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Flow-mediated dilation and heart failure: a review with implications to physical rehabilitation

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Abstract
Endothelial dysfunction plays as an important role on mismatch responses that occur during exercise in patients with congestive heart failure (CHF). However, cardiac rehabilitation, a core component of management of CHF patients, can improve endothelial function, contributing to reduce the morbidity and mortality of these patients. The primary aims of this review were to describe the importance of flow-mediated dilatation (FMD) as a non-invasive validation tool to assess endothelial dysfunction and to highlight the relevance of scientific studies that evaluated the effects of exercise interventions on peripheral vascular endothelial function as measured by FMD in patients with CHF with both preserved and reduced ejection fraction.

Keywords Endothelial function · Exercise · Physical training · Cardiac rehabilitation · Heart failure

The role of the endothelium in regulating vascular health

The endothelium plays an important role in maintaining vascular homeostasis. Endothelial cells control vascular function by responding to various hormones, neurotransmitters, and vasoactive factors which affect vasomotion, thrombosis, platelet aggregation, and inflammation [1]. In response to various chemical (acetylcholine, ACh) or physical (shear stress) stimuli, the endothelium modulates vasomotor tone, by synthesizing and releasing different vasodilators and vasoconstrictors [1, 2]. The endothelium-derived relaxing factors (EDRF), which contribute to the mechanism of endothelial function, include nitric oxide (NO), prostaglandin I_2 (PGI_2), and the purported endothelium-derived hyperpolarizing factor (EDHF). While there are also endothelium-derived contracting factors (EDCFs), this review focuses on the EDRF.

NO has been shown to play an important role in the maintenance of basal vasodilator tone of blood vessels and plays a key role in vasodilation [3, 4]. It also prevents platelet adhesion and aggregation, as well as leukocyte adhesion and migration into the arterial wall, and inhibits smooth muscle cell proliferation and intimal migration, oxidation of LDL cholesterol, apoptosis of smooth muscle cells, all key events in the development of atherosclerosis [5, 6].

Mechanism of flow-mediated vasodilation

Flow-mediated dilation (FMD) is an important physiological stimulus regulating vascular tone and homeostasis of the peripheral circulation. This important endothelial mechanism of vasodilation occurs in virtually every vascular bed. In large arteries, FMD may be critical for preventing atherosclerosis through NO release. In humans, a reduction in FMD is prognostic of cardiovascular disease (CVD). Animal studies have reported that the contribution of NO to FMD is reduced as oxidative stress increases in the presence of risk factors for CVD [5, 6]. In humans, in vivo and in vitro studies have demonstrated that relaxant factor(s), other than NO, compensate to maintain FMD when NO availability is reduced [7, 8]. Altered endothelium-dependent FMD is a hallmark of the development of CVD and is an initiating event in the development of atherosclerotic heart disease [9–11]. During coronary artery

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disease (CAD), the microcirculation exhibits altered endothelium-dependent vasodilation [12]. In humans, Phillips et al. have shown that hydrogen peroxide (H_2O_2) replaces NO as the mediator of endothelium-dependent flow-induced dilation in resistance arteries of visceral fat in the presence of CAD [8]. An increase in oxidative stress appears to be a major mechanism underlying the development of vascular endothelial dysfunction. The dominant mechanism responsible for endothelial dysfunction is the decrease in bioavailable NO, as well as the increase in reactive oxygen species (ROS) production. The generation of ROS in the endothelium includes anions (O_2), hydroxyl radicals (OH·), and hydrogen peroxide (H_2O_2). ROS modulate vascular tone by several mechanisms, directly act as EDCF, or indirectly potentiate EDCF-mediated responses by reducing the bioavailability of NO. ROS can interact with NO and reduce its bioavailability via several pathways: direct NO inactivation by superoxide with peroxynitrite ($ONOO^-$) formation, reduction in NO synthase expression and activity due to changes in their substrate or cofactors, and also endothelial NOS uncoupling [1].

Method of evaluating flow-mediated dilation

The endothelium occupies a unique position in that it is able to secrete a variety of vasoactive molecules and is also exposed to direct vascular injury. It is thus an important mediator of atherosclerosis formation and is widely perceived to be a metric of vascular risk. Previous studies have demonstrated a correlation between measures of coronary vasodilator function and FMD [13]. Early studies established that attenuated vascular responses occur prior to the development of atherosclerosis in response to a milieu of risk factors, thus making measurements attractive as a screening tool for cardiovascular (CV) risk [10, 11]. Endothelial function is dynamic and can be attenuated rapidly in response to acute oxidative stress (cigarette smoking, high fat, heavy exertion). In addition, interventions that are associated with a decrease in vascular risk will improve vasodilation within a period of weeks allowing one to determine the impact of novel interventions in a timely fashion. It is important to note that the changes in FMD over time during a treatment intervention have been found to be a prognostic marker of CV disease over a single FMD measurement [14] (Fig. 1).

The most common way to evaluate endothelial function in humans is through the technique of brachial artery flow-mediated dilation. The first report by Celermajer et al. [15] showed the measurement of peripheral artery FMD in 1992. Not only were they able to describe a new method, but also demonstrated that children with familial hypercholesterolemia had impaired function at an early age. Since then, thousands of studies have been reported using this methodology. The guidelines for measuring brachial artery FMD were previously summarized [16, 17]. Briefly, a high-resolution (> 10 MHz) linear array ultrasound probe is used to longitudinally image the brachial (or radial) artery at rest. A thin blood pressure (BP) cuff is inflated to supra-systolic pressure for 5 min on either the forearm or on the upper arm. After the cuff is released, the artery dilates in response to shear stress-mediated NO release and maximum dilation typically occurs between 45 and 120 s [18]. After a 5-min recovery period, sublingual nitroglycerine may be given to assess endothelium-independent dilation. The FMD response (with lower arm occlusion) has been shown to be mediated primarily by NO; thus, it reflects endothelium-dependent vasodilation [4, 19]. In addition, it is important to state that adhering firmly to the guidelines favors the reduction of variability between evaluations and increase reproducibility. Factors such as food intake, pretest physical exercise, caffeine, alcohol intake, drug use, sleep deprivation, and small baseline vascular diameter may interfere with the response to FMD and are important factors to be followed for better test quality [20]. Two large cohort studies, the Cardiovascular Health Study (CHS) [21] and the Multi-ethnic Study of Atherosclerosis [22], demonstrated that FMD was an independent predictor of CV outcomes. In addition, during coronary disease, reduced brachial FMD is associated with greater extent of coronary disease involvement. FMD remains the standard tool for research studies designed to understand the effects of novel risk factors or treatments on peripheral artery conduit vessel function.

Pathophysiology of endothelial function in CHF with reduced left ventricular ejection fraction

The vascular endothelium has direct influence in various physiological process related to arterial homeostasis. Particularly, NO produced by vascular endothelium is the main factor of blood flow control [23–25]. It is known that vascular dysfunction is common in CHF patients, with the reduced endothelium-derived vasodilator stimulus being the primary responsible for the endothelial dysfunction and for vasodilation-vasoconstriction imbalance [26].

In CHF, various factors are responsible for this characteristic endothelium dysfunction, such as increasing of hormone factors, with the sympathetic system [27], angiotensin II, endocrine and paracrine [28], and inflammatory cytokine (tumor necrosis factor [TNF]-α, interleukin (IL)-1, IL-6, IL-18) being responsible for increasing of inflammation, and risen by oxidative stress [29]. That stimulus culminates with increases in ROS which decrease the bioavailability of NO and negatively impact in the endothelium constitutive NO synthase (eNOS) expression and activation therefore produce endothelium dysfunction [30] (Fig. 2).

In addition to endothelial dysfunction, other studies have demonstrated that autonomic changes during heart failure including enhanced sympathetic nervous system activation

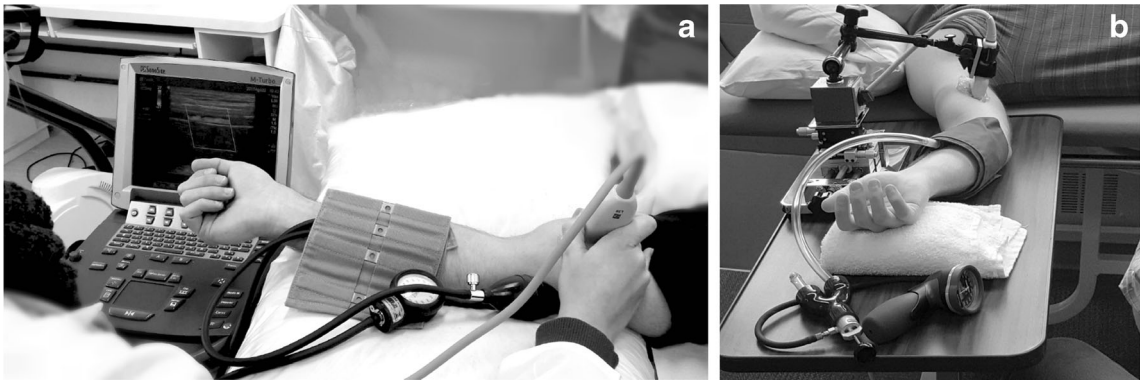

Fig. 1 Flow-mediated dilation technique

modify the vasodilatation response at rest and during exercise stimulus. [27, 31, 32]. The sympathetic system is considerably hyperactivates in CHF patients, mainly due to high catecholamine plasmatic levels which impose high vasoconstrictor status on these patients [33, 34]. In addition, inhibition of the cardiovascular sympathetic reflexes by suppression of baroreceptors reflex activity and increase of sympathetic afferent and arterial chemoreceptor reflexes are dysfunctions associated with sympathetic dysfunction in the CHF patients [35].

Study that assessed the influence of sympathetic system on endothelial activity showed that the administration of phentolamine (α adrenergic receptor blocker) with infusion of

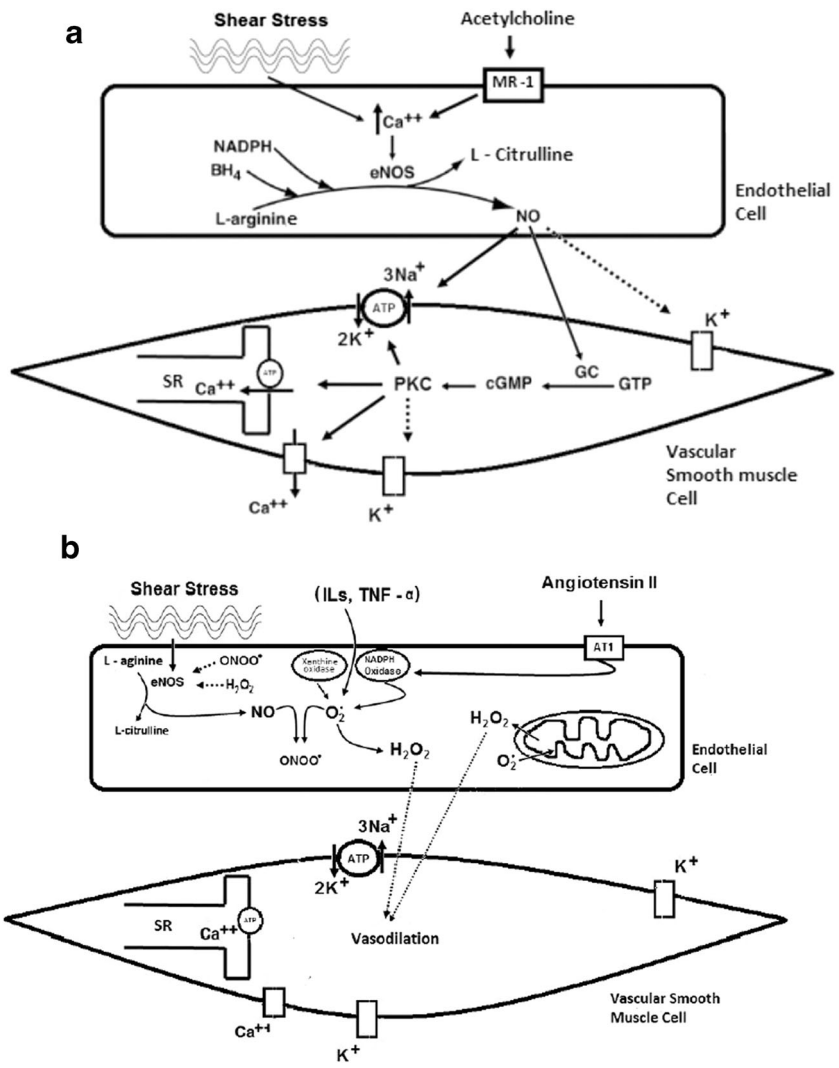

Fig. 2 Endothelial dysfunction caused by inflamatory process, endocrine system, and oxidative stress, which increase reactive oxygen species and deacrease NO and eNOS, imparing vascular smooth cell relax mediated by endothelium. ILs: interleukins, TNF-α: tumor necrosis factor α-type, AT1: type 1 angiotensin II receptor, O^-: superoxide anion, $ONOO^-$: peroxynitrite, H_2O_2: hydrogen peroxide

acetylcholine increase blood flow in vascular bed close to normal values, both at rest and after exercise, demonstrated expressive influence of sympathetic system on endothelial dysfunction [36].

In CHF, the muscle system presents sympathetic hyperactivity which produces persistent maintenance of vasoconstriction, as well as attenuated vasodilatation activity thus generates great tissue hypoxemia associated with inflammatory response, promoting great muscular dysfunction at rest as well as during physical exercise [27, 32].

An important way to investigate vascular dysfunction due to vascular endothelial changes is through FMD, which is an important and widely common non-invasive technique to assess vascular and endothelium function [15], and has a strong correlation with other vessels as coronary and arterioles functions which allows to infer the coronary function through analysis of peripheral vessels. In CHF patients, a reduction in FMD has been shown to be an important predictor of worse clinical events [37], hospitalization [37], and death [38].

Current studies have sought to clarify the difference between the severity of vascular dysfunction in patients and individuals without cardiovascular disease, and lower values of FMD (percentage) are found in individuals with CHF compared to apparently healthy volunteers [39]. However, an existing difficulty is to verify the cut-off value for better or worse prognosis given the heterogeneity of FMD response in these patients [40, 41]. Apparently, the FMD response is different among CHF etiologies, and individuals who developed CHF due to myocardial infarction have lower values of FMD when compared to non-ischemic patients [42, 43].

In addition, there is a tendency for FMD stratification according to symptoms of CHF by the New York Heart Association (NYHA) scale independent of ejection fraction. Individuals without symptom (grade I) present values close to those without heart disease, and the most symptomatic patients have lowest values of FMD [39, 44]. Even though it is known that the symptomatology is quite broad in CHF syndrome, values that facilitate the understanding of vascular dysfunction-symptom relationship also ease up the approach in intervention to cardiac patients.

A very important recent observation is related to how much shear stress the cardiac patient has and how much this stress favors the dilatation response to the conductance and resistance vessels. Due to left ventricular impairment due to CHF, there is reduction of blood flow in the peripheral arteries, which produces lower shear stress and results in lower NO production, reducting the endothelium-dependent vasodilation [29]. Studies have shown that shear stress may be as important as the vascular dilatation caused by it, which is an important stimulus to the other signs and symptoms related to CHF. Paine et al. [45] demonstrated that the flow caused by reactive hyperemia had a better correlation in the cardiac disorder and was related to greater functional impairment than the FMD itself, being an important and possible confounding variable.

Another important role of FMD in CHF is the fact that it can enlighten the disease progression. Studies demonstrated the effect of drug and physical rehabilitation on FMD, issues that will be explored ahead [46, 47]. Regarding heart transplantation and vascular reponse, Witman et al. [48] performed a longitudinal study which verified the FMD response after heart transplantation and the progression of vascular health over the years. The authors observed that FMD of patients undergoing heart transplantation was similar to those of non-heart disease patients, and obviously higher than patients with CHF. However, over the years, values tended to decrease, a fact that is still unknown and requires further investigation.

In summary, FMD is important for the recognition of vascular dysfunction, adjuvant for quantifying the severity of the disease and for its prognosis, and for follow-up of the short-, medium-, and long-term treatment of individuals with CHF.

Pathophysiology of endothelial function in CHF with preserved left ventricular ejection fraction

The pathophysiology of endothelium function in patients with CHF with reduced ejection fraction (HFrEF) has been more commonly addressed, while studies involving patients with preserved left ventricle ejection fraction (HFpEF) and its consequences on endothelium function are still scarce.

Over the time and considerations regarding the knowledge of the HFrEF, more specifically on endothelial dysfunction, due to the multiple mechanisms, however, an action of ROS triggers produced during comorbidity-induced endothelial inflammation may trigger a signaling (NO) cascade, which ultimately increases interstitial fibrosis and activates cardiac remodeling. These actions contribute to the characteristics of HFpEF: ventricular rigidity, impaired relaxation, and cardiac dysfunction in patients with HFpEF; ROS produced during comorbidity-induced endothelial inflammation may trigger signaling nitric oxide (NO) cascade, which ultimately increases interstitial fibrosis and activates cardiac remodeling. These actions contribute to the characteristics of HFpEF: ventricular rigidity, impaired relaxation, and cardiac dysfunction [49].

Moreover, it is speculated that the integration of the central (endothelial cells of the coronary vessels, but more important of the intramyocardial capillaries and endocardium), peripheral (skeletal muscle) and cardiovascular systems (risk factors) play an important role in this process [50–52]. Assuming that the peripheral endothelial cells and coronary endothelial cells can justify a preserved ejection fraction [50], in addition, the contribution of the pulmonary vascular system is substantial, since it represents a larger endothelial surface of the body, serving as a single major source of endothelial mediators [50]. Physiologically, NO represents a central piece in

homeostasis, for regulation, vasomotor permeability, and antiplatelet aggregation function, maintaining vascular integrity [53–55].

However, comorbidities may lead to endothelial dysfunction and/or to loss of physiological properties of the vessel and proinflammatory properties that induce release or deprivation of vasomotor regulatory substances [56, 57], triggers in L-arginine deprivation, eNOS, arginase [58], and reduced expression from eNOS [59]. Some risk factors such as diabetes, obesity, dyslipidemia, smoke, and hypertension have been associated with endothelial cell abnormalities in an experimental study [60]. These comorbidities induce a systemic inflammatory state, whose consequence is the production of ROS through activation of nicotinamide adenine dinucleotide phosphate oxidases [61]. Moreover, arterial hypertension has been effectively involved with the pathophysiology of HFpEF. It is believed that cardiac structures and abnormalities, including ischemia, increased arterial stiffness, myocardial fibrosis, result in chronic hypertension, resulting in chemotactic protein 1 (MCP1) and TNF-α, and fibrogenic activators, such as transforming growth factor beta (TGFb) that would be the main factor to increase inflammatory and fibrotic processes [62].

The importance of the pathophysiology of inflammatory markers has been debated. Westermann et al. [62] investigated ventricular and diastolic function in 20 patients with HFpEF and 8 controls using conduction catheter methods and echocardiography. The authors demonstrated in endomyocardial biopsy samples of right side of the ventricular septum accumulation of cardiac collagen decrease in the system of major collagenase (matrix metalloproteinase-1) and growth factor β in patients with HFpEF [62]. In addition, the authors evidenced myocardial injury with increased wall stress in the pathophysiology of patients with preserved EF. These physiological processes can explain the high oxidative stress, which was recently visualized in HFpEF myocardium using both nitrotyrosine and dihydroethidium staining [62].

In summary, the physiology pathogy of HFpEF is complex and multifactorial; however, the importance of endothelial destruction or deterioration early onset of the pathogenesis of HFpEF is notorious.

Therefore, given the importance for early and specific treatment, resources such as physical exercise can be an attractive and effective resource, acting not only on patients' quality of life but also acting on the protection of the endothelium, fibrosis, and in the inflammatory process.

Impact of rehabilitation on FMD in the CHF

Chronic heart failure is a multiorgan disease affecting all steps in the oxygen transport pathway reducing muscle O_2 supply while concurrently increasing O_2 demands [63]. Although a dysfunctional heart and impaired ability to generate cardiac output are the principal events, the harm in other systems involved in the exercise response, such as the ventilatory system, the skeletal muscle, the neurohumoral system, and the endothelial function, has encompassed the pathophysiological mechanisms that explain the exercise intolerance in HF [64]. The vascular endothelium plays an important role in the regulation of arterial tone therefore in the blood flow during exercise to the exercising muscles. The release of NO is stimulated for, e.g., by serotonin, thrombin, acethylcoline, and also by increased laminar shear stress, as occurs during exercise. The shear stress in turn produces mechanical stimulus to potassium channel activation that could facilitate calcium influx to the endothelial cells. The increasing intracellular calcium level activates endothelial NO synthase promoting NO bioavailability [64, 65].

In patients with HFrEF, there is a growing body of evidence to the date suggesting exercise training as a key tool to improve endothelial dysfunction [46, 66–70]. In order to evaluate the effects of exercise interventions on peripheral vascular endothelial function as measured by FMD, Vuckovic et al. [69] showed that different types of exercise training (aerobic, resistance, or combined) of variable duration (4 to 16 weeks) improved endothelium-dependent vasodilation, independent of age, NYHA class (I-III), and HF etiology. The same result was not found regarding endothelium-independent vasodilation though. It is not clear if the exercise can improve the response of vascular smooth muscle or if this response is affected by nitrate medications. Therefore, the mechanisms by which exercise training affects endothelium-independent vasodilation still require further explanation. Although different kinds of exercise training had a positive effect on endothelial function, different types of protocols made it difficult to recommend the optimal training intensity, duration, and frequency for patients with HFrEF, NYHA I-III. Besides, it remains unclear if combined exercise is more effective than aerobic exercise alone on endothelium function [69]. A review and meta-analysis of 51 studies ($N = 2260$) [71] investigated the effects of exercise modalities on FMD in patients with diverse health status (HF, prehypertension, hypertension-HTN, coronary artery disease-CAD, obese, overweight, postmenopause, heart transplant, type 2 diabetes, prostatectomy, metabolic syndrome, pregnancy, peripheral artery disease, and healthy). All exercise modalities improved endothelial function significantly, yet since there was a greater improvement on endothelial function in subjects with low baseline FMD, the authors suggested that combined exercise interventions are more beneficial in populations at greater cardiovascular risk.

The intensity of exercise seems to be an important factor for improving endothelial function. In a miscellaneous population [71], all intensities—light to vigorous—of aerobic exercise enhanced endothelial function and there was a dose-response relationship between aerobic exercise intensity and FMD. Every 2-MET in absolute exercise intensity or 10% increase of $\dot{V}O_2$ peak

was associated with 1% unit improvement in FMD. Because of the higher shear stress caused by greater exercise intensity, there may have been a greater release of NO [71]. Comparing the effects of aerobic interval training (AIT, walking on treadmill, bouts of 4 min at 90–95% peak heart rate (HR) interspersed by 3-min active pauses at 50–70% of peak HR, total exercise time of 38 min) and moderate continuos training (MCT, 70–75% peak HR for 47 min to make sure the trainings were isocaloric) both 3 times per week for 12 weeks, in HF patients, Wisløff et al. [46] observed a close relationship between greater aerobic capacity and improved FMD and a superior improvement on FMD by AIT than by MCT. AIT also increased the antioxidant status in blood plasma, which indicated reduced oxidative stress and therefore increased bioavailability of NO. The authors speculated that higher shear stress during the exercise bouts of AIT triggered greater responses at the cellular and molecular levels. Ramos et al. [65] also showed that high intensity interval training (HIIT—commonly used HIIT prescription was 4 × 4 at 85–95% max or peak HR interspersed by 3 min of active recovery at 60–70% peak HR, 3 times per week for 12–16 weeks) provided a more potent stimulus than MCT in enhancing vascular function in a diverse group of patients (post-myocardial infarction, HTN, metabolic syndrome, CAD, obesity, type 2 diabetes, postmenopause). On the other hand, in patients with HFrEF, a recent review and meta-analysis [70] showed that remains unclear if the magnitude of improvement in endothelial function, assessed by FMD, increases with intensity of exercise as both vigorous and moderate aerobic exercise training improved endothelial function. There was a trend toward HIIT providing a greater improvement than MCT. The same happened when HIIT and no training were compared.

Regarding resistance exercise training, Ashor et al. [71] advocated greater frequency rather than intensity enhanced endothelial function in a diverse population including HFrEF patients. The best resistance exercise prescription remains to be determined though.

Hornig et al. [66] compared 12 HFrEF stable patients (NYHA III) with seven age-matched controls after 4 weeks of handgrip training (nondominant arm, intensity at 70% of maximal workload, 30 min daily) and found the impaired FMD in patients with HF was restored by physical training most likely by increasing endothelial release of NO. However, the beneficial effect of exercise training on endothelial function was restricted to the trained extremity, suggesting a local mechanism, and was lost 6 weeks after cessation of training. In accordance with these results, although using a different exercise protocol, Kobayashi et al. [67] investigated the effects of supervised cycle ergometer exercise training, intensity at HR corresponding to ventilatory threshold or rating of 13 in the 20-grade Borg scale, for 2–3 days per week, 15 min twice a day, for 3 months in HFrEF patients (NYHA II-III) and compared with age-matched controls. The authors found an improvement on FMD in the trained lower limbs but not in the untrained upper limbs which suggests that the correction on endothelial dysfunction was particularly achieved by a rise in endothelial response to shear stress [67]. Thus, a systemic exercise program may be preferable to localized exercise training.

Patients with advanced HF may also benefit from exercise training. In 2010, Erbs et al. [68] investigated whether regular physical exercise training improves peripheral vasomotor function in patients with advanced HF (NYHA IIIb). Third, seven patients were assessed and randomly assigned to training group or control group. Eighteen patients underwent to exercise training (first 3 weeks in hospital, 3–6 times per day, 5–20 min, bicycle, intensity at 50% $\dot{V}O_2$ peak/12 weeks home-based, 20–30 min per day, bicycle, intensity at HR reached at 60% of $\dot{V}O_2$ peak, and patients were also expected to participate in one supervised group training session for 60 min each week consisting of walking, calisthenics, and noncompetitive ball games). In the training group, FMD completely normalized compared to control group so exercise training appears to be a promising therapy for patients with advanced HF. Not only did exercise training improve exercise capacity and clinical symptoms but also induced endogenous vascular repair in patients with advanced HF. However, even with evidence that therapies that improve cardiovascular outcome also seem to improve endothelial function, given the prognostic value of FMD, it would seem logical that at least some of these beneficial effects may be mediated by an improvement in endothelial function. However, it will remain difficult to promote the idea that reversal of endothelial dysfunction should be a primary target of CHF.

Unlike HFrEF, there is limited data suggesting improvement of exercise capacity in patients with HF with preserved ejection fraction (HFpEF). The primary symptom in HFpEF is severe exercise intolerance and severely reduced quality of life [72]. Central and peripheral impairments limit $\dot{V}O_2$ peak although recent data have suggested that peripheral noncardiac factors play a greater role in limiting $\dot{V}O_2$ peak thus exercise performance in HFpEF [73]. The arterial function and the skeletal muscle function compose the two main noncardiac factors that may lead to O_2 delivery-to-utilization mismatch therefore contribute to limit exercise capacity in HFpEF. Intrinsic arterial stiffness, reduced vasodilation stimuli, and reduced microvascular perfusion can cause impairment of arterial function [72] albeit abnormal FMD is not intrinsic to HFpEF patients and may not be an important contributor to severe exercise intolerance [74–76].

Lee et al. compared the resting FMD of patients with symptomatic HFpEF (NYHA II-IV) with healthy volunteers of the same age and demonstrated that a greater shear stresses compromise related to miscrovascular function than a reduction of FMD of the brachial conductance artery, which translates into a normal reduction of the event and not the impact of the syndrome itself. Haykowsky et al. compared healthy age-matched and older patients with HFpEF after cardiopulmonary exercise

test and FMD in the brachial artery and they did not find further decline in FMD beyond the one that occurs due to aging; thus, FMD may not be a fundamental component of pathophysiology of HFpEF. In addition, FMD had a modest ($r = .19$; $p = .048$) relationship with $\dot{V}O_2$ peak, and there was no significant relationship after adjustment for age, gender, and body size ($r = .009$; $p = .93$). Consequently, other peripheral factors, such as reduced oxygen utilization by the active muscles, majorly contribute to the reduced exercise capacity in elderly HFpEF patients (Haykowsky 2013). Another study analyzed the effects of endurance exercise training (ET) on FMD and carotid artery stiffness in older patients with HFpEF, NYHA II-III. Thirty-two patients underwent a 16-week ET (3 times per week, initially at 40–50% of HR reserve for 5-10 min each of walking on a track and cycle ergometry; the intensity was progressively increased until 70% of HR reserve and maintained for 20 min either walking and cycle ergometry; patients also performed isolated arm ergometry for ≥ 10 min each session to ensure upper extremity physical training). Compared to HFpEF controls, ET did not improve brachial FMD or arterial stiffness so the improvements in $\dot{V}O_2$ peak may be related to microvascular and/or skeletal muscle adaptations [73]. However, even though there is no reduction in the endothelial function of patients with this syndrome and due to the high heterogeneity of the syndrome presentation, there is still a need for better clarification about the vascular impact in this condition.

The effects of exercise intensity in HFpEF patients have not been established yet. In a pilot study, Angadi et al. [77] compared HIIT and MCT on $\dot{V}O_2$ peak, left ventricular (LV) diastolic dysfunction, and endothelial function in patients with HFpEF. The HIIT was performed on a treadmill, 4 × 4-min intervals at 85–90% peak HR, separated by 3-min active recovery at 50% peak HR, 3 days per week for 4 weeks. In turn, the MCT consisted of 15 min of continuos exercise at 60% peak HR, increasing to 30 min at 70% of peak HR by the start of second week. HIIT improved $\dot{V}O_2$ peak by an average of 9% (19.2 to 21.0 ml/kg/min) and the LV diastolic dysfunction by approximately 1 grade (2.1 to 1.3). However, FMD remained unchanged (6.9 to 7.0%). The authors attributed the latter to the relatively short period of training or possibly because baseline FMD was not so impaired. In addition, the absence of vasodilatory function effects after HIIT in HFpEF patients may be another explanation despite the small sample size.

The summary of the effects of exercise training on FMD in both HFrEF and HFpEF is shown in Table 1.

Impact of FMD on resynchronization therapy

In addition to the impact of CHF, changes caused by exacerbation and advanced HF have also been investigated on vascular endothelial function. Cardiac resynchronization therapy (CRT) is a well-recognized and highly effective treatment strategy for patients with advanced HF [78]. The use of CRT is associated with 37% relative risk reduction in HF hospitalization when compared with medical therapy alone [79]. Furthermore, CRT in selected HF patients reduced mortality by 22% and improved quality of life [79, 80]. However, at least 30% of patients receiving CRT do not respond to treatment based on current selection criteria [81]. For this, it is crucial to find other parameters that would better identify responders from nonresponders to CRT.

Akar et al. [82] focused on the novel concept that abnormal vascular endothelial function as assessed by FMD of the brachial artery may be a potential basis for predicting response to CRT in terms of functional status. FMD was measured at baseline preimplant and at 90 days postimplant in 33 HF patients (left ventricular ejection fraction [LVEF] 25 ± 9%; NYHA class III–IV) undergoing CRT. Of these, 19 (58%) patients who experienced improvements in LV ejection fraction, 6-min walk distance, and quality of life were considered responders to CRT. The authors reported that baseline FMD was significantly lower among responders compared with nonresponders. Importantly, baseline endothelial dysfunction remained a statistically significant after adjustment for QRS duration (which was prolonged in both responders and nonresponders), and cardiac dyssynchrony, suggesting that FMD may provide additive prognostic value over routine contemporary markers [82].

Damage of peripheral and coronary circulation with endothelial dysfunction has been shown to be involved in the pathogenesis of HF. Several studies have reported that peripheral endothelial dysfunction is associated with the severity of HF, clinical outcome, and mortality in patients with HF [37, 83, 84].

Yufu et al. [85] tested the hypothesis that assessment of peripheral endothelial function is associated with the long-term outcome of CRT and its linkage to coronary flow reserve (CFR). Thirty-four patients implanted with CRT for the treatment of advanced HF were evaluated at baseline (before CRT) and 6–8 months after CRT. Endothelial function was evaluated by measurement of reactive hyperemia peripheral arterial tonometry (RH-PAT). The authors demonstrated that, based on the receiver-operating characteristic curves, patients with decreased RH-PAT index (RHI) (defined as ≤ 1.5) demonstrated higher prevalence of new hospitalization due to HF progression, and RHI values were positively correlated with the 6–8-month change of CFR. The results suggest that the baseline peripheral endothelial function could predict the long-term outcome of CRT and that improvement of coronary microcirculation might be associated with the better baseline endothelial function [85].

CRT induces a significant improvement in patients with HF, who are often characterized by the presence of endothelial dysfunction (ED) with FMD. However, candidates to CRT with defibrillator (CRT-D) and its effects are still unclear.

Table 1 The summary of the effects of exercise training on FMD in both HFrEF and HFpEF

Study	Study design; participants	Exercise characteristics	Outcomes
Vuckovic et al.	Review; HFrEF	Different types of exercise training (aerobic, resistance or combined) Variable duration (4 to 16 weeks) Variable intensity (resistance: 30–65% MVC)/aerobic: MCT 50–85% peak HR, 60–80% peak $\dot{V}O_2$; 70% peak O_2 consumption at VT; AIT 90–95% peak HR)	Improvement of endothelium-dependent vasodilation, independent of age, NYHA class (I-III) and HF etiology. Endothelium-independent vasodilation did not change
Ashor et al.	Systematic review and meta-analysis; HFrEF, prehypertension, hypertension-HTN, coronary artery disease-CAD, obese, overweight, postmenopause, heart transplant, type 2 diabetes, prostatectomy, metabolic syndrome, pregnancy, peripheral artery disease, and healthy	Different types of exercise training (aerobic, resistance or combined) Variable duration (4 to 24 weeks) Variable intensity (aerobic: 50–95% HR_{max}, 50–100% peak $\dot{V}O_2$; 45–85% HRR; 3.6–6 MET, 2 ± 0.5 lactate; 12–14/20 Borg scale)	All exercise modalities improved endothelial function significantly (FMD increased by 2–2.8% units) Combined exercise interventions are more beneficial in populations at greater CV risk Dose-response relationship between aerobic exercise intensity and FMD (every 2-MET increase or 10% peak $\dot{V}O_2$ in absolute exercise intensity was associated with approximately 1% unit improvement in FMD)
Wisløff et al.	Randomized control trial; HFrEF	AIT: walking on treadmill, bouts of 4 min at 90–95% peak HR interspersed by 3-min active pauses at 50–70% of peak HR, total exercise time of 38 min/MCT: 70–75% peak HR for 47 min to make sure the trainings were isocaloric; 3 times per week for 12 weeks	Superior improvement on FMD by AIT than by MCT Close relationship between greater aerobic capacity and improved FMD
Ramos et al.	Systematic review and meta-analysis; post myocardial infarction HF, HTN, metabolic syndrome, CAD, obesity, type 2 diabetes, postmenopause	Aerobic exercise training Commonly used HIIT prescription: 4 × 4 at 85–95% max or peak HR interspersed by 3 min of active recovery at 60–70% peak HR, 3 times per week for 12–16 weeks	HIIT provided a more potent stimulus than MCT in enhancing vascular function (FMD increased 4.31% following HIIT vs 2.15% following MCT)
Pearson et al.	Systematic review and meta-analysis; HFrEF	Aerobic exercise training Variable duration (4 to 26 weeks) Variable intensity for both HIIT and MCT	Both vigorous and moderate aerobic exercise training improved endothelial function HIIT showed a trend greater than MCT on FMD improvement
Hornig et al.	Two-group experimental study; HFrEF vs healthy control	Handgrip training (non-dominant arm) at 70% max workload, 30 min, daily, for 4 weeks	Impaired FMD was restored by physical training This benefit is restricted to the trained extremity and is lost 6 weeks after cessation
Kobayashi et al.	Randomized clinical trial; HFrEF	Aerobic exercise training (cycle ergometer), 2–3 days per week, 15 min twice a day, for 3 months, intensity at HR corresponding to VT or rating 13/20 Borg scale	Improvement on FMD in the trained lower limbs but not in the untrained upper limbs
Erbs et al.	Randomized clinical trial; advanced HFrEF	Aerobic exercise training First 3 weeks in-hospital, bicycle, 3 to 6 times per day, 5 to 20 min, at 50% $\dot{V}O_2$ max/12 weeks home-based, bicycle, 20–30 min per day, at HR reached at 60% $\dot{V}O_2$ max and 1 supervised group training session for 60 min each week (walking, calisthenics, and noncompetitive ball games)	Exercise training completely normalized FMD
Kitzman et al.	Randomized clinical trial; HFpEF	Aerobic exercise training 1 h (10 min warm-up, 40 min walking, cycle ergometry and arm ergometry, 10 min recovery), 3 times per week for 16 weeks Intensity: initially at 40–50% of HR reserve for 5–10 min each of walking on a track and cycle ergometry,	Exercise training did not improve brachial FMD or arterial stiffness

Table 1 (continued)

Study	Study design; participants	Exercise characteristics	Outcomes
		progressively increased until 70% of HR reserve and maintained for 20 min either walking cycle ergometry Isolated arm ergometry for ≥ 10 min each session	
Angadi et al.	Randomized clinical trial (pilot study); HFpEF	Aerobic exercise training 3 days per week for 4 weeks HIIT: 4 × 4min, treadmill, at 85–90% peak HR interspersed by 3 min active recovery at 50% peak HR MCT: 15 min at 60% peak HR, increasing to 30 min, at 70% peak HR by the start of 2nd week	FMD remained unchanged (6.9 to 7.0%) after HIIT No changes on FMD were observed after MCT

Santini et al. [86] studied 57 consecutive patients affected by HF and undergoing CRT-D. At baseline, the authors recorded a high prevalence of ED (64.9%) with impaired FMD (4.1 ± 3.8%). After 12 months of CRT, a marked increase of the mean FMD ($P < 0.05$) with significant improvement of left ventricular ejection fraction (LVEF), left ventricular end-systolic volume (LVESV), New York Heart Association (NYHA) functional class, and 6-min walk test (6MWT) were shown. FMD was related to LVEF ($P < 0.05$), LVESV ($P < 0.05$), NYHA functional class ($P < 0.05$), and 6MWT ($P < 0.01$). The authors concluded that not only is ED an independent predictor of CRT response, but also is able to intercept the systemic effects of CRT and is an affordable marker of response to CRT [86].

The improvement of ED after CRT has been demonstrated; however, the mechanisms that determine this response have not yet been clarified. Tesselaar et al. [87] investigated whether the endothelium-dependent reactivity of the peripheral microcirculation improves in HF patients during the first 2 months of CRT. The results showed that CRT improves endothelium-dependent vasodilatory capacity in the peripheral microcirculation within 2 months of therapy, with improvement in functional capacity in patients with HF [87].

Conclusion

Endothelial dysfunction is common in CHF. However, physical exercise can positively modulate vascular function. In addition, resynchronization therapy in advanced HF can reduce deleterious effects of endothelial dysfunction. Future studies, however, should be encouraged to evaluate the potential effect of physical training, considering the types of training (purely aerobic, resisted, or combined) as well as considering the different training intensities (low, moderate, and high intensity) and duration to recommend more precise parameters of the prescription when the objective is directed to enhance positive changes of the endothelial function in these patients.

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