Blood Oxygen, Sleep Disordered Breathing, and Respiratory Instability in Patients With Chronic Heart Failure
— PROST Subanalysis —

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Background: Respiratory stability index (RSI), a semi-quantitative measure of respiratory instability, was found to reflect congestive and other clinical status of acutely decompensated heart failure in the PROST study. Given that the association between RSI and another important factor affecting respiration, such as peripheral oxygen saturation (SpO\textsubscript{2}), and the influence of oxygen inhalation on this association were undetermined, and that the association between common sleep-disordered breathing (SDB) parameters and RSI was unknown, we performed a subanalysis using PROST data.

Methods and Results: Correlation analyses were performed to evaluate the relationships between RSI, SpO\textsubscript{2}, and other SDB parameters (3% oxygen desaturation index [3%ODI], respiratory disturbance index [RDI]) using Spearman's rank correlation. RSI and overnight mean SpO\textsubscript{2} were not significantly correlated either after admission (n=38) or before discharge (n=36; r=0.27, P=0.10 and r=0.05, P=0.76, respectively). This correlation was also not affected by presence or absence of oxygen inhalation. 3%ODI, RDI and RSI were significantly and inversely correlated both after admission and before discharge.

Conclusions: RSI and blood oxygen level were not significantly correlated irrespective of oxygen inhalation, while the SDB parameters were significantly correlated, suggesting that RSI reflects lung congestion independently of blood oxygen concentration and, thus, can be a useful indicator of the non-invasive assessment of lung congestion.

Key Words: Apnea; Chronic heart failure; Respiratory instability; Sleep-disordered breathing; SpO\textsubscript{2}

Heart failure (HF) has been rapidly increasing in the developed countries. Efficient control of HF is an important issue, requiring establishment of a tool for convenient and reliable detection of the congestive state and of the other manifestations of HF in daily in-hospital clinical care or home care. HF patients are known to often have both obstructive and central sleep-disordered breathing (SDB)\textsuperscript{2,3} Aside from central SDB, typically known as Cheyne-Stokes respiration (CSR), HF patients have been reported as having abnormal respiratory rhythms characterized by shallow and irregular breathing.\textsuperscript{4,6} Such irregular breathing occurs not only during sleep, but also even when the patient is awake. Therefore, quantification of the irregular breathing and SDB may serve as an important marker of HF exacerbation and can be a useful tool in daily clinical practice. We previously proposed respiratory stability index (RSI) as a tool for quantifying irregular breathing.\textsuperscript{7} In our previous study in HF patients, RSI increased with improvement in lung congestion, and had the potential to become a marker of congestion in HF. In addition to lung congestion,\textsuperscript{9-11} however, other factors known to contribute to respiratory stability include carbon dioxide concentration,\textsuperscript{12} oxygen concentration,\textsuperscript{13,14} sensitivity of chemoreceptors,\textsuperscript{15} circulation time,\textsuperscript{16,17} and upper
airway narrowing, as well as sympathetic nervous activity regulating these factors. It is unknown whether not only lung congestion, but also any of these factors were related to the RSI changes observed at HF exacerbation. With a focus on any association between blood oxygen or oxygen inhalation, SDB, and RSI, we conducted a subanalysis using PROST study data to determine (1) the influence of oxygen level (peripheral capillary oxygen saturation, SpO₂) on RSI; (2) the influence of oxygen inhalation on any relationship between RSI and SpO₂; and (3) an association between other SDB parameters and RSI.

Methods

Patients
All patients included for analysis in the PROST study (UMIN 000019905) were examined in the present study. The study design and results of the PROST study have been reported elsewhere. In summary, PROST was a multicenter, prospective, observational study to examine the usefulness of RSI assessment during the recovery process after HF hospitalization for acute decompensated HF. All patients were aged ≥20 years and had had no respiratory assist equipment such as positive pressure ventilation or oxygen inhalation before the index admission. Key exclusion criteria were acute coronary syndrome in the last 3 months, chronic obstructive pulmonary disease, central nervous disorders, hemodialysis, and symptomatic malignancies. Enrollment began in November 2015 and ended in April 2016, with follow-up completed in June 2016. The present study is a pre-specified subanalysis using data obtained from the PROST study.

Target Sample Size
In the PROST study, patients were enrolled from 9 centers in Japan. We started enrollment from the end of November. We assumed that during the winter period (December–April), for each center, on average 2 patients would be admitted for worsening HF, and the enrollment rate was 50%. As a result, we set the target sample size at 40, and we enrolled 44 patients.

Assessment of HF
The Central Adjudication Committee, composed of 3 cardiologists, determined, in a blinded manner, clinical HF status at hospitalization (exacerbation) and at discharge (recovery) for each patient.

Assessment of SDB
All night respiratory events were recorded using a portable respiratory polygraphy (PG) device (SAS-3200, Nihon Kohden, Tokyo, Japan) on 2 occasions: soon after admission (deterioration phase) and before discharge (post-recovery phase). The PG was set in place before bedtime at night and removed on waking. An airflow sensor was placed at the oronasal area, and an SpO₂ sensor was placed on a fingertip. Nasal pressure signals were digitized and sampled at 32 Hz and SpO₂ at 2 Hz. These data were analyzed off-line using a personal computer. SpO₂ was continuously measured, and mean and minimum SpO₂ were calculated. Respiratory disturbance index (RDI) was identified as follows: apnea was defined as a drop in the peak

thermal sensor excursion >90% of baseline and lasting ≥10s, and hypopnea was defined as a >50% reduction in oronasal airflow lasting ≥10s together with a >3% drop in oxygen saturation. RDI was calculated as the sum of apnea and hypopnea episodes per hour of sleep.

RSI Measurement
The overnight airflow signals obtained by PG were full-wave rectified and detrended. The data then underwent spectral analysis (maximum entropy method) for determination of variability in the airflow component. RSI was defined as follows:

\[ RSI = \frac{1}{SD \text{ of respiratory component}} \]

The program used to calculate RSI, created by one of the authors, underwent validation by an academic research organization (ARO) of Kyushu University Hospital.

Endpoints
The primary endpoint of this pre-specified subanalysis was the association of oxygen level (peripheral capillary oxygen saturation, SpO₂) and RSI. Secondary endpoints were influence of oxygen inhalation on any relationship between RSI and SpO₂, as well as on the association between other SDB parameters (3%ODI and RDI) and the RSI. To determine whether oxygen inhalation affected the correlation between RSI and SpO₂, patients were classified into 2 groups, with and without oxygen inhalation at the first recording after admission, and the correlation between RSI and mean SpO₂ before and after treatment of HF was compared.

Statistical Analysis
Spearman’s rank correlation coefficients were calculated to determine correlations. Correlation with RSI was examined for SpO₂, minimum SpO₂, % of time with SpO₂<90% and other SDB parameters such as 3%ODI and RDI. Differences in correlation according to oxygen inhalation status were evaluated using the linear mixed-effects models including an interaction term between each parameter and oxygen inhalation status. Influence of time point for the correlations between RSI and each parameter were also evaluated on similar models. We conducted univariate and multivariate linear regression analysis to clarify the effects on RSI. Statistical significance was defined as P<0.05. Statistical analysis was performed using SAS version 9.3 (SAS Institute, Cary, CA, USA).

Results

Patients
Of a total of 44 patients who provided informed consent in the PROST study, 2 patients withdrew consent before the end of initial PG and 1 patient underwent only initial PG. Baseline patient data for the remaining 41 patients after exclusion of these 3 patients are summarized in Table 1 according to oxygen inhalation status. After-admission PG data were obtained from 38 patients, and before-discharge PG data were obtained from 36 patients. Those patients with apparent outliers from the PG data or with missing data as determined by the central review committee, were excluded from the 44 patients.

Oxygen inhalation was performed in 13 of the 39 patients after admission. Of these 13 patients, 12 patients had PG before discharge without oxygen inhalation. The flow rate
RSI and Mean SpO2:
RSI and overnight mean SpO2 were not significantly correlated after admission (n=38) or before discharge in all patients (n=36; r=0.27, P=0.10; r=0.05, P=0.76, respectively). The extent of correlation between RSI and mean SpO2 after admission did not significantly differ from that before discharge (P=0.55).

Table 1. Baseline Patient Characteristics

| Variable                        | Without oxygen (n=29) | With oxygen (n=12) | Total (n=41) |
|---------------------------------|-----------------------|--------------------|--------------|
| Age (years)                     | 74.9±12.3             | 65.7±8.8           | 72.2±12.1    |
| Sex (Male)                      | 17 (58.6)             | 8 (66.7)           | 25 (61.0)    |
| Underlying heart disease        |                       |                    |              |
| DCM                             | 6 (20.7)              | 0 (0.0)            | 6 (14.6)     |
| IHD                             | 10 (34.5)             | 5 (41.7)           | 15 (36.6)    |
| VHD                             | 3 (10.3)              | 2 (16.7)           | 5 (12.2)     |
| Hypertensive heart disease      | 8 (27.6)              | 3 (25.0)           | 11 (26.8)    |
| Others                          | 2 (6.9)               | 2 (16.7)           | 4 (9.8)      |
| Complications                   |                       |                    |              |
| AF                              | 16 (55.2)             | 7 (58.3)           | 23 (56.1)    |
| DM                              | 5 (17.2)              | 8 (66.7)           | 13 (31.7)    |
| Hypertension                    | 14 (48.3)             | 10 (83.3)          | 24 (58.5)    |
| CKD                             | 11 (37.9)             | 3 (25.0)           | 14 (34.1)    |
| Functional capacity             |                       |                    |              |
| NYHA I                          | 0 (0.0)               | 0 (0.0)            | 0 (0.0)      |
| II                              | 1 (3.4)               | 1 (8.3)            | 2 (4.9)      |
| III                             | 22 (75.9)             | 9 (75.0)           | 31 (75.6)    |
| IV                              | 6 (20.7)              | 2 (16.7)           | 8 (19.5)     |
| Specific activity scale (Mets)  | 2.4±1.1               | 2.3±1.1            | 2.3±1.1      |
| HR (beats/min)                  | 84.1±23.5             | 102.2±44.2         | 89.4±31.5    |
| Pulse rate (beats/min)          | 79.9±15.6             | 89.8±23.7          | 82.8±18.6    |
| Systolic BP (mmHg)              | 120.3±19.0            | 126.8±29.6         | 122.3±22.4   |
| Diastolic BP (mmHg)             | 71.0±13.6             | 81.5±21.6          | 74.0±16.8    |
| Rales                           |                       |                    |              |
| −                               | 14 (48.3)             | 7 (58.3)           | 21 (51.2)    |
| +                               | 15 (51.7)             | 4 (33.3)           | 19 (46.3)    |
| ++                              | 0 (0.0)               | 1 (8.3)            | 1 (2.4)      |
| CTR (%)                         | 63.8±9.1              | 61.3±4.1           | 63.1±7.9     |
| LVDD (mm)                       | 54.9±8.5              | 55.8±9.0           | 55.1±8.5     |
| LVDS (mm)                       | 42.7±11.2             | 44.0±9.3           | 43.0±10.6    |
| LVEF (%)                        | 44.6±17.9             | 42.9±11.3          | 44.2±16.3    |
| LAD (%)                         | 46.5±10.4             | 45.1±6.4           | 46.1±9.4     |
| BNP (pg/mL)                     | 808.69±544.18         | 1,375.32±2,887.18  | 974.53±1,602.43 |
| Creatinine (mg/dL)              | 1.4±0.7               | 1.0±0.4            | 1.3±0.6      |
| Medications                     |                       |                    |              |
| Diuretic                        | 20 (69.0)             | 6 (50.0)           | 26 (63.4)    |
| ACEI/ARB                        | 16 (55.2)             | 6 (50.0)           | 22 (53.7)    |
| β-blocker                       | 14 (48.3)             | 5 (41.7)           | 19 (46.3)    |
| Inotropic drug                  | 5 (17.2)              | 0 (0.0)            | 5 (12.2)     |
| Aldosterone antagonist          | 15 (51.7)             | 6 (50.0)           | 21 (51.2)    |

Data given as mean ± SD or n (%). ACEI, angiotensin-converting enzyme inhibitor; AF, atrial fibrillation; ARB, angiotensin II receptor blocker; BNP, brain natriuretic peptide; BP, blood pressure; CKD, chronic kidney disease; CTR, cardiothoracic ratio; DCM, dilated cardiomyopathy; DM, diabetes mellitus; HR, heart rate; IHD, ischemic heart disease; LAD, left atrial diameter; LVDD, left ventricular end-diastolic diameter; LVDS, left ventricular end-systolic diameter; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association class; VDH, valvular heart disease.

of oxygen in the patients who had oxygen inhalation was 1 L/min in 1 patient, 2 L/min in 10 patients and 3 L/min in 1 patient. No patient used NIPPV at the time of PG in this study. In contrast, no oxygen inhalation was performed in 26 of 39 patients after admission, of whom 24 patients underwent PG before discharge (Figure 1). Respiratory indices according to oxygen inhalation status are shown in Table 2.
Effect of Oxygen Inhalation on RSI and Mean SpO₂
Of the patients with oxygen inhalation at PG after admission, RSI and mean SpO₂ were not significantly correlated after admission (n=12; r=0.17, P=0.60; Figure 2A). Also, of the patients without oxygen inhalation at PG after admission or before discharge, RSI and mean SpO₂ were not significantly correlated (after admission, r=0.37, P=0.06; before discharge, r=0.05, P=0.76; Figure 2B). In addition, on analysis of the influence of oxygen inhalation on the extent of correlation between mean SpO₂ and RSI, there was no significant interaction (P=0.80), meaning that the correlation between mean SpO₂ (%) and RSI was not influenced by oxygen inhalation.

Other SDB Parameters and RSI
The correlation between 3%ODI or RDI and RSI was examined. 3%ODI and RSI had a significant correlation both after admission and before discharge (after admission, r=−0.63, P<0.01; before discharge, r=−0.45, P<0.01; Figure 3). Also, RDI and RSI had a significant correlation after admission and before discharge (r=−0.56, P<0.01; r=−0.45, P<0.01, respectively; Figure 4). In addition, the correlation between 3%ODI and RSI or between RDI and RSI after admission did not differ to those before discharge (P=0.54 and P=0.42, respectively).

Indicators of RSI
We conducted univariate linear regression analysis for association with RSI (Table 3). We found that only gender tended to be related to RSI (P=0.006). Other factors (age, atrial fibrillation [AF], serum Na concentration, ejection fraction [EF], angiotensin-converting enzyme inhibitor/angiotensin II receptor blocker, β-blocker, diuresis, inotropic agent) did not have a significant association with RSI. When we conducted multivariate linear regression analysis, however, using gender, age, AF and EF, only age and EF had a significant association with RSI (P=0.0034 and 0.036, respectively).

Table 2. Respiratory Indices vs. Oxygen Inhalation Status

| Variable | After admission | Before discharge |
|----------|----------------|-----------------|
|          | n All | With oxygen n | Without oxygen n | n All | With oxygen n | Without oxygen n |
| SpO₂     | 38    | 95.0±2.5 | 26             | 94.0±2.0 | 36    | 95.7±1.9 |
| RDI      | 38    | 17.2±18.6 | 26             | 18.8±19.7 | 36    | 13.8±16.2 |
| 3%ODI    | 38    | 18.2±17.6 | 26             | 21.4±18.8 | 36    | 13.3±14.5 |
| Mean RSI | 38    | 27.9±17.0 | 26             | 27.7±17.6 | 36    | 33.2±16.5 |

Data given as mean±SD. ODI, oxygen desaturation index; RDI, respiratory disturbance index; RSI, respiratory stability index; SpO₂, peripheral capillary oxygen saturation.
RSI and Minimum SpO₂ and % of Time at SpO₂<90%

Correlation between RSI and minimum SpO₂ and % of time spent at SpO₂<90% were examined (Table 4). There were no correlation between RSI and minimum SpO₂ (P=0.15 after admission, P=0.31 before discharge). There was a significant correlation, however, between RSI and % of time spent at SpO₂<90% in all patients (r=−0.33, P<0.05), and in patients without oxygen inhalation after admission (r=−0.41, P<0.05), but the correlation disappeared before discharge (P=0.33).

**Discussion**

The PROST study was a multicenter study to examine whether a marker of RSI in HF patients could be used as a surrogate marker of lung congestion and so on. In the
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Table 3. Indicators of RSI

| Variable     | Univariate analysis |                      |                     | Multivariate analysis |                      |                     |
|--------------|---------------------|----------------------|---------------------|-----------------------|----------------------|---------------------|
|              |                     | Regression coefficient | P-value | Regression coefficient | P-value |
|              |                     |                       |                     |                       |                     |
| Sex (male)   | −15.20              | 0.006                | −11.72             | 0.056                 | 0.01                |
| Age (years)  | −0.31               | 0.18                 | −0.78              | 0.0034                | 0.01                |
| AF           | −6.81               | 0.23                 | −7.68              | 0.17                  | 0.01                |
| LVEF (%)     | 0.30                | 0.15                 | 0.45               | 0.036                 | 0.01                |
| ACEI/ARB     | −0.12               | 0.98                 |                    |                       |                     |
| β-blocker    | 8.73                | 0.12                 |                    |                       |                     |
| Diuresis     | 16.22               | 0.19                 |                    |                       |                     |
| Inotropic agents | −7.69          | 0.24                 |                    |                       |                     |
| Serum Na (mEq/L) | 0.22              | 0.75                 |                    |                       |                     |

Abbreviations as in Tables 1, 2.

Table 4. Correlations Between RSI and Other SpO2 Parameters

| Correlation between RSI and | Phase | O2 inhalation | n | Coefficient | P-value |
|-----------------------------|-------|---------------|---|-------------|---------|
| Minimum SpO2 (%)            |       |               |   |             |         |
| After admission             | All   | 38            | 84.0±8.7 | 0.24 | 0.15 |
|                            | O2(+) | 12            | 88.8±7.4 | 0.39 | 0.21 |
|                            | O2(−) | 26            | 81.8±6.5 | 0.23 | 0.27 |
| Before discharge            | All O2(−) | 36   | 85.8±7.5 | 0.18 | 0.31 |
| % of time spent at SpO2<90% (%) |       |               |   |             |         |
| After admission             | All   | 38            | 9.1±14.7 | −0.33 | 0.041 |
|                            | O2(+) | 12            | 2.5±6.7 | −0.34 | 0.28 |
|                            | O2(−) | 26            | 12.1±16.5 | −0.41 | 0.04 |
| Before discharge            | All O2(−) | 36   | 3.9±10.8 | −0.17 | 0.33 |

Data given as mean±SD. O2(+), with oxygen inhalation; O2(−), without oxygen inhalation. Other abbreviations as in Table 2.

Figure 4. Respiratory stability index (RSI) vs. respiratory disturbance index (RDI) after admission (red circles; r=−0.56, P<0.01; red solid line A, regression line) and before discharge (blue triangles; r=−0.45, P<0.01; blue solid line B, regression line).
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According to the present subanalysis, however, respiratory stretch receptor stimulation, mediated stimulation through hypoxia, associated with RSI. Longer time spent at SpO₂<90% might result in the shown weak association between RSI, and this was not affected by the presence or absence of oxygen inhalation. Thus, neither blood oxygen concentration nor oxygen inhalation affected respiratory instability as measured by RSI. Thus, we may conclude that RSI can be taken as a marker that almost solely reflects the level of pulmonary congestion.

Peripheral chemoreceptors are known to monitor arterial oxygen partial pressure, and their hypoxic chemoreceptor-mediated stimulation increases the ascending impulse and thus causes increase in the respiratory rate and in sympathetic nervous activity, causing heart rate increase. According to the present subanalysis, however, respiratory control via lung congestion-related pulmonary receptor stimulation, C-fiber receptor stimulation, and pulmonary stretch receptor stimulation, appears to more strongly affect the regularity of respiration rather than chemoreceptor-mediated stimulation through hypoxia.

RSI and SpO₂: after admission were weakly (although not significantly) correlated (r=0.27, P=0.10). Before discharge, however, RSI and SpO₂ were not correlated at all. This indicates a possibility that patients with lower SpO₂ had more severe HF with more intense congestion in the acute phase, resulting in the shown weak association between RSI and SpO₂.

We found % of time spent at SpO₂<90% was significantly associated with RSI. Longer time spent at SpO₂<90% might have a stronger association than minimum SpO₂, probably because longer desaturation must mean higher congestion, and it would have a greater effect on the whole night analysis of respiratory stability than a short duration desaturation.

In the linear regression analysis between RSI and the various factors that might affect RSI, aged patients with low EF had low RSI, namely low respiratory stability. In aged patients, the respiratory feedback system tends to be impaired, and low-EF patients would have low cardiac output, both of which are known to reduce respiratory stability. As for the influence of gender, given that the current study consisted of a small number of patients, further study is needed to obtain a definitive answer on the influence of gender on RSI.

A high prevalence of obstructive and central SDB is known in HF patients. We observed significant correlation between RDI or 3%ODI and RSI. Respiratory instability during sleep in patients with HF is considered to consist of obstructive and/or central type SDB and rapid and shallow type unstable respiration, caused mainly by pulmonary receptor stimulation. The frequency of the former oscillation resides at a low and narrow range from 0.01 Hz to 0.1 Hz, whereas that of the latter oscillation, mainly due to pulmonary congestion, scatters at a higher and wide frequency range from 0.1 Hz to 0.5 Hz, and comprises the major part of RSI. Given that central SDB is considered to relate mainly to cardiac output status and that obstructive SDB may not be strongly related to HF status but is more strongly related to obesity or anatomical problems, it is possible that RSI is independent of or only slightly related to the degree of SDB. Therefore, the present finding that there was a significant correlation between 3%ODI and RDI with RSI means that RSI could reflect overall respiratory instability in patients with HF, although it mainly reflects the instability caused by pulmonary congestion. Further analyses utilizing the combinations of SDB parameters and RSI and optimization of their rate of combinations may enable more accurate monitoring of the severity of congestion in HF.

**Estimated Effect of Respiratory Disorder Pattern on RSI**

Because our analysis was based on the data from simple PG, we cannot assess the difference in the actual influence of CSR and obstructive sleep apnea (OSA) separately on the various frequency components of the data. We consider, however, that given that CSR in patients with very low cardiac output generally is very regular and periodic, and that each respiration itself is very regular, this would result in the production of 2 distinct narrow peaks in the power spectrum at lower (0.008–0.039 Hz) and higher frequency (0.08–0.5 Hz) in the area used in the calculation of RSI. In this kind of case, given that the lower frequency peak would be very tall and narrow, this power would be adopted for the calculation, resulting in a wider distribution of standard deviation of frequency (low RSI). In contrast, the breathing in OSA is usually irregular, and this would result in a broader distribution of the power in the low frequency area. As a result, this low-frequency power would not be adopted because the peak is <50% of the higher frequency peak power (from the definition of the RSI calculation), meaning that the standard deviation of frequency distribution would be lower (higher RSI). In the presence of pulmonary congestion, however, respiration would be rapid and shallow, and this would result in a broader distribution of power in the higher respiratory frequency range in CSR and OSA patients equally. In summary, the influence of CSR and OSA on RSI would be different, but the degree of influence would vary depending on the HF status of each patient.

**Study Limitations**

First, in patients with very low SpO₂ on admission, oxygen inhalation was given, resulting in normal SpO₂, and PG would have been performed after their condition had somewhat stabilized. This might have led to smaller intra-individual and inter-individual differences in SpO₂ between before and after treatment. Thus, the narrowed RSI-SpO₂ analysis range may have led to decreased precision of the analysis. From an ethical viewpoint, however, prolonged monitoring of patients with very low SpO₂ without treatment of the low oxygen status is unacceptable. One possible solution would be the analysis of very brief data recorded before the start of treatment. Further analysis with this technique may enable assessment of a broader SpO₂ range, thus producing more reliable results.

Second, blood carbon dioxide (CO₂) concentration, which also has a major effect on respiratory control, could not be measured in this study. Thus, it remains unknown whether CO₂ is correlated with RSI, or whether CO₂ affects any relationship between RSI and congestion or oxygen...
saturation. These should be analyzed in future studies with the use of monitoring of CO2.

Third, the threshold of the power in the frequency range used for calculation of RSI was decided semi-empirically. Given that the power of variability in the low frequency range, which may be related to SDB; and the power of respiratory variability in the high frequency range, which may be more related to lung congestion, were not evenly evaluated, absolute assessment of SDB influence was difficult. With improvement of the algorithm based on results from more patients in the future, the more theoretical analysis of different frequency ranges would become feasible.

Fourth, given that we assessed SDB based on PG, not on polysomnography, we could not classify SDB into central and obstructive types, and could not assess the influence of arousal. We consider that some patients may have had CSR and, given that it consists of low-frequency power, it must have affected RSI in a different way to OSA.

Fifth, the sample size with oxygen (n=12 at admission) and without oxygen (n=26 at admission) is small. We concluded that oxygen inhalation and RSI were not significantly correlated using the linear mixed-effects models, concluded that oxygen inhalation and RSI were not significantly correlated using the linear mixed-effects models, including an interaction term between each parameter and oxygen inhalation status (r=0.17, P=0.60). But we cannot completely rule out the possibility that the small sample size might have affected these results.

Sixth, we consider that the lag time from oxygenation to detection at the chemoreceptor might have an association with RSI, and the analysis would be important. Given, however, that there are various methods to measure the lag time from PG data and we did not validate any method for the current study, due to the length of time required for this, we did not analyze the lag time in the current study.

**Conclusions**

RSI, a marker of respiratory stability, was not significantly correlated with oxygen level in HF patients nor was it affected by oxygen inhalation, suggesting that RSI may be an index specifically reflecting lung congestion independently from blood oxygen concentration or oxygen inhalation. In contrast, markers of SDB, 3%ODI or RDI, and RSI were significantly and inversely correlated, suggesting a pathophysiological analogy of RSI and SDB in HF.

**Conflicts of Interest**

S.A., H.A. received research funding from Teijin Pharma; S.M. received lecture fee from Teijin Pharma; K.D. received scholarship donation from Merck & Co., Otsuka Pharmaceutical, Daichi Sankyo and Takeda Pharmaceutical. The other authors declare no conflicts of interest.

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