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Original article

A novel method for the quantitative evaluation of diurnal respiratory instability in patients with heart failure: A pilot study

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ABSTRACT

Background: There is no established method to quantitatively measure the presence and the severity of respiratory instability (RI). The purpose of this pilot study was to propose a novel index of diurnal RI as a surrogate measure of clinical severity of heart failure (HF).
Methods and results: We prospectively enrolled 60 patients with symptomatic HF [70 ± 14 years, 75% male, and New York Heart Association (NYHA) functional classes II–IV] who underwent right heart catheterization (RHC), and recorded diurnal respiration using a nasal pressure sensor during bed rest while awake within 2 days before or after RHC. Non-uniformity of the breath-by-breath respiratory slopes during 15 min calculated as the ratio of peak expiratory amplitude to corresponding peak-to-peak interval was assessed by histogram-based frequency distribution measurement, and was defined as the "RI-index". The RI-index was significantly different among NYHA functional classes and was highest in NYHA class IV. The presence of atrial fibrillation (β coefficient: 0.300, $p = 0.01$) and stroke volume index (β coefficient: −0.462, $p < 0.01$) were independently associated with RI index among hemodynamic parameters. Furthermore, the high RI index above the median value was the independent predictor of the composite outcome of death from any cause, a life-threatening arrhythmia, and an unplanned hospitalization for worsening HF.
Conclusions: The RI index stratified functional severity of HF well, and was a significant independent predictor of poor outcomes.

Introduction

Sleep-disordered breathing (SDB) has been reported to occur in more than 70% of heart failure (HF) patients [1]. Repetitive apnea induces intermittent hypoxia, systemic inflammation, excessive negative intrathoracic pressure, and sympathetic overdrive [2–4]. Importantly, abnormal breathing also occurs frequently during daytime in patients with HF [5–7]. Cheyne–Stokes respiration (CSR), a severe form of periodic breathing during daytime, is recognized as an indicator of poor prognosis of HF [6,7]. The causal link between CSR and HF has been actively investigated, and there is increasing evidence that the development of CSR reflects the clinical severity of HF [8–11].

Power spectral analysis has been applied to identify CSR and to assess its severity in the research field [5,12–14]. However, there is a broad spectrum of abnormal breathing from non-periodic irregular respiration to severe CSR in the real-world clinical setting, but no quantitative measure of severity of abnormal breathing comprehensively across all breathing patterns has been established to date.

In the present study, we propose a novel index of respiratory instability assessed by using histogram-based frequency distribution measurement of the breath-by-breath respiratory "slope" while awake in patients with HF. We hypothesized that this novel index has an advantage for assessing the severity of various forms

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of abnormal breathing irrespective of the presence or absence of respiratory periodicity, and has clinical utility for HF severity stratification and for predicting clinical outcomes.

Methods

Study population

The study was approved by the Ethical Committee of Mie University School of Medicine and all patients gave written informed consent prior to the study participation. This pilot study involved 60 patients with symptomatic HF [New York Heart Association (NYHA) functional class II–IV] who underwent hemodynamic evaluation by right heart catheterization (RHC) between June 2013 and June 2015. Exclusion criteria included age <20 years, difficulty lying supine due to orthopnea, acute coronary syndrome within the last three months, administration of intravenous inotropic agents, severe chronic obstructive lung disease, history of major stroke, or patients with advanced dementia who were uncooperative.

Study design

All patients underwent respiratory waveform analysis during daytime wakefulness for 15 min within 2 days before or after RHC and laboratory measurements including plasma brain natriuretic peptide (BNP) level and arterial blood gases. HF treatment was unchanged during the periods of respiratory waveform recording and RHC in each patient. Echocardiographic parameters including left atrial diameter, left ventricular diastolic dimension (LVDd), and left ventricular ejection fraction (LVEF) assessed on admission were used as baseline values. All patients received guideline-based HF therapy during hospitalization [15] and were followed up after hospital discharge.

Respiratory waveform recording and analysis

All subjects underwent respiratory waveform recording for 15 min in the supine position using a type 3 portable device SAS-3200® (Nihon Kohden Corp., Tokyo, Japan) before the evening meal. They were asked to relax but not to fall asleep and to breathe through their nose. Nasal airflow by pressure sensor for recording the respiratory waveform, chest wall and abdominal wall motion sensors for measuring respiratory effort, and a fingertip pulse oximeter for heart rate and oxygen saturation measurements were simultaneously monitored. Estimated oxygen desaturation index (ODI) [16] was calculated as the number of desaturation at least 4% events during the 15-minute recording and then multiplied by 4. Nasal airflow waveform signals were recorded by a pressure sensor, with an adequate sampling rate of 50 Hz and bit depth of 16-bits, via an analog-to-digital converter. MATLAB R2013b® (Mathworks, Inc., Natick, MA, USA) was employed for waveform analysis to identify the peak and its amplitude in each expiration. Fig. 1A shows an example of a CSR waveform for one minute, which shows obvious breath-by-breath changes of respiratory waveform. We identified expiratory peaks (red inverted triangles) by using the *findpeaks* MATLAB function with a setting at *minimum peak distance* and *minimum peak height* of 2 s and 5 μV, respectively. Peak expiratory amplitudes for 15 min were normalized by dividing their average to minimize the influence of inter-patient

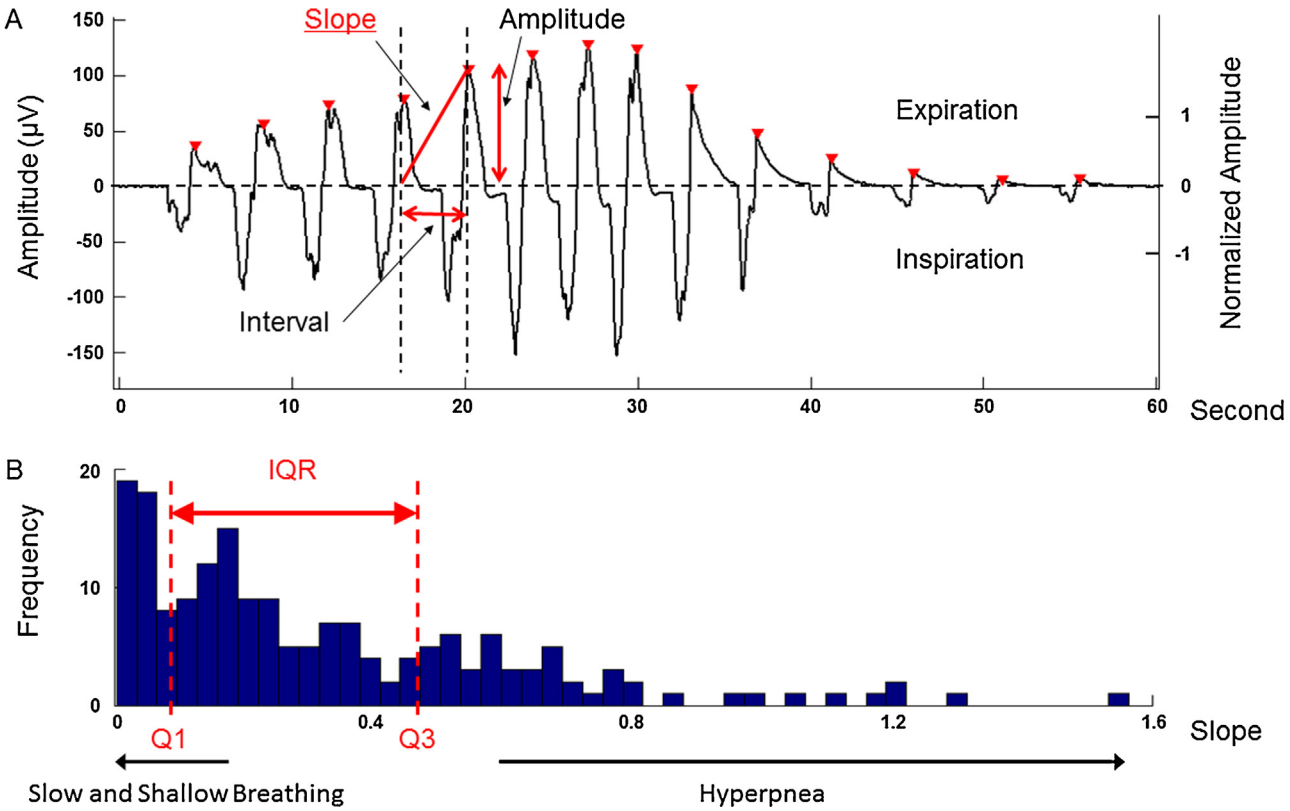

Fig. 1. Respiratory waveform analysis and histogram-based frequency distribution measurement. An example of Cheyne–Stokes respiratory waveform for one minute is shown (A). We identified expiratory peaks (red inverted triangles), and the "slope" of each expiration was calculated by normalized peak expiratory amplitude (longitudinal arrow) divided by the corresponding peak-to-peak respiratory interval (horizontal arrow). A histogram of all consecutive values of expiratory slope for 15 min in the same patient was created (B). The interquartile range (IQR) was defined as a novel index of respiratory instability (RI-index). Q1 and Q3 denote the 25th and 75th percentiles, respectively.

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