Is It Possible to Distinguish Patients with Terminal Stage of Heart Failure by Analyzing Their Breathing Patterns?

Oscillatory Breathing as a Manifestation of Poor Prognosis in Advanced Heart Failure

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The recently revised guidelines for heart failure in Japan discuss the terminal phase of heart failure.¹⁾ Severe heart failure resistant to all treatments is considered as “stage D,” treatment refractory heart failure. Generally, these patients with heart failure are repeatedly hospitalized more than twice per year so special treatments are recommended, or end-of-life care is indicated. Palliative care has developed as a terminal care for cancer and AIDS, but it has been considered for all life-threatening diseases. In such patients, early discoveries of physical and psychosocial problems, accurate assessments, and coping are important. For patients with cancer, it is usually not difficult to estimate their end of life, and patients, their families, and related medical professionals never miss the time to start hospice care. However, patients with chronic heart failure are repeatedly hospitalized because of acute worsening, and then they require terminal care in their last stage. Many cases of recovery have been observed among patients with severe heart failure by intensive acute treatments. Therefore, even for heart failure experts, it is difficult to determine which patients are entering the terminal stage and which ones should receive more intensive treatment.

Many elderly people in Japan are in a state of asymptomatic heart failure or pre-heart failure condition. Most of them have a frail condition and may easily develop severe heart failure triggered by a common cold, excessive alcohol consumption, and excessive salt intake. Cognitive function decreases in elderly patients with heart failure, which leads to a decrease in self-care ability for disease management of heart failure, and these conditions may cause acute worsening of chronic heart failure. Unfortunately, these patients are less likely to feel subjective symptoms even if their heart failure is severely worsening. This may cause patients to delay their treatment. Although B-type natriuretic peptide is a valuable biomarker to indicate the severity and prognosis of heart failure, it may be difficult to distinguish patients with end-stage heart failure. As an important physical finding to estimate the se-

verity and prognosis of heart failure, physicians could focus on oscillatory breathing in patients with advanced heart failure.

Many factors for predicting prognosis of heart failure have been established. Among them, Cheyne-Stokes breathing is a well-known predictive indicator for severe heart failure.²⁾ Central sleep apnea with Cheyne-Stokes breathing has been demonstrated as an additional highly prevalent comorbidity in heart failure with either reduced or preserved ejection fraction.^{3,4)} Cardiopulmonary exercise testing (CPX) is widely used to evaluate heart failure severity and necessary for grading one's exercise capacities.¹⁾ Furthermore, CPX provides traditional prognostic indicators.^{5,6)} The presence of oscillatory ventilation during exercise evaluated by CPX is frequently observed in patients with severe heart failure and has been reported as one of the poorest prognostic indicators.^{7,8)}

Oscillatory breathing characterized by cyclic variation of ventilation with or without interposed apnea has been observed at rest,⁹⁾ during sleep,⁹⁻¹²⁾ and during exercise¹³⁻¹⁵⁾ in heart failure. Since all forms of these abnormal breathing patterns cause similar detrimental effects on clinical outcomes, they are considered collectively as “altered breathing syndrome,” which should be recognized as a comorbid condition of heart failure.¹⁶⁾ The mechanisms of altered breathing syndrome include but are not limited to prolongation of circulation time accompanied by severe heart failure, excessive activated reflex of the chemoreceptor/baroreceptor, and increased dead space due to pleural effusion and pulmonary edema.¹⁷⁾

In chronic heart failure patients with central sleep apnea and Cheyne-Stokes breathing, hypoxemia may contribute to increased C-reactive protein levels and augment the release of inflammatory cytokines, adhesion molecules, and insulin.^{18,19)} These mechanisms may further exacerbate heart failure through hypoxia in tissues, increasing the production of inflammatory cytokines, excessive production of reactive oxygen species, sympathetic nervous system activation, vascular endothelial dysfunction,

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Figure. Conceptual classification of heart failure severity based on oscillatory breathing patterns. Stage CS indicates stage C heart failure with Cheyne-Stokes breathing at rest.

renin-angiotensin system (RAS) activation, and other ways. Therefore, detecting oscillatory breathing at rest and/or during exercise by CPX may clarify the severity and prognosis of heart failure.

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Himi, *et al.* clarified the severity of patients with heart failure by analyzing respiratory patterns of oscillatory breathing at rest and exercise.²⁰⁾ Although the pattern of breathing is altered, it is difficult to conceptualize the difference analyzed during a physical examination. As shown in p.714, Figure 1, breathing can be clearly divided into three patterns in cardiovascular patients analyzed by CPX.²⁰⁾ The details of the mechanisms and differences in oscillatory breathing at rest and during exercise are unknown; however, the prolonged circulation time is a significant determinant of oscillatory breathing, and the cycle length of oscillatory breathing is related to the circulation time and closely linked to the severity of heart failure.²⁰⁾ According to a combination of mathematical modeling and direct measurement, daytime oscillatory breathing in heart failure is closely related to chemoreflex hypersensitivity and reduced stability that predicts mortality in patients with advanced heart failure.²¹⁾ Himi, *et al.* concluded that cardiac function is more impaired in cardiac patients who manifest oscillatory breathing at rest and during exercise than in those who manifest oscillatory breathing only at rest or only during exercise.²⁰⁾ The frequent occurrence of oscillatory breathing may be a more important indicator for severe heart failure, regardless of during exercise or at rest.

In heart failure, autonomic dysregulation is positively correlated with oscillatory breathing and alterations in cardiovascular reflexes,^{22,23)} and central neural control of sympathetic nerve activity.²⁴⁾ Kruppel-like factor 2 expression in the carotid bodies may reflect oscillatory breathing,

autonomic dysregulation, and an increased incidence of arrhythmia in animal models of heart failure.²⁵⁾ Sympathetic overactivity contributes to ventricular arrhythmias²⁶⁾ and is an independent prognostic factor in chronic heart failure.²⁷⁾

Cardiac rehabilitation is safe and effective for improving exercise capacity, quality of life, and prognosis of patients with heart failure.²⁸⁻³⁰⁾ Cardiac rehabilitation reduced visceral adipose tissue in patients with chronic heart failure³¹⁾ and reduced the coronary plaque volume in patients with acute coronary syndrome.³²⁾ Notably, exercise training in cardiac rehabilitation also reduced the duration of exercise oscillatory ventilation³³⁾ and oscillation amplitude³⁴⁾ without changing the cycle length in patients with chronic heart failure. Therefore, cardiac rehabilitation improves cardiopulmonary efficiency and functional capacity in patients with heart failure, and improves prognosis by improving oscillatory breathing and autonomic imbalance.

Oscillatory breathing is considered as one of the useful indicators to estimate the severity and outcome of heart failure. Yet, it remains unknown whether this index could be improved by heart failure treatment, aside from cardiac rehabilitation. Oscillatory breathing during exercise disappears when an adaptive servo-ventilator is used for heart failure patients with Cheyne-Stokes breathing at rest,³⁵⁾ and it may have great potential if the prognosis of heart failure is improved in these patients. Especially in advanced heart failure patients with oscillatory breathing during exercise and at rest, it may help to clarify whether the patients with advanced heart failure have shifted to stage D (Figure). An abnormal breathing pattern could indicate that terminal care rather than intensive heart failure treatment should be considered in these patients to improve their quality of life. Further studies are needed to clarify the usefulness of evaluating oscillatory breathing as a prognostic indicator for advanced heart failure.

Disclosures

Conflicts of interest: None.

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