of life in patients with implantable cardioverter defibrillators. *Psychosomatics*. 2005;46:451-457.

26. Pincus SM, Goldberger AL. Physiological time-series analysis: What does regularity quantify? *Am J Physiol.* 1994;266:H1643-1656.

27. Richman JS, Lake DE, Moorman JR. Sample entropy. *Methods Enzymol*. 2004;384:172-184.

28. Richman JS, Moorman JR. Physiological time-series analysis using approximate entropy and sample entropy. *Am J Physiol Heart Circ Physiol.* 2000;278:H2039-2049.

29. Lake DE, Moorman JR. Accurate estimation of entropy in very short physiological time series: The problem of atrial fibrillation detection in implanted ventricular devices. *Am J Physiol Heart Circ Physiol*. 2011;300:H319-325.

30. Heart rate variability: Standards of measurement, physiological interpretation and clinical use. Task force of the european society of cardiology and the north american society of pacing and electrophysiology. *Circulation*. 1996;93:1043-1065.

31. Colquhoun D, Sakmann B. Fast events in single-channel currents activated by acetylcholine and its analogues at the frog muscle end-plate. *J Physiol.* 1985;369:501-557.

32. Olshansky B, Day JD, Moore S, Gering L, Rosenbaum M, McGuire M, Brown S, Lerew DR. Is dual-chamber programming inferior to single-chamber programming in an implantable cardioverter-defibrillator? Results of the INTRINSIC RV (inhibition of unnecessary RV pacing with AVSH in ICDs) study. *Circulation*. 2007;115:9-16.

33. Deisenhofer I, Kolb C, Ndrepepa G, Schreieck J, Karch M, Schmieder S, Zrenner B, Schmitt C. Do current dual chamber cardioverter defibrillators have advantages over conventional single chamber cardioverter defibrillators in reducing inappropriate therapies? A randomized, prospective study. *J Cardiovasc Electrophysiol*. 2001;12:134-142.

34. Healey JS, Connolly SJ, Gold MR, Israel CW, Van Gelder IC, Capucci A, Lau CP, Fain E, Yang S, Bailleul C, Morillo CA, Carlson M, Themeles E, Kaufman ES, Hohnloser SH. Subclinical atrial fibrillation and the risk of stroke. *N Engl J Med*. 2012;366:120-129.

35. Orlov MV, Ghali JK, Araghi-Niknam M, Sherfesee L, Sahr D, Hettrick DA. Asymptomatic atrial fibrillation in pacemaker recipients: Incidence, progression, and determinants based on the atrial high rate trial. *Pacing Clin Electrophysiol*. 2007;30:404-411.

36. Defaye P, Dournaux F, Mouton E. Prevalence of supraventricular arrhythmias from the automated analysis of data stored in the DDD pacemakers of 617 patients: The AIDA study. The AIDA multicenter study group. Automatic interpretation for diagnosis assistance. *Pacing Clin Electrophysiol*. 1998;21:250-255.

37. Moorman JR, Carlo WA, Kattwinkel J, Schelonka RL, Porcelli PJ, Navarrete CT, Bancalari E, Aschner JL, Whit Walker M, Perez JA, Palmer C, Stukenborg GJ, Lake DE, Michael O'Shea T. Mortality reduction by heart rate characteristic monitoring in very low birth weight neonates: A randomized trial. *J Pediatr*. 2011;159:900-906.

DOI: 10.1161/CIRCEP.113.000034

Table 1: Characteristics of adjudicated rhythm groups

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

*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.*

DOI: 10.1161/CIRCEP.113.000034

Table 2: AF discrimination using standard thresholds

Discriminator Threshold	Sensitivity	Specificity	Positive Likelihood Ratio	Negative Likelihood Ratio	Positive Predictive Value	Negative Predictive Value
Heart rate (bpm) <180	48 [29-68]	74 [64-84]	1.9 [1.1-3.1]	0.70 [0.48-1.03]	35 [20-53]	83 [73-90]
HRV (coefficient of variation) ≥0.10	85 [66-96]	85 [76-91]	5.6 [3.4-9.3]	0.18 [0.072-0.43]	62 [45-76]	95 [88-99]
Stability (ms) ≥30	89 [71-98]	85 [76-91]	5.8 [3.5-9.6]	0.13 [0.045-0.38]	63 [46-78]	96 [90-99]
Entropy (COSEn) ≥-1.2	85 [66-96]	100 [96-100]	156 [9.8-2489]	0.16 [0.069-0.38]	100 [85-100]	96 [90-99]

Sensitivity is the proportion of correct diagnoses of AF among shocks for AF and specificity is the proportion of correct diagnoses of non-AF rhythms among shocks not for AF. Values within brackets are 95% confidence intervals.

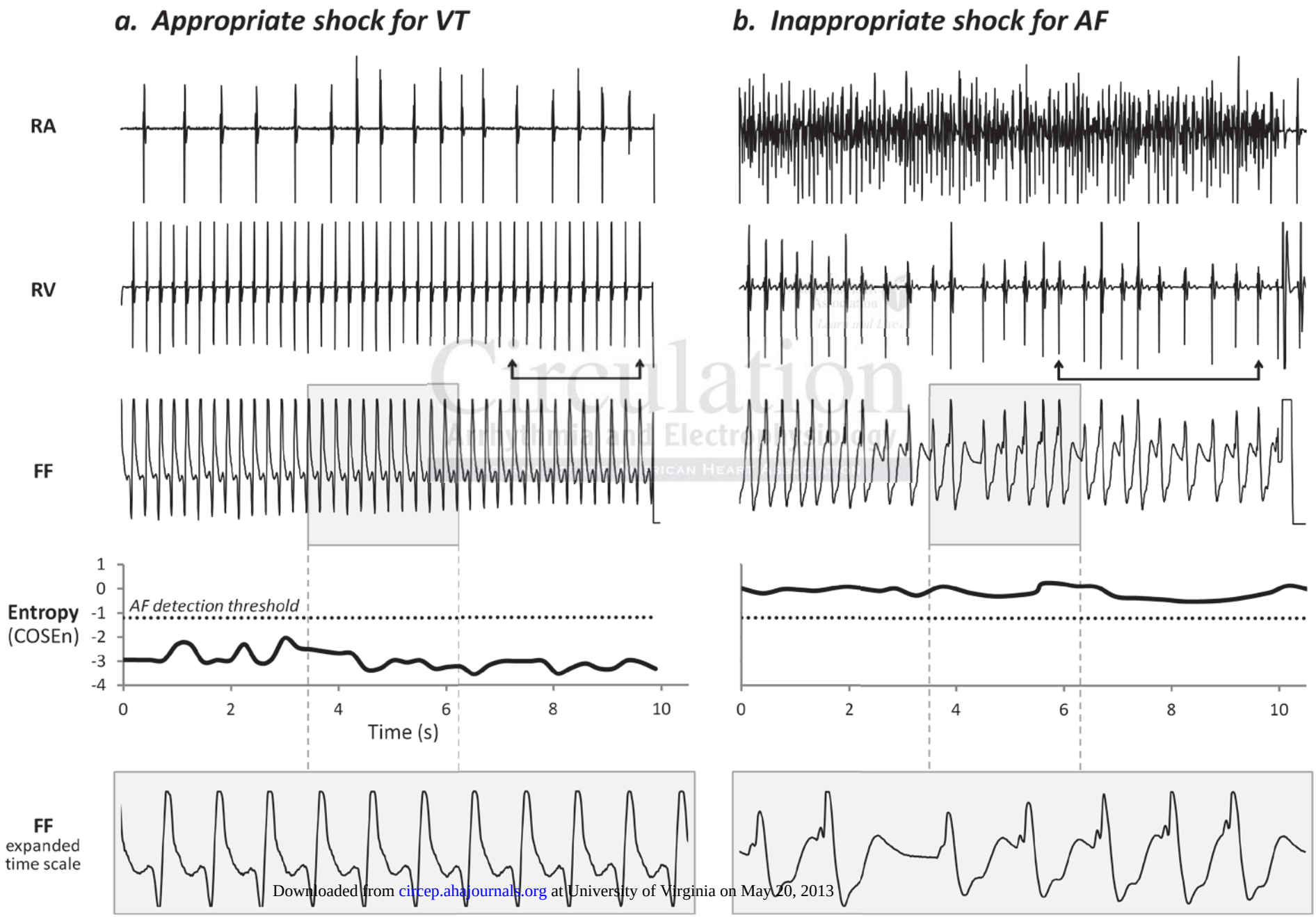
DOI: 10.1161/CIRCEP.113.000034

Figure Legends:

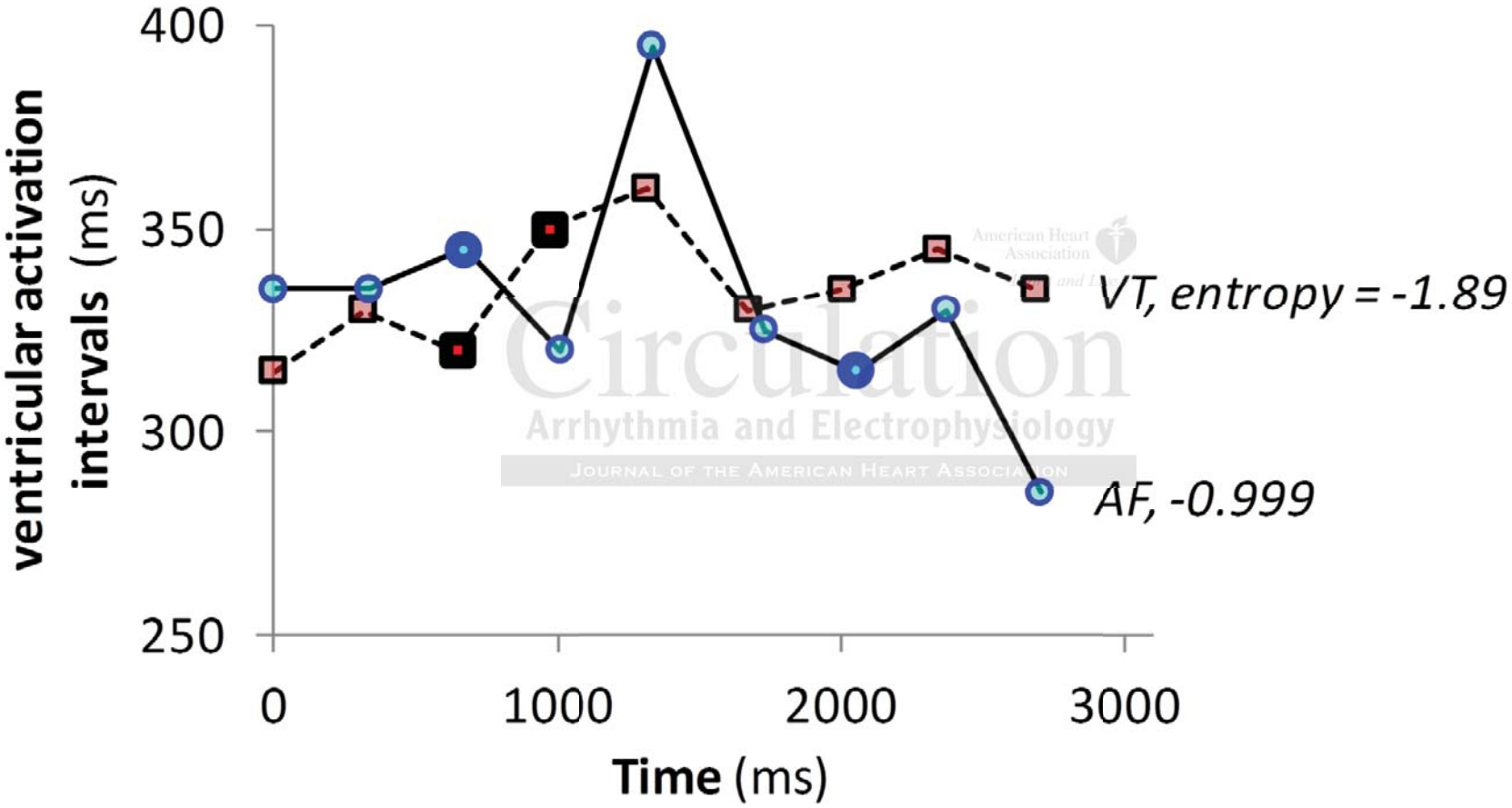
Figure 1. Representative pre-shock EGMs and corresponding entropy values. The panels show bipolar EGMs from right atrial (RA) and right ventricular (RV) leads, unipolar far field (FF) EGMs, plots of entropy values, and an expanded view of the FF EGMs from two patients. The bipolar EGMs were recorded from two poles in close proximity within the same lead. In contrast, FF EGMs were recorded using an active unipolar lead in the RV and an indifferent electrode outside the heart, and reflect electrical activity from a larger portion of the ventricle, similar to surface ECG tracings. The dotted line represents the entropy threshold for AF detection. The arrows indicate the RV EGM segment of 9 intervals immediately preceding the ICD shock that was used for the rhythm discrimination analyses. **A.** Data from a patient who received an appropriate shock for VT. The RV rate exceeded the RA rate and the FF EGM demonstrated a similar morphology among beats. At all times, the entropy values accurately indicated VT/VF. **B.** Data from a patient who received an inappropriate shock for AF. The RA EGM exhibited AF. The ICD was programmed to deliver a shock for heart rates exceeding 190 bpm. The entropy values consistently indicated AF.

Figure 2. AF discrimination. **A.** Representative examples of AF and VT with identical average heart rates (180 bpm) and stabilities (30 ms). These values are similar to the discrimination thresholds used in routine clinical practice. The ventricular activation intervals measured at the RV lead are plotted over three seconds preceding ICD shocks in two 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

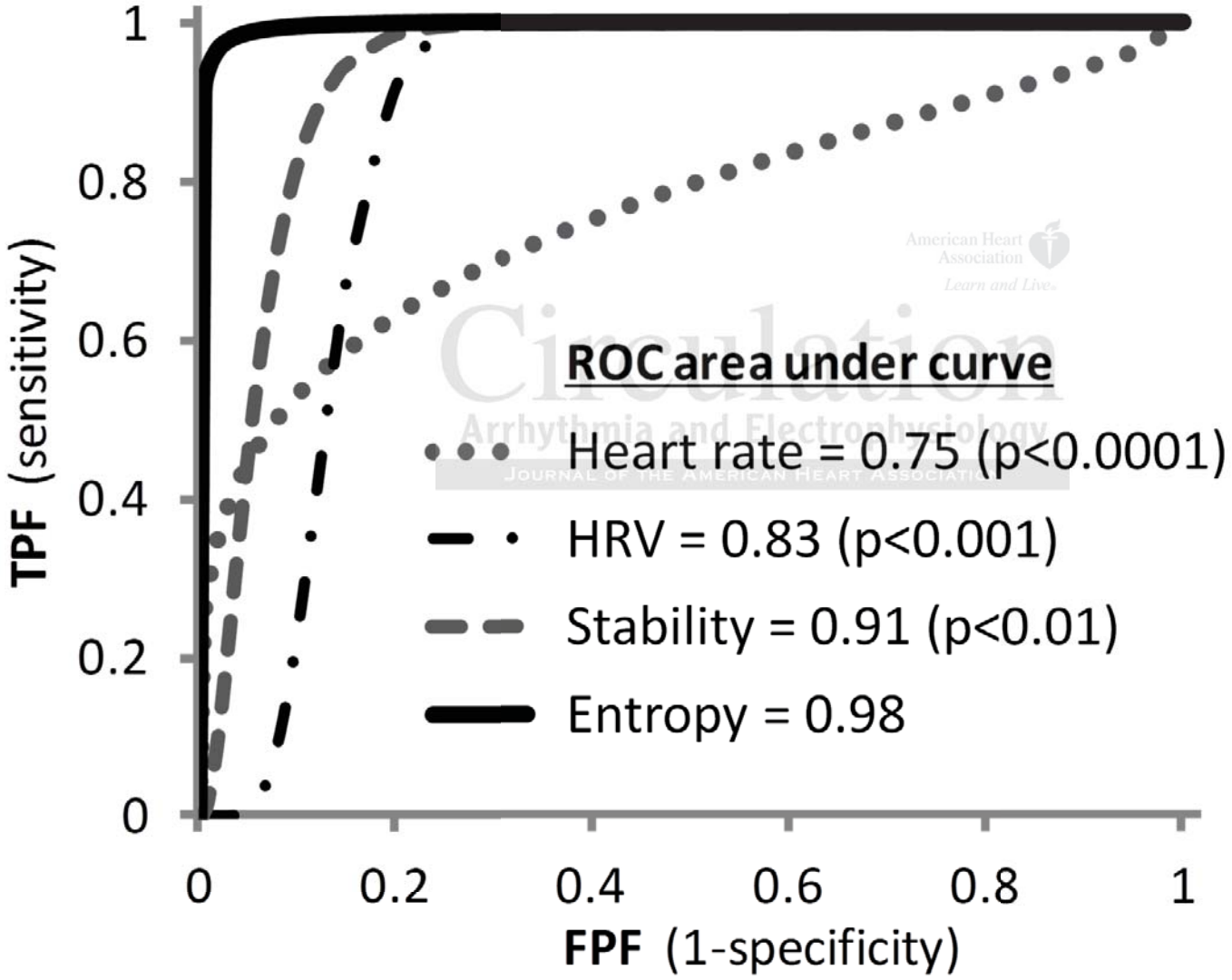
indicated by the bold symbols. Although the AF and VT were indistinguishable based on stability and heart rate, the entropy of AF (-0.999) was significantly higher than that of the VT (-1.89). **B.** The ROC curves for discrimination of AF from SVT/VT/VF by heart rate, HRV, stability, and entropy. The 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 bpm) 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.



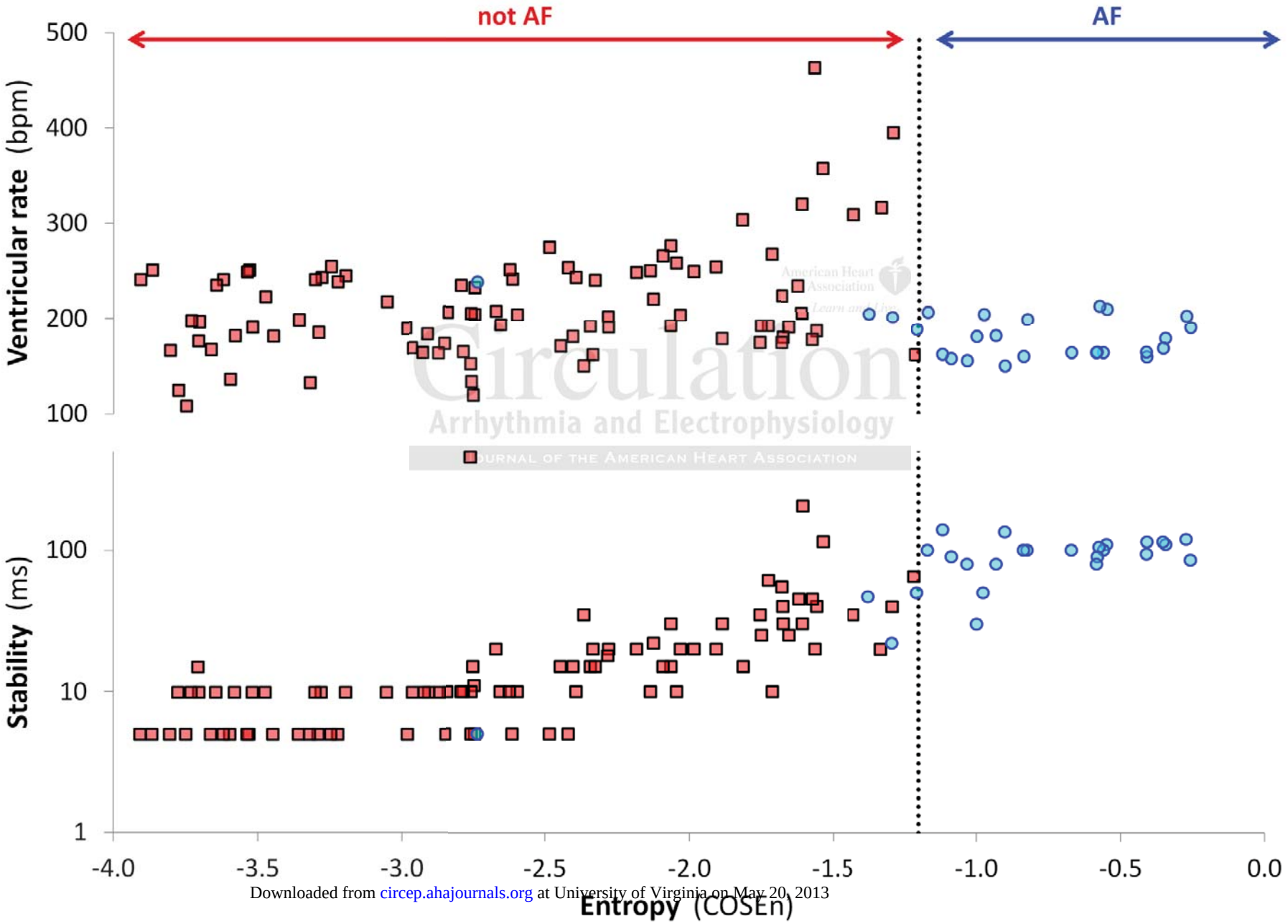
a. AF and VT with the same heart rate and stability, but distinct entropy



b. ROC curves for discrimination of AF



c. *Distribution of ventricular rate and stability as a function of entropy*



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 [8].

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 $\boldsymbol{r}$, and the degree of entropy is calculated as the adjusted conditional probability of subsequent matches exceeding a given threshold [8]. This threshold was pre-determined by applying the method of equal proportion of misclassifications [9] to a different patient dataset of 24 hour Holter surface ECG recordings [8] with a prevalence of AF that is similar to this study.

For a segment length of $\boldsymbol{n}$ beats, the entropy calculation starts with calculating the differences between the $[\boldsymbol{n} \times (\boldsymbol{n} - 1) \div 2]$ pairs of intervals (i.e., 36 pairs in a 9-beat segment), comparing each pair to the *tolerance window* $(\mathbf{2} \times \boldsymbol{r})$, and then deciding if a match has been made. The result is a conditional probability. If $\boldsymbol{A}$ is equal to the number of pairs of intervals that match and $\boldsymbol{B}$ is the subset of $\boldsymbol{A}$ in which the next pairs also match, sample entropy is $[-\ln(\boldsymbol{A} \div \boldsymbol{B})]$ where $\ln$ is the natural logarithm [10-13]. 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 $\boldsymbol{r}$ and template length $\boldsymbol{m}$, the *matching volume* is $(\mathbf{2} \times \boldsymbol{r})^{\boldsymbol{m}}$]. Normalizing for the *matching volume* allows comparison of entropy estimates made with different values of $\boldsymbol{r}$ [8].

The value of $\boldsymbol{r}$ is an important factor for determining the underlying dynamics of a segment of intervals. If $\boldsymbol{r}$ is too small (i.e., smaller than the typical noise amplitude), then pairs of intervals that are similar shall fail to match. However, if $\boldsymbol{r}$ 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 $\boldsymbol{r}$ with the scale of signal noise such that $\boldsymbol{r}$ 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

intervals	335	335	345	320	395	325	315	330	285
335	0								
335	0	0							
345	10	10	0						
320	-15	-15	-25	0					
395	60	60	50	75	0				
325	-10	-10	-20	5	-70	0			
315	-20	-20	-30	-5	-80	-10	0		
330	-5	-5	-15	10	-65	5	15	0	
285	-50	-50	-60	-35	-110	-40	-30	-45	0

Next, we seek matches within a certain tolerance $\boldsymbol{r}$ for template lengths $\boldsymbol{m}$ (a single interval) and $\boldsymbol{m} + \mathbf{1}$ (two consecutive intervals). Previously, in a different dataset of 24 hour Holter surface ECG recordings [8], we established that $\boldsymbol{m} = 1$ is suitable for AF detection. Because the resolution of the EGM data in this study is ≤5 msec, we limited values for the tolerance $\boldsymbol{r}$ 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 $\boldsymbol{r} = 22.5$ 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 $\boldsymbol{m} = 1$.

Supplementary Table 2

intervals	335	335	345	320	395	325	315	330	285
335	0								
335	1	0							
345	1	1	0						
320	1	1	0	0					
395	0	0	0	0	0				
325	1	1	1	1	0	0			
315	1	1	0	1	0	1	0		
330	1	1	1	1	0	1	1	0	
285	0	0	0	0	0	0	0	0	0

In the next step, we determine whether a match for a template of length $\boldsymbol{m} = 2$ occurs when a value of 1 has occurred for $\boldsymbol{m} = 1$ (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 ($345 - 335 < 22.5$)].

Supplementary Table 3

intervals	335	335	345	320	395	325	315	330	285
335	0								
335	1	0							
345	1	0	0						
320	0	0	0	0					
395	0	0	0	0	0				
325	1	0	1	0	0	0			
315	1	1	0	0	0	1	0		
330	0	0	0	0	0	0	0	0	
285	0	0	0	0	0	0	0	0	0

The conditional probability of matching at the $\boldsymbol{m+1}$ point having matched for $\boldsymbol{m}$ points, is $\boldsymbol{A} \div \boldsymbol{B} = 7 \div 19 = 0.36842$. The sample entropy (SampEn) is the negative natural logarithm of this probability:

$$\text{SampEn} = -\ln\left[\frac{\boldsymbol{A}}{\boldsymbol{B}}\right] = -\ln\left[\frac{7}{19}\right] = 0.99853$$

The quadratic sample entropy (QSE), which normalizes for $\boldsymbol{r}$, is:

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

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:

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

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

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 $\boldsymbol{r}$ leading to a numerator count of 5 is $\boldsymbol{r} = 17.5$ msec. The mean interval is 335.56 msec. The COSEn calculation for the VT record is:

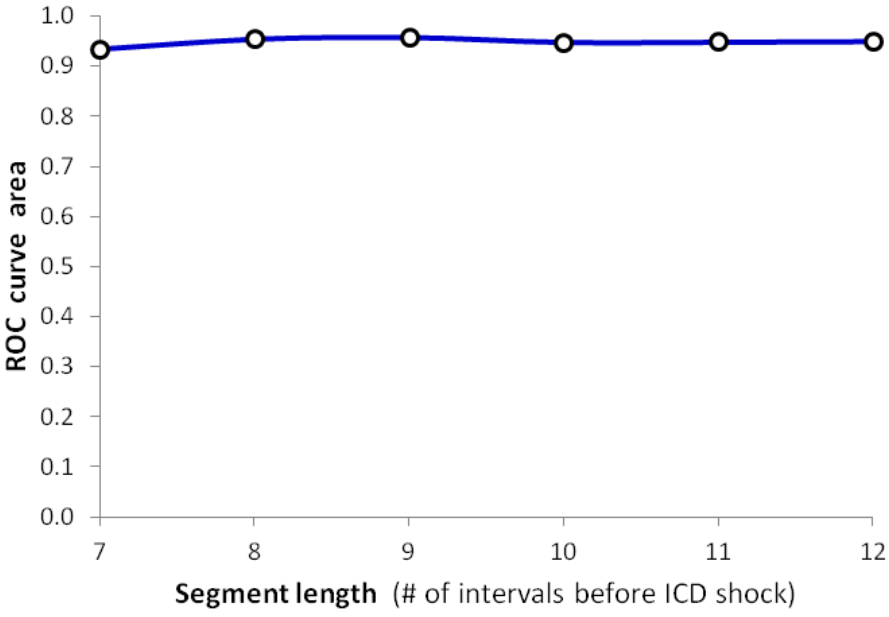
$$\mathrm{COSEn} = -\ln\left[\frac{\boldsymbol{A}}{\boldsymbol{B}}\right] + \ln[(2 \times \boldsymbol{r})^{\boldsymbol{m}}] - \ln[\text{average interval}]$$

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

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



References

1. Pincus SM, Goldberger AL. Physiological time-series analysis: What does regularity quantify? *Am J Physiol*. 1994;266:H1643-1656

2. Kaplan DT. The analysis of variability. *J Cardiovasc Electrophysiol*. 1994;5:16-19

3. Lake DE. Nonparametric entropy estimation using kernel densities. *Methods Enzymol*. 2009;467:531-546

4. Lake DE. Improved entropy rate estimation in physiological data. *Conf Proc IEEE Eng Med Biol Soc*. 2011;2011:1463-1466

5. Lake DE. Renyi entropy measures of heart rate gaussianity. *IEEE Trans.Biomed Eng.* 2006;53:21-27

6. Pincus SM. Approximate entropy as a measure of system complexity. *Proc Natl Acad Sci U S A*. 1991;88:2297-2301

7. Richman JS, Moorman JR. Physiological time-series analysis using approximate entropy and sample entropy. *Am J Physiol Heart Circ Physiol*. 2000;278:H2039-2049

8. Lake DE, Moorman JR. Accurate estimation of entropy in very short physiological time series: The problem of atrial fibrillation detection in implanted ventricular devices. *Am J Physiol Heart Circ Physiol*. 2011;300:H319-325

9. Colquhoun D, Sakmann B. Fast events in single-channel currents activated by acetylcholine and its analogues at the frog muscle end-plate. *J Physiol*. 1985;369:501-557

10. Richman JS, Moorman JR. Physiological time series analysis using approximate entropy and sample entropy. *American Journal of Physiology*. 2000;278:H2039-H2049

11. Lake DE, Richman JS, Griffin MP, Moorman JR. Sample entropy analysis of neonatal heart rate variability. *American Journal of Physiology*. 2002;283:R789-R797

12. Richman JS, Lake DE, Moorman JR. Sample entropy. *Methods Enzymol.* 2004;384:172-184

13. Richman JS. Sample entropy statistics and testing for order in complex physiological signals. *Communications in statistics - theory and methods*. 2007;36:1005-1019