



Harmonic analysis of pulse morphology variability for pulse smoothness assessment

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ABSTRACT

A non-linear physiological system leads to a change in pulse morphology variability (PMV), which can be an important feature in assessing the condition of the cardiovascular system. The smooth pulse derived from traditional East Asian medicine (TEAM) also contains chaotic features according to the temporal sequence, and such pulses usually appear during menstruation in women. Analyzing the PMV as a novel indicator of pulse smoothness can contribute not only to understanding non-linear physiological systems but also to studying the characteristics of pulse patterns. In this study, we propose an algorithm to assess pulse smoothness using a harmonic analysis approach of the PMV. First, we introduced a two-step pre-processing method that considers the applied pressure (AP) variability and outlier pulse removal (OPR) to generate a refined pulse series. Next, we performed PMV analyses using four different methods to examine the characteristics of the pulse series. Finally, we performed a spectral harmonic analysis based on the trace of the intra-class distance within each single-period pulse (TIS) to assess the pulse smoothness. We evaluated the proposed algorithms using repeated-measures ANOVA and receiver operating characteristic (ROC) analysis according to the menstrual period. Distorted pulses were automatically detected with the pre-processing method, and the maximum amplitude of the average TIS was consistently observed near the radial augmentation index point. In addition, the total adjacent harmonic peak increment (AHPI) among the proposed variables was significantly higher during the menstrual phase than during the non-menstrual phase ($P < 0.05$), and the area under the ROC curve of the AHPI was 0.742. Therefore, dissonant or disharmonic frequency components are present during menstruation, and the AHPI could be a novel indicator reflecting pulse smoothness.

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1. Introduction

The non-linear variability of bio-signals is an inevitable physiological dynamic, and investigating these features is essential for a detailed analysis of the physiological system [1]. Such physiological variability has gained increasing attention as a research topic over the past two decades in the assessment of autonomic functions and the prognosis of several disorders, such as diabetic neuropathy and myocardial infarction [2]. The pulse wave signal is also oscillatory in nature and has chaotic characteristics because this signal is generated by a non-linear internal system in humans [3,4]. Hemodynamic variability derived from the pulse signal can reflect changes in cardiac performance. For example, heart rate variability (HRV), which is measured by the variation in the time interval

between heart beats, has been studied extensively using time and frequency domain analyses to examine autonomic influences on the heart rate [5–7]. Pulse pressure variation, which represents the effect of respiration on the variation in the arterial blood pressure, is one of the most sensitive and specific predictors of fluid responsiveness, which is defined as the ability of the left ventricle to increase its stroke volume, in mechanically ventilated patients [8–10]. Moreover, pulsus alternans, a cardiovascular phenomenon characterized by alternating strong and weak pulse pressures, has been considered in the prognosis of severe ventricular failure, and several mechanisms contributing to pulsus alternans have been reported [11,12].

However, few studies have quantified changes in the morphology of the pulse waveform and blood flow variability [2,13]. Pulse morphology variability (PMV) is related to many factors, including arterial blood pressure, compliance, cardiac output and vascular resistance [14]. In addition, because uncertainties derived from non-linear behavior lead to changes in the PMV, this type of vari-

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ability can be an important feature in assessing the condition of the cardiovascular system [15]. Understanding the complicated variation in pulse morphology could contribute to scientific validation of non-linear physiological systems [16].

To quantify the non-linearity in physiological signals, non-linear analyses, including approximate entropy, Kolmogorov-Sinai entropy, correlation dimension and inner randomness, have been performed [4,14,17]. However, these methods are not intuitive and do not describe the association between the analysis variables and signal characteristics. An effective way to classify identities or determine differences is to compute class distances, and basic distance measures, such as city-block and Euclidean distances, are commonly used to compute similarities [18]. In pulse analysis studies, the percent root-mean-square difference (PRD) has been calculated to measure the similarity between two waveforms, and a dynamic time-warping algorithm has been used to detect irregular pulses [19,20]. The morphology index calculated by spectral analysis has been used for the early detection of coronary artery disease, and pulse morphology features were reported to be more efficient than pulse interval features in assessing the condition of the coronary artery [2,14]. In addition, the edit distance with real penalty has been used to classify pulse waveforms with advanced k-nearest neighbour classifiers, and time-varying frequency and an amplitude model have been used to capture the physiological facets of HRV and pulsus alternans [1,21]. The segmentation strategy using the PMV derived by intra-class distance (ICD) has been introduced to obtain the single-period pulse (SPP) sets, but most previous studies have not considered the variability derived from a pulse series [22].

The PMV in a pulse series can be an important indicator reflecting intrinsic characteristics, such as pulse self-similarity, pulse stability and blood flow variability. Furthermore, pulse smoothness, described as a non-linear chaotic feature according to the temporal sequence, could be represented by intensive analysis of variability. This clinical implication of pulse smoothness can be found in traditional East Asian medicine (TEAM). As described in TEAM, an unsmooth or rough pulse pattern is a pulse that comes and goes unsmoothly with a fluctuating pattern, whereas a slippery pulse pattern is a pulse that comes and goes smoothly. These two pulse patterns cannot be classified distinctly based solely on morphology, and thus have rarely been studied despite their clinical importance [23]. Therefore, the analysis of the PMV as a novel indicator of pulse smoothness can contribute not only to understanding non-linear physiological systems but also to studying the classification of pulse patterns. Ideally, an unsmooth pulse might have dissonant and disharmonic frequency components [24]; consequently, in this study, we propose an algorithm to assess pulse smoothness in a pulse series using harmonic analysis.

2. Methods

2.1. Experimental protocol

The observational study on the pulse waveform was performed with healthy 42 women aged 20–30 years, who had normal menstrual cycle. Participants were excluded from the study if they met the following criteria

- having myoma uteri, endometriosis, ovarian cystic tumor, or polycystic ovary syndrome
- done any medical surgeries or therapies within one month prior to study participation
- intake of any drugs that affect the autonomic nervous system or signals of the radial pulse, such as anti-depressant, anti-serotonin barbiturate and psychotropic drugs before the screening

- diet control for the purpose of weight loss within one month prior to study participation
- pregnancy or vascular malformation of the radial artery.

All participants were asked for written informed consent. All participants visited four times according to their menstrual period (menstruation phase, follicular phase, luteal phase and the subsequent menstruation phase, sequentially). These phases were defined in advance according to a previous study [25].

The Korea Institute of Oriental Medicine-pulse analysis system (KIOM-PAS), a pulse tonometric device developed at the KIOM, was used to measure the radial pulse. The electro-mechanical stability of the KIOM-PAS was certified based on IEC 60601-1 2nd edition, and the reliability and safety of the device was approved based on clinical good manufacturing practice (GMP). A pulse detection sensor is composed of six piezoresistive unit sensors within $9 \times 9 \text{ mm}^2$ and the performance of the sensor array was validated by evaluating the sensor sensitivity per channel. The sensor array was positioned in a row at the region approximately 13 mm proximal to the prominent bone, which is known as Cheok, and the responsive pulse wave (PW) and applied pressure (AP) were measured using a continuously evolving tonometric mechanism with a sampling rate of 1000 Hz [26]. The sensor was gradually moved downward, and after the pulse amplitude had reached its maximum, the sensor was stopped to maintain the AP for 60 s. The pulse series acquired for 60 s was used for the pulse morphology and spectral analyses. We expected that a pulse coming and going sporadically would be observed during the menstruation phase similar to the unsmooth pulse pattern described in TEAM [27]. This study was conducted at Kyung-Hee University Korean Medicine Hospital in Seoul, Korea, and was approved by the Ethics Committee of the Institutional Review Board (No. KOMCIRB-150622-HR-021).

2.2. Two-step pre-processing method

Calculating the average pulse waveform as a representative pulse of a participant is a fundamental and important process for pulse waveform analysis. For example, the feature points of a pulse waveform, which generally consist of a percussive wave, tidal wave and dirotic wave, can be detected from the average pulse, and the frequency-domain characteristics derived from a spectral analysis can be captured using a well-refined pulse series. Because the morphologies of each SPP in a pulse series differ from each other with respect to the detailed points, even when acquired from the same participant, a representative pulse should be averaged from the pulse series rather than selecting one SPP waveform. However, there are some uncertainties. Motion artifacts, including uncontrolled hand or body movement during pulse acquisition, and measurement noise cause distortions in the pulse waveform signal [1]. In addition, movement of the blood vessel and incorrect location of the pressure sensor during measurement lead to dramatic changes in pulse morphology [26,28]. Therefore, a reliable process to calculate an average pulse waveform or pulse series is necessary. To solve these problems, we propose a two-step pre-processing method. All pre-processing and further analyses were performed using LabVIEW 2016 (National Instruments, USA).

2.2.1. AP variability analysis

The AP is considered a distinctively important component in pulse diagnosis, and the PW according to the AP conveys various hemodynamic and physiological information [29]. Although it is expected that ideally a constant pressure is applied to the radial artery, the amplitude of the AP under actual measurement conditions can change due to various unknown factors, consequently affecting the pulse morphology. Fig. 1 illustrates the necessity of AP variability analysis. As shown in Fig. 1(a), although constant AP

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