Cardiorespiratory Coupling is Associated With Exercise Capacity in Patients With Chronic Obstructive Pulmonary Disease

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Cardiorespiratory coupling is associated with exercise capacity in patients with chronic obstructive pulmonary disease

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Abstract

Background: Although comorbidites of cardiovascular disease is common in patients with chronic obstructive pulmonary disease (COPD), the interaction between the heart and lungs in COPD patients has yet to be further elucidated. Synchrogram index is a new parameter that can quantify this interaction and has the potential to apply in COPD patients.

Aim: Our objective in this study was to characterize cardiorespiratory interactions in terms of cardiorespiratory coupling (CRC) using the synchrogram index of the heart rate and respiratory flow signals in patients with chronic obstructive pulmonary disease.

Methods: This is a cross-sectional and a preliminary data from a prospective study, examining 55 COPD patients. K-means clustering analysis was applied to cluster COPD patients based on synchrogram index. Linear regression and multivariable regression analysis were used to determine the correlation between the synchrogram index and the exercise capacity assessed by six-minute walking test (6MWT).

Results: The 55 COPD patients were separated into a synchronized group (median 0.89 (0.64-0.97), n=43) and a desynchronized group (median 0.23 (0.02-0.51), n=12) based on K-means clustering analysis. Synchrogram index was correlated significantly with six minutes walking distance (r=0.42, p=0.001) and distance saturation product (r= 0.41, p=0.001) assessed by 6MWT, and still was an independent variable by multivariable regression analysis.

Conclusion: This is the first result studying the heart-lung interaction in terms of cardiorespiratory coupling in COPD patients by the synchrogram index, and COPD patients are clustered into synchronized and desynchronized groups. Cardiorespiratory coupling is associated with exercise capacity in patients with COPD.

Key Words: Heart-lung interaction, synchrogram index, six-minute walking distance, distance saturation product.

Background

Chronic obstructive pulmonary disease (COPD) is characterized by irreversible airflow limitations resulting from the inflammation and narrowing of peripheral airway, destruction of the alveolar attachment, and loss of small airways [1-3]. Possible causes include exposure to or inhalation of noxious gases or particles and systemic inflammation. COPD has been shown to affect nutritional status, exercise tolerance, and the cardiovascular system [4].The prevalence of cardiovascular disease as a comorbidity and cause of mortality underlines the need to consider the interaction between the heart and lungs in patients with COPD [5-7].

Heart-lung interactions can be classified according to the underlying related but different mechanisms: (i) respiratory sinus arrhythmia, (ii) cardioventilatory coupling, and (iii) respiratory stroke volume synchronization [8]. For example, during inspiration, central inspiratory drive [9] and negative intrathoracic pressure [10] both contribute to an increase in heart rate [11]. Negative intrathoracic pressure promotes filling of the right ventricle and impedes filling of the left ventricle [12]. A decrease in arterial blood pressure tends to increase respiratory rate and tidal volume through the baroreflex [13]. Since heart-lung interactions was affected by several mechanisms as mentioned before, a proper quantification of cardiorespiratory coupling (CRC) is an intuitive method to depict it. It has been used to study the heart-lung interactions in control subjects [14], infants [15], and in identifying sleep stages [16].

To our knowledge, CRC has not been systematically evaluated in patients. Under the clinical observation of intimate relationship between heart and lung in patients with COPD [17], a proper quantification of CRC would be beneficial for clinical application. The aim of this study was to apply synchrogram index to evaluate the CRC in patients with COPD, and to cluster patients based on their synchrogram index.

Methods

Study Design and Patients

This observational cross-sectional study was a preliminary data from a conducting prospective study at Chang Gung Memorial Hospital since January in 2019. Included patients were those with a clinical diagnosis COPD, based on the Global Initiative for Obstructive Lung Disease Criteria (GOLD), with the exclusive criteria: patients with congestive heart failure (ejection fraction <40%), known malignancy, or atrial fibrillation as well as those using anti-arrhythmic agents for arrhythmia or oxygen. All COPD patients underwent cardiac echo analysis, biochemical analysis (eosinophils, high sensitivity C-reactive protein (HS-CRP), and IgE), pulmonary function tests, chest high-resolution CT (HRCT) scanning, a six-minute walking test

(6MWT) and a coupling test during the first visit of enrollment. Emphysema was defined based on chest HRCT report from the radiologist and one pulmonologist [18]. Clinical profiles, a list of inhalation medicines, anti-psychotic agents, result of emphysema based on HRCT and acute exacerbation history [19] were also recorded. Although there is one patient who presented high ratio of FEV_1/FVC before exercise (0.72) and after exercise (0.73), he was not excluded as the spirometry fulfilled the GOLD guideline when he was diagnosed COPD. The remaining 55 patients with COPD (69 (51-84) years old, 54 male) (Figure 1). All participants signed informed consent prior to enrollment. The study was approved by the Ethics Committee of Chang Gung Memorial Hospital, Linkou, Taiwan (201702150B0).

Six-minute walking test

The 6MWT was carried out on the smooth surface and straight aisle with interval of 30 meters. Before the exam, patients were rest in a sitting position and performed spirometry before exercise to assess the pulmonary function, including the flow volume and tidal volume based on the guideline [20]. Meanwhile, oxygen saturation, heart rate, arterial blood pressure, and Borg scale in assessing the degree of dyspnea were recorded. Then, they were instructed to walk as soon as possible in six minutes. They could stop and take the rest when they felt tired or dyspnea, then restarted if they are available as soon as possible. The instructors were avoided to walk with the subjects but stood at the fixed area giving encouraging sentences with even tone every minute and 15 second before the end of the exam according to the American Thoracic Society (ATS) guideline [21, 22]. Oxygen saturation and heart rate can be recorded in real time during the course of walking. At the end of the exam, walking distance, oxygen saturation, distance saturation product (i.e., the product of nadir saturation during exercise and walking), heart rate and Borg scale were recorded and patients performed spirometry again after exercise.

Phase synchronization analysis

Instrumentation

Experiments were performed in a quiet room with the temperature maintained at 22-24 °C. Participants were instructed to avoid inhalation short acting bronchodilators for 4 hours and oral medicines such as beta-2 agonists, xanthene derivatives for 12 hours, and alcohol or caffeine-contained drink for at least eight hours prior to the test. Otherwise, participants could intake other foods before the exam. The chest skin was abraded using gel and then cleaned using alcohol to reduce electrode impedance prior to the attachment of electrocardiogram (ECG) electrodes. Prior to the examination, recordings of blood pressure, heart rate, and oxygen saturation were obtained. The subjects wore a pulse oximeter on the index finger and ECG electrodes on the chest wall. Before the exam, the breathing tube was inserted into the subject's mouth with their lips are sealed around the mouthpiece and the nose clip of the nares was used [23]. The subject was instructed to practice breathing at tidal volume for 1 minute then complete exam in the same way when they were ready. ECG signals and flow signals were recorded continuously for 5 min using three Actiwave devices (CamNtech Ltd, Cambridge, UK). The recorded signals were transferred in European Data Format to LabChart 8 software (ADInstruments, Dunedin, New Zealand), and then exported to text files for analysis.

Signal Processing and Synchrogram index

R peaks were detected using a standard R peak detection algorithm from the ECG signal (Figure 2 (a5 and b5)). The time differences between consecutive R peaks were calculated, and then converted into an instantaneous heart rate (IHR) time series using a standard interpolation algorithm (Figure 2 (a4 and b4)) [24]. The phase of the respiratory signal (denoted as ϕ_R) was extracted using the synchrosqueezing transform (SST) (Figure 2 (a3 and b3) [25]. The phase of IHR (denoted as ϕ_H) was extracted by the same method (Figure 2 (a2 and b2). After obtaining the phases of the IHR and the respiratory signal, the synchrogram was used to quantify the cardiorespiratory coupling [14, 26]. The output is the synchrogram index, which is a non-unit quantity between 0 and 1. When the cardiorespiratory coupling is strong, the synchrogram index is close to 1; otherwise it is close to 0.

The synchrogram is a signal processing tool used to depict coupling between two oscillatory signals. In the current study, we first obtained the timestamps t_k (Figure 2 (dashed line between a2 and a3, b2 and b3)), where the IHR phase attained 0 modulo 2π. We then measured the respiratory phase at t_k as follows: $\psi(t_k) = \frac{1}{2\pi}[\phi_R(t_k) \ \ mod \ \ 2\pi]$; that is, we evaluate the phase of the respiratory signal at t_k (Figure 2 (circle points at a2 and b2)). Finally, plot $\psi(\ t_k)$ against t_k. When the cardiorespiratory coupling is strong, the phase of the respiratory signal at t_k would be fixed for all k, and hence we obtain a horizontal stripe in the plot (Figure 2 (a6)) ; otherwise, we obtained scattered points in the plot (Figure 2 (b6)). The *synchrogram index* λ [26] is aiming to quantify if the plot is scattered or fixed along a horizontal line. It is defined by $\lambda = \frac{1}{M} \ \left[\left(\sum_{t_k=1}^{M} \sin 2\pi\, \psi(t_k)\right)^2 + \left(\sum_{t_k=1}^{M} \cos 2\pi\, \psi(t_k)\right)^2\right]$, where M is the number of detected cycles in the IHR.

Statistical Analysis

All results are presented as median (range) or mean ± standard deviation. The nonparametric exact two-tailed Mann-Whitney U test was used to determine the statistical significance between two groups of continuous variables, and Fisher's exact tests were used for categorical variables. Pearson's correlation was used to examine the association between six-minute walking distance (6MWD), distance saturation product (DSP) and clinical parameter, including synchrogram index. Multivariable regression analysis was used to determine the independent parameters that predict distance. K-Means was applied to cluster COPD patients based on their synchrogram indices. Silhouette analysis was performed to select optimal cluster numbers. All reported P values were two-sided, with $P < 0.05$ considered statically significant. Signals were analyzed using Matlab.All data were analyzed using R version 3.5.2 (R foundation for statistical computing).

Results

Demographic characteristics of patient

Among 55 COPD patients, 54 (98.2%) were male, 49 (89.1%) had smoking history, 36 (65.5%) were in allergic status, 33 (60%) were confirmed with emphysema from chest HRCT, and only 1 (1.8%) patient fulfilled the criteria of Asthma-COPD overlap (ACO) [27, 28]. The median synchrogram indices in the COPD group was 0.87 and the distribution was skewed (range: 0.02-0.97). The median BMI was 24.7 (range 16.7-32.1) modified medical research council (mMRC) was 1 (range 0-4), and COPD assessment test (CAT) was 10 (range 2-29). The median ejection fraction was 65.5% (range 52-90), suggesting that there was no heart failure mid-range ejection fraction (HFmrEF) patient in COPD group. However, there were 24 patients (44.3%) presented diastolic dysfunction. The median left atrial size was 34 mm (range 23-46) and E/e' ratio (the ratio of the transmitral early peak velocity over early diastolic mitral annulus velocity) was 8.9 (4.5-20.0). In addition, the median eosinophil count was 129 (range 0-615.6), IgE level was 59.7 (2-1652) and 19 (34.5%) patients had a history of acute exacerbation one year prior to enrollment in the study. Most patients used combination therapy of long-acting β_2 agonist (LABA) with long-acting muscarinic antagonist (LAMA) (20 (36.4%)) and triple therapy of LABA with LAMA and ICS (26 (47.3%)) (Table 1).

ECG, flow signal, CRC data, and synchrogram index

Figures 2a and 2b illustrate CRC analysis based on the synchrogram of IHR and respiratory flow signals. Since there are no definitions of good or poor synchronization, we applied K-means [29]. Two clusters were identified, i.e. synchronized group (n=43) and desynchronized group (n=12) according to the optimal cluster number based on the silhouette analysis. The median synchrogram index values in these two groups were as follows: synchronized group (0.89; 0.64-0.97) and desynchronized group (0.23; 0.02-0.51) (Figure 3b). Overall, subjects in the synchronized group were younger (69 (51-84) vs 77 (52-84), p= 0.02) and had a lower BMI (24.2 (16.7-32) vs 26.2 (20.3-30.8), p =0.03). No significant between-group differences were observed in terms of gender, smoking status, allergic status, therapies, or history of acute exacerbation (Table 1).

Comparing coupling tests with six-minute walking test

In terms of 6MWT, patients in the synchronized group presented longer walking distances (468 (328-624) vs. 408 (182-517), unit=m, p =0.009) and a higher distance saturation product (DSP) (421.2 (255.6-536.6), vs 373.2 (149.2-464.6), unit=m%, p=0.02) (Table 2).The correlation of distance and DSP assessed by 6MWT with clinical parameters were listed (Table 3). The synchrogram index correlated significantly with distance (r=0.42, p =0.001) (Figure 3c) and DSP (r=0.41, p= 0.001) (Figure 3d). In the multivariable regression model, age, mMRC and synchrogram index were independent variables that could predict distance. Age, synchrogram index, mMRC, emphysema were independent variables to predict DSP (Table 4). Distance was explained by the following multivariable regression model with three independent variables: (1) Distance = 671.3+93.3×Synchrogram Index-3.1×Age-37.9×mMRC (r^2= 0.56, p <0.0001) (2) DSP= 619.2+89.1×Synchrogram Index-2.8×Age-50.7×mMRC-41.1×Emphysema (r^2= 0.63, p <0.0001).

Discussion

This is the first study to cluster COPD patients into synchronized or desynchronized patients in terms of cardiorespiratory coupling. The synchrogram index distribution was wide among COPD patients and narrow among control subjects. Patients in synchronized group presented the similar distribution of synchrogram index to that among control subjects and had higher 6MWD and DSP compared with desynchronized group. In addition to the factors previously identified, synchrogram index is a novel factor that was and independent variable to predict 6MWD and DSP.

Researchers have previously demonstrated that six-minute walking distance is an important predictor of survival in COPD patients [30, 31] and heart failure patients [32]. The poor walking distance demonstrated by COPD patients can be attributed to age [33], desaturation [34],the severity of emphysema [35], dyspnea scores [36], and inspiratory capacity [37]. Our study has the coordinate results that age and mMRC contribute to 6MWD, and reveal that synchrogram index is a factor in determining 6MWD. The influence of cardiorespiratory coupling on the prognosis of COPD patients should be further confirmed under adequate follow-up duration.

In terms of patients with heart failure, several comorbid conditions, such as skeletal muscle dysfunction, impaired autonomic regulation, and nutritional factors, may coexist and contribute to exercise intolerance [38]. Furthermore, impaired aerobic function due to negative cardiopulmonary muscular interaction contributes to low exercise intolerance in patients with COPD and in those suffering from heart failure [39]. In this study, there is no HFmrEF patient. Moreover, we found that diastolic heart failure was not related to walking distance. This is an indication that walking distance is independent of impaired pulmonary or heart function. Instead, it appears that nutritional status, peripheral muscle condition [40], oxygen utilization by peripheral muscle, and negative cardiorespiratory-muscle interactions [39] should be taken into account. Since synchrogram index is a quantification of heart lung interaction, its relationship with oxygen utilization by peripheral muscle and cardiopulmonary muscle interactions should be further explored to explain the underlying mechanism why synchrogram index was associated with walking distance.

DSP is a reliable factor to predict mortality among patients with bronchiectasis [41], interstitial lung disease [42], and COPD [43, 44]. In this study, patients in the desynchronized group present a lower DSP, implying an elevated likelihood of poor outcomes but need adequate follow-up duration to confirm. To our knowledge, this is the first study to evaluate factors that associated with DSP in COPD patients. Age, mMRC, synchrogam index and emphysema are independent variables to predict DSP. Emphysema is an independent factor in determining DSP but not 6MWD in this study, which may be related to the correlation of emphysema among desaturation during exercise [45] and its contribution to the desaturation component of DSP.

A strong heart-lung interaction may improve ventilation and perfusion matching, resulting in a better oxygen transport [46]. However, we did not observe any discrepancy between the synchronized and desynchronized groups in terms of saturation. This may be explained by the fact that we excluded patients who were using oxygen on a daily basis and by the reason that there was similar proportion of emphysema. Note that there may be a link between desaturation and coupling in those patients. In order to evaluate this relationship, it is necessary to explore COPD patients with chronic hypoxemic failure in the next program.

This study faced a number of limitations. First, despite measuring and quantifying the coupling between respiration flow signals and IHR, we found no indications of causality. Second, the strict inclusion criteria prevented us from analyzing patients using oxygen on a daily basis, thus there was small population of desynchronized subgroup in this study. Third, most of the patients in the study were male and all were of East Asian decent; i.e., this sample is not representative of COPD patients overall. Finally, this is a cross-sectional and preliminary data of a prospective-designed study. Due to the insufficient follow-up time, we cannot evaluate mortality outcomes and cardiac vascular events. We will continue monitoring the subjects in this study in order to observe the clinical impact of synchronization in heart-lung interactions.

Conclusions

This study first conducted the CRC analysis to describe heart-lung interactions of COPD patients. Asides from age and mMRC, synchrogram index is an independent variable that could predict 6MWD and DSP.

List of abbreviations: ACO: Asthma-COPD overlap; AE: acute exacerbation; BMI: body mass index; CAT: chronic obstructive pulmonary disease assessment test; COPD: chronic obstructive pulmonary disease; CRC: cardiorespiratory coupling; ECG: electrocardiogram; $ETCO_2$ sensor: end tidal CO_2 sensor; FEV_1: forced expiratory volume in 1^{st} second; FVC: forced vital capacity; GOLD: Global Initiative for Obstructive Lung Disease Criteria; HRV: heart rate variability; HS-CRP: high sensitivity C-reactive protein; ICS: inhaled corticosteroids; IHR: instantaneous heart rate; mMRC: modified medical research council; LABA: long-acting beta agonists; LAMA: long-acting antimuscarinic agents; OCS: oral corticosteroids; SST: synchrosqueezing transform

Declarations

Ethics approval and consent to participate

The study was approved by the Ethics Committee of Chang Gung Memorial Hospital, Linkou, Taiwan (201702150B0). Patients provided signed informed consent prior to screening.

Consent for publication

Not Applicable.

Availability of data and materials

The data sets analyzed during the current study are available from the corresponding author upon reasonable request.

Competing interests

All authors all declare that they have no competing interests.

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Authors' contributions

TYL, HTW, PJC, CYL and YLL conceived and designed the analysis. SML MHH, FTC, TYW and HCL contributed to the clinical and laboratory work for the study. YLL, HTW, and YCH designed and performed the statistical analyses. All authors were involved in data analysis, data interpretation, and preparation of the final manuscript. The authors read and approved the final manuscript.

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Table 1 Clinical characteristics of COPD patients, clustered into synchronized and desynchronized group

Variable median (range)	Total (n=55)	Synchronized (n=43)	Desynchronized (n=12)	p-value
Age	69 (51-84)	69 (51-84)	77 (52-84)	0.02
Gender, male	54 (98.2)	42 (97.7)	12 (100)	1
Smoker	49 (89.1)	38 (88.4)	11 (91.7)	1
Current	27 (49.1)	20 (46.5)	7 (58.3)	1
Ex-smoker	22 (40)	17 (39.5)	5 (41.7)	1
BMI	24.7 (16.7-32.1)	24.2 (16.7-32.0)	26.2 (20.3-30.8)	0.03
Eosinophil Count	129 (0-615.6)	134.5 (0-615.6)	115.0 (0-329.8)	0.74
Allergy	36 (65.5)	28 (65.1)	8 (66.7)	1
a-IgE	59.7 (2-1652)	65.2 (3.59-1652)	47.0 (2-691)	0.59
HS-CRP	1.7 (0.2-189.7)	1.64 (0.2-37.9)	1.75 (0.2-189.7)	0.65
CAT	10 (2-29)	10 (2-29)	6 (3-29)	0.99
mMRC	1 (0-4)	1 (0-3)	1 (0-4)	0.73
Emphysema	33 (60)	27 (62.7)	6 (50)	1
AE history	19 (34.5)	16 (37.2)	3 (25)	0.49
Underlying				
ACO	1 (1.8)	0 (0)	1 (8.3)	0.21
Hypertension	17 (30.9)	11 (25.6)	6 (46.2)	0.16
DM	8 (14.5)	5 (11.6)	3 (23.1)	0.35
CAD	3 (5.5)	3 (7.0)	0 (0)	1
Liver Disease	6 (10.9)	6 (14.0)	0 (0)	0.32
Kidney Disease	1 (1.8)	0 (0)	1 (7.7)	0.21
Cardiac echo				
Diastolic dysfunction	24 (43.6)	20 (46.5)	4 (33.3)	0.51
E/e' ratio	8.9 (4.5-20.0)	8.8 (4.5-13.0)	11.4 (5.2-20.0)	0.06
EF (%)	65.5 (52-90)	66.5 (52-90)	64.5 (52-78)	0.33
LA (mm)	34 (23-46)	34 (23-46)	33.5 (28-41)	0.99
Drugs				
LABA	4 (7.3)	3 (7.0)	1 (8.3)	1
LAMA	1 (1.8)	1 (2.3)	0 (0)	1
LABA+LAMA	20 (36.4)	15 (34.9)	5 (41.7)	0.74
LABA+ICS	3 (5.5)	2 (4.7)	1 (8.3)	0.54
Triple	26 (47.3)	22 (51.2)	4 (33.3)	0.35
OCS	5 (9.1)	4 (9.3)	1 (8.3)	1
Anti-psychotic agents	2 (3.6)	0 (0)	2 (4.8)	1

Significantly different from patients with synchronized and desynchronized (P < 0.05).Abbreviation: BMI (Body mass index), HS-CRP (High sensitivity C reactive protein), CAT(Chronic obstructive pulmonary disease assessment test), mMRC (modified medical research council), E/e' ratio (the ratio of the transmitral early peak velocity over early diastolic mitral annulus velocity), EF (Ejection fraction), LA (left atrial) LABA (Long acting beta agonists), LAMA (Long acting antimuscarinic agents), ICS (inhaled corticosteroids), Triple (LABA+LAMA+ICS), OCS (oral corticosteroids), AE (acute exacerbation)

Table 2 Results of 6MWT in COPD patients, synchronized and desynchronized group

	COPD (n=55)	Synchronized (n=43)	Desynchronized (n=12)	p-value
Pre-and post-exercise (6MWT)				
Median (range)				
Pre-FVC(L)	2.6 (1.2-4.4)	2.7 (1.2-4.4)	2.45 (1.3-3.3)	0.28
Pre-FVC (%)	78.7 (38-129)	82.5 (39-129)	77 (38-96)	0.89
Pre-FEV1(L)	1.5 (0.5-2.7)	1.39 (0.6-2.7)	1.43 (0.5-2.0)	0.49
Pre-FEV1(%)	56.7 (18-102)	55.5 (18-102)	62.5 (18-76)	0.79
Pre-FEV1/FVC	0.56 (0.31-0.72)	0.57 (0.31-0.72)	0.56 (0.35-0.7)	0.64
Post-FVC(L)	2.7 (1.1-4.4)	2.7 (1.1-4.4)	2.7 (1.4-3.3)	0.29
Post-FVC %	81 (42-130)	81.5 (42-130)	87 (43-96)	0.78
Post-FEV1 (L)	1.47 (0.53-2.82)	1.44 (0.67-2.82)	1.49 (0.53-2.09)	0.53
Post-FEV1(%)	60 (21-105)	57 (22-105)	60 (21-79)	0.60
Post-FEV1/FVC	0.59 (0.35-0.73)	0.59 (0.35-0.73)	0.56 (0.37-0.70)	0.62
Pre-HR	83 (57-109)	83.5 (57-109)	80.5 (60-98)	0.66
Post-HR	107 (69-149)	108 (69-149)	105 (70-122)	0.48
Pre-Borg	0 (0-3)	0 (0-3)	1 (0-3)	0.06
Post-Borg	4 (1-7)	4 (2-7)	4 (1-7)	0.77
pre-spO2	95 (88-99)	95.5 (88-99)	95 (90-98)	0.31
post-spO2	90.5 (75-96)	90.5 (75-96)	90 (80-95)	0.61
pre-IC	1.78 (0.92-2.77)	1.78 (1.07-2.77)	1.73 (0.92-2.04)	0.20
post-IC	1.73 (0.94-2.83)	1.73 (0.97-2.83)	1.7 (0.94-2.43)	0.45
ΔIC	0 (-1.1-0.55)	-0.02 (-0.49 - 0.55)	0.11(-1.1-0.28)	0.37
ΔspO2	-4.5 (-22~0)	-4.5 (-22~0)	-4.0 (-18~0)	0.97
Distance	456 (182-624)	468 (328-624)	408 (182-517)	0.03
DSP	411.1 (149.2-536.6)	421.2 (255.6-536.6)	373.2 (149.2-464.6)	0.04

Significantly different from patients with Synchronized and Desynchronized ($P < 0.05$).Abbreviation: 6MWT (six minutes walking test), FVC (Forced vital capacity), FEV1 (Forced expiratory volume in 1st second), HR (Heart rate), ΔIC (change of inspiratory capacity), ΔspO2 (change of oxyhemoglobin saturation by pulse oximetry), DSP (Distance saturation product)

Table 3 Main correlations with distance and DSP as Assessed by 6MWT

	Distance		DSP	
Variable	r Value	p Value	r Value	p Value
Age	-0.53	<0.001	-0.53	<0.001
Synchrogram Index	0.42	0.001	0.41	0.001
BMI	-0.07	0.62	-0.05	0.69
Gender	0.13	0.34	0.17	0.21
CAT	-0.44	<0.001	-0.44	<0.001
mMRC	-0.53	<0.001	-0.61	<0.001
Smoking	0.02	0.86	0.03	0.83

EF	-0.12	0.39	-0.13	0.35
E/e' ratio	-0.34	0.06	-0.35	0.06
Left atrial (mm)	0.04	0.78	0.09	0.50
Diastolic dysfunction	0.07	0.59	0.05	0.72
EOS.count	0.08	0.59	0.10	0.45
IgE	-0.13	0.37	-0.11	0.43

Abbreviation: 6MWT (Six minute walking test), BMI (Body mass index), HS-CRP (High sensitivity C reactive protein), CAT(Chronic obstructive pulmonary disease assessment test), mMRC (modified medical research council), E/e' ratio (the ratio of the trans-mitral early peak velocity over early diastolic mitral annulus velocity), EF (Ejection fraction), LA (left atrial), EOS.count (Eosinophil count)

452

Table 4-1 Multivariable regression model for distance as assessed by 6MWT

variable	Beta	*SE	t value	p-value
Age	-3.1	1.2	-2.6	0.01
Synchrogram Index	93.3	42.2	2.2	0.03
mMRC	-37.9	12.9	-2.9	0.005

r^2= 0.56, adjusted r^2 = 0.51, Residual stand error = 60.9, p<0.0001, Abbreviation: *SE: stand error of beta.

Distance = 671.3+93.3XSynchrogram Index-3.1XAge-37.9XmMRC

Table 4-2 Multivariable regression model for DSP as assessed by 6MWT

variable	Beta	*SE	t value	p
Age	-2.8	1.1	-2.4	0.02
Synchrogram Index	89.1	39.0	2.3	0.03
CAT score	-0.9	1.6	-0.6	0.57
mMRC	-40.7	14.3	-2.8	0.007
Emphysema	-41.1	19.6	-2.1	0.04

r^2= 0.63, adjusted r^2 = 0.58, Residual stand error = 56.3, p<0.0001, Abbreviation: DSP (Distance saturation product), SE: Stand error of beta. DSP = 619.2+89.1XSynchrogram Index-2.8XAge-50.7XmMRC-41.1*Emphysema

453

Legends

Figure 1 Flow chart.

Figure 2 (a1) respiratory flow signal (a2) phase of the flow signal extracted by the SST, (a3) phase of the IHR extracted by the synchrosqueezing transform (SST), (a4) instantaneous heart rate (IHR), (a5) Electrocardiogram, (a6) synchrogram during 110 (sec) to 125 (sec) (a7) synchrogram and the resulting synchrogram index (0.89) in a synchronized patient.

(b1) respiratory flow signal (b2) phase of the flow signal extracted by the SST, (b3) phase of the IHR extracted by the SST, (b4) IHR, (b5) Electrocardiogram, (b6) synchrogram during 110 (sec) to 125 (sec) (b7) synchrogram and its synchrogram index (0.35) in a desynchronized patient.

Figure 3 (a) Distribution of synchrogram index in synchronized group and desynchronized group. (b) Scatterplot of synchrogram index against distance (m) from six-minute walking test of all patients (c) Scatterplot of synchrogram index against distance saturation product (m%) from six-minute walking test of all patient

Figures

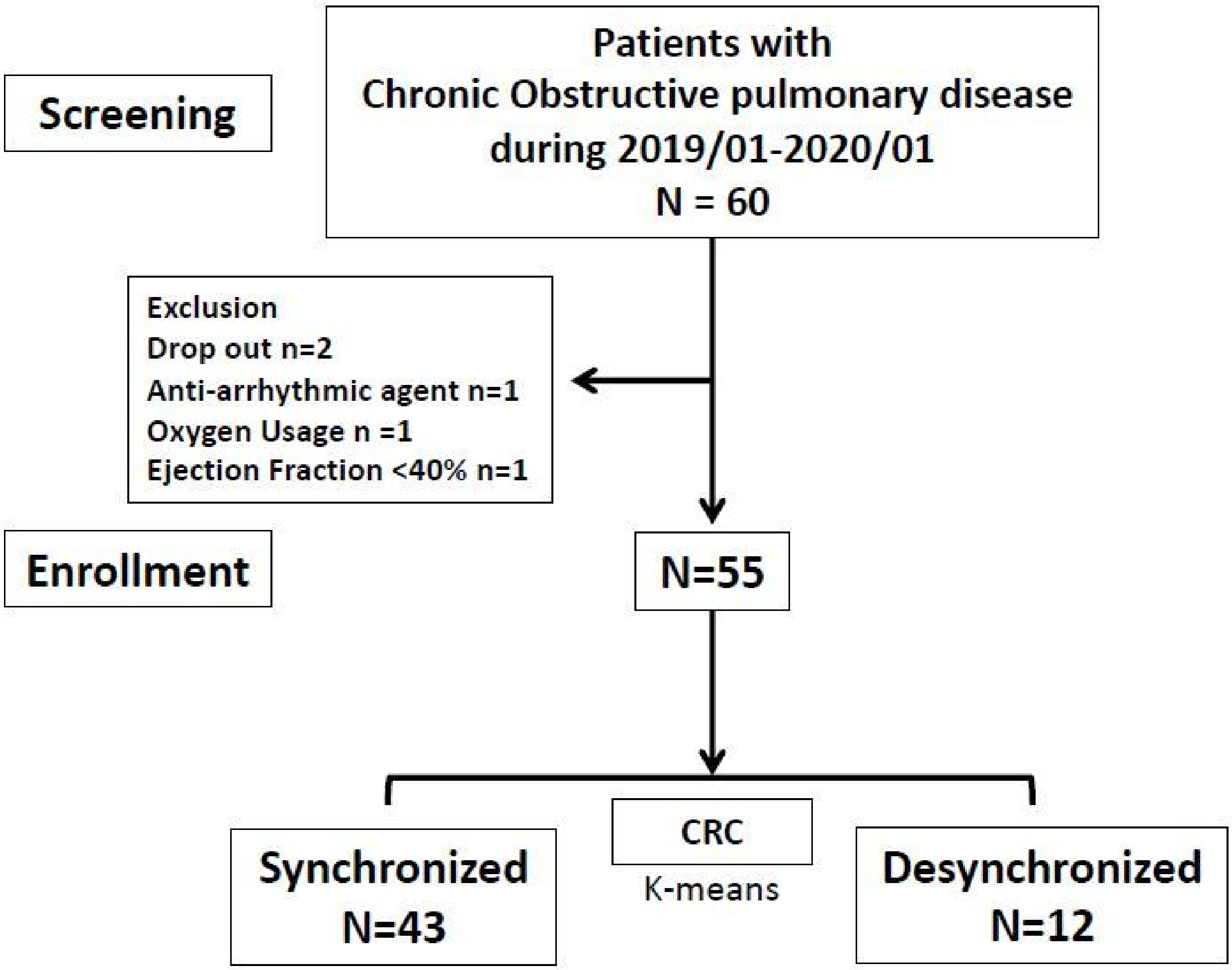

Figure 1

Flow chart.

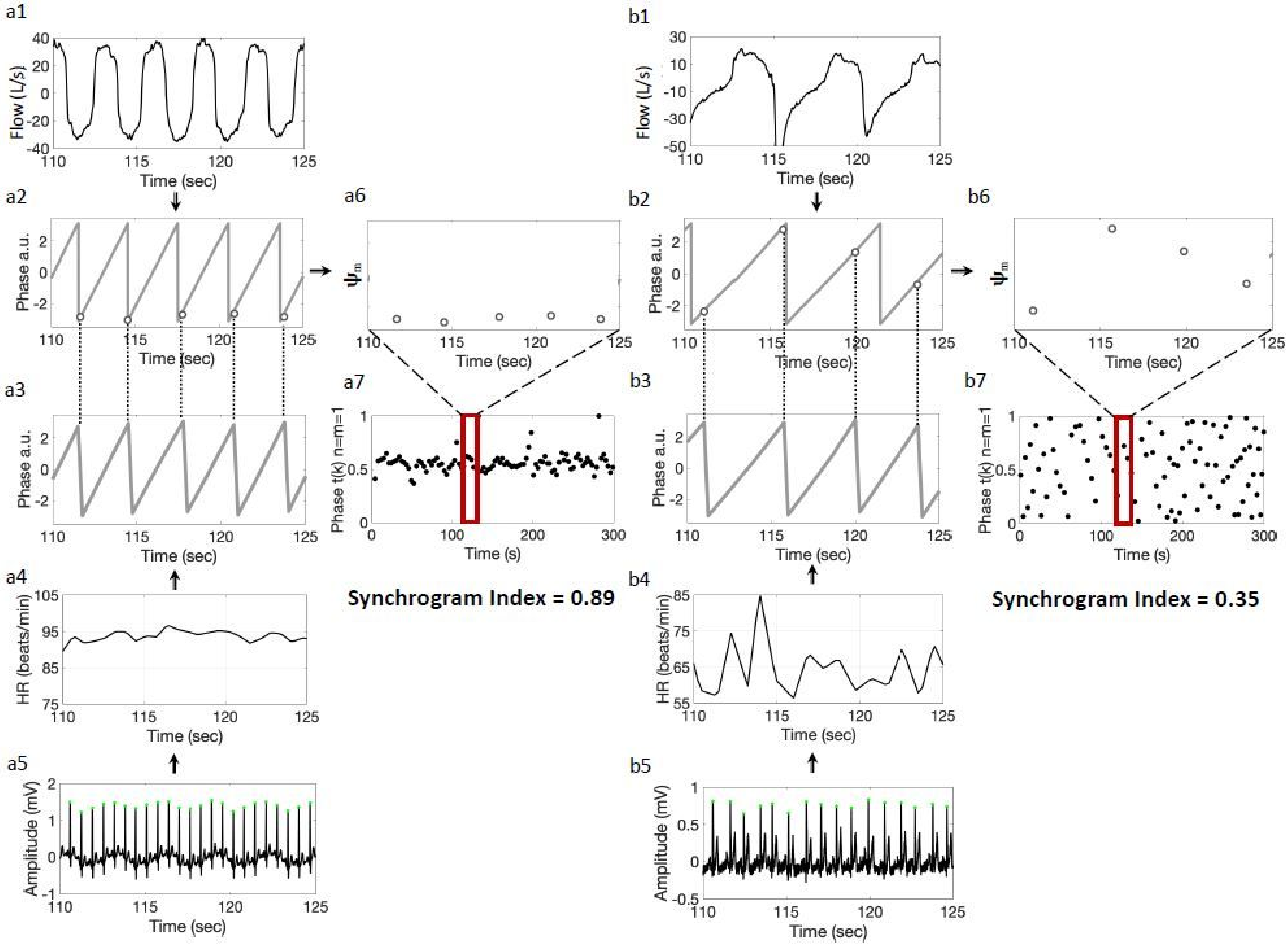

Figure 2

(a1) respiratory flow signal (a2) phase of the flow signal extracted by the SST, (a3) phase of the IHR extracted by the synchrosqueezing transform (SST), (a4) instantaneous heart rate (IHR), (a5) Electrocardiogram, (a6) synchrogram during 110 (sec) to 125 (sec) (a7) synchrogram and the resulting synchrogram index (0.89) in a synchronized patient. (b1) respiratory flow signal (b2) phase of the flow signal extracted by the SST, (b3) phase of the IHR extracted by the SST, (b4) IHR, (b5) Electrocardiogram, (b6) synchrogram during 110 (sec) to 125 (sec) (b7) synchrogram and its synchrogram index (0.35) in a desynchronized patient.

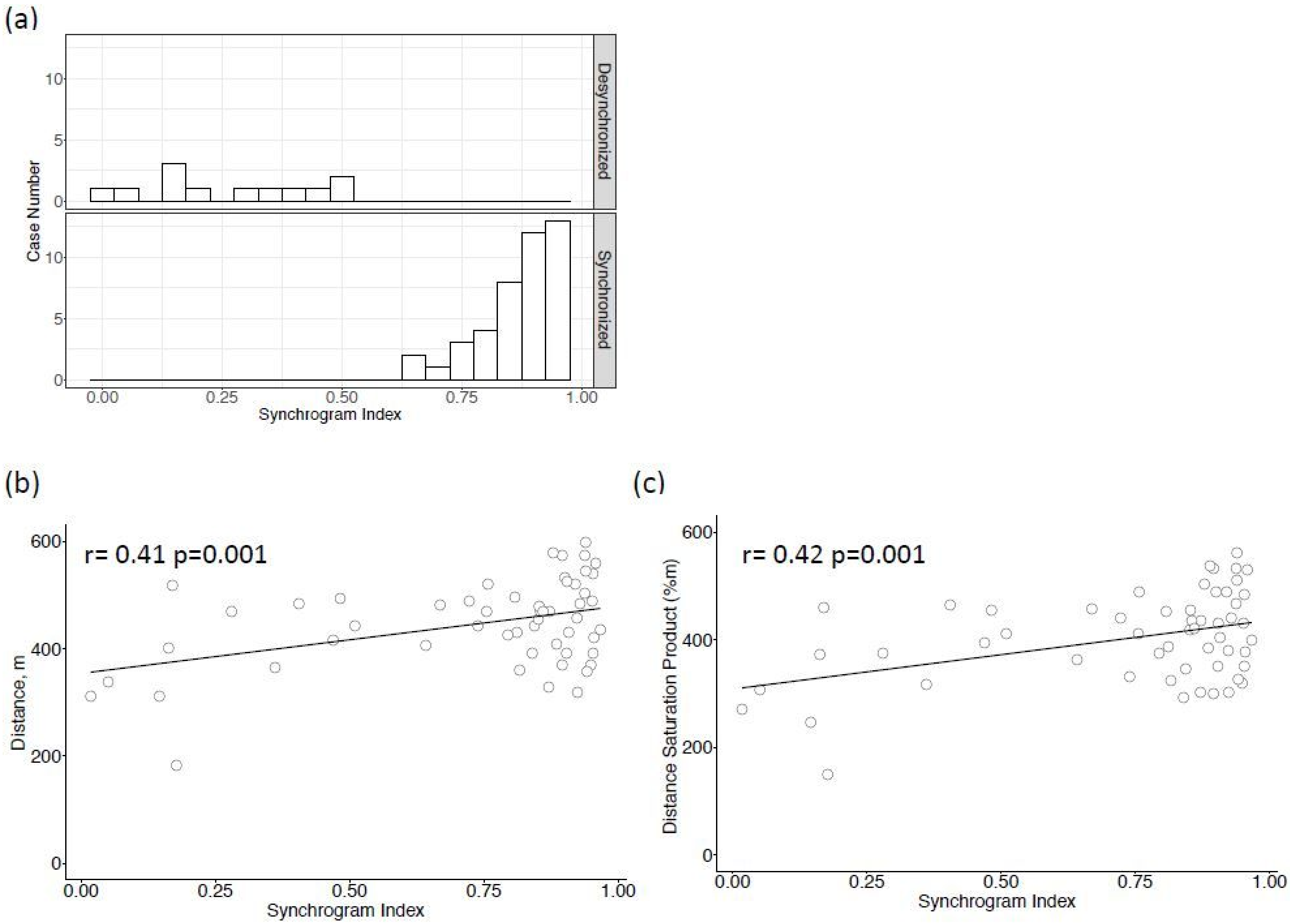

Figure 3

(a) Distribution of synchrogram index in synchronized group and desynchronized group. (b) Scatterplot of synchrogram index against distance (m) from six-minute walking test of all patients (c) Scatterplot of synchrogram index against distance saturation product (m%) from six-minute walking test of all patient