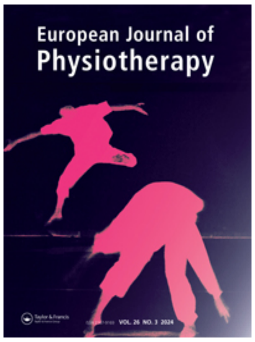

European Journal of Physiotherapy

ISSN: (Print) (Online) Journal homepage: www.tandfonline.com/journals/iejp20

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EUROPEAN JOURNAL OF PHYSIOTHERAPY
2024, VOL. 26, NO. 3, 176–184
https://doi.org/10.1080/21679169.2023.2229392

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RESEARCH ARTICLE

Aerobic exercise simultaneous with non-invasive ventilation reduces the length of stay in intensive care in patients with heart failure: a randomised clinical trial

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ABSTRACT

Introduction: Early cardiac rehabilitation using non-invasive ventilation (NIV) and aerobic exercise may reduce the length of hospital stay in patients with heart failure (HF), however, there is still no evidence of this effect on patients in the intensive care unit (ICU).

Objectives: to investigate the effects of aerobic exercise (AE) performed simultaneously with non-invasive ventilation (NIV) on the length of intensive care stay (LICUS) in patients diagnosed with decompensated heart failure (HF) admitted to the intensive care units (ICU).

Methods: Twenty-eight patients admitted to the intensive care unit (ICU) because of decompensation of HF were randomised into two groups: the intervention group (AE + NIV), and a control group. The intervention group's treatment strategy involved simultaneous AE with NIV daily. The control group performed non-simultaneous AE and NIV daily during their ICU stay. The primary outcome was LICUS. The secondary outcomes were the length of hospital stay, peripheral and respiratory muscle strength, functional status, functional classification, and exercise tolerance.

Results: The mean LICUS was shorter in AE + NIV than in the control group (6.3 ± 4.7 days *vs* 8.3 ± 3.6 days, respectively; $p = 0.015$). Secondary outcomes were similar between groups, except for exercise hemodynamics, which was improved in AE + NIV, as showed by the decreased diastolic blood pressure immediately after the exercise tolerance test.

Conclusion: The use of AE simultaneous with NIV reduced the LICUS of patients admitted to the ICU because of decompensated HF. This innovative approach is a promising tool for accelerating ICU discharge during the in-hospital rehabilitation of patients with HF.

ARTICLE HISTORY
Received 27 January 2023
Revised 14 June 2023
Accepted 16 June 2023
Published online 22 June 2023

KEYWORDS
Heart failure; Bi-level positive airway pressure ventilation; physiotherapy; aerobic exercise; hospitalization

Introduction

Heart failure (HF) is a major public health problem that affects approximately 23 million people worldwide and 2% of the adult population [1]. Despite therapeutic advances, HF remains associated with increased mortality, morbidity, and high healthcare costs. Moreover, it is the main cause of hospitalisation in South America, accounting for 21% of all cardiovascular cause-related admissions and is associated with elevated in-hospital mortality and reduced survival rates after discharge [2].

Also, critically ill patients, including those admitted in cardiac intensive care units (ICU), are susceptible to several complications related to the severity of their own illness and to the need for intensive care therapies. The main causes of ICUs' complications – healthcare-associated infections, pain, agitation, delirium, mechanical ventilation, excessive oxygen supplementation, gastrointestinal dysfunction, medications adjustment and devices, and immobility – may increase morbidity and mortality and contribute to higher health expenses and a longer stay in the ICU [3].

Among several non-pharmacological HF therapies, cardiovascular rehabilitation (CR) and non-invasive ventilation (NIV) are relevant because of their potential benefits. Aerobic exercise (AE) is a pivotal component of CR programs that reduce mortality and hospitalisation rates and improves functional capacity and quality of life in high-risk patients with poor prognosis [4–6]. AE has been recently recommended as an early intervention for critically ill patients. Daily twenty-minute sessions of early mobilisation improves exercise capacity and muscle strength at hospital discharge [7]. Also, NIV can be an important adjuvant in the treatment of HF by improving pulmonary, cardiac, and peripheral muscle function [8,9]. In outpatients patients with stable HF, the use of continuous positive end-expiratory pressure (CPAP), ranging from 4 to 6 cmH_2O, prior to exercise, improved exercise tolerance [10]. Moreover, the use of NIV with inspiratory pressure support, during exercise, reduced exertional leg

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discomfort and increased exercise endurance in patients with chronic congestive HF, suggesting the potential of NIV as an adjunct to exercise by allowing patients to train at higher workloads and for longer periods of time, which could enhance physiological training effects [11].

Physical exercise proved to be safe in hospitalised patients with acute HF, there were no hospital complications and, when associated with NIV, improved performance in the 6-minute walk test, dyspnoea and length of hospital stay [14]. Considering the congestive profile of patients admitted in ICU due to decompensation of HF, with low exercise tolerance associated with ventricular pump and gas exchange deterioration, even after initial therapeutic compensation, NIV during exercise could allow a better exercise tolerance due to increase of alveolar pressure, improving pulmonary congestion, and by ventricular afterload reduction due to the positive pleural pressure, resulting in ventricular pump improvement, however, this strategy has not been investigated in intensive care unit (ICU) scenario [12–14]. So, we hypothesised that aerobic exercise simultaneous non-invasive ventilation could reduce length of intensive care unit stay when compared to those therapies applied separately. Therefore, the present study aims to evaluate the effects of this combined protocol on the length of ICU stay (LICUS) in patients diagnosed with HF decompensation hospitalised in the ICU.

Materials and methods

Study design

The present study was designed as a two-arm randomised superiority clinical trial and conducted in the ICU of a tertiary hospital in Rio de Janeiro, Brazil.

The sample size was calculated based on the data obtained from previous literature comparing the length of hospital stay (LOHS) in patients with HF decompensation admitted to the hospital and treated with AE simultaneous NIV [14]. LOHS was used as a proxy because the literature on AE and NIV in the ICU setting was limited. Considering $\alpha = 0.05$, $\beta = 0.05$, the mean and standard deviation (39 ± 15 and 17 ± 10 days, for the control and the AE + NIV groups, respectively), and 1:1 allocation, the estimated sample size was 18 patients. Accounting for the loss during follow-up, the sample size was increased by approximately 50%, resulting in a final sample size of 28 patients.

Ethical considerations

This study was conducted in accordance with the Declaration of Helsinki amended in 2013 and approved by the Institutional Research Ethics Committee (CAAE 89480418.0.3002.5259). This clinical trial was registered in the Brazilian Registry of Clinical Trials (RBR-7pkj3q) and followed the recommendations of the Consolidated Standards of Reporting Trials (CONSORT). All the patients were notified of the possible benefits and adverse effects of the study. After acceptance, detailed verbal explanation of the procedures was provided to the subjects or their companions, with the intervention being performed only after the volunteers had read, authorised, and signed the terms of informed consent. Patients in both the groups received medical treatment following the recommendations of national and international guidelines during their hospital stay.

Participants

Patients admitted to the ICU due to decompensated HF were considered eligible for the study, and 48h post-admission, the patients were asked by a senior physiotherapist about participating as volunteers in the research. The patients willing to participate were referred to the first evaluation.

The inclusion criteria were previous diagnosis of HF, left ventricular ejection fraction (LVEF) <40%, age ≥18 years, hospitalisation due to decompensated HF, and clinical stability without need of continuous ventilatory support. The exclusion criteria were decompensated pulmonary diseases, pregnancy, head trauma, brain injury, cognitive impairment, neuromuscular disorders, hemodynamic instability with high dose of inotropes or acute coronary syndrome. Hemodynamic instability was considered if systolic blood pressure (SBP) ≤ 90 mmHg or mean arterial pressure (MAP) ≤ 65 mmHg, peripheral hypoperfusion (altered state of consciousness, cold and cyanotic extremities and/or decreased urine output ≤ 0.5 mL/kg/hour), HR < 40 or > 130 beats per minute, SpO_2 < 88%, vomiting episodes were recent, complaints of dizziness or headache, high dose dobutamine (>10mcg/kg/min, as defined by the unit's medical routine) [15].

Before beginning the study protocol, health and sociodemographic variables were collected: age, weight, body mass index (BMI), sex, race, education level, comorbidities, smoking, alcohol consumption, and medications. The aetiology of HF, functional classification (according to the New York Heart Association classification- NYHA) during admission, risk of in-hospital mortality (using the Acute Decompensated Heart Failure National Registry score- ADHERE), reason for admission, hemodynamic profile on admission (according to the classification of Stevenson in: group A- without both pulmonary congestion and signs of hypoperfusion [dry and warm]; group B- presence of pulmonary congestion without signs of hypoperfusion [wet and warm]; group C- presence of pulmonary congestion associated with hypoperfusion [wet and cold]; and group D- hypoperfusion without pulmonary congestion [dry and cold]) [2], LVEF during admission, and the dosage of dobutamine 48 h after admission were obtained from medical records. Exercise tolerance, respiratory muscle strength (RMS), peripheral muscle strength (PMS), and functional status were assessed at baseline (48 h after admission), and at ICU discharge.

Intervention

Patients were randomly allocated using a specific randomisation tool (www.random.org) into the intervention (AE + NIV)

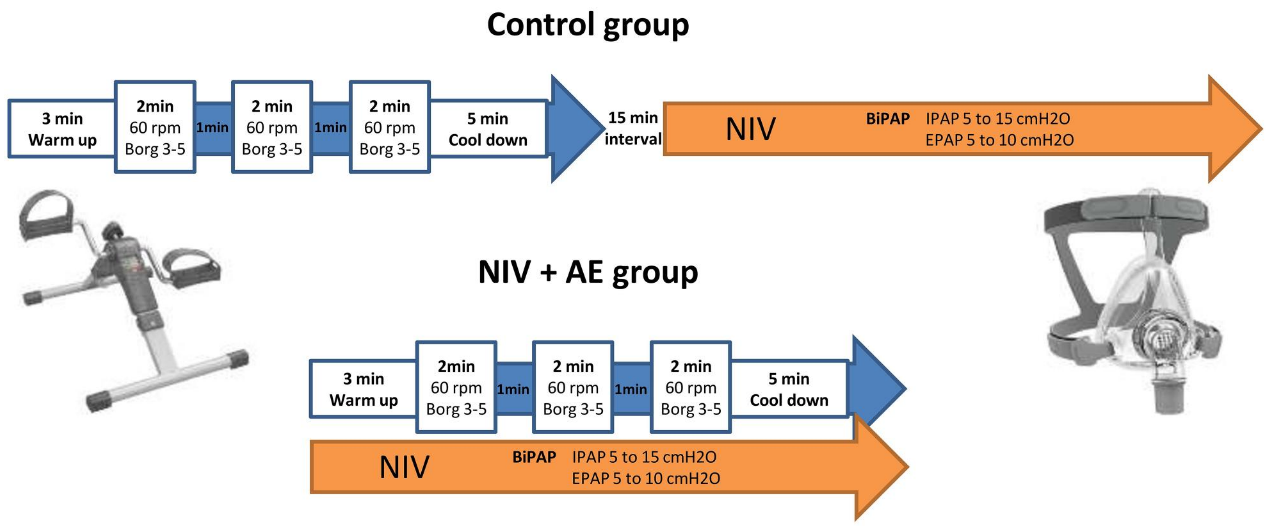

Figure 1. NIV and AE prescription during study.

or control groups. In the intervention group, the NIV was applied at the same time of AE. In the control group, the same AE and NIV protocols were performed, but at separate times by a minimum of 15 min at minimum) (Figure 1). The principal researcher trained all ICU's physiotherapy staff to prescribe both NIV and AE protocols at same way, in order to minimise the possibility of protocol deviations. The patients remained under continuous monitoring of heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP), and peripheral oxygen saturation (SpO_2) for the duration of the protocol and an additional 60 min of recovery. The subjective perceived fatigue score (Borg CR-10 scale) [16] was recorded at baseline, during the intervention, and at the end of the protocol period. The protocol was interrupted if the SBP increased or dropped $\geq$30 mmHg, HR increased to $\geq$120 bpm, the patient presented signs of excessive respiratory effort, with difficulty in supporting the protocol and/or signs of low cardiac output or precordial pain was noted. The same measurements as those described for the intervention group were recorded during the AE protocol for the control group. Both groups performed the protocol once daily until discharged from the ICU. Figure 1 shows the study protocol. Due to the nature of the procedures, neither researchers nor patients were blinded.

AE protocol

Patients underwent AE using a portable lower-limb cycle ergometer (Minibike Premium G325 Proaction, USA). Patients to pedal on the cycle ergometer without a load for a 3 min warm-up period. Thereafter, the AE training period consisted of three sets of cycling for 2 min at 60 rpm at mild to moderate intensity depending on the subjective perceived fatigue, quantified by the Borg CR-10 scale from 3 to 5, interspersed with 1 min of rest [13,17,18]. For cooldown, 5 min of cycling without a load was performed. The cycle ergometer load was increased daily according to the patient's tolerance to keep 60 rpm and subjective perceived effort from mild to moderate during the AE training period (Borg CR-10 scale from 3 to 5).

NIV protocol

NIV was prescribed using a bilevel ventilatory support (BiPAP Synchrony II, Philips Respironics, Germany) using full-face mask (Fitlife, Philips Respironics, Germany). The ventilatory pressures were adjusted according to patients' comfort and symptoms, ranging from 5 to 15 cmH_2O of inspiratory positive airway pressure (IPAP), and from 5 to 10 cmH_2O of expiratory positive airway pressure (EPAP), aiming a tidal volume of 6 mL.kg – according with the recommendations of the Mechanical Ventilation Committee of the Brazilian Intensive Care Medicine Association and the Intensive Care Committee of the Brazilian Society of Pneumology and Tisiology [19]. Supplementary oxygen flow was maintained the same as already used by the patient immediately before the begin of study protocol.

Outcome measures

Primary outcome

The primary outcome was the length of intensive care unit stay (LICUS) obtained from medical registries after patients' discharge.

Secondary outcomes

The secondary outcomes were LOHS, change in exercise tolerance, RMS, PMS, functional status, in-hospital mortality, readmissions, and mortality within 30 days of hospital discharge.

A submaximal exercise test (SET) was performed to quantify exercise tolerance and assess the safety of hemodynamic responses during training [9]. In the sitting position, the subjects were asked to keep a pedalling cadence of 60 rpm without load on a cycle ergometer. The test was stopped if the patients were unable to maintain 60 rpm, reported fatigue/-pain, or demonstrated any sign of low cardiac output. The

Table 1. Baseline characteristics of the study population.

Variable	Control ($N = 14$) mean ± SD or Number (%)	AE + NIV ($N = 14$) mean ± SD or Number (%)	p Value
Age (years)	64.1 ± 13.6	64.0 ± 8.3	0.8361
Weight (Kg)	66.9 ± 10.9	65.8 ± 14.4	0.4135
BMI (Kg/m^2)	24.3 ± 4.5	23.5 ± 3.9	0.3419
Gender			
Female	5 (35.7)	7 (50.0)	0.704
Male	9 (64.3)	7 (50.0)	
Ethnics			
White	6 (42.9)	4 (28.6)	0.507
Not-white	8 (57.1)	10 (71.4)	
Education level			
Illiterate	2 (14.3)	0	0.837
Primary school	3 (21.4)	3 (21.4)	
Intermediate school	5 (35.7)	6 (42.9)	
High school	2 (14.3)	3 (21.4)	
Complete higher education	2 (14.3)	2 (14.3)	
Comorbidities			
Hypertension	13 (92.9)	12 (85.7)	1.000
Diabetes mellitus	6 (42.9)	2 (14.3)	0.209
Dyslipidemia	1 (7.1)	1 (7.1)	1.000
Stroke	1 (7.1)	2 (14.3)	
Peripheral arterial disease	1 (7.1)	1 (7.1)	1.000
Coronary disease	5 (35.7)	7 (50.0)	
Atrial Fibrillation/Flutter	7 (50.0)	4 (28.6)	0.440
COPD	1 (7.1)	1 (7.1)	1.000
Chronic kidney disease	0	4 (28.6)	0.098
Social History			
Smoking			
Non-smoker	8 (57.1)	4 (28.6)	0.236
Smoker	2 (14.3)	2 (14.3)	
Former smoker	4 (28.6)	8 (57.1)	
Alcohol consumption			
Non-drinker	10 (71.4)	9 (64.3)	1.000
Drinker	2 (14.3)	3 (21.4)	
Former drinker	2 (14.3)	2 (14.3)	
Medications in use before admission			
Beta-blockers	11 (78.6)	11 (78.6)	1.000
Statins	4 (28.6)	6 (43.8)	0.695
Diuretics	13 (92.6)	13 (92.6)	1.000
Antiarrhythmics	1 (7.1)	2 (14.3)	1.000
ACE inhibitor	6 (42.6)	5 (35.7)	1.000
Anticoagulants/Platelet antiaggregant	11 (78.6)	7 (50)	0.236
Other	4 (28.6)	4 (28.6)	1.000
Aetiology of HF			
Ischemic	4 (28.6)	7 (50.0)	0.602
Myocarditis	2 (14.3)	1 (7.1)	
Heart valve disease	3 (21.4)	3 (21.4)	
Peripartum	1 (7.1)	0	
Alcoholic	0	1 (7.1)	
Undefined	1 (7.1)	2 (14.3)	
Hypertensive	1 (7.1)	0	
Tachycardiomyopathy	2 (14.3)	0	
NYHA			
II	1 (7.1)	2 (15.4)	0.586
III	10 (71.4)	6 (46.1)	
IV	3 (21.4)	5 (38.5)	
ADHERE			
Low	4 (28.6)	5 (35.7)	0.784
Intermediate	8 (57.1)	6 (42.9)	
High	2 (14.3)	3 (21.4)	
Reason of admission			
Dyspnoea	9 (64.3)	11 (78.6)	0.889
Tiredness	1 (7.1)	1 (7.1)	
Peripheral edoema	1 (7.1)	1 (7.1)	
Atrial fibrillation	1 (7.1)	0	
Other	2 (14.3)	1 (7.1)	
Hemodynamic profile			
Wet/warm	11 (78.6)	9 (64.3)	0.678
Wet/cold	3 (21.4)	5 (35.7)	
LVEF (%)	31.4 ± 9.4	27.8 ± 8.6	0.1663
Dobutamine dose (μg/Kg/min)	3.0 ± 3.1	2.2 ± 3.3	0.4253

Control: control group; AE + NIV: aerobic exercise simultaneously with non-invasive ventilation group. COPD : Chronic obstructive pulmonary disease; HF: heart failure; NYHA: New York heart Association classification; ADHERE: Acute Decompensated Heart Failure National Registry score, a risk stratification model to predict in-hospital mortality in patients admitted with acutely decompensated heart failure; LVEF: left ventricular ejection fraction.

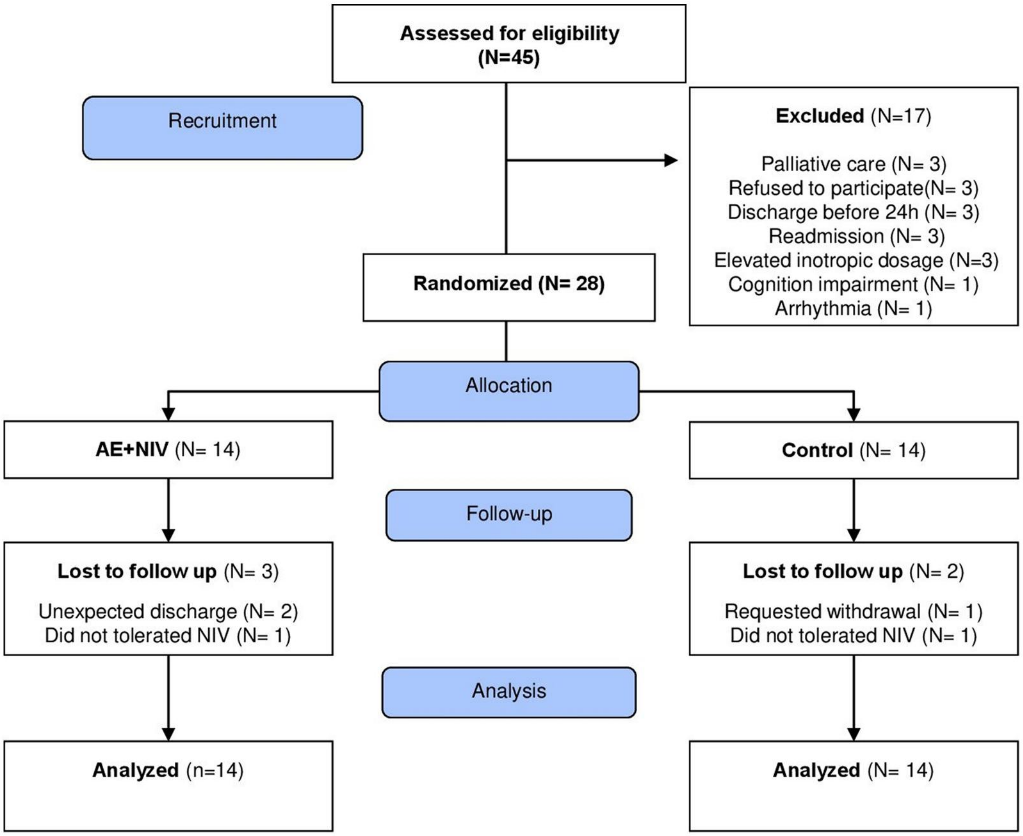

Figure 2. Study flowchart. Control = control group; AE + NIV = aerobic exercise simultaneously with NIV group; NIV = non-invasive ventilation.

HR, SBP, DBP, SpO_2, and Borg CR-10 scale were continuously monitored during the test, and till the total time of the assigned test was completed. SET was performed in the ICU, on the first day of the protocol and when the patient was discharged.

RMS was estimated by measuring maximal inspiratory pressure (MIP) and maximal expiratory pressure (MEP) using manovacuometry (Analogic Manometer, Ventcare, Brazil) according to the recommendations of the American Thoracic Society and the European Respiratory Society [20]. The test was performed by a physiotherapist, who requested the volunteers to perform a maximal inspiration effort from the residual volume and a maximum expiration effort from the total lung capacity for 1 to 2 s [21].

The PMS was assessed using manual handgrip dynamometry (MHD) and Medical Research Council (MRC) score [22]. The MHD measurement was performed in the dominant hand with the shoulder adducted and neutrally rotated, the elbow at 90° of flexion, and the forearm and wrist neutrally positioned using a digital dynamometer (WCT Fitness 600170, Brazil). The average of three successive measurements was used [23]. Additionally, the MRC score was used to assess the overall muscle strength. This score grades strength from 0 (total paralysis) to 5 (normal muscle strength) by assessing the voluntary achievement of six specific bilateral movements: shoulder abduction, elbow flexion, wrist extension, hip flexion, knee extension, and ankle dorsiflexion [22].

The functional status was evaluated using the ICU Functional Status Scale (FSS-ICU), which has been previously validated in Portuguese population and is clinically prevalent [24]. This scale determines the physical function of patients in the ICU, by assessing following five functional tasks: rolling, transferring from supine to sitting, transferring from sitting to standing, sitting at the edge of the bed, and walking. Each of these tasks was scored using an ordinal scale of 8 points, ranging from zero (incapable of performing any task) to 7 (complete independence).

Hospital and ICU readmissions, in-hospital mortality data and LOHS were recorded by analysing the medical registries 30 days after discharge from the ICU. Information on mortality within 30 days of hospital discharge was obtained from the database of the judicial court of Rio de Janeiro (http://www4.tjrj.jus.br/Portal-Extrajudicial/CNO/).

Data analysis

Descriptive data are expressed as mean ± standard deviation (SD) or number and percentual. Data distribution was analysed using the Shapiro–Wilk normality test. Comparisons between means were performed using the paired t test or the Mann–Whitney U test for parametric and nonparametric data, respectively. Longitudinal assessment was performed as intention to treat using a mixed linear model adjusted for sex, age, and LVEF at baseline, and described as a beta coefficient (β) with a 95% confidence interval. Fisher's exact test was used to assess the associations between categorical variables. All statistical analyses were performed using Stata version 13 (StataCorp LLC, College Station, TX, USA) with a significance level of 0.05.

Results

From March 2019 to February 2020, 45 patients were assessed for eligibility, and 28 were included in the study after completion of the initial assessment and randomised into the control or (AE + NIV) groups. Five patients did not complete the study and were excluded from de analysis (Figure 2).

Baseline sociodemographic characteristics of the study participants are shown in Table 1. Overall, the mean age was 64 years. Majority of the patients had received a fundamental school education. Most patients had hypertension, coronary artery disease, diabetes mellitus, and atrial fibrillation/flutter as comorbidities. Additionally, majority of the patients self-reported as non-white, sedentary, former-smokers, or non-drinkers in both groups. Most patients were classified as NYHA III or IV, with Hemodynamic profile B, and at low/moderate risk of in-hospital mortality. They also had a low mean LVEF, indicating severe left ventricular dysfunction, and had received similar dobutamine dosages 48 h post-admission. Dyspnoea was reported as the main reason for admission to the ICU.

The mean LICUS was significantly shorter for the AE + NIV group than for the control group (6.3 ± 4.7 days vs 8.3 ± 3.6 days, respectively; $p = 0.015$; Table 3), but no significant effect on LOHS (Control group, 20.4 ± 11.5 days vs AE + NIV group, 31.8 ± 22.2 days; $p = 0.095$) was found.

During their ICU stay, the patients performed the study protocol 5.1 ± 3.1 times in the control group and 4.5 ± 3.6 times in the AE + NIV group ($p = 0.547$). The mean values of the NIV were IPAP: 11.8 ± 1.5 *vs* 12.7 ± 1.1 cmH_2O for the Control and the (AE + NIV) groups, respectively ($p = 0.100$); and EPAP: 7.5 ± 1.3 *vs* 7.9 ± 0.5 cmH_2O for the Control and AE + NIV group, respectively ($p = 0.384$).

The longitudinal effects of the intervention on peripheral and respiratory muscle strength, functional status, and perceived fatigue were similar between the two groups. However, the (AE + NIV) group presented a small but significant exercise hemodynamic improvement, as shown by the reduction in DBP immediately after the exercise tolerance test at discharge (Table 2).

Finally, there were no deaths during the ICU stay, and the number of deaths (in-hospital or after 30 days of discharge) and readmissions after 30 days of hospital discharge were similar between the groups (Table 3).

Table 2. Effect of AE + NIV on PMS, functional status, RMS and exercise tolerance.

Variable	Coefficient (β)	95% CI	*p* Value
Peripheral muscle strength			
MRC	−0.4	−3.5 to +2.7	0.813
MHD	+0.6	−1.2 to +2.3	0.540
Functional Status (FSSICU)	−2.2	−5.0 to +0.5	0.107
Respiratory muscle strength			
MIP (cmH_2O)	−3.3	−19.2 to +12.6	0.255
MEP (cmH_2O)	+9.5	−4.8 to +28.4	0.163
Borg CR-10 scale	−0.5	−1.6 to +0.7	0.429
NYHA	+0.1	−0.6 to +0.7	0.999
Exercise tolerance (EET)			
Test duration (min)	−1.8	−6.9 to 3.3	0.487
HR (bpm)	+0.7	−14.0 to 15.4	0.923
SBP (mmHg)	−2.6	−18.6 to 13.3	0.745
DBP (mmHg)	−10.7	−19.4 to −2.0	0.016
DP (bpm.mmHg)	+646.9	−1446.2 to 2740.1	0.545
SpO2 (%)	−0.4	−1.5 to +0.7	0.492
Borg CR-10 scale	+0.6	−1.7 to +3.0	0.591

MRC: Medical Research Council score; MHD: Manual Handgrip dynamometry; FSSICU: Functional status score for Intensive Care Unit; MIP: Maximal Inspiratory Pressure; MEP: Maximal expiratory pressure; NYHA: New York heart Association classification; EET: Exercise effort test; HR: Heart rate; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; DP: Double-product; SpO_2: peripheral oxygen saturation. Borg CR-10 scale: perceived fatigue score. Longitudinal analysis using linear mixed models adjusted by gender, age and LVEF.

Discussion

The main finding of the present study was that the strategy of AE combined with NIV reduced LICUS by approximately 2 days in patients admitted to the ICU because of the decompensation of pre-existing severe HF. Similarly, for stable patients with HF admitted to hospital wards, it has already been demonstrated that 8 days of combined NIV and AE therapy was safe, improved exercise tolerance, and reduced perceived dyspnoea and LOHS [14]. However, despite the reduction of LICUS caused by concurrent AE and NIV, a novel finding of this study, a reduction in the LOHS was not observed. This strongly suggests the need for follow-up after ICU discharge to include physiotherapy. For our participants, concurrent AE and NIV was only available during their ICU stay. Additionally, after discharge from the ICU to the wards, patients may have to lengthen their hospital stays to accommodate complementary examinations and

Table 3. Length of stay, mortality and hospital re-admissions.

Variable	Total (28) Number (%) or Mean ± SD and median [IQ25-75]	Control (14) Number (%) or Mean ± SD and median [IQ25-75]	AE + NIV (14) Number (%) or Mean ± SD and median [IQ25-75]	*p* Value
LICUS (days)	7.4 ± 4.1	8.3 ± 3.6 7 [5.5 - 11]	6.3 ± 4.7 6 [4 - 6]	0.015
LOHS (days)	25.3 ± 18.1	20.4 ± 11.5 20 [13–23]	31.8 ± 22.2 24 [16–45]	0.095
Deaths in ICU	0	0	0	–
In-hospital deaths	2 (7.1)	0 (0)	2 (14.3)	0.481
Readmission within 30 days of discharge	7 (30.4)	3 (21.4)	4 (28.6)	1.000
Deaths after 30 days of hospital discharge	3 (13.0)	1 (7.1)	2 (14.3)	1.000

Control: control group; AE + NIV: aerobic exercise during non-invasive ventilation group; LICUS: length of intensive care stay; LOHS: ICU: Intensive Care Unit. Comparison between means was performed using Mann-Whitney test. Fisher's exact test was used for assess the association between categorical variables.

procedures dependent on the (in the public health system) schedule availability. This factor may impact the accuracy of LOHS as a secondary outcome.

Recently, a cross-sectional study demonstrated that simultaneous AE and NIV using a limb cycle ergometer improved exercise tolerance and reduced perceived dyspnoea in ICU patients with decompensated HF [9]. This could potentially explain the reduction in LICUS observed in the present study. However, our data showed that the longitudinal effect of simultaneous AE and NIV intervention did not improve SET, functional status, PMS, RMS, or NYHA, leading to the question: what aspect of this intervention could justify the early discharge from the ICU? In the present study, both groups performed NIV and AE, alone or simultaneously, which could explain the similarity in SET durations between the groups. Nevertheless, an important effect of combined AE and NIV was the reduction of DBP immediately after SET at discharge, may indicate an improvement in hemodynamics during exercise beyond the total duration of the SET. Physiologically, DBP represents systemic vascular resistance and afterload, which are keystones of HF hemodynamics. The reduction of afterload could lead to improvements in LV function and cardiac output, thereby reducing the duration of ICU stay by improving pulmonary congestion and related symptoms [25,26]. AE and NIV associated improvements in muscular function, are evident even after a few sessions. This was observed in hypertensive patients, where AE reduced both SBP and DBP [27–29]. The mechanisms related to the effect of AE on blood pressure depend on hemodynamic, humoral, and neural factors, widely studied in healthy and normotensive individuals. Significant reduction in blood pressure levels were achieved with low intensity training [30–32].

Furthermore, patients with HF have detrimental autonomic impairments, mainly sympathetic hyperactivation, which when combined with parasympathetic withdrawal may result in elevated blood pressure and increased peripheral vascular resistance [1]. Physiological adaptations that occur after exercise involve both central and peripheral mechanisms, including an increase in peak cardiac output, improvement in vascular reactivity, better utilisation of oxygen through metabolic changes in the skeletal muscle, improvement of autonomic function, and increased efficiency of ventilation mechanics [29].

Clinically, the advantage of a shorter ICU stay could be associated with a reduction in complications, like infections and delirium, but also with reduced expenditure, which tends to be much higher for ICUs than for intermediate or clinical wards. Thus, fewer days in the ICU may reduce costs for the health care system [33,34]. In fact, considering the public health system in Brazil, the estimated cost of daily hospital stay for a HF patient, in 2005, was US$52.93 in wards and US$91.45 in ICU, respectively [35]. Additional data shows that in 2019, the average cost of a daily stay in the ICU increased to US$126.22 [36]. Thus, strategies that reduce ICU and hospitalisation stays must be considered from the point of view of cost-effectiveness, not only by healthcare professionals but also by healthcare managers. This would allow expanded investment in multidisciplinary teams to ensure the best care for HF patients. In our study, the absence of regular physiotherapy follow-up during the entire hospital stay could be a possible explanation for insignificant reduction in LOHS, further emphasising the need for multidisciplinary management of HF from ICU until hospital discharge.

Likewise, patients hospitalised for HF have high event rates (>50%). Mortality ranges from 10 to 15%, hospital readmission rates within 6 months after discharge is between 30 to 40%, and hospitalisation is associated with an increased risk of death [37]. Interestingly, in the present study, no deaths were registered during ICU stay, and despite the two deaths observed during the entire hospitalisation period, and the three observed 30 days following hospital discharge, mortality and readmission rates were unaffected by our intervention. These results are similar to those previously described, with in-hospital mortality for patients with HF ranging from 2 to 7%, and between 5 to 15% after 60–90 days of discharge [38]. Despite advances in medicine, outpatients with stable chronic HF have an annual hospitalisation rate of approximately 32%, but for those hospitalised due to acute exacerbation of HF, this increases to 44% [37]. Moreover, the 5-year survival rate of patients with HF is approximately 50%, and many people die directly from HF or related cardiovascular diseases [39].

The benefits of CR follow-up for outpatients with chronic HF are well described, but there is scarce clinical research in the hospital environment. Physical inactivity is associated with a higher risk of death in all cardiac diseases, and moderate exercise is correlated with increased survival in patients with chronic HF [40]. A recent meta-analysis revealed that outpatient CR can make negligible difference in all-cause mortality in the short term (≤ one year of follow-up) but can improve all-cause mortality in the long term (> 12 months). In addition, CR reportedly reduces hospital admissions due to all causes, and hospitalisations caused by HF specifically in the short term [41].

Finally, while other guidelines merely cite the necessity of initiating phase I CR with low-intensity exercise and early mobilisation, neglecting NIV as a possible strategy for improving CR performance, the Brazilian cardiac rehabilitation guidelines report a lack of data for exercise programs for patients with advanced symptoms (NYHA IV) [42]. Thus, the present study can contribute to the indication of exercise programs for patients with advanced HF in the initial stages of in-hospital care.

In conclusion, the present study showed that AE during NIV reduced the length of ICU stay in patients admitted to the ICU with decompensated HF by a small but significant improvement in exercise tolerance. This innovative intervention could be a relevant tool for accelerating ICU discharge and in-hospital rehabilitation providing clinical and financial benefits associated with a shorter ICU stay for patients with HF.

Limitations

This study was limited by the small sample size, that despite a priori calculation of sample size, resulted in low statistical power (45% for LICUS and 66% for LOHS). Also, the presence of a control group without NIV could have offered relevant information about the possible advantages of prescribing NIV and AE in different combinations in the ICU. We are also aware that this was a single-center study, and our results may not be applicable to other settings. Additionally, the primary outcome was LICUS, which is subjective because physicians deciding discharge from the ICU were not blinded to the patient allocation, creating bias. However, to reduce subjectivity in the physician's decision to discharge, during the clinical routine of the unit, only the physiotherapists were aware of the patients' inclusion and randomisation. Finally, the absence of physiotherapy follow up in the ward, with interruption of AE + NIV therapeutic strategy, impairs the interpretation of LOHS results.

Acknowledgements

The authors thank the patients that gently accepted to participate of the study despite their current illness status.

Disclosure statement

No potential conflict of interest was reported by the author(s).

Funding

FUNDACOR- Fundação Pró-Coração.

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