Distribution Entropy for Short-term QT Interval Variability Analysis: A Comparison between the Heart Failure and Normal Control Groups

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Abstract

Previous studies have proved the beat to beat QT interval variability (QTV) helpful for evaluating the cardiac function. A common method for quantifying QTV is the QT variability index (QTVI). Owing to the nonlinear nature of QTV data, advanced entropy methods, such as the sample entropy (SampEn), were also used. Most recently, a novel distribution entropy (DistEn) has been reported to have superior performance compared with conventional methods for especially short length data. We thus aimed, in this study, to investigate the short-term QTV in heart failure (HF) patients by DistEn.

Thirty-four HF patients and 33 healthy subjects were studied, and their QTV series were analyzed by DistEn, and traditional SampEn, fuzzy entropy (FuzzyEn), and QTVI. Results demonstrated a significantly increased DistEn of QTV in HF group ($p < 0.001$). No significant difference was found in both SampEn and FuzzyEn between the two groups. In addition, results suggested a significantly increased QTVI in HF group ($p < 0.01$). Pearson correlation analysis showed that DistEn was significantly related to QTVI in HF group ($p < 0.05$), whereas there was no significant relation between them in healthy group. Results indicated that DistEn analysis of QTV may provide a valuable additional feature for evaluating the cardiac functioning in HF patients.

1. Introduction

Heart failure (HF) is a common cardiovascular disease that causes increasing morbidity and mortality throughout the world. Electrocardiography (ECG) signals are widely used for simply and non-invasively assessing the cardiac functioning. The ECG-derived QT intervals reflects the global depolarization and repolarization of the ventricular myocardium, physiologically. The prolongation and shortening of the QT interval are accepted as markers of repolarization abnormalities, delayed and accelerated myocardial repolarization, respectively [1]. In addition, previous studies have shown that elevated beat-to-beat QT interval variability (QTV) is associated with increased risk of sudden cardiac death in chronic heart failure [2].

In 1997, Berger et al. defined a QT variability index (QTVI) by combining the normalized QT variance and normalized heart rate variance [2] in order for quantifying the QTV. Till now, it has been applied in a wide spectrum of patient groups and played a dominant role in QTV analysis. However, due to the nonlinear nature of QTV data, this linear QTVI method may not entirely explain the information hidden in this complex series. Advanced nonlinear methods may be capable of unveiling the valuable hidden information. Recent publications have applied the approximate entropy (ApEn) and sample entropy (SampEn) for analysing QTV in such as schizophrenia patients [3], aging subjects [4], and subjects at different physiological states [5], etc. Most recently, Li et al. developed a novel distribution entropy (DistEn) based upon the probability density of inter-vector distances in the state space. DistEn has been shown superior, as compared with traditional SampEn, as well as its refined algorithm–fuzzy entropy (FuzzyEn), in analysing series with extremely short length. It also precludes the dependence upon input parameters of those SampEn-based measures [6].

Therefore, in the present study, we aimed to show the DistEn performance in the analysis of short-term QTV data in HF and normal control groups. The traditional SampEn and FuzzyEn, as well as the linear QTVI method, would also be performed for comparison purposes. We hypothesized that the DistEn may provide valuable additional feature for quantifying QTV data.

2. Methods

2.1. Subjects

Thirty-four HF patients (New York Heart Association class II-III) and 33 healthy volunteers were selected to ensure the age and gender comparability from one of our

previous clinical trials under full ethical approval from the Qilu Hospital of Shandong University. Their clinical characteristics are summarized in Table 1.

Table 1. Clinical characteristics of the subjects

Variables	Healthy volunteers	HF patients	*p* value
No.	33	34	
Men	18	21	0.55
Age (years)	56 ± 8	59 ± 9	0.29
BMI (kg/m^2)	24 ± 8	25 ± 4	0.16
SBP (mmHg)	114±13	118±14	0.23
DBP (mmHg)	72 ± 9	75 ± 9	0.18
LVEF (%)	65 ± 4	39 ± 7	<0.01

Data are presented as number or mean ± standard deviation. No. = number, BMI = body mass index, HR = heart rate, SBP = systolic blood pressure, DBP = diastolic blood pressure, LVEF = left ventricular ejection fraction.

2.2. Protocol

Examinations were performed in a quiet and warm measurement room (25 ± 3 °C) at Qilu Hospital of Shandong University, by a Cardiovascular Function Detection device (CV FD–I) produced by Huiyironggong Tech. Co. Ltd., Jinan, PR China. Each subject lay supine on a measurement bed for a 10 min rest period before the formal recording to allow cardiovascular stabilization. ECG electrodes were attached to the right wrist, the right and left ankles to acquire a standard lead-II ECG. Subjects were told to relax, breath regularly and move as little as possible during the whole measurement.

2.3. Data acquisition and preprocessing

Surface ECG signals were measured at a sampling frequency of 1 kHz for 5 min. R-wave locations in ECG were detected automatically and ectopic R-wave were removed by a data-adaptive template matching procedure [7]. The fore-and-aft R-wave positions formed RR interval and HR sequence was obtained from consecutive RR intervals. For beat-to-beat QT interval measurement, the algorithm proposed by Berger et al. [2] was applied in this work. The operator should choose the beginning and the end of a QT wave template. This algorithm found the QT interval for each beat by a template compressing-stretching model. Note that one QT interval should correspond with one RR interval. Besides, the QT interval corresponding to the ectopic R-wave should also be removed.

2.4. DistEn analysis of QTV data

For a series $\{u(i), 1 \le i \le N\}$ of N points, DistEn algorithm is summarized as follows [6].

1) Form $N-m$ vectors $X(i)$ by

$$\{X(i) = u(i), u(i+1), ..., u(i+m-1), 1 \le i \le N-m\} \quad (1)$$

here m indicates the embedding dimension.

2) Define the distance matrix $D = \{d_{i,j}\}$ between all possible pair of vectors $X(i)$ and $X(j)$ for $1 \le i, j \le N-m$, wherein

$$d_{i,j} = \max\{|u(i+k) - u(j+k)|, 0 \le k \le m-1\} \quad (2)$$

is the Chebyshev distance between $X(i)$ and $X(j)$.

3) The distribution characteristics of all $d_{i,j}$ for $1 \le i, j \le N-m$ is a full quantification of the information underlying the distance matrix D. The histogram approach is applied to estimate the empirical probability density function (ePDF) of D. If the histogram has M bins, we use $p_t, t = 1, 2, ..., M$ to denote the probability (frequency) of each bin. To reduce bias, elements with $i = j$ are excluded when estimating the ePDF.

4) Define the normalized DistEn of $u(i)$ as

$$DistEn(m) = -\frac{1}{\log_2(M)} \sum_{t=1}^{M} p_t \log_2(p_t) \quad (3)$$

In this study, we simply set M at 2^9 and m = 2. For more information on the effects of M and m, readers can refer to the study of Li et al. [6]

2.5. Traditional QTV analysis methods

Another two entropy methods–SampEn and FuzzyEn–were also performed here for comparison purposes. Details about these two measures can be found in [8, 9]. A tolerance level of r = 0.2 times the standard deviation of the QTV series under analysis and m = 2 were defined according to previous studies [8, 9].

Finally, we calculated the QTVI, which was defined by:

$$QTVI = \log_{10} \frac{QT_v / QT_m^2}{HR_v / HR_m^2} \quad (4)$$

where QT_v is the QT interval variance, QT_m is the mean QT interval, HR_v is the heart rate variance, and HR_m is the heart rate mean. The QTVI was proved to be elevated in patients with DCM [2] and other cardiovascular disease [10].

2.6. Statistical analysis

We used the SPSS software (Ver. 20.0, IBM, USA) to perform all the statistical analyses.

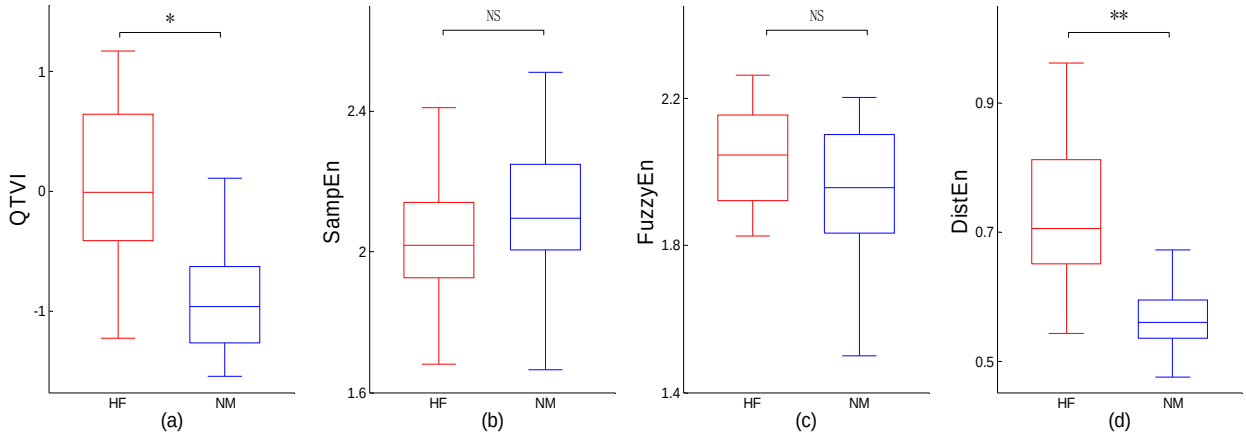

Figure 1. Box plots of QTVI (a), SampEn (b), FuzzyEn (c), and DistEn (d). HF indicates heart failure whereas NM indicates the normal control group. $**p < 0.001$; $*p < 0.01$; NS: not significant.

Four indices (QTVI, SampEn, FuzzyEn and DistEn) revealed a normal distribution after performing the Kolmogorov-Smirnov test. To examine the differences of all the four indices between HF patients and normal control groups, we performed the unpaired student's *t*-test. Furthermore, correlation between QTVI and DistEn was tested by Pearson correlation analysis. Statistical significance was accepted at $p < 0.05$.

3. Results

As shown in Figure 1 (a), significantly higher QTVI presents in HF group compared with normal control group ($p < 0.01$).

SampEn is slightly smaller in HF patients than in normal control group while there is a weak rise of FuzzyEn in HF group, as shown in Figure 1 (b) and (c). But both differences are not statistically significant (p = 0.71 and 0.32, respectively).

Figure 1 (d) shows a statistically significant increase of DistEn in HF patients compared with normal control group ($p < 0.001$).

Table 2. The correlation results.

	Normal		Heart failure	
	QTVI	DistEn	QTVI	DistEn
QTVI	1	0.016	1	0.430*
DistEn	0.016	1	0.430*	1

$*p < 0.05$

The correlation results (Table 2) show that there is no significant correlation between QTVI and DistEn in normal control group but a statistically significant correlation ($p < 0.05$) between them in HF patients.

4. Discussion and conclusion

Four methods, including the traditional QTVI, SampEn, FuzzyEn, and a novel DistEn measure, were adopted in this study for the analysis of QTV series with a view to discriminating between the HF patients and healthy control groups. Results demonstrated a statistically significantly increased QTVI in HF patients, which is in common with the previous study [11]. Besides, no significant difference was found in both SampEn and FuzzyEn between the two groups, which is probably due to the length and parameter effects. They may not perform well in short-term QTV series with relatively arbitrarily defined input parameters, including the tolerance r and the embedding dimension m. Our results revealed a statistically significantly elevated DistEn of QTV in HF patients group, which strongly support the better performance of DistEn in short data set as has already been reported by Li et al. [6].

Berger et al. first proposed QTVI in 1997 to examine QTV in patients with ischemic or non-ischemic dilated cardiomyopathies (DCM). QTVI represents a log ratio between normalized QT variance and HR variance. Since then, its clinical application has been explored in a wide spectrum of diseased states. However, two main issues that should be taken into consideration when explaining the analysis results. First, a rise in QTVI could be due to either an increase in QT variance, a decrease in HR variance, or both. It is still controversial on whether the inclusion of HR variance will dilute the performance of QTVI or not [10]. Second, it cannot explain the nonlinear feature of this complex series when only the lower-order moments are adopted.

Because of the nonlinearity of QT intervals, entropy-

based complexity analysis may provide additional insight. Note that we did not perform ApEn because the weight of self-matches in it would introduce considerable bias in small data sets [12]. However, neither SampEn nor FuzzyEn could tell the difference between heart failure and normal control groups. This may partly results from their poor statistical performances when dealing with short-term data. In data acquisition, each ECG record only lasted for 5 min (about 300–500 beats). It has been suggested that these algorithms are confined to data length and become relatively unstable in such short series [13]. Additionally, SampEn and FuzzyEn both lack consistency due to their great sensitivity to the predetermined parameters, especially threshold value *r* (similarity criterion) [14]. These limitations discount the clinical value of those traditional entropy measures. Since DistEn takes full advantage of the intrinsic information in the state space, it has significantly improved stability and consistency when analyzing series with extremely short length [6]. The increased DistEn of QTV in HF patients may indicate the lability in ventricular depolarization and repolarization. The lability is mechanically related to the increased risk of malignant ventricular arrhythmias. Thus, DistEn analysis may be potential for the clinical evaluation of cardiac dysfunction.

Our results showed a significant correlation between the DistEn and QTVI in HF group. It may partly because both the DistEn and QTVI evolve to the same direction in HR group, and partly be a chance observation. Anyway, the results indeed suggested no significant correlation between them in normal control group which strongly support our hypothesis that the DistEn analysis may be capable of providing an additional valuable feature for quantifying QTV data.

To summarize, this study suggests DistEn algorithm is a promising measure for short-term QTV analysis. It shows great potential of examining the DistEn of QTV in clinical practice for evaluating the cardiac functioning. Future studies will focus on the discriminating between the HF and normal control groups by combining DistEn and other linear or nonlinear features.

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