Journal of Cardiology xxx (2017) xxx–xxx

Contents lists available at ScienceDirect

Journal of Cardiology

journal homepage: www.elsevier.com/locate/jjcc

Original article

Independent prognostic importance of respiratory instability and sympathetic nerve activity in patients with chronic heart failure

Hidetsugu Asanoi (MD, PhD, FJCC)[a,*], Daisuke Harada (MD)[a], Yoshitaka Oda (MD, PhD)[b], Hiroshi Ueno (MD, PhD)[a], Junya Takagawa (MD, PhD)[a], Hisanari Ishise (MD, PhD)[a], Yukiko Goso (MD, PhD)[b], Shuji Joho (MD, PhD)[b], Hiroshi Inoue (MD, PhD, FJCC)[b]

[a] The Cardiology Division, Imizu Municipal Hospital, Imizu City, Toyama, Japan
[b] The Second Department of Internal Medicine, Toyama University Hospital, Toyama City, Toyama, Japan

ARTICLE INFO

Article history:
Received 19 December 2016
Received in revised form 20 February 2017
Accepted 28 February 2017
Available online xxx

Keywords:
Heart failure
Respiratory instability
Sympathetic nerve activity
Prognosis

ABSTRACT

Background: Respiratory instability in chronic heart failure (CHF) is characterized by irregularly rapid respiration or non-periodic breathing rather than by Cheyne–Stokes respiration. We developed a new quantitative measure of respiratory instability (RSI) and examined its independent prognostic impact upon CHF.

Methods: In 87 patients with stable CHF, respiratory flow and muscle sympathetic nerve activity (MSNA) were simultaneously recorded. RSI was calculated from the frequency distribution of respiratory spectral components and very low frequency components.

Results: During a mean follow-up of 85 ± 38 months, 24 patients died. Sixteen patients who died of cardiac causes had a lower RSI (16 ± 6 vs. 30 ± 21, $p < 0.01$), a lower specific activity scale (4.3 ± 1.4 Mets vs. 5.7 ± 1.4 Mets, $p < 0.005$), a higher MSNA burst area (16 ± 5% vs. 11 ± 4%, $p < 0.001$), and a higher brain natriuretic peptide (BNP) level (514 ± 559 pg/ml vs. 234 ± 311 pg/ml, $p < 0.05$) than 71 patients who did not die of cardiac causes. Multivariate analysis revealed that RSI ($p = 0.015$), followed by MSNA burst area ($p = 0.033$), was an independent predictor of subsequent all-cause deaths and that RSI ($p = 0.026$), MSNA burst area ($p = 0.001$), and BNP ($p = 0.048$) were independent predictors of cardiac deaths. Patients at very high risk of fatal outcome could be identified by an RSI < 20.

Conclusions: The daytime respiratory instability quantified by a new measure of RSI has prognostic importance independent of sympathetic nerve activation in patients with clinically stable CHF. An RSI of <20 identifies patients at very high risk for subsequent all-cause and cardiovascular death.

Introduction

Augmented sympathetic discharge, an established prognosticator of early mortality in chronic heart failure (CHF) [1,2], is known to be linked to respiration through direct coupling between the respiratory and autonomic centers and through reflexes from lungs and central hemodynamics [3–6]. In fact, sleep-disordered breathing that frequently occurs in patients with CHF is accompanied by sympathoexcitation [7], enhanced central chemoreflex [8,9], circulatory delay between the lungs and chemoreceptors [9], lung congestion [10], and eventually elevated mortality [11,12]. However, the circadian respiratory monitoring of patients with CHF revealed that daytime, rather than nocturnal Cheyne–Stokes respiration correlated more closely with the severity of CHF [12]. The daytime respiratory instability is characterized more frequently by unstable respiration such as rapid, irregular, and non-periodic respiration with transient sighing or apnea rather than Cheyne–Stokes respiration [13]. However, a quantitative and simple measure of respiratory instability that could be applicable not only to periodic breathing but also to irregular rapid and shallow respiration without periodicity has not yet been established. Furthermore, despite the close relationship between respiration and sympathetic nerve activity, it remains uninvestigated whether the respiratory instability such as non-periodic and irregular respiration has a prognostic importance independent of sympathetic nerve activation. We postulated that such daytime respiratory instability could be an integrated

* Corresponding author at: The Cardiology Division, Imizu Municipal Hospital, 20 Hohnoki, Imizu City, Toyama 934-0053, Japan.
E-mail address: hasanoi@kmh.biglobe.ne.jp (H. Asanoi).

http://dx.doi.org/10.1016/j.jjcc.2017.02.011
0914-5087/

indicator of neuroautonomic, hemodynamic, and respiratory derangement associated with worsening heart failure and thereby indicates a potential prognostic warning.

In the present study we introduce a new respiratory stability index (RSI), which is a quantitative measure of respiratory instability that faithfully reflects the magnitude of the non-periodic irregular respiratory fluctuations as well as Cheyne–Stokes respiration. We examined the independent prognostic impact of RSI on patients with CHF as compared to sympathetic nerve activity, using simultaneous recordings of respiratory flow and muscle sympathetic nerve activity (MSNA).

Materials and methods

Patient population

We retrospectively enrolled 87 consecutive patients [male, $n = 63$; female, $n = 24$; mean age, 58 (range, 21–80) years] with a history of heart failure who had undergone simultaneous measurements of respiratory flow and MSNA between July 1998 and January 2006. Among them, 66 patients had a radiographic cardio-thoracic ratio of >0.55, an echocardiographic left ventricular (LV) end-diastolic diameter of >55 mm or a LV ejection fraction of <0.45. The remaining 21 patients had a history of heart failure with a preserved LV ejection fraction and a normally sized heart. The number of patients with New York Heart Association (NYHA) functional classes I, II, and III were 21, 32, and 34, respectively. Patient-reported functional capacity was assessed using a specific activity scale [14] that averaged 5.4 ± 1.5 Mets. The causes of heart failure were ischemic heart disease, dilated cardiomyopathy, valvular heart disease, and others in 22, 33, 19, and 13 patients, respectively. All patients were under stable conditions for heart failure and none of them had experienced worsening heart failure within the previous two weeks.

Ethical approval

This study was carried out in compliance with the principles laid down in the Helsinki Declaration. Informed consent to participate in this study was provided by all patients. The study was approved by the Institutional Human Subjects Review Committee in Toyama University Hospital.

Measurements

All parameters were measured in supine, alert patients as previously described [4,6,15]. Blood pressure was measured by noninvasive tonometry (Jentow 7700, Colin, Komaki, Japan) that could accurately trace analog pressure. Respiratory flow was continuously determined on a breath-by-breath basis using the hot wire anemometer (Minato AE-300, Osaka, Japan). Multiunit records of efferent postganglionic sympathetic nerve activity to skeletal muscle district were obtained using a microelectrode inserted directly into the left peroneal nerve posterior to the fibular head. The nerve signal was amplified by a factor of 100,000 fed through a band-pass filter (500–5000 Hz), and integrated with a custom nerve traffic analysis system (Neuropack ΣMEB-5504, Nihon Kohden, Tokyo, Japan). Integrated nerve activity, blood pressure, electrocardiogram (ECG), and respiratory flow were digitized at 1000 Hz per channel by an analog-digital converter (DT9804-USB, Data Translation Inc., Marlboro, MA, USA) and directly stored on a hard-disk memory system (Latitude C600, Dell Corp., Round Rock, TX, USA). Stationary 5-min periods of data were selected for further analyses from more than 30 min recordings, while patients were asked to relax but not to fall asleep.

We identified RR intervals as well as systolic and diastolic blood pressure from each beat. Respiratory flow was resampled at 4 Hz and then integrated to obtain instantaneous ventilatory volume (IVV) (Fig. 1). All patients underwent echocardiography and blood samples were obtained from 80 of them who had remained supine for at least 30 min to measure brain natriuretic peptide (BNP).

Evaluation of muscle sympathetic nerve activity

Sympathetic neural bursts were identified in the integrated signals by their characteristic appearance and relationship to R wave of ECG and to instantaneous blood pressure. The MSNA was assessed as burst rate (bursts/min), incidence (bursts/100 beats), and area (%). The MSNA burst area is expressed as mean integrals of the MSNA normalized by the maximal amplitude, as reported previously [15]. Briefly, transient electromyographic or motor and sensory nerve activity sometimes produces slow baseline fluctuations and results in incorrect evaluation of burst areas. Therefore, baseline drift caused by such noises was detected and subtracted from the original integrated nerve activity (Fig. 2). The burst area has a considerable advantage over burst incidence or rate for MSNA quantification in that it takes amplitude distribution into account [15].

Respiratory stability index

Respiration is considered unstable if natural oscillatory behavior fails to approach a state in which every cycle is identical to every other cycle [13]. This viewpoint could encompass a variety of respiratory instability such as nonperiodic breath-to-breath fluctuation other than periodic oscillatory ventilation. By this definition, we focused on two frequency ranges to estimate RSI (Fig. 1). One was the respiratory frequency components which were retrieved from the IVV by removing high or low frequency noise through a 5th-order band-pass Butterworth filter with cut-off frequencies of 0.11 and 0.5 Hz. The other components comprised the very low frequency of periodic breathing which was obtained by tracing peaks of the IVV with its baseline adjusted to zero and then applying the band-pass filter with cut-off frequencies of 0.008 and 0.04 Hz. The maximum entropy method was applied to these two respiratory and periodic breathing curves to extract the spectral components of respiratory variations from each wave. All spectral power was normalized by the ratio (%) of the maximal power of the respiratory components (Fig. 1). In the evaluation of respiratory instability, we focused mainly on respiratory interval variations and equally adopted all respiratory frequency points as far as they have spectral power above 5% of the maximum respiratory power (Fig. 3A). The very low frequency points of the periodic breathing curve were also taken into account in evaluating RSI only when the maximal power of the very low frequency components was $>50\%$ of the maximal power of the respiratory components (Fig. 3B and C). The distribution of these respiratory frequency points was evaluated by the standard deviation and RSI was defined as the reciprocal of the standard deviation. The normal values of RSI obtained from 29 alert healthy subjects (51 ± 20 years old) in our institutes were 43 ± 21 (mean $\pm$ standard deviation).

Follow-up and documentation of end points

All 87 patients enrolled between July 1998 and January 2006 were followed up at the outpatient clinics of our hospitals, and their status was determined from medical records. The follow-up of those who had not visited the clinic as scheduled was obtained by telephone interview of the patient, patient's family, or primary care physicians. The composite end point was death due to all causes and cardiac causes (sudden death, progressive heart failure, or acute myocardial infarction).

Please cite this article in press as: Asanoi H, et al. Independent prognostic importance of respiratory instability and sympathetic nerve activity in patients with chronic heart failure. J Cardiol (2017), http://dx.doi.org/10.1016/j.jjcc.2017.02.011