PAPER

Local dynamics of heart rate: detection and prognostic implications

IOP Publishing | Institute of Physics and Engineering in Medicine Physiological Measurement

Physiol. Meas. **35** (2014) 1929–1942 doi:10.1088/0967-3334/35/10/1929

Local dynamics of heart rate: detection and prognostic implications

Travis J Moss[1,2], Douglas E Lake[1] and J Randall Moorman[1]

[1] Cardiovascular Division, Department of Internal Medicine, and Cardiovascular Research Center, University of Virginia Health System, Charlottesville, VA 22908, USA
[2] Department of Medicine, University of Colorado School of Medicine, Aurora, CO 80045, USA

E-mail: dlake@virginia.edu

Received 6 July 2013, revised 14 December 2013
Accepted for publication 08 January 2014
Published 17 September 2014

Abstract

The original observation that reduced heart rate variability (HRV) confers poor prognosis after myocardial infarction has been followed by many studies of heart rate dynamics. We tested the hypothesis that an entropy-based local dynamics measure gave prognostic information in ambulatory patients undergoing 24-h electrocardiography. In this context, entropy is the probability that short templates will find matches in the time series. We studied RR interval time series from 24-h Holter monitors of 1564 consecutive patients over age 39. We generated histograms of the count of templates as a function of the number of templates matches in short RR interval time series, and found characteristic appearance of histograms for atrial fibrillation, sinus rhythm with normal HRV, and sinus rhythm with reduced HRV and premature ventricular contractions (PVCs). We developed statistical models to detect the abnormal dynamic phenotype of reduced HRV with PVCs and fashioned a local dynamics score (LDs) that, after controlling for age, added more prognostic information than other standard risk factors and common HRV metrics, including, to our surprise, the PVC count and the HRV of normal-to-normal intervals. Addition of the LDs to a predictive model using standard risk factors significantly increased the ROC area and the net reclassification improvement was 27%. We conclude that abnormal local dynamics of heart rate confer adverse prognosis in patients undergoing 24-h ambulatory electrocardiography.

Keywords: heart rate variability, sample entropy, atrial fibrillation, risk factor, prognosis, ectopy

(Some figures may appear in colour only in the online journal)

1. Introduction

Low heart rate variability (HRV), measured by the standard deviation of normal-to-normal RR intervals (SDNN) independently predicts mortality after acute myocardial infarction and in chronic congestive heart failure (Bilchick *et al* 2002, Kleiger *et al* 1987). This phenomenon is generally understood to represent an alteration of heart rate (HR) control by the autonomic nervous system, and can result in a decreased threshold for fatal ventricular tachyarrhythmias (Kleiger *et al* 1990). Similarly, premature ventricular contractions (PVCs) portend adverse prognosis in heart failure (Le *et al* 2010). These two distinct electrocardiographic features of heart disease have contrasting influences on HRV metrics such as standard deviation (SD), range, and the pNNx family of measures (Mietus *et al* 2002). Qualitatively, though, the local dynamics (LD) of an unvarying HR punctuated by occasional outlying ectopic beats are distinctly different from both normal sinus rhythm (SR) and atrial fibrillation (AF).

When the EKG is available, it is straightforward to classify all beats in order to remove (and count) the PVCs, and to calculate the standard deviation of normal-to-normal intervals (SDNN). Cardiac monitoring, though, is increasingly available in other ways such as single lead implantable cardioverter-defibrillator devices and pulse oximeters in which ectopic beats are not labeled. Accordingly, we studied measures of local dynamics of HR that can be applied to very short series without knowing whether or not PVCs are present. We hypothesized that abnormal local dynamics, exemplified by PVCs in the setting of reduced baseline HRV, convey important prognostic information. Because of the potential utility of such a prognostic measure in cardiac implanted electronic devices, we optimized metrics for very short series measured only intermittently.

The context of this investigation is our overarching hypothesis that human illness, especially early in its course, may lead to momentary disruptions of finely adaptive physiological systems such as HR control. This has led us, as well as others, to speculate about how organs signal to each other during health (Godin and Buchman 1996), how this signaling leads to changes in variability and entropy of continuous physiological signaling during illness (Godin *et al* 1996, Goldberger *et al* 2002), and how advanced time series analysis to detect these changes can play a role in patient care (Buchman 2004, Cao *et al* 2004, Griffin *et al* 2004, 2005, Griffin, Lake and Moorman 2005). In particular, we and others have measured entropy of HR time series as a means of weighing the density of the inter-organ signaling that is the hallmark of good health (Costa, Goldberger and Peng 2005a, Lake *et al* 2002, Moorman *et al* 2011, Richman and Moorman 2000, Richman, Lake and Moorman 2004). The central exercise is to count the number of short templates of HR values that repeat in a short period of time. More repetition implies coupling of periodic processes among organs—e.g. in health the HR follows the periodicity of breathing to produce the familiar respiratory sinus arrhythmia–and leads to higher levels of HRV but lower values of entropy.

In this scheme, AF is an anomaly. The HRV is very high, but, since HR control is uncoupled from other organ function, the entropy is also very high. We have exploited this feature to develop the coefficient of sample entropy (COSEn), an optimized measure for detection of AF in very short time series (DeMazumder *et al* 2013, Lake and Moorman 2011). Here we envision a two-step approach of using entropy-based measures of heart rate in clinical practice. The first step is to detect AF; the second is to further characterize the HR time series by its local dynamics.

The new idea in this work arises not from the entropy itself, but from the ways in which templates match each other not only according to the rhythm, but also according to the presence of low HRV and PVCs. For example, low HRV should lead to frequent matching of templates with each other. The expected number of matches for a PVC or its compensatory

pause, on the other hand, is much lower. We devised an entropy-based measure that captures these abnormal local HR dynamics, and tested its relevance to outcome of patients whose physicians ordered 24-h ambulatory Holter monitoring.

2. Methods

2.1. Study population

We studied 1564 consecutive patients of age more than 39 years from a database of 2440 patients of all ages for whom University of Virginia Health System physicians ordered Holter monitoring from December 2004 to October 2010. The age criterion reflects the low incidence of chronic heart diseases such as AF and congestive heart failure (CHF) before the age of 40 (Lake and Moorman 2011, Mietus *et al* 2002). Common reasons for ordering the Holter studies included palpitations (40%) or syncope and dizziness (12%). 122 patients (7.8%) went on to have additional Holter studies during this time period, in which case we used the first. The University of Virginia Institutional Review Board gave permission for this study.

2.2. Clinical data

Common risk factors and mortality status, including date of death, were obtained using ICD-9 codes to query the University of Virginia Clinical Data Repository (CDR), an electronic data warehouse. These categorical variables included gender, hypertension, hyperlipidemia, CHF, history of AF, diabetes mellitus, history of tobacco use, presence of cardiac pacemaker, and history of coronary heart disease as manifested by either coronary artery bypass graft (CABG) or percutaneous transluminal coronary intervention (PTCI) as recorded during visits to University of Virginia cardiologists. As detailed in table 1, the prevalence of chronic disease in this otherwise unselected population with a mean age of 65 years is consistent with that seen in the general population with the exceptions of more patients with a history of atrial fibrillation (41%) and congestive heart failure (26%). 445 patients (28%) had definitive evidence of coronary heart disease and had undergone CABG or PTCI.

2.3. Heart rate metrics

We collected files of RR intervals and beat labels from the Philips Holter system, and calculated standard HR and HRV metrics such as mean and standard deviation, range, trimmed range (next-to-longest interval minus next-to-shortest), pNN20 (the mean number of times in which the change in successive normal sinus (NN) intervals exceeded 20 ms) (Mietus *et al* 2002) and number of intervals labeled as PVCs.

2.4. Detection of atrial fibrillation

We estimated entropy of the RR intervals using COSEn (Lake and Moorman 2011), a metric derived from sample entropy (SampEn) (Richman and Moorman 2000) that is optimized for the rapid detection of AF (DeMazumder *et al* 2013). These entropy metrics rely on counts of m-long templates matching within a tolerance r that also match at the next, or $m + 1$st point. Generally, AF is characterized by higher entropy than SR, and we used the value of −1.4 as the cutoff (Lake and Moorman 2011).

Table 1. Baseline characteristics of patient population.

	Atrial Fibrillation (n = 170)		Sinus Rhythm (n = 1394)	
Age (years)	71.4	±11.1	63.7	±13.2
Gender (male)	101	59%	618	44%
Hypertension	133	78%	939	67%
Hyperlipidemia	111	65%	841	60%
History of AF	155	91%	488	35%
CABG or PTCI	56	33%	389	28%
History of tobacco use	34	20%	351	25%
Diabetes mellitus	51	30%	352	25%
History of CHF	74	44%	325	23%
Prior pacemaker	29	17%	139	10%
Mean heart rate (bpm)	74.9	±12.1	84.4	±14.3
Standard Deviation (ms)	168.2	±53.7	51.7	±49.6
Range (ms)	538	±161	168	±147
Trimmed Range (ms)	379	±129	107	±109
pNN20	0.1	±0.1	0.7	±0.2
PVC	1.1	±2.1	0.6	±1.4
COSEn	–0.6	±0.4	–2.6	±0.4
Deaths	44	26%	170	12%
Follow-up time of survivors (years)	4.1	±2.0	4.5	±1.7

Age > 39 years, n = 1564. Values are expressed as either mean ± standard deviation or number and percentage. All heart rate metrics are reported as the mean of hourly 12-point samplings from a 24-h record. AF indicates atrial fibrillation; CABG, Coronary Artery Bypass Graft; PTCI, Percutaneous Transluminal Coronary intervention; bpm, beats per minute; ms, milliseconds.

2.5. Local dynamics score: an example of the analysis

Figures 1(*a*)–(*c*) show 5-min plots of RR intervals as a function of time from the canonical MIT-BIH Holter databases, for AF (*a*), SR with normal HRV (*b*) and SR with abnormal local dynamics of reduced HRV and VE in a patient with CHF (*c*). The analytic strategy was to parse the corresponding 24-h record into piecewise continuous 500-beat segments, and in each to count the number of matches for every template of length 2 beats, where the tolerance for matching was 20 ms. This corresponds to the first step of entropy estimation using parameters m = 2 beats and r = 20 ms (Richman, Lake and Moorman 2004, Richman and Moorman 2000).

Figures 1(*d*)–(*f*) show averaged histograms of the number of templates as a function of number of template matches for the corresponding 24-h Holter recordings. The ordinate is the natural logarithm of the count, and the bin width is 10 points. In AF (*d*), as expected, most templates find very few matches. In SR with normal HRV (*e*), most templates find 150 or fewer matches among the 498 other 2-beat templates.

The most important finding is shown in panel (*f*). The distribution of counts of template matches is bimodal, with some templates finding very few matches, and others finding very many, approaching the maximum of 498. The count in the left-most bin comes from beats that find the fewest matches i.e. from beats that are outliers. Clinically, we know these to be ectopic beats e.g. PVCs and the ensuing pauses. On the other hand, the counts in the right-most bins inform about points that have many matches. Clinically, we know these to belong to the low variability baseline. Taken together, these findings in the histogram detect abnormal local dynamics, or the coexistence of reduced heart rate variability with ectopic beats.

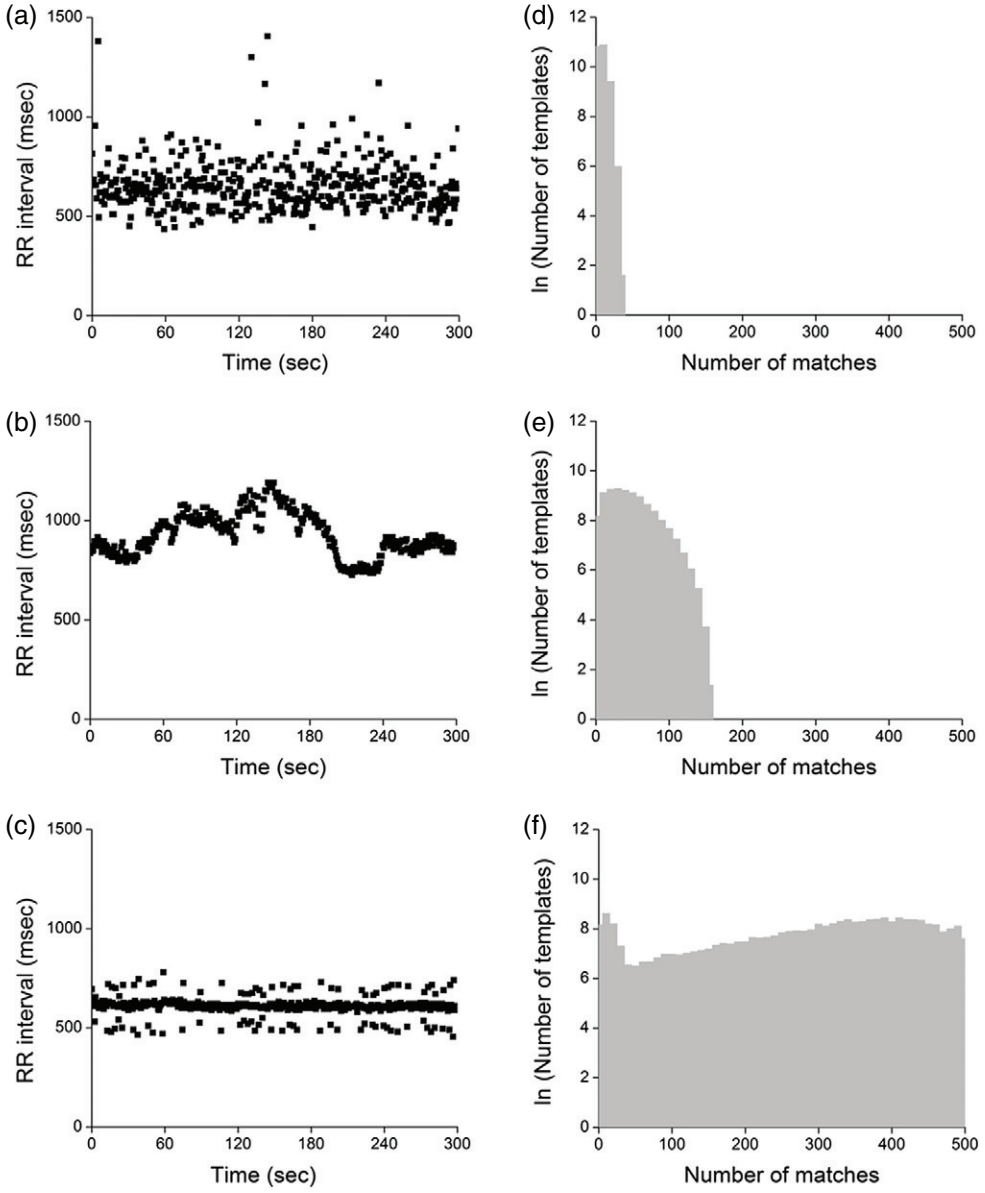

Figure 1. Left: Plots of RR intervals over 5 min segments extracted from 24-h MIT-BIH Holter database recordings from patients with AF, sinus rhythm and no heart disease, and sinus rhythm with congestive heart failure. Right: Averaged histograms of the number of templates as a function of the number of matches for all 500 beat segments of the corresponding Holter studies. The ordinate is the natural logarithm.Atrial fibrillation (panels (*a*) and (*d*)) with widely varying RR intervals produces a histogram shifted to the left, where templates find few matches.Normal sinus rhythm with normal variability (panels (*b*) and (*e*)) produces a histogram where more templates find more matches than in AF.Sinus rhythm in a patient with CHF (panels (*c*) and (*f*)) leads to abnormal local dynamics—low variability RR intervals with shorter intervals below and longer intervals above, representing PVCs and their compensatory pauses. The resulting histogram has distinctive shape, capturing both ectopic templates that find few matches on the left side, and templates in the baseline that find many matches on the right.

Motivated by the possibility of implementation in implanted devices, we investigated whether these findings were present in shorter time series. Figures 2(*a*)–(*c*) show that the distinctive histogram anatomy is preserved in the averaged histograms of 12-beat segments sampled once per hour. Because of the limited number of points, we used template length $m = 1$ beat. The bin counts represent the numbers of beats that match each other 0 times, 1 time, 2 times, et cetera, up to 11 times, respectively, as given by the bin labels. The abnormal features of figure 2(*c*) are the higher-than-expected counts in bin 0, representing ectopic beats, and in bins 10 and 11, which represent reduced HRV.

To detect this phenotype quantitatively, we used Cox proportional hazards modeling of survival and found an optimal linear combination using the counts in bins 0, 10 and 11 as predictors. The linear combination of these counts maintained statistical significance after adding age and standard HRV metrics such as mean, standard deviation (SD), and trimmed range. The resulting coefficients were normalized so as to sum to 1. The LD score is the sum of the products of the coefficients and the bin counts; thus a uniform distribution of templates matches where the counts in all bins equal 1 leads to a LD score of 1. Lower scores imply a centrally focused histogram distribution, and higher scores imply a distribution focused on either or both extremes of the histogram.

2.6. Patient groups

We divided patients into three mutually exclusive groups. As the prognosis of patients with atrial fibrillation is poorer than those without, we first selected and grouped all patients with atrial fibrillation as detected by COSEn ($n = 170$). From the remaining patients without AF, we selected and grouped all patients in the highest quintile (20%) of local dynamics score ($n = 279$). The 1115 patients that remain are without atrial fibrillation or abnormal local dynamics and comprise our reference group. Table 2 shows the baseline characteristics of the patient population.

2.7. Statistical analysis

We used analysis of variance (ANOVA; Minitab 16) to compare baseline demographics, standard risk factors for heart disease, HRV parameters and mortality rates in the three groups (AF, SR with highest quintile of LDs, and all other SR). We used the *coxph* procedure in R 3.0.0 for univariate and multivariate Cox proportional hazards modeling to test association of predictors with survival. Patients not reaching an outcome were censored at the last documented follow-up date in the CDR database. To test the significance of information added by the new measure, we compared a model based on standard risk factors alone to one that added the LDs. The level of statistical significance was a two-sided $p < 0.05$.

3. Results

3.1. Patient groups

Age, history of CHF, pNN20, COSEn, and LDs differed amongst the 3 groups (see table 2). Hypertension, diabetes mellitus, prior pacemaker, and mean HR differed between the reference

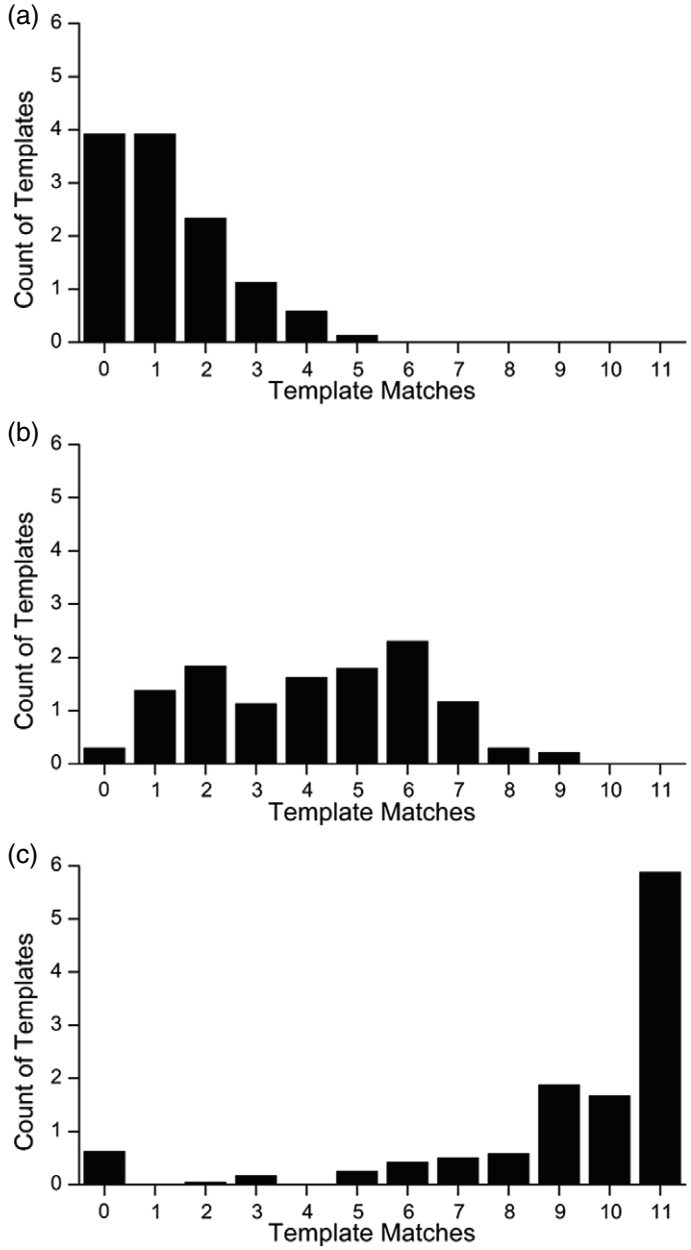

Figure 2. Averaged histograms of the number of templates as a function of the number of matches for 12 beat segments sampled hourly in the Holter studies shown in figure 1. The phenotypic differences persist among AF (*a*), SR with normal HRV (*b*) and SR with abonormal local dynamics (*c*). The LD score is the weighted sum of the counts in the bins that represent PVCs and compensatory pauses (bin 0) and low baseline HRV (bins 10 and 11).

and LD groups. These along with standard HRV metrics (SD, trimmed range, and PVC count) were considered as candidates for our multivariate models to predict death based on both clinical risk factors and Holter measures. In the analysis that follows, we describe only the 1394 patients with SR.

Table 2. ANOVA comparison of groups.

	Reference Group: SR, lower 80% LDs (n = 1115)		AF (n = 170)		LD Group: SR with highest 20% LDs (n = 279)		ANOVAresults
Age (years)	63.2	±13.2	71.4	±11.1	65.9	±12.9	RA, RL, AL
Gender (male)	488	44%	101	59%	130	47%	RA, AL
Hypertension	725	65%	133	78%	214	77%	RA, RL
Hyperlipidemia	659	59%	111	65%	182	65%	NS
History of AF	378	34%	155	91%	110	39%	RA, AL
CABG or PTCI	299	27%	56	33%	90	32%	NS
History of tobacco use	271	24%	34	20%	80	29%	AL
Diabetes mellitus	253	23%	51	30%	99	35%	RA, RL
History of CHF	241	22%	74	44%	84	30%	RA, RL, AL
Prior pacemaker	102	9%	29	17%	37	13%	RA, RL
Mean heart rate (bpm)	69.9	±9.6	74.9	±12.1	75.9	±12.5	RA, RL
Standard Deviation (ms)	51.7	±45.5	168.2	±53.7	52.1	±63.5	RA, AL
Range (ms)	167	±131	538	±161	172	±200	RA, AL
Trimmed Range (ms)	107	±100	379	±129	107	±139	RA, AL
pNN20	0.7	±0.2	0.1	±0.1	0.8	±0.2	RA, RL, AL
PVC	0.6	±1.4	1.1	±2.1	0.8	±1.4	RA, AL
COSEn	−2.5	±0.4	−0.6	±0.4	−2.8	±0.6	RA, RL, AL
LDs	0.9	±0.3	2.1	±0.5	1.6	±0.2	RA, RL, AL
Deaths	109	10%	44	26%	61	22%	
Follow-up time of survivors (years)	4.5	±1.6	4.1	±2.0	4.3	±1.9	

Values are expressed as either mean ± standard deviation or as number and percentage; total n = 1564. All heart rate metrics are reported as the mean of hourly 12-point samplings from a 24-h record. Ages < 40 years excluded. ms indicates milliseconds; ANOVA, analysis of variance; NS, not significant; RA, reference and AF groups significantly different; RL, reference and LD groups significantly different; AL, AF and LD groups significantly different.
AF indicates atrial fibrillation; CABG, coronary artery bypass grafting; PTCI, percutaneous transluminal coronary intervention; CHF, congestive heart failure; pNN20, percentage of intervals between normal beats differing by more than 20 ms; PVC, premature ventricular contraction; COSEn, coefficient of sample entropy; LDs, local dynamics score.

3.2. Survival

There were 214 deaths during the mean follow-up time of 4.5 years, 170 of them in patients with SR. Figure 3 shows the distribution in LDs for survivors and non-survivors, demonstrating the increased proportion of non-survivors with higher scores. Figure 4(*a*) shows survival by quintile of the LD score. The survival is reduced in the highest quintile, and we compared this group of patients with highest LD scores to the remaining 80%. The LDs value of 1.41 was used as a cutoff. Figure 4(*b*) shows that mortality was highest in patients with AF (26%), next-highest in patients with SR but in the highest quintile of LD scores (22%), and lowest in the remaining patients with SR (10%).

In univariate Cox proportional hazards models, age, hypertension, diabetes mellitus, history of tobacco use, history of CHF, prior pacemaker, and COSEn all achieved statistical significance, as did LDs (table 3). Surprisingly, hyperlipidemia, mean HR, pNN20, PVC count, SD, and trimmed range did not. In multivariate analysis, only age, history of tobacco use, history of CHF, and LDs retained statistical significance as mortality predictors.

3.3. Evaluation of LDs as a novel risk marker

We followed the guidelines of Hlatky and coworkers in evaluating the information added by LDs to standard risk factors for death (Hlatky *et al* 2009). We compared the results of Cox models that used standard risk factors to a model that additionally incorporated LDs and calculated change in c-statistic and net reclassification improvement. The standard risk factors

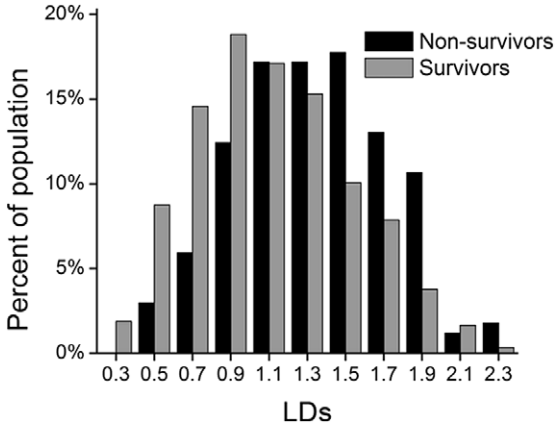

Figure 3. Frequency histograms of LD score in survivors and non-survivors. An LD score greater than 1 reflects reduced HRV and VE.

were those that met statistical significance in univariate testing–age, hypertension, diabetes, hyperlipidemia, history of tobacco use and history of CHF. The addition of LDs to the prognostic model improved the c-statistic by 0.018, from 0.758 to 0.776.

We analyzed reclassification of patients based on addition of LDs to the predictive model (table 4). Figure 4(*c*) shows survival after reclassification by adding LDs to standard risk factors. The results are consistent with the expectation of better survival prediction using LDs as an additional predictor. The net reclassification index (NRI) using LDs as a continuous variable was 26.9% (Pencina, D'Agostino Sr and Steyerberg 2011).

4. Discussion

The key finding of this study is that the local dynamics of heart rate are strong independent predictors of mortality in patients undergoing 24-h ambulatory Holter monitoring. The approach, which is based on techniques of entropy estimation in physiological time series, was to count the number of closely matching templates and to inspect the histogram of the number of templates as a function of the number of matches. The major finding was that heart rate records showing both reduced heart rate variability and the presence of ectopic beats had distinctive appearance of the histogram. These features were present even in analysis of 12-beat segments, an appealing length for use in implantable devices. We used survival analysis to devise a simple local dynamics score (LDs), and showed that it effectively identified patients at highest risk of all-cause mortality within 4 years. Since the LDs added significant information in a multivariable statistical model that included both the number of PVCs and the standard deviation of normal-to-normal beats (SDNN), we conclude there may be other dynamical features of the time series that are captured in the score.

We find promise for clinical utility for entropy-based measures of HR time series from EKG monitoring. We propose a two-step process, in which AF is first detected by the finding of high entropy. If AF is absent, then local dynamics analysis adds information about prognosis. An important strength is that the methods are based entirely on RR interval time series, and require no physician or machine interpretation of rhythm or counting of PVCs. Reports from Holter monitoring might include these kinds of findings:

'AF absent, risk of death in nth quintile' or 'AF present, no further dynamical analysis'

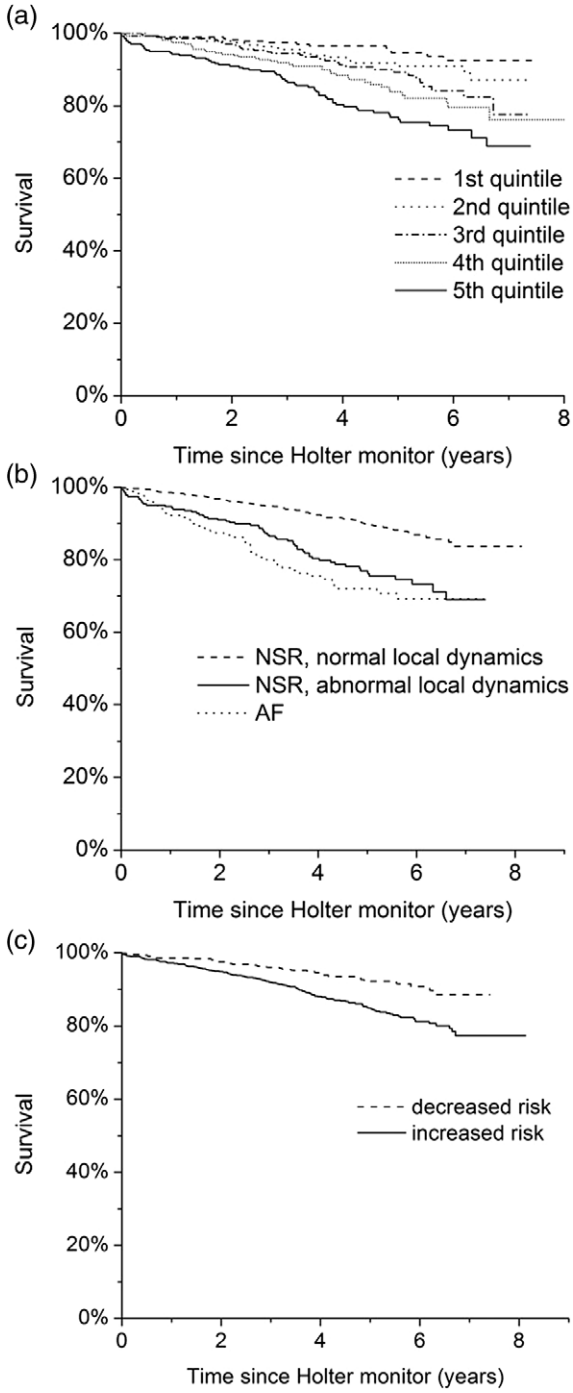

Figure 4. Survival plots based on LD score and entropy. (*a*) Survival by quintiles of LD score, lowest survial rate in patients classified in the highest LDs quintile (solid line). (*b*) Survival by diagnosis of AF (dotted line), SR with highest quintile of LD score (solid line) and SR with lower LD score (dashed line). (*c*) Survival after reclassification by adding LD score to a standard risk factor prediction model. There was a higher survival rate in patients reclassifed to lower risk (dashed line) than to high (solid line).

Table 3. Univariate & Multivariate Cox proportional hazards models.

	Univariate Model			Multivariate Model		
	Hazard Ratio	X^2	*p* Value	Hazard Ratio	X^2	*p* Value
Age (years)	1.067	103	<0.0001	1.061	67.4	<0.0001
Hypertension	2.805	21.9	<0.0001	1.229	0.7	0.4050
Diabetes mellitus	1.962	18.6	<0.0001	1.323	2.7	0.1002
History of tobacco use	2.316	29.53	<0.0001	1.752	11.2	0.0008
Hyperlipidemia	1.679	8.74	0.0031	0.899	0.3	0.5854
History of CHF	2.737	42.8	<0.0001	1.592	7.4	0.0066
Pacemaker	2.207	17.4	<0.0001	1.150	0.5	0.4825
Mean heart rate (bpm)	1.000	0.8	0.3716			
Standard Deviation	1.002	2.92	0.0876			
Trimmed Range	1.001	1.61	0.2046			
PVCs	1.082	3.11	0.0779			
PNN20	0.877	0.1	0.7522			
COSEn	0.605	7.9	0.0049	0.838	1.3	0.2504
LDs	3.242	43.9	<0.0001	2.245	16.7	<0.0001

Only variables with ANOVA showing significant difference between reference and LD groups (RL) from Table 2 were included in regression analysis along with standard HRV metrics (Standard Deviation, Trimmed Range, PVCs). $n = 1394$, deaths = 170. Patients with AF detected by COSEn > − 1.4 were excluded.
CHF indicates congestive heart failure; pNN20, percentage of intervals between normal beats differing by more than 20 ms; PVC, premature ventricular contraction; COSEn, coefficient of sample entropy; LDs, local dynamics score.

Table 4. Reclassification after addition of LDs.

Model without LDs		Risk reclassification in model with LDs	
		Lower	Higher
Deaths	170	31	139
Non-deaths	1224	388	836

In sinus rhythm, HR dynamics result from the interaction of the sinus node and multiple other systems, notably the autonomic nervous system. The overall complexity of HR patterns reflects the density of the interactions, and alteration in complexity has been proposed to signify illness in humans (Buchman 2004, Godin and Buchman 1996, Godin *et al* 1996, Goldberger *et al* 2002, Goldberger, Peng and Lipsitz 2002). In adults, loss of complexity is most clearly manifest as loss of HRV (Buchman, Stein and Goldstein 2002), whether due to less vagal activity, more sympathetic activity, or both (Porta *et al* 2007). We speculate that there may be a similar kind of mechanism for the abnormal local dynamics we describe here. Other dynamical measures also show changes, including entropy, time reversibility and multifractal structure (Costa, Goldberger and Peng 2002, 2005b, Goldberger *et al* 2002, Goldberger, Peng and Lipsitz 2002b, Havlin *et al* 1999, Ivanov *et al* 1999, Nunes Amaral *et al* 1998, Schulte-Frohlinde *et al* 2002). In adults, illness can lead to decreased or increased complexity of blood pressure variability (Porta *et al* 2012). In fetuses and newborns, loss of complexity additionally entails decelerations that can be periodic (Flower *et al* 2010, Kovatchev *et al* 2003, Moorman *et al* 2011) and may be related to neonatal apnea (Lee *et al* 2012).

We have used entropy estimates of HR time series to aid in early diagnosis of neonatal sepsis and to diagnose AF in very short time series (DeMazumder *et al* 2013, Lake and Moorman 2011, Lake *et al* 2002). The technique centers on finding matching pairs of points, and calculating the conditional probability that a matching pair will be followed by another. Generally, we assume that all points in the series contribute equally—in other words, that the time series is stationary with respect to points matching each other. Were this the case, a histogram of templates as a function of matches would show a uniform distribution, and the number of matches per template should behave as a random variable with measurable probability density.

Here we show that even a short series extracted from a patient with reduced HRV and ventricular ectopy leads to a very different distribution of template matches. While RR intervals in the non-varying baseline will find many matches, there will be no matches at all for either the PVC or its compensatory pause. These and similar kinds of non-stationarity in local dynamics of cardiac rhythm such as type II AV block, multiple atrial pacemaker sites, premature atrial beats, will all disrupt the expected distribution of template match counts. The extreme example is AF, where no template finds many matches.

Thus we expect most points in a short RR interval time series to match some but not all other points. If most points find only a few matches, we diagnose AF. If most points find many matches, we expect uninterrupted low HRV. If there is a combination of some templates with no matches and some with many matches in the same short time series, we expect dynamical disruptions that are less easy to characterize—many such series will have low HRV decorated with PVCs, but others may have less well-known disruptions of short term HR dynamics.

5. Conclusions

In this large and consecutive patient population presenting for ambulatory EKG recording, the LDs was a very significant independent predictor of all cause 4-year mortality even after controlling for age and other risk factors. The surprising lack of prognostic information in conventional HRV measures such as the canonical SDNN and the number of PVCs may be due to the very short segments that we employed—only 12 beats. Such short segments are justified by the need to capture very local dynamics, and for ease of future implementation in implanted devices.

We envision implementation of entropy-based measures in future heart rate monitoring systems and devices. Because they need as few as 12 points for meaningful calculations, processor and storage requirements are minimal. They could easily be deployed to assist clinicians by alerting them to patients at high risk for mortality, thus prompting more attentive management.

Acknowledgments

Conflicts of interest: An option for the use of local dynamics score technology has been obtained by Adult Medical Predictive Devices, Diagnostics, and Displays in Charlottesville, VA. Drs. Lake and Moorman have equity and consulting agreements.

Funding sources: Supported by an American Heart Association Mid-Atlantic grant-in-aid.

References

Bilchick K C, Fetics B, Djoukeng R, Fisher S G, Fletcher R D, Singh S N, Nevo E and Berger R D 2002 Prognostic value of heart rate variability in chronic congestive heart failure (Veterans affairs' survival trial of antiarrhythmic therapy in congestive heart failure) *Am. J. Cardiol*. **90** 24–8

Buchman T G 2004 Nonlinear dynamics, complex systems, and the pathobiology of critical illness *Curr. Opin. Crit. Care* **10** 378–82

Buchman T G, Stein P K and Goldstein B 2002 Heart rate variability in critical illness and critical care *Curr. Opin. Crit. Care*. **8** 311–15

Cao H, Lake D E, Griffin M P and Moorman J R 2004 Increased nonstationarity of neonatal heart rate before the clinical diagnosis of sepsis *Ann. Biomed. Eng*. **32** 233–44

Costa M, Goldberger A L and Peng C K 2002 Multiscale entropy analysis of complex physiologic time series *Phys. Rev. Lett*. **89** 068102

Costa M, Goldberger A L and Peng C K 2005a Multiscale entropy analysis of biological signals *Phys. Rev. E Stat. Nonlin. Soft Matter Phys*. **71** 021906

Costa M, Goldberger A L and Peng C K 2005b Broken asymmetry of the human heartbeat: loss of time irreversibility in aging and disease *Phys. Rev. Lett*. **95** 198102

Demazumder D, Lake D E, Cheng A, Moss T J, Guallar E, Weiss R G, Jones S R, Tomaselli G F and Moorman J R 2013 Dynamic analysis of cardiac rhythms for discriminating atrial fibrillation from lethal ventricular arrhythmias *Circ. Arrhythm. Electrophysiol*. **6** 555–61

Flower A A, Moorman J R, Lake D E and Delos J B 2010 Periodic heart rate decelerations in premature infants *Exp. Biol. Med. (Maywood)* **235** 531–8

Godin P J and Buchman T G 1996 Uncoupling of biological oscillators: a complementary hypothesis concerning the pathogenesis of multiple organ dysfunction syndrome *Crit. Care Med*. **24** 1107–16

Godin P J, Fleisher L A, Eidsath A, Vandivier R W, Preas H L, Banks S M, Buchman T G and Suffredini A F 1996 Experimental human endotoxemia increases cardiac regularity: results from a prospective, randomized, crossover trial *Crit. Care Med*. **24** 1117–24

Goldberger A L, Amaral L A N, Hausdorff J M, Ivanov P C, Peng C K and Stanley H E 2002a Fractal dynamics in physiology: alterations with disease and aging *Proc. Natl. Acad. Sci. U. S. A*. **99** 2466–72

Goldberger A L, Peng C K and Lipsitz L A 2002b What is physiologic complexity and how does it change with aging and disease? *Neurobiol. Aging* **23** 23–6

Griffin M P, O'Shea T M, Bissonette E A, Harrell F E Jr, Lake D E and Moorman J R 2004 Abnormal heart rate characteristics are associated with neonatal mortality *Pediatr. Res*. **55** 782–8

Griffin M P, Lake D E and Moorman J R 2005 Heart rate characteristics and laboratory tests in neonatal sepsis *Pediatrics*. **115** 937–41

Griffin M P, Lake D E, Bissonette E A, Harrell F E Jr, O'Shea T M and Moorman J R 2005 Heart rate characteristics: novel physiomarkers to predict neonatal infection and death *Pediatrics* **116** 1070–4

Havlin S, Amaral L A, Ashkenazy Y, Goldberger A L, Ivanov P Ch, Peng C K and Stanley H E 1999 Application of statistical physics to heartbeat diagnosis *Physica A* **274** 99–110

Hlatky M A *et al* 2009 Criteria for evaluation of novel markers of cardiovascular risk: a scientific statement from the American Heart Association *Circulation* **119** 2408–16

Ivanov P C, Amaral L A, Goldberger A L, Havlin S, Rosenblum M G, Struzik Z R and Stanley H E 1999 Multifractality in human heartbeat dynamics *Nature* **399** 461–5

Kleiger R E, Miller J P, Bigger J T Jr and Moss A J 1987 Decreased heart rate variability and its association with increased mortality after acute myocardial infarction *Am. J. Cardiol*. **59** 256–62

Kleiger R E, Miller J P, Krone R J and Bigger J T Jr (Multicenter Post-Infarction Research Group) 1990 The independence of cycle length variability and exercise testing on predicting mortality of patients surviving acute myocardial infarction *Am. J. Cardiol*. **65** 408–11

Kovatchev B P, Farhy L S, Cao H, Griffin M P, Lake D E and Moorman J R 2003 Sample asymmetry analysis of heart rate characteristics with application to neonatal sepsis and systemic inflammatory response syndrome *Pediatr. Res*. **54** 892–8

Lake D E and Moorman J R 2011 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*. **300** H319–25

Lake D E, Richman J S, Griffin M P and Moorman J R 2002 Sample entropy analysis of neonatal heart rate variability *Am. J. Physiol. Regul. Integr. Comp. Physiol*. **283** R789–97

Le V V, Mitiku T, Hadley D, Myers J and Froelicher V F 2010 Rest premature ventricular contractions on routine ECG and prognosis in heart failure patients *Ann. Noninvasive Electrocardiol*. **15** 56–62
Lee H *et al* 2012 A new algorithm for detecting central apnea in neonates *Physiol. Meas*. **33** 1–17
Mietus J E, Peng C K, Henry I, Goldsmith R L and Goldberger A L 2002 The pNNx files: re-examining a widely used heart rate variability measure *Heart* **88** 378–80
Moorman J R, Delos J B, Flower A A, Cao H, Kovatchev B P, Richman J S and Lake D E 2011 Cardiovascular oscillations at the bedside: early diagnosis of neonatal sepsis using heart rate characteristics monitoring *Physiol. Meas*. **32** 1821–32
Nunes Amaral L A, Goldberger A L, Ivanov P C and Stanley H E 1998 Scale-independent measures and pathologic cardiac dynamics *Phys. Rev. Lett*. **81** 2388–91
Pencina M J, D'Agostino R B Sr and Steyerberg E W 2011 Extensions of net reclassification improvement calculations to measure usefulness of new biomarkers *Stat. Med*. **30** 11–21
Porta A, Gnecchi-Ruscone T, Tobaldini E, Guzzetti S, Furlan R and Montano N 2007 Progressive decrease of heart period variability entropy-based complexity during graded head-up tilt *J. Appl. Physiol*. **103** 1143–9
Porta A *et al* 2012 Short-term complexity indexes of heart period and systolic arterial pressure variabilities provide complementary information *J. Appl. Physiol*. **113** 1810–20
Richman J S and Moorman J R 2000 Physiological time-series analysis using approximate entropy and sample entropy *Am. J. Physiol. Heart Circ. Physiol*. **278** H2039–49
Richman J S, Lake D E and Moorman J R 2004 Sample entropy *Methods Enzymol*. **384** 172–84
Schulte-Frohlinde V, Ashkenazy Y, Goldberger A L, Ivanov P Ch, Costa M, Morley-Davies A, Stanley H E and Glass L 2002 Complex patterns of abnormal heartbeats *Phys. Rev. E* **66** 031901