Reviews in Cardiovascular Medicine

Rev. Cardiovasc. Med. **2022**; 23(4): 144
https://doi.org/10.31083/j.rcm2304144

Review

Exercise Training in Patients with Heart Failure: From Pathophysiology to Exercise Prescription

Gianluigi Cuomo[1], Anna Di Lorenzo[1], Anna Tramontano[1], Francesca Paola Iannone[1], Andrea D'Angelo[1], Rita Pezzella[1], Crescenzo Testa[1], Alessandro Parlato[1], Pasquale Merone[1], Mario Pacileo[2], Antonello D'Andrea[2], Giuseppe Cudemo[1], Elio Venturini[3], Gabriella Iannuzzo[4], Carlo Vigorito[1], Francesco Giallauria[1,*]

[1]Department of Translational Medical Sciences, "Federico II" University of Naples, 80131 Naples, Italy
[2]Division of Cardiology/UTIC, "Umberto I" Hospital, Nocera Inferiore (ASL Salerno), 84014 Nocera Inferiore (SA), Italy
[3]Cardiac Rehabilitation Unit, Azienda USL Toscana Nord-Ovest, Cecina Civil Hospital, 57023 LI Cecina, Italy
[4]Department of Clinical Medicine and Surgery, "Federico II" University of Naples, 80131 Naples, Italy
*Correspondence: francesco.giallauria@unina.it (Francesco Giallauria)
Academic Editors: Kazuhiro P. Izawa and Peter H. Brubaker
Submitted: 14 December 2021 Revised: 24 January 2022 Accepted: 28 January 2022 Published: 12 April 2022

Abstract

Heart failure (HF) is a chronic, progressive, and inexorable syndrome affecting worldwide billion of patients (equally distributed among men and women), with prevalence estimate of 1–3% in developed countries. HF leads to enormous direct and indirect costs, and because of ageing population, the total number of HF patients keep rising, approximately 10% in patients >65 years old. Exercise training (ET) is widely recognized as an evidence-based adjunct treatment modality for patients with HF, and growing evidence is emerging among elderly patients with HF. We used relevant data from literature search (PubMed, Medline, EMBASE) highlighting the epidemiology of HF; focusing on central and peripheral mechanisms underlying the beneficial effect of ET in HF patients; and on frail HF elderly patients undergoing ET. Since many Countries ordered a lockdown in early stages pandemic trying to limit infections, COVID-19 pandemic, and its limitation to exercise-based cardiac rehabilitation operativity was also discussed. ET exerts both central and peripheral adaptations that clinically translate into anti-remodeling effects, increased functional capacity and reduced morbidity and mortality. Ideally, ET programs should be prescribed in a patient-tailored approach, particularly in frail elderly patients with HF. In conclusion, given the complexity of HF syndrome, combining, and tailoring different ET modalities is mandatory. A procedural algorithm according to patient's baseline clinical characteristics [i.e., functional capacity, comorbidity, frailty status (muscle strength, balance, usual daily activities, hearing and vision impairment, sarcopenia, and inability to actively exercise), logistics, individual preferences and goals] has been proposed. Increasing long-term adherence and reaching the frailest patients are challenging goals for future initiatives in the field.

Keywords: heart failure; preserved ejection fraction; exercise training; cardiac rehabilitation; continuous training; interval training; strength training; respiratory training; inspiratory muscle training; functional electrical stimulation; mortality; elderly; frailty; COVID-19

1. Introduction

Heart failure (HF) is a heterogeneous syndrome, which presents often non-specific symptoms and sign at the onset, but life-limiting with the disease progression [1]. About 64.3 million people are living with heart failure worldwide (equally distributed between men and women), with prevalence estimated at 1–3% in developed countries, but it grows to approximately 10% in people >65 years old [2]. Prevalence in Asia [3] and Latin America seems to be similar to Western countries: conversely, results difficult estimating prevalence in Africa due to scarce literature [2,4]. Furthermore, this results enormous direct and indirect costs, estimated about $108 billion per annum worldwide in 2012 [5]. However, because of ageing population, the total number of HF patients keep rising [6].

Notably, HF strongly impacts on disability and is a major determinant of frailty: it has been assessed that 8.9% of patients have extreme disability and 30.3% have severe disability in life activities, while 53.3% of patients have moderate-severe disability in participation in society [7–9]. HF has negative impact on QoL similarly to other conditions (i.e., Parkinson's disease), even though on optimal medical therapy: about 70% of patients suffer from pain and discomfort, and half of patients experience anxiety and depression [10].

HF untreated symptoms, in addition to effects on quality of life (QoL), increase hospitalizations, emergency department visits, and long-term mortality [11,12]. In fact, despite advances in both pharmacological and non-pharmacological therapeutic strategies for HF, either with reduced or preserved ejection fraction (HFrEF and HFpEF, respectively), mortality and morbidity still remain elevated [13,14].

In HF patients, structured moderate-intensity continuous exercise training is strongly recommended (Class I recommendation, level of evidence A) in order to improve symptoms relief, functional capacity and QoL and reduce hospitalization [15].

The reduction of hospitalization has been clearly documented for HF patients undergoing exercise-based cardiac rehabilitation [16–18]; interestingly, a recent study found that the acute-phase initiation of CR was associated with lower in-hospital mortality (odds ratio [OR] 0.76, 95% confidence interval [CI] 0.73–0.80), shorter hospital stays and lower incidence of 30-day readmission due to HF [19]. In addition, in a cohort of 190 elderly patients hospitalized for HF, Kono *et al.* [20] showed that early mobilization within 3 days from admission exert reduction of cardiac events in 1400 days follow-up from discharge compared to mobilization from 4th day of admission. Interestingly, early mobilization was shown as independent predictor of re-hospitalization.

However, few HF patients are referred to structured training program; and a standardized training protocol suitable for all patients has not yet been validated [21]. In HF patients, different types of training have been tested: continuous moderate training (MCT) [22], high intensity interval training (HIIT) [23] and resistance or strength training (RST) [24], alone or in combination (i.e., ARIS (Aerobic, Resistance, InSpiratory Training OutcomeS) protocol [25].

The European Society of Cardiology Guidelines recommend regular aerobic exercise in HF patients to improve functional capacity and symptoms and to reduce risk of hospitalization [15]. Similarly, Canadian Cardiovascular Society Guidelines for the Management of Heart Failure in 2017 recommended aerobic exercises in stable HF patients to improve exercise capacity [26], while American College of Cardiology Foundation/American Heart Association guidelines in 2013 recognized only exercise training effects on quality of life for these patients [27]. Nevertheless, only about half of patients for whom it would be indicated are enrolled in training protocols [28] and referral rate is quite scarce in some region.

This review discusses recent evidence on the effect of exercise training in patients with HF (HFrEF and HFpEF), moving from pathophysiology to exercise prescription.

2. Pathophysiological Effects of Exercise Training

Effects of exercise training on central cardiac and peripheral mechanisms have long been investigated. At the onset of exercise, cardiac output (the product of heart rate and stroke volume) may increase from $\sim$5 L/min at rest to $\sim$15 L/min in young (20–40 years old) females and $\sim$20 L/min in young males [29]. At early stages of exercise, rise in heart rate is the main cause of the increase in cardiac output, but the maximum heart rate may decrease during maximal exercise with training [30]. Therefore, the large increase in cardiac output after exercise training is due to a larger stroke volume.

One year of progressive endurance exercise training has shown to increase LV mass and LV end-diastolic diameters (LVEDD) in sedentary subjects. In left ventricle, the initial effect during the first 6–9 months is a concentric remodeling depending on the duration and intensity of exercise, while in the right ventricle an eccentric remodeling was seen in response to endurance training [31].

About peripheral mechanisms, exercise training showed to reduce the effects of hyperactivation of the sympathetic nervous system [32].

Higher levels of circulating catecholamines have been detected in patients with heart failure, due to dysregulation of the sino-aortic and cardiac baroceptor; this mechanism results in rising of noradrenalin circulating level [33], which may aggravate myocardial ischemia and cause arrhythmias [34].

Furthermore, ET has been shown to effect on vagal stimulation improving heart rate recovery (HRR), which is fall in heart rate during first minute after exercise and is correlated with long term prognosis in patients with HF [35–38].

In patients with HF, exercise training could stimulate favorable left atrial [39] and left ventricle reverse remodeling after myocardial infarction decreasing circulating catecholamine and natriuretic peptide levels [40–43].

Moreover, exercise training has anti-inflammatory and antioxidative effects, reducing proinflammatory cytokines concentration in skeletal muscle and increasing antioxidative molecules production [44–49].

In addition, the above-mentioned effects contribute to peripheral vasodilation, improving endothelial function through nitric oxide (NO) production [50,51].

Furthermore, exercise training plays a key role on cardiopulmonary efficiency, considering that dyspnea is one of main symptom of HF. Cardiopulmonary exercise testing (CPET) is the gold-standard method for measuring maximum exercise capacity and cardiorespiratory fitness. Oxygen uptake and ventilatory patterns obtained during the submaximal portion of CPET have strong relationship to prognosis in HF patients [52]. Several studies assessed relationship between lower cardiorespiratory fitness and risk of developing coronary artery disease and heart failure in older age [53,54].

Moreover, low cardiorespiratory fitness, assessed by treadmill test, in young adulthood is associated with smaller left ventricle size; in addition, greater cardiorespiratory fitness decline with aging should indicate higher risk of developing LV dysfunction [55].

Exercise training could improve VO_{2peak} both in patients with HF with reduced left ventricular ejection fraction (HFrEF) and in patients with HF with preserved left ventricular ejection fraction (HFpEF), offering a further therapeutic option especially in the latter [56,57]. Notably, it is

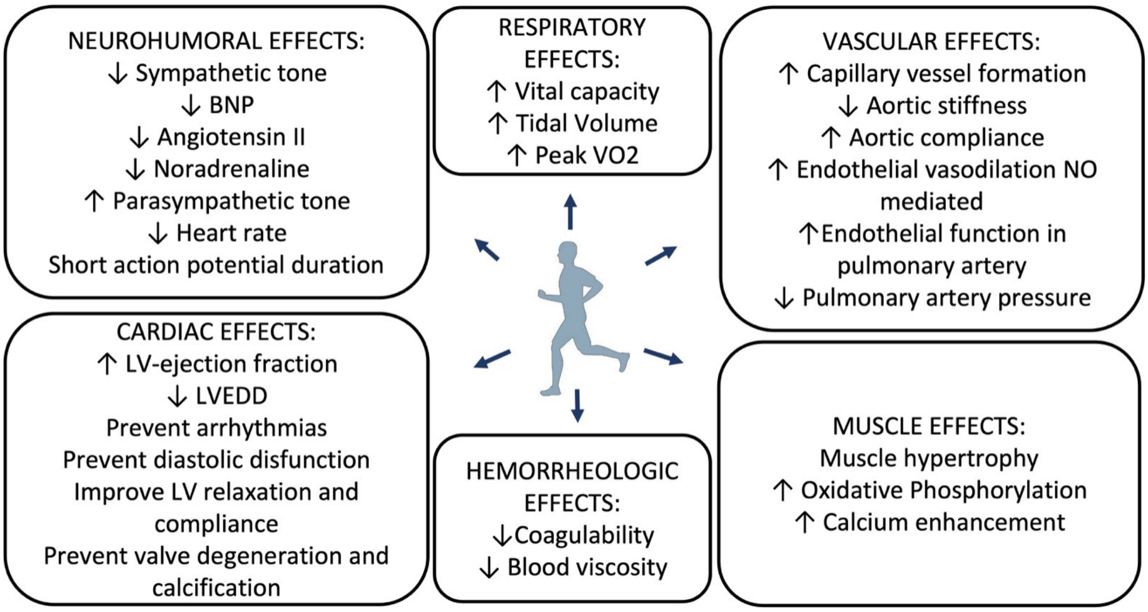

Fig. 1. Effects of exercise training in Heart failure. BNP, brain natriuretic peptide; LV, left ventricular; LVEDD, left ventricular end diastolic diameter; NO, nitric oxide; peakVO2, peak oxygen consumption.

crucial that exercise training should be performed life-long after acute event for maintaining long-term cardiovascular fitness [39].

The main effects of exercise training in heart failure are summarized in Fig. 1.

3. Exercise Prescription in Heart Failure with Reduced Ejection Fraction (HFrEF)

Although most recent European Society of Cardiology guidelines recommend regular aerobic exercise in HF patients to improve functional capacity and symptoms and to reduce risk of hospitalization [15], only about half of patients for whom it would be indicated are enrolled in training protocols [28].

However, an exercise training program is only recommended in stable patients, in NYHA class II–III, undergoing optimal medical treatment, while it is contraindicated in a number of cardiac (first 2 days after acute coronary syndrome, untreated life-threatening cardiac arrhythmias, uncontrolled hypertension, acute heart failure, acute myocarditis and pericarditis, symptomatic aortic stenosis, severe hypertrophic obstructive cardiomyopathy) and non-cardiac diseases (acute systemic illness, uncontrolled diabetes mellitus, thrombophlebitis, severe COPD) [58].

Nevertheless, to date there are still no standardized training protocols. Several studies investigated different exercise training types, methods, and settings, to identify pathophysiological effects and benefits of various types of intervention. Anyway, it is recommended to carry out submaximal exercise test (6-Minute Walking Test or CPET) to evaluate exercise capacity and determine training intensity before starting any training protocol.

Six-Minute Walking Test (6MWT) is an easy to perform and widely used test, which may provide reliable information about HF prognosis and patient capacity to perform daily activities, but it suffers from physician ability, place where it is performed and patient condition [59].

Cardiopulmonary exercise testing (CPET) has been established to be safe in HF patients [60] and it is considered gold standard to assess exercise capacity and to determine exercise training intensity, measuring directly O2 consumed during exercise until this peak (VO_{2peak}) and providing an estimate of transition from aerobic to anaerobic metabolism, the ventilatory anaerobic threshold (VAT) [58,61].

The first and more investigated form of training is endurance aerobic training or moderate continuous training (MCT) [22]. This modality can be performed by cycling or treadmill, without reaching maximum effort; after estimating exercise intensity through VO_{2peak} measurement, it is recommended to start at low intensity (about 5–10 minutes twice a week) and then increase according to patient's tolerance (up to 20–60 minutes on 3–5 days a week) [58].

In HF-ACTION trial, continuous moderate training showed, after adjustment for highly prognostic predictors of the primary endpoint, a modest significant reduction for mortality and hospitalization in HF patients (HR = 0.85 for cardiovascular mortality or HF hospitalization; 95% CI, 0.74–0.99; $p = 0.03$) [22].

Interval training (IT) is based on short bouts alternating with recovery phases, using treadmill or electrically braked cycle. According to patient's clinical features, two different programs are possible: high intensity interval training (HIIT) includes few (about three or four) hard work phases (3–4 minutes) performed at 90–95% of maximal exercise capacity, interspersed with recovery phases (3 minutes) performed at low or no workload; the whole is preceded by a warm-up and followed by a cool-down phase; low intensity interval training (LIT) consists in 15 minutes exercise alternating hard (about 30 seconds at 50% of achieved power output) and recovery (about 60 seconds) phases, and intensity should be increased accord to patient's exercise conditioning (until 30 minutes training session).

Several studies in recent times compared MCT and HIIT [23,62–65], without reaching univocal results; although HIIT appears to be more effective than MCT in improving left ventricular function, possibly due to challenge on heart's pumping ability caused by short bouts of exercise, recently SMARTEX-HF randomized multicenter trial by Ellingsen *et al*. [66] showed that HIIT was not superior to MCT in improving left ventricular end-diastolic diameter and VO_{2peak}.

Resistance or strength training (RST) is based on muscle contraction exercises against specific resistances, with aim of increasing muscle strength and endurance [24]. Therefore, it is an anaerobic exercise, widely used to prevent wasting syndrome; in this instance, more subjective parameters are used to determine exercise intensity, such as % of one repetition (% 1-RM, i.e., maximum weight that can be lifted only once [25]) or Borg scale [67].

Due to possible negative effects on remodeling and ventricular overload and the poor evidence of efficacy, RST has been underused for long [68–70]; however, its use has recently been increased in association with aerobic endurance and interval training, showing additional benefits on respiratory parameters (particularly VO_{2peak}) and vascular flow [71,72].

Respiratory training, and in particular inspiratory muscle training (IMT), is a type of training which aims to improve respiratory muscle endurance, through use of specific devices (the most used apply a resistive load or a threshold load about 30% of maximal inspiratory pressure) [73]. The rationale behind use of this type of training is the finding of changes in muscle fibers of diaphragm [74] and ventilatory abnormalities at cardiopulmonary exercise test in HF patients [52].

Several studies examined role of IMT in heart failure, showing improvement in VO_{2peak}, maximal inspiratory pressure, QoL and other parameters [75–78].

Combined with aerobic training, IMT showed additional benefits in serum biomarkers, such as C-reactive protein and NT-proBNP [78].

Functional electrical stimulation (FES) is a technique which uses surface electrodes to stimulate muscle activity. This technique represents an opportunity for patients with reduced mobility or who cannot tolerate exercise [79]. In 2013, a meta-analysis exploring the effects of FES in HF patients showed that, although with a lower effect size than other training modalities, FES significantly improved 6-Minute-Walking distance (6MWD) and VO_{2peak} compared to controls. In this view, FES could be used as a bridge-method to make patients able to perform conventional exercise training [80].

In Table 1 key elements of above-mentioned training modalities are shown. In recent years, the attitude to use the different training methods in combination with each other has become increasingly widespread. In a 2016 meta-analysis, Cornelis *et al*. [81] compared different training modalities, alone and in combination, to evaluate the effects on VO_{2peak}, left ventricular ejection fraction (LVEF), left ventricular end-diastolic diameter (LVEDD) and QoL; no significant effects were found regarding CPET parameters, while there was a significant improvement in QoL in combined continuous and strength training, and a significant improvement in LVEF and LVEDD in interval training compared to continuous training

In ARISTOS-HF trial [25], a new model of training, based on combined aerobic training/resistance training/inspiratory muscle training named ARIS (12 weeks, 3 times/week, 10 minutes/week, respectively) have been proposed. The idea behind this training modality was to improve functional capacity, which is impaired in HF patients, i.e., low aerobic capacity, reduced respiratory muscle function and pathological peripheral muscle strength. Although no statistically significant results were found in ARISTOS-HF trial, positive trend for increased VO_{2peak} and additional benefits in peak circulatory power (the product of VO_{2peak} and peak systolic blood pressure), LVEDD and QoL were shown in ARIS group; in particular, peak circulatory power showed to be a stronger predictor for cardiovascular events in HF patients [82,83]. These findings allowed authors to encourage use of ARIS training in HF patients.

In Fig. 2, different rehabilitative modalities according to clinical stability and functional capacity, individual possibilities, and frailty status of HF patients have been proposed.

4. Prescription of Exercise Training in Patients with Heart Failure with Preserved Ejection Fraction (HFpEF)

Although HFrEF and HFpEF are two different entities in terms of pathophysiology and background disease, they both present a common range of symptoms and reduced exercise tolerance is a hallmark. HFpEF is the most common form of HF in older population and in people with hypertension and other cardiovascular risk factors [14]. Surprisingly, few studies have been conducted to assess the beneficial effects of ET in HFpEF patients.

According to pathophysiological perspective, the main causes of exercise intolerance and reduction in VO_{2peak} in these patients are related either to cardiac or not cardiac patterns.

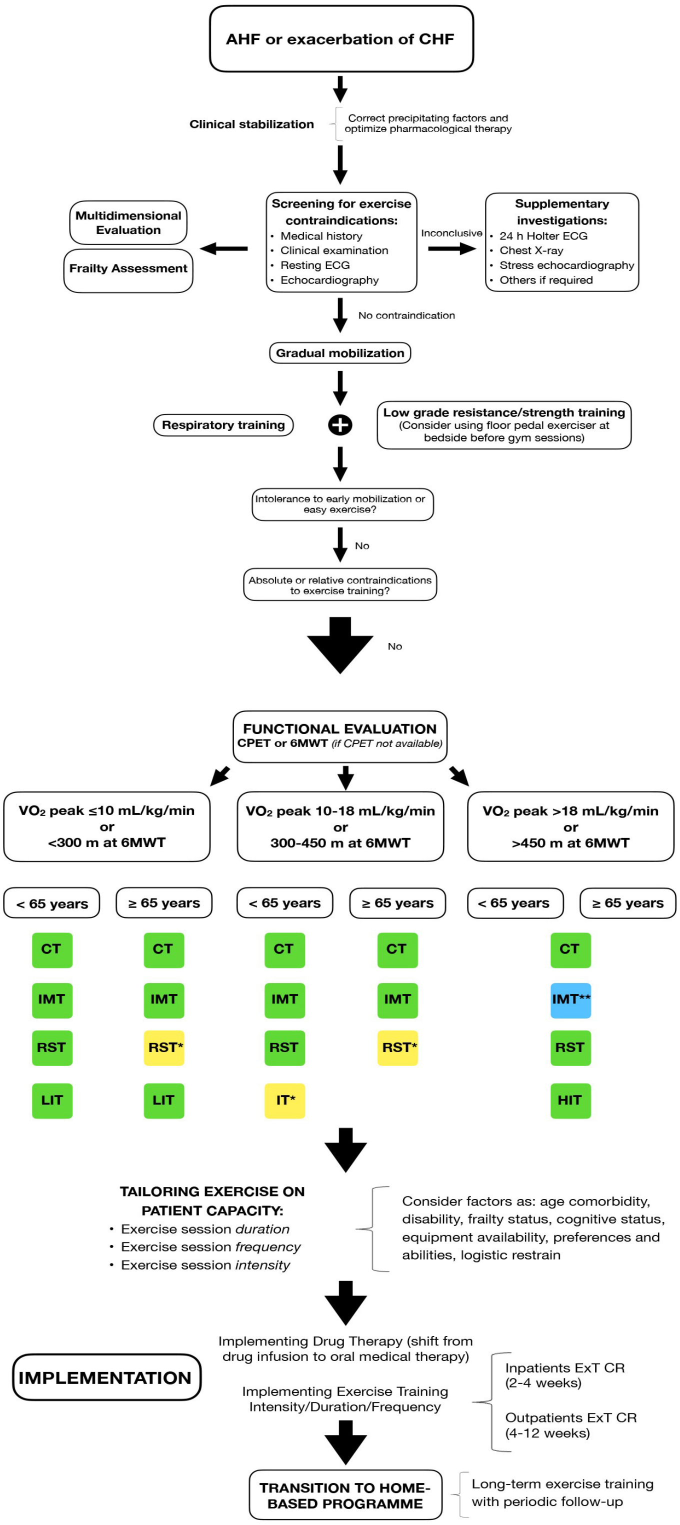

Fig. 2. Procedural algorithm of exercise training in Heart failure *(continue on next page)*. 6MWT, 6-Minute Walking Test; AHF, acute heart failure; CHF, chronic heart failure; CPET, cardiopulmonary exercise testing; CR, cardiac rehabilitation; CT, continuous training; ExT, Exercise Training; HIT, high intensity interval training; IMT, inspiratory muscle training; IT, interval training; LIT, low intensity interval training; RST, resistance strength training; VO_2 peak, peak oxygen consumption. * (yellow): consider it in active lifestyle patients. ** (blue): consider it only if respiratory muscle weakness is present.

Table 1. Key elements for exercise training modalities.

	Starting protocol	Progression scheme	Main Effects
Moderate continuous training	10–15 minutes. Intensity: 40–50% of VO_{2peak}.	30 minutes. Intensity: >60–70% of VO_{2peak}.	Improve exercise tolerance, 6MWD, VO_{2peak}, VE/VCO_2; Improve cardiac output and diastolic function.
Interval training	High intensity: 4 minutes bouts at 90% of maximal exercise capacity, interspersed with 3 minutes recovery period. 5–10 minutes of warm–up and cool–down phases. Exercise duration: 35–45 minutes.	Increase bouts intensity.	Improve exercise tolerance, 6MWD, VO_{2peak}; Improve resting LVEF, LVEDD.
	Low intensity: Bout of 10 seconds and recovery period of 80 seconds. Exercise duration: 5–10 minutes.	Bout of 30 seconds and recovery period of 60 seconds. Exercise duration: 30 minutes.	
Strength training	5–10 repetitions. 1–3 circuit each session. 2–3 sessions/week. Intensity: <30%. 1-RM or Borg scale <12.	15–25 repetitions. 1 circuit each session. 2–3 sessions/week. Intensity: 30–50%. 1-RM or Borg scale 12–15.	Improve muscle mass; improve intramuscular co-ordination; increase resting LVEF.
Inspiratory muscle training	Use of threshold device at 20–30% of MIP for 15–30 minutes/day. 5–6 days/week.	Readjust weekly. It is possible practice 2 session daily, 30 minutes each session, 7 days/week.	Improve respiratory muscle strength and endurance, 6MWD, VO_{2peak}.
Functional electrical stimulation	10 Hz frequency. 20 second stimulation-20 second rest. 60 minutes/day. 7 days/week.		Improve 6MWD, exercise duration, VO_{2peak}.

1-RM, 1 repetition maximum; 6MWD, 6-Minute walking distance; LVEDD, left ventricular end diastolic diameter; LVEF, left ventricular ejection fraction; MIP, maximal inspiratory pressure; VO_{2peak}, peak oxygen consumption; VE/VCO_2, minute ventilation/carbon dioxide production.

As for the former, in HFpEF patients undergoing exercise, alterations in LV stiffness and LV relaxation determine an increase in pulmonary capillary pression and, consequently, dyspnea and lower VO_{2peak} [84,85].

Regarding peripheral mechanisms, it has been reported that arterial velocity pulse index (AVI), which is associated with VO_{2peak}, is lower in HFpEF patients, suggesting importance of impaired vascular function in exercise intolerance genesis in this cohort [86]. Underlying mechanisms of reduced exercise tolerance in HFpEF patients are not fully elucidated; a reduced skeletal muscle hyperemia and a marked reduction in muscle mass replaced by an increase in intermuscular adipose tissue may play a key role [87–89].

In a randomized, controlled, single-blind study Kitzman *et al*. [82] enrolled 53 elderly patients with isolated HEpEF and evaluated them during 16 weeks of MCT; VO_{2peak} increased significantly in patients undergoing to exercise training (+2.3 ± 2.2 mL/kg/min, p = 0.0002), as well as 6-MWD (p = 0.0002) [90].

In a meta-analysis including 6 randomized controlled trials in which patients performed MCT, Pandey *et al*. [83] observed an improvement in VO_{2peak} and QoL, but not in echocardiographic parameters (E/A, deceleration time and ejection fraction) [91]. Different studies were concordant to the meta-analysis findings [92,93], thus suggesting that improvements in exercise tolerance were independent from changes in systolic or diastolic function; while effects on peripheral mechanisms, as improved oxygen extraction by skeletal muscles, could be implicated.

In 2015, Angadi *et al*. [86] compared HIIT vs. MCT exercise in HFpEF patients reporting an increase in VO_{2peak} (from 19.2 ± 5.2 to 21.0 ± 5.2 mL/kg/min; p = 0.04) and a statistically significant improvement in diastolic markers (E and deceleration time, p = 0.02) in patients undergoing 4 weeks HIIT, while no significant changes were observed in patients undergoing MCT. Although sample size was limited and designed a short follow-up period (4 weeks), these findings paved the way for considering short-term HIIT protocol in HFpEF patients [94].

Moreover, Donelli da Silveira *et al*. [95] in randomized clinical trial demonstrated the superiority of HIIT vs. MCT in HFpEF patients after 12 weeks exercise program. In particular, this trial showed that the increase in VO_{2peak} is two times higher in the HIIT compared to MCT group [3.5 (3.1 to 4.0) vs. 1.9 (1.2 to 2.5) mL/kg/min, $p < 0.001$]; while similar improvements in diastolic function and QoL have been reached through both training modalities [95].

These findings highlight that HIIT is more effective in HFpEF compared to MCT, probably due to the improvement in diastolic dysfunction; however, conflicting results have been reported [96].

In a recent meta-analysis, IMT was effective in HFpEF patients in improving 6MWD (mean difference 83.97 meters, 95% CI, 59.18–108.76; $p < 0.0001$) and VO_{2peak} (mean difference 2.82 mL/kg/min, 95% CI, 1.90–3.74; $p < 0.0001$) [97].

Although older age and poor effort tolerance could make exercise difficult to perform, the proven efficacy in different trials and the shortage of therapeutic options for this condition strongly suggest using these exercise training protocol in HFpEF patients.

5. Exercise Training in HF Elderly Patients

Prevalence of HF rise to approximately 10% among people >70 years old [2,6]. In addition, regardless of comorbidities, a reduction in VO_{2peak} from 45 mL/kg/min in young people (25 years old) to 25 mL/kg/min in older people (75 years old) have been described [98].

Practicing ET is quite difficult in HF elderly patients although they represent the majority of HF cohort. In Fig. 2, a procedural algorithm exploring all rehabilitative modalities according to clinical stability and functional capacity, individual possibilities, and frailty status of HF patients has been proposed. Notably, elderly HF patients should be carefully evaluated for tailoring exercise session according to their peculiar characteristics (disability, frailty, cognitive impairment, falls risk, sarcopenia, visual and ear impairment, etc.).

ET has been largely investigated in older patients [99–101]. Austin *et al*. [99] enrolled 200 patients >60 years old with NYHA class II–III and randomized to ET group or usual care: patients performed aerobic endurance training and low resistance strength training 2.5 hours for session, 2/week for 8 weeks, and afterwards other 16 weeks exercise sessions consisting of 1 hour/week. After 24 weeks training, ET group showed a significant improvement in functional capacity [6MWD increases significantly by 16% in ET group (from 275.5 ± 21.4 meters to 320.4 ± 21.9 meters; $p < 0.001$)], in functional status [NYHA class (from 2.44 to 2.01)] and QoL, while hospital admissions were fewer and lasted less compared to usual care controls.

More recently, Antonicelli *et al*. [100] investigated ET effect in 343 older HF patients (<70 years, mean age 76.90 ± 5.67): patients performed endurance training 3 times/week for 3 months in hospital settings and next 3 months in home-monitored settings; 6MWD improved from 299 ± 120 meters to 394.1 ± 123.6 meters after 6 months in exercise group ($p < 0.001$), all-cause hospitalizations adjusted for clinical covariates reduced by 44.2% (B = 0.558, 95% CI, 0.326–0.954, p = 0.033) and was shown improvement in QoL (28.6 ± 12.3 vs. 44.5 ± 12.3, p = 0.001). Furthermore, it was found a significant reduction in NT-proBNP plasma levels in ET group from 1236 to 440 pg/mL ($p < 0.001$), while this level increased in control group.

In a cohort of 40 postinfarction older patients, Giallauria *et al*. [102] reported that 3-month ET program was associated to a reduction in NT-pro-BNP levels (from 1446 ± 475 to 435 ± 251 pg/mL, $p < 0.001$) and an overall improvement of exercise capacity, without LV remodeling and with improvement in early LV filling. Interestingly, an inverse correlation between changes in NT-pro-BNP levels and in VO_{2peak} (r = –0.67, $p < 0.01$), E-wave (r = –0.42, $p < 0.01$) and E/A ratio (r = –0.60, $p < 0.01$) have been reported; suggesting that ET can exert its beneficial effects by improving myocardial efficiency with no detrimental effects even in elderly patients.

Although aerobic endurance training has been more investigated in elderly HF patients, skeletal muscle wasting is a precipitating factor in clinical conditions in these patients, causing increase in type II muscular fibers and consequently an earlier shift to anaerobic metabolism and fatigue onset [103,104].

Reduced VO_{2peak} and lower exercise time were found associated with sarcopenia in type I muscular fiber area was predictive of changes in 6M [105]. Pu *et al.* [101] investigated progressive resistance training in 16 HF patients (100% women, mean age 77 $\pm$ 6 years) compared to non-HF individuals with comparable aerobic capacity. All patients performed 60 minutes session, 3 session/week, for 10 weeks. After 10 weeks, exercise group showed a significant improvement in 6MWD (+49 $\pm$ 14 meters; $p < 0.03$) and muscle strength (33.5 $\pm$ 7.3% increase on leg press and 68.0 $\pm$ 13.2% on knee extension); notably, change WD (r = 0.612; $p = 0.026$).

Combined muscle strength and aerobic training programs have been proved to increase VO_{2peak} and to improve other CPET indexes [106]. A recent meta-analysis investigated the ET effects in older patients with HF and evaluated relationship between training modalities and efficacy [107]. ET improved QoL (effect size = –0.69; $p < 0.001$), aerobic capacity (measured as 6MWD, effect size = 0.47; $p = 0.002$) and cardiac function (measured as LVEF, effect size = 0.91; $p = 0.001$). In addition, resistance training had greatest effect on aerobic capacity, while aerobic training had greatest effect on cardiac function. Duration of intervention, duration of single session and weekly frequency showed to have no predictive influence on aerobic capacity and cardiac function adaptation.

Although it would be desirable to have more trials, data available suggest that ET have similar benefits in older HF patients compared to younger cohort. Combined strength and aerobic training should be recommended to prevent wasting syndrome in older patients in addition to effects on aerobic capacity [108–110].

6. Low Intensity Exercise Training for Frail Patients with Heart Failure

Patients with poorer clinical condition are often excluded by most trials; although in these specific patients, low-intensity exercise have major impact on quality of life favorably changing perspectives for daily life activities [111]. In HF patients, ET exerts beneficial effects not only improving physical performance, but also restoring basic abilities, particularly in patients with poorest conditions. Early gradual mobilization in patients with cachexia or after recent acute event is strongly recommended [58]. These movements are performed using only resistance opposed by their own weight, aiming at increasing strength, at improving coordination, respiratory capacity. These protocols should be performed at low intensity, with gradual increase according to patient' perceived exertion.

In the REHAB-HF pilot study [112], 27 patients older than 60 years which experienced acute decompensated heart failure were assigned to an intervention group performing multi-domain rehabilitation which included combined strength (sit to stand), balance (stand and reach), endurance (continuous walking) and mobility (dynamic start and stop) exercises compared to control group. Starting objectives were rise from chair using hands, stand with feet apart and walk for at least 10 minutes; at the last level of intensity patients were able to sit to stand behind chair with arms across chest, stand in semi-tandem and walk for 30 minutes quickly changing direction. The primary outcome was change in Short Physical Performance Battery (SPPB) test, which assess speed over 4 meters, time to complete 5 chair rises and standing balance: after 3 months SPPB score in intervention group increased from 4.8 $\pm$ 2.8 to 6.9 $\pm$ 3.0 units compared to increase from 6.0 $\pm$ 3.0 to 6.8 $\pm$ 3.3 units in control group; moreover, it was shown an increase in 6MWD from 170 $\pm$ 83 meters to 232 $\pm$ 113 meters in exercise group. Also, inversely correlation in SPPB score with 6 months all cause rehospitalizations (–0.60; $p < 0.01$) was observed. Of note, SPPB is a very common test among geriatricians for great predictive power, and could be easily adopted as outcome measure in frail elderly patients when cardiopulmonary exercise stress testing is not feasible or available [113]; and the adoption of other outcomes measures to evaluate the effects of exercise training in specific cohorts of patients (i.e., frail elderly patients) should be encouraged [8].

Therefore, in elderly HF patients, exercise prescription must be tailored on patient's status and reach patient's individualized targets (Patients Reported Outcomes, PROs) (Fig. 3). When feasible, undergoing CPET is considered the gold standard for evaluating functional capacity; otherwise 6MWT distance should be considered (Figs. 2,3). Both tests are strongly related to patient' outcome. In elderly HF patients, functional capacity progressively worsens; and patients might not be able to complete these tests in several conditions such as pre-frailty, frailty, comorbidity, physical disability, polypharmacy, cognitive status, sedentary behavior, work abilities, etc. In these patients, geriatric multidimensional evaluation is mandatory (Figs. 2,3).

7. Impact of Exercise Training on Mortality

Despite the rationale and biological plausibility in favor of ET in HF, trials often fail to demonstrate a reduction in mortality. The large HF-ACTION trial failed to show a

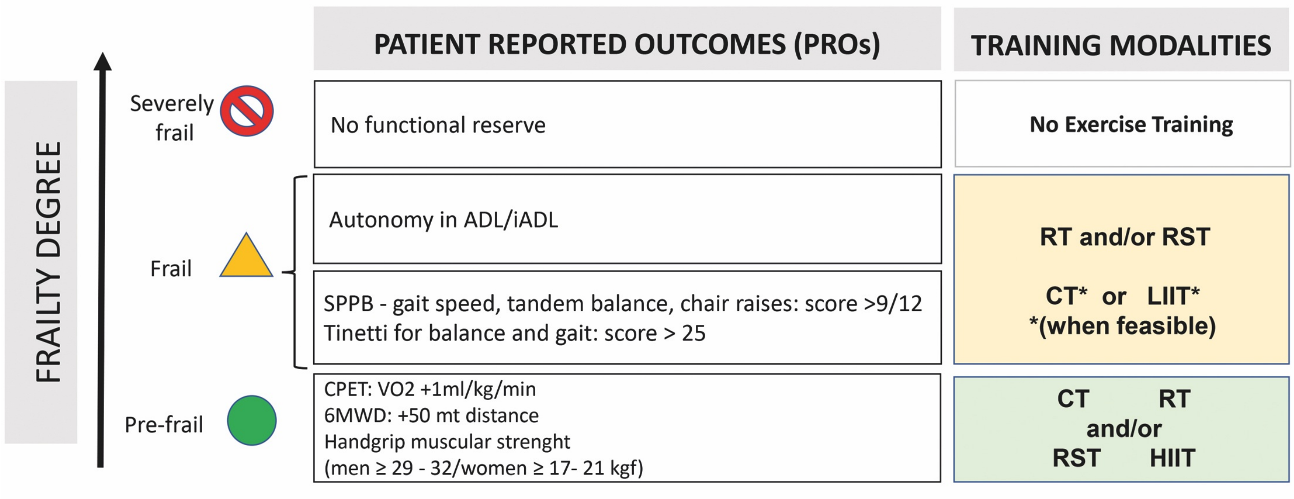

Fig. 3. Patients Reported Outcomes (PROs) and training modalities according to Frailty degree. 6MWD, 6-minute walking distance; ADL, activities of daily living and iADL, instrumental activities of daily living; CPET, cardio-pulmonary exercise test; CT, continuous training; HIIT, high intensity interval training; LIIT, low intensity interval training; RST, resistance/strength training; RT, respiratory training; SPPB, short physical performance battery.

reduction in all-cause (HR = 0.96 [95% CI, 0.79–1.17]; $p = 0.70$) and cardiovascular mortality (HR = 0.92 [95% CI, 0.83–1.03]; $p = 0.14$) in exercise training group vs. usual care group in primary analysis, and only after supplementary analyses adjusting for highly prognostic baseline characteristics a statistically significant reduction in all–cause mortality was found (HR = 0.89 [95% CI, 0.81–0.99]; $p = 0.03$) [22].

The ExTraMATCH meta-analysis aimed at assessing exercise training effect on mortality in 801 HF patients, 396 assigned to exercise group and 406 assigned to control group; in exercise training group, mortality resulted significantly lower (log rank $\chi^2 = 5.9$, $p = 0.015$) [114].

More recently, in order to include more patients and to more thoroughly evaluate the effects of exercise training in Heart Failure, the ExTraMATCH II meta-analysis was conducted [18]; although no reduction in mortality and hospitalizations was observed, a statistically significant improvement in exercise capacity and QoL was found (mean improvement at 6-MWT 21 m, 95% CI, 1.57–40.4 m, $p = 0.034$; mean difference at Minnesota Living with Heart Failure Questionnaire score –5.94, 95% CI, –1.0 to –10.9, $p = 0.018$) and positive trend in VO_{2peak} was observed (1.01 mL/kg/min, 95% CI, –0.42 to 2.44 mL/kg/min; $p = 0.168$).

A recent meta-analysis reported that an exercise-based cardiac rehabilitation program had no impact on mortality in first 12 months but obtaining additional data by contacting the study authors resulted in a reduction in all-cause mortality at a follow-up of more than 12 months in patients who performed ET compared to control group (intervention 244/1418 (17.2%) vs. control 280/1427 (19.6%) events): RR 0.88, 95% CI, 0.75–1.02; $p = 0.09$) [115].

Even if mortality data do not lead to univocal results, the improvement in VO_{2peak} and 6MWD could be reliable surrogate parameters for assessing exercise effect on final outcomes in HF patients.

8. SARS CoV-2: Heart Failure Rehabilitation during Pandemic

The severe acute respiratory syndrome coronavirus 2 (SARS CoV-2) in 2020 started a pandemic which created major difficulties for Health Systems of worldwide countries in recent years and risks changing health care in the future.

SARS CoV-2 infection and its disease "COVID-19", demonstrated more severe course and higher mortality in patients with cardiovascular comorbidities [116,117]. The discovery that SARS CoV-2 enters human cells through angiotensin-converting enzyme 2 (ACE2) receptor created several concerns particularly in patients treated with renin angiotensin system (RAS) inhibitors (drugs largely used in cardiovascular diseases and especially HF) that in early phases where deemed to promote COVID-19 disease [118]. Notably, several studies demonstrated that use of ACE inhibitors (ACEI) or angiotensin-receptor blockers (ARBs) is not associated with risk of more severe COVID-19 disease [119,120].

Although COVID-19 is prevalently a respiratory disease, systemic involvement (cardiovascular, gastrointestinal, neurological, renal, thromboembolic, etc.) has been clearly documented [121–125]. Cardiovascular manifestations may be secondary to lung disease, which causes respiratory failure, hypoxia and increasing cardiac workload: however also other mechanisms have been shown, as coronary microvascular damage [126] and direct cardiac injury due to virus capacity to directly infects human cardiomyocytes, causing increase of cardiac troponins [127–129].

Therefore, patients who already present cardiovascular comorbidities should be particularly beware for risk of a SARS CoV-2 infection. This is particularly valid for those suffering from HF: Matsushita *et al*. [130] randomized 889 French patients with previous acute coronary syndrome, dividing them in a reduced LVEF group (EF $<$40%, n = 91) and moderated reduced and preserved LVEF group (EF $\geq$40%, n = 798); higher incidence of COVID-19 related hospitalization or death resulted in reduced LVEF group (9% vs. 1%, $p < 0.001$), regardless discontinuation of ACEI or ARBs. Moreover, it has been supposed that COVID-19 through proinflammatory cytokines activation could unmask asymptomatic HFpEF or contribute to progression in patients with already known disease [131].

In addition to the direct damage caused by COVID-19, reorganizations of healthcare resources to deal with the pandemic emergency has also caused difficulties for patients with HF. Many countries ordered a lockdown in early stages of pandemic trying to limit infections, with obvious limitations to outdoor exercise training and to cardiac rehabilitation programs participation for cardiac patients.

Cunha *et al*. [132] evaluated lockdown impact on physical activities and vital sign in HF patients with an implantable cardioverter defibrillator (ICD) or cardiac resynchronization device (CRT) highlighting marked reduction in physical activity, especially in patients with performed low exercise before lockdown: this may lead to worsening of clinical status of these patients in future, increasing hospitalization and mortality.

Worldwide, scientific societies proposed different modalities, either in telemedicine or through protocols to be implemented in hospital setting, trying to guarantee cardiac rehabilitation programs continuation during pandemic [133–136]. The effectiveness of solutions implemented will certainly be one of most important challenges that healthcare systems will have to face in this century to ensure survival and quality of life in patients with cardiovascular diseases.

9. Exercise Training Limitations

Although ET programs are strongly recommended by Guidelines, recent RCT are showing less significant results regarding ET effects in heart failure. One explanation is that in previous trials, particularly those prior to 1990s, many patients were not treated on OMT, which includes beta-blockers, aldosterone antagonists or angiotensin receptor Neprilysin inhibitors.

The impossibility of being performed in the most fragile patients and in which exercise would represent a risk than a therapeutic alternative is one of the flaws of exercise training protocols. Cardiac and non-cardiac diseases in which exercise is contraindicate have been defined in a consensus document of the Heart Failure Association and the European Association for Cardiovascular Prevention and Rehabilitation [58]. However, this issue could be limited in certain patients through use of functional electrical stimulation (FES) which is also suitable for patients with reduced mobility [79].

Unfortunately, HF women are often denied to cardiac rehabilitation programs [137,138]; specific CR programs specifically designed for women are eagerly awaited.

Finally, the poor patient's adherence to training programs is likely the most important limiting factor for the lack of benefit observed in trials [139]. The HF-ACTION trial, a larger multicenter RCT which aimed to investigate effects of exercise training on mortality and safety, failed to meet expectations, probably because patient's participation in training programs was on average 1.8 times/week compared to 3 times/week foreseen by protocol [22].

In EXERT trial HF patients performed aerobic and resistance training for 30 minutes 2 times/week for at least 9 months, of which first 3 months under supervision; the investigator found a reduction in number of training sessions when performed at home [140].

Therefore, trying to improve patients' adherence to training program could be the best way to improve its effectiveness. It is mandatory to consider that adherence to training program is always more difficult than pharmacological therapy, as it requires more dedicated time.

Furthermore, adherence is affected by patient-related factors, such as severity of symptoms, age, sex, comorbidities and socioeconomic status, and by factors related to the rehabilitation center, such as logistics and availability of physician [141–146].

To improve patient's adherence, it is important to be very clear in explaining the number of training sessions, the effort to be made during exercise and its duration and, above all, the exercise modalities. Supervised and encouraged exercise is the best way to keep patients motivated [139], so it is advisable to increase duration of supervised exercise phase during trials.

Initiatives aiming at encouraging patients' adherence to cardiac rehabilitation, such as TAKEheart (Training Awareness Knowledge Engagement) by AHRQ (Agency for Healthcare Research and Quality, more information to https://takeheart.ahrq.gov) pave the way for improving attendance to exercise-based cardiac rehabilitation programs.

Promoting exercise group sessions and psychological support for patient without family/friends support could represent a valid strategy for improving adherence to training programs. This modality has been successfully used in other conditions (i.e., cancer) [147], but data are still lacking for cardiovascular diseases. However, during COVID-19 pandemic, this option does not seem preferable at present and it is discouraged by Healthcare stakeholders [133–136].

Finally, it is important to ensure that training benefits are clear to patients; the self-efficacy technique was investigated to keep compliance high [148,149]. Questionnaires and diaries filled in by patients can be used to monitor progress of training protocol.

10. Conclusions

Exercise training is widely recognized as an evidence-based adjunct treatment modality for patients with HF, and growing evidence is emerging among elderly patients with HF. Exercise training exerts both central and peripheral adaptations that clinically translate into anti-remodeling effects, increased functional capacity and reduced morbidity and mortality. Ideally, exercise training programs should be prescribed in a patient-tailored approach, particularly in frail elderly patients with HF. Increasing long-term adherence and reaching the frailest patients are challenging goals for future initiatives in the field.

Author Contributions

Conceptualization—FG and GiaC; methodology—FG and GiaC; validation—FG and GiaC; resources—ADL, RP, MP; data curation—GiuC, FPI, AT; writing—original draft preparation—GiaC, AT, ADL, CV, GI, RP, AndD, CT, FG, AP; writing—review and editing—GiaC, PM, AntD, GiuC, EV, GI, FG; visualization—FG, CV, GI, EV; supervision—GiaC, CV, FG; project administration—FG. All authors have read and agreed to the published version of the manuscript.

Ethics Approval and Consent to Participate

Not applicable.

Acknowledgment

Not applicable.

Funding

This research received no external funding.

Conflict of Interest

The authors declare no conflict of interest. Francesco Giallauria is serving as one of the Editorial Board members of this journal. We declare that Francesco Giallauria had no involvement in the peer review of this article and has no access to information regarding its peer review. Full responsibility for the editorial process for this article was delegated to Kazuhiro P. Izawa and Peter H. Brubaker.

References

[1] Gheorghiade M, Ambrosy A. Heart failure in 2010: one step forward, two steps back. Nature Reviews Cardiology. 2011; 8: 72–73.

[2] Groenewegen A, Rutten FH, Mosterd A, Hoes AW. Epidemiology of heart failure. European Journal of Heart Failure. 2020; 22: 1342–1356.

[3] Guo L, Guo X, Chang Y, Yang J, Zhang L, Li T, *et al*. Prevalence and Risk Factors of Heart Failure with Preserved Ejection Fraction: A Population-Based Study in Northeast China. International Journal of Environmental Research and Public Health. 2016;13: 770.

[4] GBD 2017 Disease and Injury Incidence and Prevalence Collaborators. Global, regional, and national incidence, prevalence, and years lived with disability for 354 diseases and injuries for 195 countries and territories, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017. Lancet. 2018; 392: 1789–1858.

[5] Cook C, Cole G, Asaria P, Jabbour R, Francis DP. The annual global economic burden of heart failure. International Journal of Cardiology. 2014; 171: 368–376.

[6] Ferrucci L, Giallauria F, Guralnik JM. Epidemiology of aging. Radiologic Clinics of North America. 2008; 46: 643–652, v.

[7] García-Olmos L, Batlle M, Aguilar R, Porro C, Carmona M, Alberquilla A, *et al*. Disability and quality of life in heart failure patients: a cross-sectional study. Family Practice. 2019; 36: 693–698.

[8] Giallauria F, Di Lorenzo A, Venturini E, Pacileo M, D'Andrea A, Garofalo U, *et al*. Frailty in Acute and Chronic Coronary Syndrome Patients Entering Cardiac Rehabilitation. Journal of Clinical Medicine. 2021; 10: 1696.

[9] Marinus N, Vigorito C, Giallauria F, Haenen L, Jansegers T, Dendale P, *et al*. Frailty is highly prevalent in specific cardiovascular diseases and females, but significantly worsens prognosis in all affected patients: a systematic review. Ageing Research Reviews. 2021; 66: 101233.

[10] Calvert MJ, Freemantle N, Cleland JGF. The impact of chronic heart failure on health-related quality of life data acquired in the baseline phase of the CARE-HF study. European Journal of Heart Failure. 2005; 7: 243–251.

[11] Alpert CM, Smith MA, Hummel SL, Hummel EK. Symptom burden in heart failure: assessment, impact on outcomes, and management. Heart Failure Reviews. 2017; 22: 25–39.

[12] Lewis EF, Lamas GA, O'Meara E, Granger CB, Dunlap ME, McKelvie RS, *et al*. Characterization of health-related quality of life in heart failure patients with preserved versus low ejection fraction in CHARM. European Journal of Heart Failure. 2007; 9: 83–91.

[13] Murphy SP, Ibrahim NE, Januzzi JL. Heart Failure with Reduced Ejection Fraction: A Review. Journal of the American Medical Association. 2020; 324: 488–504.

[14] Dunlay SM, Roger VL, Redfield MM. Epidemiology of heart failure with preserved ejection fraction. Nature Reviews Cardiology. 2017; 14: 591–602.

[15] McDonagh TA, Metra M, Adamo M, Gardner RS, Baumbach A, Böhm M, *et al*. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. European Heart Journal. 2021; 42: 3599–3726.

[16] Adachi T, Iritani N, Kamiya K, Iwatsu K, Kamisaka K, Iida Y, *et al*. Prognostic Effects of Cardiac Rehabilitation in Patients with Heart Failure (from a Multicenter Prospective Cohort Study). The American Journal of Cardiology. 2022; 164: 79–85.

[17] Kamiya K, Sato Y, Takahashi T, Tsuchihashi-Makaya M, Kotooka N, Ikegame T, *et al*. Multidisciplinary Cardiac Rehabilitation and Long-Term Prognosis in Patients with Heart Failure. Circulation Heart Failure. 2020; 13: e006798.

[18] Taylor RS, Walker S, Ciani O, Warren F, Smart NA, Piepoli M, *et al*. Exercise-based cardiac rehabilitation for chronic heart failure: the EXTRAMATCH II individual participant data meta-analysis. Health Technology Assessment. 2019; 23: 1–98.

[19] Kaneko H, Itoh H, Kamiya K, Morita K, Sugimoto T, Konishi M, *et al*. Acute-phase initiation of cardiac rehabilitation and clinical outcomes in hospitalized patients for acute heart failure. International Journal of Cardiology. 2021; 340: 36–41.

[20] Kono Y, Izawa H, Aoyagi Y, Ishikawa A, Sugiura T, Mori E, *et al*. Predictive impact of early mobilization on rehospitalization for elderly Japanese heart failure patients. Heart and Vessels. 2020; 35: 531–536.

[21] Dalal HM, Wingham J, Palmer J, Taylor R, Petre C, Lewin R. Why do so few patients with heart failure participate in cardiac rehabilitation? A cross-sectional survey from England, Wales and Northern Ireland. BMJ Open. 2012; 2: e000787.

[22] O'Connor CM, Whellan DJ, Lee KL, Keteyian SJ, Cooper LS, Ellis SJ, *et al*. Efficacy and Safety of Exercise Training in Patients with Chronic Heart Failure: HF-ACTION randomized controlled trial. Journal of the American Medical Association 2009; 301: 1439–1450.

[23] Wisløff U, Støylen A, Loennechen JP, Bruvold M, Rognmo Ø, Haram PM, *et al*. Superior cardiovascular effect of aerobic interval training versus moderate continuous training in heart failure patients: a randomized study. Circulation. 2007; 115: 3086–3094.

[24] Mandic S, Myers J, Selig SE, Levinger I. Resistance versus aerobic exercise training in chronic heart failure. Current Heart Failure Reports. 2012; 9: 57–64.

[25] Laoutaris ID, Piotrowicz E, Kallistratos MS, Dritsas A, Dimaki N, Miliopoulos D, *et al*. Combined aerobic/resistance/inspiratory muscle training as the 'optimum' exercise programme for patients with chronic heart failure: ARISTOS-HF randomized clinical trial. European Journal of Preventive Cardiology. 2021; 28: 1626–1635.

[26] Ezekowitz JA, O'Meara E, McDonald MA, Abrams H, Chan M, Ducharme A, *et al*. 2017 Comprehensive Update of the Canadian Cardiovascular Society Guidelines for the Management of Heart Failure. The Canadian Journal of Cardiology. 2017; 33: 1342–1433.

[27] Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE, Drazner MH, *et al*. 2013 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. Journal of the American College of Cardiology. 2013; 62: e147–e239.

[28] Brown TM, Hernandez AF, Bittner V, Cannon CP, Ellrodt G, Liang L, *et al*. Predictors of Cardiac Rehabilitation Referral in Coronary Artery Disease Patients: findings from the American Heart Association's Get with The Guidelines Program. Journal of the American College of Cardiology. 2009; 54: 515–521.

[29] Hellsten Y, Nyberg M. Cardiovascular Adaptations to Exercise Training. Comprehensive Physiology. 2015; 6: 1–32.

[30] Zavorsky GS. Evidence and possible mechanisms of altered maximum heart rate with endurance training and tapering. Sports Medicine. 2000; 29: 13–26.

[31] Arbab-Zadeh A, Perhonen M, Howden E, Peshock RM, Zhang R, Adams-Huet B, *et al*. Cardiac remodeling in response to 1 year of intensive endurance training. Circulation. 2014; 130: 2152–2161.

[32] Acanfora D, Scicchitano P, Casucci G, Lanzillo B, Capuano N, Furgi G, *et al*. Exercise training effects on elderly and middle-age patients with chronic heart failure after acute decompensation: a randomized, controlled trial. International Journal of Cardiology. 2016; 225: 313–323.

[33] Braith RW, Edwards DG. Neurohormonal abnormalities in heart failure: impact of exercise training. Congestive Heart Failure. 2003; 9: 70–76.

[34] Tanai E, Frantz S. Pathophysiology of Heart Failure. Comprehensive Physiology. 2015; 6: 187–214.

[35] Giallauria F, Vitale G, Pacileo M, Di Lorenzo A, Oliviero A, Passaro F, *et al*. Sacubitril/Valsartan Improves Autonomic Function and Cardiopulmonary Parameters in Patients with Heart Failure with Reduced Ejection Fraction. Journal of Clinical Medicine. 2020; 9: E1897.

[36] Giallauria F, De Lorenzo A, Pilerci F, Manakos A, Lucci R, Psaroudaki M, *et al*. Long-term effects of cardiac rehabilitation on end-exercise heart rate recovery after myocardial infarction. European Journal of Cardiovascular Prevention and Rehabilitation. 2006; 13: 544–550.

[37] Giallauria F, Lucci R, Pietrosante M, Gargiulo G, De Lorenzo A, D'Agostino M, *et al*. Exercise-Based Cardiac Rehabilitation Improves Heart Rate Recovery in Elderly Patients after Acute Myocardial Infarction. Journals of Gerontology - Series A Biological Sciences and Medical Sciences. 2006; 61: 713–717.

[38] Giallauria F, Del Forno D, Pilerci F, De Lorenzo A, Manakos A, Lucci R, *et al*. Improvement of heart rate recovery after exercise training in older people. Journal of the American Geriatrics Society. 2005; 53: 2037–2038.

[39] Giallauria F, Galizia G, Lucci R, D'Agostino M, Vitelli A, Maresca L, *et al*. Favourable effects of exercise-based Cardiac Rehabilitation after acute myocardial infarction on left atrial remodeling. International Journal of Cardiology. 2009; 136: 300–306.

[40] Passino C, Severino S, Poletti R, Piepoli MF, Mammini C, Clerico A, *et al*. Aerobic training decreases B-type natriuretic peptide expression and adrenergic activation in patients with heart failure. Journal of the American College of Cardiology. 2006; 47: 1835–1839.

[41] Rengo G, Galasso G, Femminella GD, Parisi V, Zincarelli C, Pagano G, *et al*. Reduction of lymphocyte G protein-coupled receptor kinase-2 (GRK2) after exercise training predicts survival in patients with heart failure. European Journal of Preventive Cardiology. 2014; 21: 4–11.

[42] Smart NA, Meyer T, Butterfield JA, Faddy SC, Passino C, Malfatto G, *et al*. Individual patient meta-analysis of exercise training effects on systemic brain natriuretic peptide expression in heart failure. European Journal of Preventive Cardiology. 2012; 19: 428–435.

[43] Giallauria F, Cirillo P, Lucci R, Pacileo M, De Lorenzo A, D'Agostino M, *et al*. Left ventricular remodelling in patients with moderate systolic dysfunction after myocardial infarction: favourable effects of exercise training and predictive role of N-terminal pro-brain natriuretic peptide. European Journal of Cardiovascular Prevention and Rehabilitation. 2008; 15: 113–118.

[44] Parker L, Trewin A, Levinger I, Shaw CS, Stepto NK. Exercise-intensity dependent alterations in plasma redox status do not reflect skeletal muscle redox-sensitive protein signaling. Journal of Science and Medicine in Sport. 2018; 21: 416–421.

[45] Gielen S, Adams V, Möbius-Winkler S, Linke A, Erbs S, Yu J, *et al*. Anti-inflammatory effects of exercise training in the skeletal muscle of patients with chronic heart failure. Journal of the American College of Cardiology. 2003; 42: 861–868.

[46] Giallauria F, Cirillo P, D'agostino M, Petrillo G, Vitelli A, Pacileo M, *et al*. Effects of Exercise Training on High-Mobility Group Box-1 Levels after Acute Myocardial Infarction. Journal of Cardiac Failure. 2011; 17: 108–114.

[47] Rengo G, Parisi V, Femminella GD, Pagano G, de Lucia C, Cannavo A, *et al*. Molecular aspects of the cardioprotective effect of exercise in the elderly. Aging Clinical and Experimental Research. 2013; 25: 487–497.

[48] Vega RB, Konhilas JP, Kelly DP, Leinwand LA. Molecular Mechanisms Underlying Cardiac Adaptation to Exercise. Cell Metabolism. 2017; 25: 1012–1026.

[49] Franzoni F, Ghiadoni L, Galetta F, Plantinga Y, Lubrano V, Huang Y, *et al*. Physical activity, plasma antioxidant capacity, and endothelium-dependent vasodilation in young and older men. American Journal of Hypertension. 2005; 18: 510–516.

[50] Erbs S, Höllriegel R, Linke A, Beck EB, Adams V, Gielen S, *et al*. Exercise training in patients with advanced chronic heart failure (NYHA IIIb) promotes restoration of peripheral vasomotor function, induction of endogenous regeneration, and improvement of left ventricular function. Circulation Heart Failure. 2010; 3: 486–494.

[51] Pedralli ML, Marschner RA, Kollet DP, Neto SG, Eibel B, Tanaka H, *et al*. Different exercise training modalities produce similar endothelial function improvements in individuals with prehypertension or hypertension: a randomized clinical trial Exercise, endothelium and blood pressure. Scientific Reports. 2020; 10: 7628.
[52] Malhotra R, Bakken K, D'Elia E, Lewis GD. Cardiopulmonary Exercise Testing in Heart Failure. JACC: Heart Failure. 2016; 4: 607–616.
[53] Berry JD, Pandey A, Gao A, Leonard D, Farzaneh-Far R, Ayers C, *et al*. Physical Fitness and Risk for Heart Failure and Coronary Artery Disease. Circulation Heart Failure. 2013; 6: 627–634.
[54] Pandey A, Garg S, Khunger M, Darden D, Ayers C, Kumbhani DJ, *et al*. Dose-Response Relationship between Physical Activity and Risk of Heart Failure: A Meta-Analysis. Circulation. 2015; 132: 1786–1794.
[55] Pandey A, Allen NB, Ayers C, Reis JP, Moreira HT, Sidney S, *et al*. Fitness in Young Adulthood and Long-Term Cardiac Structure and Function: the CARDIA Study. JACC: Heart Failure. 2017; 5: 347–355.
[56] Dieberg G, Ismail H, Giallauria F, Smart NA. Clinical outcomes and cardiovascular responses to exercise training in heart failure patients with preserved ejection fraction: a systematic review and meta-analysis. Journal of Applied Physiology. 2015; 119: 726–733.
[57] Gomes Neto M, Durães AR, Conceição LSR, Saquetto MB, Ellingsen Ø, Carvalho VO. High intensity interval training versus moderate intensity continuous training on exercise capacity and quality of life in patients with heart failure with reduced ejection fraction: a systematic review and meta-analysis. International Journal of Cardiology. 2018; 261: 134–141.
[58] Piepoli MF, Conraads V, Corrà U, Dickstein K, Francis DP, Jaarsma T, *et al*. Exercise training in heart failure: from theory to practice. a consensus document of the Heart Failure Association and the European Association for Cardiovascular Prevention and Rehabilitation. European Journal of Heart Failure. 2011; 13: 347–357.
[59] Giannitsi S, Bougiakli M, Bechlioulis A, Kotsia A, Michalis LK, Naka KK. 6-minute walking test: a useful tool in the management of heart failure patients. Therapeutic Advances in Cardiovascular Disease. 2019; 13: 1753944719870084.
[60] Keteyian SJ. Exercise training in congestive heart failure: risks and benefits. Progress in Cardiovascular Diseases. 2011; 53: 419–428.
[61] Corrà U. Cardiopulmonary exercise testing in systolic heart failure: from basic to advanced practice. Monaldi Archives for Chest Disease. 2016; 86: 757.
[62] Smart NA, Dieberg G, Giallauria F. Intermittent versus continuous exercise training in chronic heart failure: a meta-analysis. International Journal of Cardiology. 2013; 166: 352–358.
[63] Freyssin C, Verkindt C, Prieur F, Benaich P, Maunier S, Blanc P. Cardiac rehabilitation in chronic heart failure: effect of an 8-week, high-intensity interval training versus continuous training. Archives of Physical Medicine and Rehabilitation. 2012; 93: 1359–1364.
[64] Iellamo F, Manzi V, Caminiti G, Vitale C, Castagna C, Massaro M, *et al*. Matched dose interval and continuous exercise training induce similar cardiorespiratory and metabolic adaptations in patients with heart failure. International Journal of Cardiology. 2013; 167: 2561–2565.
[65] Koufaki P, Mercer TH, George KP, Nolan J. Low-volume high-intensity interval training vs continuous aerobic cycling in patients with chronic heart failure: a pragmatic randomised clinical trial of feasibility and effectiveness. Journal of Rehabilitation Medicine. 2014; 46: 348–356.
[66] Ellingsen Ø, Halle M, Conraads V, Støylen A, Dalen H, Delagardelle C, *et al*. High-Intensity Interval Training in Patients with Heart Failure with Reduced Ejection Fraction. Circulation. 2017; 135: 839–849.
[67] Pollock ML, Franklin BA, Balady GJ, Chaitman BL, Fleg JL, Fletcher B, *et al*. AHA Science Advisory. Resistance exercise in individuals with and without cardiovascular disease: benefits, rationale, safety, and prescription: an advisory from the Committee on Exercise, Rehabilitation, and Prevention, Council on Clinical Cardiology, American Heart Association; Position paper endorsed by the American College of Sports Medicine. Circulation. 2000; 101: 828–833.
[68] Mitchell JH, Wildenthal K. Static (isometric) exercise and the heart: physiological and clinical considerations. Annual Review of Medicine. 1974; 25: 369–381.
[69] Volaklis KA, Tokmakidis SP. Resistance exercise training in patients with heart failure. Sports Medicine. 2005; 35: 1085–1103.
[70] Jewiss D, Ostman C, Smart NA. The effect of resistance training on clinical outcomes in heart failure: a systematic review and meta-analysis. International Journal of Cardiology. 2016; 221: 674–681.
[71] Georgantas A, Dimopoulos S, Tasoulis A, Karatzanos E, Pantsios C, Agapitou V, *et al*. Beneficial effects of combined exercise training on early recovery cardiopulmonary exercise testing indices in patients with chronic heart failure. Journal of Cardiopulmonary Rehabilitation and Prevention. 2014; 34: 378–385.
[72] Anagnostakou V, Chatzimichail K, Dimopoulos S, Karatzanos E, Papazachou O, Tasoulis A, *et al*. Effects of Interval Cycle Training with or without Strength Training on Vascular Reactivity in Heart Failure Patients. Journal of Cardiac Failure. 2011; 17: 585–591.
[73] Cahalin LP, Arena RA. Breathing exercises and inspiratory muscle training in heart failure. Heart Failure Clinics. 2015; 11: 149–172.
[74] Tikunov B, Levine S, Mancini D. Chronic congestive heart failure elicits adaptations of endurance exercise in diaphragmatic muscle. Circulation. 1997; 95: 910–916.
[75] Mello PR, Guerra GM, Borile S, Rondon MU, Alves MJ, Negrão CE, *et al*. Inspiratory muscle training reduces sympathetic nervous activity and improves inspiratory muscle weakness and quality of life in patients with chronic heart failure: a clinical trial. Journal of Cardiopulmonary Rehabilitation and Prevention. 2012; 32: 255–261.
[76] Palau P, Domínguez E, Núñez E, Schmid J, Vergara P, Ramón JM, *et al*. Effects of inspiratory muscle training in patients with heart failure with preserved ejection fraction. European Journal of Preventive Cardiology. 2014; 21: 1465–1473.
[77] Marco E, Ramírez-Sarmiento AL, Coloma A, Sartor M, Comin-Colet J, Vila J, *et al*. High-intensity vs. sham inspiratory muscle training in patients with chronic heart failure: a prospective randomized trial. European Journal of Heart Failure. 2013; 15: 892–901.
[78] Adamopoulos S, Schmid J, Dendale P, Poerschke D, Hansen D, Dritsas A, *et al*. Combined aerobic/inspiratory muscle training vs. aerobic training in patients with chronic heart failure: the Vent-HeFT trial: a European prospective multicentre randomized trial. European Journal of Heart Failure. 2014; 16: 574–582.
[79] Dobsák P, Nováková M, Fiser B, Siegelová J, Balcárková P, Spinarová L, *et al*. Electrical stimulation of skeletal muscles. an alternative to aerobic exercise training in patients with chronic heart failure? International Heart Journal. 2006; 47: 441–453.
[80] Smart NA, Dieberg G, Giallauria F. Functional electrical stimulation for chronic heart failure: a meta-analysis. International Journal of Cardiology. 2013; 167: 80–86.

[81] Cornelis J, Beckers P, Taeymans J, Vrints C, Vissers D. Comparing exercise training modalities in heart failure: a systematic review and meta-analysis. International Journal of Cardiology. 2016; 221: 867–876.
[82] Cohen-Solal A, Tabet JY, Logeart D, Bourgoin P, Tokmakova M, Dahan M. A non-invasively determined surrogate of cardiac power ('circulatory power') at peak exercise is a powerful prognostic factor in chronic heart failure. European Heart Journal. 2002; 23: 806–814.
[83] Nicholls D. Circulatory power—a new perspective on an old friend. European Heart Journal. 2002; 23: 1242–1245.
[84] Borlaug BA. The pathophysiology of heart failure with preserved ejection fraction. Nature Reviews Cardiology. 2014; 11: 507–515.
[85] Obokata M, Olson TP, Reddy YNV, Melenovsky V, Kane GC, Borlaug BA. Haemodynamics, dyspnoea, and pulmonary reserve in heart failure with preserved ejection fraction. European Heart Journal. 2018; 39: 2810–2821.
[86] Fujiwara K, Shimada K, Nishitani-Yokoyama M, Kunimoto M, Matsubara T, Matsumori R, *et al*. Arterial Stiffness Index and Exercise Tolerance in Patients Undergoing Cardiac Rehabilitation. International Heart Journal. 2021; 62: 230–237.
[87] Thompson RB, Tomczak CR, Haykowsky MJ. Evaluation of Cardiac, Vascular, and Skeletal Muscle Function with MRI: Novel Physiological End Points in Cardiac Rehabilitation Research. The Canadian Journal of Cardiology. 2016; 32: S388–S396.
[88] Haykowsky MJ, Brubaker PH, Morgan TM, Kritchevsky S, Eggebeen J, Kitzman DW. Impaired aerobic capacity and physical functional performance in older heart failure patients with preserved ejection fraction: role of lean body mass. Journals of Gerontology - Series A Biological Sciences and Medical Sciences. 2013; 68: 968–975.
[89] Haykowsky MJ, Kouba EJ, Brubaker PH, Nicklas BJ, Eggebeen J, Kitzman DW. Skeletal muscle composition and its relation to exercise intolerance in older patients with heart failure and preserved ejection fraction. The American Journal of Cardiology. 2014; 113: 1211–1216.
[90] Kitzman DW, Brubaker PH, Morgan TM, Stewart KP, Little WC. Exercise training in older patients with heart failure and preserved ejection fraction: a randomized, controlled, single-blind trial. Circulation Heart Failure. 2010; 3: 659–667.
[91] Pandey A, Parashar A, Kumbhani D, Agarwal S, Garg J, Kitzman D, *et al*. Exercise training in patients with heart failure and preserved ejection fraction: meta-analysis of randomized control trials. Circulation Heart Failure. 2015; 8: 33–40.
[92] Haykowsky MJ, Brubaker PH, Stewart KP, Morgan TM, Eggebeen J, Kitzman DW. Effect of endurance training on the determinants of peak exercise oxygen consumption in elderly patients with stable compensated heart failure and preserved ejection fraction. Journal of the American College of Cardiology. 2012; 60: 120–128.
[93] Fujimoto N, Prasad A, Hastings JL, Bhella PS, Shibata S, Palmer D, *et al*. Cardiovascular effects of 1 year of progressive endurance exercise training in patients with heart failure with preserved ejection fraction. American Heart Journal. 2012; 164: 869–877.
[94] Angadi SS, Mookadam F, Lee CD, Tucker WJ, Haykowsky MJ, Gaesser GA. High-intensity interval training vs. moderate-intensity continuous exercise training in heart failure with preserved ejection fraction: a pilot study. Journal of Applied Physiology. 2015; 119: 753–758.
[95] Donelli da Silveira A, Beust de Lima J, da Silva Piardi D, dos Santos Macedo D, Zanini M, Nery R, *et al*. High-intensity interval training is effective and superior to moderate continuous training in patients with heart failure with preserved ejection fraction: a randomized clinical trial. European Journal of Preventive Cardiology. 2020; 27: 1733–1743.
[96] Mueller S, Winzer EB, Duvinage A, Gevaert AB, Edelmann F, Haller B, *et al*. Effect of High-Intensity Interval Training, Moderate Continuous Training, or Guideline-Based Physical Activity Advice on Peak Oxygen Consumption in Patients with Heart Failure with Preserved Ejection Fraction: A Randomized Clinical Trial. Journal of the American Medical Association. 2021; 325: 542–551.
[97] Baral N, Changezi HU, Khan MR, Adhikari G, Adhikari P, Khan HMW, *et al*. Inspiratory Muscle Training in Patients with Heart Failure with Preserved Ejection Fraction: A Meta-Analysis. Cureus. 2020; 12: e12260.
[98] Jackson AS, Beard EF, Wier LT, Ross RM, Stuteville JE, Blair SN. Changes in aerobic power of men, ages 25–70 yr. Medicine and Science in Sports and Exercise. 1995; 27: 113–120.
[99] Austin J, Williams R, Ross L, Moseley L, Hutchison S. Randomised controlled trial of cardiac rehabilitation in elderly patients with heart failure. European Journal of Heart Failure. 2005; 7: 411–417.
[100] Antonicelli R, Spazzafumo L, Scalvini S, Olivieri F, Matassini MV, Parati G, *et al*. Exercise: a "new drug" for elderly patients with chronic heart failure. Aging. 2016; 8: 860–872.
[101] Pu CT, Johnson MT, Forman DE, Hausdorff JM, Roubenoff R, Foldvari M, *et al*. Randomized trial of progressive resistance training to counteract the myopathy of chronic heart failure. Journal of Applied Physiology. 2001; 90: 2341–2350.
[102] Giallauria F, Lucci R, De Lorenzo A, D'Agostino M, Del Forno D, Vigorito C. Favourable effects of exercise training on N-terminal pro-brain natriuretic peptide plasma levels in elderly patients after acute myocardial infarction. Age and Ageing. 2006; 35: 601–607.
[103] Drexler H, Riede U, Münzel T, König H, Funke E, Just H. Alterations of skeletal muscle in chronic heart failure. Circulation. 1992; 85: 1751–1759.
[104] Vigorito C, Giallauria F. Effects of exercise on cardiovascular performance in the elderly. Frontiers in Physiology. 2014; 5: 51.
[105] Suzuki T, Palus S, Springer J. Skeletal muscle wasting in chronic heart failure. ESC Heart Failure. 2018; 5: 1099–1107.
[106] Maiorana A, O'Driscoll G, Cheetham C, Collis J, Goodman C, Rankin S, *et al*. Combined aerobic and resistance exercise training improves functional capacity and strength in CHF. Journal of Applied Physiology. 2000; 88: 1565–1570.
[107] Slimani M, Ramirez-Campillo R, Paravlic A, Hayes LD, Bragazzi NL, Sellami M. The Effects of Physical Training on Quality of Life, Aerobic Capacity, and Cardiac Function in Older Patients with Heart Failure: A Meta-Analysis. Frontiers in Physiology. 2018; 9: 1564.
[108] Anker SD, Ponikowski P, Varney S, Chua TP, Clark AL, Webb-Peploe KM, *et al*. Wasting as independent risk factor for mortality in chronic heart failure. Lancet. 1997; 349: 1050–1053.
[109] Ponikowski P, Piepoli M, Chua TP, Banasiak W, Francis D, Anker SD, *et al*. The impact of cachexia on cardiorespiratory reflex control in chronic heart failure. European Heart Journal. 1999; 20: 1667–1675.
[110] Ponikowski PP, Chua TP, Francis DP, Capucci A, Coats AJ, Piepoli MF. Muscle ergoreceptor overactivity reflects deterioration in clinical status and cardiorespiratory reflex control in chronic heart failure. Circulation. 2001; 104: 2324–2330.
[111] Ridda I, Lindley R, MacIntyre RC. The challenges of clinical trials in the exclusion zone: the case of the frail elderly. Australasian Journal on Ageing. 2008; 27: 61–66.
[112] Reeves GR, Whellan DJ, O'Connor CM, Duncan P, Eggebeen JD, Morgan TM, *et al*. A Novel Rehabilitation Intervention for Older Patients with Acute Decompensated Heart Failure: the REHAB-HF Pilot Study. JACC: Heart Failure. 2017; 5: 359–

366.
[113] Pavasini R, Guralnik J, Brown JC, di Bari M, Cesari M, Landi F, *et al*. Short Physical Performance Battery and all-cause mortality: systematic review and meta-analysis. BMC Medicine. 2016; 14: 215.
[114] Piepoli MF, Davos C, Francis DP, Coats AJS. Exercise training meta-analysis of trials in patients with chronic heart failure (ExTraMATCH). British Medical Journal. 2004; 328: 189.
[115] Long L, Mordi IR, Bridges C, Sagar VA, Davies EJ, Coats AJ, *et al*. Exercise-based cardiac rehabilitation for adults with heart failure. Cochrane Database of Systematic Reviews. 2019; 1: CD003331.
[116] Figliozzi S, Masci PG, Ahmadi N, Tondi L, Koutli E, Aimo A, *et al*. Predictors of adverse prognosis in COVID-19: A systematic review and meta-analysis. European Journal of Clinical Investigation. 2020; 50: e13362.
[117] Ssentongo P, Ssentongo AE, Heilbrunn ES, Ba DM, Chinchilli VM. Association of cardiovascular disease and 10 other pre-existing comorbidities with COVID-19 mortality: A systematic review and meta-analysis. PLoS ONE. 2020; 15: e0238215.
[118] Kuster GM, Pfister O, Burkard T, Zhou Q, Twerenbold R, Haaf P, *et al*. SARS-CoV2: should inhibitors of the renin-angiotensin system be withdrawn in patients with COVID-19? European Heart Journal. 2020; 41: 1801–1803.
[119] Mancia G, Rea F, Ludergnani M, Apolone G, Corrao G. Renin-Angiotensin-Aldosterone System Blockers and the Risk of Covid-19. New England Journal of Medicine. 2020; 382: 2431–2440.
[120] Bean DM, Kraljevic Z, Searle T, Bendayan R, Kevin O, Pickles A, *et al*. Angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers are not associated with severe COVID-19 infection in a multi-site UK acute hospital trust. European Journal of Heart Failure. 2020; 22: 967–974.
[121] Guzik TJ, Mohiddin SA, Dimarco A, Patel V, Savvatis K, Marelli-Berg FM, *et al*. COVID-19 and the cardiovascular system: implications for risk assessment, diagnosis, and treatment options. Cardiovascular Research. 2020; 116: 1666–1687.
[122] Hunt RH, East JE, Lanas A, Malfertheiner P, Satsangi J, Scarpignato C, *et al*. COVID-19 and Gastrointestinal Disease: Implications for the Gastroenterologist. Digestive Diseases. 2021; 39: 119–139.
[123] Montalvan V, Lee J, Bueso T, De Toledo J, Rivas K. Neurological manifestations of COVID-19 and other coronavirus infections: a systematic review. Clinical Neurology and Neurosurgery. 2020; 194: 105921.
[124] Vakili K, Fathi M, Pezeshgi A, Mohamadkhani A, Hajiesmaeili M, Rezaei-Tavirani M, *et al*. Critical complications of COVID-19: a descriptive meta-analysis study. Reviews in Cardiovascular Medicine. 2020; 21: 433.
[125] Wool G, Miller J. The Impact of COVID-19 Disease on Platelets and Coagulation. Pathobiology. 2021; 88: 15–27.
[126] Siddiqi HK, Libby P, Ridker PM. COVID-19 - A vascular disease. Trends in Cardiovascular Medicine. 2021; 31: 1–5.
[127] Zou X, Chen K, Zou J, Han P, Hao J, Han Z. Single-cell RNA-seq data analysis on the receptor ACE2 expression reveals the potential risk of different human organs vulnerable to 2019-nCoV infection. Frontiers of Medicine. 2020; 14: 185–192.
[128] Bojkova D, Wagner JUG, Shumliakivska M, Aslan GS, Saleem U, Hansen A, *et al*. SARS-CoV-2 infects and induces cytotoxic effects in human cardiomyocytes. Cardiovascular Research. 2020; 116: 2207–2215.
[129] Dong N, Cai J, Zhou Y, Liu J, Li F. End-Stage Heart Failure with COVID-19: Strong Evidence of Myocardial Injury by 2019-nCoV. JACC: Heart Failure. 2020; 8: 515–517.
[130] Matsushita K, Marchandot B, Carmona A, Curtiaud A, El Idrissi A, Trimaille A, *et al*. Increased susceptibility to SARS-CoV-2 infection in patients with reduced left ventricular ejection fraction. ESC Heart Failure. 2021; 8: 380–389.
[131] Freaney PM, Shah SJ, Khan SS. COVID-19 and Heart Failure with Preserved Ejection Fraction. Journal of the American Medical Association. 2020; 324: 1499.
[132] Cunha PS, Laranjo S, Lourenço A, Rodrigues L, Cardoso I, Portugal G, *et al*. Lockdown measures for COVID-19 outbreak and variation in physical activity in patients with heart failure and cardiac implantable devices. IJC Heart & Vasculature. 2021; 37: 100906.
[133] Khera A, Baum SJ, Gluckman TJ, Gulati M, Martin SS, Michos ED, *et al*. Continuity of care and outpatient management for patients with and at high risk for cardiovascular disease during the COVID-19 pandemic: a scientific statement from the American Society for Preventive Cardiology. American Journal of Preventive Cardiology. 2020; 1: 100009.
[134] Grossman GB, Sellera CAC, Hossri CAC, Carreira LTF, Avanza AC Jr, Albuquerque PF, *et al*. Position Statement of the Brazilian Society of Cardiology Department of Exercise Testing, Sports Exercise, Nuclear Cardiology, and Cardiovascular Rehabilitation (DERC/SBC) on Activities Within its Scope of Practice During the COVID-19 Pandemic. Arquivos Brasileiros de Cardiologia. 2020; 115: 284–291.
[135] Mureddu GF, Ambrosetti M, Venturini E, La Rovere MT, Mazza A, Pedretti R, *et al*. Cardiac rehabilitation activities during the COVID-19 pandemic in Italy. Position Paper of the AICPR (Italian Association of Clinical Cardiology, Prevention and Rehabilitation). Monaldi Archives for Chest Disease. 2020; 90.
[136] Nakayama A, Takayama N, Kobayashi M, Hyodo K, Maeshima N, Takayuki F, *et al*. Remote cardiac rehabilitation is a good alternative of outpatient cardiac rehabilitation in the COVID-19 era. Environmental Health and Preventive Medicine. 2020; 25: 48.
[137] Yoo BW, Wenger NK. Gender Disparities in Cardiac Rehabilitation among Older Women: Key Opportunities to Improve Care. Clinics in Geriatric Medicine. 2019; 35: 587–594.
[138] Mathews L, Brewer LC. A Review of Disparities in Cardiac Rehabilitation: Evidence, Drivers, And Solutions. Journal of Cardiopulmonary Rehabilitation and Prevention. 2021; 41: 375–382.
[139] Conraads VM, Deaton C, Piotrowicz E, Santaularia N, Tierney S, Piepoli MF, *et al*. Adherence of heart failure patients to exercise: barriers and possible solutions: a position statement of the Study Group on Exercise Training in Heart Failure of the Heart Failure Association of the European Society of Cardiology. European Journal of Heart Failure. 2012; 14: 451–458.
[140] McKelvie RS, Teo KK, Roberts R, McCartney N, Humen D, Montague T, *et al*. Effects of exercise training in patients with heart failure: the Exercise Rehabilitation Trial (EXERT). American Heart Journal. 2002; 144: 23–30.
[141] Wingham J, Dalal HM, Sweeney KG, Evans PH. Listening to patients: choice in cardiac rehabilitation. European Journal of Cardiovascular Nursing. 2006; 5: 289–294.
[142] Jolly K, Taylor R, Lip GY, Greenfield S, Raftery J, Mant J, *et al*. The Birmingham Rehabilitation Uptake Maximisation Study (BRUM). Home-based compared with hospital-based cardiac rehabilitation in a multi-ethnic population: cost-effectiveness and patient adherence. Health Technology Assessment. 2007; 11: 1–118.
[143] Marzolini S, Mertens DJ, Oh PI, Plyley MJ. Self-reported compliance to home-based resistance training in cardiac patients. European Journal of Cardiovascular Prevention & Rehabilitation. 2010; 17: 35–49.
[144] Farley RL, Wade TD, Birchmore L. Factors influencing attendance at cardiac rehabilitation among coronary heart disease pa-

tients. European Journal of Cardiovascular Nursing. 2003; 2: 205–212.
[145] Parkosewich JA. Cardiac rehabilitation barriers and opportunities among women with cardiovascular disease. Cardiology in Review. 2008; 16: 36–52.
[146] Daly J, Sindone AP, Thompson DR, Hancock K, Chang E, Davidson P. Barriers to participation in and adherence to cardiac rehabilitation programs: a critical literature review. Progress in Cardiovascular Nursing. 2002; 17: 8–17.
[147] Sautier L, Mehnert A, Höcker A, Schilling G. Participation in patient support groups among cancer survivors: do psychosocial and medical factors have an impact? European Journal of Cancer Care. 2014; 23: 140–148.
[148] Gorodeski EZ, Goyal P, Cox ZL, Thibodeau JT, Reay RE, Rasmusson K, *et al*. Virtual Visits for Care of Patients with Heart Failure in the Era of COVID-19: a Statement from the Heart Failure Society of America. Journal of Cardiac Failure. 2020; 26: 448–456.
[149] Tierney S, Mamas M, Woods S, Rutter MK, Gibson M, Neyses L, *et al*. What strategies are effective for exercise adherence in heart failure? A systematic review of controlled studies. Heart Failure Reviews. 2012; 17: 107–115.