



Case Report

## The efficacy and safety of high-intensity interval training in chemotherapy-related cardiomyopathy: Report of two cases

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### ABSTRACT

Studies suggest that exercise regimens are beneficial across all phases of cancer treatment and rehabilitation. However, studies on the efficacy and safety of cardiac rehabilitation in patients with chemotherapy-related cardiomyopathy are lacking. Herein, we present two patients diagnosed with chemotherapy-related cardiomyopathy who participated in a cardiac rehabilitation program, including eight weeks of high-intensity interval training, and their exercise capacity was monitored. Both patients showed significant increases in peak oxygen consumption and 6-min walk distance. High-intensity interval training results in objective improvements in aerobic exercise capacity without serious cardiovascular complications in patients with chemotherapy-related cardiomyopathy.

**Keywords:** Cardiac rehabilitation cardiomyopathy, chemotherapy, high-intensity interval training, oxygen consumption.

The adverse effects associated with various cancer therapies have become important concerns for cancer survivors.<sup>[1]</sup> Cardio-oncology is a recently developed field aimed at significantly reducing cardiovascular morbidity and mortality and improving quality of life in cancer survivors.<sup>[2]</sup> One of the most severe complications of chemotherapy is chemotherapy-related cardiomyopathy (CRC).<sup>[3]</sup> Chemotherapy-related cardiomyopathy may appear early or late in the course of treatment and can vary from subclinical myocardial dysfunction to sudden heart failure (HF).<sup>[4]</sup> Compared with idiopathic dilated cardiomyopathy, CRC has a three-fold higher rate of mortality.<sup>[5]</sup>

Cardiac rehabilitation (CR) is a comprehensive program that includes doctor-prescribed exercises, education, or counseling about cardiac risk factors

and psychosocial assessments. Cardiac rehabilitation programs have been shown to reduce the overall risk of hospitalization for recurring cardiovascular diseases and reduce cardiovascular mortality.<sup>[6]</sup> High-intensity interval training (HIIT) is one of the CR protocols that includes repeated intervals of high-intensity activity arranged between rest or low-intensity active recovery intervals.

Exercise has beneficial effects during the early and late stages of cancer therapy, as well as during rehabilitation.<sup>[1]</sup> The American Heart Association recently outlined the need for a comprehensive cardio-oncology rehabilitation model that uses a multimodal approach to prevent or alleviate cardiovascular disease and the requirement to identify high-risk cardiovascular patients, including those with cardiotoxicity associated with cancer treatment.<sup>[7]</sup>

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Recent trials have suggested that exercise training can have numerous positive effects without major adverse effects in CRC and other cardiomyopathies patients.<sup>[8,9]</sup> However, little attention has been focused on CR protocols in patients with CRC. This case report describes improvements in exercise capacity over two months of CR with HIIT protocol in two patients with CRC.

### CASE REPORT

Cardiac rehabilitation consisted of a cardiopulmonary exercise test (CPET), aerobic and resistance exercises, and education on cardiac risk factors. The individual exercises prescribed were based on CPET results and medical records (Table 1). The first two weeks served as an adaptation period for HIIT. The following six weeks of HIIT consisted of a 10-min warm-up at 50 to 60% of the heart rate reserve (HRR), followed by four intervals (4-min each) of walking on a treadmill (MT7; Motus, Paju-si, Korea) at 85% of the HRR with three active rest periods of 3-min walking at 50 to 60% of the HRR, and a final 10-min cool-down at 50 to 60% of the HRR. The treadmill speed and grade were constantly adjusted to. Blood pressure, HR, oxygen saturation, and electrocardiographic

parameters were strictly monitored. The exercises were supervised by an experienced physical therapist and a rehabilitation medicine specialist. After the eight-week HIIT program was completed, home exercise prescriptions were provided.

### Outcome measurements

Improvement (change from the baseline) of maximal oxygen uptake ( $VO_{2max}/kg$ ), resting HR, maximal HR, double product (HR multiplied by systolic blood pressure), the slope of ventilatory equivalent for carbon dioxide (VE/ $VCO_2$  slope), rate of perceived exertion at stage 3 of CPET, and respiratory exchange ratio at  $VO_{2max}$  were utilized as CPET parameters (Table 2).<sup>[10]</sup> We adopted improvement of left ventricular ejection fraction (LVEF) as an echocardiographic parameter and 6-min walk distance (6MWD) as a supplemental parameter of exercise capacity. In addition, the hand-grip power was measured as a parameter of upper extremity muscle strength using a JAMAR® Plus+ hand dynamometer (Performance Health, Warrenville, IL, USA).

For pulmonary function test parameters in one patient, we utilized improvement of forced vital capacity (FVC), forced expiratory volume in 1 second

**TABLE 1**  
Characteristics of the patients

	Case 1	Case 2
Sex	Female	Female
Age (year)	45	53
Initial $VO_{2max}$ (mL·kg <sup>-1</sup> ·min <sup>-1</sup> )	18.5	19.4
Hypertension	-	-
Diabetes mellitus	-	-
Hyperlipidemia	-	-
Smoking (Current/Ex/Never)	Never	Never
Body mass index	24.0	24.8
LVEF (%)		
Baseline	49	25
LVEF (%)		
Post CR & discontinuation CTx	53	57
Duration (month)		
Time from the start of CR	9	7
CTx-Monoclonal antibody	+	+
CTx-Taxanes	+	+
CTx-Doxorubicin, cyclophosphamide	-	+
CTx-Tamoxifen	-	-

$VO_{2max}$ : Maximal oxygen consumption; LVEF: Left ventricular ejection fraction; CTx: Chemotherapy; CR: Cardiac rehabilitation.

**TABLE 2**  
Outcome variables before and after cardiac rehabilitation

Variables	Case 1	Case 2
$VO_{2max}$ (mL·kg <sup>-1</sup> ·min <sup>-1</sup> )		
Baseline	18.5	19.4
8-weeks later	24.2	30.3
Rate of change (%)	+30.8	+56.1
Double product (mmHg·beat·min <sup>-1</sup> )		
Baseline	18.669	17.280
8-weeks later	16.560	13.452
VE/ $VCO_2$ slope		
Baseline	27.6	36.1
8-weeks later	29.9	22.3
HR <sub>max</sub> (beat/min)		
Baseline	150	162
8-weeks later	171	176
HR <sub>rest</sub> (beat/min)		
Baseline	86	83
8-weeks later	70	66
RPE <sub>stage3</sub>		
Baseline	13	11
8-weeks later	11	9
RER at $VO_{2max}$		
Baseline	1.1	1.06
8-weeks later	1.08	1.32

$VO_{2max}$ : Maximal oxygen consumption; VE/ $VCO_2$  slope: Minute ventilation/carbon dioxide production slope; HR<sub>max</sub>: Maximal heart rate; HR<sub>rest</sub>: Resting heart rate; RPE<sub>stage3</sub>: Rate of perceived exertion at stage 3; RER: Respiratory exchange ratio.

(FEV1), maximal inspiratory pressure (MIP), maximal expiratory pressure (MEP), and peak cough flow (PCF). Spirometry was performed with a VMAX 22 spirometer (Sensormedics, Yorba Linda, California, USA) used in the sitting position. Peak cough flow was assessed using an Asthma Mentor Peak flow meter (Respironics, Murrysville, PA, USA).<sup>[11]</sup>

For patients' safety, all possible adverse effects, such as musculoskeletal problems, asymptomatic cardiac rhythms, asymptomatic HR, and blood pressure changes during rehabilitation training, were investigated.

**Case 1-** A 46-year-old female patient who had undergone conservation surgery for cancer of the left breast in 2009 was referred to our CR clinic for CRC on January 4, 2019. Prior to the referral, the patient was treated with palliative chemotherapy consisting of intravenous pertuzumab, trastuzumab, and docetaxel at the oncology department after diagnosis of recurrent breast cancer with lung and neck lymph node metastases in 2017. After 13 cycles of chemotherapy, concluded in July 2018, echocardiography revealed LVEF of 49%. When the patient was first referred to the CR clinic, the patient was classified as New York Heart Association (NYHA) class II, Eastern Cooperative Oncology Group performance status (ECOG PS) 1. The patient was given an individual exercise prescription after CPET and underwent HIIT three times a week for eight weeks without significant cardiovascular complications. After eight weeks of HIIT, the patient's  $VO_{2max}$  increased from 18.5 to 24.2 mL/kg/min (+30.8%), and 6MWD increased from 573 to 648 m (+13.1%). On echocardiography, LVEF was mildly elevated, ranging from 49 to 53%. The right-hand grip power increased from 24 to 27 kg, and the left from 18.8 to 25.1 kg.

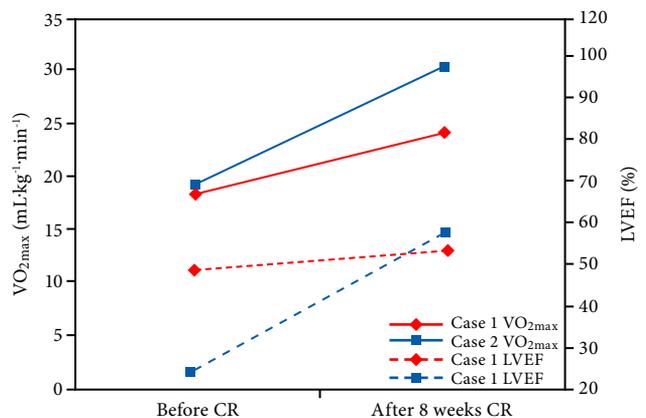
**Case 2-** A 53-year-old female patient who had undergone conservation surgery for cancer of the left breast in 2015 and had subsequently received oral tamoxifen, radiation therapy, and a total of six cycles of chemotherapy was referred to our CR clinic on April 23, 2019. Prior to the referral, the patient also underwent a left simple mastectomy for recurrent breast cancer in August 2018 and was prescribed intravenous paclitaxel, doxorubicin, cyclophosphamide, and trastuzumab in September 2018 at the breast surgery department. The patient complained of dyspnea upon exertion on April 4, 2019. Echocardiography, conducted on April 19, 2019, revealed an LVEF of 25% with global hyperkinesia,

and chemotherapy, including trastuzumab, was discontinued. At the time of the referral, the patient was classified as NYHA class II, ECOG PS 1. The patient underwent HIIT three times a week for eight weeks without significant cardiovascular complications. After eight weeks of HIIT, the patient's  $VO_{2max}$  increased from 19.4 to 30.3 mL/kg/min (+56.1%), and 6MWD increased from 592 to 830 m (+40.2%). In addition, LVEF increased from 25 to 57% over eight months, inclusive of the CR period. A pulmonary function test revealed that FVC increased from 1.65 to 2.10 L (+27.2%), and FEV1 from 1.44 to 1.97 L (+36.8%). Furthermore, MIP increased from 62 cm H<sub>2</sub>O to 74 cm H<sub>2</sub>O (+19.3%), MEP from 62 cm H<sub>2</sub>O to 89 cm H<sub>2</sub>O (+43.5%), and PCF from 300 to 350 L/min (+16.6%). The right-hand grip power increased from 23.4 kg to 25.8 kg, and the left from 21.9 kg to 24.5 kg.

## DISCUSSION

This is a case report on CR using a HIIT protocol in patients with CRC in which the maximal oxygen consumption, maximal HR, pulmonary function, and peripheral and respiratory muscle strength were compared before and after CR. In both cases, the overall exercise capacity improved after eight weeks of the program, with increases in  $VO_{2max}$ , 6MWD, and LVEF (Figure 1). Moreover, no major cardiovascular or other musculoskeletal complications arose during CR.

Recent trials have suggested that oxygen consumption in patients with coronary artery disease improves by 11-25% after CR.<sup>[12]</sup> In addition, as CR protocols, HIIT has shown a relatively low rate of



**Figure 1.** Change in exercise capacity after cardiac rehabilitation

$VO_{2max}$ : Maximal oxygen consumption; LVEF: Left ventricular ejection fraction; CR: Cardiac rehabilitation.

significant cardiovascular complications compared with low-to moderate-intensity continuous exercise training for patients with coronary artery disease or HF.<sup>[13]</sup> Considering that HIIT objectively improved  $VO_{2max}$  by up to 56.1% without any significant cardiovascular events in this case report, this could be a noteworthy change. Furthermore, considerations need to be made for the different pathophysiology of CRC compared to coronary artery disease, and that CRC is related to reversible changes in the heart after the discontinuation of chemotherapy. Initiation of standard HF treatment and discontinuation of cardiotoxic agents enhances left ventricular functional recovery.<sup>[4]</sup> In this case report, the improvements in cardiac function were highly associated with drug discontinuation, whereas the HIIT program led to increases in aerobic exercise capacity, pulmonary function, and skeletal and respiratory muscle strength. Additionally, as  $VO_{2max}$  is a powerful predictor of all-cause cardiac mortality in HF, CR with HIIT could be recommended in patients with CRC.<sup>[6,9]</sup>

The mortality of cancer survivors with cardiomyopathy is significantly higher than that of patients with idiopathic nonischemic cardiomyopathy.<sup>[3]</sup> The importance of this problem was highlighted in a cohort study published in 2011, which demonstrated that cardiovascular disease is a greater cause of mortality in breast cancer survivors than recurrent malignant diseases.<sup>[14]</sup> On the prophylactic side, blood pressure control, healthy diet, smoking cessation, and moderate aerobic exercise are significant nonpharmacological strategies to prevent chemotherapy-induced cardiotoxicity.<sup>[15]</sup> Furthermore, it is necessary to monitor the occurrence of HF during chemotherapy to discontinue and change the drug after early diagnosis and prescribe a CR program in the future, particularly in breast cancer patients.

In conclusion, HIIT could be used as a safe and efficient CR protocol in CRC patients; however, the small number of patients enrolled makes it difficult to provide definitive conclusions. Therefore, large-scale multicenter randomized studies are required to confirm the long-term effectiveness and safety of HIIT in patients with CRC.

**Patient Consent for Publication:** Written informed consent was obtained from both patients for the publication of their cases.

**Data Sharing Statement:** The data that support the findings of this study are available from the corresponding author upon reasonable request.

**Author Contributions:** Conceptualization: C.H.E., K.C.; Data curation: K.M.J.; Investigation: C.H.E, P.J.H.; Methodology: C.H.E.; Writing - original draft: P.J.H.; Writing - review & editing: C.H.E, K.C, K.M.J.

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