ARTICLE IN PRESS

Progress in Cardiovascular Diseases xxx (xxxx) xxx

Contents lists available at ScienceDirect

Progress in Cardiovascular Diseases

journal homepage: www.onlinepcd.com

Effect of physical exercise-based cardiac rehabilitation on frail patients with heart failure: focus on endothelial dysfunction

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ARTICLE INFO

Keywords:
Cardiac rehabilitation
Frailty
Heart failure
Endothelial dysfunction

ABSTRACT

This narrative review examines the interplay between frailty, heart failure (HF), and endothelial dysfunction, with a specific focus on the role of exercise-based cardiac rehabilitation (CR) in older and frail adults. Frailty and HF frequently coexist and share pathophysiological mechanisms — including chronic inflammation, oxidative stress, and impaired nitric oxide (NO) signaling — that exacerbate endothelial dysfunction and contribute to reduced functional capacity and poor prognosis. We synthesize current evidence linking endothelial impairment to both frailty and HF progression, and we evaluate findings from clinical trials investigating exercise-centered CR, hybrid CR, and cardiac telerehabilitation in this population.

Across studies, CR consistently improves physical performance, exercise tolerance, and quality of life, with several trials reporting measurable enhancements in endothelial function, such as improved flow-mediated dilation or increased mobilization of endothelial progenitor cells. Benefits appear strongest when programs are multidomain and individualized to the frailty phenotype, integrating aerobic, resistance, balance, and mobility training. However, heterogeneity in study designs, limited enrollment of frail older adults, and the frequent designation of endothelial outcomes as secondary endpoints constrain the ability to draw firm mechanistic conclusions. Overall, available evidence indicates that CR is a feasible and effective therapeutic strategy to counteract vascular dysfunction, reduce frailty severity, and potentially disrupt the negative cycle that accelerates HF progression in older patients. Future studies should prioritize frail populations, adopt standardized endothelial assessments as primary outcomes, and evaluate long-term clinical impact. Tailored CR models, including hybrid and telerehabilitation programs, are likely essential to improve access, adherence, and vascular outcomes in this vulnerable group.

Introduction

Frailty defines a multidimensional, chronic status of increased vulnerability to stressors due to decreased physiological reserve and resistance to disease. It often manifests as weakness, fatigue, and decreased physical activity while affecting virtually all body's organs and systems. Frailty is a common consequence of aging and is associated with higher risks of falls, hospitalization, cardiovascular diseases, mortality, and other adverse health events.[1]

Chronic heart failure (CHF) is a complex and debilitating syndrome characterized by the heart's inability to effectively meet the blood body's demands, affecting millions of individuals and placing a heavy burden on healthcare system worldwide.[2] CHF is a common condition in the elderly individuals, often coexisting with frailty.[3] Due to the global population aging, the prevalence of CHF among older adults continues to rise, creating a growing public health challenge. Notably, it is

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https://doi.org/10.1016/j.pcad.2026.05.001

Available online 6 May 2026

Please cite this article as: Rosanna Maniscalco et al., *Progress in Cardiovascular Diseases,* https://doi.org/10.1016/j.pcad.2026.05.001

estimated that up to 50% of elderly patients with CHF also experiences frailty,[4] highlighting the intricate link between these two geriatric syndromes.[4] The coexistence of CHF and frailty presents a complex clinical scenario characterized by a synergistic, detrimental impact on patient outcomes.[4]

While CHF can contribute to the development of frailty through mechanisms such as reduced physical activity, fatigue, and muscle wasting (cachexia), frailty itself can exacerbate CHF progression by limiting a patient's capacity for self-care, medication adherence, and tolerance to standard therapies.[5] This bidirectional relationship creates a vicious cycle, fueled by shared underlying pathophysiological pathways including chronic inflammation, hormonal imbalances, and oxidative stress, ultimately leading to a decline in overall health and functional status.[6,7] As a result, the concomitant presence of the two conditions represents a key risk factor for all-cause mortality and other poor outcomes.[8]

CHF is commonly classified according to left ventricle ejection fraction (LVEF), i.e. the proportion of blood pumped out by left ventricle during one contraction. When LVEF is less than 40%, the condition is defined as heart failure with reduced ejection fraction (HFrEF). Conversely, in heart failure with preserved ejection fraction (HFpEF), the LVEF is typically normal (i.e., $\geq$50%), but the heart's structural alterations impair ventricle relaxation during diastole.[9]

Among other mechanisms, endothelial dysfunction (ED) is central to the pathogenesis of HF, particularly in HFpEF.[10] Characterized by impaired nitric oxide (NO) production, increased vascular oxidative stress, and systemic inflammation, ED ultimately promoting vasoconstriction, high blood pressure, and a pro-thrombotic status.[11] ED is emerging also as a key driver of frailty, possibly linking cardiovascular diseases to organismal decline. Indeed, ED is a common condition in a plethora of diseases associated with an increased prevalence of frailty, e.g. hypertension, diabetes, and atherosclerosis.[12]

As a corollary, it is conceivable that targeting ED through lifestyle modifications and cardiovascular drugs might potentially mitigate frailty and its adverse outcomes in older adults. These interventions may include exercise training to improve muscle strength and endurance, nutritional support to prevent muscle wasting, innovative interventions and careful management of comorbidities to optimize overall health.[13,14] In particular, Cardiac Rehabilitation (CR) is considered a crucial component of the management strategies to improve or limit frailty in people with cardiovascular diseases.[6]

Here we briefly synthesize the role of ED in the pathogenesis of CHF in frail individuals to then review the literature reporting the effect of CR as an intervention for frail patients with CHF. Finally, we discuss the underlying mechanisms through which CR may exert its beneficial effects, as well as the challenges and future perspectives in integrating CR into standard care for CHF frailty patients.

ED in frail patients with CHF

ED is a recognized hallmark of CHF and plays a central role in its progression, particularly in frail older adults. The endothelium, the inner lining of blood vessels, regulates vascular tone, inflammation, and hemostasis through the balanced production of bioactive molecules, notably nitric oxide. In HF, endothelial cells exhibit impaired NO synthesis, reduced NO bioavailability, and increased oxidative stress. This critical imbalance leads to heightened vascular stiffness, abnormal vasodilation, and a pervasive pro-inflammatory state.[15,16] These phenomena profoundly contribute to the pathogenesis and progression of HF through several interconnected mechanisms.

Vasoconstriction and increased arterial stiffness elevate systemic blood pressure, significantly raising the workload on an already compromised heart and accelerating its functional decline.[17] Furthermore, ED in coronary arteries limits blood flow to the myocardium, especially during stress, promoting myocardial ischemia and contributing to further cardiac dysfunction.[18] Lastly, pro-inflammatory cytokines released from the dysfunctional endothelium directly impact cardiac muscle, fueling myocardial inflammation, promoting fibrosis and adverse cardiac remodeling.[19]

In frail patients, these pathophysiological processes are amplified. Indeed, frailty is characterized by systemic inflammation, sarcopenia (muscle wasting), and a decreased physiological reserve, overall promoting endothelial damage.[20] Elevated levels of inflammatory molecules such as interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α), commonly observed in frail HF patients, promote oxidative stress and reduce the activity of endothelial nitric oxide synthase (eNOS), the key enzyme for nitric oxide (NO) production.[21] The resulting decrease in NO availability disrupts vascular homeostasis, leading to impaired flow-mediated dilation (FMD), increased arterial stiffness, and reduced tissue perfusion.[22]

Moreover, mitochondrial dysfunction in endothelial cells further exacerbates oxidative stress in HF patients, especially those with frailty. Studies suggest that impaired mitochondrial dynamics result in excessive production of reactive oxygen species (ROS), which directly damage the endothelium and inhibit NO signaling pathways (Fig. 1).

This vicious cycle of oxidative damage and NO deficiency perpetuates endothelial dysfunction, contributing to reduced exercise tolerance and worsening frailty through several key mechanisms. Primarily, endothelial dysfunction compromises vasodilation in the skeletal muscle microvasculature, thereby limiting the adequate supply of oxygen and nutrients to active muscles during physical exertion. This inadequate perfusion directly leads to premature fatigue and reduced exercise performance.[23] Furthermore, ED can negatively influence mitochondrial function within skeletal muscle cells, disrupting cellular energy metabolism and resulting in reduced adenosine triphosphate (ATP) production. This bioenergetic impairment consequently diminishes the muscle's capacity for sustained activity and overall exercise tolerance.[24] Additionally, the combination of suboptimal muscle perfusion with chronic inflammation and oxidative stress associated with endothelial dysfunction significantly contributes to the development and progression of sarcopenia and generalized muscle weakness, further amplifying the severity of frailty in affected patients.[25]

Frailty itself profoundly impacts vascular function through multiple interconnected mechanisms. The sedentary lifestyle commonly associated with frailty significantly diminishes beneficial endothelial shear stress, reducing NO production and compromising vascular homeostasis.[26] Simultaneously, chronic low-grade inflammation elevates pro-inflammatory cytokines (IL-6, TNF-α), while mitochondrial dysfunction generates excessive oxidative stress, both directly impairing endothelial NO synthase activity. Furthermore, hormonal imbalances (reduced anabolic hormones IGF-1 and DHEA) and nutritional deficiencies (L-arginine, folate, vitamins C and D) inherent to the frail state further contribute to ED, establishing a self-reinforcing cycle of systemic decline. This intricate interdependence between frailty, sedentary behavior, and endothelial dysfunction underscores the critical need for tailored interventions to break this detrimental cycle[27] (Fig. 2). (See Fig. 3.)

An additional hallmark of vascular endothelial dysfunction is the altered number and functionality of both endothelial progenitor cells (EPCs) and circulating endothelial cells (CECs).[28] CECs are mature, terminally differentiated endothelial cells that are released in the bloodstream in response to endothelial damage or cardiovascular injury. An elevated CECs number is often considered a biomarker of endothelial injury and dysfunction, as their increased presence in circulation reflects ongoing vascular damage, impaired endothelial integrity, and reduced regenerative capacity.[29] On the other hand, EPCs originate from the bone marrow and act as key contributors to endothelial repair, vascular regeneration, and angiogenesis. These progenitor cells are mobilized into circulation in response to endothelial injury and are held to restore endothelial function and promote neovascularization.[30] EPCs exert their beneficial effects through the secretion of pro-angiogenic factors, such as vascular endothelial growth factor and stromal-derived factor-1,

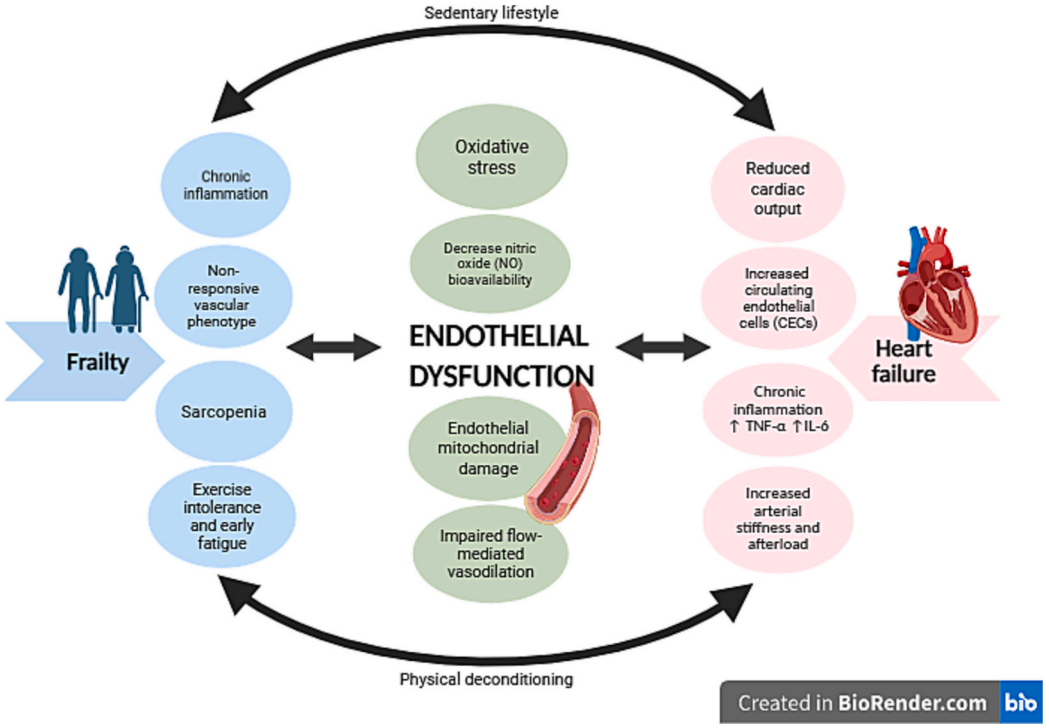

Fig. 1. Mechanisms of ROS overproduction and its effects on endothelial and myocardial function. Reduced signaling through AT1R and AT2R decreases anti-inflammatory, antifibrotic, and anti-apoptotic responses, as well as ADMA regulation, leading to reactive oxygen species (ROS) accumulation. ROS overproduction activates NF-κB, increasing ICAM-1 and VCAM-1 expression and endothelial permeability. In cardiomyocytes, ROS induces mitochondrial damage and poor exercise tolerance. ROS-mediated inhibition of the NO–sGC–cGMP–PKG pathway results in myocardial hypertrophy, dilation, diastolic and systolic dysfunction, and fibrosis, while also impairing extracellular matrix (ECM) synthesis.

which enhance endothelial survival, proliferation, and migration.[31] In patients with endothelial dysfunction, including those with HF, the number and functionality of EPCs are significantly reduced, possibly contributing to an impaired vascular repair.[28]

Assessment of ED

Various techniques are employed to evaluate the functional status of the endothelium.[32] Many of these approaches examine the systemic function of the endothelium by measuring its capacity for dilation in both major peripheral arteries and the microcirculation. Flow-mediated dilation (FMD), venous occlusion plethysmography, peripheral arterial tonometry (PAT), and laser Doppler flowmetry (LDF) are the most commonly used tool to assess endothelial function.[33]

FMD represent the most commonly used approach to assess systemic endothelial function in a non-invasive manner. This technique measures the variations in the diameter of a peripheral artery through ultrasound, triggered by a peak increase in blood circulation resulting from reactive hyperemia. When blood flow velocity rises, it triggers endothelial cells to produce nitric oxide as a response to increased shear stress, leading to blood vessel dilation. FMD is calculated by evaluating the maximum percentage variation in the brachial artery's diameter during hyperemia against its baseline measurement.[34,35] Ras et al. conducted an exhaustive meta-analysis highlighting the reliability of FMD as a predictive marker of future cardiovascular events.[36] Its use may therefore be particularly valuable in secondary prevention and in the clinical monitoring of patients with cardiovascular risk factors or established disease.[37–39]

The PAT examines the expansion of peripheral microcirculation by assessing variations in pulsatile arterial volume through finger plethysmography (EndoPAT). A pressure cuff is applied to the forearm and inflated beyond systolic levels, inducing five minutes of restricted blood flow, which is then followed by a period of increased blood flow after the cuff is released. The use of a pneumatic probe on the fingertip of the same arm allows the measurement of arterial blood volume variations at rest and during hyperemia by tracking the amplitude of the digital pulse wave (PWA). During hyperemia, the enhancement of blood flow is indicated by the reactive hyperemia index (RHI), which is calculated as the ratio of post-occlusion to pre-occlusion pulse wave amplitude (PWA) readings.[40] However, it has been suggested that PAT has a low-moderate reliability, an aspect that has limited its diffusion in clinical settings.[41]

Beyond these tools, also surrogate, blood-based biomarkers of endothelial function have been proposed.[42] Among them, elevated circulating levels of vascular cell adhesion molecule-1 (VCAM-1) and intercellular adhesion molecule-1 (ICAM-1), which are over expressed by activated endothelial cells in response to inflammatory stimuli, have been associated with the onset of new HF symptoms following acute myocardial infarction. Moreover, up-regulation of their receptors on monocyte subsets in HF patients has been proposed as potential prognostic indicator of disease severity.[43] Intercellular adhesion molecule-2 (ICAM-2) and junctional adhesion molecule-A (JAM-A), both known mediators of leukocyte-endothelial interactions, have emerged as promising biomarkers in CVD population. Specifically, elevated plasma levels and dynamic longitudinal changes over time have been independently associated with the occurrence of adverse clinical events.[44–46] *E*-selectin has also been found to be increased in individuals affect by HF, likely reflecting inflammation-driven endothelial activation, particularly in the presence of comorbidities such as diabetes mellitus.[47] Similarly, von Willebrand factor (vWf), a marker of acute vascular dysfunction, is significantly elevated in HF across phenotype, contributing to further endothelial structure alteration.[48] However, these biomarkers do not consistently correlate with tradition clinical indicator, suggesting they may reflect specific and independent pathogenic mechanisms related to endothelial health. To date, their clinical usefulness remains limited due to the small number of available studies and their intrinsic biological variability.[46]

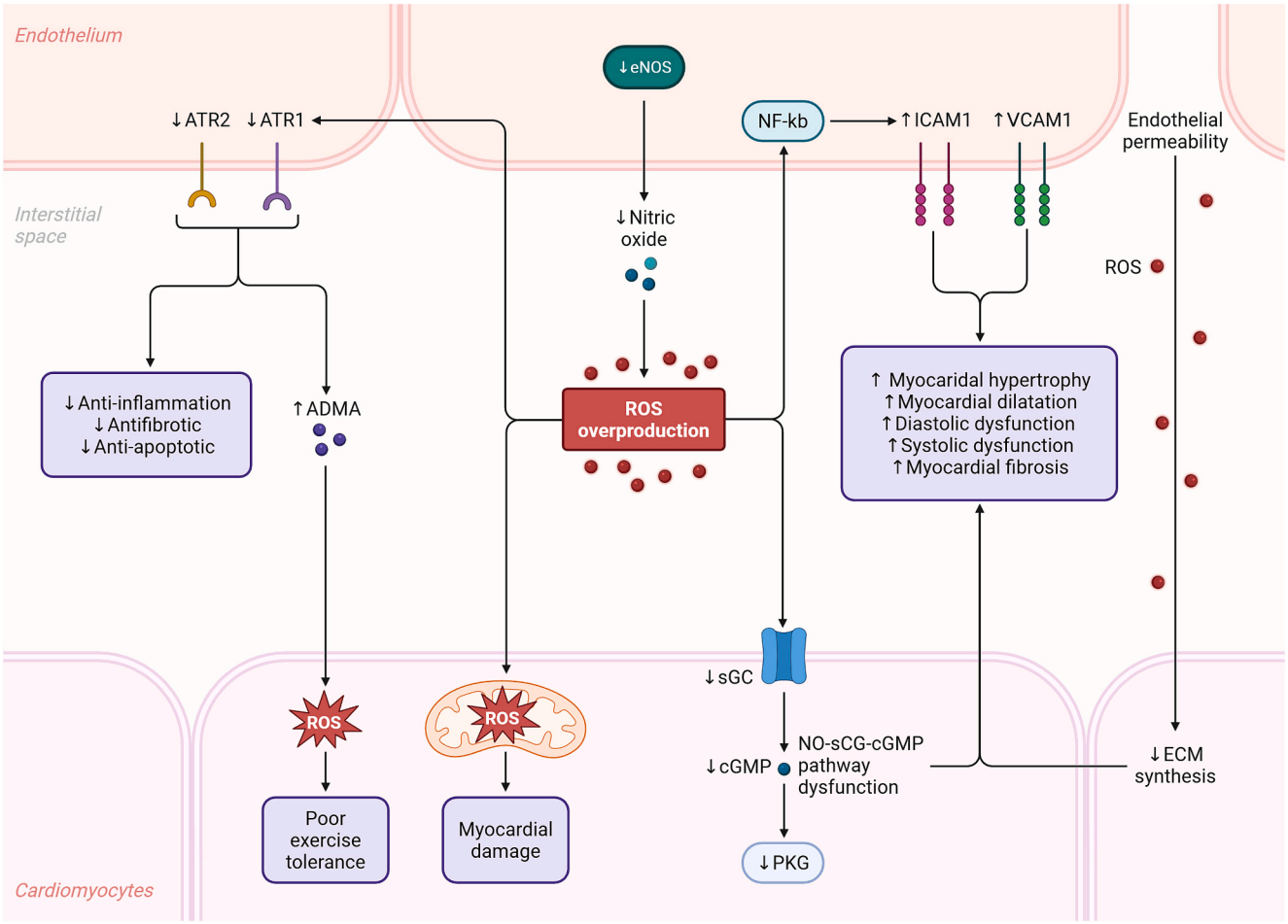

Fig. 2. Comparison of skeletal muscle and endothelial function between non-frail and frail individuals.
In non-frail individuals (left), endothelial NO production from L-arginine via eNOS supports glucose uptake (via GLUT4), mitochondrial biogenesis (via PGC-1α), reduced oxidative stress, and anti-inflammatory myokine release, contributing to healthy skeletal muscle function. In contrast, frailty (right) is associated with reduced NO bioavailability due to endothelial dysfunction and increased pro-inflammatory cytokines. This leads to impaired vasodilation, insulin resistance, mitochondrial dysfunction, reduced angiogenesis and aerobic capacity, increased reactive oxygen species (ROS), and skeletal muscle damage, contributing to sarcopenia and functional decline.

Cardiac rehabilitation

Definition and core components

Cardiac rehabilitation (CR) is defined as a supervised, evidence-based program designed to help individuals with CVD in recovering and promoting their health. It usually combines structured physical activity with education on healthy living, risk factor management, and psychological support. The goal is to enhance clinical stability, reduce the risk of future cardiovascular events, and improve quality of life.[49,50] CR is inherently multidimensional, extending beyond the recovery of cardiac function to encompass physical, psychological, and social well-being.[51] A multidisciplinary team, including physicians, nurses, physiotherapists, dietitians, and psychologists, collaborates closely with the patient and their family to develop a personalized rehabilitation plan that optimizes long-term outcomes.[52] Key components include comprehensive assessment and risk stratification, optimized pharmacotherapy, management of comorbidities, and sustained non-pharmacological interventions. As a result, an individualized treatment plan is structured for each patient, developed and signed by a physician, and reviewed at least every 30 days to ensure continued clinical relevance. Additional, programs must meet specific regulatory requirements regarding qualifying medical diagnoses, prescribed number and duration of sessions, and structural criteria for intensive CR models.[53]

Several international organizations have defined and refined CR core components and standards, reflecting a holistic approach to cardiovascular recovery. The British Association for Cardiovascular Prevention and Rehabilitation (BACPR), the European Society of Cardiology (ESC), and the American Heart Association/American Association of Cardiovascular and Pulmonary Rehabilitation (AHA/AACVPR) have established widely recognized guidelines and frameworks.[53–55] Complementing these, the World Health Organization promotes CR integration into primary care and universal health coverage (WHO,1993), while the Canadian Association of Cardiovascular Prevention and Rehabilitation (CACPR) emphasizes program quality, equity, and innovation, including technology adoption.[56] The National Institute for Health and Care Excellence (NICE) provides evidence-based guidance tailored to post-myocardial infarction care, and the International Council of Cardiovascular Prevention and Rehabilitation (ICCPR) fosters global collaboration, particularly supporting low-resource settings (Table 1).

The cornerstone of CR is physical exercise, with the primary objective of improving cardiorespiratory fitness. Exercise activity prescription is guided by four key parameters: frequency, intensity, duration, and mode. To individualize exercise intensity, cardiopulmonary exercise testing (CPET) is commonly employed. CPET is the gold standard for assessing integrated cardiopulmonary and metabolic responses to

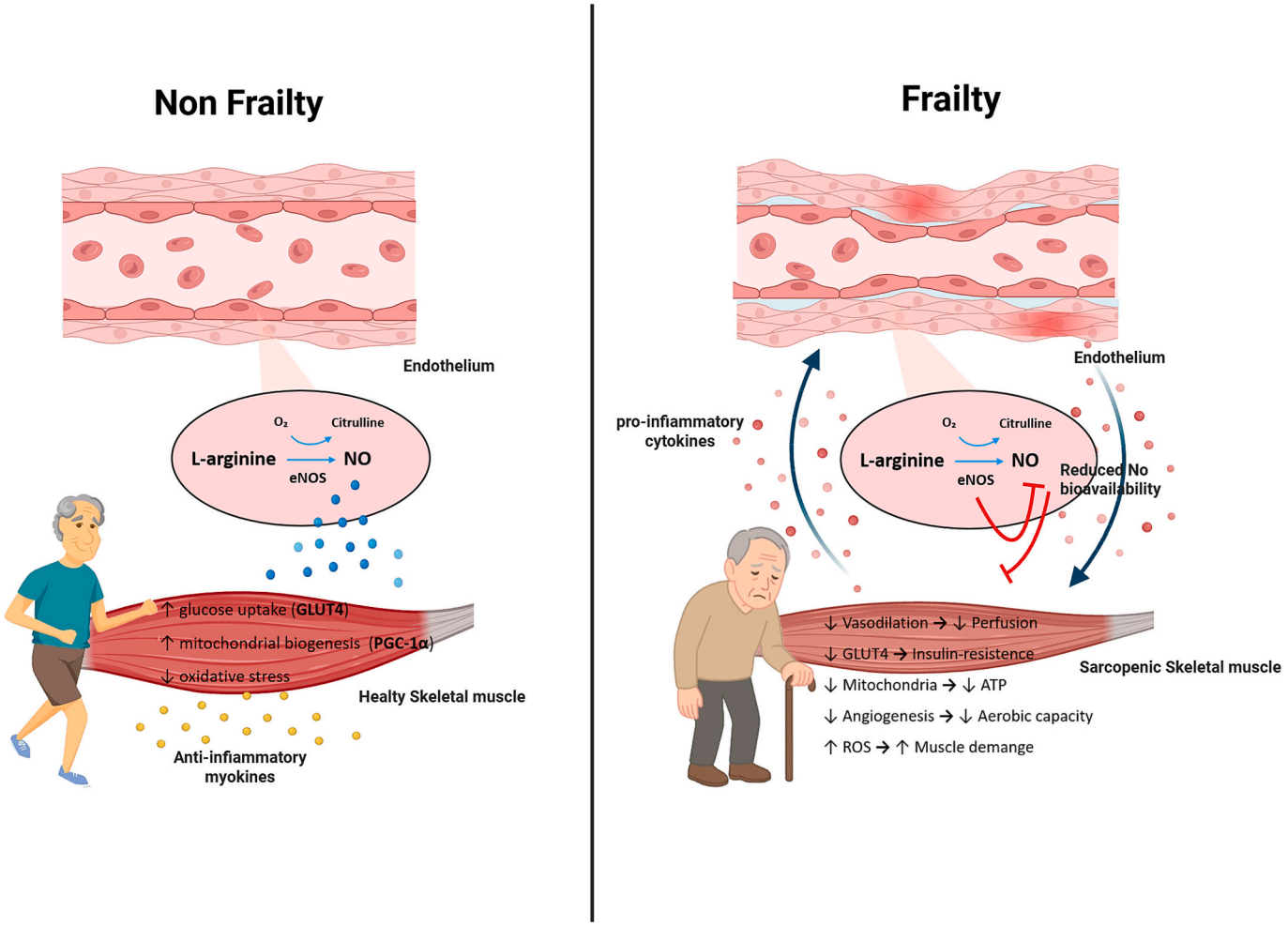

Fig. 3. Schematic overview comparing non-frail (left) and frail (right) conditions.
In the non-frail state, preserved endothelial function and a favorable muscle microenvironment sustain adequate tissue perfusion and optimal skeletal muscle performance. In contrast, frailty is characterized by endothelial dysfunction and heightened systemic inflammation, which reduce nitric oxide bioavailability. These alterations impair tissue perfusion, disrupt muscle metabolism, and diminish functional capacity, ultimately contributing to progressive muscle mass loss, decreased strength, and impaired physical performance, with increased vulnerability to disability.

Table 1
Exercise Intensity Prescription Methods in Cardiac Rehabilitation: Clinical Application in Heart.

Method	Parameters for Intensity Prescription	Physiological Rationale	Clinical Application in HF and Frailty	Key References
Cardiopulmonary Exercise Testing (CPET)	VO_2 peak; Ventilatory Thresholds (VT1, VT2);	Gold standard for integrated cardiopulmonary and metabolic assessment; identifies precise aerobic and anaerobic thresholds	Enables individualized MICT and HIIT prescription; may be limited in very frail	71
Moderate-Intensity Continuous Training (MICT)	60–70% VO_2 peak or HRR (up to 80% in selected HFpEF)	Promotes stable shear stress, improves endothelial function, reduces sympathetic overactivation	Safest and most widely used model in HF; suitable for elderly and frail populations	72
High-Intensity Interval Training (HIIT)	>85% VO_2 peak with active recovery intervals	Enhances endothelial adaptation; superior reduction of oxidative stress and inflammatory markers compared to MICT	Effective in stable HF; requires careful supervision in frail patients	75
Heart Rate Reserve (HRR)	60–80% HRR	Accounts for resting HR and blunted chronotropic response common in HF	Practical when CPET unavailable	78
Rate of Perceived Exertion (RPE – Borg 6–20)	12–13 for aerobic training; 9–11 in frail HF patients	Reflects subjective cardiorespiratory strain when HR is unreliable	Essential chronotropic incompetence; useful in home-based CR	76,77

exercise, providing objective measures such as peak oxygen uptake (VO_2 peak), carbon-dioxide consumption, anaerobic threshold, and continuous monitoring of heart rate, blood pressure, oxygen saturation, and ECG.[57] Alternatively, simpler tools such as the Talk Test, a subjective method estimating exercise intensity based on a patient's ability to speak comfortably during activity, can be used. This test correlates moderately with ventilatory thresholds and is practical for guiding aerobic exercise intensity in settings lacking advanced testing or for patients requiring low-technology solutions.[58] Another option is the 6-min walk test (6MWT), which evaluates submaximal functional capacity by measuring the distance walked in six minutes along a standardized course. The 6MWT is widely utilized for baseline assessment, monitoring functional

changes, and prognostic evaluation in patients with cardiovascular and pulmonary diseases. A walked distance >400 m is associate to good physical functionality conversely to a distance <300 m often correlated to high mortality risk and re-hospitalization.[59,60] Silverii et al. published an exhaustive paper that provides the clinical rationale behind the choice of exercise training protocols.[61] The authors emphasize that each training plan should be individualized based on a multidimensional assessment, encompassing clinical, functional, cognitive, nutritional, and social domains. This may include the use of validated tools such as the Short Physical Performance Battery (SPPB), Fried's criteria, the Essential Frailty Toolset (EFT), and assessments of Activities of Daily Living (ADL). These tools allow for the stratification of older patients into robust, pre-frail, and frail categories, enabling the design of progressive, safe, and tailored training programs. Ideally, for robust and pre-frail individuals, a combined training approach is recommended, involving light-to-moderate intensity aerobic exercise for 15–30 min, supplemented with resistance training 2–3 times per week. Intensity can be progressively increased to moderate-to-vigorous levels, up to 40–60 min per session, if tolerated. Conversely, for cardiovascular patients identified as frail, the focus should be on balance, coordination, and gait training, gradually integrated with aerobic and resistance exercises. For this population, programs typically span 8–12 weeks, with 3–5 sessions per week lasting approximately 30 min.[62–64]

A core element of CR is the comprehensive assessment, particularly crucial in older adults with comorbidities, frailty, and psychosocial issues. Initial evaluation includes medical history, cardiovascular function, comorbidities, fall risk, medications, and symptoms. Social, behavioral and environmental factors are also assessed to identify barriers to participation or suitability for remote care.[53] This leads to a functional assessment and the creation of an Individualized Treatment Plan (ITP) summarizing clinical status, goals, and interventions.[65]

Nutritional education is another key component of CR. Interventions should be food-based, personalized, and culturally appropriate, using accessible language. Commonly recommended patterns include the Mediterranean and DSH diets.[66,67] Referral to a dietitian is essential for cardiovascular patients with diabetes, malnutrition, or frailty.[68]

Finally, psychological assessment is equally critical. Depression, anxiety, stress, isolation, sleep issue, and cognitive decline are common in CVD patients and independently affect outcomes.[69] Though mechanisms remain unclear,[70] early screening and intervention are essential. Psychological support may overlap with other CR elements and be delivered in various formats by psychologists, trained nurses, or psychiatrists for complex cases.[71,72]

Cardiac telerehabilitation

Although evidence supports the positive impact of CR on capacity range markers and hard outcomes, a significant number of patients do not participate due to barriers like education, socioeconomic status, or lack of motivation.[73] Consequently, there has been increasing interest in alternative CR models, such as cardiac telerehabilitation (CTR) (or home-based CR). This approach allows remote participation, with personalized exercise plans, education on heart disease prevention, and psychological support.[74] CTR leverages digital technologies such as telemedicine platforms, wearable devices, and remote consultations, providing continuous monitoring and interventions without the need for frequent in-person visits.[75] This is especially useful for patients with limited mobility and for those living in rural areas. The flexibility and convenience offered by home-based rehabilitation improve the completion rates for prescribed rehabilitation sessions when compared with traditional in-person rehabilitation programs.[76,77] These findings are supported by Fukuta et al., which showed that CTR, when combined with remote monitoring and personalized feedback (e.g., heart rate, physical activity level, exercise progress, or the experiences during the rehabilitation program), results in improvements in exercise tolerance and self-reported clinical outcomes comparable to those achieved through center-based rehabilitation.[78] As CR, the core intervention of CTR is the physical training. To ensure exercise safety, specialists track exercise intensity by monitoring heart rate, oxygen consumption, and perceived exertion, along with the patient's general health status at the start, during, and at the end of each session.[79] This aspect emphasizes the role of remote supervision in CTR, where telemonitoring systems and online communication allow real-time adjustments. This digital approach ensures safe exercise levels, with no risk of adverse cardiac events, hospitalizations, or deaths reported during remotely monitored sessions.[80] Additionally, remote supervision can engage more patients, creating a sense of community and motivation. Therefore, home-based CR programs promote long-term adherence, allowing patients to incorporate exercise into their routines, minimize hospital visits, and encourage lasting lifestyle changes.[81,82] Physical training programs in CTR integrate aerobic exercises, strength training, and respiratory techniques, resulting on one hand in significant improvements in functional recovery of patients with heart failure, and on the other hand in promoting patient autonomy through active participation in the rehabilitation program. Real-time transmission of biometric data via mobile networks enables continuous and personalized supervision by healthcare professionals, ensuring both the efficacy and safety of the exercises performed.[83] Beyond physical training, CTR incorporates psychological support and stress management. However, literature often lacks clarity on this aspect. Some studies, such as Piotrowicz et al., describe remote counseling via telephone, addressing illness acceptance, treatment adherence, and emotional well-being.[84]

Overall, the available literature highlights that CTR significantly improves functional status, psychological well-being, and overall quality of life. However, evidence regarding its impact on reducing cardiovascular mortality remains limited.[85] Likewise, there is limited evidence regarding the effectiveness and safety of digital interventions in older cardiovascular patients with a frailty phenotype. The available data mostly come from small-scale studies, partly due to the persistently low referral rates to rehabilitation programs within this patient population.[85] Therefore, larger studies are needed to assess the impact of CTR on short- and long-term clinical and functional outcomes, as well as to evaluate its effectiveness, safety, and acceptability in frail elderly patients.[86]

Hybrid cardiac rehabilitation

Hybrid Cardiac Rehabilitation (Hybrid-CR) represents a progressive model that integrates center-based and home-based rehabilitation, combining their strengths to overcome individual limitations.[87] This model is especially beneficial for patients facing physical, logistical, or psychological barriers to traditional CR.[88] The structure of Hybrid-CR is not yet standardized.[89] Typically, an initial phase occurs in a specialized center for counseling, followed by a home-based phase.[89] Wearable fitness trackers, heart rate monitors, and mobile apps provide real-time progress tracking, allowing healthcare providers to personalize exercise intensity while ensuring safety.[90] Hybrid-CR offers a structured yet adaptable approach, merging the direct supervision of in-person rehabilitation with the convenience of home-based care. While traditional CR ensures close monitoring and structured sessions, it is often limited by accessibility and logistical constraints. Hybrid-CR balances these factors, improving patient engagement while maintaining clinical effectiveness.[91]

Hybrid-CR programs are not inferior compared to traditional CR programs in term of improvement of functional capacity, tested by 6MWT or VO2peak, and psychological status, and increased of adherence to treatment.[92]

Marchionni et al.[93] evaluated functional capacity (measured by a symptom-limited exercise test on a cycle ergometer), health-related quality of life (measured by the Sickness Impact Profile), and healthcare costs as endpoints in patients who had experienced a myocardial infarction (mean age 66 years), comparing traditional center-based CR

with a Hybrid-CR intervention. The traditional program consisted of 40 supervised exercise sessions, whereas the hybrid model included four in-clinic and four home-based sessions, both supported by regular physiotherapist. After 6- and 12-month follow-up, the authors reported that the Hybrid-CR intervention led to reduced healthcare system costs and improved adherence to the rehabilitation program, with no significant differences observed between groups in the other two outcomes.

The study conducted by Campo et al.[94] involving patients with ischemic heart disease and a median age of 76 years demonstrated that both traditional outpatient intervention (CR) and hybrid CR program produced comparable improvements in quality of life, as measured by the EuroQol Visual Analogue Scale, as well as in physical mobility. These results indicate that the Hybrid-CR model may serve as an effective alternative to conventional CR, particularly by improving accessibility and adherence among this patient population.

Overall, Hybrid-CR represents an effective alternative to traditional CR, potentially offering greater accessibility and flexibility for patients. However, many authors emphasize the need for further well-designed studies to validate these results, particularly regarding long-term outcomes and clinical parameters associated with heart failure.

Exercise-centered cardiac rehabilitation in frail older adults: shared findings and key differences across studies

The progressive decline in cardiovascular, musculoskeletal, and metabolic function associated with aging significantly increases the risk of frailty, falls, and loss of independence.[95] Although no pharmacological interventions have yet proven effective in reversing age-related physical or cognitive deterioration, a growing body of evidence highlights the pivotal role of structured exercise programs in mitigating these adverse outcomes (.[96,97] Multicomponent exercise regimens—combining aerobic, resistance, balance, and flexibility training—have consistently demonstrated efficacy in enhancing physical performance and reducing frailty among older adults with cardiovascular disease (.[96,98,99] These interventions confer systemic physiological benefits, including improved endothelial function, reduced arterial stiffness, and modulation of systemic inflammation and oxidative stress.[97,100,101] Numerous randomized controlled trials (summarized in Table 2) and systematic reviews have reported significant improvements in functional metrics such as gait speed, chair-rise time, and Short Physical Performance Battery (SPPB) scores in frail or pre-frail older adults undergoing tailored cardiac rehabilitation (CR) programs.[102–104] For instance, the PEARL trial demonstrated superior improvements in gait speed and balance using a multimodal CR approach incorporating resistance, balance, and aerobic training in older patients hospitalized for heart failure,[102] while Tamulevičiūtė-Prascienė et al. observed reductions in frailty status among elderly patients post-valvular surgery when standard CR was supplemented with additional resistance and balance exercises.[103] Despite consistent positive outcomes, variability exists across studies in the design and delivery of interventions. Some trials emphasize moderate-intensity aerobic training (e.g., brisk walking or cycling 150 min/week) as a core component,[96,105] whereas others prioritize progressive resistance training targeting lower-limb musculature to combat sarcopenia and improve postural control.[99,106] Balance training emerges as particularly important in fall-prevention strategies, especially among the oldest-old.[95,98]The duration and frequency of interventions also vary considerably, ranging from 8-week programs with thrice-weekly sessions to 6-month protocols with more intensive follow-up.[103,104] In some cases, integration of nutritional support and behavioral strategies adds further complexity but may provide additional benefits in frail populations.[96,101] More recently, clinical trials have increasingly targeted older adults with heart failure (HF), addressing both systolic and diastolic phenotypes across acute and chronic stages. Trials such as REHAB-HF, PACE SETTER, and REHAB-HFpEF have evaluated multidomain or personalized CR protocols—incorporating strength, endurance, mobility, and balance components—particularly after acute decompensated HF (ADHF), with the aim of improving physical function and reducing rehospitalization. Investigations such as FUNNEL+ and another trial (titled “Identifying Markers of Exercise Training in Heart Failure”) have focused on peak VO_2 and proteomic responses, while BAMS-HF and CHF-CaRe explored changes in physical and cognitive function, respectively. Telerehabilitation has emerged as a feasible and promising alternative, as demonstrated by TELEREHAB-HF and BAMS-HF, offering digitally supported or remote home-based CR. Other trials, such as CAMCO, investigated novel modalities (e.g., orienteering versus conventional walking) in inpatient CR settings. Recruitment feasibility and behavioral components have also been addressed, as in another trial guided by Emily C Gathright (NCT05575375), which tested a values-affirmation intervention integrated with CR. Additionally, studies such as PREHAB extended CR to preoperative HF patients, while ExCR in Vulnerable ADHF focused on early post-discharge rehabilitation. Collectively, the evidence supports the feasibility and efficacy of exercise-based CR in frail older adults, with multidimensional, individualized interventions yielding the most substantial functional gains. Nonetheless, further research is warranted to optimize exercise prescriptions by identifying the ideal intensity, frequency, and combination of training components for this vulnerable population.

Table 2
Expected Quantitative Outcomes of Cardiac Rehabilitation on Physical Function.

Functional parameter	Expected quantitative outcome	Clinical and Prognostic Significance	References
SPPB	Increase of +2.2 to +4 points	Improved mobility; reduced risk of falls and functional disability.	78,79
6MWD	Increase of +30 to +50 m	Achievement of the MCID; enhanced daily autonomy and reduced hospitalization risk	82
Peak VO2	Increase of ≥6% (avg. gain up to +2.16 mL/kg/min)	threshold for improved long-term prognosis and survival	84,85
Frailty Status	Prevalence reduction	Mitigation of Frailty status	81

Abbreviations: 6MWD: 6-Minute Walk Distance; MCID: Minimal Clinically Important Difference; SPPB: Short Physical Performance Battery; Peak VO_2: Peak Oxygen Consumption.
Notes: Expected outcomes are based on mean improvements observed in the cited clinical trials for frail older populations.

In addition to the conventional outcomes described above, a number of recent studies, summarized in the table below (Table 3), have investigated specific pathophysiological markers, particularly endothelial dysfunction, which is widely recognized as an early marker of vascular disease and a modifiable therapeutic target in patients with HF.[107] Several of these studies have assessed endothelial function using FMD or other related vascular imaging techniques, though the results remain heterogeneous and appear to depend on HF phenotype, training modality, and intervention characteristics. For instance, Erbs et al. (NCT00176384) demonstrated that a 12-week program combining inpatient and home-based training improved FMD and was associated with enhanced regenerative capacity of circulating progenitor cells (CPCs) in older patients with NYHA IIIb HF.[108] Similar improvements in brachial artery vasodilation were observed in another study[109] after three months of home-based aerobic training in patients with NYHA II HF. Likewise, LEICA study reported enhanced FMD following four weeks of supervised aerobic exercise in stable HF patients aged ≥65.[110] Furthermore, (15)O-water PET was employed to assess coronary vasomotion in patients with non-ischemic dilated cardiomyopathy, demonstrating improved coronary endothelial responsiveness after a center-based CR program combined with optimal medical therapy.[111] The type and intensity of exercise also seem to influence outcomes. A greater

Table 3
Selected Clinical Trials on Endothelial Dysfuction and Exercise in Older Adults with Heart Failure.

PATIENT CHARACTERISTICS	MIN AGE	INTERVENTION	OUTCOME	FINDINGS
NYHA IIIb CHF	≥70	12-week (intial phase in hospital followed by home exercise training)	Endothelial function related to endogenous regenerative capacity of circulating progenitor cells (CPCs)	Enhanced FMD associated with increased regenerative capacity of CPCs
HFpEF	70	16-week endurance exercise training (walking, arm and leg ergonometry)	Endothelial-dependent flow-mediated arterial dilatation	No changes in endothelial function
NYHA II HF	66	3 month of aerobic training at home, 5 session/ week of 30 min of cyckle ergonometry	Endotelial dysfunction	Improvement in endothelial-mediated vasodilatation of the brachial artery
HF from non-ischaemic dilated cardiomyopathy and without coronary risk factors	54	12-week center-based CR (warm-up, low intensity weight resistance activity, aerobic activity) associated with medical therapy	Coronary vasomotion by using (15)O water PET	Improvement of coronary vasomotion
HFpEF	70	3 days/week for 4-week comparing high-intensity interval training (HIIT) with moderate-intensity aerobic continuos training (MI-ACT)	Endothelial function via FMD	Greater FMD improvement with HIIT vs. MI-ACT
NYHA II-III HF	65	12-week Moderate-intensity continuous training or High intensity interval training	Superficial femoral artery endothelial function via FMD	No significant changes in FMD
Stable CHF	≥65	4-week supervised aerobic exercise training (sessions per weekday of 15–20 min)	Endothelial function via FMD	Increase in FDM
CHF	56	36 session of exercise training (HIIT and HIIT combined with muscle strengh training)	Increase of EPCs at rest and the acute response	EPCs long term mobilization
Hemodynamically stable NYHA I–II HF	56	12-week, 36 training sessions, HIIT, Circuit-Resistance Training	Endothelial function via FMD	vascular function improvement mediated by HIIT
Clinically stable NYHA II-III HF	60	3 time week, 12-week at hospital clinical research center	Endothelial function via FMD	No significant changes in FMD

FMD improvements was found with high-intensity interval training (HIIT) compared to moderate-intensity continuous training in patients with HFpEF[112] and similarly was reported a vascular function improvements following HIIT or circuit-resistance training in stable NYHA I–II HF.[113] Kourek et al. added mechanistic insight by demonstrating increased endothelial progenitor cell mobilization after combined HIIT and strength training.[114] Conversely, other studies did not find significant changes in endothelial function, despite well-structured exercise protocols, pointing to variability in response.[115–117] It is important to note, however, that only a minority of these studies considered endothelial dysfunction as a primary outcome, with most including it as a secondary or exploratory endpoint. This limits the ability to draw definitive conclusions about the vascular effects of exercise-based CR interventions. Additionally, there is considerable variability in the age of participants across studies, with mean ages ranging from mid-50s to ≥70 years. While some trials specifically targeted older adults, others included relatively younger populations, potentially limiting the generalizability of results to the older, frail HF population that is the main focus of this review. Given that endothelial function is strongly influenced by age-related vascular changes, future research should prioritize the inclusion of older adults and explicitly assess vascular outcomes as primary endpoints to better understand exercise-induced adaptations in this vulnerable group.

Conclusion

The interplay between frailty and HF in older adults represents a major clinical challenge, underpinned by a complex web of shared pathophysiological mechanisms, with endothelial dysfunction emerging as a pivotal contributor. As highlighted, the bidirectional relationship between frailty and HF exacerbates systemic inflammation, oxidative stress, and vascular dysfunction, leading to a vicious cycle that worsens both conditions and adversely affects patient outcomes.[118] The role of endothelial dysfunction is not only mechanistic but also prognostic, as demonstrated by multiple studies showing an association between measures of endothelial function and poor outcomes in multiple populations.[119] Molecular mediators and the imbalance between circulating EPCs and CECs further delineate the pathophysiological substrate linking endothelial dysfunction to the frailty-HF dyad.[120] These insights suggest that endothelial health serves as both a biomarker and a therapeutic target to disrupt the deleterious cascade affecting these patients.

From a clinical perspective, available evidence underscores the urgent need for comprehensive, multidisciplinary approaches that extend beyond pharmacological treatments. Interventions such as structured exercise programs, nutritional optimization, and CR have shown promise in mitigating endothelial dysfunction and its downstream consequences.[121] Specifically, CR emerges as a valuable, yet underutilized, strategy to improve endothelial function, enhance NO bioavailability, and ultimately reverse the downward spiral of frailty in HF patients. Cardiac rehabilitation, in both traditional and innovative formats such as cardiac telerehabilitation (CTR) and hybrid-CR, demonstrates multidimensional benefits extending beyond physical recovery to psychological well-being and long-term risk reduction.[6] CTR, in particular, has shown to be a viable alternative to in-person programs, addressing common barriers to CR participation and maintaining comparable outcomes in exercise tolerance, cardiovascular risk profiles, and quality of life.

Nevertheless, several challenges remain. Despite the established efficacy of exercise-based interventions and CR programs, participation and adherence rates, especially among frail and elderly patients, remain suboptimal. A deeper issue lies in the logistical and systemic barriers to implementing these advanced and individualized CR programs, particularly in healthcare systems with constrained resources or limited access to specialized services. Factors such as geographic disparities, staffing shortages, financial limitations, and insufficient telehealth infrastructure hinder the widespread adoption and scalability of tailored CR interventions.[122] This further emphasizes the need for health policy reforms and resource allocation to facilitate equitable access to these potentially life-changing programs.

Moreover, the clinical response heterogeneity, mainly due to age and comorbidities,[123] emphasizes the imperative for increasingly individualized and flexible therapeutic strategies. In this context, the synergistic integration of pharmacological interventions with cardiac rehabilitation and lifestyle modifications emerges as a key approach to optimize systemic inflammation control, promote vascular health, and enhance functional capacity in elderly and frail patients.

Future research should focus on personalizing CR programs to the frailty phenotype, integrating molecular markers to guide intervention intensity and types, as well as to monitor progress and individual's

response to intervention. The translation of these findings into real-world settings requires addressing the aforementioned barriers, tailoring interventions to the functional capacity and psychosocial needs of frail individuals.

CRediT authorship contribution statement

Rosanna Maniscalco: Writing – original draft. **Rina Recchioni:** Writing – original draft, Conceptualization. **Sara Caccese:** Visualization. **Valeria Pellegrini:** Writing – review & editing. **Rosalba La Grotta:** Data curation, Writing – review & editing, Formal analysis, Visualization. **Angelica Giuliani:** Writing – review & editing. **Lorenzo Pimpini:** Writing – review & editing. **Daniele Caraceni:** Supervision. **Gaia Cattadori:** Writing – review & editing. **Andrea Passantino:** Writing – review & editing. **Fabiola Olivieri:** Writing – review & editing, Funding acquisition. **Francesco Prattichizzo:** Writing – review & editing, Funding acquisition. **Giulia Matacchione:** Writing – review & editing, Writing – original draft, Conceptualization.

Funding

This work was funded by the European Union – Next Generation EU - NRRP M6C2 - Investment 2.1 Enhancement and strengthening of biomedical research in the NHS - PNRR-MAD-2022–12376806. This work was also supported by the Italian Ministry of Health (Ricerca Corrente to IRCCS INRCA and IRCCS MultiMedica).

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

1. Kim DH, Rockwood K. Frailty in older adults. *N Engl J Med*. 2024;391(6):538–548.
2. Sapna F, et al. Advancements in heart failure management: a comprehensive narrative review of emerging therapies. *Cureus*. 2023;15(10), e46486.
3. Heckman GA, Rockwood K. Frailty, risk, and heart failure care: commission or omission? *J Am Coll Cardiol*. 2022;80(12):1144–1146.
4.. Beghini A, et al. 2024 update in heart failure. *ESC Heart Fail*. 2025;12(1):8–42.
5. Uchmanowicz I, et al. Coexisting frailty with heart failure. *Front Physiol*. 2019;10:791.
6. Pandey A, Kitzman D, Reeves G. Frailty is intertwined with heart failure: mechanisms, prevalence, prognosis, assessment, and management. *JACC Heart Fail*. 2019;7(12):1001–1011.
7. Bhattarai U, et al. Frailty and chronic diseases: a bi-directional relationship. *Aging Med (Milton)*. 2024;7(4):510–515.
8. Talha KM, et al. Frailty and heart failure: state-of-the-art review. *J Cachexia Sarcopenia Muscle*. 2023;14(5):1959–1972.
9. Bozkurt B, et al. Universal definition and classification of heart failure: a report of the Heart Failure Society of America, Heart Failure Association of the European Society of Cardiology, Japanese Heart Failure Society and Writing Committee of the Universal Definition of Heart Failure. *J Card Fail*. 2021;23(3):352–380.
10. Drera A, et al. Endothelial dysfunction in heart failure: what is its role? *J Clin Med*. 2024;13(9).
11. Xu S, et al. Endothelial dysfunction in atherosclerotic cardiovascular diseases and beyond: from mechanism to pharmacotherapies. *Pharmacol Rev*. 2021;73(3):924–967.
12. Calila H, et al. Endothelial dysfunction as a key link between cardiovascular disease and frailty: a systematic review. *J Clin Med*. 2024;13(9).
13. Dugal JK, et al. Non-pharmacological therapy in heart failure and management of heart failure in special populations-a review. *J Clin Med*. 2024;13(22).
14.. Vacca A, et al. Lifestyle interventions in cardiometabolic HFpEF: dietary and exercise modalities. *Heart Fail Rev*. 2025;30(4):637–655.
15.. Rech DA, et al. Frailty influences the vascular responsiveness of elderly individuals with chronic heart failure. *Microvasc Res*. 2022;141, 104316.
16.. Lindgren M, Borjesson M. The importance of physical activity and cardiorespiratory fitness for patients with heart failure. *Diabetes Res Clin Pract*. 2021;176, 108833.
17. Obokata M, Reddy YNV, Borlaug BA. Diastolic dysfunction and heart failure with preserved ejection fraction: understanding mechanisms by using noninvasive methods. *JACC Cardiovasc Imaging*. 2020;13(1 Pt 2):245–257.
18. Saavedra-Alvarez A, et al. Vascular dysfunction in HFpEF: potential role in the development, maintenance, and progression of the disease. *Front Cardiovasc Med*. 2022;9, 1070935.
19. Alcaide P, et al. Myocardial inflammation in heart failure with reduced and preserved ejection fraction. *Circ Res*. 2024;134(12):1752–1766.
20.. Perazza LR, Brown-Borg HM, Thompson LV. Physiological Systems in Promoting Frailty. *Compr Physiol*. 2022;12(3):3575–3620.
21. D'Amato A, et al. Implications of oxidative stress in the pathophysiological pathways of heart failure. *Int J Mol Sci*. 2025;26(11).
22. Penna C, Pagliaro P. Endothelial dysfunction: redox imbalance, NLRP3 inflammasome, and inflammatory responses in cardiovascular diseases. *Antioxidants (Basel)*. 2025;14(3).
23.. Socha MJ, Segal SS. Microvascular mechanisms limiting skeletal muscle blood flow with advancing age. *J Appl Physiol (1985)*. 2018;125(6):1851–1859.
24.. Zong Y, et al. Mitochondrial dysfunction: mechanisms and advances in therapy. *Signal Transduct Target Ther*. 2024;9(1):124.
25.. Amarasekera AT, et al. Does vascular endothelial dysfunction play a role in physical frailty and sarcopenia? A systematic review. *Age Ageing*. 2021;50(3):725–732.
26.. Fasipe B, Li S, Laher I. Exercise and vascular function in sedentary lifestyles in humans. *Pflugers Arch*. 2023;475(7):845–856.
27. Battista F, et al. Sedentary lifestyle and physical inactivity: a mutual interplay with early and overt frailty. *Nutr Metab Cardiovasc Dis*. 2025;35(6), 103971.
28. Lopes J, et al. Reduced levels of circulating endothelial cells and endothelial progenitor cells in patients with heart failure with reduced ejection fraction. *Arch Med Res*. 2022;53(3):289–295.
29.. Ng CY, Cheung C. Origins and functional differences of blood endothelial cells. *Semin Cell Dev Biol*. 2024;155(Pt C):23–29.
30. Cavalcante S, et al. Maximal exercise improves the levels of endothelial progenitor cells in heart failure patients. *Curr Issues Mol Biol*. 2023;45(3):1950–1960.
31. Schneller D, et al. Cytokine-like 1 is a novel proangiogenic factor secreted by and mediating functions of endothelial progenitor cells. *Circ Res*. 2019;124(2):243–255.
32. Chia PY, Teo A, Yeo TW. Overview of the assessment of endothelial function in humans. *Front Med (Lausanne)*. 2020;7, 542567.
33. Lanza GA, et al. Cardiac rehabilitation and endothelial function. *J Clin Med*. 2020;9(8).
34. Ghiadoni L, et al. Assessment of flow-mediated dilation reproducibility: a nationwide multicenter study. *J Hypertens*. 2012;30(7):1399–1405.
35. Nerla R, et al. Effect of bariatric surgery on peripheral flow-mediated dilation and coronary microvascular function. *Nutr Metab Cardiovasc Dis*. 2012;22(8):626–634.
36. Ras RT, et al. Flow-mediated dilation and cardiovascular risk prediction: a systematic review with meta-analysis. *Int J Cardiol*. 2013;168(1):344–351.
37.. Anderson TJ, Phillips SA. Assessment and prognosis of peripheral artery measures of vascular function. *Prog Cardiovasc Dis*. 2015;57(5):497–509.
38. Yeboah J, et al. Predictive value of brachial flow-mediated dilation for incident cardiovascular events in a population-based study: the multi-ethnic study of atherosclerosis. *Circulation*. 2009;120(6):502–509.
39. Villano A, et al. Endothelial dysfunction and cardiovascular outcome in asymptomatic patients with type 2 diabetes: a pilot study. *Diabetes Metab Res Rev*. 2020;36(1), e3215.
40.. McCrea CE, et al. Test-retest reliability of pulse amplitude tonometry measures of vascular endothelial function: implications for clinical trial design. *Vasc Med*. 2012;17(1):29–36.
41. Nil M, et al. Reproducibility of peripheral arterial tonometry measurements in male cardiovascular patients. *Eur J Clin Invest*. 2014;44(11):1065–1071.
42.. Sena CM, Goncalves L, Seica R. Methods to evaluate vascular function: a crucial approach towards predictive, preventive, and personalised medicine. *EPMA J*. 2022;13(2):209–235.
43. Reina-Couto M, et al. Endothelitis profile in acute heart failure and cardiogenic shock patients: endocan as a potential novel biomarker and putative therapeutic target. *Front Physiol*. 2022;13, 965611.
44. Luissint AC, Nusrat A, Parkos CA. JAM-related proteins in mucosal homeostasis and inflammation. *Semin Immunopathol*. 2014;36(2):211–226.
45. Reglero-Real N, et al. Endothelial cell junctional adhesion molecules: role and regulation of expression in inflammation. *Arterioscler Thromb Vasc Biol*. 2016;36(10):2048–2057.
46. Bouwens E, et al. Circulating biomarkers of cell adhesion predict clinical outcome in patients with chronic heart failure. *J Clin Med*. 2020;9(1).
47. Chong AY, et al. Increased circulating endothelial cells in acute heart failure: comparison with von Willebrand factor and soluble E-selectin. *Eur J Heart Fail*. 2006;8(2):167–172.
48. Gibbs CR, et al. Abnormalities of hemorheological, endothelial, and platelet function in patients with chronic heart failure in sinus rhythm: effects of angiotensin-converting enzyme inhibitor and beta-blocker therapy. *Circulation*. 2001;103(13):1746–1751.
49. Piepoli MF, et al. ExtraHF survey: the first European survey on implementation of exercise training in heart failure patients. *Eur J Heart Fail*. 2015;17(6):631–638.
50. Corra U, et al. Executive summary of the position paper of the Working Group on Cardiac Rehabilitation and Exercise Physiology of the European Society of Cardiology (ESC): core components of cardiac rehabilitation in chronic heart failure. *Eur J Cardiovasc Prev Rehabil*. 2005;12(4):321–325.
51.. Taylor RS, et al. Global perspectives on heart disease rehabilitation and secondary prevention: a scientific statement from the Association of Cardiovascular Nursing and Allied Professions, European Association of Preventive Cardiology, and

International Council of Cardiovascular Prevention and Rehabilitation. *Eur Heart J*. 2023;44(28):2515–2525.
52.. Kourek C, et al. Latest updates on structure and recommendations of cardiac rehabilitation programs in chronic heart failure. *World J Clin Cases*. 2024;12(8):1382–1387.
53. Brown TM, et al. Core Components of Cardiac Rehabilitation Programs: 2024 Update: a scientific statement from the American Heart Association and the American Association of Cardiovascular and Pulmonary Rehabilitation. *Circulation*. 2024;150(18):e328–e347.
54. Piepoli MF, et al. Challenges in secondary prevention after acute myocardial infarction: a call for action. *Eur J Prev Cardiol*. 2016;23(18):1994–2006.
55. European Association of Cardiovascular, P, et al. Secondary prevention through cardiac rehabilitation: physical activity counselling and exercise training: key components of the position paper from the Cardiac Rehabilitation Section of the European Association of Cardiovascular Prevention and Rehabilitation. *Eur Heart J*. 2010;31(16):1967–1974.
56.. Canadian Association of Cardiovascular Prevention and Rehabilitation (CACPR) 2025 spring conference abstracts. *J Cardiopulm Rehabil Prev*. 2025;45(4):E26–E34.
57. Ruzzolini M, Ambrosetti M. Cardiopulmonary exercise testing in cardiac rehabilitation: from the reporting form to structured exercise prescription. A proposal from the Italian alliance for cardiovascular rehabilitation and prevention (Itacare-P). *Int J Cardiol Cardiovasc Risk Prev*. 2023;18, 200191.
58. Reed JL, Pipe AL. The talk test: a useful tool for prescribing and monitoring exercise intensity. *Curr Opin Cardiol*. 2014;29(5):475–480.
59. Laboratories, A.T.S.C.o.P.S.f.C.P.F. ATS statement: guidelines for the six-minute walk test. *Am J Respir Crit Care Med*. 2002;166(1):111–117.
60. Boxer R, et al. The 6-minute walk is associated with frailty and predicts mortality in older adults with heart failure. *Congest Heart Fail*. 2010;16(5):208–213.
61.. Silverii MV, et al. Cardiac rehabilitation protocols in the elderly. *Monaldi Arch Chest Dis*. 2020;90(4).
62. Chiarantini D, et al. Lower extremity performance measures predict long-term prognosis in older patients hospitalized for heart failure. *J Card Fail*. 2010;16(5):390–395.
63. Fried LP, et al. Frailty in older adults: evidence for a phenotype. *J Gerontol A Biol Sci Med Sci*. 2001;56(3):M146–M156.
64. Dunlay SM, et al. Activities of daily living and outcomes in heart failure. *Circ Heart Fail*. 2015;8(2):261–267.
65. Brown TM, et al. Core Components of Cardiac Rehabilitation Programs: 2024 update: a scientific statement from the American Heart Association and the American Association of Cardiovascular and Pulmonary Rehabilitation: endorsed by the American College of Cardiology. *J Cardiopulm Rehabil Prev*. 2025;45(2):E6–E25.
66. Mehra VM, et al. Systematic review of cardiac rehabilitation guidelines: quality and scope. *Eur J Prev Cardiol*. 2020;27(9):912–928.
67.. Van Horn L, et al. Recommended Dietary Pattern to Achieve Adherence to the American Heart Association/American College of Cardiology (AHA/ACC) Guidelines: A Scientific Statement From the American Heart Association. *Circulation*. 2016;134(22):e505–e529.
68.. Marques-Vidal P, et al. Dietary measures among patients with coronary heart disease in Europe. ESC EORP Euroaspire V. *Int J Cardiol*. 2020;302:5–14.
69.. Richards SH, et al. Psychological interventions for coronary heart disease. *Cochrane Database Syst Rev*. 2017;4(4):CD002902.
70. Tully PJ, Cosh SM, Baumeister H. The anxious heart in whose mind? A systematic review and meta-regression of factors associated with anxiety disorder diagnosis, treatment and morbidity risk in coronary heart disease. *J Psychosom Res*. 2014;77(6):439–448.
71. Levine GN, et al. Psychological health, well-being, and the mind-heart-body connection: a scientific statement from the American Heart Association. *Circulation*. 2021;143(10):e763–e783.
72.. Bush M, et al. Psychosocial services provided by licensed cardiac rehabilitation programs. *Front Rehabil Sci*. 2023;4, 1093086.
73. Vonk T, et al. Temporal trends in cardiac rehabilitation participation and its Core components: a Nationwide cohort study from the Netherlands. *J Cardiopulm Rehabil Prev*. 2024;44(3):180–186.
74. Zheng Y, et al. Effect of home-based cardiac telerehabilitation in patients after percutaneous coronary intervention: a randomized controlled trial. *Comput Inform Nurs*. 2024;42(12):898–904.
75.. Mitropoulos A, et al. Exploring the effects of real-time online cardiac telerehabilitation using wearable devices compared to gym-based cardiac exercise in people with a recent myocardial infarction: a randomised controlled trial. *Front Cardiovasc Med*. 2024;11, 1410616.
76. Krishnamurthi N, et al. Predictors of patient participation and completion of home-based cardiac rehabilitation in the Veterans Health Administration for patients with coronary heart disease. *Am J Cardiol*. 2019;123(1):19–24.
77. Lundgren KM, et al. Exercise-based telerehabilitation for heart failure patients declining outpatient rehabilitation-a randomized controlled trial. *Med Sci Sports Exerc*. 2025;57(3):449–460.
78.. Fukuta Y, et al. Effects of real-time remote cardiac rehabilitation on exercise capacity and quality of life: a quasi-randomised controlled trial. *BMC Geriatr*. 2023;23(1):388.
79. Batalik L, et al. Benefits and effectiveness of using a wrist heart rate monitor as a telerehabilitation device in cardiac patients: a randomized controlled trial. *Medicine (Baltimore)*. 2020;99(11), e19556.
80. Chan C, et al. Exercise telemonitoring and telerehabilitation compared with traditional cardiac and pulmonary rehabilitation: a systematic review and Meta-analysis. *Physiother Can*. 2016;68(3):242–251.
81.. Serves N, et al. Adherence to rehabilitation and home exercise after myocardial infarction: a qualitative study of expectations, barriers and drivers. *BMC Sports Sci Med Rehabil*. 2023;15(1):98.
82. Xu D, et al. The effectiveness of remote exercise rehabilitation based on the "SCeiP" model in homebound patients with coronary heart disease: randomized controlled trial. *J Med Internet Res*. 2024;26, e56552.
83. Piotrowicz E, et al. Effects of a 9-week hybrid comprehensive telerehabilitation program on long-term outcomes in patients with heart failure: the telerehabilitation in heart failure patients (TELEREH-HF) randomized clinical trial. *JAMA Cardiol*. 2020;5(3):300–308.
84. Spindler H, et al. Conventional rehabilitation therapy versus telerehabilitation in cardiac patients: a comparison of motivation, psychological distress, and quality of life. *Int J Environ Res Public Health*. 2019;16(3).
85. Cavalheiro AH, et al. Effectiveness of tele-rehabilitation programs in heart failure: a systematic review and meta-analysis. *Health Serv Insights*. 2021;14, 11786329211021668.
86. Scherrenberg M, et al. The need for long-term personalized management of frail CVD patients by rehabilitation and telemonitoring: a framework. *Trends Cardiovasc Med*. 2023;33(5):283–297.
87. Imran HM, et al. Home-based cardiac rehabilitation alone and hybrid with center-based cardiac rehabilitation in heart failure: a systematic review and meta-analysis. *J Am Heart Assoc*. 2019;8(16), e012779.
88. Thomas RJ, et al. Home-based cardiac rehabilitation: a scientific statement from the American Association of Cardiovascular and Pulmonary Rehabilitation, the American Heart Association, and the American College of Cardiology. *Circulation*. 2019;140(1):e69–e89.
89. Heindl B, et al. Hybrid cardiac rehabilitation - the state of the science and the way forward. *Prog Cardiovasc Dis*. 2022;70:175–182.
90. Chong MS, et al. A theory-based, technology-assisted intervention in a hybrid cardiac rehabilitation program for patients with coronary heart disease: a feasibility study. *Asian Nurs Res (Korean Soc Nurs Sci)*. 2023;17(3):180–190.
91.. Racodon M, et al. Comparison between hybrid cardiac rehabilitation and center-based cardiac rehabilitation: a noninferiority randomized controlled trial. *Int J Rehabil Res*. 2025;48(1):25–30.
92.. Wu C, Li Y, Chen J. Hybrid versus traditional cardiac rehabilitation models: a systematic review and meta-analysis. *Kardiol Pol*. 2018;76(12):1717–1724.
93. Marchionni N, et al. Improved exercise tolerance and quality of life with cardiac rehabilitation of older patients after myocardial infarction: results of a randomized, controlled trial. *Circulation*. 2003;107(17):2201–2206.
94.. Campo G, et al. Exercise intervention improves quality of life in older adults after myocardial infarction: randomised clinical trial. *Heart*. 2020;106(21):1658–1664.
95.. Ushijima A, et al. Effects of cardiac rehabilitation on physical function and exercise capacity in elderly cardiovascular patients with frailty. *J Cardiol*. 2021;77(4):424–431.
96. Schoenenberger AW, et al. Predictors of functional decline in elderly patients undergoing transcatheter aortic valve implantation (TAVI). *Eur Heart J*. 2013;34(9):684–692.
97.. Nakaya Y, et al. Early cardiac rehabilitation for acute decompensated heart failure safely improves physical function (PEARL study): a randomized controlled trial. *Eur J Phys Rehabil Med*. 2021;57(6):985–993.
98.. Valenzuela PL, et al. Physical strategies to prevent disuse-induced functional decline in the elderly. *Ageing Res Rev*. 2018;47:80–88.
99. Izquierdo M, et al. International exercise recommendations in older adults (ICFSR): expert consensus guidelines. *J Nutr Health Aging*. 2021;25(7):824–853.
100.. Fiuza-Luces C, et al. Exercise benefits in cardiovascular disease: beyond attenuation of traditional risk factors. *Nat Rev Cardiol*. 2018;15(12):731–743.
101.. Sherrington C, et al. Exercise to prevent falls in older adults: an updated systematic review and meta-analysis. *Br J Sports Med*. 2017;51(24):1750–1758.
102.. Bull FC, et al. World Health Organization 2020 guidelines on physical activity and sedentary behaviour. *Br J Sports Med*. 2020;54(24):1451–1462.
103.. Russomanno G, et al. The anti-ageing molecule sirt1 mediates beneficial effects of cardiac rehabilitation. *Immun Ageing*. 2017;14:7.
104. Caicedo-Pareja M, et al. Physical exercise intervention characteristics and outcomes in frail and pre-frail older adults. *Geriatrics (Basel)*. 2024;9(6).
105.. Kidd T, et al. What are the most effective interventions to improve physical performance in pre-frail and frail adults? A systematic review of randomised control trials. *BMC Geriatr*. 2019;19(1):184.
106.. Tamuleviciute-Prasciene E, et al. The impact of additional resistance and balance training in exercise-based cardiac rehabilitation in older patients after valve surgery or intervention: randomized control trial. *BMC Geriatr*. 2021;21(1):23.
107. Premer C, et al. Rethinking endothelial dysfunction as a crucial target in fighting heart failure. *Mayo Clin Proc Innov Qual Outcomes*. 2019;3(1):1–13.
108. Erbs 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. *Circ Heart Fail*. 2010;3(4):486–494.
109. Eleuteri E, et al. Aerobic training and angiogenesis activation in patients with stable chronic heart failure: a preliminary report. *Biomarkers*. 2013;18(5):418–424.
110. Sandri M, et al. Chronic heart failure and aging - effects of exercise training on endothelial function and mechanisms of endothelial regeneration: Results from the Leipzig Exercise Intervention in Chronic heart failure and Aging (LEICA) study. *Eur J Prev Cardiol*. 2016;23(4):349–358.
111. Legallois D, et al. Cardiac rehabilitation improves coronary endothelial function in patients with heart failure due to dilated cardiomyopathy: a positron emission tomography study. *Eur J Prev Cardiol*. 2016;23(2):129–136.

112. Angadi SS, et al. High-intensity interval training vs. moderate-intensity continuous exercise training in heart failure with preserved ejection fraction: a pilot study. *J Appl Physiol (1985)*. 2015;119(6):753–758.
113. Turri-Silva N, et al. High-intensity interval training versus progressive high-intensity circuit resistance training on endothelial function and cardiorespiratory fitness in heart failure: a preliminary randomized controlled trial. *PloS One*. 2021; 16(10), e0257607.
114. Kourek C, et al. The acute and long-term effects of a cardiac rehabilitation program on endothelial progenitor cells in chronic heart failure patients: comparing two different exercise training protocols. *IJC Heart Vasc*. 2021;32, 100702.
115. Kitzman DW, et al. Effect of endurance exercise training on endothelial function and arterial stiffness in older patients with heart failure and preserved ejection fraction: a randomized, controlled, single-blind trial. *J Am Coll Cardiol*. 2013;62(7): 584–592.
116. Benda NM, et al. Effects of high-intensity interval training versus continuous training on physical fitness, cardiovascular function and quality of life in heart failure patients. *PloS One*. 2015;10(10), e0141256.
117.. do Nascimento DM, et al. Functional training improves peak oxygen consumption and quality of life of individuals with heart failure: a randomized clinical trial. *BMC Cardiovasc Disord*. 2023;23(1):381.
118. Mirkowski K, et al. Frailty and heart failure: clinical insights, patient outcomes and future directions. *Card Fail Rev*. 2025;11, e05.
119.. Tsigkou V, et al. The prognostic role of galectin-3 and endothelial function in patients with heart failure. *Cardiol J*. 2023;30(5):725–733.
120. Kourek C, et al. The effects of a cardiac rehabilitation program on endothelial progenitor cells and inflammatory profile in patients with chronic heart failure of different severity. *J Clin Med*. 2023;12(20).
121.. Sun WT, et al. Potential preservative mechanisms of cardiac rehabilitation pathways on endothelial function in coronary heart disease. *Sci China Life Sci*. 2025;68(1):158–175.
122. Ritchey MD, et al. Tracking cardiac rehabilitation participation and completion among medicare beneficiaries to inform the efforts of a national initiative. *Circ Cardiovasc Qual Outcomes*. 2020;13(1), e005902.
123.. Santiago de Araujo Pio C, et al. Interventions to promote patient utilisation of cardiac rehabilitation. *Cochrane Database Syst Rev*. 2019;2(2), CD007131.