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Original Article

Changes of heart rate variability predicting patients with acute exacerbation of chronic obstructive pulmonary disease requiring hospitalization after Emergency Department treatment

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Abstract

Background: Indexes of heart rate variability (HRV) appear to reflect severity and may have prognostic value in patients with acute exacerbation of chronic obstructive pulmonary disease (AECOPD). We hypothesized that AECOPD without adequate treatment response would demonstrate impaired cardiac autonomic regulation and changes in HRV after emergency department (ED) treatment.
Methods: A prospective study of measuring HRV in admitted and discharged patients with AECOPD shortly after ED arrival and again 24 h after treatment.
Results: Total consecutive 33 patients (18 admitted and 15 discharged, age 77.1 ± 1.6 years) were enrolled. Among admitted patients, high frequency in normalized unit (HF%) was significantly lower ($P < 0.001$) while Ratio of LF to HF (LF/HF ratio) was significantly higher ($P < 0.001$) than discharged. 24 h after treatment, admitted patients had a significantly larger increase in HF% ($P < 0.002$) and larger decrease in LF/HF ratio ($P < 0.05$) than discharged. ROC curve analysis show the relative potential of the ΔHF% and ΔLF/HF% in the discrimination of groups. The area under the ROC curve between the 2 groups was 0.807 ($P < 0.01$) and 0.722 ($P < 0.05$), respectively. The best cut-off value for the admission between groups was ΔHF% >7.1 and ΔLF/HF% ≦−0.39.
Conclusion: Patients with AECOPD requiring admission after ED treatment had a greater increase in HF% and greater decrease in LF/HF ratio compared to those discharged. Our study demonstrates patient with ΔHF% was >7.1 or a ΔLF/HF% ≦−0.39 require admission despite 24 h of ED treatment.

Keywords: Acute exacerbation; Chronic obstructive pulmonary disease; Emergency department; Heart rate variability

1. Introduction

Chronic obstructive pulmonary disease (COPD) is still responsible for over 9000 hospital admissions, and the mean duration of hospital stay for COPD acute exacerbation (AECOPD) patients is about 11 days, in the United Kingdom.[1] The national inpatient burden of AECOPD is considerable.[2] The risk of mortality for AECOPD patients in the hospital

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and one year after discharge were 8% and 23% respectively.[3] Traditionally, emergency physicians decide whether to discharge or admit a patient with AECOPD, from the emergency room, based on clinical symptoms/signs such as relief from dyspnea, absence of wheezing, and degree of respiratory distress. If the patients do not respond adequately to treatment, hospitalization is recommended. Objective tests, like as arterial blood gas (ABG) and the pulmonary function test, can help clinical physicians determine disease severity[4–6]; however, they cannot aid in determining if patients should be admitted. In addition, spirometric measurements are not sensitive enough to detect relief from dyspnea over the course of an ED visit.[7] Hence, non-invasive and novel measures that enable the risk-stratification of AECOPD patients' response to treatment are highly desirable for ED physicians.

Some specific spectral components of heart rate variability (HRV) are considered to be associated with the autonomic modulation of the heart. In a previously conducted study, the increase in total power, low frequency (LF) component, and low LF/high frequency (HF) ratio (LF/HF ratio) pointed to the fact that intermittent hypoxic training increased the response of the autonomic nervous system, predominantly through increased sympathetic activity.[8] The indexes of HRV appear to reflect severity and may have prognostic value in COPD patients.[9] Patients with AECOPD have increased HRV parameters than those with stable COPD.[10] However, it has not been reported if the indexes of HRV enable the identification of AECOPD patients who do not respond adequately to treatment. The aim of the present study was to noninvasively evaluate cardiac autonomic modulation in patients with COPD, during acute exacerbation. We hypothesized that AECOPD patients, without adequate response to treatment, would demonstrate impaired cardiac autonomic regulation.

2. Methods

2.1. Definition of COPD and AECOPD

Patients were diagnosed as having COPD according to the internationally accepted criteria determined by the Global Initiative for Chronic Obstructive Lung Disease (GOLD).[11] The spirometric criterion for airflow limitation remains a post-bronchodilator fixed ratio of FEV1/FVC <0.70. Patients were then divided into the mild (GOLD stage 1), moderate (GOLD stage 2), severe (GOLD stage 3), and very severe (GOLD stage 4) groups, according to the predicted FEV1. AECOPD was defined by the symptoms of increased dyspnea and sputum volume with or without purulent sputum, coughing or wheezing.[12]

2.2. Study setting and population

We enrolled 33 consecutive patients who presented to the emergency department (ED) of Taipei Veterans General Hospital, Taiwan. The inclusion criteria were: a physician's diagnosis of COPD; presence of moderate (GOLD stage 2) to severe (GOLD stage 3) COPD; presentation to the ED for AECOPD treatment; age >50 year; and ability to provide informed consent. Exclusion criteria were: presence of mild (GOLD stage 1) and very severe (GOLD stage 4); not being able to perform spirometry; presence of decompensated congestive heart failure; history of lung cancer or surgery; presence of diabetic neuropathy; presence of an implanted cardiac pacemaker; frequent occurrence of atrial fibrillation; and premature atrial or ventricular contractions or other forms of arrhythmia. These patients were not on any medication other than those required for control of COPD control, such as inhaled bronchodilators (salbutamol and ipratropium bromide) and corticosteroids (budesonide, beclomethasone or fluticasone). Patients taking methylxanthines were excluded.

Institutional review board in Veterans General Hospital Taipei approved the protocol (VGHIRB No.: 97-07-20A), and written informed consent was obstained from all patients.

2.3. Treatment

Treatment comprised a combination of bronchodilators, corticosteroids, antibiotics if necessary, controlled oxygenation, and non-invasive or, if required, invasive ventilation. An inhaled short-acting beta$_2$-agonist (salbutamol) and anticholinergic (ipratropium) were given upon arrival to the ED, followed by 6-h intervals, when additional dosages were given, on a pro re nata basis. Intravenous methylprednisolone (31.25 mg) was given upon presentation to the ED, followed by 31.25 mg once or twice daily. Methylxanthines was not used as they may interfere with HRV. An empiric antibiotic was administered to patients with at least two of the following symptoms: increased dyspnea, sputum purulence or sputum volume. Oxygen was delivered in a controlled manner to achieve a maximal oxygen saturation (90%–92%).

2.4. Assessment and hospital admission

The factors taken into consideration for hospital admission included a marked increase in the intensity of symptoms, onset of new physical signs, altered mental status, signs of respiratory failure, hemodynamic instability and a failure to respond to treatment after 24 h of ED observation.

2.5. Physiological parameters and processing of electrocardiogram signals

Arterial blood oxygen saturation (SpO_2) was recorded using an NPB-40 Handheld Pulse Oximeter (Nellcor Puritan Bennett Inc, Pleasanton, California). The HRV of all the participants was measured upon arrival at the ED before medical treatment, after 1 h of treatment, and 24-h after treatment. The detailed procedures used for HRV analysis have been described in other articles.[13] A precordial electrocardiogram (ECG) was taken and recorded for 5 min, with the participants in a semi-recumbent posture. Electrocardiogram signals were recorded using an analog-to-digital converter with a sampling rate of 256 Hz. The digitized ECG signals were analyzed online and were simultaneously stored on a hard disk for

off-line verification. Signal acquisition, storage, and processing were performed on an IBM-compatible portable personal computer. A computer algorithm then identified each QRS complex and rejected each ventricular premature complex or noise according to its likelihood in a standard QRS template. Continuity in the time domain was produced by re-sampling stationary R–R values while interpolating at a rate of 7.11 Hz. A frequency-domain analysis of HRV was performed using fast Fourier transformation (FFT). A Hamming window was used to attenuate the leakage effect while the direct current component was deleted.[14] For each time segment (288 s; 2048 data points), our algorithm estimated the power spectral density based on FFT. The resulting power spectrum was corrected for attenuation resulting from the sampling and the Hamming window. The power spectrum was subsequently quantified into standard frequency-domain measurements,[15] including total variance, HF (0.15–0.40 Hz), LF (0.04–0.15 Hz), very low frequency (VLF) (0.016–0.04 Hz) LF:HF ratio, HF% and LF%. The LF% denotes the LF power in normalized units (nu): LF/(total power−VLF) × 100 to detect the sympathetic influence on HRV.[13] Similarly, HF% was defined as HF/(total power−VLF) × 100. Logarithmic transformation (ln) was performed to achieve normal distribution, and correct skewed distributions of the original total variance, HF, LF, VLF, and LF/HF.[16] The HF component is considered to represent cardiac parasympathetic activity,[17] whereas the LF component is considered to be a marker of both sympathetic and parasympathetic activities.[4] The LF/HF ratio, and LF% describe the sympathovagal balances and reflect sympathetic modulations.[15,17,18]

2.6. Statistical analyses

Data were analyzed using SPSS 15.0 for Windows (SPSS Inc, Chicago, Illinois). Results were expressed as mean ± SEM. Statistical analysis between groups was performed either by one-way analysis of variance followed using Scheffe multiple range test, for the post hoc assessment of individual means or Fisher exact test. $P < 0.05$ was considered statistically significant.

3. Results

A total of 33 patients with GOLD stage 2 (n = 16, 48.5%) and GOLD stage 3 (n = 17, 51.5%) COPD were recruited and the mean age was 77.1 ± 1.6 years (SE). Upon presentation to the ED, patients were rated based on the severity of shortness of breath, on a Medical Research Council (MRC) dyspnea scale. Before treatment, the severity of dyspnea of nine patients (27.3%) was rated grade 3, 17 patients (51.5%) as grade 4, and seven patients (21.2%) as grade 5 (Table 1). The indexes of HRV were measured before, 1-hour after, and 24-hours after treatment, and are shown in Table 2. The total variance (ms^2), HF% (nu), and LF% (nu) significantly increased in all patients 24 h after treatment, compared to before treatment ($^{\$}P < 0.05$, T_0 vs. T_2).

Table 1
The severity of shortness of breath on a Medical Research Council (MRC) dyspnea scale in patients with acute exacerbation of chronic obstructive pulmonary disease.

	Before treatment N = 33 (%)	24 h after treatment N = 33 (%)
Grade 1	0 (0)	1 (3.0)
Grade 2	0 (0)	14 (42.4)
Grade 3	9 (27.3)	14 (42.4)
Grade 4	17 (51.5)	3 (9.1)
Grade 5	7 (21.2)	1 (3.0)

Table 3 shows the comparison of the patients who were admitted and those discharged; no significant difference was observed between the groups, in terms of age, body temperature, hemogram (hemoglobin and white count), level of C-reactive protein, arterial blood gas (pH, PCO_2, PO_2, HCO_3^-, SaO_2) and GOLD stage 2/3 (%). There was no difference in the patient-rated MRC scale between the patients who were admitted and those who were discharged (4.0 ± 0.2 vs. 3.9 ± 0.2, $P > 0.05$). Admitted patients had a significantly longer hospital stay (1.8 ± 0.2 vs. 17.1 ± 2.6, $P < 0.001$).

Of the 33 patients, 15 patients with a good response to treatment were discharged after a 24-h observation in the ED, while 18 patients required hospital admission. Upon presentation to the ED, admitted patients had a lower HF% (nu) (19.2 ± 2.1 vs. 35.6 ± 3.7, $P < 0.001$) and higher LF/HF ratio (0.7 ± 0.2 vs. −0.2 ± 0.2, $P < 0.001$) than discharged patients (Fig. 1). However, at 1-h and 24-h post treatment, there was no significant difference in the various HRV indexes including the RR intervals (ms), total variance (ms^2), HF [$ln(ms^2)$], HF% (nu), LF [$ln(ms^2)$],LF/HF ratio and VLF [$ln(ms^2)$] between the admitted and discharged patients. When comparing the time points after 24 h of treatment and the initial presentation in the ED, a significant increase in the HF% (nu) was observed in admitted patients after 24 h of treatment (33.4 ± 3.1 vs. 19.2 ± 2.1, $P < 0.01$), along with a significant decrease in the LF/HF ratio (0.3 ± 0.2 vs. 0.7 ± 0.2, $P < 0.05$). Significant

Table 2
Comparison of heart rate variability before, 1-hour after and 24-hours after treatment.

	Before treatment[a] (T_0) (N = 33)	1 h after treatment (T_1) (N = 33)	24 h after treatment (T_2) (N = 33)
RR intervals (ms)	664.9 ± 30.0[b]	663.3 ± 26.8	676.8 ± 23.2
Total variance (ms^2)	6.1 ± 0.4	6.2 ± 0.4	6.6 ± 0.4$^{\$}$
HF [$ln(ms^2)$]	4.1 ± 0.5	4.2 ± 0.5	4.7 ± 0.4
HF% (nu)	28.1 ± 2.6	31.8 ± 2.3	35.4 ± 2.3$^{\$}$
LF [$ln(ms^2)$]	4.2 ± 0.5	4.2 ± 0.5	4.7 ± 0.4
LF% (nu)	34.9 ± 3.5	32.5 ± 3.3	37.4 ± 2.7$^{\$}$
LF/HF ratio	20.1 ± 15.3	−4.8 ± 15.0	4.2 ± 15.1$^{\hat{}}$
VLF [$ln(ms^2)$]	4.9 ± 0.4	4.9 ± 0.4	5.3 ± 0.3

$^{\$}P < 0.05$, T_0 vs. T_2.
$^{\hat{}}P < 0.05$, T_1 vs. T_2.
HF, high frequency; LF, low frequency; VLF, very low frequency.
[a] Treatment: drugs inhalation and intravenous treatment.
[b] Mean ± SE.

Table 3
Demographic information, laboratory findings in discharged and admitted patients with acute exacerbation of chronic obstructive pulmonary disease in the ED.

	Discharged (N = 18)	Admitted (N = 15)	*P*
Age	77.5 ± 2.1	76.6 ± 2.5	NS
Male/female	17/1	15/0	NS
Respiratory rate	25.7 ± 1.2	27.7 ± 1.3	NS
Systolic blood pressure	162.7 ± 7.5	156.1 ± 5.4	NS
Body temperature	36.5 ± 0.2	36.8 ± 0.3	NS
WBC	10,688.9 ± 755.4	10,533.3 ± 1106.8	NS
Hb	13.1 ± 0.4	13.5 ± 0.4	NS
Hematocrit	36.9 ± 1.7	40.4 ± 0.9	NS
CRP	3.1 ± 0.8	2.1 ± 1.0	NS
Arterial blood gas			
PH	7.4 ± 0.1	7.4 ± 0.1	NS
PCO_2	38.2 ± 2.0	37.3 ± 2.2	NS
PO_2	123.2 ± 10.8	129.7 ± 9.7	NS
HCO_3^-	25.1 ± 0.9	23.1 ± 1.1	NS
SaO_2	97.9 ± 0.5	98.3 ± 0.4	NS
GOLD stage 2/3 (%)	8/10 (44.4/55.6)	8/7 (53.3/45.5)	NS
MRC dyspnea scale	4.0 ± 0.2	3.9 ± 0.2	NS
Hospital stay (day)	1.8 ± 0.2	17.1 ± 2.6	<0.001

Value are presented as mean ± standard error or no (%) WBC, white blood cell; Hb, hemoglobin; CRP, C-reactive protein; MRC, Medical Research Council.

differences in the HF% or LF/HF were not noted in discharged patients after 24 h of treatment ($P > 0.05$).

The ΔHF% is defined as the difference between the HF% 24 h after treatment and before treatment (ΔHF% = (T_2−T_0) HF%) (Table 4). On comparing patients who were admitted and those discharged, it was found that the magnitude of change in the HF% (ΔHF%) among those admitted was significantly larger (14.2 ± 3.5 vs. 1.4 ± 5.1 $P < 0.005$). The ΔLF/HF% describes the difference between the LF/HF% 24 h after treatment compared and before treatment (ΔLF/HF % = (T_2−T_0) LF/HF%). The magnitude of change in the LF/HF% (ΔLF/HF%) was significantly lower in the admitted patients than those discharged (−0.4 ± 0.2 vs. 0.0 ± 0.3, $P < 0.05$). ROC curve analysis was performed to show the relative potential of the ΔHF% and ΔLF/HF% in the discrimination of the groups (Fig. 2). The areas under the ROC curve in the two groups were 0.807 (95% confidence interval, CI, 0.644−0.971, $P < 0.01$) and 0.722 (95% CI, 0.540−0.905, $P < 0.05$), respectively. The best cut-off values for admission were ΔHF% >7.1 and ΔLF/HF% ≦−0.39. When the ΔHF% was >7.1, the sensitivity and specificity were 86.7% and 77.8%. When the ΔLF/HF% was ≦−0.39, the sensitivity and specificity were 66.7% and 77.8%, respectively.

Table 4
Changes in the discharged and admitted patients with acute exacerbation of chronic obstructive pulmonary disease, in the ED, before treatment and 24 h after treatment.

	Discharged (N = 18)	Admitted (N = 15)	*P*
ΔMRC	1.2 ± 0.2	1.4 ± 0.2	NS
ΔHF%	1.4 ± 5.1	14.2 ± 3.5	<0.005
ΔLF%	3.1 ± 3.6	1.7 ± 4.5	NS
ΔLF/HF%	0.0 ± 0.3	−0.4 ± 0.2	<0.05

ΔMRC = MRC (before treatment (T_2) − 24 h after treatment (T_0)).
ΔHF% = (T_2−T_0) HF%.
ΔLF% = (T_2−T_0) LF%.
ΔLF/HF% = (T_2−T_0) LF/HF%.
MRC, Medical Research Council; HF, high frequency; LF, low frequency.

4. Discussion

In the case of AECOPD, the decision regarding discharge is a clinical challenge for emergency physicians, as the modalities available in the ED, such as arterial blood gas, or the pulmonary function test do not fully reflect the severity of disease.[19] The aim of the present study was to noninvasively evaluate HRV in order to risk-stratify AECOPD patients with

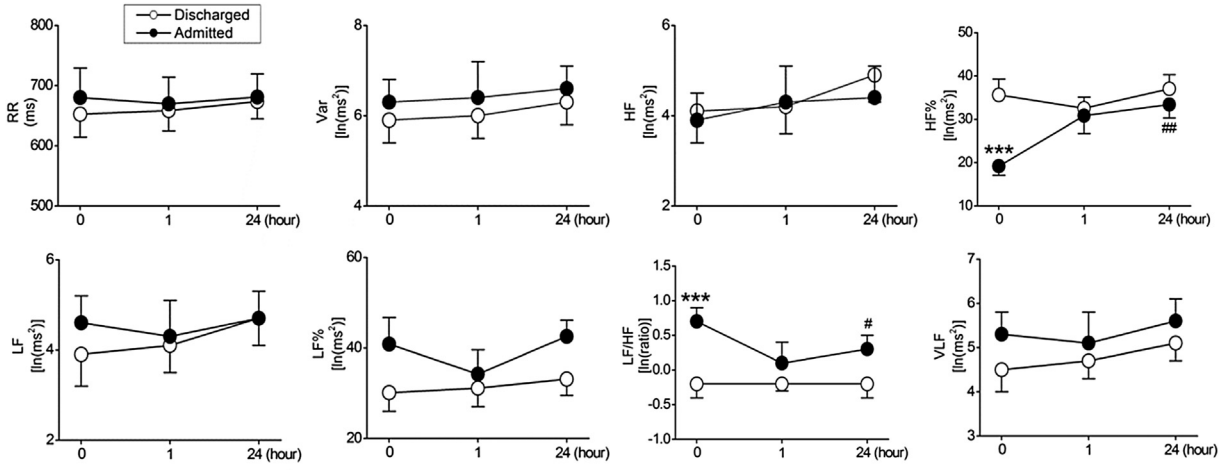

Fig. 1. Comparison of R−R, variance of the R−R interval (Var), high-frequency (HF) power, low-frequency (LF) power, normalized HF (HF%, in normalized units [nu]), normalized LF (LF%, in normalized units [nu]), LF/HF ratio, and very low frequency (VLF), power of heart rate variability (HRV) between before initial treatment (T_0), after initial treatment (T_1) and after 24 h treatment (T_2) in AECOPD patients, in the ED. Values are presented as mean ± SEM. * admitted vs. discharged patients, ***$P < 0.001$. # admitted patients at initial (T_0) vs. after 24 h treatment (T_2), #$P < 0.05$, ##$P < 0.01$.

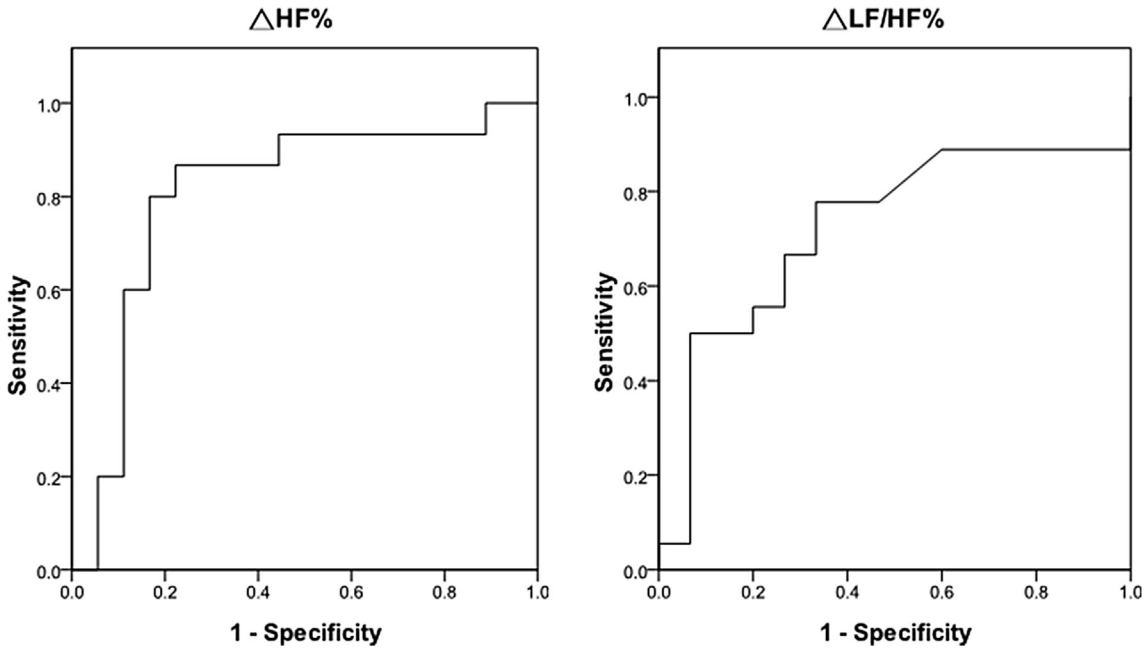

Fig. 2. Receiver-operating characteristic (ROC) curve for the cutoff level of the ΔHF % and ΔLF/HF % in differentiating admitted and discharged AECOPD patients in the ED.

or without a response to adequate treatment, prior to ED discharge. In our study, a significant increase in HF% and decrease in LF/HF ratio after 24 h of treatment (T_2) was observed in admitted patients. The ROC curve analysis showed the relative potential of the ΔHF% ($P < 0.005$) and ΔLF/HF% ($P < 0.05$) in the discrimination of the discharged and admitted groups. Our study demonstrated that, after 24-h ED treatment, patients with AECOPD, with either ΔHF% >7.1 or a ΔLF/HF% ≦−0.39, may not adequately respond to treatment and may require hospital admission.

4.1. Significant increase in total variance, HF% and LF % 24 h after treatment

In Table 2, lower values for all the HRV indexes were observed, which were compatible with those observed in a previously conducted study,[9] and were consistent with the reduction in phasic cardiac responsiveness to sympathetic stimulation.[20] This chronic sympathetic stimulation may be associated with a down-regulation of beta-receptors.[21] In our study, an increase in the HF% was observed after 24 h of treatment, suggesting an increase in the vagal modulation in response to treatment. A decrease in the LF% and LF/HF was initially observed 1 h after treatment, followed by a significant increase after 24 h, in concordance with the observation that COPD patients have chronically high tonic intrinsic and extrinsic sympathetic stimulation.[21]

COPD patients are less able to respond to sympathetic and parasympathetic stimuli,[21] while AECOPD patients have increased autonomic activity.[10] In our study, COPD patients responded to treatment with a shift toward parasympathetic modulation, through an increase in the HF%. The increase in the parasympathetic tone was offset by a concomitant increase in the sympathetic tone LF%; this is in accordance with the impaired response to parasympathetic stimuli and high tonic sympathetic stimulation observed in COPD patients.[22]

4.2. Age, respiratory rate, temperature, hematogram, arterial blood gas, and GOLD classifications did not differ between admitted and discharged patients

No significant difference was observed comparing the GOLD stage 2/3 ratios between the two groups. This is compatible with the observation that, despite current guidelines defining the severity of COPD through the GOLD classification, its correlation with severity, in the case of acute exacerbation, is modest.[23] The average duration of hospital stay (including observation in the ED and admission to the ward) among cases of admitted AECOPD was about 11.7 days, in a previous conducted study,[3] and 17.1 days in our study. Admitted patients had a significant longer total hospital stay compared to discharged patients (17.1 ± 2.6 vs. 1.8 ± 0.2, $P < 0.001$).

4.3. Significant increase in the ΔHF% and a significant decrease in the ΔLF/HF% of admitted patients who did not response to treatment

Fig. 1 showed that, at initial presentation in the ED, before treatment (T_0), admitted patients had a significant lower HF% ($P < 0.001$) and higher LF/HF ratio ($P < 0.001$) compared to discharged patients. This suggested that admitted AECOPD patients needed longer treatment, had a sympathovagal balance towards an increase in sympathetic and decrease in parasympathetic modulation at the initial ED presentation, and were under more severe stress than discharged patients. After 24 h of

treatment, no significant differences in the HRV indexes were noted between the admitted and discharged patients, making it difficult for clinical physicians to differentiate the cases.

In the study (Table 4), the MRC scale was useful in describing patient cohorts and stratifying them for interventions.[24] However, no significant difference was noted in the ΔMRC between the two groups ($P > 0.05$), and, therefore, it could not readily assist clinical emergency physicians in the risk stratification of AECOPD patients, in terms of ED discharge. On the other hand, a significant increase in the ΔHF% ($P < 0.005$) and significant decrease in the ΔLF/HF% ($P < 0.05$) after 24 h of treatment can help to identify patients who should be admitted. ED physicians could discharge AECOPD patients from the ED after treatment for 24 h, if their ΔHF% ≦ 7.1 or ΔLF/HF% > −0.39. This strategy may help to decrease the length of stay in AECOPD patient in the ED.

4.4. Study limitations

There are a few limitations to this study. First, it used a small sample size and from only one tertiary referral center. Second, as ours was a veterans' hospital, the average age of the patients was about 77.1 years, which was too old to be representative of the general population. Many of the AECOPD patients were too weak to perform spirometry. Third, due to ethical consideration, this study included only GOLD stage 2 and 3 AECOPD patients. Fourth, in order to reduce the confounding factors, we also excluded AECOPD patients who were suspected of having pneumonia in the ED, initially. Fifth, due to AECOPD patient's emergent situation, we recorded and checked the quality of 5-min HRV at the same time. We chose one acceptable and optimal 5-min HRV before initial treatment, after initial treatment and after 24 h treatment. In addition, the study included patients who did not have severe or unstable cardiac disease. As many COPD patients have concomitant cardiac disorders, the study result may not be applicable to these patients.

In conclusion, non-invasive modalities such as HRV merit consideration when evaluating therapeutic response during AECOPD, for better risk-stratification of patients with or without adequate response to treatment, prior to ED discharge. A significant increase in the ΔHF% and significant decrease in ΔLF/HF% were observed in admitted patients after 24 h of treatment, compared to before treatment. Our study demonstrated that patients with ΔHF% >7.1 or ΔLF/HF% ≦−0.39 require admission despite 24 h of ED treatment. These significant changes may serve to risk-stratify patients in the ED setting prior to discharge.

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