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# Multi-Frequency Components Entropy as Novel Heart Rate Variability Indices in Congestive Heart Failure Assessment

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**ABSTRACT** In this paper, novel heart rate variability (HRV) indices were extracted for the autonomic nervous system (ANS) activity assessment in congestive heart failure (CHF). It has been reported that CHF is a chronic cardiovascular syndrome along with ANS dysfunction, and HRV is a useful tool for ANS assessment. The multi-frequency components Entropy (MFC-En), which is obtained by the Hilbert–Huang transform and the entropy algorithm, was proposed as novel HRV indices for analyzing ANS with CHF. This paper included 24-h HRV signals of 98 subjects collected with Holter (54 healthy, 12 low-risk CHF, and 32 high-risk CHF subjects). The MFC-En indices successfully showed a statistical significance between the control and CHF groups ($p < 0.001$). The CHF classification accuracy of the MFC-En was 86.7%, while the ratio of the low- and high-frequency power was only 79.6%. Moreover, statistical significances were found among the control, low-risk CHF, and high-risk CHF groups ($p < 0.01$). Therefore, the MFC-En is a useful tool for CHF assessment that revealed the ANS of CHF patient is more activated by measuring the complexity of the rhythms changes of the ANS throughout the day.

**INDEX TERMS** Congestive heart failure (CHF), heart rate variability (HRV), Hilbert-Huang transform (HHT), instantaneous frequency (IF), multi-frequency components analysis (MFCA).

## I. INTRODUCTION

Congestive heart failure (CHF) is one of the most fatal cardiovascular diseases that is characterized by the heart losing the ability to pump enough blood to meet the metabolic requirements [1] Nearly 26 million people suffer from CHF globally [2]. The main characteristic of CHF disease is the imbalanced activity of the autonomic nervous system (ANS) [3]. The ANS can modulate the physiological arousal of a human body to meet the environmental demands through its two branches: the sympathetic nervous system (SNS) and parasympathetic nervous system (PNS) [4]

Heart rate variability (HRV) signal extracted from electrocardiogram (ECG) is widely used to assess the activity of the ANS for CHF investigation [5]. Multiple HRV indices have been used for CHF investigation because the HRV analysis is a noninvasive and useful tool for reflecting the status of the ANS [6], [7]. The standard HRV analysis methods focus on the time and frequency domain. Takase *et al.* [8] found that the values of the time domain HRV indices were significantly lower in the CHF subjects. Binkley *et al.* [9] revealed that the frequency domain HRV indices reflected the changes of the ANS and the significant difference between the healthy and CHF subjects. Yu and Lee [10] reported that the frequency domain indices were useful for discriminating the CHF subjects from the healthy subjects. Moreover, the entropy has been studied as a non-linear analysis method for CHF investigation [11]–[13]. Zhao *et al.* [14] reported that the sample entropy and fuzzy measure entropy showed a significant difference between the healthy and CHF subjects.

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These studies supported that the HRV analysis was a useful tool for CHF diagnosis.

Various studies focused on the power of HRV [15]–[17], which can reflect the tone of the ANS, may have neglected the rhythms changes of the ANS. The Hilbert-Huang transform (HHT) is a self-adaptive data analysis method that can reveal the instantaneous frequency (IF) changes of the data. Bajaj and Pachori [18] proposed a method based on the HHT for separating the rhythms of ECG signal for seizure detection, they found that each intrinsic mode function (IMF) was corresponding to different rhythms [18], which implied that the HHT may useful for rhythms analysis of bio-signal. The HHT consists of the empirical mode decomposition (EMD) method and the Hilbert transform (HT) algorithm [19]. The EMD method has been proven to be suitable for analyzing the HRV signal of ECG and decomposing the signal into a set of intrinsic mode functions (IMFs) [20]. Then, the HT can be adopted at the IMFs to reveal the instantaneous information of the signal in different frequency components. Griffel *et al.* [21] found that the HHT shows a greater sensitivity to the PNS analysis than that of the spectral analysis. Jarchi and Casson [22] showed that the HHT can be used for instantaneous heart rate estimation. Altan *et al.* [23] used the mean instantaneous frequency (MIF) of the HRV signal for CHF diagnosis. These studies supported that the HHT is a useful tool for HRV analysis, even for analyzing the rhythms changes of ANS. However, the MIF can only reflect the average level of the rhythms changes of the ANS.

Hence, multi-frequency components analysis (MFCA) was proposed to investigate the rhythms changes of the ANS and the complexity of the ANS throughout the day in this study. First, the instantaneous frequency of each component of a 5-min HRV segments were extracted by the HHT algorithm, these IF reflect the instantaneous rhythms changes of each part of the ANS. Then, the MIF of the frequency components were extracted to reflect the average level of the rhythms changes of the ANS in a 5-min period. Third, the mean value and entropy of each MIF in a 24-h period were extracted to reflect the average level and complexity of the rhythms changes of the ANS throughout the day, respectively. Finally, the indices extracted by the MFCA method were validated by CHF assessment.

## II. SYSTEM AND METHODS

In this study, a long-term HRV analysis system was proposed. The framework of the system is shown in Fig.1. First, the ECG signals were collected and the HRV signals were extracted. Then, the corrected 5-min HRV segments were obtained by preprocessing. After that, standard HRV measurements and the MFCA method were used to calculate the indices. Finally, these long-term indices were validated by a statistical analysis and CHF assessment.

### A. DATA COLLECTION

Holter is one of the most wildly used portable ambulatory electrocardiography device for monitoring the long-term

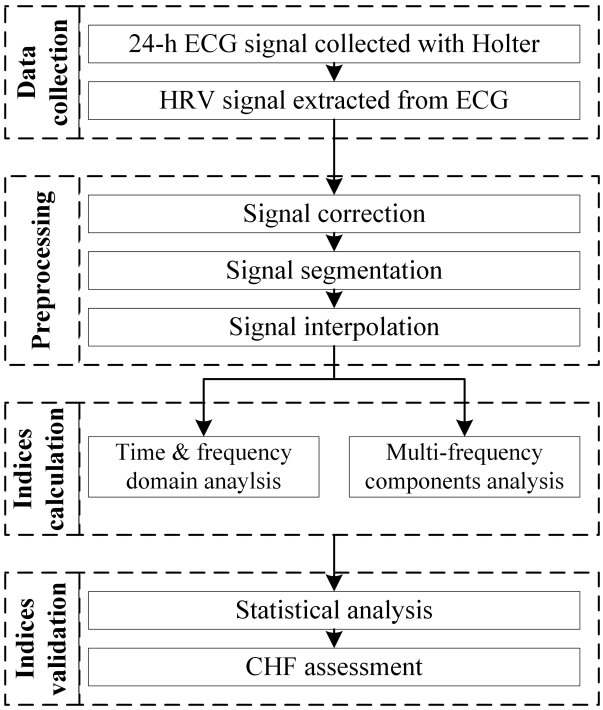


**FIGURE 1.** Framework of the proposed HRV analysis system.

(over 24-h) ECG in clinic application. In this study, the HRV signals extracted from ECG signals which collected with Holter are used for investigating [24].

The 24-h HRV signals for 54 healthy subjects (Age: 61.38 ± 11.63 years) were collected from the Normal Sinus Rhythms RR Interval database, and 44 CHF subjects (Age: 55.51 ± 11.44 years) were collected from two different databases: 15 from the Beth Israel Deaconess Medical Center (BIDMC) Congestive Heart Failure database and the remaining 29 from the Congestive Heart Failure RR Interval database. All these databases are open source in Physionet [24]–[26].

Subjects from the CHF databases were classified into 4 classes following the criterion proposed by the New York Heart Association (NYHA). Class-I represented subjects with cardiac disease; however, they did not have symptoms during physical activities. Class-II represented subjects with cardiac disease resulting in slight symptoms during physical activities. Class-III represented subjects with cardiac disease resulting in marked symptoms during physical activities, and Class-IV represented subjects that had symptoms or discomfort during both rest and daily physical activities [27]. According to the NYHA criterion, 44 CHF patients were classified: 4 for Class-I, 8 for Class-II, 17 for Class-III, and 15 for Class-III∼IV.

In this study, 54 healthy subjects were categorized into the control group, and 44 CHF subjects were categorized into the CHF group (CHF) for CHF assessment. Furthermore, 12 mild-to-moderate CHF subjects in Class-I and Class-II were categorized into a low-risk (LR) group, and 32 advanced

CHF subjects in Class-III and Class-IV were categorized into a high-risk (HR) group for further assessment [28].

### B. LONG-TERM HRV ANALYSIS

#### 1) PREPROCESS

For obtaining noiseless signal for standard short-term HRV analysis, the 24-h HRV signals were preprocessed. First, the first and last RR intervals and the intervals longer than 3s were excluded in each 24-h HRV signal for removing the noises. Then, the 24-h signals were divided into multiple non-overlapping 5-min segments in each subject for standard short-term HRV analysis [5]. Finally, all 5-min segments were resampled to 2 Hz by interpolation.

#### 2) TIME/FREQUENCY DOMAIN ANALYSIS

In this study, the long-term time/frequency domain indices were calculated using two steps. (1) The short-term indices were obtained from the 5-min HRV segments. (2) The mean value of the short-term indices in 24-h were treated as long-term indices.

The short-term time/frequency analysis of each 5-min HRV segment was based on the standard method [15]. Three time domain indices we used as follows: the standard deviation of the normal-to-normal (NN) intervals (SDNN), the root mean square of successive differences between the adjacent NN intervals (RMSSD), and the percentage of NN intervals greater than 50 ms (PNN50) [29]. For an $N$ point 5-min HRV segment, the time domain indices were defined as follows.

$$SDNN = \sqrt{\frac{1}{N}\sum_{i=1}^{N}\left(HRV_i - \frac{1}{N}\sum_{i=1}^{N} HRV_i\right)^2} \quad (1)$$

$$RMSSD = \sqrt{\frac{1}{N-1}\sum_{i=1}^{N-1}(HRV_{i+1} - HRV_i)^2} \quad (2)$$

$$PNN50 = \frac{num\left[(HRV_{i+1} - HRV_i) > 50\text{ms}\right]}{N-1} \quad (3)$$

There are four frequency components in the HRV signal: the very-high frequency (VHF, 0.4–1 Hz), high frequency (HF, 0.15–0.4 Hz), low frequency (LF, 0.04–0.15 Hz), and very-low frequency (VLF, 0.003–0.04 Hz) [17], [30]–[33]. Therefore, five frequency domain indices were obtained in these four components. The power spectral density of each 5-min HRV segment was computed using a fast Fourier transform. The power of the VLF, LF, HF, and VHF bands were denoted as VLFP, LFP, HFP, VHFP, respectively. The ratio of LF and HF was denoted as LF/HF [16], [34].

Finally, the mean value of each index in 24-h was calculated as the corresponding long-term time/frequency domain index.

#### 3) MULTI-FREQUENCY COMPONENTS ANALYSIS

In a previous HHT-based HRV study, the mean value of instantaneous frequency (MIF) of the HRV signal was used for CHF diagnosis [23]. However, the MIF can only reflect the average level of the rhythms changes of the ANS. The HHT can reveal the instantaneous rhythms changes in the cardiac system [18], [22], and the entropy can reveal the complexity of the HRV signal [11], [12], [29]. Thus, the MFCA was proposed as a novel HRV analysis method to determine the long-term dynamic rhythms changes of the ANS.

The MFCA was based on the HHT algorithm and entropy measurement. First, the HHT algorithm was adopted to obtain the IF of the 5-min HRV segments in different scales of frequency components to reveal changes of the signal. Then, the IF was further processed, and the entropy measurement was adopted to quantitatively investigate the complexity of these changes. The scheme of the MFCA is shown in Fig. 2, and the details of the MFCA were as follows.

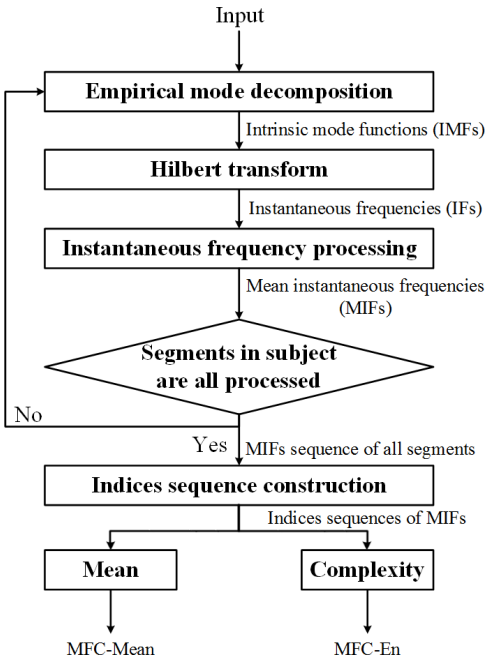


**FIGURE 2.** Scheme of multi-frequency components analysis (MFCA).

*Step 1 (Empirical Mode Decomposition):* The EMD method was proposed by Huang *et al.* [19] and has been proven as a self-adaptive non-linear and non-stationary data analysis method. The main characteristic of EMD is that it can decompose any non-linear and non-stationary data into a set of monocomponent frequency data called intrinsic mode functions (IMFs) and a trend component [35]. The IMFs satisfy two requirements: (1) the number of zero crossing and extremes must be the same in each IMF, and (2) the mean value of the envelope defined by the local maxima and the envelope defined by the local minima at any point should be zero in each IMF. In EMD, a sifting process is necessary for selecting the IMF that satisfies the requirements. The input data $x$ subtracting its mean value $m_1$ produced $h_1 = x - m_1$. The $h_1$ was treated as the new input data $x'$, and the sifting process was repeated $l$ times. After the sifting process, $h_{1l} = h_{1(l-1)} - m_{1l}$ was obtained and was denoted as the first IMF component of the input data. Here, $l$ was constrained by a

stopping criterion that was defined as shown below [19].

$$0.2 \leq \sum_t \frac{\left|h_{1(l-1)}(t) - h_{1l}(t)\right|^2}{h^2_{1(l-1)}(t)} \leq 0.3 \tag{4}$$

After EMD, a data $x$ was decomposed into a finite number of IMFs and the trend component as follows.

$$x(t) = \sum_{i=1}^{n} IMF(t)_i + trend \tag{5}$$

where $n$ is the total number of IMFs of the data $x$.

Here, the 5-min HRV segment was treated as the input data $x$, then IMFs of the HRV segment were obtained.

*Step 2 (Hilbert Transform):* The HT is a useful tool for calculating instantaneous attributes of a time series, especially the envelope amplitude and IF of the signal [36]. Because of the strict requirement that the signal must be monocomponent in frequency, the HT cannot be used in the HRV signal directly. The EMD method expanded the use of the HT because the IMF decomposed by EMD was a monocomponent real-valued signal [20], [35].

For a signal $IMF(t)_i$, its HT $\overline{IMF}(t)_i$ was given as shown below.

$$\begin{aligned}\overline{IMF}(t)_i &= H\left[IMF(t)_i\right] = \frac{1}{\pi} P \int_{-\infty}^{+\infty} \frac{IMF(t)_i}{t-\tau} d\tau \\ &= \lim_{\varepsilon \to 0^+} \frac{1}{\pi} \int_{|t-\tau| \geq \varepsilon} \frac{IMF(t)_i}{t-\tau} d\tau\end{aligned} \tag{6}$$

The parameter $P$ is the Cauchy principal value of the integral.

Generally, the HT of an IMF signal is written as an analytic signal of the IMF (AIMF), as shown below.

$$AIMF(t)_i = IMF(t)_i + j \cdot \overline{IMF}(t)_i = A(t) e^{j\theta_i} \tag{7}$$

where $j$ is the imaginary unit.

$$A(t) = \sqrt{IMF(t)_i^2 + \overline{IMF}(t)_i^2}, \theta_i(t) = \tan^{-1}\left(\frac{\overline{IMF}(t)_i}{IMF(t)_i}\right) \tag{8}$$

Hence, the IF sequence of $IMF(t)_i$ is defined as follows.

$$IF_i = d\theta_i(t)/dt \tag{9}$$

The IF sequence of all the IMFs in a 5-min HRV segment were obtained in this step.

*Step 3 (Instantaneous Frequency Processing):* The IF sequence of each signal was further processed by calculating the MIF to reflect the average level of the frequency changes. For an $N$ point IF sequence, the MIF was defined as shown below.

$$MIF_i = \frac{1}{N} \sum_{j=1}^{N} IF_i(j) \tag{10}$$

The MIF of all IF sequences in a 5-min HRV segment were calculated in this step. Step 1 to step 3 were repeated until all 5-min segments in the subject were processed.

*Step 4 (Indices Sequence Construction):* For each subject, the MIFs were calculated from all 5-min HRV segments in 24-h. Hence, multiple 5-min indices of each subject were obtained. An indices sequence (IS) to represent the index over 24-h was constructed as follows.

$$IS(index) = \{I_1, I_1, \ldots, I_n\} \tag{11}$$

The parameter $I_n$ is a 5-min index, and $n$ is the amount of $I$ over 24-h.

*Step 5 (Indices Calculation):* The indices calculation in the MFCA consisted of the mean value calculation and the complexity measurement of each IS. The definitions of the MFCA-based indices are shown as follows.

*MFC-Mean:* The MFC-mean was calculated from the mean value of the IS for the robustness improvement. An IS of $MIF_i$ was denoted as $IS(MIF_i) = \{I_1, I_2, \ldots, I_n\}$. The $MFC - mean(MIF_i)$ was defined as shown below.

$$MFC - mean(MIF_i) = \frac{\sum IS(MIF_i)}{n} = \frac{\sum \{I_1, I_2, \ldots, I_n\}}{n} \tag{12}$$

The parameter $n$ is the amount of the index in $24-$h.

*MFC-En:* The MFC-En was the entropy of the IS, which reflected the complexity of the index in 24-h. In this study, the fuzzy entropy (FuzzyEn) algorithm proposed by Chen *et al.* was used as the complexity measurement. The fuzzy membership function of FuzzyEn was selected as exponential function $\exp\left[-((d_{ij}^m))/r^n\right]$. The parameters $n$, $m$, and $r$ were selected as 2, 2, and 0.25 times the standard deviation of the input data in this study, respectively [37], [38].

The pseudo-code of the MFCA is described as follows.

**Algorithm 1** Multi-Frequency Components Analysis.

**Input:**
$\{HRV_j, j = 1, \ldots, m\}$ : long–term HRV signal $m$ : total number of 5-*min* segments of $\{HRV_j\}$ $n$ : total number of IMFs

```
for i ← 1 to n do
    IMF_i ← EMD(HRV)
    for j ← 1 to m do
        IF_ij ← HT(IMF_ij)
        MIF_ij ← mean(IF_ij)
        IS(MIF_ij) ← {MIF_ij}
    end for
    MFC − Mean(MIF_i) ← mean(IS(MIF_i))
    MFC − En(MIF_i) ← FuzzyEn(IS(MIF_i))
end for
return
MFC − Mean(MIF_1−n)
MFC − En(MIF_1−n)
```

Here, the input series $\{HRV_j, j = 1, \ldots, m\}$ is the 24-h HRV signal. $m$ and $n$ is total numbers of 5-min segments in 24-h period, and the numbers of IMF we selected, respectively. The algorithm returns the $MFC-mean$ and $MFC-En$ indices of each IMF.

### C. VALIDATION

The HRV indices used in this study were validated in three aspects. First, a t-test was used to analyze the significant difference of the control group and CHF group. Then, a one-way ANOVA followed by a post hoc analysis with the least significant difference test was used to analyze the statistical significance among the control, LR, and HR groups. A $p < 0.05$ was considered statistically significant, and the values of the statistical analysis were expressed as the mean ± standard deviation (SD) [39]. Further, for validating the performance of these HRV indices, the Fisher discriminant function from SPSS was used for CHF assessment. The results were expressed as the accuracy, sensitivity, and specificity. These tests were performed using SPSS version 22.0.0.0 (SPSS Inc., Chicago, IL, USA).

## III. RESULTS

The significant difference among the control, LR, and HR groups of the indices and the performance of the indices are shown in this section. In total, 16 long-term HRV indices were calculated, including 3 time-domain indices (SDNN, RMSSD and PNN50), 5 frequency-domain indices (VLFP, LFP, HFP, VHFP, and LF/HF), and 8 MFCA-based indices (MFC-Mean and MFC-En calculated from $IMF_1$, $IMF_2$, $IMF_3$, and $IMF_4$).

### A. HRV ANALYSIS BY THE HHT

The results of EMD of a typical 5-min HRV segment are shown in Fig. 3 (a). The first 4 IMFs contained almost the entire energy of the HRV signal. Hence, the first 4 IMFs of the HRV signal of each subject were selected for further analysis. Fig. 3 (b) shows the IF sequence of the first 4 IMFs. The MIF and SD of each IF sequence were also represented as the mean ± SD. The red lines indicated the value of the MIF, which showed the average level of the rhythms changes of the corresponding IMF. From Fig. 3 (b), the MIF showed that the $IMF_1$ corresponded to the VHF component (0.431 Hz). $IMF_2$ was the HF component (0.199 Hz). $IMF_3$ was the LF component (0.076 Hz), and $IMF_4$ was the VLF component (0.027 Hz). Therefore, the first 4 IMFs corresponded to 4 frequency components of the HRV signal, respectively.

Fig. 4 shows the distribution of the normalized MIF in a 24-h period of the first 4 IMFs. The complexities of the color distribution increased with the severity of CHF. Therefore, the complexity of the MIF in a 24-h period may have potential for early stage CHF detection.

### B. STATISTICAL ANALYSIS AMONG THE GROUPS WITH LONG-TERM TIME AND FREQUENCY DOMAIN INDICES

The mean ± SD values of the time/frequency domain indices for the control, LR, and HR groups are listed in TABLE 1. The VHFP and LF/HF showed a significant difference ($p < 0.001$), and PNN50 showed a significant difference ($p < 0.01$) between the control and CHF groups. In addition,

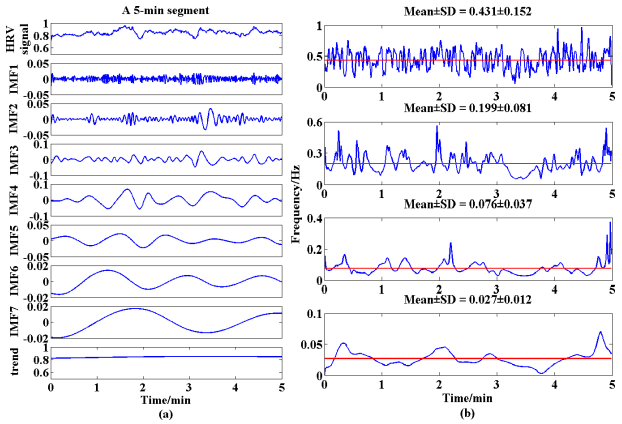


**FIGURE 3.** HHT analysis of a typical 5-min HRV segment, (a) results of EMD method, (b) instantaneous frequency sequences of the first 4 IMFs.

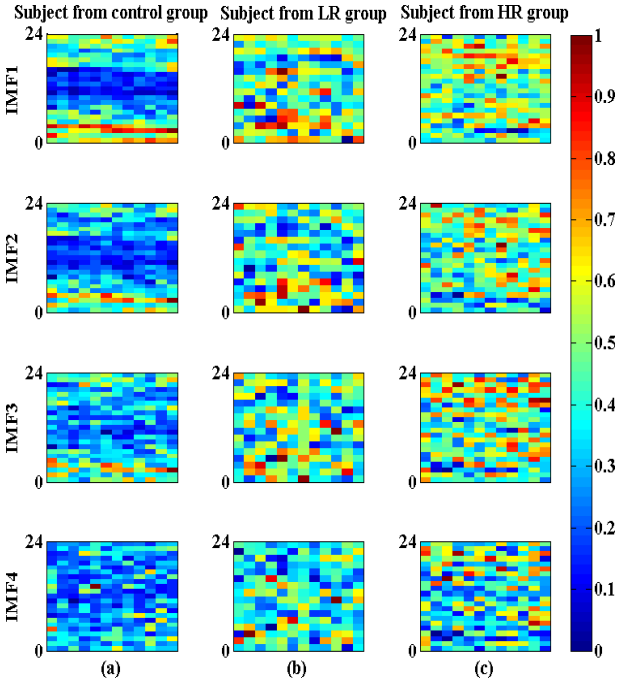


**FIGURE 4.** Distributions of normalized MIF in 24-h period for a typical subject from (a) control group, (b) LR group, and (c) HR group.

no index showed a significant difference ($p < 0.05$) among the control, LR, and HR groups. For the control versus the LR groups and the control versus the HR groups, LF/HF showed a better statistical significance than that of the other indices. Fig. 5 shows the results of the RMSSD, PNN50, VHFP, and LF/HF among the control, LR, and HR groups. The LF/HF was the only index that showed a stepwise change with the severity of CHF. Hence, the LF/HF was considered the representative index among the time/frequency domain indices in this study.

### C. STATISTICAL ANALYSIS AMONG THE GROUPS WITH THE MFCA-BASED INDICES

In total, 8 MFCA-based indices were obtained by the MFCA method. The mean ± SD values are listed in TABLE 2. The MFCA-based indices showed significant

**TABLE 1.** Long-term time/frequency domain indices for control, LR and HR groups.

| Indices | Control group (mean ± SD) | LR group (mean ± SD) | HR group (mean ± SD) | *p*-value C versus LR | *p*-value C versus HR | *p*-value LR versus HR |
|---|---|---|---|---|---|---|
| SDNN | 0.053±0.016 | 0.062±0.035 | 0.043±0.023 | 0.223 | 0.038* | 0.013* |
| **RMSSD$^{\#\#\#}$** | **0.023±0.146** | **0.057±0.035** | **0.042±0.032** | **0.000*****| **0.001**** | **0.166** |
| **PNN50$^{\#\#}$** | **2.727±4.491** | **8.670±8.283** | **7.367±12.229** | **0.026*** | **0.013*** | **0.642** |
| VLFP | 0.032±0.027 | 0.049±0.053 | 0.024±0.024 | 0.074 | 0.263 | 0.016* |
| LFP | 0.856±0.815 | 1.637±1.841 | 0.780±0.894 | 0.017* | 0.737 | 0.014* |
| HFP | 0.569±1.133 | 1.539±1.902 | 0.801±0.916 | 0.012* | 0.383 | 0.069 |
| **VHFP$^{\#\#\#}$** | **0.257±0.468** | **1.517±1.598** | **1.136±1.167** | **0.001**** | **0.001**** | **0.332** |
| **LF/HF$^{\#\#\#}$** | **3.045±1.198** | **1.578±0.677** | **1.196±0.791** | **0.000***** | **0.000***** | **0.275** |

SDNN: the standard deviation of the normal-to-normal (NN) intervals; RMSSD: the root mean square of successive differences between the adjacent NN intervals; PNN50: the percentage of NN intervals greater than 50 ms; VLFP, LFP, HFP, and VHFP: the power in VLF, LF, HF, and VHF band of HRV, respectively; SD: standard deviation; C: control group, LR: low-risk group, HR: high-risk group; #, ##, ### represent $p < 0.05$, $p < 0.01$, and $p < 0.001$ between control and CHF group, respectively; *, **, *** represent $p < 0.05$, $p < 0.01$, and $p < 0.001$ among control, LR, and HR groups, respectively.

C: control group, LR: low-risk group, HR: high-risk group

**TABLE 2.** MFCA-based indices for control, LR and HR groups.

| Indices | Control group (mean ± SD) | LR group (mean ± SD) | HR group (mean ± SD) | *p*-value C versus LR | *p*-value C versus HR | *p*-value LR versus HR |
|---|---|---|---|---|---|---|
| MFC-Mean($MIF_1$)$^{\#\#}$ | 0.419±0.042 | 0.462±0.070 | 0.460±0.065 | 0.016* | 0.001** | 0.910 |
| MFC-Mean($MIF_2$)$^{\#\#\#}$ | 0.195±0.025 | 0.252±0.048 | 0.248±0.036 | 0.000*** | 0.000*** | 0.702 |
| MFC-Mean($MIF_3$)$^{\#\#\#}$ | 0.093±0.012 | 0.140±0.037 | 0.140±0.026 | 0.000*** | 0.000*** | 0.985 |
| MFC-Mean($MIF_4$)$^{\#\#\#}$ | 0.049±0.006 | 0.077±0.025 | 0.077±0.017 | 0.000*** | 0.000*** | 0.945 |
| **MFC-En($MIF_1$)$^{\#\#\#}$** | **0.943±0.151** | **1.221±0.342** | **1.396±0.232** | **0.000***** | **0.000***** | **0.015*** |
| **MFC-En($MIF_2$)$^{\#\#\#}$** | **1.255±0.149** | **1.426±0.238** | **1.600±0.195** | **0.003**** | **0.000***** | **0.004**** |
| MFC-En($MIF_3$)$^{\#\#\#}$ | 1.437±0.163 | 1.545±0.239 | 1.666±0.174 | 0.060 | 0.000*** | 0.046* |
| MFC-En($MIF_4$)$^{\#}$ | 1.621±0.121 | 1.618±0.157 | 1.719±0.152 | 0.941 | 0.002** | 0.030* |

MFC-Mean: mean value of multi-frequency components, MFC-En: multi-frequency components entropy; MIF: the mean instantaneous frequency; SD: standard deviation; C: control group, LR: low-risk group, HR: high-risk group; #, ##, ### represent $p < 0.05$, $p < 0.01$, and $p < 0.001$ between control and CHF group, respectively; *, **, *** represent $p < 0.05$, $p < 0.01$, and $p < 0.001$ among control, LR, and HR groups.

differences ($p < 0.01$) between the control and CHF groups. The MFC-Mean indices showed significant differences among the control versus LR groups and the control versus HR groups ($p < 0.05$). The MFC-En indices showed significant differences between the LR and HR groups ($p < 0.05$). Moreover, the MFC-En($MIF_1$) and MFC-En($MIF_2$) showed significant differences among the control, LR, and HR groups ($p < 0.05$). Fig. 6 shows the results of the MFC-Mean and MFC-En of $IMF_1$ and $IMF_2$ among the control, LR, and HR groups. MFC-En($MIF_1$) and MFC-En($MIF_2$) showed monotonicity among the control, LR, and HR groups.

### D. PERFORMANCE OF THE MFC-EN INDICES

The performance of the MFC-En indices and LF/HF were validated by CHF assessment. The Fisher discriminant function in SPSS was used for classifying each sample as a healthy or CHF subject. The accuracy (ACC), sensitivity (SEN), and specificity (SPE) values of the MFC-En indices and LF/HF were computed and are listed in TABLE 3. The ACC was defined as the percentage of correctly classified samples. The SEN was defined as the percentage of correctly classified CHF samples. The SPE was defined as the percentage of correctly classified healthy samples. As shown in Table 3,

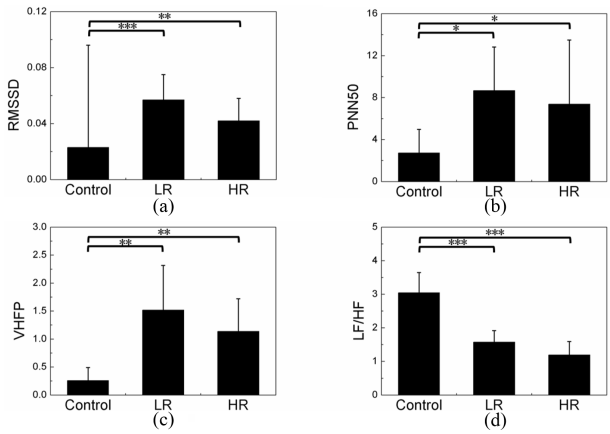


**FIGURE 5.** Indices for control, LR and HR groups, (a) RMSSD, (b) PNN50, (c) VHFP, and (d) LF/HF; *, **, *** represents $p < 0.05$, $p < 0.01$, and $p < 0.001$, respectively.

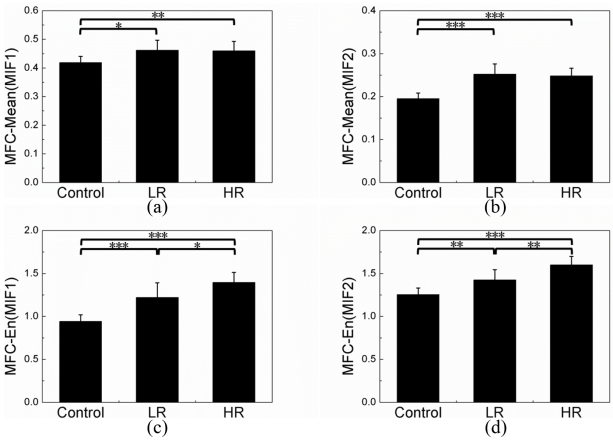


**FIGURE 6.** Indices for control, LR and HR groups, (a) MFC-Mean(MIF1), (b) MFC-Mean(MIF2), (c) MFC-En(MIF1), and (d) MFC-En(MIF2); *, **, *** represents $p < 0.05$, $p < 0.01$, $p < 0.001$, respectively.

**TABLE 3.** Performance of indices for CHF screening.

| Indices | ACC (%) | SEN (%) | SPE (%) |
|---|---|---|---|
| MFC-En($MIF_1$) | 86.7 | 79.5 | 92.6 |
| MFC-En($MIF_2$) | 80.6 | 72.7 | 87.0 |
| MFC-En($MIF_3$) | 71.4 | 70.5 | 72.2 |
| MFC-En($MIF_4$) | 60.2 | 63.6 | 57.5 |
| LF/HF | 79.6 | 86.4 | 74.1 |

for 98 samples, the MFC-En($MIF_1$) achieved 86.7% ACC and 92.6% SPE, and MFC-En($MIF_2$) achieved 80.6% ACC and 87.0% SPE, while the LF/HF only achieved 79.6% ACC and 74.1% SPE.

Moreover, the receiver operating character (ROC) curve and area under the curve (AUC) of MFC-En($MIF_1$), MFC-En($MIF_2$), and LF/HF are shown in Fig. 7. MFC-En($MIF_1$) achieved the highest AUC value (0.8742), while MFC-En($MIF_2$) and LF/HF achieved lower values (0.8026 and 0.8030, respectively).

The results showed that MFC-En($MIF_1$) was the most accurate index for distinguishing the CHF subjects from

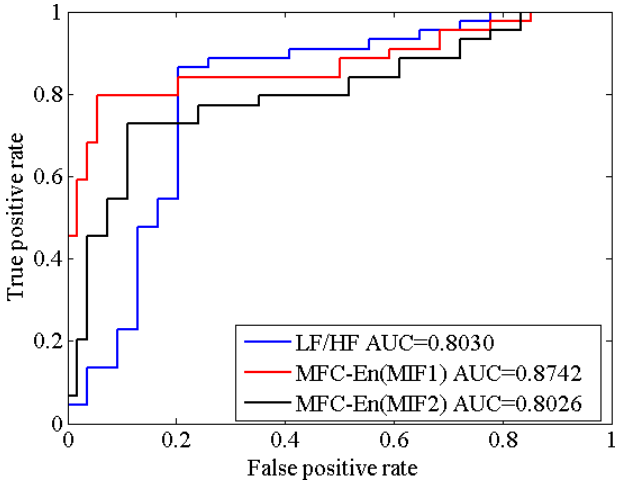


**FIGURE 7.** The ROC curves of MFC-En(MIF1), MFC-En(MIF2), and LF/HF.

the healthy subjects among the time/frequency domain and MFCA-based indices in this study.

## IV. DISCUSSION

### A. COMPARISON AND SUMMARY

In this study, most of the time/frequency domain indices showed significant differences between the control and CHF groups, as previous studies have reported [8]–[10]. Among all indices, LF/HF had the greatest statistical significance among the control versus LR and the control versus HR groups ($p < 0.001$) (TABLE 1). Therefore, LF/HF was selected as the representative index for comparison among the time/frequency domain indices in this study.

Previous study showed mean instantaneous frequency (MIF) of each IMF of HRV signal can be used as indices for CHF diagnosis. Bajaj and Pachori [18] used a bunch of indices including MIF with complex machine learning technic for diagnosing the CHF from normal subjects with over 90% accuracy. In this study, we proposed MFCA method for analyzing the HRV with CHF, and analyzed the physiological significance with each single index. Results showed that the MFC-En ($MIF_1$) and MFC-En ($MIF_2$) have statistical significance among the control, LR, and HR groups, while the time/frequency domain indices had no significant differences (TABLE 2) [6], [28], [40]. Moreover, MFC-En($MIF_1$) achieved a higher classification ACC than that of LF/HF (86.7% versus 79.6%) (TABLE 3). Briefly, MFC-En has potential for CHF classification and early stage CHF detection.

### B. MOTIVATION OF THE MFCA METHOD

This study proposed the MFCA method as a novel HRV analysis method for CHF assessment. The MFCA method was developed on the HHT algorithm and entropy measurement. The HHT revealed the rhythms changes of the ANS by monitoring the IF changes of the HRV signal, and the entropy measurement revealed the complexity of the rhythms changes of the ANS.

The HHT algorithm that consisted of the EMD and HT revealed the instantaneous changes of the signal in different scales of frequency components [41]. It has been reported that the HRV signal had four components: the VHF, HF, LF, and VLF component [17], [30]–[33]. The EMD method can decompose the non-linear and non-stationary HRV signal into a set of monocomponent frequency signals called IMFs [20], [35]. Each IMF contains information for a different frequency component of the HRV signal. The HT can reveal the instantaneous rhythms of the signal by the IF changes of each IMF [18]. The results of EMD of a typical 5-min HRV segment showed that the first 4 IMFs corresponded to the VHF, HF, LF, and VLF component of the HRV signal, respectively (Fig. 3). Then, the first 4 IMFs of the HRV signal were selected. Therefore, the HHT revealed the rhythms changes of the ANS by monitoring the IF changes of the first 4 IMFs of the HRV signal, and the MIF of the 5-min HRV segment reflected the average level of the rhythms changes of the ANS in a 5-min period.

The MFC-Mean indices showed significantly larger values in the CHF group with $p < 0.001$, revealing that the rhythms changes of the ANS in the CHF patients were more rapid throughout the day (TABLE 2). The complexities of the MIF values increased from the control to the LR to the HR groups (Fig. 4). The daily activity level of the CHF patients was irregular and was related to the severity of the disease [27], and the entropy revealed the intrinsic complexity of the HRV signal [11], [12], [29]. Therefore, the entropy was introduced to investigate these complexities. FuzzyEn is a proven, powerful tool for measuring the complexity of the signal owing to its insensitivity to noise and data length [37]. Thus, FuzzyEn was selected as the complexity measurement method. MFC-En showed a statistical significant among the control, LR, and HR groups with $p < 0.05$, which revealed that the rhythms changes of the ANS throughout the day were more complex in the CHF groups, especially in the HR group. Moreover, MFC-En achieved a higher ACC in CHF classification than that of LF/HF (86.7% versus 79.6%). Therefore, the MFCA method has potential for CHF classification and early stage CHF detection.

The 5-min HRV segment was used for the indices calculation because the 5-min segment was suitable for the time and frequency domain analysis [15]. The complexity of the indices in 24-h was analyzed because the circadian rhythms led the ANS changes throughout the day [41]–[44].

### C. PHYSIOLOGICAL SIGNIFICANCE

It has been reported that CHF disease is a chronic cardiovascular syndrome along with ANS dysfunction, and HRV is a useful tool for ANS assessment [3]. Previous studies have investigated the power changes of the HRV signal, which revealed the tone of the ANS is different between the healthy and CHF subjects [15]–[17]. The HHT reveals the rhythms changes of the bio-signal by monitoring the instantaneous frequency changes of the signal [18]. In this study, the rhythms changes of the ANS were more rapid and complex in the CHF subjects.

MFC-En($MIF_1$) and MFC-En($MIF_2$) reflected that the rhythms changes of the VHF and HF component of the HRV signal were more complex in the CHF groups, respectively. The VHF and HF components were related to the cardiac contractility and PNS activity [31]–[33], and these complexities increased with the severity of CHF Thus, MFC-En($MIF_1$) and MFC-En($MIF_2$) revealed the rhythms of the cardiac contractility and respiratory pattern are were more complex in the CHF patients, especially in the HR patients (TABLE 2). This result showed that the rapid and disordered respiratory pattern of the CHF patients was consistent with previous studies [45], [46] MFC-Mean($MIF_3$) and MFC-Mean($MIF_4$) showed significant differences ($p < 0.001$) among the control and LR groups while MFC-En($MIF_3$) and MFC-En($MIF_4$) had no significant differences (TABLE 2) Thus, although the rhythms of the SNS changed, the changes were not obvious at the beginning stage of CHF disease [47]

In conclusion, the MFCA-based indices indicated that the rhythms changes and complexities of each component of the HRV signal increased in the CHF group, thus revealed that the ANS in CHF patients are more activated, even in the early stage of disease [47]. These results showed that the rhythms of cardiac contractility and the modulation of the ANS were more rapid and complex in CHF patients.

### D. LIMITATIONS

This study had some limitations. First, the ages of the subjects in the control and CHF groups were significantly different, which may have influenced the results. Second, the study in the large sample found that the EMD method failed to completely decompose the HRV signal into four frequency components for the first 4 IMFs. Third, the performances of MFC-En in CHF early stage detection were not ideal. MFC-En achieved a higher ACC than that of LF/HF (65.91% versus 54.55%), which may be related to the effects of the imbalances in the data and the performance of the classifier. Finally, the algorithms should to be improved. Therefore, these limitations should be considered in future studies.

## V. CONCLUSION

This study proposed the MFCA method as a novel HRV analysis method for analyzing HRV with CHF. The MFC-Mean and MFC-En indices were nonlinear HRV indices and were significantly higher in the CHF patients. These indices showed that disordered rhythms changes of the ANS occurred in the CHF patients. The MFC-En values were also significantly different among the three classes of subjects. Therefore, this study was able to propose a novel method for CHF assessment.

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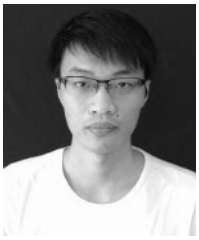

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