Is Exercise Training Appropriate for Patients With Advanced Heart Failure Receiving Continuous Inotropic Infusion? A Review

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ABSTRACT: Exercise-based rehabilitation programs have been reported to have beneficial effects for patients with heart failure. However, there is little evidence about whether this is the case in patients with more severe heart failure. In particular, there is a question in the clinical setting whether patients with advanced heart failure and continuous inotropic infusion should be prescribed exercise training. In contrast, many studies conclude that prolonged immobility associated with heart failure profoundly impairs physical function and promotes muscle wasting that could further hasten the course of heart failure. By contrast, exercise training has various effects not only in improving exercise capacity but also on vascular function, skeletal muscle, and autonomic balance. In this review, we summarize the effectiveness and discuss methods of exercise training in patients with advanced heart failure receiving continuous inotropic agents such as dobutamine.

KEYWORDS: Exercise training, advanced heart failure, inotropic infusion, skeletal myopathy, cardiac cachexia

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Introduction

End-stage heart failure (HF), which is medically intractable, became an important problem in the setting of HF. In such cases, heart transplantation is a radical cure, and left ventricular assist device (LVAD) is another helpful support and used as either a bridge to heart transplantation or destination therapy. However, the sources of these surgical therapies were limited so that inotrope support is easily used to maintain the flow to vital organs as a bridge or alternate to the surgical interventions.[1] The use of inotrope might sometimes lead to the correction of appropriate hemodynamic balance, resulting in the weaning off of inotrope agents, whereas the state of inotrope dependency could not be taken off in some cases. There was little epidemiologic data about the dependency of inotrope; however, there are many opportunities of the use of inotrope in various clinical settings. However, the discussion about the efficacy of inotropic agents had not led to definitive conclusions because of lacking well-designed investigations that were practically difficult.[2,3] In addition, the continuous inotropic infusion therapy could have various influences, such as suppressing the physical activities, leading to skeletal muscle atrophy, which might aggravate the course of HF.

Several reports discuss the effect of exercise-based rehabilitation programs for patients with New York Heart Association (NYHA) class I to III HF.[4,5] However, there is little evidence about the effect of cardiac rehabilitation (CR) for patients with more severe HF. Recently, several studies investigated the effect of exercise in patients with left ventricle (LV) dysfunction and subsequent improvements in exercise capacity without an adverse effect on LV remodeling or other serious complications.[3] Rather than having a detrimental effect, exercise was reported to decrease abnormal remodeling in cases of HF with impaired LV function.[4] However, studies that investigated the effect of exercise in patients with HF excluded patients with NYHA class IV, those who were hemodynamically unstable, or those who received continuous inotropic agents.[6] Whether exercise training should be avoided until stabilization of HF has not been clearly elucidated yet. On the other hand, delayed CR significantly affects fitness outcomes.[7] For every 1 day of waiting time for instituting CR, patients are 1% less likely to show improvement across all fitness-related measures.[7]

In particular, patients who were dependent on inotropic agents were the most problematic. Inotropic agents such as dobutamine are used for acute or subacute decompensation of HF due to severely impaired cardiac output, or these agents are used for hemodynamic support as a pharmacologic bridge to a more definitive intervention such as a ventricular assist device or cardiac transplantation. Inotrope dependence means that withdrawal of inotropes leads to symptomatic hypotension, recurrent congestive symptoms, or worsening renal function.[8] As a result, the duration of continuous dobutamine infusion is highly variable; if used for a long period of time, exercise restriction may worsen the atrophic change of skeletal muscle and decrease the adaptive response to exercise. These detrimental effects may easily aggravate the course of HF itself.

In this review, we summarize the methodology of exercise training in stable patients with advanced HF receiving continuous inotropic agents, which can be represented by the patients with the Interagency Registry for Mechanically

Assisted Circulatory Support (INTERMACS) profile 3 in other words.

Pathophysiological Change in Advanced HF

In patients with advanced HF, there are much systemic influences, which affect the course of HF. One important site affected by the presence of HF is skeletal muscle and it has been reported to be abnormal. A change in size of skeletal muscle fiber or type was detected in one study.[9] An anabolic/catabolic imbalance affects muscle loss as a result of reduced muscle anabolism, increased muscle catabolism, or both.[10] In addition, muscle consists of slow-twitch type I and fast-twitch type II muscle fibers, and the fiber type distribution was distributed toward type II fibers in patients with HF; their capillary length density of skeletal muscle was also reduced.[9] These intrinsic alterations of skeletal muscle are the main contributors of limited exercise capacity in patients with HF. These skeletal muscle abnormalities are often complicated in cases of severe HF. In addition, the patient's condition sometimes worsens to cardiac cachexia. Cardiac cachexia is characterized by increase in inflammatory cytokine and neuroendocrine factors, such as tumor necrosis factor α, norepinephrine, and cortisol; muscle wasting; and loss of muscle protein.[11] The presence of skeletal myopathy and cardiac cachexia suggests a poor prognosis in patients with HF. For instance, reduced muscle mass or muscle power suggests poor prognosis in HF patients undergoing ventricular assist device placement.[12] Therefore, prevention of these complications may improve the course of HF and become one critical target of HF therapy in the clinical viewpoint.[13–15] However, it remains unknown how suppression of the pathways leading to skeletal myopathy or cardiac cachexia contributes to reduce risk of HF or increase the survival rate.

According to vascular function, endothelial dysfunction and increased vascular tone were also complicated with HF and these complications further worsened the hemodynamic compromise in HF.[16] The decrease in endothelial dysfunction in patients with HF complicates the coordination of hemodynamic compromise, leading to increased mortality and worse prognosis.[17] Increased vascular tone, which is mediated by several pathways, such as autonomic nerve system or renin-angiotensin pathways, also becomes a burden to the compromised hemodynamics in HF.[18]

Beneficial or Evil Effects of Inotrope Agents on Exercise in Advanced HF

Few published reports discuss exercise in patients receiving continuous inotropic support.[19,20] The safety and efficacy of exercise training in patients with intravenous inotropic support have been described; however, there is insufficient evidence for the benefits of exercise training in this setting because of the small numbers of subjects included in the studies. According to the safety, the appropriate assessments for the feasibilities of exercise training significantly reduce the risk of exercise training for patients with inotropic infusion who were awaiting for heart transplantation. However, more critical evaluation of exercise training for these patients should be performed by longer follow-up duration. Indeed, several reports on exercise training in patients with advanced HF showed unchanged exercise capacity.[21] The ability to perform exercise testing itself means a capacity for maintained exercise. By contrast, there are little data on the effect of exercise training in patients with severely impaired exercise capacity, those who are dependent on continuous inotropic support, or those who are unable to perform exercise testing.

The physiology of dobutamine infusion results in an efficient reduction in pulmonary wedge pressure with a mild increase in heart rate,[22] lowering the risk of worsening HF during exercise. Milrinone (phosphodiesterase inhibitor) infusion, another commonly used inotrope, also has similar beneficial effects on exercise.[3] In addition, milrinone has another pleiotropic effect and suppresses the inflammatory cytokines, such as tumor necrosis factor or interleukin 8, which are increased in patients with HF.[23] In contrast, arrhythmic events reportedly increased during inotropic infusion.[24] However, the effect of inotropic agents' infusion on exercising skeletal muscle was described previously, demonstrating that the increased cardiac output and blood flow to limbs does not necessarily improve oxygen delivery to working skeletal muscle in patients with HF.[25,26] In another study, a metabolic change in skeletal muscle occurred during inotropic infusion and it increased glucose production and uptake to adapt higher levels of muscular carbohydrate use during exercise.[27,28] In addition, β-adrenergic signaling has been proposed as an important regulator of skeletal muscle regenerations and it may have some effects on the increase in skeletal muscle mass through its anabolic properties.[29,30] Among β-agonists, β_2-adrenergic pathway had been reported to have beneficial impact on skeletal muscle.[31] Indeed, β_2-adrenergic agonists can change the composition of skeletal muscle fiber type and increase maximal isometric force production.[32,33] There are several reports demonstrating that β-agonists can exert a protective effect on skeletal muscle in patients with HF by antagonizing the protein degradation associated with cachexia.[34] Histologically, β_2-agonists induced hypertrophy of fast-twitch muscles, resulting in slow to fast alterations in skeletal muscle fibers.[35] Dobutamine has some effects through β_2-receptor as compared with dopamine[36] so that dobutamine may have some powers against muscle wasting through β_2-pathways. By contrast, dopamine also has powers of increasing skeletal muscle mass through dopamine receptor.[37] These protective effects have been associated with an inhibition of proteolysis (calcium-dependent proteolysis and adenosine triphosphate–dependent proteolysis) and an activation of protein synthesis signaling pathways,[38] whereas milrinone may have negative impact on skeletal muscle contractility.[39] However, there had been no clinical data about the comparison of the effect of catecholamine infusion on skeletal muscle.

According to the vascular function and autonomic nerve balance, there reported to be some effects by dobutamine

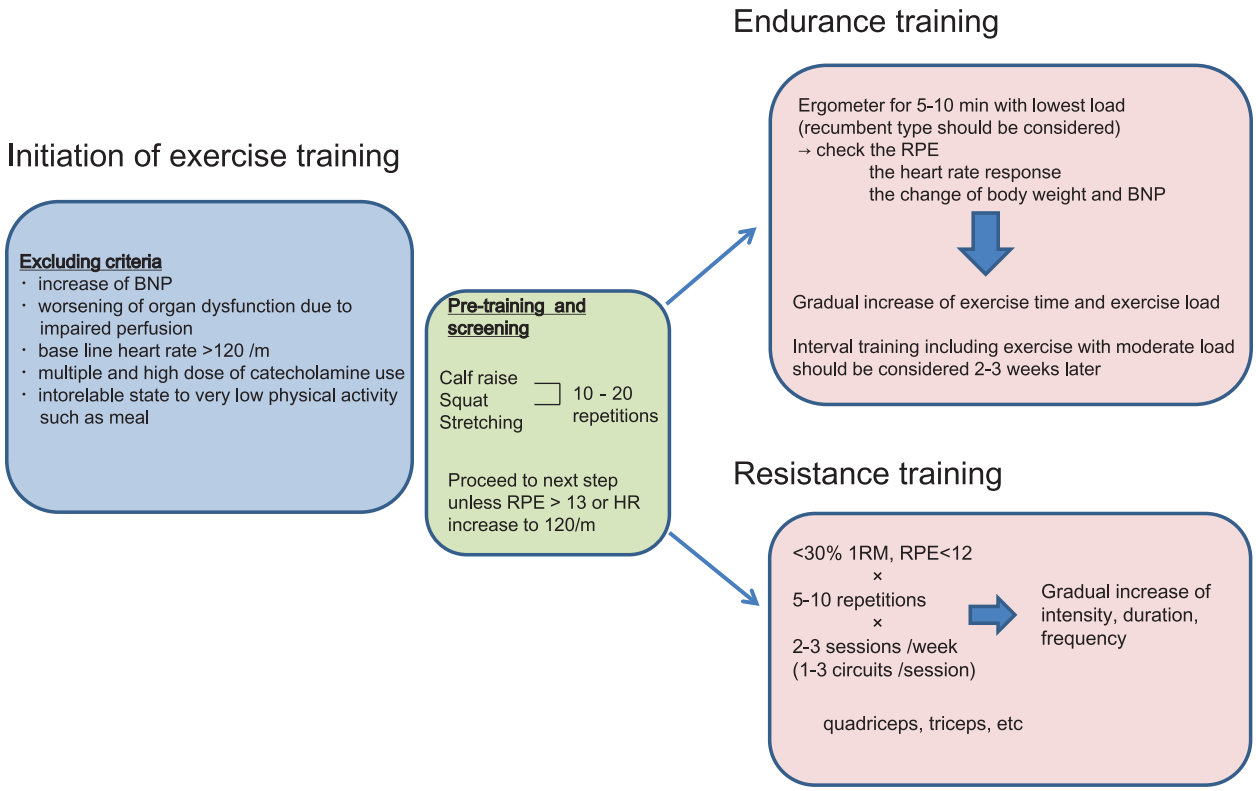

Figure 1. The course of exercise training for patients with advanced heart failure. BNP indicates brain natriuretic peptide.

infusion.[40] Freimark et al[41] demonstrated dobutamine infusion beneficially affected endothelial function that may have a beneficial effect on exercise. Al-Hesayen et al[40] reported that dobutamine infusion caused a significant sympatholytic response in patients with HF unexpectedly, other than sympathoexcitatory effects. The comparative study of dopamine and dobutamine demonstrated that both have comparable therapeutic effects in patients with HF; however, low-dose dopamine had more favorably affects cardiac autonomic function.[42] Dopamine even restored the depressed circadian change in patients with HF. By these effects, exercise training may be induced with ease or reducing its risk. However, little was found about the association between exercise and dobutamine or milrinone infusion.

Consideration of the Start of Rehabilitation

Prescribing exercise in critically hemodynamically unstable patients enhances the risk of exercise more than its benefit. The appropriate timing to initiate exercise training has been poorly investigated and described.[43,44] The state of continuous inotropic infusion has been cited as an increased risk for exercise training, not as a contraindication.[43] However, once the decompensation of HF is stabilized even with using inotropic agents, exercise training can be initiated at a very low level of intensity. One example of exercise protocol regimen is presented in Figure 1. Indeed, a consensus document of the HF Association and the European Association for Cardiovascular Prevention and Rehabilitation mentions that early mobilization through an individualized exercise program may prevent further disability after hospitalization due to HF.[43] In addition, just 1 week is sufficient to start substantial muscle atrophy and induce whole-body insulin resistance in the absence of skeletal muscle lipid accumulation.[45–47] To reduce the detrimental effect of bed rest, exercise training should be started as early as possible and balancing the risk and benefit of exercise is of utmost importance.

The identification of clinical stability is most critical for the induction of exercise training and it is defined by stable symptoms, absence of resting symptoms and postural hypotension, stable fluid balance, freedom from evidence of congestion, stable renal function, and normal electrolyte value.[48] The level of B-type natriuretic peptide (BNP) also offers information about the clinical stability in HF treatment. BNP–guided decisions may reduce the risk of prescribing an exercise protocol too early; however, there is insufficient evidence for it.[49] Measuring the change of BNP can offer some information about clinical stability in HF.

Patients with INTERMACS profile 3, who are dependent on continuous inotropic support, may progress in a short time to the next stage of surgical HF therapies, such as an LVAD or heart transplantation. Exercise training before surgery may have the beneficial effect of reducing operative risk; however, there is no concise protocol regarding this. Early initiation of exercise training after implantation of an LVAD has been reported to be associated with improvements in exercise capacity.[50] Several reports support the effectiveness of exercise training after the implantation of VAD, but this discussion is beyond the scope of this article.[51]

Methodology of Exercise Training in Patients With Advanced HF

The difficulty in this situation is uncertainty of appropriate exercise protocol. The appropriate intensity of exercise is generally determined by an exercise test; however, patients with severe HF cannot perform the exercise test at the initiation of training[52] because of their low exercise capacity and lack of conditioning.

Indeed, sufficient and effective exercise training protocols differ by the expected results of exercise training. For instance, high-intensity protocols promote superior improvements of VO_2max,[28,29] whereas muscle mass, metabolic capacity, and proteasome activation were sufficiently improved by moderate-intensity exercise.[30] However, the most critical point in the initiation of CR in patients with severe HF is safety. Care must be taken especially with frail older populations because of the increased risk of adverse events, including injuries and falls, associated with exercise training.[53,54]

Aerobic training of the lowest intensity still provides a training effect in cardiac patients with a markedly reduced exercise capacity.[55] Therefore, the lowest load of intensity (such as 10 W × 5-20 minutes) should be prescribed first and, as the exercise is tolerated, it should be increased gradually. Indeed, we certified that there was no case in which low-level and short-term (such as 5 minutes) ergometer exercise exacerbated the status of HF after appropriate screening for the candidate of exercise training in patients with inotropic infusion (unpublished data). In the absence of exercise tests, an exercise program can be developed using Borg scales and/or subjective tools such as the talk test.[56] A subjective rating of perceived exertion Borg scale rating of 9 to 12 should be sufficient for the patient to tolerate light to moderate exertion. The patient's heart rate response may also suggest the tolerability of exercise, and abrupt increase in heart rate after the initiation of exercise or dull normalization of heart rate after the termination of exercise may suggest intolerable excess exercise load and has to be carefully managed. According to the principles of endurance training, cycle ergometer training at the lowest intensity for 5 to 10 minutes may be tried with continuous electrophysiological monitoring and observing the response of vital signs to the prescribed load. A recumbent ergometer may have a hemodynamically milder load than an upright ergometer.[57] Each response to exercise should be monitored for abnormal responses, such as postexercise hypotension, atrial and ventricular arrhythmias, and worsening HF symptoms.

Resistance training can be safely used for training small muscle groups. Short bouts of work are applied, and the number of repetitions is limited.[43] In resistance training, small loads, such as those outlined in a pretraining protocol in a consensus document, should be performed first.[43] This type of resistance training is performed before the start of endurance training, and the intensities of endurance and resistance training are then increased with caution. Some reports conclude that resistance training may be more effective than aerobic training in attenuating or reversing skeletal muscle atrophy in patients with HF.[58]

Interval training, which has characteristics of both endurance and resistance training, may be a promising method of exercise. Interval training can be defined as repeated bouts of short-duration, high-intensity exercise separated by brief periods of constant, lower-intensity work rate exercise. Indeed, interval training has been reported to improve skeletal muscle function in addition to exercise capacity; however, appropriate protocols have not been developed yet.[59,60] Recently, lactate ambulation induced by high-intensity interval training can lead to mitochondrial adaptations in skeletal muscle.[61] It may be helpful to begin with intermittent instead of continuous exercise in patients with severely impaired exercise capacity.

In addition to these protocols, electrical muscle stimulation (EMS) and inspiratory muscle training are other effective methods of rehabilitation for advanced HF. Indeed, several reports demonstrated the efficacy of EMS in patients with advanced HF.[62,63] For instance, Forestieri et al[64] demonstrated the improvement of exercise capacity in patients by EMS, and EMS demonstrated a significantly higher dose reduction in dobutamine infusion. By contrast, the addition of inspiratory muscle training was reported to improve quality of life in patients with HF.[65] However, there had been only insufficient evidence for these interventions. How these methods are added to regular aerobic exercise should be considered according to each individual case.

When exercise capacity improves up to the level in which walking in a short distance is available, 6-minute walk test is increasingly implemented to assess the exercise capacity.[66] Monitoring and coordination of physical activity using a pedometer step count may also be beneficial in the process of CR in HF.[67]

Expected Results of Exercise Training

Exercise training in CR is generally performed to improve exercise capacity. However, there are various expected results of exercise, and exercise training in patients with severe HF who are on continuous inotropic support should be approached in a different way. There were several studies dealing with the efficacies of exercise training on patients with moderately impaired cardiac function (Table 1). Among them, there were little studies for patients with inotropic agents, and the effect derived from exercise training should be resumed by the reports of patients with reduced cardiac function, which are presented in Table 1.

First, the prevention of skeletal myopathy or cardiac cachexia is the primary goal for this phase of exercise.[83] Oxidative stress is one of main pathways leading to sarcopenia and cardiac cachexia. Exercise training could modify this oxidative stress and overactivity of the ubiquitin-proteasome system thereby reversing skeletal muscle atrophy in HF in experimental animals.[84] These effects may lead to the improvement of cardiac

Table 1. Clinical trials of exercise training that include patients with advanced heart failure.

FIRST AUTHOR	PATIENTS	RATIO OF DCM	MEAN LVEF	N	PROTOCOL	DURATION	EFFECT	
Selig[68]	LVEF < 40%, NYHA I-IV	NA	27 ± 7	39	Leg cycling, elbow extension/flexion, stair climbing, arm cycling, knee extension/flexion, shoulder press/pull	3 mo	Peak VO_2, skeletal muscle strength, HRV	*J Card Fail*. 2004:;21-30
Belardinelli[69]	LVEF < 40%	15	28 ± 6	99	Leg cycling	14 mo	Peak VO_2	*Circulation*. 1999;99:1173-82
Wisløff[70]	Stable postinfarction heart failure	0	26 ± 8	27	10 min at ≈60% to 70% of peak heart rate + walking 4-min intervals at 90% to 95% of peak heart rate vs walking at 70% to 75% of peak heart rate	12 mo	Peak VO_2, endothelial function, LVEF LV reverse remodeling	*Circulation*. 2007;115:3086-94
Arad[71]	Advanced CHF (NYHA III, stage D)	23	27 ± 4	30	45 min of exercise on a treadmill, a stair machine, a bicycle, targeting 60%-70% of the HRR	18 wk	6-min walk, exercise duration, peak VO_2, cardiac index, LVEF, pulmonary artery pressure	*Int J Cardiol*. 2008:114-119
Pu[72]	NYHA I to III, LVEF ≤ 45%	NA	36 ± 3	16	Dynamic contractions of the large upper- and lower-body muscle groups (seated leg press, chest press, knee extension, triceps and knee flexion) 5 exercises/3 sets/8 reps/80% of 1 RM	12 wk	Skeletal muscle strength, 6-min walk	*J Appl Physiol*. 2001:2341-2350
Conraads[73]	Stable HF	50	NA	23	RT (9 exercises/2 sets/6-10 reps/50% of 1 RM) + ET	4 mo	Inflammatory marker, NYHA class, peak VO_2	*Eur Heart J*. 2002:1854-1860
Maiorana[74]	NYHA I to III	46	26 ± 3	13	Cycle ergometry, treadmill walking, and RT (7 exercises/1 set/12 reps/55%-65% of 1 RM)	8 wk	Peak VO_2 exercise test duration, ventilatory threshold	*J Appl Physiol*. 2000:1565-1570
O'Connor[75]	NYHA II to IV, LVEF < 35%	51	25 ± 5	2331	15-30 min/session at an HR of 60% of HRR After 6 sessions, 30-35 min, and 70% of HRR	12 wk	Cardiovascular mortality↓ or heart failure hospitalization ↓	*JAMA*. 2009;301:1439-1450

(Continued)

Table 1. (Continued)

FIRST AUTHOR	PATIENTS	RATIO OF DCM	MEAN LVEF	N	PROTOCOL	DURATION	EFFECT	
Erbs[76]	NYHA IIIb	46	24±2	37	3 to 6 times daily for 5 to 20 min on ergometer adjusted to 50% of VO_{2max} (3 wk)→training target HR for home training (HR at 60% of VO_{2max})	12 wk	Peak VO_2, LVEF, endothelial function, skeletal muscle capillary density	*Circulation: Heart Failure*. 2010:486-494
Passino[77]	LVEF<45%, peak VO_2<25 mL/min/kg	41	35±2	85	For a minimum of 3 d/wk 30 min/d keeping HR at 65% of peak VO_2 HR	9 mo	Peak VO_2, LVEF, QoL, serum BNP level	*JACC*. 2006:1835-1839
Scrutinio[78]	Symptoms of HF for at least 6 mo, LVEF<40%	46	27±6	275	Tailored low-intensity individual exercise program, consisting of respiratory, mobilization, musculoskeletal flexibility, movement coordination, and/or calisthenic exercises	NA	All-cause mortality, urgent heart transplantation at 1 y ↓	*J Cardiopulm Rehabil Prev*. 2012:71-77
Gielen[79]	NYHA II-III, LVEF<40%	65	25±2	20	4 to 6 times daily for 10 min on a bicycle ergometer Workloads 70% of VO_{2max} After discharge, bicycle ergometers for daily home exercise training	6 mo	Peak VO_2, skeletal muscle inflammatory marker expression (TNF-α, IL-6, IL-1β)	*JACC*. 2003:861-868
Hambrecht[80]	NYHA II-III, LVEF<40%	89	26±9	22	Supervised in hospital—home-based training ET (4-6 sessions/wk 10-60 min/session. 70% VO_{2max}) + RT	6 mo	Peak VO_2, peak leg oxygen consumption, changes in cytochrome c oxidase–positive mitochondria	*JACC*. 1995:1239-1249
Hambrecht[81]	NYHA I-III, LVEF<40%	84	27±9	137	Supervised in hospital—home-based training ET (4-6 sessions/wk 10-60 min/session. 70% VO_{2max}) + RT	6 mo	Heart rate, VO_{2max}, VE_{max}, total peripheral resistance	*JAMA*. 2000:3095-3101
Klocek[82]	YHA II-III, LVEF<40%	NA	34±4	42	Group A with constant workload, group B with progressive/increasing workload	6 mo	Peak VO_2, QoL score (cardiac symptom, emotional distress, peripheral circulatory symptoms, dizziness)	*Int J Cardiol*. 2005:323-329

Abbreviations: BNP, brain natriuretic peptide; CHF, chronic heart failure; DCM, dilated cardiomyopathy; ET, endurance training; HF, heart failure; HR, heart rate; HRR, heart rate response; LVEF, left ventricular ejection fraction; NA, not applicable; NYHA, New York Heart Association classification; QoL, quality of life; reps, repetitions; RT, resistance training.

cachexia, in which skeletal muscle atrophy is a consequence of protein synthesis and degradation imbalance.[85] Improvements in skeletal muscle function after training have been explained by corrections made to the oxidative capacity of impaired muscle, as well as to a reversal of chronic heart failure–mediated decline in skeletal muscle mass. Exercise training has also been reported to have some effects on neurohormonal factors, such as angiotensin II.[86] Angiotensin II was reported to be a contributing factor to skeletal muscle atrophy[87] so that exercise may have beneficial effects on sarcopenia through modifying these neurohormonal pathways.

Increased coordination of adaptive response to exercise is required to increase exercise capacity. Patients with severe HF generally have an exaggerated ventilator response and decreased adaptive response to exercise,[88] resulting in further decrease in exercise capacity. Proposed causes of the increased ventilator response to exercise include mismatching of ventilation relative to pulmonary perfusion[89] and exaggerated ergoreflex response originating in the exercising skeletal muscles during effort.[90] Indeed, there is reported to be a close association between abnormal reflex response and reduced skeletal muscle mass.[91] These responses can be corrected by endurance and variation in resistant training tasks through skeletal muscle reinforcement.[92]

Exercise training has also a marked beneficial impact on vascular function. Linke et al[93] demonstrated the lower-limb exercise improved the systemic endothelial function in patients with HF. Anagnostakou et al reported that strength training in addition to interval cycle training had a marked impact on the improvement of vascular function in patients with HF. These improvements of vascular function would work for the amelioration of HF.[16]

Exercise training affects physical activity as well as emotional stability.[94] The effect of mood may have a tremendous effect on the improvement of HF; emotional mood has a close association with autonomic balance,[95] and a depressed mood certainly aggravates the state of HF.[96] These effects can be expected more intensely in patients with advanced HF, in particular, patients with continuous inotropic infusion, who has a tendency to become depressive.[97] In addition, physical inactivity itself increases the risk of depression.[98] A gradual increase in physical activity seems to have meaningful impact during the course of HF treatment.

Moreover, exercise training may affect endothelial function and improve the flow of nutritive blood and oxygen to the skeletal muscle,[99] leading to a partial shifting from type II to type I muscle fibers and resulting in greater oxidative capacity.[100] Endothelial dysfunction had been reported to have some contributions on the worsening of HF,[101] which is expected to be improved by exercise training.[102]

Conclusions

In addition to increasing exercise capacity, several expected benefits result from exercise training. These effects, including the prevention of skeletal muscle atrophy and cardiac cachexia, possibly have a positive effect on the course of HF. Therefore, exercise training should be considered in patients with advanced HF with continuous inotropic infusion therapy. However, there had been little evidence about the methodology of exercise training in patients with advanced HF. The association between the effects of exercise training and the course of advanced HF should be further investigated.

Author Contributions

EA wrote the first draft of the manuscript. MT made critical revisions and approved the final version.

REFERENCES

1. Nauman DJ, Hershberger RE. The use of positive inotropes in end-of-life heart failure care. *Curr Heart Failure Rep*. 2007;4:158–163.
2. Hauptman PJ, Mikolajczak P, George A, et al. Chronic inotropic therapy in end-stage heart failure. *Am Heart J*. 2006;152:1096.e1-1096.e8. doi:10.1016/j.ahj.2006.08.003.
3. Gorodeski EZ, Chu EC, Reese JR, Shishehbor MH, Hsich E, Starling RC. Prognosis on chronic dobutamine or milrinone infusions for stage D heart failure. *Circ Heart Fail*. 2009;2:320–324. doi:10.1161/CIRCHEARTFAILURE.108.839076.
4. Pina IL, Apstein CS, Balady GJ, et al. Exercise and heart failure: a statement from the American Heart Association Committee on exercise, rehabilitation, and prevention. *Circulation*. 2003;107:1210–1225.
5. Hambrecht R, Gielen S, Linke A, et al. Effects of exercise training on left ventricular function and peripheral resistance in patients with chronic heart failure: a randomized trial. *JAMA*. 2000;283:3095–3101.
6. Roveda F, Middlekauff HR, Rondon MU, et al. The effects of exercise training on sympathetic neural activation in advanced heart failure: a randomized controlled trial. *J Am College Cardiol*. 2003;42:854–860.
7. Fell J, Dale V, Doherty P. Does the timing of cardiac rehabilitation impact fitness outcomes? an observational analysis. *Open Heart*. 2016;3:e000369. doi:10.1136/openhrt-2015-000369.
8. Stevenson LW. Clinical use of inotropic therapy for heart failure: looking backward or forward? part II: chronic inotropic therapy. *Circulation*. 2003;108:492–497. doi:10.1161/01.CIR.0000078349.43742.8A.
9. Drexler H, Riede U, Munzel T, Konig H, Funke E, Just H. Alterations of skeletal muscle in chronic heart failure. *Circulation*. 1992;85:1751–1759.
10. von Haehling S, Steinbeck L, Doehner W, Springer J, Anker SD. Muscle wasting in heart failure: an overview. *Int J Biochem Cell Biol*. 2013;45:2257–2265. doi:10.1016/j.biocel.2013.04.025.
11. Akashi YJ, Springer J, Anker SD. Cachexia in chronic heart failure: prognostic implications and novel therapeutic approaches. *Current Heart Fail Rep*. 2005;2:198–203.
12. Chung CJ, Wu C, Jones M, et al. Reduced handgrip strength as a marker of frailty predicts clinical outcomes in patients with heart failure undergoing ventricular assist device placement. *J Cardiac Fail*. 2014;20:310–315. doi:10.1016/j.cardfail.2014.02.008.
13. Fulster S, Tacke M, Sandek A, et al. Muscle wasting in patients with chronic heart failure: results from the studies investigating co-morbidities aggravating heart failure (SICA-HF). *Eur Heart J*. 2013;34:512–519. doi:10.1093/eurheartj/ehs381.
14. Kenchaiah S, Pocock SJ, Wang D, et al; CHARM Investigators. Body mass index and prognosis in patients with chronic heart failure: insights from the Candesartan in Heart failure: assessment of Reduction in Mortality and morbidity (CHARM) program. *Circulation*. 2007;116:627–636. doi:10.1161/CIRCULATIONAHA.106.679779.
15. Anker SD, Ponikowski P, Varney S, et al. Wasting as independent risk factor for mortality in chronic heart failure. *Lancet*. 1997;349:1050–1053. doi:10.1016/S0140-6736(96)07015-8.
16. Marti CN, Gheorghiade M, Kalogeropoulos AP, Georgiopoulou VV, Quyyumi AA, Butler J. Endothelial dysfunction, arterial stiffness, and heart failure. *J Am College Cardiol*. 2012;60:1455–1469. doi:10.1016/j.jacc.2011.11.082.
17. Katz SD, Hryniewicz K, Hriljac I, et al. Vascular endothelial dysfunction and mortality risk in patients with chronic heart failure. *Circulation*. 2005;111:310–314. doi:10.1161/01.CIR.0000153349.77489.CF.
18. Ledoux J, Gee DM, Leblanc N. Increased peripheral resistance in heart failure: new evidence suggests an alteration in vascular smooth muscle function. *Br J Pharmacol*. 2003;139:1245–1248. doi:10.1038/sj.bjp.0705366.
19. Kataoka T, Keteyian SJ, Marks CR, Fedel FJ, Levine AB, Levine TB. Exercise training in a patient with congestive heart failure on continuous dobutamine. *Med Sci Sports Exercise*. 1994;26:678–681.

20. Arena R, Humphrey R, Peberdy MA. Safety and efficacy of exercise training in a patient awaiting heart transplantation while on positive intravenous inotropic support. *J Cardiopulm Rehabil*. 2000;20:259–261.
21. Karapolat H, Engin C, Eroglu M, et al. Efficacy of the cardiac rehabilitation program in patients with end-stage heart failure, heart transplant patients, and left ventricular assist device recipients. *Transplant Proce*. 2013;45:3381–3385. doi:10.1016/j.transproceed.2013.06.009.
22. Wilson JR, Martin JL, Ferraro N. Impaired skeletal muscle nutritive flow during exercise in patients with congestive heart failure: role of cardiac pump dysfunction as determined by the effect of dobutamine. *Am J Cardiol*. 1984;53:1308–1315.
23. Hayashida N, Tomoeda H, Oda T, et al. Inhibitory effect of milrinone on cytokine production after cardiopulmonary bypass. *Ann Thorac Surg*. 1999;68:1661–1667.
24. Capomolla S, Febo O, Opasich C, et al. Chronic infusion of dobutamine and nitroprusside in patients with end-stage heart failure awaiting heart transplantation: safety and clinical outcome. *Eur J Heart Fail*. 2001;3:601–610.
25. Mancini DM, Schwartz M, Ferraro N, Seestedt R, Chance B, Wilson JR. Effect of dobutamine on skeletal muscle metabolism in patients with congestive heart failure. *Am J Cardiol*. 1990;65:1121–1126.
26. Drexler H, Faude F, Hoing S, Just H. Blood flow distribution within skeletal muscle during exercise in the presence of chronic heart failure: effect of milrinone. *Circulation*. 1987;76:1344–1352.
27. Kreisman SH, Ah Mew N, Arsenault M, et al. Epinephrine infusion during moderate intensity exercise increases glucose production and uptake. *Am J Physiol Endocrinol Metab*. 2000;278:E949–E957.
28. Qvisth V, Hagstrom-Toft E, Enoksson S, Bolinder J. Catecholamine regulation of local lactate production in vivo in skeletal muscle and adipose tissue: role of -adrenoreceptor subtypes. *J Clin Endocrinol Metabol*. 2008;93:240–246. doi:10.1210/jc.2007-1313.
29. Ryall JG, Church JE, Lynch GS. Novel role for ss-adrenergic signalling in skeletal muscle growth, development and regeneration. *Clin Exp Pharmacol Physiol*. 2010;37:397–401. doi:10.1111/j.1440-1681.2009.05312.x.
30. Lynch GS, Ryall JG. Role of beta-adrenoceptor signaling in skeletal muscle: implications for muscle wasting and disease. *Physiol Rev*. 2008;88:729–767. doi:10.1152/physrev.00028.2007.
31. George I, Xydas S, Mancini DM, et al. Effect of clenbuterol on cardiac and skeletal muscle function during left ventricular assist device support. *J Heart Lung Transplant*. 2006;25:1084–1090. doi:10.1016/j.healun.2006.06.017.
32. Dodd SL, Powers SK, Vrabas IS, Criswell D, Stetson S, Hussain R. Effects of clenbuterol on contractile and biochemical properties of skeletal muscle. *Med Sci Sports Exerc*. 1996;28:669–676.
33. Joassard OR, Durieux AC, Freyssenet DG. β2-Adrenergic agonists and the treatment of skeletal muscle wasting disorders. *Int J Biochem Cell Biol*. 2013;45:2309–2321. doi:10.1016/j.biocel.2013.06.025.
34. Busquets S, Figueras MT, Fuster G, et al. Anticachectic effects of formoterol: a drug for potential treatment of muscle wasting. *Cancer Res*. 2004;64:6725–6731.
35. Zeman RJ, Ludemann R, Easton TG, Etlinger JD. Slow to fast alterations in skeletal muscle fibers caused by clenbuterol, a beta 2-receptor agonist. *Am J Physiol*. 1988;254:E726–E732.
36. Tibayan FA, Chesnutt AN, Folkesson HG, Eandi J, Matthay MA. Dobutamine increases alveolar liquid clearance in ventilated rats by beta-2 receptor stimulation. *Am J Respir Crit Care Med*. 1997;156:438–444.
37. Reichart DL, Hinkle RT, Lefever FR, et al. Activation of the dopamine 1 and dopamine 5 receptors increase skeletal muscle mass and force production under non-atrophying and atrophying conditions. *BMC Musculoskelet Disord*. 2011;12:27. doi:10.1186/1471-2474-12-27.
38. Navegantes LC, Resano NM, Migliorini RH, Kettelhut IC. Role of adrenoceptors and cAMP on the catecholamine-induced inhibition of proteolysis in rat skeletal muscle. *Am J Physiol Endocrinol Metab*. 2000;279:E663–E668.
39. Seow CY, Morishita L, Bressler BH. Milrinone inhibits contractility in skinned skeletal muscle fibers. *Am J Physiol*. 1998;274:C1306–C1311.
40. Al-Hesayen A, Azevedo ER, Newton GE, Parker JD. The effects of dobutamine on cardiac sympathetic activity in patients with congestive heart failure. *J Am College Cardiol*. 2002;39:1269–1274.
41. Freimark D, Feinberg MS, Matezky S, Hochberg N, Shechter M. Impact of short-term intermittent intravenous dobutamine therapy on endothelial function in patients with severe chronic heart failure. *Am Heart J*. 2004;148:878–882. doi:10.1016/j.ahj.2004.04.013.
42. Hsueh CW, Lee WL, Chen CK, et al. Dopamine and dobutamine have different effects on heart rate variability in patients with congestive heart failure. *Zhonghua yi xue za zhi*. 1998;61:199–209. (Free China ed.).
43. Piepoli MF, Conraads V, Corra U, et al. Exercise training in heart failure: from theory to practice. A consensus document of the Heart Failure Association and the European Association for Cardiovascular Prevention and Rehabilitation. *Eur J Heart Fail*. 2011;13:347–357. doi:10.1093/eurjhf/hfr017.
44. Fleg JL, Cooper LS, Borlaug BA, et al. Exercise training as therapy for heart failure: current status and future directions. *Circulation Heart Fail*. 2015;8:209–220. doi:10.1161/CIRCHEARTFAILURE.113.001420.
45. Dirks ML, Wall BT, van de Valk B, et al. One week of bed rest leads to substantial muscle atrophy and induces whole-body insulin resistance in the absence of skeletal muscle lipid accumulation. *Diabetes*. 2016;65:2862–2875. doi:10.2337/db15-1661.
46. Wall BT, Dirks ML, Snijders T, Senden JM, Dolmans J, van Loon LJ. Substantial skeletal muscle loss occurs during only 5 days of disuse. *Acta Physiologica*. 2014;210:600–611. doi:10.1111/apha.12190.
47. Callahan DM, Toth MJ. Skeletal muscle protein metabolism in human heart failure. *Curr Opin Clin Nutr Metab Care*. 2013;16:66–71. doi:10.1097/MCO.0b013e32835a8842.
48. Stevenson LW, Massie BM, Francis GS. Optimizing therapy for complex or refractory heart failure: a management algorithm. *Am Heart J*. 1998;135:S293–S309.
49. Packer M. Should B-type natriuretic peptide be measured routinely to guide the diagnosis and management of chronic heart failure? *Circulation*. 2003;108:2950–2953. doi:10.1161/01.CIR.0000109205.35813.8E.
50. Humphrey R. Exercise physiology in patients with left ventricular assist devices. *J Cardiopulmonary Rehabil*. 1997;17:73–75.
51. Kerrigan DJ, Williams CT, Ehrman JK, et al. Cardiac rehabilitation improves functional capacity and patient-reported health status in patients with continuous-flow left ventricular assist devices: the Rehab-VAD randomized controlled trial. *JACC Heart Fail*. 2014;2:653–659. doi:10.1016/j.jchf.2014.06.011.
52. Working Group on Cardiac Rehabilitation & Exercise Physiology, Working Group on Heart Failure of the European Society of Cardiology. Recommendations for exercise testing in chronic heart failure patients. *Eur Heart J*. 2001;22:37–45. doi:10.1053/euhj.2000.2388.
53. Giallauria F, Vigorito C, Tramarin R, et al; ISYDE-2008 Investigators of the Italian Association for Cardiovascular Prevention, Rehabilitation, and Prevention. Cardiac rehabilitation in very old patients: data from the Italian Survey on Cardiac Rehabilitation-2008 (ISYDE-2008)—official report of the Italian Association for Cardiovascular Prevention, Rehabilitation, and Epidemiology. *J Gerontol A Biol Sci Med Sci*. 2010;65:1353–1361. doi:10.1093/gerona/glq138.
54. Faber MJ, Bosscher RJ, Chin APMJ, van Wieringen PC. Effects of exercise programs on falls and mobility in frail and pre-frail older adults: a multicenter randomized controlled trial. *Arch Phys Med Rehabil*. 2006;87:885–896. doi:10.1016/j.apmr.2006.04.005.
55. Mezzani A, Hamm LF, Jones AM, et al; European Association for Cardiovascular Prevention and Rehabilitation; American Association of Cardiovascular and Pulmonary Rehabilitation; Canadian Association of Cardiac Rehabilitation. Aerobic exercise intensity assessment and prescription in cardiac rehabilitation: a joint position statement of the European Association for Cardiovascular Prevention and Rehabilitation, the American Association of Cardiovascular and Pulmonary Rehabilitation and the Canadian Association of Cardiac Rehabilitation. *Eur J Prev Cardiol*. 2013;20:442–467. doi:10.1177/2047487312460484.
56. Fletcher GF, Balady GJ, Amsterdam EA, et al. Exercise standards for testing and training: a statement for healthcare professionals from the American Heart Association. *Circulation*. 2001;104:1694–1740.
57. Bonzheim SC, Franklin BA, DeWitt C, et al. Physiologic responses to recumbent versus upright cycle ergometry, and implications for exercise prescription in patients with coronary artery disease. *Am J Cardiol*. 1992;69:40–44.
58. Braith RW, Stewart KJ. Resistance exercise training: its role in the prevention of cardiovascular disease. *Circulation*. 2006;113:2642–2650. doi:10.1161/CIRCULATIONAHA.105.584060.
59. Haykowsky MJ, Timmons MP, Kruger C, McNeely M, Taylor DA, Clark AM. Meta-analysis of aerobic interval training on exercise capacity and systolic function in patients with heart failure and reduced ejection fractions. *Am J Cardiol*. 2013;111:1466–1469. doi:10.1016/j.amjcard.2013.01.303.
60. Ellingsen O, Halle M, Conraads VM, et al. High intensity interval training in heart failure patients with reduced ejection fraction. *Circulation*. 2017;136:611–612. doi:10.1161/CIRCULATIONAHA.116.022924.
61. Hoshino D, Tamura Y, Masuda H, Matsunaga Y, Hatta H. Effects of decreased lactate accumulation after dichloroacetate administration on exercise training-induced mitochondrial adaptations in mouse skeletal muscle. *Physiol Rep*. 2015;3:e12555. doi:10.14814/phy2.12555.
62. Groehs RV, Antunes-Correa LM, Nobre TS, et al. Muscle electrical stimulation improves neurovascular control and exercise tolerance in hospitalised advanced heart failure patients. *Eur J Prev Cardiol*. 2016;23:1599–1608. doi:10.1177/2047487316654025.
63. Ennis S, McGregor G, Hamborg T, et al. Randomised feasibility trial into the effects of low-frequency electrical muscle stimulation in advanced heart failure patients. *BMJ Open*. 2017;7:e016148. doi:10.1136/bmjopen-2017-016148.
64. Forestieri P, Bolzan DW, Santos VB, et al. Neuromuscular electrical stimulation improves exercise tolerance in patients with advanced heart failure on continuous intravenous inotropic support use—randomized controlled trial [published online ahead of print June 21, 2017]. *Clin Rehabil*. doi:10.1177/0269215517715762.
65. Neto MG, Martinez BP, Conceição CS, Silva PE, Carvalho VO. Combined exercise and inspiratory muscle training in patients with heart failure: a systematic review and meta-analysis. *J Cardiopulm Rehabil Prev*. 2016;36:395–401.

66. Conraads VM, Beckers PJ. Exercise training in heart failure: practical guidance. *Heart*. 2010;96:2025–2031. doi:10.1136/hrt.2009.183889.
67. Amiya E, Taya M, Watanabe M. Physical activity. A useful marker for cardiac rehabilitation? *Int Heart J*. 2015;56:583–584. doi:10.1536/ihj.15-301.
68. Selig SE, Carey MF, Menzies DG, et al. Moderate-intensity resistance exercise training in patients with chronic heart failure improves strength, endurance, heart rate variability, and forearm blood flow. *J Card Fail*. 2004; 10:21–30.
69. Belardinelli R, Georgiou D, Cianci G, Purcaro A. Randomized, controlled trial of long-term moderate exercise training in chronic heart failure: effects on functional capacity, quality of life, and clinical outcome. *Circulation*. 1999;99: 1173–1182.
70. Wisløff U, Støylen A, Loennechen JP, et al. Superior cardiovascular effect of aerobic interval training versus moderate continuous training in heart failure patients: a randomized study. *Circulation*. 2007;115:3086–3094.
71. Arad M, Adler Y, Koren-Morag N, et al. Exercise training in advanced heart failure patients: discordance between improved exercise tolerance and unchanged NT-proBNP levels. *Int J Cardiol*. 2008;126:114–119.
72. Pu CT, Johnson MT, Forman DE, et al. Randomized trial of progressive resistance training to counteract the myopathy of chronic heart failure. *J Appl Physiol*. 1985;90:2341–2350.
73. Conraads VM, Beckers P, Bosmans J, et al. Combined endurance/resistance training reduces plasma TNF-alpha receptor levels in patients with chronic heart failure and coronary artery disease. *Eur Heart J*. 2002;23:1854–1860.
74. Maiorana A, O'Driscoll G, Cheetham C, et al. Combined aerobic and resistance exercise training improves functional capacity and strength in CHF. *J Appl Physiol*. 1985;88:1565–1570.
75. O'Connor CM, Whellan DJ, Lee KL, et al. Efficacy and safety of exercise training in patients with chronic heart failure: HF-ACTION randomized controlled trial. *JAMA*. 2009;301:1439–1450.
76. Erbs S, Höllriegel R, Linke A, et al. Exercise training in patients with advanced chronic heart failure (NYHA IIIb) promotes restoration of peripheral vasomotor function, induction of endogenous regeneration, and improvement of left ventricular function. *Circ Heart Fail*. 2010;3:486–494.
77. Passino C, Severino S, Poletti R, et al. Aerobic training decreases B-type natriuretic peptide expression and adrenergic activation in patients with heart failure. *J Am Coll Cardiol*. 2006;47:1835–1839.
78. Scrutinio D, Passantino A, Catanzaro R, et al. Inpatient cardiac rehabilitation soon after hospitalization for acute decompensated heart failure: a propensity score study. *J Cardiopulm Rehabil Prev*. 2012;32:71–77.
79. Gielen S, Adams V, Möbius-Winkler S, et al. Anti-inflammatory effects of exercise training in the skeletal muscle of patients with chronic heart failure. *J Am Coll Cardiol*. 2003;42:861–868.
80. Hambrecht R, Niebauer J, Fiehn E, et al. Physical training in patients with stable chronic heart failure: effects on cardiorespiratory fitness and ultrastructural abnormalities of leg muscles. *J Am Coll Cardiol*. 1995;25:1239–1249.
81. Hambrecht R, Gielen S, Linke A, et al. Effects of exercise training on left ventricular function and peripheral resistance in patients with chronic heart failure: randomized trial. *JAMA*. 2000;283:3095–3101.
82. Klocek M, Kubinyi A, Bacior B, Kawecka-Jaszcz K. Effect of physical training on quality of life and oxygen consumption in patients with congestive heart failure. *Int J Cardiol*. 2005;103:323–329.
83. Brum PC, Bacurau AV, Cunha TF, Bechara LR, Moreira JB. Skeletal myopathy in heart failure: effects of aerobic exercise training. *Experiment Physiol*. 2014;99:616–620. doi:10.1113/expphysiol.2013.076844.
84. Cunha TF, Bacurau AV, Moreira JB, et al. Exercise training prevents oxidative stress and ubiquitin-proteasome system overactivity and reverse skeletal muscle atrophy in heart failure. *PLoS ONE*. 2012;7:e41701. doi:10.1371/journal.pone.0041701.
85. Glass DJ. Signalling pathways that mediate skeletal muscle hypertrophy and atrophy. *Nature Cell Biol*. 2003;5:87–90. doi:10.1038/ncb0203-87.
86. Mousa TM, Liu D, Cornish KG, Zucker IH. Exercise training enhances baroreflex sensitivity by an angiotensin II-dependent mechanism in chronic heart failure. *J Appl Physiol*. 2008;104:616–624. doi:10.1152/japplphysiol.00601.2007.
87. Du Bois P, Pablo Tortola C, Lodka D, et al. Angiotensin II induces skeletal muscle atrophy by activating TFEB-mediated MuRF1 expression. *Circulation Res*. 2015;117:424–436. doi:10.1161/CIRCRESAHA.114.305393.
88. Clark AL, Volterrani M, Swan JW, Coats AJ. The increased ventilatory response to exercise in chronic heart failure: relation to pulmonary pathology. *Heart*. 1997;77:138–146.
89. Wasserman K, Zhang YY, Gitt A, et al. Lung function and exercise gas exchange in chronic heart failure. *Circulation*. 1997;96:2221–2227.
90. Piepoli M, Clark AL, Volterrani M, Adamopoulos S, Sleight P, Coats AJ. Contribution of muscle afferents to the hemodynamic, autonomic, and ventilatory responses to exercise in patients with chronic heart failure: effects of physical training. *Circulation*. 1996;93:940–952.
91. Piepoli MF, Kaczmarek A, Francis DP, et al. Reduced peripheral skeletal muscle mass and abnormal reflex physiology in chronic heart failure. *Circulation*. 2006;114:126–134. doi:10.1161/CIRCULATIONAHA.105.605980.
92. Brassard P, Poirier P, Martin J, et al. Impact of exercise training on muscle function and ergoreflex in Fontan patients: a pilot study. *Int J Cardiol*. 2006;107:85–94. doi:10.1016/j.ijcard.2005.02.038.
93. Linke A, Schoene N, Gielen S, et al. Endothelial dysfunction in patients with chronic heart failure: systemic effects of lower-limb exercise training. *J Am College Cardiol*. 2001;37:392–397.
94. Niset G, Coustry-Degre C, Degre S. Psychosocial and physical rehabilitation after heart transplantation: 1-year follow-up. *Cardiology*. 1988;75:311–317.
95. Emani S, Binkley PF. Mind-body medicine in chronic heart failure: a translational science challenge. *Circ Heart Fail*. 2010;3:715–725. doi:10.1161/CIRCHEARTFAILURE.110.951509.
96. Adelborg K, Schmidt M, Sundboll J, et al. Mortality risk among heart failure patients with depression: a nationwide population-based cohort study. *J Am Heart Assoc*. 2016;67:1318. doi:10.1161/JAHA.116.004137.
97. Pantilat SZ, Steimle AE. Palliative care for patients with heart failure. *JAMA*. 2004;291:2476–2482. doi:10.1001/jama.291.20.2476.
98. Horne D, Kehler DS, Kaoukis G, et al. Impact of physical activity on depression after cardiac surgery. *Canad J Cardiol*. 2013;29:1649–1656. doi:10.1016/j.cjca.2013.09.015.
99. Yang HT, Prior BM, Lloyd PG, et al. Training-induced vascular adaptations to ischemic muscle. *J Physiol Pharmacol*. 2008;59:57–70.
100. Corra U, Mezzani A, Giannuzzi P, Tavazzi L. Chronic heart failure-related myopathy and exercise training: a developing therapy for heart failure symptoms. *Prog Cardiovasc Dis*. 2002;45:157–172.
101. Fischer D, Rossa S, Landmesser U, et al. Endothelial dysfunction in patients with chronic heart failure is independently associated with increased incidence of hospitalization, cardiac transplantation, or death. *Eur Heart J*. 2005;26:65–69. doi:10.1093/eurheartj/ehi001.
102. Hambrecht R, Fiehn E, Weigl C, et al. Regular physical exercise corrects endothelial dysfunction and improves exercise capacity in patients with chronic heart failure. *Circulation*. 1998;98:2709–2715.