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Diastolic dysfunction in exercise and its role for exercise capacity

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Abstract Diastolic dysfunction is frequent in elderly subjects and in patients with left ventricular hypertrophy, vascular disease and diabetes mellitus. Patients with diastolic dysfunction demonstrate a reduced exercise capacity and might suffer from congestive heart failure (CHF). Presence of symptoms of CHF in the setting of a normal systolic function is referred to as heart failure with normal ejection fraction (HFNEF) or, if evidence of an impaired diastolic function is observed, as diastolic heart failure (DHF). Reduced exercise capacity in diastolic dysfunction results from a number of pathophysiological alterations such as slowed myocardial relaxation, reduced myocardial distensibility, elevated filling pressures, and reduced ventricular suction forces. These alterations limit the increase of ventricular diastolic filling and cardiac output during exercise and lead to pulmonary congestion. In healthy subjects, exercise training can enhance diastolic function and exercise capacity and prevent deterioration of diastolic function in the course of aging. In patients with diastolic dysfunction, exercise capacity can be enhanced by exercise training and pharmacological treatment, whereas improvement of diastolic function can only be observed in few patients.

Keywords Diastolic dysfunction · Diastolic heart failure · Exercise capacity

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The importance of diastole for cardiac function in terms of cardiac output and exercise capacity has been elucidated in the past few years. Isolated diastolic dysfunction is frequent in elderly subjects and in patients with left ventricular hypertrophy, diabetes, and vascular disease. Diastolic dysfunction with preserved systolic function has been identified as a cause for exertional dyspnea and exercise intolerance, and nearly half of the patients with new onset of congestive heart failure (CHF) demonstrate isolated diastolic dysfunction [1]. Thus, diastolic dysfunction represents a pathologic entity with high prevalence and morbidity which needs early dedicated treatment in order to prevent progression to severer grades. It is well known that exercise intolerance due to cardiac dysfunction can be ameliorated by exercise training. This accounts for systolic as well as for diastolic impairment of cardiac function.

The purpose of this article is to thoroughly review the literature in order to provide an overview of the role of diastole for cardiac function at exercise in normal subjects and the physiologic alterations that limit cardiac output and exercise capacity in patients with diastolic dysfunction. Furthermore, the possibilities of exercise training and pharmacological interventions for the treatment of patients with diastolic dysfunction are described and recommendations for exercise training are given.

Definition of diastolic dysfunction

Diastole is referred to as the phase of the cardiac cycle during which myocardial fibers relax and return to their non-contracted length and geometry, and during which left ventricular filling takes place. Left ventricular pressure during diastole takes a bidirectional course. Onset, velocity, and extent of myocardial relaxation and left ventricular

untwisting determine the drop of left ventricular pressure during early diastole, whereas the time course of left ventricular filling and myocardial elastic properties (distensibility and stiffness) are the determinants of the reincrease of left ventricular pressure during late diastole.

To establish the diagnosis of diastolic dysfunction, evidence of a slow left ventricular relaxation, an abnormal left ventricular filling, a reduced diastolic distensibility, or an increased left ventricular stiffness is required [2]. Parameters that are used to evaluate diastolic function are usually obtained at rest. However, there is evidence that diastolic dysfunction can be present at exercise in patients with normal diastolic function at rest [3, 4]. The finding of diastolic dysfunction by abnormal mechanical properties of the left ventricle in diastole does not imply the presence of clinical symptoms. Patients with clinical symptoms that are related to an impaired diastolic function might be classified as patients with diastolic heart failure (DHF).

Definition of diastolic heart failure

Different propositions have been made to establish the diagnosis of DHF. The criteria proposed by the European Study Group on Diastolic Heart Failure comprise (a) signs or symptoms of CHF; (b) a normal or only mildly abnormal left ventricular systolic function, generally defined as an ejection fraction (EF) $\geq$ 45%; and (c) an abnormal diastolic function [2]. This definition has been challenged by a study that examined diastolic function by simultaneous cardiac catheterization and echocardiography in 63 patients with a history of CHF and echocardiographic evidence of normal systolic function (EF $\geq$ 50%) and LV hypertrophy [5]. It could be shown that all 63 patients showed at least one abnormal parameter of diastolic function. The authors concluded that measurements of diastolic function are not necessary to make the diagnosis of DHF in patients with symptoms and signs of CHF and a normal systolic function. The term DHF is not used uniformly throughout literature. Often, the same clinical syndrome is referred to as heart failure with normal ejection fraction (HFNEF) of which the definition rather emphasizes the presence of symptoms of CHF and a normal systolic function and neglects the evidence of an abnormal diastolic function. However, in patients with HFNEF, a slow myocardial relaxation and an increased left ventricular stiffness were observed as evidence for an impaired diastolic dysfunction [6]. Since it does not seem of importance for the issue that is addressed in this manuscript whether DHF and HFNEF are different entities or synonyms for one syndrome, the term DHF will be used throughout the manuscript for both.

Diagnosis of diastolic dysfunction

Since extensive review of the modalities to diagnose an impaired diastolic function has been provided elsewhere [7–9], only a brief synopsis is given.

Invasive measurement of intracardiac pressures

An increase of the time constant τ of the left ventricular pressure decay [10] with a value $>$ 48 ms [9], a left ventricular end-diastolic pressure (LVEDP) $>$ 16 mmHg [11], and a mean pulmonary capillary wedge pressure (PCWP) $>$ 12 mmHg [12] are indicative of an impaired diastolic function. Prolongation of τ is suggestive for a slow myocardial relaxation, whereas elevated values for LVEDP and PCWP indicate a reduced myocardial distensibility. An increase in muscle stiffness can be identified by an increase of the slope of the pressure-volume relationship (dP/dV) in the pressure-volume plot.

Echocardiography

Doppler flow measurements can reveal a prolonged isovolumetric relaxation time (IVRT) as a measure of a slow relaxation. A ratio of peak mitral flow velocity during early (E) and late (A) diastolic filling $<$ 1 and a deceleration time of the early flow velocity (DT) $>$ 220 ms [13] represent evidence of a slow early left ventricular filling. A ratio of systolic (S) and diastolic (D) pulmonary vein peak flow velocity $<$ 1 indicates an elevated left atrial pressure resulting in a reincrease of the early mitral flow velocity and thus normalizing the E/A-ratio. Therefore, Doppler analysis of the pulmonary vein flow allows to distinguish between a normal mitral valve flow pattern and a "pseudonormal" pattern with elevated left atrial pressure [8]. A reduction of the A-wave velocity due to an increased myocardial stiffness results in an abnormally high increase of the E/A-ratio $>$ 2. This "restrictive filling pattern" is associated with a poor prognosis [14]. The mitral anular velocity during early diastolic filling (E′) correlates closely with LV relaxation kinetics and with age, whereas E from transmitral flow is dependent on LV filling pressure, on age, and on LV relaxation kinetics. Therefore, the ratio of E/E′ eliminates the influence of age and left ventricular relaxation kinetics and can be interpreted as the ratio of LV-filling pressure and early left ventricular filling. An E/E′-ratio $>$ 15 indicates diastolic dysfunction with high LV-filling pressures whereas an E/E′-ratio $<$ 8 excludes DHF [9, 15].

Biomarkers

The degree of diastolic dysfunction is closely related to the plasma level of natriuretic peptides such as atrial natriuretic

peptide (ANP) and brain natriuretic peptide (BNP). Increasing values of BNP could be found with increasing degree of diastolic dysfunction by means of Doppler measurements of transmitral flow [16, 17]. However, due to a low specificity and multiple conditions with presence of elevated BNP levels, such as pulmonary disease [18], pulmonary embolism [19], renal dysfunction [20], and sepsis [21], BNP does not serve as a screening tool to detect diastolic dysfunction but is rather recommended to exclude DHF in patients with exertional dyspnea [9].

Normal diastolic function in exercise

During physical exercise, cardiac output can increase several times over the value at rest [22]. The increase in cardiac output is achieved by an increase in heart rate and stroke volume [23]. Increases in heart rate result in a shortening of the time for diastolic filling, and increases in stroke volume demand that higher volumes of blood be shifted from the left atrium to the left ventricle during that time period. In fact, acceleration of diastolic left ventricular filling has been observed in healthy subjects and greater increases of diastolic filling rate were found in endurance trained athletes compared to normal subjects [24]. Acceleration of diastolic filling during exercise in normal subjects is provided by a shortened myocardial relaxation [25] due to an increased calcium uptake by the sarcoplasmic reticular [26], an increased elastic recoil after a more complete systolic contraction, a higher myocardial untwisting rate, and a faster intraventricular pressure decay in early diastole [27]. Also, sympathetic stimulation causes a downward shift of the early diastolic portion of the left ventricular pressure loop [28]. These mechanisms create a suction force in the left ventricle resulting in an increase of the transmitral pressure gradient [29], enhancement of transmitral flow, and acceleration of left ventricular filling without elevation of left atrial pressures.

Diastolic dysfunction in exercise

In diastolic dysfunction, the mechanical properties of the left ventricle are altered to an extent that diastolic filling is delayed, slowed, shortened, or associated with elevated left-ventricular pressures. The ability to enhance transmitral flow and accelerate diastolic filling at exercise is therefore reduced.

A number of studies compared the response of diastolic transmitral flow to resistance exercise in patients with diastolic dysfunction and in normal subjects. In these studies, resistance exercise led to an increase of late diastolic filling velocity of $6 \pm 5\%$ [30] and the late proportion of diastolic filling [31] and caused a drop of early diastolic flow velocity and of the early proportion of total diastolic filling of $16 \pm 4\%$ [32] in patients compared to normals. In diabetic patients without diastolic dysfunction at rest a greater increase of the ratio of late to early diastolic flow velocity was shown compared to normal subjects (0.29 ± 0.2 vs. 0.09 ± 0.07) suggesting that latent diastolic dysfunction can be unmasked by resistance exercise [33].

Other studies examined the diastolic transmitral flow pattern at aerobic exercise. In a group of patients with hypertension and diastolic dysfunction at rest with a reduced E/A ratio, the transmitral flow pattern became pseudonormal with increase of the E/A-ratio at maximal exercise indicating an exercise induced rise in atrial pressure[34]. Another study group showed an increase of the E/A-ratio up to 2.4 ± 1.5 with a S/D-ratio < 1 and a smaller increase of flow propagation velocity after exercise in patient with CHF compared to normals suggesting an increase of diastolic filling pressures and reduced suction forces [35]. In one study an elevated E/E′-ratio at rest in patients with exertional dyspnea was a good predictor of a short exercise duration in a symptom-limited exercise test compared to patients with a normal E/E′-ratio (426 vs. 625 s) [36]. Since no differences of transmitral flow velocities could be found between patients with elevated and normal E/E′-ratio, left ventricular filling pressures might reveal diastolic dysfunction earlier than the transmitral flow pattern alone.

Diastolic dysfunction is accompanied by neurohumoral activation which might be triggered or intensified by exercise. In patients with normal left ventricular function at rest but elevated filling pressures at exercise as measured by cardiac catheterization, elevated NT-proBNP levels were found compared to controls with normal filling pressures at exercise (median 145. 2 pg/ml [range 69.7–273.4] vs. 38.3 pg/ml [range 22.1–64.7]) [37]. Also, an elevated E/E′-ratio is associated with increased BNP levels after exercise in patients with diastolic dysfunction [38] or suspected DHF [39]. Exercise activates the renin-angiotensin-aldosteron system and causes increased plasma levels of angiotensin II (AT II) [40–42]. AT II prolongs the time constant τ of myocardial relaxation mediated through activation of AT_1 receptors. In CHF, prolongation of τ is even stronger and myocardial contractility is depressed by AT II [43]. Elevated plasma levels of AT II could, therefore, play a role for exercise intolerance in patients with DHF and might be a target for pharmacological treatment.

Diastolic dysfunction is associated with a number of other alterations at exercise. It is correlated with an increase of pulmonary blood volume at exercise [44] and a reduced coronary flow velocity reserve at peak dose dobutamine [45]. Furthermore, the submaximal ventilation

equivalent for carbon dioxide is higher, whereas peak oxygen consumption and tidal volume are lower in patients with diastolic dysfunction compared to normal subjects [46]. Also, patients with diastolic dysfunction report greater dyspnea at submaximal exercise than controls. Inspiratory muscle weakness and a breathing pattern with rapid shallow breaths were found compared to the controls which might account for the perception of dyspnea [47].

Certain clinical conditions are associated with a normal diastolic function at rest but an impaired diastolic function during or after exercise. Evidence of an exercise induced impairment of diastolic function caused by myocardial ischemia was found in patients with coronary artery disease [48] and angina pectoris [49]. Exercise induced diastolic dysfunction could also be found in patients with type 1 diabetes mellitus [4] and in patients with hyperlipidemia and a normal stress ECG [3]. It was hypothesized that exercise induced diastolic dysfunction in these patients might be an early sign of subclinical myocardial ischemia. However, impairment of diastolic dysfunction by exercise is not only limited to the time of exercise. In a number of studies persistence of exercise induced diastolic dysfunction was described 30 min [50, 51], 1 h [52], and up to 2 days [53] after stress testing in patients with coronary artery disease. The incidence and magnitude of diastolic impairment was determined by the severity of the exercise induced ischemia [52] suggesting that ischemia results in myocardial stunning which can persist even a long time after resolution of the ischemic condition.

Diastolic dysfunction and exercise capacity

The enhancement of diastolic left ventricular filling is a crucial determinant for the increase of cardiac output at exercise. Impairment of diastolic function can result in the inability to increase cardiac output adequately and can limit exercise capacity. Hypertensive rats developing left ventricular hypertrophy with normal systolic function but abnormal diastolic function can lose more than 25% of their initial exercise capacity suggesting that exercise intolerance was caused by diastolic dysfunction [54]. Similar observations are made in humans. Patients with isolated diastolic dysfunction due to type 2 diabetes [55] and arterial hypertension [56] demonstrate maximal workloads that are 1.9 and 2.5 metabolic equivalents (METs), respectively, lower than matched controls without diastolic dysfunction. In another study, maximal workloads were more than 80 watts and maximal specific oxygen uptake 41% lower in patients with diastolic dysfunction than in normals [46] (Table 1). Also, a negative correlation exists between exercise capacity and left ventricular stiffness in hypertensive patients [57] and an index of left ventricular filling pressure at exercise (duration of diastolic reverse pulmonary vein flow and mitral flow at atrial contraction) in patients with acromegaly [58].

In patients with symptoms of congestion due to DHF, reduction of exercise capacity is even more severe. The extent of exercise intolerance in DHF is even comparable to patients with systolic heart failure [59]. Comparative studies of patients with DHF and matched controls revealed a reduction of maximal specific oxygen uptake between 38 and 29% and a reduction of maximal workload between 31% and 50% [59–63] (Table 2). Therefore, reduction of exercise capacity represents a major clinical problem in patients with diastolic dysfunction and, more pronounced, in DHF. Hence, reversal of exercise intolerance constitutes a main target for treatment in these patients.

Pathological left ventricular filling pressures are consequence of diastolic dysfunction. The importance of elevated filling pressures for the limitation of exercise capacity is well known for patients with impaired systolic function [64]. More recent results claim a relation between filling pressure and exercise capacity also for patients with diastolic dysfunction. A study with a larger number of patients found that a reduced exercise capacity was even better related to elevated left ventricular filling pressures at rest than to an impaired myocardial relaxation. In that study, an E/E'-ratio ≥ 10 was the best predictor of a low maximal metabolic equivalent [65]. In another study, E/E' was the most powerful predictor not only of exercise capacity but also of reduced peak oxygen uptake. An E/E'-ratio > 7.5 was able to predict a reduction of peak oxygen uptake ≤ 14 ml/min per kg with high sensitivity and specificity [66].

Table 1 Studies comparing exercise capacity of patients with diastolic dysfunction and matched controls

Diastolic dysfunction	No. of patients and controls ($N =$)	Age (years)	VO2 (ml/kg/min)	Exercise duration (s)	Workload
Dekleva 2000	40 vs. 20	53 vs. 47	12.1 vs. 12.7	–	4.6 vs. 7.1 METs
Poirier 2000	10 vs. 9	52 vs. 50	–	662 vs. 803	9.5 vs. 11.4 METs
Palmieri 2006	18 vs. 55	45 vs. 38	–	825 vs. 895	6.8 vs. 7.1 METs
Arruda 2007	40 vs. 47	66 vs. 63	18.7 vs. 31.7	390 vs. 684	138 vs. 220 W

Values for specific oxygen uptake (VO2), exercise duration, and workload represent values at maximal exercise. Workload is either given in metabolic equivalents (METs) or in watts. All values are given for patients and controls

Table 2 Studies comparing exercise capacity of patients with diastolic heart failure in New York Heart Association classes I–III and matched controls

Diastolic heart failure	No. of patients and controls ($N = $)	Age (years)	VO2 (ml/kg/min)	Exercise duration (s)	Workload
Hundley 2001	10 vs. 10	77 vs. 71	13.2 vs. 20.3	360 vs. 840	–
Kitzman 2002	59 vs. 28	70 vs. 68	14.2 vs. 19.9	449 vs. 637	58 vs. 83 W
Borlaug 2006	17 vs. 19	65 vs. 65	9.0 vs. 14.4	180 vs. 455	37 vs. 74 W
Brubaker 2006	59 vs. 28	70 vs. 68	14 vs. 20	368 vs. 619	47 vs. 80 W
Witte 2006	61 vs. 102	69 vs. 63	22.5 vs. 36.2	562 vs. 846	–

Values for specific oxygen uptake (VO2), exercise duration, and workload represent values at maximal exercise. All values are given for patients and controls

Since diastolic dysfunction and elevated filling pressures are associated with elevated levels of natriuretic peptides, the level of BNP in relation to exercise capacity was investigated in patients with exertional dyspnea and isolated diastolic dysfunction. It could be shown that patients with BNP $\geq$ 50 pg/ml had a lower peak oxygen uptake and anaerobic threshold than patients with BNP $<$ 50 pg/ml [67]. Therefore, the degree of neurohumeral activation by diastolic dysfunction seems to be correlated to the severity of exercise intolerance.

However, reduced exercise capacity in patients with diastolic dysfunction does not seem to be merely related to diastolic function itself. Comparing matched groups of patients with diastolic dysfunction and DHF, the latter showed a more profound reduction of exercise capacity, a smaller increase in heart rate and cardiac output, and less systemic vasodilation despite a similar rise in end-diastolic volume, stroke volume, and contractility [60]. Other studies found a greater intraventricular conduction delay (IVCD) in patients with diastolic dysfunction and increase of aortic stiffness in patients with DHF compared to normals. Exacerbation of dyssynchrony after exercise was noted in the group of patients with DHF which was positively correlated with post-exercise NT-pro BNP [68]. Therefore, exercise intolerance in DHF can be caused by alterations that might be associated with diastolic dysfunction but are not related to the mechanical myocardial properties determining diastole.

Treatments to improve exercise capacity in diastolic dysfunction

Since a reduced exercise capacity is frequent in patients with diastolic dysfunction and represents a major limitation of their quality of life, numerous studies have investigated the possibilities to improve exercise capacity in those patients. Interventions that have been examined comprise exercise training and pharmacological treatment.

Exercise training

It is well known that exercise training improves diastolic function in healthy subjects. Trained subjects demonstrate a higher increase of peak diastolic filling rate during exercise compared to untrained subjects [69]. Especially, endurance training shows beneficial effects on diastolic function. An interventional study with 6 months of intensive aerobic endurance training in young and elderly subjects demonstrated improvement of diastolic function at rest and exercise. Remarkably, in both groups improvement of the early part of diastolic filling was achieved, whereas only in the group of elderly subjects reduction of the initially elevated atrial filling rate could be shown [70]. A number of observational studies compared diastolic function in highly trained endurance athletes and in normal subjects. At rest, despite an increased left ventricular mass in endurance athletes, early to late diastolic filling ratio was either unchanged [71] or even slightly increased [72]. During exercise, endurance athletes demonstrate an up to 71% higher ventricular filling rate at corresponding heart rates compared to normal subjects resulting in a higher stroke volume [24]. Also, enhanced peak early diastolic filling [71, 73], an increased early to late diastolic filling ratio [71], and greater peak lengthening rate, filling volume, and filling fraction of the left ventricle during the first 100 ms of diastole [74] were found in endurance athletes. In addition, it could be shown that diastolic filling dynamics in endurance-trained elderly subjects are more similar to younger subjects than to untrained elderly subjects [75, 76], which provides evidence that endurance training not only improves diastolic function in healthy subjects but also prevents deterioration of diastolic function in the course of aging.

However, the effect of exercise training on diastolic function and exercise capacity in patients with preexisting diastolic dysfunction has only been examined in few studies (Table 3). Patients with diastolic dysfunction show an improvement of exercise tolerance by training but the effects of training on diastolic function are less clear. In a study with patients with

Table 3 Studies examining exercise training or medical treatment in patients with isolated diastolic dysfunction with regard to exercise capacity

	No. of patients	Intervention + Duration	Frequency + Intensity	Improvement of exercise capacity
Exercise training				
Yu 2004	127	Aerobic exercise 8 weeks Thereafter: Walking 6 months	2 × per week for 2 h 65–80% of max. HR Daily for 1 h	Exercise duration and MET improved No numeric values are given
Loimaala 2007	24	Jogging or walking 12 months	2 × per week for 2 h 65–70% of VO2max	VO2 2.7 ml/kg/min
Smart 2007	18	Cycle ergometry 16 weeks	3 × per week for 1 h 60–70% of VO2max	VO2 3.7 ml/kg/min
Braasard 2007	11	Cycle ergometry 12 weeks	3 × per week for 1 h 60–70% of VO2max	VO2 4.1 ml/kg/min
Medical treatment				
Warner 1999	20	Losartan 50 mg/d 2 weeks	–	Exercise duration 60 s
Nodari 2003	26	(A) Nebivolol 5 mg/d or (B) Atenolol 100 mg/d 6 months	–	VO2max (A) 1.2 ml/kg/min (B) No improvement
Little 2004	21	Candesartan 16 mg/d 2 weeks	–	Exercise duration 52 s
Little 2006	19	Losartan 50 mg/d 6 months	–	Exercise duration 57 s
Mottram 2004	15	Spironolactone 25 mg/d 6 months	–	Exercise duration No improvement
Yip 2008	151	Diuretics alone or D + Irbesartan 75 mg/d or D + Ramipril 10 mg/d 24 weeks	–	6-minute-walking-distance No improvement

Values for exercise duration, metabolic equivalent (MET), and specific oxygen uptake (VO2) represent the mean difference to baseline

coronary artery disease who underwent a rehabilitation program with regular exercise training for at least 8 weeks, only the subgroup of patients with an abnormal left ventricular relaxation pattern showed significant improvement of diastolic function [77]. Another study in patients with type 2 diabetes mellitus and diastolic dysfunction who performed exercise training 4 times weekly for 12 months could not find a change in tissue Doppler indices of diastolic function but a significant improvement of maximal specific oxygen uptake of 8% [78]. Also, a recent study of patients with diastolic dysfunction and exercise intolerance who underwent a 16-week aerobic training program 3 times per week demonstrated a significant increase of exercise capacity of 19% and of peak oxygen uptake of 30% but no change of diastolic function [79]. Therefore, the gain in exercise capacity seems to be related rather to peripheral mechanisms, such as improvement of muscular aerobic metabolism, muscular mass, vasculature, and coordination. Only a small study of type 2 diabetics with diastolic dysfunction found an improvement of diastolic function after 3 months of exercise [80]. Therefore, despite improvement of exercise capacity and evidence for the beneficial effect of exercise training on diastolic function in healthy subjects, the subgroups of patients with diastolic dysfunction who respond to exercise training with improvement of diastolic function are not yet identified.

Pharmacological treatment

The effect of pharmacological treatment on exercise tolerance and diastolic function in patients with impaired diastole has been evaluated in a number of studies (Table 3). In patients with diastolic dysfunction by means of Doppler echocardiography and a hypertensive response to exercise, increased exercise tolerance and improved quality of life was found after only 2 weeks of treatment with losartan [81]. Similar effects on the blood pressure response were found with short-term verapamil and long-term hydrochlorotiazide compared to candesartan [82] and losartan [83], respectively, but improvement of exercise tolerance and quality of life was only found in the patients treated with candesartan and losartan. It was hypothesized that increase of AT II during exercise might be responsible for a slowed left ventricular relaxation and can

be antagonized by AT II antagonism. This would explain the beneficial effect of AT II antagonists already after short-term treatment. AT II increase during exercise is not suppressed by ACE-inhibition [84] which might lead to the assumption that ACE-inhibition could be less effective in improving exercise tolerance in patients with diastolic dysfunction than AT II antagonism. However, in a study comparing diuretics alone and the combination of diuretics with ramipril and irbesartan, respectively, no significant advantage regarding exercise capacity and quality of life was found for any of the treatment arms [85]. Only indices of left ventricular long axis motion and BNP-levels were slightly improved under ramipril and irbesartan compared to diuretics alone. In a small study improvement of resting and post-exercise diastolic function could be observed in a group of 11 patients with borderline hypertension after 24 weeks of ACE-blockade [86]. Unfortunately, no data on exercise performance were reported in that study. Therefore, other mechanisms than mere AT II antagonism such as reduction of afterload or myocardial fibrosis might be the mode of action for all inhibitors of the renin-angiotensin-aldosteron-system. Consequently, it could be shown that treatment with aldosterone receptor antagonists improved E/A ratio and deceleration time in elderly patients with diastolic dysfunction [87]. In another study, increased exercise tolerance in patients with isolated diastolic dysfunction could be achieved by treatment with an aldosteron antagonist but no significant change of the indices of diastolic function could be observed and the improvement of exercise tolerance was attributed to an enhancement of systolic function [88]. ß-blockers have also shown to improve exercise capacity and E/A ratio in patients with diastolic dysfunction. However, no change of left ventricular filling pressures at rest and during exercise could be achieved [89]. Therefore, similar to exercise training, pharmacological treatment of patients with diastolic dysfunction enhances exercise capacity but improvement of diastolic function is limited and occurs only in few patients.

Recommendations for exercise training in diastolic dysfunction

To date no guideline or consensus document explicitly addresses the prescription of exercise training in patients with isolated diastolic dysfunction. However, since there is growing evidence of the beneficial effects of exercise training in patients with diastolic dysfunction, exercise prescription is likely to be suited to maintain or regain quality of life for these patients. However, patients with isolated diastolic function are rather of higher age and show a considerable prevalence of relevant comorbidities. Therefore, care must be taken to exclude patients with contraindications for exercise training (Table 4).

Table 4 Contraindications for exercise training

Acute congestive heart failure
Symptomatic or severe aortic stenosis
Recent electrocardiogram changes or recent myocardial infarction
Unstable angina
Resting ST displacement (>3 mm)
Resting systolic blood pressure > 200 mmHg or resting diastolic blood pressure > 110 mmHg
Resting systolic pulmonary arterial blood pressure > 60 mmHg
Aortic dissection
Uncontrolled atrial or ventricular arrhythmias
Third-degree heart block without pacemaker
Active pericarditis or myocarditis
Recent embolism
Thrombophlebitis
Orthopaedic problems that would prohibit exercise
Acute systemic illness or fever
Uncontrolled metabolic disease (e.g. uncontrolled diabetes mellitus)

Recommendations for exercise prescription in patients with CHF and other cardiovascular diseases have been published in the past [90, 91]. As long as no specific statements for patients with diastolic dysfunction are available, these recommendations represent the best evidence for beneficial effects in these patients. In brief, aerobic exercise is the training of choice since it demonstrates the best balance between beneficial cardiovascular, muscular, metabolic, and respiratory effects and associated risks such as cardiovascular or orthopedic events. It should be performed 3–5 times per week and should comprise a warm-up period of 10–15 min, an exercise time of 20–30 min, and a cool-down period. Exercise intensity can be low at 40–60% of peak VO2 [90] or moderate at 70–80% of peak VO2 [91]. Heart rate should be between 50% and 70% of maximal heart rate.

Resistance training also exerts beneficial effects on the musculo-skeletal system, on the glucose- and lipid-metabolism, and on the quality of life in CHF patients. Recently, the updated AHA statement for resistance exercise [92] pointed out the safety of resistance training in patients with cardiovascular disease, if performed correctly and at submaximal level. Resistance training should be performed 2–3 times per week with 8–10 different exercises. For each exercise a set of 8–12 repetitions with 70–80% of the maximal power is recommended for patients <50 years of age. Patients >50 years of age should perform sets of 10–15 repetitions at reduced levels of resistance.

Summary

Diastolic dysfunction can be caused by an abnormal myocardial relaxation or impaired left ventricular filling

dynamics. Patients with diastolic dysfunction can be asymptomatic or show clinical signs of DHF. However, diastolic dysfunction is associated with a reduced exercise capacity due to a slowed myocardial relaxation, reduced left ventricular suction forces, and elevated ventricular filling pressures. Exercise training and pharmacological treatment can enhance exercise capacity in patients with diastolic dysfunction, but the beneficial effect on diastolic function is small and is only observed in few patients.

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