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RESEARCH ARTICLE

SAFETY AND EFFICACY OF EARLY SUPERVISED MOBILIZATION AFTER RECENT DECOMPENSATION OF HEART FAILURE

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ABSTRACT

Heart failure is a complex clinical syndrome in which structural or functional cardiac disorders result in an impaired cardiac function causing symptoms that vary according to the underlying pathology of heart failure. Patients with heart failure are often challenged by the loss of independence and compromised functional abilities associated with the symptoms. This is why comprehensive cardiac rehabilitation including supervised exercise is advised. Indeed, the favorable effects of exercise training in chronic heart failure are widely recognized and exercise training is recommended in international guidelines. However, the application early exercise intervention in patients hospitalized for acute decompensation or acute worsening in cardiac function has not been sufficiently explored and, as a result, knowledge about the effects of exercise training in the inpatient setting of acute HF remained limited regardless of the research efforts made in this area. For this reason, this work aimed at reviewing and collecting previous literature to support the effectiveness and the safety of early mobilization in this patient group.

INTRODUCTION

Cardiac rehabilitation is a complex intervention offered to patients diagnosed with heart disease. A comprehensive cardiac rehabilitation program includes components of health education, advice on cardiovascular risk reduction, physical activity and stress management. It is evident that cardiac rehabilitation reduces mortality, morbidity, and unplanned hospital admissions. Moreover, it leads to noticeable improvements in exercise capacity, quality of life and psychological well-being and it is now recommended in international Guidelines (1). According to The American College of Sports Medicine (ACSM), cardiac rehabilitation (CR) can be divided into 4 phases; Phase Ⅰ, known as the hospital phase, aims to minimize the effects of restriction to bed and ends with hospital discharge. Phase Ⅱ (up to 12 week) starts immediately after discharge and is known as the early out-patient phase, the aim is to develop activities that simulate the metabolic expense of everyday activities. Phase Ⅲ, known as the late out-patient phase (variable duration) aims to develop exercises with more intensity, The fourth and final phase is known as the preventive phase and should have a starting date but not a finishing one, where the patient will choose a cyclical activity of greater affinity, carrying out the program at least 3 times a week throughout one's lifetime (2)

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EXERCISE TRAINING IN CARDIAC REHAB

Exercise training is a core component of CR.(3) Over the past decades, evidences of the need for CR in HF patients have accumulated, and the American Heart Association and American College of Cardiology guidelines recommend CR as a class I indication for HF (4). The European society of cardiology also recommended exercise Rehabilitation to improve exercise tolerance, and health-related QoL in patients with HF. Clinical trials and meta-analyses in people with HF show that exercise rehabilitation improves exercise capacity and QoL. Several meta-analyses also show that it reduces HF Hospitalization (class of evidence 1, level A) (5)

VALUE OF EXERCISE IN HEART FAILURE

Reduced Mortality and Hospitalization: According to the Exercise Training Meta-Analysis of Trials in patients with CHF (ExTraMATCH) study, the mortality rate in the CR group was reduced by 35% compared with that in the control group during the 2-year-follow-up period Also, the HF: A Controlled Trial Investigating Outcomes of Exercise Training (HF-ACTION) study was a randomized controlled 30-month study of 2,331 patients with HF with reduced ejection fraction (HFrEF) (6). The overall mortality or readmission decreased by 11% in the CR group compared with those in the control group, although the results were significant only after adjustment for high prognostic risk factors. Another meta-analysis results reported by Smart and Marwick also showed

that the exercise treatment group had a 39% reduction in mortality (7). CR in patients with HFpEF has also been reported to improve exercise performance and quality of life and to reduce hospitalization rates (8)

Improved Cardiovascular Structure and Function: The improvement of vascular endothelial cell function, in part as a result of regular exercise, is known to have the potential to improve the reduced cardiac output and peripheral vasoconstriction in patients with HF. In addition, exercise slows down the secretion of cytokines and the activation of neurohormonal systems, improves the utilization of oxygen in mitochondria of peripheral muscle cells, increases muscle mass, increases respiratory efficiency without a deleterious effect on left ventricular remodeling, and ultimately improves the clinical outcome of patients with HF , also it decreases the resting heart rate and increase the chronotropic reserve through a beneficial effect on the sympathetic nervous system, even in patients with HF taking a beta-blocker.(9) The beneficial effects on left ventricular function in patients with HF remain controversial, as previous studies showed either no effect or only a slight improvement.(10) However, exercise training enhances the vagal tone by decreasing the central sympathetic nerve outflow, and is associated with a significant reduction of tumor necrosis factor-alpha, interleukin 1-beta, interleukin-6, and brain natriuretic peptide levels.(11)

Improved Plasma BNP Levels: To date, several variables have been assessed in patients with HF. Peak oxygen consumption (peak VO2), the slope of the ratio of minute ventilation to carbon dioxide production (VE/VCO2), the exercise oscillatory ventilation (EOV), and B-type natriuretic peptide (BNP), among others, have emerged as independent diagnostic and prognostic markers in HF. Furthermore, there has been a growing interest in the additional benefit of applying multivariate scores to evaluate patients with HF.(12) Plasma BNP level is a reliable and established prognostic biomarker. Moreover, patients with HF with a high BNP level have a worse prognosis. In patients with such advanced HF, it remains uncertain whether an exercise training programme can safely improve the multivariate indicators of cardiopulmonary function, as well as the N-terminal proBNP (NT-pro-BNP) improvements. Moreover, there are very few systematic studies measuring the impact of AEx on NT-pro-BNP.(11) Another Meta-analysis of Q1 RCTs by Santoso et al. reviewed the effect of aerobic exercise on the N-terminal Pro-B-type Natriuretic Peptide and Cardiopulmonary function in Patients with Heart Failure and included Eight RCTs including 247 cases and 232 controls, confirmed that AEX significantly lowered NT-pro-BNP.(12)

EARLY MOBILIZATION IN ACUTE HEART FAILURE

Patients with acute HF may benefit from exercise training. The impact of exercise training in chronic HF has already been described in literature. However, only a few number of studies was conducted on the impact of early exercise rehabilitation in acute heart failure.(13) Early rehabilitation can be defined as a number of interventions to rebuild briefly the patient's independence, which should be implemented as soon as the clinical state allows it, and last during the whole period of Hospitalization (14). Acute HF is defined as the rapid development of HF signs and symptoms, which requires immediate hospitalization and has a high risk of readmission. In this case, medical treatment predominantly aims to tackle hemodynamic changes and fluid overload.

Acute HF includes both de novo acute HF and ADHF patients (15) About 25–33% of the acute HF patients present with de novo acute HF while the remainder of patients present with decompensation of their ADHF disease. (16)Furthermore, acute HF is the leading cause of hospitalization in older adults and is associated with high morbidity and mortality rates and costs for society. (17)

HIGHLIGHTS ON DECOMPENSATED HEART FAILURE: Decompensated heart failure (HF) is characterized by the inability of the heart to eject and/or accommodate blood within physiological pressure levels, causing severe symptoms such as breathlessness, oedema, great functional dependence, impairment of performance in activities of daily living (ADL) as well as limitations in social life and, consequently, decreased quality of life.(18)This requires immediate therapeutic intervention in hospital. Besides guideline-recommended drugs, treatment of HF involves non-pharmacological interventions such as cardiac rehabilitation (CR), in which physical exercise plays an important role.(19) Early rehabilitation can be defined as a number of interventions to rebuild briefly the patient's independence, which should be implemented as soon as the clinical state allows it, and last during the whole period of hospitalization (20). Exercise training (ET) has been shown to be a safe, economic and feasible therapeutic resource, and is a crucial component of CR.(21) Indeed, regular physical activity is associated with a decrease in cardiovascular mortality, improvement in quality of life and a decrease in the rate of hospitalization.(19) Therefore, HF patients should be enrolled in aerobic exercise training (AET) to increase functional capacity and improve symptoms. 3–5 Unfortunately, there is a lack of knowledge regarding exercise during the phase of stabilization. No studies, until now, have enrolled such patients in structured ET programs existing only in imprecise recommendations.(22) New knowledge about this issue is needed, in order to have a variety of responses and tools to improve better HF patients' functional capacity and quality of life, in a safe and feasible way. The ET prescription is based on frequency, intensity, time and type of exercise (FITT), which must be adjusted according to locations where the exercise takes place (inpatient or outpatient), the stage of the disease (acute or chronic) and the patient's limitations or motivations. AET is the most well established non-pharmacological method for the treatment of patients with chronic HF. (23) However, ET has not been evaluated in patients admitted with decompensated HF, who have been typically excluded from studies of AET in HF. This is underpinned by safety concerns, and thus strict adherence to safety criteria is paramount in AET in inpatient settings.

PHASE (I) CARDIAC REHAB & EARLY MOBILIZATION: As patients with chronic heart failure transition to acute decompensated heart failure, physical function worsens further, and this decline is exacerbated by hospitalization and bed rest. 8 These deficits often persist. Many patients never recover baseline function, lose independence, and have high risks of rehospital-ization and death after discharge (sometimes referred to as "post-hospital syndrome") (8). However, management guidelines do not address physical dysfunction in patients hospitalized for heart failure, 15 and previous exercise training trials excluded patients with heart failure who had recently been hospitalized (17)

Phase Ⅰ of cardiac rehabilitation has become a challenge for evidence based physiotherapy, having the means for success with the adjustment of a new exercise prescription model as long as this model is based on the principles of the clinical physiology of exercise, in the individualizing of the prescription. At this early phase, the focus of physical therapy is prescription to avoid inactivity, and to maintain or improve pulmonary capacities and muscular strength.(24) The ACSM recommendations for the prescription of exercises in phase I of cardiac rehabilitation are stated in table 1. GWTG-HF defines EA as a patient ambulating without assistance. The use of a cane or other device still meets this definition. Even if actual ambulation is not documented in the medical record, privileges to walk to and from the bathroom and evidence of the patient getting out of the bed unassisted are considered to meet the definition (25)

Table 1. Early mobilization protocol according to the ACMS

Intensity	TPE below 13 (scale 6-20)
Heart rate	<120 bpm or resting HR + 20 bpm Post-surgery: resting HR + 30 bpm Up to tolerance if non-symptomatic
Duration	Intermittent sessions lasting 3-5 min
Resting periods	As the patient wishes
Frequency Early mobilization	3 to 4 times per day (1st to 3rd days)
Subsequent mobilization	twice per day (As from the 4th day)

SAFETY AND EFFICACY OF EARLY MOBILIZATION

IN AHF: Improving outcomes in this subset of patients are of high priority. From literature, it is known that exercise training during hospitalization is clinically relevant since prolonged bed rest is associated with muscle weakness, atrophy and wasting, both affecting the patient's long-term outcome on functional capacity, quality of life, and survival.(25) In the setting of HF, it is Imperative to ensure hemodynamic stabilization and the congestion in the process of early mobilization to prevent the in-hospital worsening of HF.(26)

HF patients often have multiple comorbidities such as anemia, cognitive impairment, and skeletal muscle atrophy (sarcopenia) , all of which contribute to limit activities of daily living (ADL). (27) When such patients are hospitalized with acute HF, restricted mobilization and prolonged bed rest for the treatment or due to the congestive symptoms are likely to cause physical deconditioning, which leads to further impairment in ADL.(28) The following is a review of the previously documented effects of initiating an early exercise program in patients with acute heart failure listed based on the benefits obtained from measuring the main outcome.

Reversing Effects of Prolonged Bed-rest: Exercise intervention during hospitalization may counteract these malignant effects of immobility. For example, in ICU patients with various illnesses, it has been shown that early mobilization improves the return to independent functional status at hospital discharge.(29) A systematic review revealed that physical therapy, or any active mobilization of the patient, is key to recovery in ICU patients. Of fourteen studies examining seven interventions that targeted physical function, only those including exercise training positively influenced physical function in critically ill patients (30). One of these studies has shown that, compared with usual care, daily exercise training using a bedside ergometer resulted in a 259 greater 6-min walking distance (6MWD) (196 m in intervention group vs. 143 m in control group, $p < 0.05$) at hospital discharge.(31) In addition, Literature using data from mechanically ventilated inpatients suggests that EA improves outcomes. Patients undergoing a relatively inexpensive and low intensity monitored exercise program with a trained physical therapist have higher rates of discharge to home and fewer days in the intensive care unit.(32) Although some of these studies were retrospective, and therefore subject to confounding by patient frailty, there was a subsequent small randomized trial that also associated early exercise therapy with improved outcomes including better functional status at discharge and reduced rates of intensive care unit delirium.(32) Furthermore, small randomized trials have shown improved outcomes when stroke patients are mobilized 24 to 48 hours after admission. 14–18 However, it does seem that very early mobilization (within 24 hours) may not be associated with the same improvement in outcomes and could potentially result in harm.(33). The knowledge from these prior studies suggests that careful study in the HF population is warranted before EA is universally implemented beginning with documentation of current practices. However, based on these findings, exercise training may also be beneficial to hospitalized acute HF patients. Until now, literature regarding the safety and clinical effects of exercise training in hospitalized acute HF patients is limited because these patients are often excluded from clinical trials (31) The relevant clinical studies concerning exercise training in hospitalized acute HF patients are listed in Table 3 with their respective methods, primary outcomes, and results and conclusion.

Improving Functional Capacity: Oliveira et al. investigated the effect of combining exercise training with non-invasive ventilation during the hospitalization of acute HF patients and showed that exercise training improves 6MWD and reduces the length of hospital stay. When exercise training is combined with noninvasive ventilation, this beneficial effect is even more pronounced, showing an additional reduction in dyspnea (34) Finally, exercise training should be initiated as soon as possible, preferably from the inpatient setting, because it was demonstrated that the one-year transplantation-free survival in HF patients improves when cardiac rehabilitation is initiated during hospitalization, compared with controls (35). Another study by Delgado et al., demonstrates that an AET program can be safe to be implement even in inpatients recovering from acutely decompensated HF. Furthermore, it showed that Aerobic Exercise Training (AET) can improve exercise capacity in those patients, which may contribute to greater functional recovery and Independence after an episode of acute decompensation. Regarding feasibility and efficacy, the results demonstrate a significant difference in the distance walked in the 6MWT and ADL and it is safe if performed under careful monitoring and adhering to guideline recommendations (36). To address these issues, the Rehabilitation Therapy in Older Acute Heart Failure Patients (REHAB-HF) trial, the largest multicenter, randomized, single-blind, controlled trial of an early, transitional, tailored, progressive rehabilitation intervention that included multiple physical-function domains. The results of this trial concluded that the physical rehabilitation intervention improves physical function and reduces rehospitalizations compared to usual care in older patients hospitalized with ADHF. And it was the first HF clinical trial to employ a multi-domain physical rehabilitation intervention beginning during ADHF hospitalization (30).

Table 2. Summary of previous studies that investigated the effect of early mobilization program on different outcomes in patients with heart failure

Study	Sample	Protocol	Main outcome measures	Results
Kitzman et.al., (2021)(30) RCT	Total of 349 patients (175 intervention and 174 control) both genders	Start: At hospital & continued at home or at outpatient clinic Frequency: 3 days/w for 12 weeks Duration: 60 mins Intensity: Low Type: physical- function exercises (strength, balance, mobility, and endurance). + home program	physical function using the score of the Short Physical Performance Battery 6-minute walk distance frailty status quality of life depression Hospitalization for any cause within 6 months	All measures improved only incidence of hospitalization was high in both groups
Reeves et.al., (2017)(17) RCT	360 patients	Frequency : 3 times/week for 12 weeks Duration : 60 min/session Intensity: (RPE ≤ 12) gradually increased to 13	Short Physical Performance Battery score secondary outcome: 6-month all-cause rehospitalization, quality of life and costs.	Improvement in all outcomes
Delgado et.al., 2020 (38) RCT	100 patients (50 intervention and 50 control)	ERIC-HF protocol of staged exercise	The London chest activity of daily living (LCADL) scale the Barthel index (BI) the 6 minute walking test (6MWT)	Improvement in 6MWD and LCADL No improvement in BI
Martínez-Velillaet.al., (2019) (39) RCT	370 patients	2 daily sessions (morning and evening) of 20 minutes' duration for 5 to 7 consecutive days	Short Physical Performance Battery (SPPB). And Barthel Index (BI)	Improved SPPB and BI scores in the exercise group
Cops *et al*., (2020) (40) Review	14 studies	Studies included all contained Interventions in acute decompensated HF	variable	Overall inclusion recommended the effectiveness of exercise training in AHF patients with co-morbidity
Motoki *et al*., (2019)(41) Retrospective study	171 patients admitted for ADHF	CR included resistance training and aerobic exercise.	Patient disability was evaluated usingBarthel Index (BI) Patient disability was evaluated using Barthel Index (BI) scores at pre- (BIpre) and post-(BIpost) rehabilitation. All-cause mortality was retrospectively recorded after discharge	Improvements in disabilities among patients with ADHF. Baseline disabilities were associated with a poor prognosis. Greater improvements in BI to inpatient CR were significantly related to better outcomes Improved BI scores compared to baseline (ΔBI > 15)
Oliveira et al., 2017 (34)	- 29 acute HF patients	3 experimental groups: 1) ET+NIV (n = 11) 2) ET+sham (n = 9) 3) Control (n = 9) - 8 days of aerobic exercise with in-bed cycle ergometer, during hospitalization	6 minutes walk test before discharge and length of hospital stay + safety of early ET in hospitalized acute heart failure patients	Exercise training in acute HF is safe as there were no adverse events Exercise training improves functional capacity and improves clinical outcomes

Decreased Hospital Stay and Re-Admission Rate: Re-admissions and prolonged hospitalization are a large proportion of this cost spurring various and variably effective efforts to reduce them. If EA is successful in HF as it is with mechanically ventilated and stroke patients, the benefit to patients, as well as the cost savings, could be substantial. Indeed, according to recent large-scale registry data, early ambulation of HF patients is associated with a reduction in the length of hospital stay and HF readmission rate (25) Thus, minimizing the length of hospital stay is encouraged in the clinical guidelines for the treatment of acute HF and a promising intervention for this purpose is a mobilization program during the early stage of HF (26) A study by Fleming et al., concluded that Early ambulation (EA) is associated with decreased hospital length of stay (LOS) and post discharge 30-day re-admissions among hospitalized patients with HF and could be a simple, low-cost intervention to improve care in this patient population. And it was followed by a study by Kakutani et al., and insured that ,the progressive mobilization program for acute HF was feasible and was associated with better ADL and reduced hospital stay, leading to improvement of clinical outcome.(37)

Decreased Mortality Rate: According to the findings of Fleming et. al., exercise was associated with reductions in mortality and hospitalizations as well as improvement in quality of life. Despite the paucity of published data, the American College of Cardiology/American Heart Association guidelines recommend exercise in outpatients with HF. Fleming et al., indicated that close to two thirds (65.5%) of hospitalized HF patients were already participating in EA. (25)

CONCLUSION

Based on previous researches, early supervised rehabilitation programs can effectively improve functional and clinical outcomes, reduce risk of mortality and shorten hospital stay in patients with de-compensated heart failure. Adverse effects can be controlled or even reversed by providing proper supervision and set an individualized rehabilitation plan on case-by-case

basis. However, further research is required to determine the long-term effects of early rehabilitation.

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