29. Heart failure

Authors

Åsa Cider, PT, PhD, Physiotherapy Department, Sahlgrenska University Hospital, Gothenburg, Sweden

Raija Tyni-Lenné, PT, PhD, Associate Professor, Department of Physical Therapy, Karolinska University Hospital, Stockholm, Sweden

Maria Schaufelberger, MD, PhD, Associate Professor, Sahlgrenska University Hospital, Gothenburg, Sweden

Summary

Chronic heart failure has a multifactorial origin and reduced physical performance capacity is common in those who suffer from it. Changes in the peripheral blood circulation are likely just as important as left ventricular function in the reduction of physical performance capacity. Research from the past decade has shown that exercise clearly improves function in patients with heart failure, which is why exercise should be offered to these patients today as a part of treatment.

The table below gives a description of training methods with the levels of intensity, frequency and duration that have been scientifically studied. In day-to-day clinical work, we strive for a combination of aerobic central circulatory training and peripheral muscle training, 2–3 times per week, together with home training.

Table 1. Description of training methods investigated in different scientific studies in patients with chronic heart failure.

Training method	Intensity	RPE*	Frequency	Duration (min./session)
Aerobic central circulatory training	(40) 60–80% of VO_2 max**	11–15 central	1 time/week to several times/day	1–60
Peripheral muscle training	35–80% of 1 RM***	13–15 local	2 times/week to 1 time/day	15–60
Combination of aerobic central circulatory training and peripheral muscle training	60–80% of VO_2 max** 60–80% of 1 RM	13–15 central and local	3 times/week	45–60
Hydrotherapy	40–80% of HRR****	11–15	3 times/week	45
Respiratory muscle training	30% of max. inspiratory pressure		3 times/week to daily	30–60

* RPE = Rating of Perceived Exertion (Borg scale 6–20).

** VO_2 max = Maximal Oxygen Uptake.

*** RM = Repetition Maximum. 1 RM corresponds to the maximum weight that can be lifted through the entire exercise movement one time.

**** HRR = Heart Rate Reserve.

Suitable activities are aerobic exercise, for example, walking, exercising on land or in water, and cycling combined with peripheral muscle training with, for example, resistance bands (Thera-Band®) or weights and exercise pulleys. The latter form of training is especially suited in cases of pronounced impairment of physical performance capacity. During the exercise session, light to moderate exertion and light to moderate breathlessness are suitable levels of load.

Patients with stable heart failure with predominant systolic dysfunction, New York Heart Association (NYHA) class (I)-II-III, are best suited for exercise. Before training begins, there should be contact with a knowledgeable physiotherapist so that the patient can undergo aerobic and muscular physical function testing. Based on the outcomes of this, a suitable training programme is then drawn up.

Definition

The syndrome of heart failure has been defined in a number of ways, but no one definition is complete. A common definition is: Heart failure is a condition where the heart's pumping capacity is unable to meet the metabolic needs of the peripheral tissues (1).

Cause

In the Western world, ischaemic heart disease and hypertension (elevated blood pressure) are predominant causes of heart failure (2). Other etiological factors include diabetes, valvular disease, endocrine disorders, toxic effect, arrhythmia and systemic disease. There is also an idiopathic type, that is, where the cause is not known (1).

Prevalence/Incidence

The prevalence of heart failure varies between 0.3–2 per cent according to different sources and rises with increasing age, to approximately 10 per cent at 80 years of age (3, 4). The incidence of heart failure is also age-dependent and varies between 1–5 new cases per 1000 individuals per year (2). A Swedish registry study indicates that the incidence of heart failure is decreasing, in part due to improved medical care (5).

Pathophysiology

Loss of myocardial cells, changes in heart muscle tissue and contractility reduce the resting stroke volume. This is compensated for by activation of the neuroendocrine system through increased sympathetic system activity and activation of the renin-angiotensin system. This leads to a pathological remodeling in both the heart and the peripheral vascular system, progressive weakening of arterial and cardiopulmonary baroreflexes and a down-regulation of beta receptors in the heart. The parasympathetic heart activity is also reduced (1). The cause of the reduced exercise capacity in heart failure is complex. Haemodynamic variables at rest correlate poorly to maximal exercise capacity (6), while the correlation during exercise is better (7). It has been proposed that diastolic dysfunction may be more important for exercise capacity than systolic dysfunction (8). However, it is likely factors in the skeletal muscle that have the most significance for the reduction in exercise capacity (9). Peripheral blood flow is decreased due to reduced cardiac output and increased peripheral vascular resistance, which is mediated via changes in endothelial function and directly via vasoactive agents (10–12). Insulin resistance is reduced (13) in chronic heart failure and peripheral skeletal muscle mass is reduced (14, 15). Skeletal muscle strength and endurance are also reduced (16, 17). A change in muscle fibre composition and reduced oxidative capacity in skeletal muscle have also been reported. It moreover appears that inflammatory cytokines play an important role in loss of skeletal muscle mass and fatigue in chronic heart failure (18, 19). Skeletal muscle receptors that are sensitive to exercise, that is, ergoreceptors, are overactive. One of the tasks of these receptors is to control vascular constriction, which can be affected by exercise (20, 21). Whether these changes are contingent on physical inactivity or are a consequence of the heart failure syndrome itself is a topic of discussion (9, 22).

Symptoms and diagnosis

The diagnostic criteria recommended by the Task Force on Heart Failure of the European Society of Cardiology (23) are as follows:

1. Symptoms consistent with heart failure at rest or during exercise.
2. Objective evidence of cardiac dysfunction at rest.
3. Improvement in symptoms in response to treatment directed towards heart failure.

Points 1 and 2 should be met, while point 3 substantiates the diagnosis in cases where there is doubt. Fatigue, shortness of breath and reduced physical performance capacity are cardinal symptoms of heart failure. Functional capacity is often classified with NYHA criteria (24). Typical signs of heart failure are crackling sounds from the lungs, tachycardia, ventricular gallop, peripheral oedema, enlarged liver and stasis of the neck veins.

   Heart failure can be caused by systolic and/or diastolic dysfunction. In systolic dysfunction, the ventricular pumping capacity is impaired. Systolic function is usually measured as an ejection fraction (i.e. the stroke volume in relation to the total diastolic volume). Diastolic dysfunction is characterised by typical symptoms or signs of heart failure despite a normal ejection fraction, with concurrent signs of decrease in myocardial compliance. The diagnosis for systolic and/or diastolic dysfunction is made with the aid of a patient history, clinical examination, echocardiogram, x-ray and laboratory tests. Stress tests have limited diagnostic value in heart failure, but a normal stress test in an untreated patient rules out the diagnosis (25).

Prognosis

Despite the fact that the prognosis has improved in recent years (5), it is still poor, with a 5-year survival rate of approximately 50 per cent. The more symptoms a patient has, the worse the prognosis (2).

Treatment principles

The drugs most commonly used in the treatment of heart failure are diuretics, ACE inhibitors and beta blockers. Diuretics are used primarily to relieve symptoms. In addition to relieving symptoms, ACE inhibitors also have a prognostic effect. Beta blockers have a prognostic and symptomatic effect in moderate and severe heart failure. In patients with severe heart failure, spironolactone has a favourable prognostic effect. Angiotensin receptor blockers have been shown to reduce mortality in moderate and severe heart failure.

Effects of physical activity

Acute effects of aerobic exercise

The maximal oxygen uptake (VO_2 max) during arm exercise, cycling and walking in people with heart failure can be 30–40 per cent lower than in healthy individuals (26, 27). Maximal cardiac output is also decreased due to a decrease in maximal stroke volume and insufficient capacity to increase heart rate normally (28, 29). Systolic blood pressure does not increase normally (30), while the sympathetic activity increases more during exercise in patients with heart failure than in healthy individuals (31).

The respiratory minute volume (VE) is increased in patients with heart failure at every given load compared with healthy individuals. At maximal exertion, however, VE is approximately 50 per cent of predicted value, suggesting that this does not limit the exercise capacity (32). The ratio between minute ventilation and carbon dioxide production (VE/VCO_2) increases, and it is most often shortness of breath that is the limiting factor for physical activity in these patients.

The peripheral resistance during exercise decreases in patients with heart failure but is still higher than in healthy individuals. Normally, the blood flow in the skeletal muscle increases during aerobic exercise. In heart failure, the blood flow to the working muscles is reduced when large muscle mass is involved, which is the case with aerobic exercise (11). This results in anaerobic metabolism early on in the physical activity (33). Normal blood flow can be maintained, however, if the exercise is performed using a sufficiently small muscle mass (34).

Acute effects of muscle exercise

Isometric muscle exercise (static exercise)
In healthy individuals, the blood flow in the skeletal muscle in an isometric contraction is inhibited due to increased intramuscular pressure, which compresses the blood vessels (35). During isometric exercise, heart rate and systolic and diastolic blood pressure increase more in patients with heart failure than in healthy individuals (36). The increased afterload (the pressure that the ventricle is subjected to during the ejection phase, i.e. the expulsion resistance) that isometric exercise leads to could be harmful to patients with heart failure. However, in two Swedish studies patients with heart failure performed isometric exercise without any complications (16, 37).

Isotonic muscle exercise (dynamic exercise)
Exercise in the form of leg press at 60–80 per cent of maximum exertion does not yield a larger effect on haemodynamic variables than cycling. Neither does it yield a negative effect on left ventricular function (38, 39).

Acute effects of hydrotherapy

When the body is immersed in water, significant physiological changes occur. The physiological changes are due in part to the temperature and depth of the water. The pressure the body is subjected to is 0.74 mm Hg/1 cm H_2O. Immersion in thermoneutral water, approximately 35¡ C, to the upper edge of the sternum (suprasternal fossa) results in an increase in venous return that gives an increased blood volume in the heart. The increased preload results in a haemodynamic improvement with increased stroke volume and ejection fraction, while the heart rate remains unchanged or is somewhat lower. The result is an increase in cardiac output, while the mean arterial pressure is unchanged and the total peripheral resistance decreases due to vasodilatation in the peripheral tissues and abdominal organs (40).

The increased volume in the heart also stimulates cardiopulmonary receptors, which in turn signal the kidneys (via the brain) to reduce sympathetic stimulation and increase urine secretion (diuresis) and reduce the neurohormones renin, aldosteron and angiotensin II (41). This means that warm baths have a similar effect as that sought in modern drug treatment of heart failure. Even an increase in cardiac output, stroke volume and ejection fraction together with a decrease in peripheral resistance has been shown after warm baths. There is at present scientific debate regarding the benefits of hydrotherapy in heart failure. A group of German researchers (42) suggests that certain patients with severe mitral insufficiency (poorly functioning valve between the left atrium and ventricle) should not exercise in water, as they have measured a market increase in preload in these patients. Studies conducted in Sweden have not been able to confirm this, so further research in this area is needed.

Long-term effects

Aerobic exercise, muscle exercise and hydrotherapy

The long-term effects of exercise in patients with heart failure (Table 2) are in many respects in line with those measured in healthy individuals and patients with heart disease without heart failure (43, 44). The exercise methods studied include central circulatory training, cycling in particular but also exercise classes, walking and peripheral muscle training. Hydrotherapy, tai chi and respiratory muscle training have also been studied.

Table 2. Long-term effects of aerobic central circulatory training and peripheral muscle endurance training in patients with chronic heart failure.

Effect variable	Result	Effect variable	Result
VO$_2$ max	↑	Sympathetic activity	↓
Workload		Muscle blood flow	↑
		Oxidative capacity	↑
watt	↑	Capillarisation	↑
		Muscle fibre area	↑
exercise time	↑		
Heart rate		Muscle strength and endurance	↑
resting	↓		
	↔		
maximal	↑		
Stroke volume		Endotheliumindependent	↑
resting	↑	and	
exercise	↑	endothelium-dependent vascular function	↑
Cardiac output		Dyspnoea	↓
exercise	↑	Fatigue	↓
Ejection fraction*	↔	NYHA class	↓
	↑		
Systolic blood pressure		6-minute walk test	↑
resting	↔		
exercise	↓		
Respiratory minute volume	↓	Quality of life	↑
			↔
Inflammatory cytokines	↓	Mortality	↓

↑ = Increase, ↔ = No change, ↓ = Decrease.
* Ejection fraction = Ratio of stroke volume to total end-diastolic volume.

Indications

Patients with stable heart failure with predominant systolic dysfunction in NYHA class (I)-II-III. Experience from exercise training of patients in NYHA Class IV and patients with diastolic dysfunction is limited (43, 44).

Primary prevention

For patients with asymptomatic left ventricular dysfunction or myocardial infarction, training increases exercise capacity and cardiac output (45, 46). Whether training in asymptomatic patients with reduced left ventricular function is able to prevent the development of heart failure is not known.

Secondary prevention

Exercise training improves several of the pathophysiological findings found in heart failure disease. Two meta-analyses have shown that longer periods of exercise can have an impact on mortality and morbidity (44, 47). Exercise also has positive effects on underlying factors such as diabetes and hypertension (48, 49).

Prescription

Different types of exercise
Central circulatory training/aerobic exercise, peripheral/local muscle training on land and in water, and respiratory muscle training, are the most evaluated techniques (see Table 3).

Central circulatory training, which has been studied the most, involves the engagement of large muscle groups at the same time, for example, cycling, walking and/or exercise classes (44).

Table 3. Description of training methods investigated in different scientific studies in patients with chronic heart failure.

Training method	Intensity	RPE*	Frequency	Duration (min./session)
Aerobic central circulatory training	(40) 60–80% of VO_2 max**	11–15 central	1 time/week to several times/day	10–60
Peripheral muscle training	35–70% of 1 RM***	13–15 local	2 times/week to 1 time/day	15–60
Combination of aerobic central circulatory training and peripheral muscle training	60–80% of VO_2 max** 60–80% of 1 RM	13–15 central and local	3 times/week	45–60
Hydrotherapy	40–80% of HRR****	11–15	3 times/week	45
Respiratory muscle training	30% of max. inspiratory pressure		3 times/week to daily	30–60

* RPE = Rating of Perceived Exertion (Borg scale 6–20).

** VO_2 max = Maximal Oxygen Uptake.

*** RM = Repetition Maximum. 1 RM corresponds to the maximum weight that can be lifted through the entire exercise movement one time.

**** HRR = Heart Rate Reserve

In *peripheral muscle training*, the skeletal muscle is exercised locally at a relatively high load. Techniques for peripheral/local muscle training include endurance training with different types of weights and bands, for example, Thera-Band® (HCM, Hygenic Corporation, Malaysia) (50).

Respiratory training comprises both inspiratory and expiratory resistance training (51, 52).

In the studies of exercise training conducted until now, there is large variation when it comes to intensity, duration, frequency and exercise model. Empirically, patients with more severe heart failure (NYHA III) are considered to need a longer rehabilitation period than patients with ischaemic heart disease without heart failure, for example, in order to develop the habit of incorporating exercise into daily life. Individually adapted exercise programs where consideration is given to functional capacity and recovery time are very important for this patient group. Considering the disease's pathology, both central circulatory training and peripheral muscle training are probably important. Peripheral muscle training performed in sequences is probably of value to patients with more advanced heart failure, in order to regain lost muscle mass. This is an important step before commencing an exercise programme that engages the central circulation (53). It is essential for the patient's functional capacity that not only the leg muscles but also the arm and trunk muscles are exercised. Patients with chronic heart failure should always be referred to a physiotherapist for an individually adapted training programme. An intensity corresponding to between 60–80 per cent of VO_2 max, that is, 11–15 on the Borg RPE scale, is effective (54, 55). Two to three sessions per week are suitable for out-patient exercise training, while training at home and in hospital can be conducted more frequently.

Functional mechanisms

Oxygen uptake (VO$_2$)

Oxygen uptake improves by an average of about 15 per cent (2–34%), which is explained by the impact on several interacting factors such as improved heart muscle function, reduced vasoconstriction in the arterioles of the active skeletal muscle, along with an increased oxygen extraction and metabolic function in the active skeletal muscles. The measuring methods and measures of effect in the different studies vary, however, which can make it difficult to compare results between the studies. The effect of exercise training reported in the studies enable the patients to increase their activities at home, during leisure time and at work if applicable (43, 44).

Cardiac function

Cardiac function may be improved by exercise training due to better stroke volume and reduced chronotropic response during acute exercise (44).

Peripheral blood circulation and skeletal muscle function

Exercise normalises the peripheral blood circulation, probably mediated in part by improved endothelial function (56). Increased muscle strength gained through exercise is a result of both increased blood circulation to the muscles, increased muscle volume, and improved metabolic function in the muscle cells themselves. The oxidative capacity improves due to an increase in the amount of oxidative enzymes, mitochondrial volume and the number of type I fibres. Occlusion of intramuscular vessels begins already at 15 per cent of maximal voluntary contraction. The improved muscle function means that the patient is able to perform his or her daily activities at a lower percentage of maximal voluntary contraction, which theoretically results in reduced load on the heart (50).

Respiratory function

Respiratory minute volume (VE) and the ratio between minute ventilation and carbon dioxide production (VE/VCO2) decreases, blood flow to the respiratory muscles increases, and the metabolic situation improves after exercise training (57). These could possibly be some of the reasons for the reduced breathlessness (dyspnoea) the patient experiences after exercise.

Neuroendocrine and autonomic function, and inflammatory cytokines

Exercise reduces the neuroendocrine activation and the number of inflammatory cytokines (58). The autonomic function also improves (59).

Mortality and hospitalisation

Two meta-analyses suggest that exercise can reduce mortality and hospitalisations in chronic heart failure. As in every case, the results from a meta-analysis must be interpreted with caution (60, 61).

Quality of life and symptoms

Quality of life and symptoms improve through training (44, 62). The underlying cause of this phenomenon may be of both a physical and psychological nature.

Functional tests

A functional test should always be performed to determine the appropriate individual exercise level before an exercise period begins. The same test should in addition always be conducted at the end of an exercise period to evaluate the effect of the exercise programme and for continued prescription.

Cycle/Treadmill test

A standardised maximal or submaximal cycle/treadmill test, preferably with analysis of maximal oxygen uptake, forms the basis for an appropriate design of an exercise programme (55, 63). It is also a way of ascertaining whether the patient tolerates increased physical exertion.

6-minute walk test

A standardised 6-minute walk test (64, 65) is often used to assess exercise capacity in relation to activities of daily life (ADL). The patient is encouraged to walk as far as possible for six minutes on a measured stretch of hallway. Measurement variables are the distance walked, perceived exertion measured on the Borg scale (66), and heart rate.

Muscle function

Strength and endurance, both isometric and isotonic, can be measured with an isokinetic instrument such as KINCOM (KINetic COMmunicator) (37). Clinical endurance tests can also be performed, for example, through one-legged toe raises or shoulder flexion test with weights (67).

Rating of symptoms, quality of life and physical activity

General health-related quality of life can be measured with the SF-36 questionnaire (68), while disease-specific quality of life is often measured with the Minnesota Living with

Heart Failure Questionnaire (69). An example of a survey that measures the level of physical activity is Frändin and Grimby's activity scale (76).

Symptom severity can be assessed with the visual analogue scale (VAS) (70) or the Borg scale (66). Level of function may be evaluated using, for example, NYHA classification criteria (24).

Interactions with drugs

Beta blockers
Maximal heart rate is lower in patients with heart failure treated with beta blockers than in patients not receiving beta blockers (71). Exercise capacity increases and the ejection fraction improves both at rest and during exertion after chronic treatment with beta blockers. No effect on the skeletal muscle has been found (72).

ACE inhibitors
ACE inhibitors have a moderate effect on exercise capacity. Cardiac output increases and the left ventricular filling pressure falls during exertion (73). The effect of ACE inhibitor therapy on skeletal muscle is not unambiguous. Increased muscle fibre area and changes in myosin composition in skeletal muscle fibres have been described earlier (71, 72).

Digitalis
Digitalis increases contractility in the myocardium and thereby the stroke volume, while heart rate decreases. Exercise capacity increases under digitalis therapy (74, 75).

Diuretics
An open study of severely symptomatic patients showed increased oxygen uptake during exertion after eight days of treatment with diuretics (76). Diuretics can have potentially negative effects through an increased risk of dehydration and electrolyte disturbances in warm weather.

Contraindications

Uncompensated heart failure, obstructive hypertrophic cardiomyopathy, significant valve disease (above all aortic stenosis), active myocarditis, a drop in blood pressure, serious arrhythmia or severe ischaemia during exertion. Other serious diseases such as ongoing infection, uncontrolled diabetes, uncontrolled hypertension or recent pulmonary embolism (54) are also contraindications.

Risks

No serious incidents have occurred during or after training of patients with heart failure (44, 62). However, the heart failure patients who have participated in exercise studies to date have been selected. The mortality is in general high in this patient group, which is why it is important that exercise initially should be implemented in a medical setting in case a serious complication should occur.

References

1. Libby PB, Mann RO, Zipes DL. Brunwald's heart disease. London: Saunders; 2007.
2. Cowie MR, Mosterd A, Wood DA, Deckers JW, Poole-Wilson PA, Sutton GC, et al. The epidemiology of heart failure. Eur Heart J 1997;18:208-25.
3. Eriksson H. Heart failure. A growing public health problem. J Intern Med 1995 Feb;237:135-41.
4. Ho KK, Pinsky JL, Kannel WB, Levy D. The epidemiology of heart failure. The Framingham Study. J Am Coll Cardiol 1993;22:6A-13A.
5. Schaufelberger M, Swedberg K, Koster M, Rosen M, Rosengren A. Decreasing one-year mortality and hospitalization rates for heart failure in Sweden. Data from the Swedish Hospital Discharge Registry 1988 to 2000. Eur Heart J 2004;25:300-7.
6. Franciosa JA, Park M, Levine TB. Lack of correlation between exercise capacity and indexes of resting left ventricular performance in heart failure. Am J Cardiol 1981;47:33-9.
7. Metra M, Raddino R, Dei Cas L, Visioli O. Assessment of peak oxygen consumption, lactate and ventilatory thresholds and correlation with resting and exercise hemodynamic data in chronic congestive heart failure. Am J Cardiol 1990;65:1127-33.
8. Miyashita T, Okano Y, Takaki H, Satoh T, Kobayashi Y, Goto Y. Relation between exercise capacity and left ventricular systolic versus diastolic function during exercise in patients after myocardial infarction. Coron Artery Dis 2001;12:217-25.
9. Clark AL, Poole-Wilson PA, Coats AJ. Exercise limitation in chronic heart failure. Central role of the periphery. J Am Coll Cardiol 1996;28:1092-102.
10. Drexler H. Reduced exercise tolerance in chronic heart failure and its relationship to neurohumoral factors. Eur Heart J 1991;12:21-8.
11. Sullivan MJ, Knight JD, Higginbotham MB, Cobb FR. Relation between central and peripheral hemodynamics during exercise in patients with chronic heart failure. Muscle blood flow is reduced with maintenance of arterial perfusion pressure. Circulation 1989;80:769-81.
12. Zelis R, Longhurst J, Capone RJ, Mason DT. A comparison of regional blood flow and oxygen utilization during dynamic forearm exercise in normal subjects and patients with congestive heart failure. Circulation 1974;50:137-43.
13. Swan JW, Walton C, Godsland IF, Clark AL, Coats AJ, Oliver MF. Insulin resistance in chronic heart failure. Eur Heart J 1994;15:1528-32.
14. Schaufelberger M, Eriksson BO, Grimby G, Held P, Swedberg K. Skeletal muscle fiber composition and capillarization in patients with chronic heart failure. Relation to exercise capacity and central hemodynamics. J Card Fail 1995;1:267-72.
15. Volterrani M, Clark AL, Ludman PF, Swan JW, Adamopoulos S, Piepoli M, et al. Predictors of exercise capacity in chronic heart failure. Eur Heart J 1994;15:801-9.
16. Magnusson G, Isberg B, Karlberg KE, Sylven C. Skeletal muscle strength and endurance in chronic congestive heart failure secondary to idiopathic dilated cardiomyopathy. Am J Cardiol 1994;73:307-9.

17. Stibrant Sunnerhagen K, Cider A, Schaufelberger M, Hedberg M, Grimby G. Muscular performance in heart failure. J Card Fail 1998;4:97-104.

18. Tejero-Taldo MI, Kramer JH, Mak Iu T, Komarov AM, Weglicki WB. The nerve–heart connection in the pro-oxidant response to Mg-deficiency. Heart Fail Rev 2006;11:35-44.

19. von Haehling S, Doehner W, Anker SD. Nutrition, metabolism, and the complex pathophysiology of cachexia in chronic heart failure. Cardiovasc Res 2007;73:298-309.

20. Ponikowski PP, Chua TP, Francis DP, Capucci A, Coats AJ, Piepoli MF. Muscle ergoreceptor overactivity reflects deterioration in clinical status and cardiorespiratory reflex control in chronic heart failure. Circulation 2001;104:2324-30.

21. Witte KK, Clark AL. Why does chronic heart failure cause breathlessness and fatigue? Prog Cardiovasc Dis 2007;49:366-84.

22. Piepoli MF, Scott AC, Capucci A, Coats AJ. Skeletal muscle training in chronic heart failure. Acta Physiol Scand 2001;171:295-303.

23. Swedberg K, Cleland J, Dargie H, Drexler H, Follath F, Komajda M, et al. Guidelines for the diagnosis and treatment of chronic heart failure. Executive summary (update 2005). Task Force for the Diagnosis and Treatment of Chronic Heart Failure of the European Society of Cardiology. Eur Heart J 2005;26:1115-40.

24. New York Heart Association. Nomenclature and criteria of the heart and great vessels. New York: Little and Brown Company; 1973.

25. Remme WJ, Swedberg K. Guidelines for the diagnosis and treatment of chronic heart failure. Eur Heart J 2001;22:1527-60.

26. Keteyian SJ, Marks CR, Brawner CA, Levine AB, Kataoka T, Levine TB. Responses to arm exercise in patients with compensated heart failure. J Cardiopulm Rehabil 1996;16:366-71.

27. Clark AL, Davies LC, Francis DP, Coats AJ. Ventilatory capacity and exercise tolerance in patients with chronic stable heart failure. Eur J Heart Fail 2000;2:47-51.

28. Feigenbaum M. Cardiopulmonary, hemodynamic and neurohormonal responses to acute exercise in patients with chronic heart failure. Florida: University of Florida; 1997.

29. Higginbotham MB, Morris KG, Conn EH, Coleman RE, Cobb FR. Determinants of variable exercise performance among patients with severe left ventricular dysfunction. Am J Cardiol 1983;51:52-60.

30. Stone GW, Kubo SH, Cody RJ. Adverse influence of baroreceptor dysfunction on upright exercise in congestive heart failure. Am J Med 1986;80:799-802.

31. Colucci WS, Ribeiro JP, Rocco MB, Quigg RJ, Creager MA, Marsh JD, et al. Impaired chronotropic response to exercise in patients with congestive heart failure. Role of postsynaptic beta-adrenergic desensitization. Circulation 1989;80:314-23.

32. Weber KT, Kinasewitz GT, Janicki JS, Fishman AP. Oxygen utilization and ventilation during exercise in patients with chronic cardiac failure. Circulation 1982;65:1213-23.

33. Massie B, Conway M, Yonge R, Frostick S, Ledingham J, Sleight P, et al. Skeletal muscle metabolism in patients with congestive heart failure. Relation to clinical severity and blood flow. Circulation 1987;76:1009-19.

34. Magnusson G, Kaijser L, Sylven C, Karlberg KE, Isberg B, Saltin B. Peak skeletal muscle perfusion is maintained in patients with chronic heart failure when only a small muscle mass is exercised. Cardiovasc Res 1997;33:297-306.

35. Shephard RJ, Balady GJ. Exercise as cardiovascular therapy. Circulation 1999;99:963-72.

36. Mangieri E, Tanzilli G, Barilla F, Ciavolella M, Serafini G, Nardi M, et al. Isometric handgrip exercise increases endothelin-1 plasma levels in patients with chronic congestive heart failure. Am J Cardiol 1997;79:1261-3.

37. Cider A, Tygesson H, Hedberg M, Seligman L, Wennerblom B, Sunnerhagen KS. Peripheral muscle training in patients with clinical signs of heart failure. Scand J Rehabil Med 1997;29:121-7.

38. McKelvie RS, McCartney N, Tomlinson C, Bauer R, MacDougall JD. Comparison of hemodynamic responses to cycling and resistance exercise in congestive heart failure secondary to ischemic cardiomyopathy. Am J Cardiol 1995;76:977-9.

39. Meyer K, Hajric R, Westbrook S, Haag-Wildi S, Holtkamp R, Leyk D, et al. Hemodynamic responses during leg press exercise in patients with chronic congestive heart failure. Am J Cardiol 1999;83:1537-43.

40. Cider A, Svealv BG, Tang MS, Schaufelberger M, Andersson B. Immersion in warm water induces improvement in cardiac function in patients with chronic heart failure. Eur J Heart Fail 2006;8:308-13.

41. Gabrielsen A, Bie P, Holstein-Rathlou NH, Christensen NJ, Warberg J, Dige-Petersen H, et al. Neuroendocrine and renal effects of intravascular volume expansion in compensated heart failure. Am J Physiol Regul Integr Comp Physiol 2001;281:R459-67.

42. Meyer K, Bucking J. Exercise in heart failure. Should aqua therapy and swimming be allowed? Med Sci Sports Exerc 2004;36:2017-23.

43. Rees K, Taylor RS, Singh S, Coats AJ, Ebrahim S. Exercise based rehabilitation for heart failure. Cochrane Database Syst Rev 2004;3:CD003331.

44. van Tol BA, Huijsmans RJ, Kroon DW, Schothorst M, Kwakkel G. Effects of exercise training on cardiac performance, exercise capacity and quality of life in patients with heart failure. A meta-analysis. Eur J Heart Fail 2006;8:841-50.

45. Conn EH, Williams RS, Wallace AG. Exercise responses before and after physical conditioning in patients with severely depressed left ventricular function. Am J Cardiol 1982;49:296-300.

46. Dubach P, Myers J, Dziekan G, Goebbels U, Reinhart W, Vogt P, et al. Effect of exercise training on myocardial remodeling in patients with reduced left ventricular function after myocardial infarction. Application of magnetic resonance imaging. Circulation 1997;95:2060-7.

47. Piepoli MF, Davos C, Francis DP, Coats AJ. Exercise training meta-analysis of trials in patients with chronic heart failure (ExTraMATCH). BMJ 2004;328:189.

48. Boule NG, Haddad E, Kenny GP, Wells GA, Sigal RJ. Effects of exercise on glycemic control and body mass in type 2 diabetes mellitus. A meta-analysis of controlled clinical trials. JAMA 2001;286:1218-27.

49. Pescatello LS, Franklin BA, Fagard R, Farquhar WB, Kelley GA, Ray CA. American College of Sports Medicine Position Stand. Exercise and hypertension. Med Sci Sports Exerc 2004;36:533-53.

50. Delagardelle C, Feiereisen P. Strength training for patients with chronic heart failure. Eura Medicophys 2005;41:57-65.

51. Laoutaris I, Dritsas A, Brown MD, Manginas A, Alivizatos PA, Cokkinos DV. Inspiratory muscle training using an incremental endurance test alleviates dyspnea and improves functional status in patients with chronic heart failure. Eur J Cardiovasc Prev Rehabil 2004;11:489-96.

52. Mancini DM, Henson D, La Manca J, Donchez L, Levine S. Benefit of selective respiratory muscle training on exercise capacity in patients with chronic congestive heart failure. Circulation 1995;91:320-9.

53. McKelvie R. Exercise training in heart failure. How? Heart Failure Reviews 1999;3: 263-73.

54. Pina IL, Apstein CS, Balady GJ, Belardinelli R, Chaitman BR, Duscha BD, et al. Exercise and heart failure. A statement from the American Heart Association Committee on exercise, rehabilitation, and prevention. Circulation 2003;107:1210-25.

55. Corra U, Giannuzzi P, Adamopoulos S, Bjornstad H, Bjarnason-Weherns B, Cohen-Solal A, 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;12:321-5.

56. Sabelis LW, Senden PJ, Fijnheer R, de Groot PG, Huisveld IA, Mosterd WL, et al. Endothelial markers in chronic heart failure. Training normalizes exercise-induced vWF release. Eur J Clin Invest 2004;34:583-9.

57. European Heart Failure Training Group. Experience from controlled trials of physical training in chronic heart failure. Protocol and patient factors in effectiveness in the improvement in exercise tolerance. Eur Heart J 1998;19:466-75.

58. Gielen S, Adams V, Linke A, Erbs S, Mobius-Winkler S, Schubert A, et al. Exercise training in chronic heart failure. Correlation between reduced local inflammation and improved oxidative capacity in the skeletal muscle. Eur J Cardiovasc Prev Rehabil 2005;12:393-400.

59. Myers J, Hadley D, Oswald U, Bruner K, Kottman W, Hsu L, et al. Effects of exercise training on heart rate recovery in patients with chronic heart failure. Am Heart J 2007;153:1056-63.

60. Hagerman I, Tyni-Lenne R, Gordon A. Outcome of exercise training on the long-term burden of hospitalisation in patients with chronic heart failure. A retrospective study. Int J Cardiol 2005;98:487-91.

61. Taylor A. Physiological response to a short period of exercise training in patients with chronic heart failure. Physiother Res Int 1999;4:237-49.

62. Rees K, Bennett P, West R, Davey SG, Ebrahim S. Psychological interventions for coronary heart disease. Cochrane Database Syst Rev 2004;2:CD002902.

63. Thompson PD, Buchner D, Pina IL, Balady GJ, Williams MA, Marcus BH, et al. Exercise and physical activity in the prevention and treatment of atherosclerotic cardiovascular disease. A statement from the Council on Clinical Cardiology (Subcommittee on Exercise, Rehabilitation, and Prevention) and the Council on Nutrition, Physical Activity, and Metabolism (Subcommittee on Physical Activity). Circulation 2003;107:3109-16.

64. Guyatt G. Use of the six-minute walk test as an outcome measure in clinical trials in chronic heart failure. Heart Failure 1987;21:211-7.

65. Lipkin DP, Scrivin AJ, Crake T, Poole-Wilson PA. Six minute walk test for assessing exercise capacity in chronic heart failure patients. BMJ 1986;292:653-5.

66. Borg G. Perceived exertion as an indicator of somatic stress. Scand J Rehab Med 1970;2:92-8.

67. Cider A, Carlsson S, Arvidsson C, Andersson B, Stibrant Sunnerhagen K. Reliability of clinical muscular endurance tests in patients with chronic heart failure. Eur J Cardiovasc Nurs 2006;5:122-6.

68. Ware JE Jr, Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. Med Care 1992;30:473-83.

69. Rector TS, Cohn JN. Assessment of patient outcome with the Minnesota Living with Heart Failure Questionnaire. Reliability and validity during a randomized, double-blind, placebo-controlled trial of pimobendan. Pimobendan Multicenter Research Group. Am Heart J 1992;124:1017-25.

70. Carlsson AM. Assessment of chronic pain. I. Aspects of the reliability and validity of the visual analogue scale. Pain 1983;16:87-101.

71. Schaufelberger M, Andersson G, Eriksson BO, Grimby G, Held P, Swedberg K. Skeletal muscle changes in patients with chronic heart failure before and after treatment with enalapril. Eur Heart J 1996;17:1678-85.

72. Schaufelberger M, Eriksson BO, Grimby G, Held P, Swedberg K. Skeletal muscle alterations in patients with chronic heart failure. Eur Heart J 1997;18:971-80.

73. Swedberg K. Exercise testing in heart failure. A critical review. Drugs 1994;47:14-24.

74. Slatton ML, Irani WN, Hall SA, Marcoux LG, Page RL, Grayburn PA, et al. Does digoxin provide additional hemodynamic and autonomic benefit at higher doses in patients with mild to moderate heart failure and normal sinus rhythm? J Am Coll Cardiol 1997;29:1206-13.

75. Vescovo G, Dalla Libera L, Serafini F, Leprotti C, Facchin L, Volterrani M, et al. Improved exercise tolerance after losartan and enalapril in heart failure. Correlation with changes in skeletal muscle myosin heavy chain composition. Circulation 1998;98:1742-9.

76. Mattioli AV, Castellani ET, Casali E, Mattioli G. Symptomatic achievements with diuretics in congestive heart failure. Cardiology 1994;84:131-4.