

Neuromuscular Electrical Stimulation and Inspiratory Muscle Training as Potential Adjunctive Rehabilitation Options for Patients With Heart Failure

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- Aerobic and resistance exercise training programs produce an abundance of physiologic and clinical benefits in patients with heart failure (HF). Improved maximal aerobic capacity, submaximal aerobic endurance, muscle force production, perceived quality of life, and skeletal muscle characteristics are among the more established outcomes resulting from these rehabilitation techniques. Moreover, both aerobic and resistance exercise training appear to portend a low risk to patients with HF when appropriate exercise prescription methods are followed. While the aforementioned training techniques will undoubtedly continue to be at the center of a well-formulated rehabilitation program, other adjunctive interventions, which are presently underutilized in clinical practice, may prove beneficial in patients with HF. Specifically, both neuromuscular electrical stimulation (NMES) and inspiratory muscle training (IMT) appear to significantly improve several physiologic, exercise, symptomatologic, and quality-of-life parameters. NMES targets skeletal muscle abnormalities, whereas IMT primarily targets the weakened respiratory musculature, both often encountered in patients with HF. A PubMed search using relevant key words identified 19 original investigations examining the impact of NMES (13 studies) and IMT (6 studies) training programs in patients with HF. The resultant review (1) provides a summary of the original research outcomes of both NMES and IMT in patients with HF; (2) addresses current research gaps, providing a direction for future investigations; and (3) provides clinical scenarios where NMES and IMT may prove to be beneficial during the rehabilitation of patients with HF.

KEY WORDS

aerobic capacity

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Aerobic and resistance exercise training are safe and beneficial lifestyle interventions for patients with heart failure (HF).¹⁻⁴ Improvements in peak aerobic capacity, submaximal aerobic endurance, muscle force production, symptomatology, and quality of life are well-documented benefits of aerobic and resis-

tance training in patients with HF. Given the robust body of scientific evidence consistently demonstrating its benefits, these interventions are justifiably considered integral components of cardiac rehabilitation.⁵ While these interventions will continue to serve as the core components of rehabilitation programs,

evidence demonstrating the potential benefits of adjunctive treatment options is accumulating. Both neuromuscular electrical stimulation (NMES) and inspiratory muscle training (IMT) demonstrate a positive impact on numerous variables in patients with HF, including physiologic function, aerobic capacity, muscle force production, symptoms, and quality of life. While evidence supporting the implementation of NMES and IMT in patients with HF is compelling, neither approach is considered in clinical practice. This may partly be due to the lack of awareness of the evidence supporting NMES and IMT in patients with HF by clinicians delivering rehabilitation services. This is understandable given that there is no presently available review that summarizes the potential benefits of NMES or IMT in this chronic disease population. The purpose of the present review is to therefore: (1) identify the physiologic abnormalities that contribute to the functional limitations often observed in patients with HF; (2) provide a comprehensive summary of the research investigations implementing NMES and IMT programs in patients with HF; (3) address current research gaps, providing a direction for future investigations; and (4) provide clinical scenarios where NMES and IMT may prove to be beneficial during the rehabilitation of patients with HF.

PHYSIOLOGIC ABNORMALITIES LIMITING FUNCTIONAL CAPACITY IN PATIENTS WITH HF

Aerobic Exercise

The physiologic response to a bout of aerobic exercise is dependent on the ability of the pulmonary, cardiovascular, and skeletal muscle systems to augment oxygen uptake (pulmonary), delivery (cardiovascular), and utilization (muscle) in an effort to meet the increased energy requirements of working muscle. The connection between aerobic capacity and physiologic function is most commonly expressed through a modification of the Fick equation such that oxygen uptake ($\dot{V}O_2$) is the product of cardiac output and the difference in oxygen concentration between arterial and venous blood. Through this equation, it is readily apparent that peak $\dot{V}O_2$ is dependent on the augmentation of heart rate and stroke volume as well as the ability of working skeletal muscle to extract a greater amount of oxygen for energy production. While the proper physiologic function of both is important, it is the former (maximal cardiac output) that primarily dictates aerobic capacity in healthy individuals as well as in those with cardiac disease.⁶ While the role of the pulmonary system is not readily apparent in the Fick equation, its normal response is

nonetheless of paramount importance to the aerobic exercise response. A dramatic rise in both respiratory rate and tidal volume is necessary to increase inspired oxygen and expired carbon dioxide during aerobic exercise. Moreover, an increase in pulmonary perfusion must match the increase in pulmonary ventilation to ensure the pressure-differential-driven transfer of oxygen and carbon dioxide from the alveoli to blood and vice versa.

On average, patients with HF present with age/sex-predicted peak $\dot{V}O_2$ values that are 50% and 25% lower than the apparently healthy and coronary artery disease populations, respectively.⁷ The reason for this often-encountered profound reduction in aerobic capacity in the population with HF is multifactorial and involves the cardiovascular, skeletal muscle, and pulmonary systems. As the diagnosis implies, patients with HF present with diminished cardiac function, reducing cardiac output both at rest and during exercise. Not surprisingly, a significant positive correlation between peak $\dot{V}O_2$ and cardiac output has been consistently demonstrated in patients with HF.⁸⁻¹¹ Skeletal muscle abnormalities are well documented in patients with HF, collectively reflecting a diminished capacity for aerobic energy production.^{3,12-16} Studies have reported a 10% to 20% reduction in type I (aerobic) fiber composition with a concomitant increase in the percentage of type IIb fibers in patients with HF than in control subjects.¹⁷ The skeletal muscle abnormalities associated with HF are coupled with a reduction in capillary density.^{17,18} Both of these phenomena negatively impact the peripheral component of the Fick equation and contribute to the reduction in peak $\dot{V}O_2$. Finally, there are a number of pulmonary abnormalities involving both the respiratory musculature and interstitial tissues that have been reported in the population with HF. These include (1) respiratory muscle weakness^{19,20} and endurance,²¹ (2) elevated airway resistance,²² (3) altered diaphragmatic positioning,²³ (4) diminished alveolar-capillary perfusion capacity,²⁴ and (5) ventilation-perfusion abnormalities.²⁵⁻²⁷ Moreover, several measures of pulmonary function have been shown to correlate with aerobic exercise capacity in patients with HF.^{20,28,29} Given that patients with HF do not commonly exhibit arterial oxygen desaturation during aerobic exercise, an inability to augment pulmonary oxygen uptake is rarely the culprit for a diminished peak $\dot{V}O_2$ response. However, alterations to respiratory musculature function and positioning in conjunction with increased airway resistance likely contribute to the sensation of exertional dyspnea often encountered in the population with HF.^{28,30}

In summary, the reduction in aerobic capacity frequently observed in patients with HF is a multifactorial phenomenon, involving the pulmonary, cardiovascular,

and skeletal muscle systems to varying degrees. Improving the physiologic function of one or more of these systems through various interventions is therefore necessary to improve aerobic capacity. Moreover, improving the physiologic function of all 3 systems through focused training regimens may optimize clinical outcome.

Resistance Exercise

Describing resistance exercise is more complex than its aerobic counterpart. Simply stated, resistance exercise involves movement against a load. Resistance exercise may be further dichotomized into activities involving movement against a heavier load for fewer repetitions and movement against a lighter load for a greater number of repetitions. The former type of resistance exercise typically increases muscular strength, whereas the latter is designed to improve muscular endurance, although both approaches yield improvements in strength and endurance. Moreover, resistance exercise directed toward muscular strength primarily utilizes anaerobic energy production pathways, whereas muscular endurance activities utilize a greater degree of aerobic energy production.² A primary determinant of muscular strength is cross-sectional area,³¹ whereas the aerobic characteristics of skeletal muscle have a greater influence on endurance performance.

The skeletal muscle abnormalities described above include a decreased cross-sectional area in patients with HF compared with healthy controls.^{32–36} In addition, a progressive decrease in muscle mass is associated with increasing HF disease severity.^{33,34} While maximal force production per unit area of muscle seems to be preserved in patients with HF, a decrease in overall muscle cross-sectional area compared with apparently healthy individuals leads to diminished muscular strength in this chronic disease population.¹⁷ The well-documented decrease in aerobic characteristics of skeletal muscle plays a major role in the decreased muscular endurance observed in patients with HF.^{37–39}

In summary, patients with HF frequently present with a decreased ability to perform activities requiring muscle strength and endurance. The decline in muscular strength appears to be primarily influenced by a smaller cross-sectional area, whereas the decrease in muscular endurance is impacted by a diminished aerobic capacity of skeletal muscle.

Impact of Traditional Aerobic and Resistance Exercise Training in Patients With HF

There is a wealth of evidence demonstrating positive outcomes associated with aerobic and resistance training in patients with HF.^{1,3,40–42} Aerobic exercise training programs clearly improve peak $\dot{V}O_2$ and $\dot{V}O_2$ at the ventilatory threshold, as well as a host of other phys-

iological measures reflecting both an improved capacity to produce energy aerobically and improved autonomic and cardiovascular function. In addition, there is evidence to suggest that aerobic exercise training reduces morbidity and mortality in patients with HF.⁴³ Resistance exercise training consistently elicits improved muscular strength and endurance and potentially has a positive impact on cardiac function.⁴² Contrary to training studies in apparently healthy subjects, resistance exercise programs, particularly those focusing on improving muscular endurance, may also significantly improve peak $\dot{V}O_2$ in patients with HF.⁴² This latter finding may be related to the fact that patients with HF are, in general, profoundly deconditioned and have a host of skeletal muscle abnormalities at the initiation of an exercise program. Thus, any type of conditioning program (aerobic or resistance) may have a significant impact on aerobic performance. Given the vast amount of evidence supporting aerobic and resistance training in patients with HF, it is clear that these 2 rehabilitation options should remain the centerpiece of any lifestyle intervention program. The following sections of this review will address NMES and IMT as potential complimentary rehabilitation options in patients with HF.

NEUROMUSCULAR ELECTRICAL STIMULATION IN PATIENTS WITH HF

Original investigations assessing the effects of chronic NMES programs are summarized in Table 1. All 13 investigations included small cohorts, which is partially overcome by the consistency among each study findings. Ten of the 13 investigations included a control group with random assignment. Only 1 investigation completely blinded research personnel performing baseline/follow-up assessments. Moreover, the groups with HF enrolled in the trials (1) were predominantly men, (2) were all diagnosed with systolic HF confirmed by echocardiography, and (3) had a mean age between 53 and 63 years. The NMES training protocols employed were somewhat diverse among the studies. Individual session time, number of sessions per week, and total training duration ranged from 30 minutes to 4 hours, 3 to 7 days per week, and 5 to 10 weeks, respectively. In addition, the type of muscle contraction elicited by NMES (titanic vs twitch) varied among the investigations. All 13 investigations performed NMES on the quadriceps bilaterally and a majority also included the calf muscles.

None of the 13 investigations reported the occurrence of adverse events with NMES. Seven of 9 investigations assessing changes in peak $\dot{V}O_2$ following NMES reported a significant increase, which ranged from 4% to 20%. Interestingly, subjects in the 2 trials

Table 1 • SUMMARY OF STUDIES ASSESSING CHRONIC FUNCTIONAL ELECTRICAL STIMULATION IN PATIENTS WITH HEART FAILURE

Author, year	Number of subjects and characteristics	Age in years (mean ± SD); gender (male/female)	Training protocol	Major findings
Maillefert et al, 1998 ⁴⁴	N = 14 NYHA II–IV, LVEF < 40%	56.4 ± 9.1; 13/1	<ul style="list-style-type: none"> • Bilateral quadriceps and calves • 10 Hz, biphasic • Pulse duration: 200 μs • On/off time: 20/20 s • Intensity: Maximum tolerated by patient • 60 min/d, 5 d/wk, 5 wk 	<p>No adverse events reported</p> <p>Significant increase:</p> <ul style="list-style-type: none"> • Peak $\dot{V}O_2$ (13.9%), • $\dot{V}O_2$ at ventilatory threshold (23.6%) • 6MWT (9.5%) • Gastrocnemius muscle volume (5.4%) • Soleus muscle volume (6.0%) <p>Cardiac output did not vary during NMES or improve significantly following the intervention</p>
Vaquero et al, 1998 ⁴⁵	2 groups: NMES, n = 7 Control, n = 7 All subjects were following-heart transplant Random assignment	57 ± 7; 11/4	<p>NMES</p> <ul style="list-style-type: none"> • Bilateral quadriceps • 30–50 Hz, biphasic • On/off time: 6–10/30–50 s • Intensity: Maximum tolerated by patient • 30 min/d, 3 d/wk, 8 wk <p>Control</p> <ul style="list-style-type: none"> • No electrical stimulation 	<p>No adverse events reported</p> <p>Significant increase in the NMES group:</p> <ul style="list-style-type: none"> • Peak $\dot{V}O_2$ (9.1%) <p>No change in the control group</p>
Quittan et al, 1999 ⁴⁶	N = 7 NYHA II–III, LVEF 20 ± 10%	56 ± 5; 6/1	<ul style="list-style-type: none"> • Bilateral quadriceps • 50 Hz, biphasic • Pulse width: 0.7 ms • On/off time: 2/6 s • Intensity: 25%–30% of maximal voluntary contraction • 30 min/d, 5 d/wk, for first 2 wk • 60 min/d, 5 d/wk, for next 6 wk 	<p>No adverse events reported</p> <p>Significant increase:</p> <ul style="list-style-type: none"> • Maximal knee extensor isometric contraction at 60° (9.0%) • Maximal knee extensor isometric contraction at 90° (20.4%) • Peak isokinetic knee extensor torque at 60°/s (12.4%)
Quittan et al, 2001 ⁴⁷	2 groups: NMES, n = 17 Control, n = 16 NYHA II–IV, LVEF < 20%	NMES: 59 ± 6; 12/5 Control: 57 ± 8; 9/7	<p>NMES</p> <ul style="list-style-type: none"> • Bilateral hamstrings and quadriceps • 50 Hz, biphasic • Pulse width: 0.7 ms • On/off time: 2/6 s • 30 min/d, 5 d/wk, for first 2 wk • 60 min/d, 5 d/wk, for next 6 wk <p>Control</p> <ul style="list-style-type: none"> • No electrical stimulation 	<p>No adverse events reported</p> <p>Significant increase in the NMES group:</p> <ul style="list-style-type: none"> • Peak isokinetic knee extensor torque (22.9%) • Peak isokinetic knee flexor torque (35.4%) • Quadriceps cross-sectional area (15.5%) • Physical, emotional, and social quality-of-life scores <p>No change in the aforementioned variables in the control group</p>
Harris et al, 2003 ⁴⁸	2 groups: NMES, n = 22 Bicycle, n = 24 NYHA II and III, LVEF < 40% Random assignment	NMES: 63 ± 10; 17/5 Bicycle: 61.8 ± 10.8; 21/3	<p>NMES</p> <ul style="list-style-type: none"> • Bilateral quadriceps, calves • 25 Hz, biphasic • On/off time: 5/5 s • Intensity set by patient to achieve muscle contraction without joint movement or discomfort • 30 min/d, 5 d/wk, 6 wk 	<p>No adverse events reported</p> <p>Significant increase in the NMES group:</p> <ul style="list-style-type: none"> • Exercise time (13.4%) • 6MWT (8.1%) • Quadriceps strength (12.5%) • Quadriceps fatigue (14.3%) <p>Significant increase in the bicycle group:</p>

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Table 1 • SUMMARY OF STUDIES ASSESSING CHRONIC FUNCTIONAL ELECTRICAL STIMULATION IN PATIENTS WITH HEART FAILURE (Continued)

Author, year	Number of subjects and characteristics	Age in years (mean ± SD); gender (male/female)	Training protocol	Major findings
Nuhr, 2004 ⁴⁹	2 groups: NMES, <i>n</i> = 15 Control, <i>n</i> = 17 NYHA II–IV, LVEF 22 ± 5% Random assignment	NMES: 53 ± 7; 14/1 Control: 53 ± 13; 14/3	Bicycle • 30 min/d, 5 d/wk, 6 wk • 70% of maximum HR NMES • Bilateral hamstrings and quadriceps • 15 Hz, biphasic • On/off time: 2/4 s • Pulse width: 0.5 ms • Intensity: 25%–30% maximal voluntary contraction • 4 h/d (2 AM; 2 PM), 7 d/wk, 10 wk Control Sensory electrical stimulation only	Exercise time (20.2%) 6MWT (9.0%) Quadriceps strength (10.9%) Quadriceps fatigue (10.5%) Peak $\dot{V}O_2$ did not improve in either group Quality-of-life score improved for the entire study group (NMES + bicycle) but did not improve for each group independently Aforementioned improvements were not statistically significant between groups
Deley et al, 2005 ⁵⁰	2 groups: NMES, <i>n</i> = 12 Conventional exercise, <i>n</i> = 12 NYHA II–III, LVEF < 40% Random assignment	NMES: 56 ± 8; 9/3 Conventional exercise: 57 ± 6; 11/1	NMES • Bilateral quadriceps and calves • 10 Hz, biphasic • On/off time: 12/8 s • Pulse duration: 200 μ s • Amplitude set to highest tolerable to patient • 60 min/d, 5 d/wk, 5 wk Conventional exercise • Aerobic exercise (treadmill, bicycle and arm cycling) at 60%–70% peak HR; target exertion by Borg scale 13–15 • 60 min/d, 5 d/wk, 5 wk	No adverse events reported Significant increase in the NMES group: Peak $\dot{V}O_2$ (8.2%) $\dot{V}O_2$ at ventilatory threshold (16.8%) 6MWT (11.9%) Maximal knee extensor isometric contraction at 90° (9.7%) Significant increase in the bicycle group: Peak $\dot{V}O_2$ (21.8%) $\dot{V}O_2$ at ventilatory threshold (19.3%) 6MWT (15.3%) Maximal knee extensor isometric contraction at 90° (11.3%) Aforementioned improvements were not statistically significant between groups

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Table 1 • SUMMARY OF STUDIES ASSESSING CHRONIC FUNCTIONAL ELECTRICAL STIMULATION IN PATIENTS WITH HEART FAILURE (Continued)

Author, year	Number of subjects and characteristics	Age in years (mean \pm SD); gender (male/female)	Training protocol	Major findings
Dobsak et al, 2006 ⁵¹	2 groups: NMES, $n = 15$ Bicycle, $n = 15$ NYHA II–III, LVEF $34.7 \pm 5\%$ Random assignment	Not reported per group; aggregate data as follows: 56.3 ± 6 ; 23/7	NMES <ul style="list-style-type: none"> Bilateral quadriceps and calves 10 Hz, biphasic On/off: 20/20 s Pulse width: 200 ms Maximal stimulation amplitude: 60 mA 60 min/d, 7 d/wk, 8 wk Bicycle <ul style="list-style-type: none"> Alternating cycling with a workload and without (1 min with/2 min without) 40 min/d, 3 d/wk, 8 wk 	No adverse events reported Significant increase in the NMES group: Peak $\dot{V}O_2$ (4.6%) Peak workload (13.8%) Significant increase in the bicycle group: Peak $\dot{V}O_2$ (6.6%) $\dot{V}O_2$ at ventilatory threshold (22.5%) Peak workload (23.8%) Quality-of-life score (34.0%) Improvement in peak $\dot{V}O_2$ significantly greater in the bicycle group
Dobsak et al, 2006 ⁵²	$N = 15$ NYHA III–IV, LVEF $18.7 \pm 3.3\%$	56.5 ± 5.2 ; 14/1	<ul style="list-style-type: none"> Bilateral quadriceps and calves 10 Hz, biphasic On/off time: 20/20 s Pulse width: 200 ms Maximal stimulation amplitude: 60 mA 60 min/d, 7 d/wk, 6 wk 	No adverse events reported Significant increase in the NMES group: Maximal knee extensor isometric contraction at 90° (51.0%) Peak isokinetic knee extensor torque at 90°/s (43.0%) Peripheral blood flow velocity (35.4%)
Karavidas et al, 2006 ⁵³	2 groups: NMES, $n = 16$ Controls, $n = 8$ NYHA II–III, LVEF < 40% Random assignment	NMES: 57.4 ± 15.3 ; 14/2 Control: 63.8 ± 8.1 ; 7/1	NMES <ul style="list-style-type: none"> Bilateral quadriceps, calves 25 Hz, biphasic On/off time: 5/5 s Intensity: visible muscle contraction not strong enough to elicit discomfort or joint movement 30 min/d, 5 d/wk, 6 wk Control <ul style="list-style-type: none"> Sensory electrical stimulation only 30 min/d, 5 d/wk, 6 wk 	No adverse events reported Significant increase in the NMES group: 6MWT (11.9%) Quality-of-life score (18.4%) TNF α (17.5%) sICAM-1 (15.6%) sVCAM-1 (13.1%) Baseline brachial artery diameter (2.0%) Hyperemic brachial artery diameter (3.5%) Flow mediated dilatation (29.6%) No change in the aforementioned variables in the control group Peak $\dot{V}O_2$ and LVEF did not significantly improve in either group
Deley et al, 2008 ⁵⁴	2 groups: NMES, $n = 22$ Treadmill, $n = 22$ NYHA II–IV, LVEF < 40% Random assignment	NMES: 55 ± 10 ; 16/6 Treadmill: 56 ± 7 ; 19/3	NMES <ul style="list-style-type: none"> Bilateral quadriceps and calves 10 Hz, biphasic On/off time: 12/8 s Pulse duration: 200 μs Amplitude set to highest tolerable to patient 60 min/d, 5 d/wk, 5 wk Treadmill exercise <ul style="list-style-type: none"> Heart rate corresponding to ventilatory threshold on baseline exercise test 60 min/d, 5 d/wk, 5 wk 	No adverse events reported Significant increase in the NMES group: Peak $\dot{V}O_2$ (12.2%) $\dot{V}O_2$ at ventilatory threshold (15.4%) 6MWT (13.8%) Significant increase in the bicycle group: Peak $\dot{V}O_2$ (16.7%) $\dot{V}O_2$ at ventilatory threshold (17.4%) 6MWT (16.5%)

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Table 1 • SUMMARY OF STUDIES ASSESSING CHRONIC FUNCTIONAL ELECTRICAL STIMULATION IN PATIENTS WITH HEART FAILURE (Continued)

Author, year	Number of subjects and characteristics	Age in years (mean ± SD); gender (male/female)	Training protocol	Major findings
Karavidas et al, 2008 ⁵⁵	2 groups: NMES, <i>n</i> = 20 Control, <i>n</i> = 10 NYHA II–IV, LVEF < 35% Random assignment, personnel performing 6MWT were blinded	NMES: 62 ± 12; 16/4 Control: 64 ± 8; 8/2	NMES • Bilateral quadriceps and calves • 25 Hz, biphasic • On/off time: 5/5 s • Amplitude set to elicit a muscle contraction without discomfort or significant movement at knee or ankle joints • 30 min/d, 5 d/wk, 6 wk Control • Same NMES protocol but amplitude set at level that did not elicit a muscle contraction	Aforementioned improvements were not statistically significant between groups The greatest improvements were realized by those with the lowest exercise capacity at baseline in both groups No adverse events reported Significant increase in the NMES group: 6MWT (9.3%) Quality-of-life score (37.2%) No change in the aforementioned variables in the control group Nonsignificant trend toward a reduction in B-type natriuretic peptide in only the NMES group (6%, <i>P</i> = .053)
Banerjee et al, 2009 ⁵⁶	Crossover design with <i>n</i> = 10 subjects randomized into 2 groups 8 wk of NMES followed by a 2-wk washout, then 8 wk of habitual activity or 8 wk of habitual activity followed by a 2-wk washout, then 8 wk of NMES NYHA II–III, LVEF 34.0 ± 6%	66 ± 6.5; 9/1	NMES • Bilateral quadriceps, hamstrings, calves, and gluteals • 4 Hz, rhythmic contraction • Maximum current: 300 mA • Intensity: 90% of heart rate reserve, determined individually • 60 min/d, 5 d/wk, 8 wk Washout phase • Return to habitual physical activity level	No adverse events reported Significant increase in the NMES group: Peak $\dot{V}O_2$ (10%) 6MWT (9.6%) Maximal knee extensor isometric contraction at 90° (7.1%) No significant difference in aforementioned variables between baseline and washout The greatest improvements were realized by those with the lowest exercise capacity and strength at baseline

Abbreviations: HR, heart rate; LVEF, left ventricular ejection fraction; NMES, neuromuscular electrical stimulation; NYHA, New York Heart Association; 6MWT, 6-minute walk test distance; sICAM, soluble intercellular adhesion molecule; sVCAM, soluble vascular cell adhesion molecule; TNF, tumor necrosis factor; $\dot{V}O_2$, oxygen uptake.

not reporting a significant improvement had an average baseline peak $\dot{V}O_2$ of 18.6 mL · kg⁻¹ · min⁻¹ or more. Two of the investigations reporting a significant improvement in peak $\dot{V}O_2$ following NMES also found the greatest improvements were among those subjects with the lowest baseline exercise capacity.^{54,56} Four investigations compared NMES with conventional aerobic exercise training programs (ie, bicycle/treadmill), 3 of which reported a significant improvement in peak $\dot{V}O_2$ in the NMES arm. While the improvements in peak $\dot{V}O_2$ were statistically significant with both NMES and conventional training in each trial, the percentage

improvement was consistently greater with the latter intervention. From a statistical perspective, however, the difference in peak $\dot{V}O_2$ improvement between NMES and conventional training was only significant in 1 of the 3 trials.⁵¹ All 6 of the investigations assessing the impact of NMES on lower extremity muscle force production reported a significant increase. The 1 investigation that used conventional aerobic exercise training as a control and also assessed quadriceps strength and fatigue reported comparable improvements in these variables.⁴⁸ Other noted improvements that reached statistical significance following NMES

were (1) calf muscle volume (1 investigation), (2) quadriceps cross-sectional area (1 investigation), (3) 6-minute walk test distance (8/8 investigations), (4) $\dot{V}O_2$ at ventilatory threshold (4/5 investigations), (5) quality of life (4/4 investigations), (6) skeletal muscle fiber and enzyme characteristics shifting toward a greater aerobic capacity (1 investigation), (7) endothelial function (2/2 investigations), and (8) peripheral inflammatory markers (1 investigation).

IMT IN PATIENTS WITH HF

Investigations assessing the effect of IMT programs are summarized in Table 2. All 6 investigations were limited by small cohorts, again, partially overcome by the consistency among the study findings. Five of the 6 investigations included a control group but only 2 used a randomized design. Only 1 investigation completely blinded research personnel performing baseline/follow-up assessments. Consistent with the NMES investigations, the groups with HF enrolled in the IMT trials (1) were predominantly men, (2) were all diagnosed with systolic HF confirmed by echocardiography, and (3) had a mean age between 53 and 66 years. The IMT training protocols employed were largely consistent among studies. This is partially due to the fact that the same research group conducted 3 of the investigations. Despite the improved consistency in IMT training characteristics, no clear statements can be made regarding an optimal treatment paradigm. The number of sessions per week and total training duration ranged from 3 to 7 days per week and 10 to 12 weeks, respectively. All 6 investigations incorporated inspiratory maneuvers against a resistance ranging from 30% of maximum static inspiratory capacity to 60% of sustained maximal inspiratory pressure. Only the investigation by Mancini et al⁵⁷ incorporated other inspiratory and expiratory exercises into the program.

None of the 6 investigations reported any adverse event with IMT. All 6 investigations reported a significant improvement in maximal inspiratory pressure following IMT, ranging from 8% to 115%. Five of the investigations reported a significant increase in peak $\dot{V}O_2$ following IMT, which ranged from 11% to 23%. One investigation reported a significant correlation between the improvement in peak $\dot{V}O_2$ and the improvement in maximal inspiratory pressure.⁶⁰ The single investigation reporting no change in peak $\dot{V}O_2$ assessed the smallest intervention and control cohorts ($n = 10/\text{group}$).⁵⁸ Moreover, the investigators noted that 3 of the 10 subjects in the IMT group demonstrated an improvement in peak $\dot{V}O_2$ following the intervention. All 6 investigations reported a significant reduction in dyspnea on exertion following IMT. Other

noted improvements that reached statistical significance following IMT included the following: (1) increased 6- or 12-minute walk test distance (6/6 investigations), (2) lowered minute ventilation/carbon dioxide production slope (1 investigation), (3) improved quality of life (3/3 investigations), and (4) improved respiratory muscle endurance (6/6 investigations).

SUMMARY OF EVIDENCE SUPPORTING NMES AND IMT IN PATIENTS WITH HF

The present body of research provides compelling evidence that both NMES and IMT improve aerobic capacity in patients with HF. The physiologic mechanism for improvements in peak $\dot{V}O_2$ appears to be different for NMES and IMT with the former modality improving blood flow and the aerobic capacity of skeletal muscle while the latter ameliorates respiratory muscle weakness/endurance and the resultant sensation of exertional dyspnea. NMES also appears to favorably improve the strength and endurance of muscle groups undergoing stimulation. The improvements in strength are likely attributable to an increase in cross-sectional area, whereas improvements in endurance are again linked to enhanced aerobic capacity in skeletal muscle. Both NMES and IMT also appear to consistently improve perceived quality of life in this patient population, an important rehabilitation metric.⁵

CURRENT KNOWLEDGE GAPS AND FUTURE RESEARCH DIRECTIONS

While the current body of evidence supports both NMES and IMT in the population with HF, substantial knowledge gaps exist, indicating the need for additional research in the following areas: (1) Although the incidence and prevalence of HF is well-balanced according to sex,⁶³ all of the NMES and IMT investigations recruited a small percentage of women. Moreover, the mean age of these studies indicates that a small percentage of subjects were of an advanced age (ie, >70 years). (2) Although patients with diastolic HF present with a diminished exercise capacity,⁶⁴ none of the NMES and IMT trials to this point include subjects diagnosed with this condition. (3) Initial research indicates that the combination of conventional aerobic and resistance exercise training elicits a favorable synergistic effect.⁶⁵ To date, no investigation has assessed the impact of combining NMES and IMT with each other or conventional exercise training programs. (4) There is no consensus on optimal NMES or IMT training characteristics (ie, intensity, frequency, and duration). In addition, these training characteristics

Table 2 • SUMMARY OF STUDIES ASSESSING INSPIRATORY MUSCLE TRAINING IN PATIENTS WITH HEART FAILURE

Author, yr	Number of subjects and characteristics	Age in years (mean ± SD); gender (male/female)	Training protocol	Major findings
Mancini et al, 1995 ⁵⁷	Total sample, N = 14, NYHA I–IV Training group, n = 8 Comparison group (dropouts from original total sample), n = 6	Training group: 56 ± 15 Comparison group: 55 ± 15	Training group <ul style="list-style-type: none"> • Isocapnic hyperpnea: 20 min per session • Resistive breathing: 30% P_{imax} for 20 min • Strength training: 10 maximal inspiratory and 10 maximal expiratory efforts; 10-s hold for each repetition with 15-s rest in between • Breathing calisthenics: Targeting abdominal muscles; 4 supine exercises for 8 repetitions each • 90 min/d, 3 supervised sessions/wk, 12 wk • 15 min twice daily, 4 unsupervised sessions/wk, 12 wk Comparison group <ul style="list-style-type: none"> • Subjects withdrew from training program after an average of 3 sessions 	No adverse events reported Significant increase in the IMT group: P _{imax} (37.5%) Maximal expiratory pressure (62.0%) Maximal voluntary ventilation (15.0%) Maximal sustainable ventilatory capacity (57.0%) Tidal volume (45.4%) 6MWT (29%) Peak $\dot{V}O_2$ (16.7%) Significant decrease in the IMT group: Perceived dyspnea during isocapnic hyperpnea (~25 L/min increase in minute ventilation at comparable dyspnea rating) No change in the aforementioned variables in the comparison group
Weiner et al, 1999 ⁵⁸	2 groups: IMT, n = 10 Sham IMT, n = 10 NYHA II–III, LVEF < 30%, P _{imax} < 70%-predicted Random assignment	IMT: 66.2 ± 4.6, 9/1 Sham IMT: 63.8 ± 4.0, 9/1	IMT <ul style="list-style-type: none"> • Started at 15% of P_{imax} until 60% at the end of 4 wk • 60% P_{imax} maintained throughout remainder of the study • 30 min/d, 6 d/wk (all supervised), 12 wk Sham IMT <ul style="list-style-type: none"> • Same as above only trained without resistance 	No adverse events reported Significant increase in the IMT group: P _{imax} (36.8%) Respiratory muscle endurance (41.6%) Forced vital capacity (7.3%) 12MWT (22.7%) Significant decrease in the IMT group: Dyspnea Index: 0–4 scale (58.8%) No change in the aforementioned variables in the Sham IMT group Maximal expiratory pressure and peak $\dot{V}O_2$ did not improve in either group
Laoutaris et al, 2004 ⁵⁹	2 groups: Training group, n = 20 Control, n = 17 NYHA II–III, LVEF 24 ± 1.3% Nonrandom assignment	Training group: 57.6 ± 2.3, 18/2 Control: 60 ± 2.6, 13/2	Training group <ul style="list-style-type: none"> • 60% of sustained maximal inspiratory pressure to fatigue • >6 stages with 6 inspiratory efforts per stage; rest periods between efforts decreased from 60 to 5 s over first 6 stages • 3 sessions/wk (all supervised), 10 wk Control <ul style="list-style-type: none"> • 15% of sustained maximal inspiratory pressure 	No adverse events reported Significant increase in the IMT group: P _{imax} (35.1%) Sustained maximal inspiratory pressure (43.7%) Inspiratory volume (30%) Peak $\dot{V}O_2$ (15.6%) Maximal ventilation during exercise testing (22.5%)

(continues)

Table 2 • SUMMARY OF STUDIES ASSESSING INSPIRATORY MUSCLE TRAINING IN PATIENTS WITH HEART FAILURE (Continued)

Author, yr	Number of subjects and characteristics	Age in years (mean ± SD); gender (male/female)	Training protocol	Major findings
Dall'Ago et al, 2006 ⁶⁰	2 groups: IMT, n = 16 Placebo IMT, n = 16 LVEF < 45%, PI _{max} < 70%-predicted Random assignment, personnel performing assessments were blinded	IMT: 54 ± 3, 11/5 Placebo-IMT: 58 ± 2, 10/6	<ul style="list-style-type: none"> 6 stages with 6 inspiratory efforts per stage; rest periods between efforts decreased from 60 to 5 s over first 6 stages 3 sessions/wk (all supervised), 10 wk <p>IMT</p> <ul style="list-style-type: none"> 30% of PI_{max} at a respiratory rate of 15–20 breaths/min 30 min/d, 7 d/wk (1 supervised/6 unsupervised), 12 wk <p>Placebo IMT</p> <ul style="list-style-type: none"> Same as IMT with no inspiratory resistance 	<p>6MWTD (18.1%)</p> <p>Quality of life (16.3%)</p> <p>Significant decrease in the IMT group:</p> <p>Maximal dyspnea during exercise testing: 6–20 scale (9.9%)</p> <p>Maximal dyspnea during 6MWTD: 6–20 scale (14.3%)</p> <p>Significant increase in the control group:</p> <p>PI_{max} (10.5%)</p> <p>With exception of maximal inspiratory pressure; no change or significant decrease in the aforementioned variables in the control group</p> <p>No adverse events reported</p> <p>Significant increase in the IMT group:</p> <p>PI_{max} (115.0%)</p> <p>PI_{max} remained significantly higher 9 mo after completion of training program than baseline</p> <p>Maximal inspiratory pressure sustained for 1 min (8.6%)</p> <p>Peak $\dot{V}O_2$ (23.5%)</p> <p>Change in peak $\dot{V}O_2$ significantly correlated with change in maximal inspiratory pressure ($r = 0.62$)</p> <p>Maximal ventilation during exercise testing (29.2%)</p> <p>6MWTD (22.5%)</p> <p>Quality of life (77.8%)</p> <p>Quality of life remained significantly better 9 mo after completion of training program compared with baseline</p> <p>Significant decrease in the IMT group:</p> <p>Minute ventilation to carbon dioxide production slope (14.3%)</p> <p>Maximal dyspnea during exercise testing: 6–20 scale (9.9%)</p> <p>Maximal dyspnea during 6MWTD: 6–20 scale (14.3%)</p>

(continues)

Table 2 • SUMMARY OF STUDIES ASSESSING INSPIRATORY MUSCLE TRAINING IN PATIENTS WITH HEART FAILURE (Continued)

Author, yr	Number of subjects and characteristics	Age in years (mean ± SD); gender (male/female)	Training protocol	Major findings
Laoutaris et al, 2007 ⁶¹	2 groups: High-intensity IMT, n = 15 Low-intensity IMT, n = 23 NYHA II–III, LVEF 28 ± 1% Nonrandom assignment	High-intensity IMT: 53 ± 2, 12/3 Low-intensity IMT: 59 ± 2, 20/3	High-intensity IMT <ul style="list-style-type: none"> • 60% of sustained maximal inspiratory pressure to fatigue • >6 stages with 6 inspiratory efforts per stage; rest periods between efforts decreased from 60 to 5 s over first 6 stages • 3 sessions/wk (all supervised), 10 wk • Performed as many levels of training as able until exhaustion achieved Low-intensity IMT <ul style="list-style-type: none"> • 15% of sustained maximal inspiratory pressure • 6 stages with 6 inspiratory efforts per stage; rest periods between efforts decreased from 60 to 5 s over first 6 stages • 3 sessions/wk (all supervised), 10 wk 	No change in the aforementioned variables in the control group No adverse events reported Significant increase in the high-intensity IMT group: PI_{max} (31.7%) Sustained maximal inspiratory pressure (61.5%) Inspiratory volume (30%) Peak $\dot{V}O_2$ (12.1%) 6MWTD (6.9%) Significant decrease in the IMT group: Maximal dyspnea during exercise testing: 6–20 scale (13.0%) Significant increase in the low-intensity IMT group: PI_{max} (12.6%) With exception of maximal inspiratory pressure; no change in the aforementioned variables in the low-intensity IMT group No significant changes were detected in inflammatory or apoptotic markers in either group
Laoutaris et al, 2008 ⁶²	2 groups: High-intensity IMT, n = 14 Low-intensity IMT, n = 9 NYHA II–III, LVEF 29 ± 2% Nonrandom assignment, personnel performing assessments were blinded	High-intensity IMT: 53.4 ± 2.1 Low-intensity IMT: 57.3 ± 4	High-intensity IMT <ul style="list-style-type: none"> • 60% of sustained maximal inspiratory pressure to fatigue • >6 stages with 6 inspiratory efforts per stage; rest periods between efforts decreased from 60 to 5 s over first 6 stages • 3 sessions/wk (all supervised), 10 wk • Performed as many levels of training as able until exhaustion achieved Low-intensity IMT <ul style="list-style-type: none"> • 15% of sustained maximal inspiratory pressure • 6 stages with 6 inspiratory efforts per stage; rest periods between efforts decreased from 60 to 5 s over first 6 stages • 3 sessions/wk (all supervised), 10 wk 	No adverse events reported Significant increase in the high-intensity IMT group: PI_{max} (~33.0%) Sustained maximal inspiratory pressure (~61.0%) Peak $\dot{V}O_2$ (11.1%) 6MWTD (6.9%) Quality of life (16.3%) Significant decrease in the IMT group: Maximal dyspnea during exercise testing: 6–20 scale (2.8%) Significant increase in the low-intensity IMT group: PI_{max} (~12.0%) No significant changes were detected in N-terminal B-type natriuretic peptide, endothelial function, or heart rate variability in either group

Abbreviations: IMT, inspiratory muscle training; LVEF, left ventricular ejection fraction; 6MWTD, 6-minute walk test distance; 12MWTD, 12-minute walk test distance; NYHA, New York Heart Association; PI_{max} , maximum static inspiratory capacity.

Table 3 • PATIENT EXAMPLES ILLUSTRATING THE APPROPRIATENESS OF NMES AND/OR IMT IN INDIVIDUAL PATIENT WITH HEART FAILURE

Key baseline findings during baseline assessment	Baseline submaximal exercise tolerance	Recommendations for rehabilitation program
Patient 1		
<p>Clinical information</p> <p>Female</p> <p>Age 50 y</p> <p>NYHA: Class III</p> <p>LVEF: 20%</p> <p>BMI: 20.5 kg/m²</p> <p>Minnesota Living with Heart Failure Questionnaire (0–105 scale)⁶⁸: 80/105</p> <p>Cardiopulmonary exercise test</p> <p>Peak $\dot{V}O_2$: 10.2 mL · kg⁻¹ · min⁻¹</p> <p>Percent-predicted peak $\dot{V}O_2$⁶⁹: 34.6%</p> <p>Peak respiratory exchange ratio: 1.12</p> <p>Ventilatory threshold not detectable</p> <p>Peak dyspnea (0–10 scale)⁷⁰: 9/10</p> <p>Dyspnea key reason for test termination</p> <p>Electrocardiogram: Frequent premature ventricular contractions</p> <p>Respiratory muscle function</p> <p>PI_{max}: 32.2 cm H₂O</p> <p>Percent-predicted PI_{max}: 52.1%⁷¹</p>	<p>Patient only able to complete a 5-min exercise session on a treadmill at 1.5 mph and 0% grade before requiring rest</p>	<p>Conventional exercise training</p> <p>Supervised</p> <p>Interval aerobic exercise program on treadmill; progress duration as tolerated</p> <p>Resistance exercise training</p> <p>NMES</p> <p>Initially supervised to ensure compliance—progress to home program</p> <p>Bilateral quads and calves</p> <p>10 Hz, biphasic</p> <p>On/off: time 12/8 s</p> <p>Pulse duration 200 μs</p> <p>Amplitude set to highest tolerable to patient</p> <p>60 min/d, 5 d/wk, 5 wk</p> <p>IMT</p> <p>Initially supervised to ensure compliance—progress to home program</p> <p>30% of PI_{max} at a respiratory rate of 15–20 breaths/min</p> <p>30 min/d, 7 d/wk</p>
Patient 2		
<p>Clinical Information</p> <p>Female</p> <p>Age 50 y</p> <p>NYHA: Class III</p> <p>LVEF: 30%</p> <p>BMI: 24.2 kg/m²</p> <p>Minnesota Living with Heart Failure Questionnaire (0–105 scale)⁶⁸: 45/105</p> <p>Cardiopulmonary exercise test</p> <p>Peak $\dot{V}O_2$: 14.2 mL · kg⁻¹ · min⁻¹</p> <p>Percent-predicted peak $\dot{V}O_2$⁶⁹: 54.9%</p> <p>Peak respiratory exchange ratio: 1.15</p> <p>Ventilatory threshold: 8.0 mL · kg⁻¹ · min⁻¹</p> <p>Peak dyspnea (0–10 scale)⁷⁰: 4/10</p> <p>Leg fatigue key reason for test termination</p> <p>Electrocardiogram: Occasional premature ventricular contractions</p> <p>Respiratory muscle function</p> <p>PI_{max}: 62.2 cm H₂O</p> <p>Percent-predicted PI_{max}: 88.3%⁷¹</p>	<p>Patient able to complete a 20-min exercise session on a treadmill at 2.0 mph and 0% grade before requiring rest</p>	<p>Conventional exercise training</p> <p>Supervised</p> <p>Interval aerobic exercise program on treadmill; progress duration as tolerated</p> <p>Resistance exercise training</p> <p>NMES</p> <p>Initially supervised to ensure compliance—progress to home program</p> <p>Bilateral quads and calves</p> <p>10 Hz, biphasic</p> <p>On/off time: 12/8 s</p> <p>Pulse duration 200 μs</p> <p>Amplitude set to highest tolerable to patient</p> <p>60 min/d, 5 d/wk, 5 wk</p> <p>IMT</p> <p>Not indicated</p>
Patient 3		
<p>Clinical Information</p> <p>Female</p> <p>Age 50 y</p> <p>NYHA: Class I</p> <p>LVEF: 40%</p> <p>BMI: 24.2 kg/m²</p> <p>Minnesota Living with Heart Failure Questionnaire (0–105 scale)⁶⁸: 15/105</p> <p>Cardiopulmonary exercise test</p> <p>Peak $\dot{V}O_2$: 19.5 mL · kg⁻¹ · min⁻¹</p> <p>Percent-predicted peak $\dot{V}O_2$⁶⁹: 72.2%</p> <p>Peak respiratory exchange ratio: 1.20</p> <p>Ventilatory threshold: 12.0 mL · kg⁻¹ · min⁻¹</p> <p>Peak dyspnea (0–10 scale)⁷⁰: 2/10</p> <p>Leg fatigue key reason for test termination</p> <p>Electrocardiogram: No arrhythmias</p> <p>Respiratory muscle function</p> <p>PI_{max}: 65.0 cm H₂O</p> <p>Percent-predicted PI_{max}: 92.2%⁷¹</p>	<p>Patient able to complete a 30-min exercise session on a treadmill at 3.0 mph and 0% grade before requiring rest</p>	<p>Conventional exercise training</p> <p>Supervised</p> <p>Interval aerobic exercise program on treadmill; progress duration as tolerated</p> <p>Resistance exercise training</p> <p>NMES</p> <p>Not indicated</p> <p>IMT</p> <p>Not indicated</p>

Abbreviations: BMI, body mass index; IMT, inspiratory muscle training; LVEF, left ventricular ejection fraction; NMES, neuromuscular electrical stimulation; NYHA, New York Heart Association; PI_{max}, maximum static inspiratory capacity; $\dot{V}O_2$, oxygen uptake.

will most likely differ according to the primary rehabilitation goal (ie, optimization of aerobic capacity or muscle strength). (5) Although the use of peripheral electrical stimulation devices appears to be safe in patients with pacemakers, resynchronization devices, and/or implanted defibrillators,^{66,67} there is no clear consensus on this important safety issue. (6) A majority of NMES studies employed a randomized design. However, less than half of the IMT investigations randomized subjects to either the interventional or the control arm. Moreover, few investigations blinded research personnel performing assessments. Finally, all investigations examined a relatively small number of subjects, diminishing the strength of results drawn from any single investigation. Addressing these areas in future research endeavors will greatly augment the support for NMES and IMT in the rehabilitation of patients with HF. Until these research gaps are addressed, the widespread clinical use of NMES and IMT cannot be advocated.

CLINICAL SCENARIOS WHERE NMES AND IMT MAY BE BENEFICIAL

The evidence supporting NMES and IMT in the population with HF, while compelling, has not reached the level needed to recommend widespread implementation of these adjunctive rehabilitation options. However, optimal delivery of rehabilitation services is achieved when the program is individualized, targeting the unique set of physiologic/functional limitations that each patient presents with during the initial assessment. In patients with HF who present with a greater baseline functional impairment, NMES and/or IMT may therefore assist in their rehabilitation. The 3 patient examples listed in Table 3 assist in illustrating when the use of NMES and/or IMT may be appropriate.

- Patient 1 presents with a severely diminished aerobic exercise capacity, maximal inspiratory pressure (ie, respiratory muscle function), and quality of life. Moreover, submaximal exercise tolerance at the initiation of the rehabilitation allows only for a short bout of continuous aerobic exercise before the onset of fatigue necessitates rest. In this subject, the addition of NMES to conventional aerobic and resistance training allows for prolonged, continuous bouts of skeletal muscle stimulation with minimal stress on the cardiac system. Moreover, a low maximal inspiratory pressure indicates that an IMT program may assist in alleviating the sensation of dyspnea brought about by respiratory muscle fatigue at low exercise workloads.

- Patient 2 presents with a slightly higher aerobic exercise capacity and quality of life. However, maximal inspiratory pressure is significantly better than that for patient 1. In this case, only the addition of NMES to conventional training may be warranted.
- Finally, patient 3 demonstrates a substantially higher aerobic capacity and quality of life at baseline than the preceding cases. Moreover, maximal inspiratory pressure is approaching age/sex-predicted normal values. While the implementation of conventional aerobic and resistance training is warranted, the addition of NMES and/or IMT may provide little additional value.

The authors would again like to reiterate the fact that these clinical scenarios are not meant to endorse routine clinical implementation of NMES or IMT in patients with HF and specific characteristics. Rather, these scenarios serve to illustrate where these complementary rehabilitation options may be beneficial (ie, patients with more severe functional impairments and NYHA Class III/IV). Both NMES and IMT are medically approved treatment options that appear to pose low adverse event risk to patients when properly implemented. It is up to the clinician to design an individualized rehabilitation program based on the impairments identified during the baseline evaluation, using all approved treatment options at his or her disposal.

CONCLUSIONS

Cardiac rehabilitation, with traditional aerobic and resistance training at its core, continues to be a standard of care for patients with HF. The addition of NMES and IMT may serve a role as adjunctive rehabilitation options in the population with HF, particularly in those patients who present with a greater degree of functional impairment at baseline. Future research is required to better elucidate the clinical value of NMES and IMT in patients with HF.

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