



# Cardiac transplant and exercise cardiac rehabilitation

Ray W. Squires<sup>1</sup>

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## Abstract

Cardiac transplantation is the final therapeutic option for patients with end-stage heart failure. Most patients experience a favorable functional ability post-transplant. However, episodes of acute rejection, and multiple comorbidities such as hypertension, diabetes mellitus, chronic kidney disease and cardiac allograft vasculopathy are common. The number of transplants has increased steadily over the past two decades with 3,817 operations performed in the United States in 2021. Patients have abnormal exercise physiologic responses related to surgical cardiac denervation, diastolic dysfunction, and the legacy of reduced skeletal muscle oxidative capacity and impaired peripheral and coronary vasodilatory reserve resulting from pre-transplant chronic heart failure. Cardiorespiratory fitness is below normal for most patients with a mean peak  $\text{VO}_2$  of approximately 60% of predicted for healthy persons. Cardiac transplant recipients are therefore excellent candidates for Exercise-Based Cardiac Rehabilitation (CR). CR is safe and is a recommendation of professional societies both before (pre-rehabilitation) and after transplantation. CR improves peak  $\text{VO}_2$ , autonomic function, quality of life, and skeletal muscle strength. Exercise training reduces the severity of cardiac allograft vasculopathy, stroke risk, percutaneous coronary intervention, hospitalization for either acute rejection or heart failure, and death. However, there are deficits in our knowledge regarding CR for women and children. In addition, the use of telehealth options for the provision of CR for cardiac transplant patients requires additional investigation.

**Keywords** Cardiac transplant · Exercise responses · Exercise training

## Introduction

Cardiac transplantation is the final therapeutic option for patients with end-stage heart failure with markedly improved survival, functional status, and quality of life compared to alternative treatments [1]. The number of transplants has steadily increased over the past two decades. In 2021, there were 3,817 operations in the US (513 children). For the past ten years, 31,238 transplants were performed in the US [2]. For North America, one-year and five-year survival after transplantation is 90% and 87%, respectively [3]. After transplantation, episodes of acute rejection and multiple comorbidities such as hypertension, diabetes mellitus, chronic kidney disease, and cardiac allograft vasculopathy are common [4]. Causes of death in the early years after cardiac

transplantation include graft failure (primary graft dysfunction and acute rejection), infection, and multi organ failure. Late mortality is due primarily to malignancy, cardiac allograft vasculopathy and renal failure [1]. Cardiac transplantation continues to be limited by a relative lack of donor organs despite increased acceptance of marginal hearts once considered unacceptable [5]. The relative paucity of donor hearts will be improved with the continued use of marginal organs and genetically modified porcine hearts, potentially expanding the numbers of transplant recipients referred to Exercise-Based Cardiac Rehabilitation (CR) [6].

Cardiac transplant patients are excellent candidates for CR given their pre-transplant heart failure syndrome and multiple comorbidities. CR after heart transplantation has been recommended since the early 1980s and has received endorsement from multiple professional societies [7, 8]. CR services for heart transplant patients are reimbursed by government and commercial payors in the US. Recently, exercise training prior to transplant with the goal of maintaining or improving exercise capacity to potentially reduce postoperative complications (pre-habilitation) has been

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✉ Ray W. Squires  
squires.ray@mayo.edu

<sup>1</sup> Professor of Medicine Division of Preventive Cardiology Department of Cardiovascular Medicine, Mayo Clinic, 200 First Street SW, Rochester, MN 55905, USA

advocated [9]. This review will focus on the responses to exercise, exercise training and associated benefits after heart transplantation. Other components of comprehensive CR, such as psychological assessment and intervention, medication compliance, healthy nutrition, avoidance of tobacco and nicotine, and symptom surveillance will not be discussed.

## Responses to acute exercise

Cardiac transplant patients exhibit abnormal exercise physiologic responses. These include both central abnormalities of surgical cardiac denervation during organ harvesting, no intact pericardium, diastolic dysfunction (elevated filling pressures at rest and during exercise) and impaired coronary artery vasodilatory capacity; and the peripheral abnormalities of reduced skeletal muscle oxidative capacity, decreased skeletal muscle contractile force development, and impaired peripheral vasodilatory capacity (lingering effects of chronic heart failure) [10–12]. Table 1 lists common abnormal exercise physiologic findings in cardiac transplant patients. These abnormalities result in a reduced ability to perform both aerobic and resistance exercise and directly affect the process of exercise prescription in CR as discussed later.

## Heart rate during graded exercise testing

Because of the loss of autonomic innervation of the donor heart, the heart rate at rest, during graded exercise and during recovery is different for heart transplant recipients compared to the general population observed during exercise

testing. As a result of the loss of parasympathetic innervation of the donor heart with transplantation, heart rate at rest is elevated at approximately 95 to 115 beats/min and represents the inherent rate of depolarization of the sinoatrial node [10]. With graded exercise, the heart rate typically does not increase during the first several minutes (delayed increase), followed by a gradual rise with peak heart rates slightly lower than normal (mean of approximately 150 beats/min, 80% of age predicted) due to sympathetic nervous system denervation [10]. Many patients achieve their highest exercise heart rate during the first few minutes of recovery from exercise, rather than at the point of peak exercise intensity. Heart rate may remain near peak values for several minutes during recovery before gradually returning to resting levels (delayed decrease) [10]. The chronotropic or heart rate reserve (the difference between peak and resting heart rates) is less than normal. Regulation of heart rate during exercise is dependent upon circulating catecholamines [10]. Figure 1 shows the heart rate response during graded exercise in the same patient one year before and three months after orthotopic transplantation. Note the delayed increase in heart rate during the first few minutes of exercise and the highest rate during recovery after transplantation. Partial cardiac sympathetic efferent re-innervation occurs in some patients (approximately 35% to 40%) during the first several months to years after surgery and results in relative normalization of the heart rate response during exercise [13, 14]. Figure 2 shows the heart rate responses during graded exercise for the same patient at 3 and 12 months after transplantation. Note the typical denervated response at 3 months and the partially normalized response at 12 months.

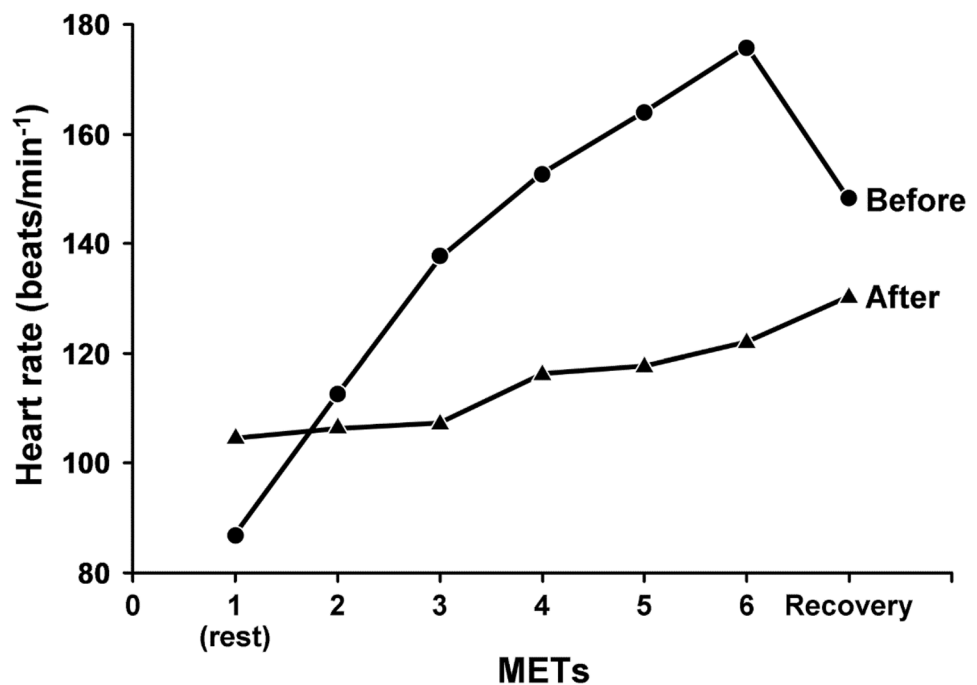
**Table 1** Abnormal Exercise Physiologic Findings in Heart Transplant Patients (from Squires [20])

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Increased resting heart rate
Delayed increase in heart rate at onset of exercise
Blunted maximal heart rate
Delayed return of heart rate to resting level after cessation of exercise
Reduced heart rate reserve
Increased exercise left ventricular end-diastolic pressure (diastolic dysfunction)
Increased exercise pulmonary artery pressure, pulmonary capillary wedge pressure, right atrial pressure
Increased left ventricular end-systolic and end-diastolic volume indices
Impaired increase in stroke volume during exercise
Reduced exercise cardiac output
Decreased exercise arterial-mixed venous oxygen difference
Slowed oxygen uptake kinetics during exercise
Decreased maximal oxygen uptake
Impaired peripheral and coronary vasodilatory reserve
Reduced maximal power output during exercise testing
Decreased ventilatory anaerobic threshold
Increased exercise ventilatory equivalents for oxygen and carbon dioxide

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**Fig. 1** Heart rates measured during graded exercise in the same patient 1 year before and 3 months after orthotopic cardiac transplantation. Note the elevated resting heart rate and the delayed increase in heart rate during exercise after transplantation consistent with complete denervation. METs = metabolic equivalents. (From Squires [10])



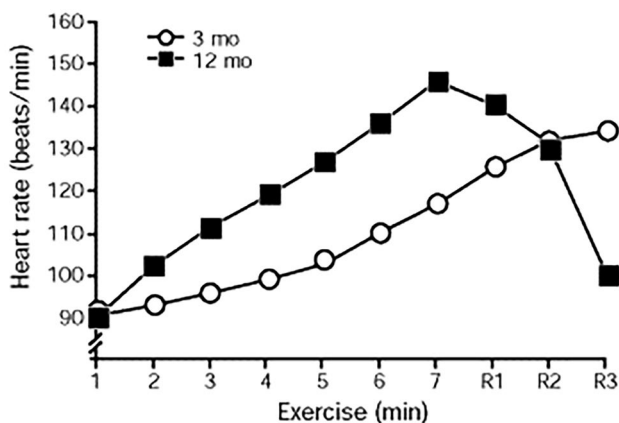
### Peak oxygen uptake (peak $\text{VO}_2$ ), athletic potential

Left ventricular ejection fraction is generally normal at rest and during exercise [12]. However, left ventricular diastolic function is often impaired as evidenced by an elevated filling pressure for a given end-diastolic volume. This impairment results in a below normal increase in stroke volume during exercise. The impaired rise in stroke volume, coupled with a below normal heart rate reserve, results in impaired exercise cardiac output [10].

Because of the dual abnormalities of an impaired exercise cardiac output and a reduced arterial-mixed venous oxygen

difference, peak exercise  $\text{VO}_2$  is usually below normal for transplant patients. In a series of 95 patients (18 women) with a mean age of 49 years who performed a cardiopulmonary exercise test approximately one year after transplantation, the mean peak  $\text{VO}_2$  was  $20 \text{ ml}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$  (62% of age- and sex-predicted) [13]. Marked variability in response was evident with a range for peak  $\text{VO}_2$  of  $11$  to  $38 \text{ ml}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$  (39% to 110% of age- and sex-predicted). Similar average peak  $\text{VO}_2$  values measured at 3 months ( $19.4 \text{ ml}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ ) and nearly five years after transplant ( $19.3 \text{ ml}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ ) have been reported [15]. The high variability of cardiorespiratory fitness after transplant, with most patients exhibiting a considerably below normal fitness, highlights the importance of individualization of the exercise prescription for this population. Important determinants of peak  $\text{VO}_2$  after transplantation include oxygen pulse ( $\text{VO}_2/\text{heart rate}$ , a surrogate measure for stroke volume), heart rate reserve, skeletal muscle strength, body mass index, and sex which together explain 84% of the variance [15].

Select, very highly exercise-trained transplant patients may achieve much higher values for peak  $\text{VO}_2$ : average peak  $\text{VO}_2$  of  $40$  to  $54 \text{ ml}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$  in a cohort of 26 men (mean age 45 years) [16, 17]. Although rare, impressive athletic performances have been reported after transplant. For example, a 45-year-old male endurance athlete developed non-ischemic cardiomyopathy with a pre-transplant peak  $\text{VO}_2$  of  $9 \text{ ml}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ . After transplantation he trained extensively and completed three ironman triathlons (peak  $\text{VO}_2$   $56 \text{ ml}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ , 149% of predicted) [18]. A 44-year-old endurance athlete trained 10 to 12 h per week after recovering from heart transplantation. He completed a seven-day



**Fig. 2** Heart rate responses to graded exercise in the same patient at 3 months and 12 months after cardiac transplantation demonstrating both denervation (at 3 months) and partial reinnervation (at 12 months). (From Squires [13])

two-person, team-based trans-alpine ultra-endurance run of 257 km (160 miles) in 43.1 h (he was paired with a healthy runner), placing 133<sup>rd</sup> of 300 teams- [19].

Cardiac transplant recipients are excellent candidates for CR for several reasons [20]:

1. Pre-transplant syndrome of chronic heart failure with poor exercise capacity due to central and peripheral circulatory abnormalities, skeletal muscle pathology and chronic heart failure-related cachexia
2. Deconditioning due to inactivity before and after transplant as well as the healing process with open-heart surgery as observed with conventional coronary bypass or valvular surgery
3. Post-transplant use of corticosteroid medications with resultant skeletal muscle atrophy and weakness as well as increased body fat

CR provides impressive benefits in terms of improved cardiorespiratory fitness and skeletal muscle function as discussed in the next section.

## Responses to exercise training

### Aerobic exercise training in adults

There have been relatively few studies on the topic of aerobic exercise training after transplantation. In addition, studies have been limited by methodological differences. For example, investigators have employed heterogeneous approaches to exercise training with differences in intensity, session duration, frequency of exercise sessions and length of the training program. Also, the time interval between transplantation and starting exercise training varied widely between studies from a few days to several years, and the number of women included in the studies was limited.

A Cochrane Systematic Review, published in 2017, included only 10 randomized, controlled trials of CR versus usual care [21]. One study was a randomized crossover trial comparing moderate intensity continuous aerobic training with high-intensity interval training. The 10 trials included only 300 patients (<25% women) with a median age of 54.4 years who began CR a median of 12 months (range: 0.5 to 61 months) after transplantation. The median follow-up interval was 12 months. Three CR models were employed by investigators: traditional medical center-based exercise training (5 studies), hybrid CR (combination of center-based and home-based exercise training, 2 studies) and home-based CR (3 studies). CR appeared to be safe for transplant recipients. Peak  $\text{VO}_2$  improved by an average of  $2.5 \text{ ml}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$  with CR versus the usual care. There were no data on CR adherence, mortality rates or

hospitalizations. Thus, randomized, controlled trials have demonstrated that exercise training results in improved cardiorespiratory fitness when compared to usual care.

Observational studies have demonstrated a wide range of improvement in peak  $\text{VO}_2$  depending upon the amount of exercise training that was accomplished. A review of 12 observational studies of exercise training after transplantation reported a range of 1.3 to  $5.6 \text{ ml}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$  improvements in peak  $\text{VO}_2$  [22]. However, some individual trials demonstrated much greater improvements in aerobic capacity. In 1988, Kavanagh and associates reported the results of a 16-month exercise training program in 36 transplant recipients (no control group) [23]. Exercise training (walk/jog; goal of 45 min, 5 days per week) began approximately 7 months after surgery and was carefully supervised. Patients improved exercise capacity with training, including an average 27% increase in peak  $\text{VO}_2$  (21.7 to  $25.9 \text{ ml}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ ; a difference of  $4.2 \text{ ml}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ ). In a subset of subjects who performed a much greater amount of training (mean walk/jog distance of 32 km/week versus 24 km/week for the entire cohort), peak  $\text{VO}_2$  increased by 54% (21.3 to  $32.2 \text{ ml}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ ; a mean difference of  $10.9 \text{ ml}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ ).

Women and men appear to experience a similar percent increase in peak  $\text{VO}_2$  after CR [24]. A greater number of CR sessions performed is an independent predictor of peak  $\text{VO}_2$  [25]. Additional factors predicting post-transplant peak  $\text{VO}_2$  include transplant-related complications, chronotropic incompetence, and impaired diastolic function [26].

CR may begin successfully soon after surgery. Haykowsky et al. performed an observational study of early outpatient CR in 18 transplant recipients (mean age  $57 \pm 6$  years, sex not reported) who began CR  $24 \pm 7$  days after surgery [27]. Supervised exercise training consisted of 30–40 min of moderate intensity aerobic exercise and lower extremity resistance exercise, five sessions per week for 12 weeks. Peak  $\text{VO}_2$  improved from approximately 14 to  $19 \text{ ml}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ .

High-intensity aerobic interval training (HIIT) has emerged as an attractive alternative to continuous moderate intensity exercise training (MICT) for transplant recipients. Traditional MICT in CR is prescribed by a target heart rate range of 60% to 85% of peak (corresponding to 50% to 75% of peak  $\text{VO}_2$ ) and Borg perceived exertion ratings (RPE) of 11–14 on the 6 to 20 scale [28]. HIIT may be prescribed as two or more periods of 10 seconds to 4+ minutes at 85% to 95% of peak heart rate (75% to 85% of peak  $\text{VO}_2$ , RPE 15–17) interspersed with 1 to 3 minutes of MICT during a 30–40 minute exercise session [28]. The precise HIIT exercise prescription requires individualized based on patient characteristics such as time from surgery, baseline fitness level, evidence of partial normalization of heart rate response to exercise, and patient goals.

The HITTS multicenter trial randomized 81 patients 11 weeks after transplant (range 7–16 weeks) to 9 months

of either HIIT (4×4 min intervals at 85% to 95% of peak effort [Borg perceived exertion ratings of 16–18] interspersed with 3 min of lower intensity exercise [perceived exertion ratings of 11–13]) or MICT (60% to 70% of peak effort [perceived exertion ratings of 12–15]) [29]. Subjects were 73% men with an average age of 49 ± 13 years. Exercise session duration was approximately 40 min, 2–3 times per week, and included resistance exercises for the large muscle groups. All sessions were directly supervised by physical therapists in the subjects' local communities in Norway, Sweden, and Denmark. At one year, both HIIT and MICT resulted in improvements in peak  $\text{VO}_2$ , with HIIT superior, 25% versus 15% (mean difference HIIT versus MICT of +1.8  $\text{ml}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ ). There were no serious exercise-related adverse events. The HIIT group demonstrated a greater increase in leg extensor strength. Two years after completion of HIIT, patients were evaluated for exercise training amounts (unsupervised, and independent from the investigators) and peak  $\text{VO}_2$  [30]. Weekly amounts of exercise training, both intensity and duration, were similar in both groups. A high percentage of both HIIT and MICT subjects exercised  $\geq 2$  times per week. There was no significant between group difference in peak  $\text{VO}_2$  (24  $\text{ml}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ , 66% of predicted for healthy persons), however, the anaerobic threshold and skeletal muscle endurance remained significantly higher in the HIIT group. Although patients appear to have difficulty continuing with HIIT without direct supervision, HIIT may provide sustainable positive effects.

HIIT, without concurrent resistance exercise training, has been shown to improve lower extremity muscle strength (quadriceps + 15%, hamstrings + 19%) [31]. Younger age in transplant patients (28 ± 7 years versus 54 ± 8 years) is associated with greater increases in peak  $\text{VO}_2$  for both HIIT (7.0 versus 2.2  $\text{ml}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ ) and MICT (4.7 versus 1.2  $\text{ml}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ ) [32]. HIIT does not impact

echocardiographic features of left ventricular function, however it does increase peak exercise  $\text{O}_2$  pulse and improves health-related quality of life [33, 34].

Thus, while both MICT and HIIT improve cardiorespiratory fitness after transplantation, HIIT appears to be the most effective form of training. Additional potential benefits of aerobic exercise training after heart transplantation are provided in Table 2.

### Resistance exercise training in adults

Skeletal muscle atrophy and weakness as well as bone demineralization are common side effects of the immunosuppressant prednisone commonly used after transplantation for at least a period of several months. Long-standing chronic heart failure also results in skeletal muscle adverse changes including reduced contractile force development. Resistance exercise training partially reverses corticosteroid-related myopathy and improves skeletal muscle strength. Horber et al. found definite evidence of skeletal muscle wasting and weakness in the lower extremities of renal transplant patients who received prednisone [36]. Fifty days of isokinetic strength training substantially increased muscle mass and strength in these patients. There are a limited number of key studies regarding the benefits of resistance training after heart transplantation. Braith et al. pioneered the assessment of the results of six months of supervised resistance exercise training after transplantation. In a series of papers, Braith et al. reported important clinical benefits, including substantially improved skeletal muscle strength, partial reversal of skeletal muscle myopathy with increased numbers of type I fibers (slow twitch, more aerobic) and reduced numbers of type II fibers (fast twitch, more anaerobic), and improved bone mineral density [37–39]. Therefore, resistance training during CR should be emphasized.

**Table 2** Additional potential benefits of aerobic exercise training for heart transplant recipients (from Squires and Bonikowske [35])

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Improved submaximal exercise endurance
Increased peak treadmill exercise workload or peak cycle power
Increased peak heart rate
Decreased exercise heart rate at the same absolute submaximal workload
Increased ventilatory (anaerobic) threshold
Decreased submaximal exercise minute ventilation
Reduced exercise ventilatory equivalent for $\text{CO}_2$
Lessened symptoms of fatigue and/or dyspnea
Reduced rest and submaximal exercise systolic and diastolic blood pressures
Decreased peak exercise diastolic blood pressure
Reduced ratings of perceived exertion at a fixed submaximal workload
Improved psychosocial function
Increased lean body mass
Reduced body fat mass
Increased bone mineral content

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## Exercise training in children

There are only limited data for exercise training in pediatric heart transplant recipients. Patel et al. enrolled 11 patients (8 girls), a mean of  $5.3 \pm 5.3$  years after transplantation, age  $14.7 \pm 5.3$  years of age (range: 8–25 years), in a 12-week home-based exercise program [40]. Two patients were adults, ages 24 and 25 years. Exercise training involved moderate intensity aerobic exercise for 30 min, three times per week and resistance exercise (elastic bands for upper extremities only) two times per week. Peak  $\text{VO}_2$  increased from  $24.5 \pm 3.8 \text{ ml} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$  to  $28.2 \pm 4.2 \text{ ml} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ . Muscle strength increased significantly for the triceps, biceps, and quadriceps groups.

Chen et al. studied 14 children (median age 15.2 years, 9 girls) at a median of 3.3 years post-transplant who participated in 12-to-16-week video conference supervised CR [41]. Supervised aerobic and resistance exercise sessions of approximately 60 min duration occurred 3 times per week. Compared with baseline, peak  $\text{VO}_2$  improved by a median of  $2 \text{ ml} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ . Additional 12 to 16 weeks of maintenance exercise (1 video-supervised session and 2 unsupervised sessions per week) resulted in further improvement in peak  $\text{VO}_2$  (median of  $3.2 \text{ ml} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ ).

## Effect of exercise training on immune function and adverse cardiovascular events

An important question concerning exercise training in immunosuppressed cardiac transplant recipients is the effect of training on immune function. Although the available data are limited, traditional moderate-intensity training does not appear to increase or decrease the number of episodes of acute rejection [42]. In addition, training does not complicate medical treatment and does not require changes in immunosuppressant dosage. Infection risk is not changed by exercise training [35]. However, additional research on the effects of exercise training on immune function is needed.

To date there has been only one investigation examining the impact of exercise training in CR on mortality [43]. Rosenbaum et al. investigated 201 heart transplant recipients in the modern era of transplantation, 2000 to 2013 [43]. The number of CR sessions attended during the first 90 days after transplantation predicted survival to 10 years (82% survival overall) with a hazard ratio of 0.31 (69% reduction) for mortality if patients participated in  $\geq 8$  sessions. Thus, CR participation appears to be associated with improved survival.

Cardiac graft vasculopathy (CAV) is a highly prevalent and potentially lethal long-term complication after transplantation [4]. Nytroen et al. assessed CAV with intravascular ultrasound at baseline and after one year in patients randomized to HIIT versus standard care [44]. Although CAV

progressed in both groups, HIIT resulted in a significantly reduced rate of progression of CAV.

Bachman et al. studied the 595 patients who underwent transplantation in the United States during 2013 and received Medicare coverage for CR [45]. Participation in CR (55% participation rate, mean number of sessions: 26.7) was associated with a 29% lower one-year risk of re-hospitalization.

Uithoven et al. evaluated the relationship between the number of CR sessions performed and major adverse cardiac events (MACE) in 140 heart transplant recipients (41 women, age  $52 \pm 12$  years) [46]. Based on recursive partitioning, patients were divided into two groups:  $\leq 23$  sessions (group 1) and  $\geq 23$  sessions (group 2). Group 1 attended an average of  $13 \pm 6$  sessions and group 2 attended  $28 \pm 5$  sessions. MACE was defined as stroke, percutaneous coronary intervention, heart failure requiring hospitalization, acute myocardial infarction, acute rejection resulting in hospitalization, and death. After a mean follow-up interval of  $4.1 \pm 2.7$  years and with adjustment for age, sex, diabetes, body mass index and pre-transplant peak  $\text{VO}_2$ , group 2 experienced an approximately 60% lower rate of the MACE composite endpoint than group 1. Thus, CR participation is associated with a substantially lower rate of MACE.

## Exercise-based cardiac rehabilitation specifics for heart transplantation: pre-habilitation, inpatient and outpatient cardiac rehabilitation

### Pre-habilitation

The International Society for Heart and Lung Transplantation recommends CR both before (pre-habilitation) and after surgery [47]. Cardiac transplant candidates who require prolonged hospitalization while awaiting a suitable donor heart, if stable, may participate in supervised stationary cycling and mild strength training [9]. The specific amount of exercise prescribed for hospitalized patients requires individualization, is dependent on multiple clinical factors, and follows exercise prescription guidelines for patients with symptomatic chronic heart failure. Outpatients awaiting heart transplantation may be referred for outpatient CR (including patients supported with a left ventricular assist device as a bridge to transplant) and follow exercise training guidelines (both aerobic and resistance exercise) appropriate for individuals with chronic heart failure [48]. The goals of pre-habilitation for both inpatients and outpatients include familiarization with exercise training procedures, assisting patients in developing the habit of regular exercise, providing medical surveillance, and maintaining or improving exercise capacity to facilitate recovery from surgery. CR may be particularly challenging for these patients due to

profound deconditioning with limited exercise capacity, low cardiac output state, fatigue, and skeletal muscle weakness. Nonetheless, pre-habilitation for stable patients awaiting transplantation should be encouraged.

### **Inpatient exercise cardiac rehabilitation**

Inpatient CR is standard care after transplantation and may begin very soon after surgery [20]. Passive range-of-motion exercises for both the upper and lower extremities, sitting up in a chair, and slow ambulation may begin and progress gradually after extubation (typically within 24 h after surgery) [49]. Walking or cycle ergometry may begin at <5 min and gradually increase to 20 to 30 min, as tolerated. Exercise intensity is guided using the Borg perceived exertion scale ratings of 11 to 13 (“fairly light” to “somewhat hard”) on the 6–20 scale, keeping the respiratory rate below 30 breaths per minute and arterial oxygen saturation above 90%. Exercise frequency is two to three sessions per day [10]. Patients whose postoperative courses are uncomplicated are typically discharged from the hospital in approximately 7 days.

### **Outpatient exercise cardiac rehabilitation**

Cardiac transplant recipients may begin outpatient CR program as soon as they are dismissed from the hospital [10]. Most CR programs strive to enroll patients within one to two weeks after dismissal. However, there may be a delay in starting outpatient CR due to a variety of health system level as well as patient level factors [50]. Participation in CR after transplantation appears to be suboptimal with approximately 55% of Medicare-age patients attending programs [45]. Additional investigation of CR participation rates for non-Medicare patients is needed.

Exercise prescription for cardiac transplant patients follows methods used with patients who have undergone recent conventional coronary bypass, coronary valve, or other cardiothoracic surgery [35]. The one exception is that a target heart rate is not used, unless the patient exhibits a partially normalized heart rate response to exercise as discussed previously. Borg perceived exertion scale ratings of 11 to 14 (“fairly light” to “somewhat hard”) may be used to prescribe moderate intensity exercise [10]. HIIT may be introduced within the first 2–3 weeks of CR, using perceived exertion ratings of 15–17 for the higher-intensity intervals, as discussed previously. The exercise prescription should include standard 5–10 min aerobic warm-up and cool-down activities (a prolonged aerobic warm-up and cool-down in patients with evidence of cardiac denervation is not needed), a gradual increase in aerobic exercise duration to 30 to 60 min, with a frequency of four to six sessions per week. Typical modes of aerobic exercise used during the early outpatient

recovery period include walking (treadmill, indoors, or outdoors), cycle ergometry, and stair climbing.

Since ratings of perceived exertion, rather than a target heart rate, are used to prescribe exercise intensity It is not necessary to perform graded exercise testing before beginning the outpatient exercise program. Performance of a 6-min walk is helpful in assessing functional capacity, however. Graded exercise testing may be performed 6 to 8 weeks after surgery for patients without complicated recoveries, when the patient has recovered sufficiently from surgery to assess the cardiopulmonary responses to exercise and to refine the exercise prescription. Because of the sternal incision, special emphasis on upper extremity active range of motion exercises to maintain normal flexibility is recommended during early outpatient CR. Additionally, at approximately 6 weeks after surgery, when sternal healing is nearly completed, rowing, arm cranking, combination arm/leg ergometry, outdoor cycling, hiking, and jogging become additional options, depending on the patients’ exercise capacity [51]. Please note that these guidelines may be surgeon specific. Some cardiothoracic surgeons recommend restriction of arm exercise for a full 12 weeks after the operation.

Skeletal muscle weakness in cardiac transplant recipients is very common, as discussed previously. Muscle strengthening exercises should be incorporated into the exercise program. For approximately the first 6 weeks after surgery (surgeon dependent), bilateral arm lifting may be restricted to less than 10 pounds to avoid sternal nonunion. During this early stage of rehabilitation, light hand weights are an excellent method of introducing resistance exercise. After at least 6 weeks of healing, patients may be started on standard weight machines, emphasizing moderate resistance, 10 to 20 slow repetitions per set, one to three sets of exercises for the major muscle groups, with a frequency of two or three sessions per week [10, 51]. Elastic band exercises are also another excellent mode of resistance training for these patients. Borg perceived exertion scale ratings of 12 to 14 to may be used gauge the intended moderate intensity of lifting. Strength gains of 25% to 50% or greater commonly occur after 8 weeks of strength training in these patients. Because cardiac transplant recipients are likely to require anti-hypertensive medications, periodic blood pressure measurement during both aerobic and strengthening exercise is recommended.

Patients must be counseled to maintain a life-time exercise routine to maintain the benefits of exercise training. Patients should continue either in a supervised exercise program indefinitely (maintenance cardiac rehabilitation program), exercise independently, or use a combination of supervised and unsupervised exercise. Periodic adjustment of the exercise prescription should occur, as needed.

## Summary

CR is recommended by professional societies both before (pre-habilitation) and after heart transplantation. Patients have abnormal exercise physiologic responses related to surgical cardiac denervation, diastolic dysfunction, and the legacy of reduced skeletal muscle oxidative capacity and impaired vasodilatory reserve resulting from pre-transplant chronic heart failure. Most patients have a below predicted baseline peak  $\text{VO}_2$ . For adults, CR improves peak  $\text{VO}_2$ , autonomic function, quality of life, and skeletal muscle strength. In addition, CR reduces the severity cardiac allograft vasculopathy, stroke risk, percutaneous coronary intervention, hospitalization for either acute rejection or heart failure, and death. Data regarding CR in children are very limited. Further study of alternative delivery modes for CR using telemedicine and other technologies to improve long-term adherence with exercise is needed. Additional exercise training methods, such as inspiratory muscle training, are attractive targets for investigation [52].

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## Declarations

**Ethical approval** Not applicable-the current paper is a review.

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## References

- Lund LH, Edwards LB, Kucheryavaya AY et al (2015) The registry of the International Society for Heart and Lung Transplantation: Thirty-second official adult heart transplant report—2015; focus theme: Early graft failure. *J Heart Lung Transplant* 34:1244–1254
- Heart transplant sets all-time record in 2021 - UNOS
- Khush KK, Hisch E, Potena L et al (2021) The International Thoracic Organ Transplant Registry of the International Society for Heart and Lung Transplantation: thirty-eighth adult heart transplant report 2021; focus on recipient characteristics. *J Heart Lung Trans* 40:1035–1049
- Lund LH, Khush KK, Cherikh WS et al (2017) The registry of the International Society for Heart and Lung Transplantation: Thirty-fourth adult heart transplant report—2017; focus theme: Allograft ischemic time. *J Heart Lung Transplant* 36:1037–1046
- Khush KK, Potena L, Cherikh WS et al (2020) The international thoracic organ transplant registry of the International Society for Heart and Lung Transplantation: 37<sup>th</sup> adult heart transplantation report-2020; focus on deceased donor characteristics. *J Heart Lung Trans* 10:1003–1015
- Griffith BP, Goerlich CE, Singh AK et al (2022) Genetically modified porcine-to-human cardiac xenotransplantation. *N Engl J Med* 387:35–44
- Squires RW, Arthur PA, Gau GT et al (1983) Exercise after cardiac transplantation: a report of two cases. *J Cardiac Rehabil* 3:570–574
- Thomas RJ, King M, Lui K et al (2007) AACVPR/ACC/AHA 2007 performance measures on cardiac rehabilitation for referral to and delivery of cardiac rehabilitation/secondary prevention services. *Circulation* 116:1611–1642
- Gimeno-Santos E, Coca-Martinez M, Arguis MJ et al (2020) Multimodal prehabilitation as a promising strategy for preventing physical deconditioning on the heart transplant waiting list. *Eur J Prev Card* 27:2367–2370
- Squires RW (1990) Cardiac rehabilitation issues for heart transplantation patients. *J Cardiopulmonary Rehabil* 10:159–168
- Pope SE, Stinson EB, Daughters GT et al (1980) Exercise response of the denervated heart in long-term cardiac transplant recipients. *Am J Cardiol* 46:213–218
- Kao AC, Van Trigt P, Shaeffer-McCall GS et al (1994) Central and peripheral limitations to upright exercise in untrained cardiac transplant recipients. *Circulation* 89:2605–2615
- Squires RW, Leung TC, Cyr NS et al (2002) Partial normalization of the heart rate response to exercise after cardiac transplantation: Frequency and relationship to exercise capacity. *Mayo Clin Proc* 77:1295–1300
- Schwaiblmair M, von Scheidt W, Uberfuhr B et al (1999) Functional significance of cardiac reinnervation in heart transplant recipients. *J Heart Lung Transplant* 18:838–845
- Rolid K, Andreassen AK, Yardley M et al (2018) Clinical features and determinants of  $\text{VO}_{2\text{peak}}$  in de novo heart transplant recipients. *World J Transplant* 10:188–197
- Richard R, Verdier JC, Duvallet A et al (1999) Chronotropic competence in endurance trained heart transplant recipients: Heart rate is not a limiting factor for exercise capacity. *J Am Coll Cardiol* 33:192–197
- Pokan R, Von Duvillard SP, Ludwig J et al (2004) Effect of high-volume and -intensity endurance training in heart transplant recipients. *Med Sci Sports Exerc* 36:2011–2016
- Haykowski MJ, Halle M, Baggish A (2018) Upper limits of aerobic power and performance in heart transplant recipients: Legacy effect of prior endurance training. *Circulation* 137:650–652
- Esefeld K, Fricke H, Haykowsky M, Halle M (2020) Ultra-endurance exercise in a heart transplant athlete: influence on myocardial function and biomarkers. *Eur J Prev Cardiol* 27:885–887
- Squires RW (2021) Heart Transplantation. In: American Association of Cardiovascular and Pulmonary Rehabilitation. Guidelines for Cardiac Rehabilitation Programs. 6<sup>th</sup> edition. Champaign, IL: Human Kinetics, pp.175–186
- Anderson L, Nguyen TT, Dell CH et al (2017) Exercise-based cardiac rehabilitation in heart transplant recipients. *Cochrane Database of Systematic Reviews*, issue 4. Art. No.: CD012264
- Nytroen K, Gullestad L (2013) Effect of exercise in heart transplant recipients. *Am J Transplant* 13:527
- Kavanagh T, Yacoub MH, Mertens DJ et al (1988) Cardiorespiratory responses to exercise training after orthotopic cardiac transplantation. *Circulation* 77:162–171
- Uithoven KE, Smith JR, Medina-Inojosa JR et al (2020) The influence of sex differences on cardiopulmonary exercise metrics following heart transplant. *Can J Cardiol* 36:54–59
- Uithoven KE, Smith JR, Medina-Inojosa JR et al (2019) Clinical and rehabilitative predictors of peak oxygen uptake following cardiac transplantation. *J Clin Med* 8:119. <https://doi.org/10.3390/jcm8010119>
- Schmidt T, Bjarnason-Wehrens B, Predel HG, Reiss N (2021) Exercise after heart transplantation: typical alterations, diagnostics and interventions. *Br J Sports Med* 42:103–111



27. Haykowsky M, Eves N, Figgures L et al (2005) Effect of exercise training on  $VO_{2peak}$  and left ventricular systolic function in recent cardiac transplant recipients. *Am J Cardiol* 95:1002–1004
28. Squires RW, Kaminsky LA, Porcari JP et al (2018) AACVPR Statement: Progression of exercise training in early outpatient cardiac rehabilitation. An official statement from the American Association of Cardiovascular and Pulmonary Rehabilitation. *J Cardiopulmonary Rehabil Prev* 38:139–146
29. Nytroen K, Rolid K, Andreassen AK et al (2019) Effect of high-intensity interval training in de novo heart transplant recipients in Scandinavia: one-year follow-up of the HIITS randomized, controlled trial. *Circulation* 139:2198–2211
30. Rolid K, Andreassen AK, Yardley M et al (2020) Long-term effects of high-tensity training vs moderate intensity training in heart transplant recipients: a 3-year follow-up study of the randomized-controlled HITTS study. *Am J Transplant* 20:3538–3549
31. Nytroen K, Rustad LA, Aukrust P et al (2012) High-intensity interval training improves peak oxygen uptake and muscular exercise capacity in heart transplant recipients. *Am J Transplant* 12:3134–3142
32. Nytroen K, Rolid K, Yardley M, Gullestad L (2020) Effect of high-intensity interval training in young heart transplant recipients: results from two randomized controlled trials. *BMC Sports Sci Med Rehab* 12:35–44
33. Rustad LA, Nytroen K, Amundsen BH et al (2014) One year of high-intensity interval training improves exercise capacity, but not left ventricular function in stable heart transplant recipients. *Eur J Prev Cardiol* 21:181–191
34. Nytroen K, Gullestad L (2013) Exercise after heart transplantation: an overview. *World J Transplant* 24:78–90
35. Squires RW, Bonikowske AR (2022) Cardiac rehabilitation for heart transplant patients: considerations for exercise training. *Prog Cardiovasc Dis* 70:40–48
36. Horber FF, Scheidegger JR, Grunig BF et al (1985) Evidence that prednisone-induced myopathy is reversed by physical training. *J Clin Endocrinol Metab* 61:83–88
37. Braith RW, Mills RM, Welsch MA et al (1996) Resistance exercise training restores bone mineral density in heart transplant recipients. *J Am Coll Cardiol* 28:1471–1477
38. Braith RW, Welsch MA, Keller JW, Pollock ML (1998) Resistance exercise prevents glucocorticoid-induced myopathy in heart transplant recipients. *Med Sci Sports Exerc* 30:483–489
39. Braith RW, Magyar PM, Pierce GL et al (2005) Effects of resistance exercise on skeletal muscle myopathy in heart transplant recipients. *Am J Cardiol* 95:1192–1198
40. Patel JN, Kavey R-E, Pophal SG et al (2008) Improved exercise performance in pediatric heart transplant recipients after home exercise training. *Pediatr Transplantation* 12:336–340
41. Chen AC, Ramirez FD, Rosenthal DN et al (2020) Healthy hearts via live videoconferencing: an exercise and diet intervention in pediatric heart transplant recipients. *JAHA* 9:e013816
42. Kavanagh T, Yacoub MH, Mertens DJ et al (1989) Exercise rehabilitation after heterotopic cardiac transplantation. *J Cardiopulmonary Rehabil* 9:303–310
43. Rosenbaum AN, Kremers WK, Schirger JA et al (2016) Association between early cardiac rehabilitation and long-term survival in cardiac transplant recipients. *Mayo Clin Proc* 91:149–156
44. Nytroen K, Rustad LA, Erikstad I et al (2013) Effect of high-intensity interval training on progression of cardiac allograft vasculopathy. *J Heart Lung Transplant* 32:1073–1080
45. Bachman JM, Shah AS, Duncan MS et al (2018) Cardiac rehabilitation and readmissions after heart transplantation. *J Heart Lung Transplant* 37:467–476
46. Uithoven KE, Smith JR, Medina-Inojosa JR et al (2020) The role of cardiac rehabilitation in reducing major adverse cardiac events in heart transplant patients. *J Cardiac Failure* 26:645–651
47. Costanzo MR, Dipchand A, Starling R et al (2010) The International Society of Heart and Lung Transplantation guidelines for the care of heart transplant recipients. *J Heart Lung Trans* 29:914–956
48. Keteyian SJ, Squires RW, Ades PA, Thomas RJ (2014) Incorporating patients with chronic heart failure into outpatient cardiac rehabilitation: practical recommendations for exercise and self-care—a clinical review. *J Cardiopulmonary Rehabil Prev* 34:223–232
49. McGregor CGA (1992) Cardiac transplantation: Surgical considerations and early postoperative management. *Mayo Clin Proc* 67:577–585
50. Marzolini S, Grace SL, Brooks D et al (2015) Time-to-referral, use, and efficacy of cardiac rehabilitation after heart transplantation. *Transplantation* 99:594–601
51. Keteyian SJ, Brawner C (1997) Cardiac transplant. In: American College of Sports Medicine. *ACSM's Exercise Management for Persons with Chronic Diseases and Disabilities*. Champaign, IL: Human Kinetics, pp. 54–58
52. Smith JR, Taylor BJ (2022) Inspiratory muscle weakness in cardiovascular diseases: Implications for cardiac rehabilitation. *Prog Cardiovasc Dis* 70:49–57

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