

# Chapter 11

## Cardiopulmonary Rehabilitation in Heart Failure



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### Clinical Case

A 63-year-old frail woman with a history of coronary artery disease (CAD), poorly controlled type 2 diabetes mellitus, hypertension, ischemic cardiomyopathy [left ventricular ejection fraction (LVEF) of 25%], status post cardiac resynchronization therapy with a defibrillator (CRT-D) presented with acute decompensated heart failure (HF). Bedside echocardiogram revealed biventricular failure with significant anterior wall hypokinesis and no valvulopathy. She underwent percutaneous coronary intervention (PCI) of the left anterior descending artery and was discharged on dual antiplatelet therapy (DAPT), torsemide, metoprolol succinate, sacubitril/valsartan, and spironolactone. She was then referred to cardiac rehabilitation (CR) for exercise training and risk factor modification.

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229

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## 11.1 What Is the History of Cardiac Rehabilitation?

Prior to the advent of CR and PCI, patients who suffered myocardial infarction (MI) were routinely prescribed 6 weeks of bed rest and inactivity. This strategy sought to minimize further insult to the infarcted cardiac tissue and to closely monitor for ventricular tachyarrhythmia, pump failure, and/or cardiac wall rupture [1]. These patients were hospitalized for upwards of 2 weeks followed by months of activity restriction. CR programs were developed in the 1970s to negate the effects of prolonged inactivity [1]. These programs played an integral role in both preventing deconditioning during inpatient hospitalization and in promoting ongoing reconditioning post-discharge. Over time, there was increased evidence that CR decreased cardiovascular-related and all-cause mortality, cardiovascular events, and hospitalizations [2, 3].

Presently, early ambulation and PCI has shortened the length of stay after MI and patients are typically discharged within 2–3 days. Thus, patients often leave the hospital with relatively little insight into their condition and often struggle to manage their comorbidities. There is strong literature suggesting that CR is a safe, cost-effective, and sustainable adjunct to current therapies to improve quality of life (QoL), morbidity, and mortality in these patients. Unfortunately, CR remains underutilized [4, 5], as only 10% of HF patients are referred to CR at discharge [4].

## 11.2 What Are the Components of a Cardiac Rehabilitation Program?

Cardiac rehabilitation, in addition to therapeutic exercise, is a comprehensive program designed to improve both the mental and physical health of an individual. Programs that focus only on exercise training without risk factor modification and HF teaching are not considered comprehensive CR. A CR

**Phase One**

Inpatient physical therapy assessment after acute event, introduction to cardiac rehabilitation program with referral at discharge

**Phase Two**

Outpatient, closely monitored cardiac rehabilitation and education for management of cardiac conditions and risk factor modification

**Phase Three**

Outpatient independent self management of cardiac conditions and exercise at a community gym or cardiac rehabilitation facility

FIGURE 11.1 Phases of cardiac rehab

program consists of many phases as shown in Fig. 11.1. Phase one begins during index hospitalization when patients are assessed by physical and occupational therapy for specific needs. At discharge, patients enter phase two, an outpatient monitored program focusing on exercise training and addressing cardiovascular risk factors. Ultimately, the goal after a 12-week program is for patients to enter phase three which is independent lifestyle modification and management of their cardiac conditions.

A baseline assessment of each patient includes an intake history and physical examination followed by a pre-enrollment symptom limited exercise treadmill test (ETT) to assess exercise tolerance and safety prior to initiation of exercise training. Medications and diet should be reviewed and documented. The physician works with exercise physiologists to design an exercise prescription usually based on the peak heart rate (HR). Exercise intensity is targeted between 70 and 85% of peak HR and adjusted according to the Borg perceived exertion scale to a difficulty level of 12–14. This is equivalent to moderate level of activity as shown in Fig. 11.2 [6].

The exercise training regimen typically consists of a 5–10 min warm-up, 20–60 min of aerobic exercise, and a 5–10 min cool down 3 days per week along with resistance training of major muscle groups. Patients are encouraged to maintain physical activity on the days that they are not in

FIGURE 11.2 The Borg RPE scale. Borg Scale is routinely used in cardiac rehabilitation programs to adjust patients exercise prescription ((© Gunnar Borg, 1970, 1998, 2017). Scale printed with permission)

Borg Perceived Exertion Scale	
6	
7	Very, very light
8	
9	Very light
10	
11	Fairly light
12	
13	Somewhat hard
14	
15	Hard
16	
17	Very hard
18	
19	Very, very hard
20	Maximum exertion

monitored sessions. Cardiac patients also receive either individual or group education regarding how to manage their cardiac condition, the importance of medication adherence, stress management, healthy heart nutrition, and other modifiable risk factors. Assessment for depression and other psychosocial factors interfering with patients’ ability to perform self-care is also important and routinely performed by the CR staff. When positive, patients are referred to appropriate professionals for evaluation and treatment. Each patient receives an individualized treatment plan that is reassessed every 30 days for the duration of their participation in CR.

### 11.3 What Are the Indications for Cardiac Rehabilitation?

Currently there are seven indications for CR that are reimbursed by the Center for Medicare/ Medicaid Services (CMS) (see Table 11.1). Among HF patients, only those with LVEF  $\leq 35\%$  are covered by CMS although there is compelling data

TABLE 11.1 Reimbursable indications for cardiac rehabilitation (cms.org)

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Coronary artery disease (includes stable angina/acute coronary syndrome)

Percutaneous Coronary Intervention (PCI)

Coronary Artery Bypass Graft Surgery (CABG)

Systolic congestive heart failure (EF <35%)

Cardiac transplant and left ventricular assist devices (LVAD)

Valve surgery (includes minimally invasive valve replacements)

Peripheral artery disease (must have claudication)

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for benefit in patients with HF with preserved ejection fraction (HFpEF), and the aforementioned indications may expand in the future. Currently no payers cover CR specifically for right sided HF. In Europe, patients with the following conditions are eligible for CR: coronary artery disease, chronic heart failure, left ventricular assist device (LVAD), heart transplantation, peripheral artery disease, post-PCI, after surgical procedures such as coronary artery bypass grafting, valve surgery and correction of congenital heart disease, and those with cardiac devices such as defibrillators, and pacemakers [7, 8].

### Case Continued

Our patient qualified for cardiac rehab based on CAD and HF with LVEF<35%. On enrollment in CR, our patient underwent a symptom-limited ETT under the standard Bruce protocol. She walked for 4 min and 35 s and achieved a maximum heart rate of 136 beats per min without any angular symptoms, but was dyspneic. She underwent diabetes teaching and medication review with the CR nurse. Initial exercise prescription was based on the Karvonen formula. Her estimated maximum heart rate was  $(220 - \text{age}) = (220 - 63) = 157$  beats per min. Her heart rate reserve (estimated maximum heart rate - resting heart rate) =  $157 - 87 = 70$  beats

per min. We targeted 70% of her heart rate reserve, hence, her targeted heart rate (70% heart rate reserve + resting heart rate) =  $49 + 87 = 136$  beats per min. She was started on the treadmill walking at a speed of 2.5 mph for 20 min followed by a short break before continuing on the recumbent stationary bike for an additional 20 min. Resistance training was deferred due to fatigue but the plan was to gradually introduce light weights to her routine.

## 11.4 What Are the Benefits of Cardiac Rehabilitation in Heart Failure with Reduced Ejection Fraction (HFrEF)?

In 2009, Heart Failure: A Controlled Trial Investigating Outcomes of Exercise Training (HF-ACTION) demonstrated the importance CR in patients with LVEF  $\leq 35\%$ . This landmark trial was the first large-scale study to show the efficacy (11% reduction in 2-year all-cause mortality and hospitalizations) and safety of moderate intensity exercise in patients with HFrEF. Part of the exercise regimen was performed in the home setting [9]. Those who were adherent to their exercise regimen had a lower depression score and also noted improvement in their functional status by at least one NYHA class. These findings subsequently led to the change in the 2013 ACCF/AHA Guideline for the Management of Heart Failure, with Exercise training becoming a Class 1a indication for patients with stable chronic systolic heart failure [10]. CR is recognized as a Class IIa indication in the United States [10], but has a class 1 indication in Europe [11] for HF.

In February 2014, the CMS added HFrEF (EF  $\leq 35\%$ ) as a covered indication. The caveat was patients must be stable and on GDMT for 6 weeks prior to enrollment in the program as per the HF-ACTION protocol (Memo: CAD-00437N). Currently only HFrEF is covered by insurers for participation in CR. However, there is compelling evidence that other types of HF also benefit.

Beneficial effects of exercise in chronic heart failure include but not limited to improvement in peak oxygen consumption ( $\text{VO}_2$ ), QoL, ventilatory responses, oxidative capacity of skeletal muscle, exercise capacity, endurance, endothelium dependent vasodilation, and muscle strength [12]. Exercise also confers a significant decrease in neurohormonal and sympathetic nervous system activation, HF hospitalizations, and all-cause mortality. It is estimated that the number needed to treat to save one life in HFrEF patients was 17 over 2 years [13].

When compared with CRT, CR appeared to be a non-inferior therapy in a parallel study comparing CRT versus implantable cardioverter defibrillation (ICD) plus supervised rehabilitation in HFrEF with NYHA III class symptoms. Patients in the ICD plus exercise group showed improvement in all parameters on cardiopulmonary exercise testing except for anaerobic threshold. There were similar reductions in right and left ventricular diameters and improvement in LVEF from 25% to 30% in both groups after 6 months of therapy. Thus, CR with target of moderate exertional level and Borg score 11–12 is comparable to CRT [14].

Although a majority of study participants in clinical trials are men, the benefit of CR does not seem to discriminate by gender or age. In HF-ACTION, 28% of participants were women. A post-analysis showed no significant difference in the change in  $\text{VO}_2$  between men and women, but there was a larger reduction in all-cause mortality and all-cause hospitalization after just 3 months of exercise training in women [15]. Although elderly patients have a greater risk for progressive functional decline, frail patients tend to be excluded from exercise-based clinical trials. Rehabilitation Therapy in Older Acute Heart Failure Patients (REHAB-HF) studied supervised exercise training in older patients (age > 60 years) with decompensated HF. Investigators initiated inpatient physical rehabilitation and extended it to 12 weeks post discharge. All-cause hospitalization rate decreased by 52% [16]. These findings corroborate the importance of CR in our patient (female, elderly).

Notably, while many of the aforementioned trials showed a positive benefit, there have been some equivocal results as well. ExTraMATCH II, a meta-analysis of 18 randomized exercise training trials of at least 3 weeks, did not show any significant benefit on the risk of mortality and HF hospitalization [17]. A Cochrane Systematic Review by Long et al. of 5783 HFpEF patients with  $\geq 6$  month follow up post exercise training showed no impact on short-term ( $<12$  month) mortality. There was a low-moderate evidence of reduction in all-cause hospitalizations and HF-specific admissions [18]. Recently, early hospital-based CR was shown to significantly reduce HF-specific mortality and HF readmissions in a review of 140,552 incident cases of HF admissions. These latter results were consistent with the findings from REHAB-HF [19]. Such conflicting results suggest heterogeneity amongst quality of trials, duration of follow up, variable patient compliance, and perhaps quality of CR centers.

## 11.5 Is There Evidence for Benefit of CR in Heart Failure with Preserved Ejection Fraction (HFpEF)?

Comorbidities and risk factors such as obesity, obstructive sleep apnea, insulin resistance / diabetes mellitus, hypertension, coronary artery disease, chronic kidney disease, atrial fibrillation, chronic obstructive pulmonary disease, and aging are risk factors for HFpEF. The treatment for HFpEF is targeted at blood pressure control, risk factor modification and the management of underlying conditions.

Existing data has shown that exercise training improves physical function. A meta-analysis of six randomized control trials including 276 patients showed that participation in exercise training improved cardiorespiratory fitness (mean difference  $+2.72$  L/min) and QoL using the Minnesota Living with Heart Failure score (mean difference  $-3.97$ ) compared to the control group. There were no changes in LVEF or diastolic function [20]. Similarly, Kitzman et al. randomized 100



patients with HFpEF and obesity into four groups including exercise, caloric restriction, exercise + caloric restriction, and control. While all intervention groups showed improvement in peak  $\text{VO}_2$ , exercise + caloric restriction group showed the greatest amount of change, 2.5 mg/kg/min increase in  $\text{VO}_2$  with no observed serious adverse events [21].

Currently, the ACCF/ AHA and the European Society of Cardiology recommend at least 150 min of moderate level of activity per week. This could be a brisk walk, dancing, active recreation, or any activity that reaches between 3 and 6 metabolic equivalents of task. HFpEF is not a CMS-reimbursable indication for CR in the United States. A large randomized control trial similar to HF-ACTION would likely be required before HFpEF would become a CMS-reimbursable indication in the United States.

## 11.6 What Is the Effect of Exercise Training on Pulmonary Hypertension and Right Ventricular Failure?

The role of CR in the patients discussed in Chaps. 2 and 7 is highlighted below. To date, there are no clinical trials specifically studying the effects of exercise training on right heart failure (RHF). Most of what is presented in this chapter is extrapolated from the pulmonary hypertension (PH) literature. RHF is a complex disease process and an important predictor of morbidity and mortality. Similar to patients with HF, moderate level exercise training in primary PH patients have been shown in pulmonary rehabilitation (PR) literature to be an effective, safe, and cost-effective treatment [18]. In a large meta-analysis including 784 patients, 6-min walk distance (6MWD) increased by  $96 \pm 61$  m after 15 weeks compared to a control group [22]. The positive effects of exercise are similar to HF patients and appear to be dose-dependent.

In a more recent study, Ehlken et al. studied the impact of exercise training in 85 patients with severe PH due to inoper-

able chronic thrombo-embolic pulmonary hypertension with NYHA class III-IV symptoms [23]. These patients who were stable on targeted medications for at least 2 months were randomized into a control group of usual care versus a 15-week moderate exercise training group. The training program started in a monitored setting for 1.5 h in divided intervals consisting of cycling, walking, dumbbell training with low weights <1 kg for 7 days per week, and respiratory training on 5 days per week for a total of 3 weeks. For the remaining 12 weeks, patients were recommended to continue exercises  $\geq 15$  min per day for at least 5 days per week at home. These patients also received counseling and mental training to improve their perception of physical limitations. After the 15 weeks, peak  $\text{VO}_2/\text{kg}$  linearly associated with right ventricular function increased by 15–20%. Cardiac index increased by 1 L/min/m<sup>2</sup> (19%) in the training group versus a decrease in 0.2 L/min/m<sup>2</sup> (–4.3%) in the control group. QoL and perception of physical limitations were also improved in the training group [23]. The results of this hemodynamic study are consistent with prior studies using 6MWD as a surrogate for improvement in functional status during exercise training. More research specifically geared towards RHF with other etiologies is needed. However, it does appear that exercise training may potentially have a positive effect on RV remodeling and function.

### 11.7 What Is the Evidence of Benefit of CR in Patients with Left Ventricular Assist Devices and Heart Transplant?

Although our patient neither has a left ventricular assist device nor is a heart transplant recipient, it is worth mentioning the role of cardiac rehabilitation in the patient discussed in Chaps. 9 and 10.

These patients' response to exercise can be quite different and requires special consideration before enrollment

into a CR program. The Cardiac Rehabilitation in Patients with Continuous Flow Left Ventricular Assist Devices (Rehab VAD) Trial randomized 26 patients with continuous flow LVAD into 6 weeks of CR or usual care (2:1) [24]. Patients in the CR group engaged in aerobic exercise targeting 60–80% of their heart rate reserve compared to the usual care group who were not prescribed an individualized plan and told to follow physician instructions regarding care as well as to walk daily. A 10% increase in peak  $\text{VO}_2$ , 17% increase in muscle strength, 23% increase in the Kansas City Cardiomyopathy Questionnaire (KCCQ), and 52.3-m increase in 6 MWD were noted in the CR group compared to the control group. These results are consistent with prior studies reporting the safety and improved  $\text{VO}_2$ , pulmonary function tests, muscle strength, QoL while decreasing depression scores in LVAD patients [25]. Reduction of the risk of hospitalization and mortality has also been confirmed with CR [26].

Studies in post-cardiac transplant patients also show similar benefits from CR. Peak  $\text{VO}_2$  in heart transplanted patients are on average 40–50% lower than normal healthy subjects. This drop in physical function is due to multiple factors including muscle loss due to inactivity and steroid usage, diastolic dysfunction, cardiac rejection, and other systemic derangements. It is important to note that re-innervated hearts have better exercise capacity than denervated hearts, which have higher resting heart rates contributing to chronotropic incompetence [27]. For the most part, the recommended exercise regimen is routine, a combination of aerobic and strength training 3 days per week followed by home maintenance exercise on the remaining days. Exercise training has been shown to increase peak  $\text{VO}_2$  between 10 and 17%. There is also an improvement in autonomic imbalance, prevention of sympathetic over-activation improving chronotropic responses, and early heart rate recovery [28]. Clearly, exercise training is a crucial element to the recovery of cardiac transplant patients.

## 11.8 What Are the Barriers to Cardiac Rehabilitation Participation?

There is compelling evidence that comprehensive cardiac rehabilitation is a safe and effective form of therapy to improve functional status and QoL in patients with different forms of HF. Despite clear benefits, there are gaps in referrals, enrollment, and patient retention. Currently, participation in CR remains low, with only about 20–30% of qualified patients enrolled in a program [29].

Medical barriers to referrals include physician misconceptions about benefits of the program, concern for safety in frail and elderly patients, and lack of access to geographically feasible CR programs. Patient barriers to participate include lack of education regarding the benefits of CR, psychosocial determinants such as transportation difficulties or inability to take time off from work, and lack of motivation for exercise training. For CR to be effective, participants must adopt lifestyle changes and continue self-training at home.

Several solutions have been proposed to increase the rates of referral, enrollment, and retention of patients in CR programs. Methods to enhance referrals include integrating an automatic referral into the electronic medical record (EMR) where clinicians must opt out when a qualifying diagnosis has been coded. While this strategy has been effective at capturing many patients, it has not been foolproof. One study compared four different strategies including an automated EMR, use of a CR liaison, a combination of automatic referral + liaison, and usual care. The combination of “automatic referral + a CR program liaison” was more effective at increasing CR participation, increasing participation greater than threefold compared to the control group [30].

This data supports the importance of having a discussion and initiation of enrollment prior to discharge. The Centers for Disease Control and Prevention (CDC) and CMS currently have an initiative called Million Hearts. Their goal is to increase CR participation from 20 to 70% and prevent one million cardiovascular events by 2022. This increase in CR participation is projected to save 25,000 lives and prevent 180,000 hospitalizations annually [29].

### **Case Conclusion**

Our patient completed a 12-week CR program. At the conclusion of the program, she was stable on her heart failure regimen without the need for uptitration of her diuretics and she was able to tolerate 40 min of continuous aerobic exercise in addition to resistance training. Upon discharge, she underwent a second ETT which showed that her exercise capacity had improved. Our patient exercised for 5 min and 49 s on a standard Bruce protocol, which is 1 min and 14 s longer than her pre-CR testing and she has had no hospital admissions for recurrent heart failure since she joined the program.

At this time there are no plans for LVAD or transplantation evaluation because she is stable on guideline-directed medical therapy. Her mood has improved with regular psychiatric follow-up. Her dietary habits have improved, and her A1C declined from 10.2 to 9.1. She feels empowered to make changes and has transitioned to phase 3 of CR.

### **Clinical Pearls**

- Strong data supports improved quality of life and reduced hospital admissions in HFrEF patients participating in CR.
- Exercise training is a Class 1a indication for patients with stable chronic systolic heart failure. CR is recognized as a Class IIa indication in the United States but as a class 1 indication in Europe for HF.
- There are no specific trials studying the effects of CR in right sided HF, but data extrapolated from pulmonary hypertension patients suggests improvement in cardiac output, quality of life, and longer 6MWT.
- LVAD and post-transplant patients participating in CR have improved autonomic dysfunction, chronotropic incompetence, cardiorespiratory fitness, and retention of muscle mass.
- Currently participation in CR remains low, with only about 20–30% of qualified individuals enrolled. Cardiac rehabilitation has highest participation rates when patients are referred while inpatient after the index cardiac event.

## References

1. Pashkow FJ. Issues in contemporary cardiac rehabilitation: a historical perspective. *J Am Coll Cardiol*. 1993;21:822–34.
2. Ades PA. Cardiac rehabilitation and secondary prevention of coronary heart disease. *N Engl J Med*. 2001;345:892–902.
3. Oldridge NB, Guyatt GH, Fischer ME, Rimm AA. Cardiac rehabilitation after myocardial infarction. Combined experience of randomized clinical trials. *JAMA*. 1988;260:945–50.
4. Golwala H, Pandey A, Ju C, et al. Temporal trends and factors associated with cardiac rehabilitation referral among patients hospitalized with heart failure: findings from get with the guidelines-heart failure registry. *J Am Coll Cardiol*. 2015;66:917–26.
5. Rengo JL, Savage PD, Shaw JC, Ades PA. Directly measured physical function in cardiac rehabilitation. *J Cardiopulm Rehabil Prev*. 2017;37:175–81.
6. Borg G. Psychophysical scaling with applications in physical work and the perception of exertion. *Scand J Work Environ Health*. 1990;16(Suppl 1):55–8.
7. Abreu A, Mendes M, Dores H, et al. Mandatory criteria for cardiac rehabilitation programs: 2018 guidelines from the Portuguese Society of Cardiology. *Rev Port Cardiol*. 2018;37:363–73.
8. Piepoli MF, Corra U, Adamopoulos S, et al. Secondary prevention in the clinical management of patients with cardiovascular diseases. Core components, standards and outcome measures for referral and delivery: a policy statement from the cardiac rehabilitation section of the European Association for Cardiovascular Prevention & rehabilitation. Endorsed by the Committee for Practice Guidelines of the European Society of Cardiology. *Eur J Prev Cardiol*. 2014;21:664–81.
9. O'Connor CM, Whellan DJ, Lee KL, et al. Efficacy and safety of exercise training in patients with chronic heart failure: HF-ACTION randomized controlled trial. *JAMA*. 2009;301:1439–50.
10. Yancy CW, Jessup M, Bozkurt B, et al. ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol*. 2013;62:e147–239.

11. Piepoli MF, Hoes AW, Agewall S, et al. European guidelines on cardiovascular disease prevention in clinical practice: The Sixth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of 10 societies and by invited experts) Developed with the special contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR). *Eur Heart J*. 2016;37:2315–81.
12. Ades PA, Keteyian SJ, Balady GJ, et al. Cardiac rehabilitation exercise and self-care for chronic heart failure. *JACC Heart Fail*. 2013;1:540–7.
13. Piepoli MF, Davos C, Francis DP, Coats AJ, ExTra MC. Exercise training meta-analysis of trials in patients with chronic heart failure (ExTraMATCH). *BMJ*. 2004;328:189.
14. Smolis-Bak E, Chwyczko T, Kowalik I, et al. Exercise training program in patients with NYHA III class systolic heart failure - parallel comparison to the effects of resynchronization therapy. *Adv Med Sci*. 2019;64:241–5.
15. Pina IL, Bittner V, Clare RM, et al. Effects of exercise training on outcomes in women with heart failure: analysis of HF-ACTION (heart failure-a controlled trial investigating outcomes of exercise TraiNing) by sex. *JACC Heart Fail*. 2014;2:180–6.
16. Reeves GR, Whellan DJ, O'Connor CM, et al. A novel rehabilitation intervention for older patients with acute decompensated heart failure: the REHAB-HF pilot study. *JACC Heart Fail*. 2017;5:359–66.
17. Taylor RS, Walker S, Smart NA, et al. Impact of exercise-based cardiac rehabilitation in patients with heart failure (ExTraMATCH II) on mortality and hospitalisation: an individual patient data meta-analysis of randomised trials. *Eur J Heart Fail*. 2018;20:1735–43.
18. Long L, Mordi IR, Bridges C, et al. Exercise-based cardiac rehabilitation for adults with heart failure. *Cochrane Database Syst Rev*. 2019;1:CD003331.
19. Scalvini S, Grossetti F, Paganoni AM, Teresa La Rovere M, Pedretti RF, Frigerio M. Impact of in-hospital cardiac rehabilitation on mortality and readmissions in heart failure: a population study in Lombardy, Italy, from 2005 to 2012. *Eur J Prev Cardiol*. 2019;26:808–17.
20. Pandey A, Parashar A, Kumbhani D, et al. Exercise training in patients with heart failure and preserved ejection fraction:



- meta-analysis of randomized control trials. *Circ Heart Fail*. 2015;8:33–40.
21. Kitzman DW, Brubaker P, Morgan T, et al. Effect of caloric restriction or aerobic exercise training on peak oxygen consumption and quality of life in obese older patients with heart failure with preserved ejection fraction: a randomized clinical trial. *JAMA*. 2016;315:36–46.
  22. Keteyian SJ, Leifer ES, Houston-Miller N, et al. Relation between volume of exercise and clinical outcomes in patients with heart failure. *J Am Coll Cardiol*. 2012;60:1899–905.
  23. Ehlken N, Lichtblau M, Klose H, et al. Exercise training improves peak oxygen consumption and haemodynamics in patients with severe pulmonary arterial hypertension and inoperable chronic thrombo-embolic pulmonary hypertension: a prospective, randomized, controlled trial. *Eur Heart J*. 2016;37:35–44.
  24. Kerrigan DJ, Williams CT, Ehrman JK, et al. Cardiac rehabilitation improves functional capacity and patient-reported health status in patients with continuous-flow left ventricular assist devices: the Rehab-VAD randomized controlled trial. *JACC Heart Fail*. 2014;2:653–9.
  25. Marko C, Danzinger G, Kaferback M, et al. Safety and efficacy of cardiac rehabilitation for patients with continuous flow left ventricular assist devices. *Eur J Prev Cardiol*. 2015;22:1378–84.
  26. Bachmann JM, Duncan MS, Shah AS, et al. Association of Cardiac Rehabilitation with Decreased Hospitalizations and Mortality after Ventricular Assist Device Implantation. *JACC Heart Fail*. 2018;6:130–9.
  27. Kavanagh T, Yacoub MH, Mertens DJ, Kennedy J, Campbell RB, Sawyer P. Cardiorespiratory responses to exercise training after orthotopic cardiac transplantation. *Circulation*. 1988;77:162–71.
  28. Karapolat H, Eyigor S, Zoghi M, et al. Effects of cardiac rehabilitation program on exercise capacity and chronotropic variables in patients with orthotopic heart transplant. *Clin Res Cardiol*. 2008;97:449–56.
  29. Ades PA, Keteyian SJ, Wright JS, et al. Increasing cardiac rehabilitation participation from 20% to 70%: a road map from the million hearts cardiac rehabilitation collaborative. *Mayo Clin Proc*. 2017;92:234–42.
  30. Grace SL, Russell KL, Reid RD, et al. Effect of cardiac rehabilitation referral strategies on utilization rates: a prospective, controlled study. *Arch Intern Med*. 2011;171:235–41.