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RESEARCH ARTICLE

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Averaged oxygen desaturation improves the prognostic value of the six-minute walk test in elderly patients with heart failure

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Abstract

Heart failure (HF) is a major cause of hospitalization, and exercise capacity is a key prognostic marker. The six-minute walk test (6MWT) is widely used to assess exercise capacity, but six-minute walk distance (6MWD) varies among individuals, especially the elderly. This study aimed to assess the hypothesis that ΔSp_{O_2}-Ex, the average oxygen desaturation during the 6MWT, could enhance the prognostic value of 6MWD in elderly patients with HF for cardiovascular risk prediction. In this single-center, prospective observational study, 55 patients aged ≥65 yr with acute HF were evaluated before discharge. Patients were divided into small and large ΔSp_{O_2}-Ex groups and short and long 6MWD groups based on cutoff values of 6.7% and 220 m, respectively, obtained from the receiver operating characteristics curve analysis. Patients were followed up for 1 yr to assess major adverse cardiovascular events, including rehospitalization for heart failure or cardiovascular death. The mean ΔSp_{O_2}-Ex was 5.8 ± 4.3%, and the mean 6MWD was 237.5 ± 106.7 m. Patients with large ΔSp_{O_2}-Ex had significantly higher event rates [hazard ratio (HR) = 6.66; $P < 0.001$], whereas those with short 6MWD had HR of 2.40 ($P = 0.03$). Combining ΔSp_{O_2}-Ex with 6MWD improved predictive accuracy [area under the curve (AUC) = 0.78] compared with either marker alone (AUC = 0.72 for ΔSp_{O_2}-Ex and 0.62 for 6MWD). Importantly, patients with both large ΔSp_{O_2}-Ex and short 6MWD had the highest event rates, indicating the additive prognostic value of combining both markers. In conclusion, ΔSp_{O_2}-Ex is a complementary marker to 6MWD, improving risk stratification in elderly patients with HF.

NEW & NOTEWORTHY This study evaluates the use of ΔSp_{O_2}-Ex, measured during the six-minute walk test (6MWT), as a complementary prognostic marker to the six-minute walk distance (6MWD) in elderly patients with heart failure. We hypothesize that combining ΔSp_{O_2}-Ex with 6MWD will improve the predictive accuracy for cardiovascular outcomes, offering a practical, noninvasive method for risk stratification and enhancing clinical decision-making for this patient population.

heart failure; peripheral oxygen saturation; prognostic marker; rehospitalization; six-minute walk test

INTRODUCTION

Heart failure (HF) is estimated to affect 38 million individuals worldwide (1). Despite notable advancements in treatment over the past couple of decades, HF continues to be a predominant cause of hospitalizations (2). Because a significant fraction of these hospitalizations are due to acute exacerbation of chronic HF (3), it is crucial to develop novel approaches to identify high-risk patients who need to be subjected to intense care to prevent rehospitalization.

Exercise capacity is a widely accepted clinical index that is strongly correlated with the prognosis of patients with HF (4). The index, including peak oxygen consumption ($\dot{V}O_2$) and lactate threshold, determined by the cardiopulmonary exercise test (CPET) remains the gold standard to evaluate the exercise capacity and prognosis of patients with HF. Meanwhile, because CPET requires substantial materials and resources, the six-minute walk test (6MWT) is frequently used as a preferable alternative, as it is a noninvasive and cost-effective test that demonstrates daily activity energy expenditure (5, 6). The distance covered during this test, termed six-minute walk distance (6MWD), is a pivotal index of a patient's functional status and prognosis (7–10). However, 6MWD is affected by individual patients' physical capability, especially among the elderly with prevalent comorbid conditions (11–13), and, therefore, reliable comparisons of 6MWD can be performed only among patients whose cardiopulmonary capacity is the bottleneck of the

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distance. The 6MWT also showed considerable variability among individuals (14–17). Given these considerations, there is a compelling need to introduce new metrics beyond 6MWD to ensure a more comprehensive and consistent evaluation of an exercise capacity and condition in elderly patients with HF.

Our spotlight is on the exercise-induced desaturation during the 6MWT, namely novel metric averaged decrease in peripheral oxygen saturation during exercise (ΔSp_{O_2}-Ex), representing the average of the disparity between the maximum Sp_{O_2} in the resting phase and the average Sp_{O_2} during the 6MWT. We hypothesize that combining ΔSp_{O_2}-Ex with 6MWD will offer additional prognostic value, potentially improving risk stratification and guiding clinical decision-making. Therefore, the objective of this study is to assess whether ΔSp_{O_2}-Ex can complement 6MWD as a prognostic marker in elderly patients with HF. This endeavor could potentially set the foundation for more individualized therapeutic strategies.

METHODS

Study Design and Population

This clinical study is single-center, prospective, observational study. We assessed 229 patients aged ≥65 yr with a confirmed diagnosis of acute HF based on the Framingham criteria between August 2020 and August 2022. The patients were selected based on their readiness for discharge and clinical stability as judged by the board-certified attending cardiologist. Of the initially registered patients, 174 individuals were excluded based on predefined criteria. Exclusion criteria included patient refusal to participate, inability to provide informed consent due to severe communication disorders or cognitive impairments, dependence on physical assistance for walking (excluding mobility aids), unavailability of the wearable pulse oximeter primarily due to prior commitments by other participants, patients deemed unlikely to complete a 6MWT based on the assessment by certified physical therapists due to any reason including frailty, or the presence of missing data. Ultimately, a cohort of 55 patients met the inclusion criteria and underwent evaluation for the study.

Ethics Approval

The study complied with the principles of the Declaration of Helsinki and was approved by the committee of the institutional review board at Hyogo Medical University (Approval No. 3531). All patients signed the informed consent forms.

Data Collection

We obtained medical records regarding age, gender, body mass index (BMI), heart rate, blood pressure, current medications, coronary artery disease, valvular disease, atrial fibrillation, hypertension, diabetes mellitus, and pulmonary disease. We also collected the data of laboratory examination, including serum levels of N-terminal pro-B-type natriuretic peptide (NT-proBNP), creatinine, estimated glomerular filtration rate (eGFR), hematocrit, and the levels of hemoglobin, and echocardiographic data, including left ventricular diastolic diameter (LVDd), tricuspid regurgitation velocity (TRV), and left ventricular ejection fraction (LVEF) by Teichholz or Simpson's method. We obtained medical records regarding rehospitalization due to HF and cardiovascular death within 365 days. If we could not obtain information from the medical records, we collected it by telephone interview. A chest X-ray was performed to confirm the absence of pulmonary congestion. The Get With the Guidelines-Heart Failure (GWTG-HF) score (18) and the AHEAD [A-atrial fibrillation, H-hemoglobin <130 g/L for men and 120 g/L for women (anemia), E-elderly (age >70 yr), A-abnormal renal parameters (creatinine >130 μmol/L), D-diabetes mellitus] (19) score were calculated based on previously published reports.

Pulmonary Function Tests

The participants underwent comprehensive pulmonary function tests (PFTs) to assess the lung function.

The PFTs were performed using an electric spirometer (DISCOM-21FX; CHEST MI, Tokyo, Japan). The PFTs were performed under the supervision of a certified pulmonary technologist. The primary parameters of interest were the percent vital capacity (%VC) and the forced expiratory volume in 1 s as a percentage of predicted (FEV1%). The measurement protocols followed the standard guidelines (20).

6MWT

The 6MWT was performed before discharge, after confirming hemodynamic stability. The 6MWT was conducted using a standardized approach (21, 22). In brief, patients were instructed to walk at their own pace while attempting to cover as much ground as possible within 6 min. The participants were allowed to use their usual mobility aids. Experienced physiotherapists timed the walk test, calling out the time every 2 min. They encouraged patients every 30 s in a standardized manner, facing the patient and using one of two phrases: "You're doing well" or "Keep up the good work." Patients were allowed to slow or stop and rest during the walk but were asked to resume walking as soon as they felt they were able to.

ΔSp_{O_2}-Ex

To determine the alterations in Sp_{O_2} with precision, we utilized a wearable pulse oximeter (Anypal Walk, ATP-W03; Fukuda Denshi Co., Ltd., Tokyo, Japan). This device was engineered to record and store Sp_{O_2} values continuously, second by second. Obtained Sp_{O_2} data were entered into a computer viewer software (FHM-02 V; Fukuda Denshi). Initially, in the first phase, Sp_{O_2} measurements were taken 30 min prior to the 6MWT, which was defined as the "resting phase." Subsequently, in the second phase, Sp_{O_2} was continuously monitored during the 6MWT to detect any dynamic changes as patients were engaged in the activity. After collecting data from both phases, the maximum Sp_{O_2} during the resting phase and the average Sp_{O_2} during the 6MWT were measured. ΔSp_{O_2}-Ex was defined as the value obtained by subtracting the averaged Sp_{O_2} during the 6MWT from the maximum Sp_{O_2} in the resting phase.

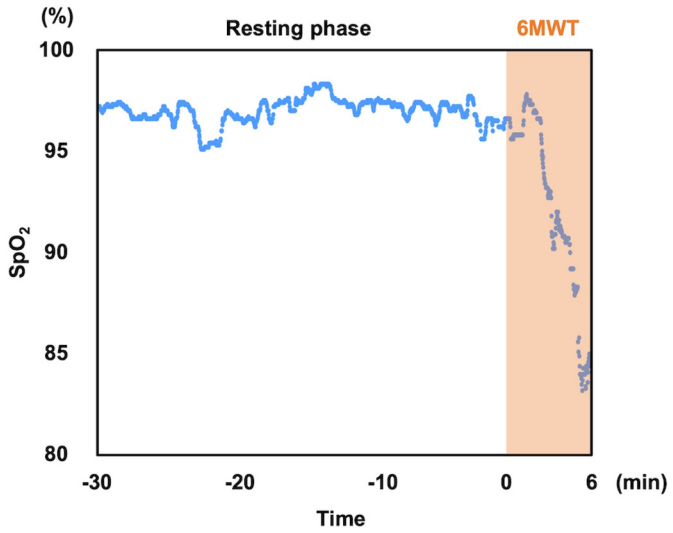

Figure 1. Second-by-second measurement of Sp_{O_2} from the resting phase to the end of In the first phase, Sp_{O_2} measurements were taken 30 min prior to the 6MWT, which was defined as the "resting phase." In the second phase, Sp_{O_2} was continuously monitored during the 6MWT to detect any dynamic changes as patients were engaged in the activity. 6MWT, six-minute walk test.

Clinical Outcomes

The primary outcome measure was 1-yr major adverse cardiovascular outcomes, including rehospitalization due to HF exacerbation, or cardiovascular death. The secondary outcome was a comparison of the usefulness of the 6MWD and ΔSp_{O_2}-Ex as prognostic factors for patients with HF.

Statistical Analysis

Patient data were expressed as means ± SD for normally distributed variables or as median and interquartile range (IQR) for non-normally distributed variables. Comparisons between groups were conducted using independent sample *t* tests for normally distributed variables and Mann–Whitney *U* tests for non-normally distributed variables. Categorical variables were compared using the chi-square test.

A receiver operating characteristic (ROC) analysis was performed to evaluate the ability of ΔSp_{O_2}-Ex and 6MWD to predict major adverse cardiovascular events, including rehospitalization and cardiovascular death within 1 yr. The area under the curve (AUC) was calculated to assess the predictive capability of these parameters. To identify optimal cutoff points for ΔSp_{O_2}-Ex and 6MWD, we used the Youden index, maximizing the sum of sensitivity and specificity.

The Kaplan–Meier survival analysis with log-rank tests was used to compare time-to-event outcomes for the primary and secondary endpoints. Cox proportional hazard models were used to calculate hazard ratios (HRs) with 95% confidence intervals (CIs) for the variables of interest, adjusting for known risk factors. To avoid multicollinearity, ΔSp_{O_2}-Ex and 6MWD were examined in separate models.

A multivariable ROC curve analysis was conducted to assess the combined prognostic value of ΔSp_{O_2}-Ex and 6MWD for predicting major adverse cardiovascular events. In this analysis, we constructed a logistic regression model incorporating these variables and used the predicted probabilities from this model to generate a multivariable ROC curve. The AUC from the multivariable ROC curve was compared against the AUCs of ΔSp_{O_2}-Ex and 6MWD individually to evaluate whether the combination of these variables provided superior prognostic information. The DeLong test was used to statistically compare the AUCs and determine whether the multivariable model offered a significant improvement in predictive capability over the individual parameters.

Statistical significance was assessed using two-tailed *P* values, with a threshold of <0.05 considered significant. All analyses were performed using EZR software (Saitama Medical Center, Jichi Medical University, Japan, v1.41.1), a modified version of the R commander (v2.7-1) (23).

RESULTS

The measurement of ΔSp_{O_2}-Ex was conducted for 55 patients with HF before discharge between August 2020 and August 2022. Figure 1 shows representative data of the temporal changes in Sp_{O_2} every second in the resting phase and during the 6MWT.

The distributions of the 6MWD and ΔSp_{O_2}-Ex are shown in Fig. 2. The mean 6MWD was 237.5 ± 106.7 m and the mean ΔSp_{O_2}-Ex was 5.8 ± 4.3%. As shown in Supplemental Fig. S1, there was no correlation between the maximum Sp_{O_2} levels in the resting phase and ΔSp_{O_2}-Ex ($r = 0.06$, $P = 0.66$).

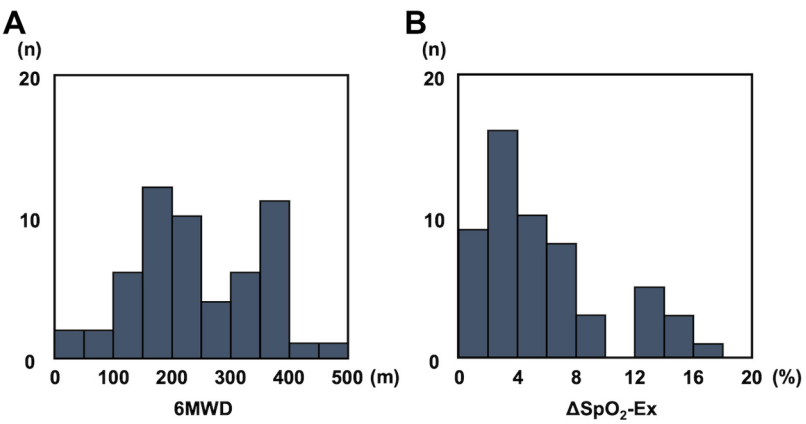

Figure 2. The distribution of 6MWD and ΔSp_{O_2}-Ex. *A*: distribution of 6MWD. *B*: distribution of ΔSp_{O_2}-Ex. The mean 6MWD was 237.5 ± 106.7 m and the mean ΔSp_{O_2}-Ex was 5.8 ± 4.3%. 6MWD, six-minute walk distance; ΔSp_{O_2}-Ex, averaged decrease in peripheral oxygen saturation during exercise.

Table 1. *Cutoff values of ΔSp_{O_2}-Ex and 6MWD*

Parameters	Cutoff Value	AUC	Sensitivity	Specificity
ΔSp_{O_2}-Ex, %	6.7	0.72	0.57	0.96
6MWD, m	220	0.62	0.68	0.63

6MWD, six-minute walk distance; ΔSp_{O_2}-Ex, averaged decrease in peripheral oxygen saturation during exercise; AUC, area under the curve.

Similarly, no correlation was found between ΔSp_{O_2}-Ex and 6MWD ($r = -0.04$, $P = 0.78$) (Supplemental Fig. S2).

For analysis, patients were dichotomized based on their 6MWD and ΔSp_{O_2}-Ex values. The cutoff values for these classifications were determined using specific cutoff values derived from ROC curve analysis. The ΔSp_{O_2}-Ex cutoff value was set at 6.7%, leading to classification into small-ΔSp_{O_2}-Ex (<6.7%; $n = 38$) and large-ΔSp_{O_2}-Ex (≥6.7%; $n = 17$) groups, and the 6MWD cutoff value was established at 220 m, leading to classification into long-6MWD (>220 m; $n = 26$) and short-6MWD (≤220 m; $n = 29$) groups (Table 1).

The baseline characteristics according to the ΔSp_{O_2}-Ex classification are shown in Table 2. The average age of the participants was 80.7 ± 6.7 yr, and 45% were female. At the time of the study, the mean BMI was 21.3 ± 4.3 kg/m^2, the average heart rate was 73.0 ± 15.4 beats/min, and the average blood pressure was 111.2 ± 19.0/63.2 ± 11.5 mmHg. Among all, 44% of the participants had coronary artery disease, 56% had atrial fibrillation, 82% had hypertension, 29% had diabetes, and 22% had pulmonary disease. Laboratory findings included a median NT-proBNP level of 3,084 (1,373, 5,781) pg/mL, a mean

Table 2. *Baseline characteristics of the small- and large-ΔSp_{O_2}-Ex groups*

Characteristics	All	Small-ΔSp_{O_2}-Ex	Large-ΔSp_{O_2}-Ex	*P* Value
Subjects, *n*	55	38	17	
Age, yr	80.7 ± 6.7	80.4 ± 7.3	81.6 ± 5.3	0.54
Gender (female)	25 (45%)	15 (39%)	10 (59%)	0.25
Body mass index, kg/m^2	21.3 ± 4.3	20.7 ± 3.4	22.6 ± 5.7	0.12
Vital signs				
Heart rate, beats/min	73.0 ± 15.4	70.9 ± 14.5	77.7 ± 16.7	0.13
Systolic blood pressure, mmHg	111.2 ± 19.0	113.7 ± 18.9	105.6 ± 18.6	0.14
Diastolic blood pressure, mmHg	63.2 ± 11.5	63.2 ± 11.1	61.1 ± 12.5	0.53
Medical history				
Coronary artery disease, *n*	24 (44%)	17 (45%)	7 (41%)	1.00
Valvular disease, *n*	23 (42%)	18 (47%)	5 (29%)	0.25
Atrial fibrillation, *n*	31 (56%)	22 (58%)	9 (53%)	0.78
Hypertension, *n*	45 (82%)	31 (82%)	14 (82%)	1.00
Diabetes mellitus, *n*	16 (29%)	12 (32%)	4 (24%)	0.75
Pulmonary disease, *n*	12 (22%)	7 (18%)	5 (29%)	0.48
Laboratory measurements				
NT-proBNP, pg/mL	3,084 (1,373, 5,781)	2,738 (1,253, 5,133)	4,081 (2,065, 5,843)	0.24
Creatinine, mg/dL	1.8 ± 1.3	1.7 ± 1.1	2.2 ± 1.6	0.21
eGFR, mL/min/1.73 m^2	34.3 ± 18.3	37.6 ± 19.7	26.9 ± 12.0	0.04
Hematocrit, %	35.8 ± 6.1	36.0 ± 6.5	35.2 ± 5.2	0.66
Hemoglobin, g/dL	11.5 ± 2.1	11.7 ± 2.2	11.1 ± 1.8	0.30
Echocardiography parameters				
LVEF, %	45.7 ± 18.0	44.6 ± 17.6	46.1 ± 19.5	0.92
≤40%, *n*	25 (45%)	17 (45%)	8 (47%)	1.00
>40%, *n*	30 (55%)	20 (55%)	10 (53%)	
LVDd, mm	53.9 ± 10.4	53.6 ± 10.8	54.6 ± 9.8	0.73
TRV, m/s	2.6 ± 1.3	2.6 ± 1.3	2.5 ± 1.4	0.57
<2.9 m/s, *n*	48 (87%)	37 (87%)	11 (88%)	1.00
≥2.9 m/s, *n*	7 (13%)	5 (13%)	2 (12%)	
Pulmonary function tests				
%VC, %	73.2 ± 22.0	72.9 ± 20.8	73.8 ± 25.3	0.89
FEV 1%, %	74.5 ± 11.6	75.0 ± 11.8	73.6 ± 11.6	0.70
Drug therapy				
ACE inhibitor or ARB, *n*	27 (49%)	18 (47%)	9 (53%)	0.78
MRA, *n*	25 (45%)	18 (47%)	7 (41%)	0.77
β-blocker, *n*	48 (87%)	33 (87%)	15 (88%)	1.00
SGLT2 inhibitor, *n*	14 (25%)	11 (29%)	3 (18%)	0.51
ARNI, *n*	14 (25%)	8 (21%)	6 (35%)	0.32
Loop diuretic, *n*	50 (91%)	34 (89%)	16 (94%)	1.00
6-minute walk test				
6MWD, m	237.5 ± 106.7	238.9 ± 112.2	234.1 ± 96.5	0.88
Sp_{O_2} at rest, %	98.3 ± 1.5	98.3 ± 1.6	98.3 ± 1.4	0.97
Sp_{O_2} during the 6MWT, %	92.5 ± 4.4	94.9 ± 2.3	87.2 ± 3.2	<0.001
ΔSp_{O_2}-Ex, %	5.8 ± 4.3	3.4 ± 1.7	11.1 ± 3.4	<0.001

Data are presented as the means ± SD or median with interquartile range (IQR). 6MWD, six-minute walk distance; 6MWT, six-minute walk test; ΔSp_{O_2}-Ex, averaged decrease in peripheral oxygen saturation during exercise; ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blockers; ARNI, angiotensin receptor-neprilysin inhibitor; eGFR, estimated glomerular filtration rate; FEV1 %, forced expiratory volume in 1 s as a percentage of predicted; LVDd, left ventricular end-diastolic dimension; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; NT-proBNP, N-terminal pro-B-type natriuretic peptide; SGLT2, sodium glucose cotransporter 2; TRV, tricuspid regurgitant velocity; %VC, percent vital capacity.

creatinine level of 1.8 ± 1.3 mg/dL, and a mean eGFR of 34.5 ± 18.3 mL/min/1.73 m^2. Echocardiographic measurements showed a mean LVEF of 45.7 ± 18.0%. From the pulmonary function tests, %VC and FEV1% were determined to be 73.2 ± 22.0% and 74.5 ± 11.6%, respectively. Regarding medication, 49% were on angiotensin-converting enzyme (ACE) inhibitors or angiotensin II receptor blockers (ARB), 45% on mineralocorticoid receptor antagonist (MRA), 87% on β-blockers, 91% on loop diuretics, and 25% on sodium glucose cotransporter 2 (SGLT2) inhibitors and angiotensin receptor-neprilysin inhibitor (ARNI). Both ΔSp_{O_2}-Ex groups showed similar vital signs and medical history, including conditions such as coronary artery disease, valvular disease, atrial fibrillation, and hypertension. Most laboratory and echocardiographic parameters were consistent, except for eGFR. Medication patterns, including the use of ACE inhibitors, β-blockers, and other medications, were consistent across both groups (Table 2). We examined the relationship between ΔSp_{O_2}-Ex and LVEF to determine if ΔSp_{O_2}-Ex serves as a prognostic predictor independent of heart failure subtype. The proportion of the patients with LVEF ≤40% and with LVEF >40% were comparable between the large- and small-ΔSp_{O_2}-Ex groups. Also, there was no significant difference in ΔSp_{O_2}-Ex between patients with LVEF ≤40% ($n = 25$) and those with LVEF >40% ($n = 30$), with values of 6.1 ± 4.0% and 5.5 ± 4.5%, respectively ($P = 0.60$). This suggests that ΔSp_{O_2}-Ex may be a useful prognostic marker regardless of LVEF value.

We also assessed the potential impact of pulmonary hypertension on ΔSp_{O_2}-Ex by evaluating TRV obtained from echocardiography. Only seven patients in our cohort had a TRV ≥2.9 m/s, the threshold recommended by major guidelines to indicate possible pulmonary hypertension. Of these seven patients, five were in the small-ΔSp_{O_2}-Ex group and two were in the large-ΔSp_{O_2}-Ex group, with no statistically significant difference observed between the groups ($P = 0.65$). This indicates that elevated pulmonary artery pressures were not associated with higher ΔSp_{O_2}-Ex values in our population. Furthermore, all enrolled patients were confirmed to be free of pulmonary congestion prior to discharge, as verified by chest X-rays indicating resolution of pulmonary edema. Therefore, neither pulmonary edema nor pulmonary hypertension appeared to be significant contributors to the observed differences in ΔSp_{O_2}-Ex within our patient population.

The long-6MWD and short-6MWD groups showed similar vital signs and medical histories (Table 3). However, notable differences were observed in laboratory measurements, where the long-6MWD group had lower NT-proBNP levels and higher hematocrit and hemoglobin values compared with the short-6MWD group (NT-proBNP: $P = 0.01$, hematocrit: $P = 0.02$, hemoglobin: $P = 0.01$). Echocardiography parameters and pulmonary function tests generally indicated better outcomes for the long-6MWD group. No significant differences were observed in the use of various medications.

Prognostic Implications: Kaplan–Meier Analysis and Hazard Ratios

The Kaplan–Meier analysis indicated that the hazard ratio (HR) for patients in the short-6MWD group was 2.40 (95% CI: 1.08–5.32; $P = 0.03$) (Fig. 3*A*), whereas the HR for the large-ΔSp_{O_2}-Ex group was 6.66 (95% CI: 2.96–15.01; $P < 0.001$) (Fig. 3*B*).

In analyzing the predictors of rehospitalization due to HF and cardiovascular death within a year after discharge, the univariate analysis showed that ΔSp_{O_2}-Ex ≥6.7%, 6MWD ≤220 m, increased heart rate, reduced eGFR, decreased hemoglobin, and decreased %VC were notable predictors. In particular, ΔSp_{O_2}-Ex stood out with a hazard ratio (HR) of 6.66. In multivariate analysis, ΔSp_{O_2}-Ex ≥6.7% was an independent risk factor with an HR of 6.04 ($P < 0.001$) (Table 4).

Composite Risk Stratification

When combining ΔSp_{O_2}-Ex with 6MWD, the rates of cardiac events, including rehospitalization due to HF exacerbation and cardiovascular death within 1 yr, were as follows for each group: 16% (3/19) for the long-6MWD and the small-ΔSp_{O_2}-Ex groups, 47% (9/19) for the short-6MWD and the small-ΔSp_{O_2}-Ex groups, 86% (6/7) for the long-6MWD and the large-ΔSp_{O_2}-Ex groups, and 100% (10/10) for the short-6MWD and the large-ΔSp_{O_2}-Ex groups (Fig. 4).

To further quantify the predictive performance, we computed the area under the curve (AUC) values for the prediction performance of ΔSp_{O_2}-Ex alone and in combination with 6MWD. The AUC for ΔSp_{O_2}-Ex was 0.72, with a sensitivity of 0.96 and a specificity of 0.57. Although ΔSp_{O_2}-Ex showed a greater predictive ability compared with 6MWD (AUC = 0.62) and NT-proBNP (AUC = 0.69), the differences were not statistically significant ($P = 0.37$ and $P = 0.83$, respectively). The combination of 6MWD and ΔSp_{O_2}-Ex yielded an AUC of 0.78, which is significantly higher compared with the AUC of 6MWD alone ($P = 0.04$) (Fig. 5*A*). To compare its prognostic ability with previously reported scores, we calculated the AUC for the GWTG-HF risk score to be 0.65, which was consistent with the reported value [0.687 (24)]. The AUC for the AHEAD score was 0.67, also similar to the reported range [0.639–0.655 (19)]. Thus, in the current analysis population, the combination of ΔSp_{O_2}-Ex and 6MWD demonstrated a higher AUC compared with existing scores, indicating superior prognostic capability (Fig. 5*B*).

DISCUSSION

The most significant finding of this study is that ΔSp_{O_2}-Ex complements 6MWD and that their combination increases the predictive value of 6MWT. As it is also suggested that ΔSp_{O_2}-Ex alone may have substantial prognostic value, this study uniquely demonstrates the clinical implications of ΔSp_{O_2}-Ex specifically measured during the 6MWT in elderly patients with heart failure.

In addition to ΔSp_{O_2}-Ex, we compared the prognostic value of the combination of 6MWD and ΔSp_{O_2}-Ex with well-established risk scores: the GWTG-HF risk score, originally developed to predict in-hospital mortality, and the AHEAD score, to predict mortality in acute heart failure. In our cohort, the AUC for the GWTG-HF score was 0.65 and for the AHEAD score, it was 0.67, both indicating moderate predictive ability. In contrast, the combination of 6MWD and ΔSp_{O_2}-Ex yielded a higher AUC of 0.78, suggesting superior predictive accuracy for rehospitalization risk (Fig. 5*B*).

Table 3. *Baseline characteristics of the long- and short-6MWD groups*

Characteristics	All	Long-6MWD	Short-6MWD	*P* Value
Subjects, *n*	55	26	29	
Age, yr	80.7 ± 6.7	79.2 ± 6.7	82.2 ± 6.6	0.10
Gender (female)	25 (45%)	9 (35%)	16 (55%)	0.18
Body mass index, kg/m^2	21.3 ± 4.3	21.0 ± 3.4	21.6 ± 5.0	0.61
Vital signs				
Heart rate, beats/min	73.0 ± 15.4	71.7 ± 15.7	74.2 ± 15.3	0.56
Systolic blood pressure, mmHg	111.2 ± 19.0	112.5 ± 18.6	110.0 ± 19.7	0.64
Diastolic blood pressure, mmHg	63.2 ± 11.5	62.8 ± 12.2	62.4 ± 11.0	0.88
Medical history				
Coronary artery disease, *n*	24 (44%)	15 (58%)	9 (31%)	0.06
Valvular disease, *n*	23 (42%)	7 (27%)	16 (55%)	0.06
Atrial fibrillation, *n*	31 (56%)	16 (62%)	15 (52%)	0.59
Hypertension, *n*	45 (82%)	19 (73%)	26 (90%)	0.16
Diabetes mellitus, *n*	16 (29%)	7 (27%)	9 (31%)	0.78
Pulmonary disease, *n*	12 (22%)	5 (19%)	7 (24%)	0.75
Laboratory measurements				
NT-proBNP, pg/mL	3,084 (1,373, 5,781)	1,690 (1,078, 4,038)	4,332 (2,322, 6,146)	0.01
Creatinine, mg/dL	1.8 ± 1.3	1.6 ± 0.8	2.0 ± 1.6	0.36
eGFR, mL/min/1.73 m^2	34.3 ± 18.3	36.3 ± 17.3	32.5 ± 19.2	0.45
Hematocrit, %	35.8 ± 6.1	37.7 ± 5.7	34.0 ± 6.0	0.02
Hemoglobin, g/dL	11.5 ± 2.1	12.3 ± 2.0	10.9 ± 1.9	0.01
Echocardiography parameters				
LVEF, %	45.7 ± 18.0	47.3 ± 18.3	44.3 ± 17.9	0.54
≤40%, *n*	25 (45%)	12 (46)	13 (45%)	1.00
>40%, *n*	30 (55%)	14 (54%)	16 (55%)	
LVDd, mm	53.9 ± 10.4	56.3 ± 10.1	51.8 ± 10.5	0.11
TRV, m/s	2.6 ± 1.3	2.5 ± 1.4	2.6 ± 1.3	0.53
<2.9 m/s, *n*	48 (87%)	23 (88%)	25 (86%)	1.00
≥2.9 m/s, *n*	7 (13%)	3 (12%)	4 (14%)	
Pulmonary function tests				
%VC, %	73.2 ± 22.0	82.1 ± 17.8	65.0 ± 22.7	<0.01
FEV 1%, %	74.5 ± 11.6	74.7 ± 11.7	74.4 ± 11.8	0.91
Drug therapy				
ACE inhibitor or ARB, *n*	27 (49%)	14 (54%)	13 (45%)	0.59
MRA, *n*	25 (45%)	14 (54%)	11 (38%)	0.26
β-blocker, *n*	48 (87%)	22 (85%)	26 (90%)	0.23
SGLT2 inhibitor, *n*	14 (25%)	8 (31%)	6 (21%)	0.54
ARNI, *n*	14 (25%)	8 (31%)	6 (21%)	0.54
Loop diuretic, *n*	50 (91%)	24 (92%)	26 (90%)	1.00
6-minute walk test				
6MWD, m	237.5 ± 106.7	333.3 ± 59.4	151.6 ± 51.4	<0.001
Sp_{O_2} at rest, %	98.3 ± 1.5	98.5 ± 1.7	98.2 ± 1.3	0.53
Sp_{O_2} during the 6MWT, %	92.5 ± 4.4	93.0 ± 4.1	92.1 ± 4.8	0.49
ΔSp_{O_2}-Ex, %	5.8 ± 4.3	5.5 ± 3.8	6.1 ± 4.7	0.62

Data are presented as the means ± SD or median with interquartile range (IQR). 6MWD, six-minute walk distance; 6MWT, six-minute walk test; ΔSp_{O_2}-Ex, averaged decrease in peripheral oxygen saturation during exercise; ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blockers; ARNI, angiotensin receptor-neprilysin inhibitor; eGFR, estimated glomerular filtration rate; FEV1 %, forced expiratory volume in 1 s as a percentage of predicted; LVDd, left ventricular end-diastolic dimension; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; NT-proBNP, N-terminal pro-B-type natriuretic peptide; SGLT2, sodium glucose cotransporter 2; TRV, tricuspid regurgitant velocity; %VC, percent vital capacity.

Risk stratification of patients with HF to reduce the risk of rehospitalization remains challenging. Evaluating exercise capacity, an essential factor for determining the severity of HF, is important but not always straightforward. Historically, the CPET has been regarded as the gold standard for appraising exercise capacity. However, the financial implications, the need for specialized equipment and personnel, and the demands it places on patients, particularly those with more severe HF symptoms, have curtailed its widespread adoption. In addition, a substantial workload beyond the lactate threshold is generally required, limiting the number of cases in which CPET can be executed (25, 26). This necessitates a simpler method of assessing submaximal exercise capacity, which is currently fulfilled by the 6MWT, and the 6MWD has been widely accepted to be correlated with HF prognosis (7, 27–31). Meanwhile, the 6MWD is affected by orthopedic issues, preventing some patients from undergoing the test. The test also showed considerable variability among individuals; for example, 6MWD was 381 ± 84 m in the RESOLVD trial (14), 249.0 ± 113.8 m in the PRESERVED-HF trial (15), 303.3 ± 105.4 m in the PARALLAX trial (16), and 304.1 ± 111.5 m in the INOVATE-HF trial (17) (Supplemental Table S1). Likewise, the standard deviation varies among studies but is substantially large to determine the absolute impact and standard value (32). Hence, although evaluation of sequential changes in 6MWD within an individual can provide useful longitudinal information about disease severity control with good reproducibility (14–17), estimation of the absolute prognosis of individual cases using 6MWD requires careful attention, and in most cases, especially

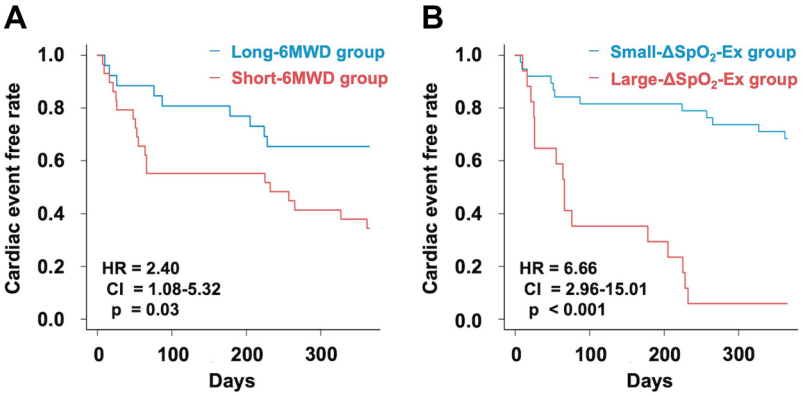

Figure 3. Prognostic implications shown by the Kaplan–Meier analysis and hazard ratios. *A*: the Kaplan–Meier analysis of cardiovascular outcomes in long- and short-6MWD group. *B*: the Kaplan–Meier analysis of cardiovascular outcomes in the small- and large-ΔSp_{O_2}-Ex groups. HR for patients in the large-ΔSp_{O_2}-Ex group was 6.66 (95% CI: 2.96–15.01; $P < 0.001$), whereas the HR for the long-6MWD group was 2.40 (95% CI: 1.08–5.32; $P = 0.03$). 6MWD, six-minute walk distance; ΔSp_{O_2}-Ex, averaged decrease in peripheral oxygen saturation during exercise; CI, confidential interval; HR, hazard ratio.

among the elderly, additional evaluation using other clinical information should be considered (33).

In our study, ΔSp_{O_2}-Ex was correlated with the prognosis of patients with HF; those with a higher ΔSp_{O_2}-Ex had significantly more HF rehospitalizations compared with those with a lower ΔSp_{O_2}-Ex. Importantly, ΔSp_{O_2}-Ex was not associated with 6MWD, suggesting that ΔSp_{O_2}-Ex could be a surrogate for pathophysiology different from that of 6MWD, at least in part. This may result in highly accurate predictions of HF readmissions by combining these two values. Because the increase in stroke volume (SV) in patients with HF reaches a plateau during milder exercise, cardiac output during exercise is often dependent on the heart rate (34). However, in patients with HF, the heart rate response during exercise is limited, sometimes due to administration of β-blocker, making it difficult to maintain sufficient cardiac output and oxygen supply to meet the elevation of systemic oxygen demand. This is consistent with the finding that ΔSp_{O_2}-Ex was not associated with LVEF (Table 2) because changes in cardiac output during exercise are correlated with SV enlargement and heart rate elevation, but not with LVEF at rest (35). Overall, mixed venous oxygen saturation (Sv_{O_2}) starts to drop at a certain intensity of exercise (36), and desaturation is supposed to begin at a point where $\dot{V}O_2$ cannot fulfill the requirement for oxygenation of venous blood in the lungs. In addition, it is known that exercise capacity per oxygen consumption is reduced in patients with HF due to progressive deconditioning (37). In other words, the skeletal muscle oxygen demand for submaximal loading is increased, which may also be a factor in lowering Sv_{O_2} in patients with HF. Recent studies have emphasized the importance of skeletal muscle abnormalities in contributing to exercise intolerance and impaired oxygen utilization in patients with HF. Niemeijer et al. (38) reported that type I muscle fiber

Table 4. *Predictors of cardiovascular events within 1 yr after discharge by the Cox proportional hazard model*

Predictor	Univariable Analysis		Multivariable Analysis	
	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
ΔSp_{O_2}-Ex $\geq$ 6.7%	6.66 (2.96–15.01)	<0.001	6.04 (2.62–13.92)	<0.001
6MWD $\leq$ 220 m	2.40 (1.08–5.32)	0.03	1.82 (0.70–4.72)	0.22
Age, yr	1.00 (0.95–1.06)	0.98		
Gender (female)	0.72 (0.34–1.51)	0.39		
Body mass index	1.07 (0.99–1.16)	0.09		
Heart rate	1.03 (1.00–1.05)	0.03	1.03(1.00–1.05)	0.05
Systolic blood pressure	0.99 (0.97–1.01)	0.18		
Diastolic blood pressure	0.99 (0.96–1.02)	0.56		
Coronary artery disease	0.71 (0.33–1.52)	0.38		
Valvular disease	0.91 (0.43–1.95)	0.81		
Atrial fibrillation	1.27 (0.59–2.71)	0.54		
Hypertension	0.58 (0.23–1.43)	0.23		
Diabetes mellitus	0.90 (0.39–2.04)	0.80		
Pulmonary disease	1.23 (0.52–2.90)	0.63		
NT-proBNP	1.00 (1.00-1.00)	0.53		
Creatinine	1.18 (0.94–1.48)	0.16		
eGFR	0.97 (0.94–1.00)	0.02	0.98 (0.95–1.01)	0.23
Hemoglobin	0.78 (0.63–0.95)	0.02	0.92 (0.72–1.17)	0.47
LVEF	0.99 (0.97–1.01)	0.31		
LVDd	1.00 (0.97–1.04)	0.99		
TRV	0.98 (0.27–3.61)	0.98		
%VC	0.97 (0.95–0.99)	0.01	0.97 (0.95–1.00)	0.06
FEV 1%	1.01 (0.98–1.04)	0.64		

6MWD, six-minute walk distance; ΔSp_{O_2}-Ex, averaged decrease in peripheral oxygen saturation during exercise; CI, confidence interval; eGFR, estimated glomerular filtration rate; FEV1 %, forced expiratory volume in 1 s as a percentage of predicted; HR, hazard ratio; LVDd, left ventricular end-diastolic dimension; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro-B-type natriuretic peptide; TRV, tricuspid regurgitant velocity; %VC, percent vital capacity.

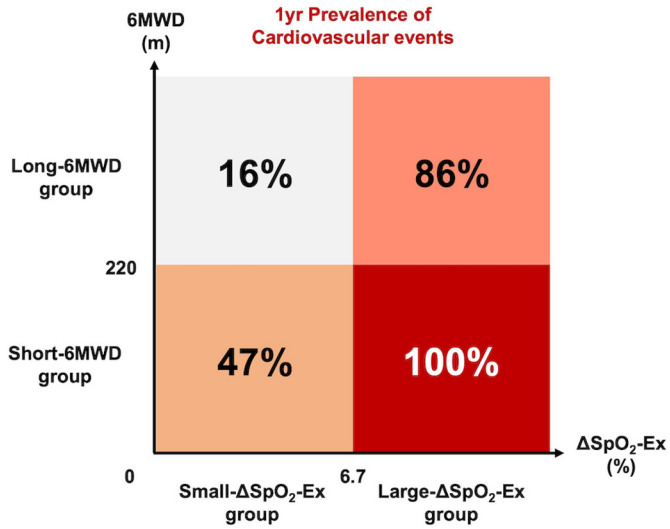

Figure 4. Incidence of cardiac events by 6MWD and ΔSp_{O_2}-Ex categories. When combining ΔSp_{O_2}-Ex with 6MWD, the rates of cardiac events, including heart failure readmission and death within 1 yr, were as follows for each group: 16% (3/19) for the long-6MWD and the small-ΔSp_{O_2}-Ex groups, 47% (9/19) for the short-6MWD and the small-ΔSp_{O_2}-Ex groups, 86% (6/7) for the long-6MWD and the large-ΔSp_{O_2}-Ex groups, and 100% (10/10) for the short-6MWD and the large-ΔSp_{O_2}-Ex groups. 6MWD, six-minute walk distance; ΔSp_{O_2}-Ex, averaged decrease in peripheral oxygen saturation during exercise.

capillarization is more prevalent in patients with HF compared with healthy individuals, enhancing oxidative capacity in this population. However, in cases of severe HF, capillarization is reduced, correlating with a lower $\dot{V}O_2$. Therefore, patients in the larger ΔSp_{O_2}-Ex group may have greater impairment in muscle capillarization, suggesting that ΔSp_{O_2} could reflect underlying skeletal muscle pathophysiology. The decrease in Sv_{O_2} causes hypoxic pulmonary vasoconstriction due to decreased pulmonary tissue oxygen pressure, resulting in reduced oxygen uptake in the lungs. If the left ventricular filling pressure rises during exercise according to underlying left heart disease, subsequent pulmonary edema also limits oxygenation, which is supported by the recent evidence provided by pulmonary echo in patients with HF (39, 40) and findings from CardioMEMS (41). Elevated filling pressure leads to alveolar and interstitial congestion, which impairs gas exchange efficiency and decreases oxygenation (42, 43). In addition, reduced lung compliance and ventilation efficiency (44) further contribute to decreased oxygen uptake, increasing ΔSp_{O_2} during exercise (ΔSp_{O_2}-Ex). In patients with HF, the hemoglobin oxygen dissociation curve shifts to the right due to lactate accumulation and hypercapnia, especially at exercise loads above the lactate threshold, leading to a lower oxygen saturation as oxygen release increases at a given partial pressure of oxygen (45). This may further enlarge ΔSp_{O_2}-Ex in patients with HF. Collectively, ΔSp_{O_2}-Ex is a value that can be evaluated by integrating such a balance of systemic oxygen demand and supply over the entire 6MWT and is a more comprehensive index of exercise capacity than a simple distance. Measuring ΔSp_{O_2}-Ex before discharge may serve as a cost-effective, objective, and safe indicator of latent pulmonary congestion.

To the best of our knowledge, this is the first study to evaluate exercise-induced desaturation (ΔSp_{O_2}-Ex) during the 6MWT as a complementary prognostic marker to 6MWD in elderly patients with HF. Previously, exercise-induced desaturation has been investigated in patients with COPD (46–49). Takigawa et al. (49) studied 144 COPD patients with or without lung volume reduction surgery and found that a reduction in oxygen saturation during the 6MWT, defined by ΔSp_{O_2}-Ex $\geq$6% (median of the participants), was an independent predictor of poor prognosis. They also found no correlation between ΔSp_{O_2}-Ex and 6MWD, which is consistent with our findings. Several studies have also demonstrated a correlation between desaturation during the 6MWT and poor prognosis in patients with COPD, although the involvement of patients with HF was not (46–49). The underlying mechanism for exercise-induced desaturation in patients with COPD is thought to involve hyperinflation leading to insufficient increase in ventilation, as well as insufficient upregulation of cardiac output and increased peripheral oxygen extraction (48). These findings suggest that a desaturation of ~6–7% during exercise may be clinically significant across different patient populations. In our current study, both the large- and small-ΔSp_{O_2}-Ex groups had resting Sp_{O_2} levels of ~98%. The ΔSp_{O_2}-Ex cutoff of 6.7% corresponds to an Sp_{O_2} of ~91%, aligning with the steep slope of the oxygen dissociation curve. This implies that patients in the large-ΔSp_{O_2}-Ex group experienced significantly prolonged periods of substantially lower Pa_{O_2}, leading to the reasonable conclusion that their prognosis was worse. In addition, recent studies have unveiled the importance of latent pulmonary vascular diseases in pulmonary hypertension with left heart disease, which is revealed

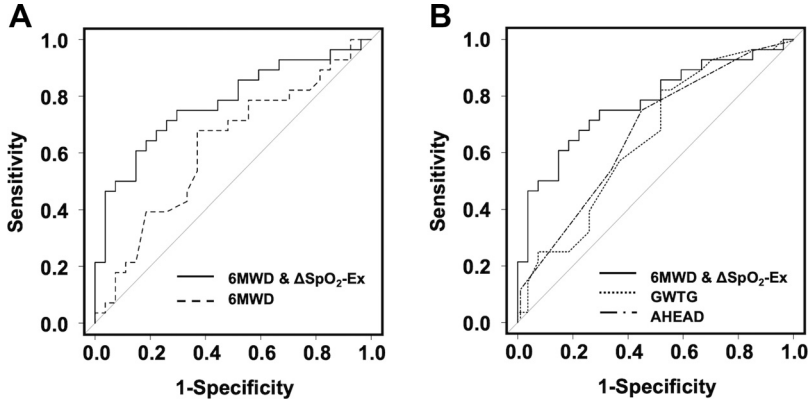

Figure 5. Receiver operating characteristics (ROC) curve analysis to predict 1-yr major adverse cardiovascular outcomes. Multivariable ROC curve analysis was conducted to evaluate the prognostic accuracy of the combined measures. *A*: the combination of 6MWD and ΔSp_{O_2}-Ex yielded an AUC of 0.78, which is significantly higher compared with the AUC of 6MWD alone of 0.62 ($P = 0.04$), as assessed by the DeLong test. *B*: the combination of 6MWD and ΔSp_{O_2}-Ex showed an AUC of 0.78, higher than that of the GWTG-HF score (0.65) and the AHEAD score (0.67). 6MWD, six-minute walk distance; ΔSp_{O_2}-Ex, averaged decrease in peripheral oxygen saturation during exercise; AUC, area under the curve.

by invasive hemodynamic tests under exercise (50). The results of our study are concordant with those of previous studies because they share, at least in part, the same pathophysiological mechanisms, and ΔSp_{O_2}-Ex is determined as a cumulative surrogate marker for cardiac, pulmonary, and skeletal muscular function, as described earlier. As for 6MWD, a cutoff of 220 m aligns with previous studies that have identified similar thresholds for predicting adverse outcomes in patients with heart failure. Most studies agree that a 6MWD $\leq$300 m is indicative of poor prognosis (7, 28, 30), whereas an even lower 6MWD <200 m could identify patients at markedly increased risk of death or rehospitalization (31). Our identified cutoff of 220 m falls within this clinically relevant range and corresponds with findings from previous research indicating that reduced 6MWD is strongly associated with adverse outcomes.

In our study, the maximum Sp_{O_2} value recorded during a 30-min rest period was selected as the baseline for calculating ΔSp_{O_2}-Ex, as this approach might be expected to minimize the influence of transient desaturation events, such as minor movements or technical artifacts, and ensure that the baseline accurately reflects the patient's true resting state. The ΔSp_{O_2}-Ex was calculated as the difference between this maximum resting Sp_{O_2} value and the overall average Sp_{O_2} measured throughout the 6MWT. The use of an average Sp_{O_2} during the 6MWT was intended to capture the cumulative impact of exercise on oxygen saturation, reflecting the patient's cardiopulmonary response over the entire period of activity. This method provides a comprehensive assessment of desaturation trends throughout the test, rather than focusing on minimum or end point values, which may not fully capture the dynamic changes in Sp_{O_2} during physical exertion that vary among patients (Supplemental Fig. S3). There have been studies analyzing Sp_{O_2} measured continuously (51) or ones in that the minimum or final Sp_{O_2} during the 6MWT were focused on (49), whereas our study focuses on exercise-induced desaturation as a complementary metric to 6MWD, aiming to provide a more comprehensive assessment of exercise capacity through measurement and analysis of second-by-second change in Sp_{O_2} during the test.

Limitations

Although this study has shed light on the significant aspects of HF prognosis, it is essential to acknowledge its limitations. The study was conducted at a single center, and the sample size was small. This was an exploratory study trying to demonstrate the potential prognostic impact of ΔSp_{O_2}-Ex on the outcome, and, therefore, our result has not been confirmed through external validation, indicating that future validation study will be required to overcome these limitations to confer the generalizability to our results. Although this study included elderly patients, we excluded those who were unable to perform the 6MWT based on the assessment by certified physical therapists. This exclusion criteria may limit the applicability of our findings to the frailest or exercise-intolerant individuals. Our assessments primarily focused on the phase immediately before discharge after acute heart failure treatment, indicating a stable phase. This raises questions about how well our results might translate into an outpatient setting. In addition, our study was not able to analyze the possibility of heart rate response suppression by β-blockers due to their design. Further investigation will be required to address this issue.

Conclusions

As a novel parameter for risk stratification, ΔSp_{O_2}-Ex might have a substantial predictive impact on the prognosis of patients with elderly HF, especially when it was combined with 6MWD. A larger multicenter study and a deeper understanding of the implications and potential applications of our findings will be required. This research serves as a steppingstone toward enhancing our capabilities in predicting and managing the prognosis of patients with HF in daily practice with minimal resources.

DATA AVAILABILITY

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

SUPPLEMENTAL MATERIAL

Supplemental Table S1 and Supplemental Figs. S1–S3: https://doi.org/10.5281/zenodo.13943096.

GRANTS

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DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the authors.

AUTHOR CONTRIBUTIONS

I.S. and Y.O. conceived and designed research; I.S., K.-D.M., Y.O., J.O., Y.M., A.D., Y.S., E.M. M.O., K.A., M.S., A.E., and Y.N. performed experiments; I.S. analyzed data; I.S., K.-D.M., S.S., M.A., and M.I. interpreted results of experiments; I.S. prepared figures; I.S., M.A., and M.I. drafted manuscript; I.S., K.-D.M., M.A., and M.I. edited and revised manuscript; I.S., K.-D.M., M.A., M.I. and approved final version of manuscript.

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