Progress in Cardiovascular Diseases xxx (xxxx) xxx

Contents lists available at ScienceDirect

Progress in Cardiovascular Diseases

journal homepage: www.onlinepcd.com

Inspiratory muscle weakness in cardiovascular diseases: Implications for cardiac rehabilitation

Joshua R. Smith [a,*], Bryan J. Taylor [b]

[a] Department of Cardiovascular Medicine, Mayo Clinic, Rochester, MN, United States of America
[b] Department of Cardiovascular Medicine, Mayo Clinic, Jacksonville, FL, United States of America

ARTICLE INFO

Available online xxxx

Keywords:
Diaphragm
Respiratory muscle strength
Exercise training
Inspiratory muscle training
Expiratory muscle strength

ABSTRACT

Exercise limitation is a cardinal manifestation of many cardiovascular diseases (CVD) and is associated with poor prognosis. It is increasingly well understood that exercise-based cardiac rehabilitation (CR) is an intervention that portends favorable clinical outcomes, including improvements in exercise capacity. The etiology of exercise limitation in CVD is multifactorial but is typically governed by terminal sensations of pain, fatigue, and/or breathlessness. A known but perhaps underestimated complication of CVD that contributes to breathlessness and exercise intolerance in such patients is inspiratory muscle dysfunction. For example, inspiratory muscle dysfunction, which encompasses a loss in muscle mass and/or pressure generating capacity, occurs in up to ~40% of patients with chronic heart failure and is associated with breathlessness, exertional intolerance, and worse survival in this patient population. In this review, we define inspiratory muscle weakness, detail its prevalence in a range of CVDs, and discuss how inspiratory weakness impacts physiological function and clinical outcomes in patients with CVD often referred to CR. We also evaluate the available evidence addressing the effects of exercise-based CR with and without concurrent specific inspiratory muscle training (IMT) on inspiratory muscle function, general physiological function, and clinical outcomes in patients with CVD. Finally, we consider whether the assessment of *global* respiratory muscle function should become standard as part of the patient intake assessment for phase II CR programs, giving practical guidance on the implementation of such measures as well as IMT as part of phase II CR.

Contents

Abbreviation: CABG, coronary artery bypass graft; CR, cardiac rehabilitation; CV, cardiovascular; CVD, cardiovascular disease; HF, heart failure; HFrEF, heart failure with reduced ejection fraction; HTxp, heart transplant; IMT, inspiratory muscle training; LVAD, left ventricular assist device; MI, myocardial infarction; MIP, maximal inspiratory pressure; MEP, maximal expiratory pressure; PR, pulmonary rehabilitation; $\dot{V}_E/\dot{V}CO_2$, ventilatory equivalent for carbon dioxide slope.

* Corresponding author at: Department of Cardiovascular Medicine, Mayo Clinic, 200 First Street SW, Rochester, MN 55905, United States of America.
E-mail address: smith.joshua1@mayo.edu (J.R. Smith).

https://doi.org/10.1016/j.pcad.2021.10.002
0033-0620/

Please cite this article as: J.R. Smith and B.J. Taylor, Inspiratory muscle weakness in cardiovascular diseases: Implications for cardiac rehabilitation, Progress in Cardiovascular Diseases, https://doi.org/10.1016/j.pcad.2021.10.002

Cardiovascular (CV) diseases (CVD) are a collective group of pathophysiologic disorders that affect the heart and blood vessels, including coronory heart disease, heart failure, congenital and valvular heart disease, peripheral artery disease, and cerebrovascular disease. As reported in 2021, CVD remains a leading cause of death nationally (United States) and globally including people of most racial and ethnic groups.[1] Cardiac rehabilitation (CR), a comprehensive multidisciplinary program that includes exercise training, patient education, behavior modification, and stress management, is a cornerstone in the provision of care for patients with CVD[2]. An ever-increasing evidence base continues to highlight the extensive benefits of this intervention, supporting CR as a service that efficaciously improves health-related quality-of-life and physical function, and reduces hospital readmissions, adverse secondary events, and mortality in patients with CVD[3].

Exercise limitation is a cardinal manifestation of CVD, and an increasing degree of exercise intolerance is associated with poor prognosis.[4,5] The etiology of exercise limitation in CVD is multifactorial in nature. Indeed, such limitation may occur secondary to deleterious alterations in cardiac, vascular, musculoskeletal, endocrine, and/or pulmonary function, ultimately resulting in worsening breathlessness, diminished capacity of the CV system to supply oxygen to the skeletal muscles, an inability of the skeletal muscles to use the delivered oxygen, or some combination of all three.[6] Exercise training facilitates advantageous health benefits across multiple organ-systems with resultant improvements in exercise capacity and the short-term physiological responses to exercise as well as substantial reductions in the risk of hospitalization and death in individuals with established CVD[7]. It is perhaps unsurprising, therefore, that exercise-centered CR portends clear physiological and clinical benefits in patients with CVD.

Of the pulmonary system maladies associated with CVD, inspiratory muscle weakness may be particularly key. For example, in chronic heart failure (HF), inspiratory muscle weakness is associated with heightened breathlessness, exercise intolerance, and worse health-related quality-of-life, and maximal inspiratory pressure (MIP) (i.e. *inspiratory muscle 'strength'*) is a strong predictor of survival in such patients.[8–12] In this review we define inspiratory muscle weakness before detailing its prevalence in a range of CVDs that represent covered diagnoses for referral to phase II CR. In doing so, we also discuss how such inspiratory muscle weakness impacts physiological function and clinical outcomes in patients with CVD. Next, we evaluate the effect of exercise-based CR with and without concurrent specific inspiratory muscle training (IMT) on inspiratory muscle function, general physiological function, and clinical outcomes in patients with CVD. Finally, we consider whether the assessment of *global* respiratory muscle function should become standard as part of the patient intake assessment for phase II CR programs, giving practical guidance on the implementation of global respiratory muscle function and IMT as part of phase II CR.

Inspiratory muscle weakness in CVD

Diaphragm and/or global inspiratory muscle size and function can be assessed using a variety of different techniques, including lung function testing, magnetically or electrically evoked muscle pressure(s), and ultrasound or CT imaging.[13] Likely owing to their relative simplicity, measurements of MIP remain the most used assessment of global inspiratory muscle strength in the clinical setting. In the absence of clearly defined lower limits of normal, inspiratory muscle weakness is generally defined as a reduced MIP either as an absolute value (80 and 70 cmH_2O for men and women, respectively) or relative to a normalized value (e.g., <70% predicted).[14,15] Importantly, inspiratory muscle weakness is associated with impaired mobility and higher risk of myocardial infarction (MI) as well as greater rates of all-cause and CVD mortality in the general population and patients with CVD.[10,15–19] Furthermore, inspiratory muscle weakness precipitates reductions in pulmonary function,[17] which is also associated with higher risk and incidence of CVD, as well as CVD and all-cause mortality.[20–23] Inspiratory muscle weakness also contributes to abnormal exercise ventilatory responses and exertional dyspnea.[13,24] Taken together, inspiratory muscle weakness has important clinical implications for the general population as well as patients with CVD. Below we discuss how inspiratory muscle weakness impacts clinical and physiological outcomes in patients with CVD with a specific focus on patients with an indication for CR.

HF

Inspiratory muscle weakness is a common and clinically important consequence of chronic heart failure that may be particularly prevalent in those patients with a lower left ventricular ejection fraction, lower systolic blood pressure, and smoking history.[25] To date, most of the research investigating inspiratory muscle weakness in CVD has focused on HF with reduced ejection fraction (HFrEF). Inspiratory muscle weakness is prevalent in patients with HFrEF with ~40% of these patients exhibiting MIP <70% of predicted,[15] and patients with HFrEF commonly exhibit lower MIP compared to healthy adults.[10,26–29] Importantly, inspiratory muscle weakness is associated with worse long-term outcomes (e.g., mortality) in patients with HFrEF.[10,15,30] Specifically, in a study of 445 patients with HFrEF, Hamazaki and colleagues found that inspiratory muscle weakness was independently associated with all-cause mortality (adjusted HR: 2.85, 95% CI: 1.17–3.38) (see Fig. 1).[15] Moreover, patients with HFrEF and inspiratory muscle weakness had higher rates of CVD and non-CVD mortality compared to patients with HFrEF but without inspiratory muscle weakness.[15] As further evidence for its clinical relevance in patients with HFrEF, inspiratory muscle weakness is associated with heightened exertional dyspnea, impaired exercise tolerance, poor functional status, and worse disease severity.[8–10,28,29,31] Impaired inspiratory muscle strength may also, at least in part, contribute to the abnormal alterations in the ventilatory response to exercise in HFrEF, including a relatively 'rapid and shallow' breathing pattern, increased dead space ventilation, and increased minute ventilation ($\dot{V}_E$) for a given metabolic demand (greater $\dot{V}_E/\dot{V}CO_2$), often considered as evidence of ventilatory 'inefficiency'.[8,10,32] In fact, a recent study in 256 patients with HF found that inspiratory muscle weakness was a significant predictor of a $\dot{V}_E/\dot{V}CO_2$ slope of >34,[32] which is important as a $\dot{V}_E/\dot{V}CO_2$ slope greater than 34 is an excellent prognostic indicator of mortality for patients with HF[33]. The augmented ventilatory response combined with the inspiratory muscle weakness likely leads to an imbalance between muscle load relative to muscle capacity during exercise, consequently necessitating a greater blood flow 'demand' from the respiratory muscles in HF.[34,35] This has the potential to redistribute cardiac output away from the locomotor muscles impairing exercise tolerance in these patients.[36–38] In summary, the aforementioned data clearly illustrate that inspiratory muscle weakness is prevalent in patients with HFrEF and is associated with adverse clinical and physiological outcomes; that is, inspiratory muscle weakness is an important marker for detection and intervention in patients with chronic HF.

Cardiac transplantation/left ventricular assist device (LVAD)

Heart transplantation (HTxp) is the gold standard treatment for select patients with what would otherwise be fatal end-stage heart

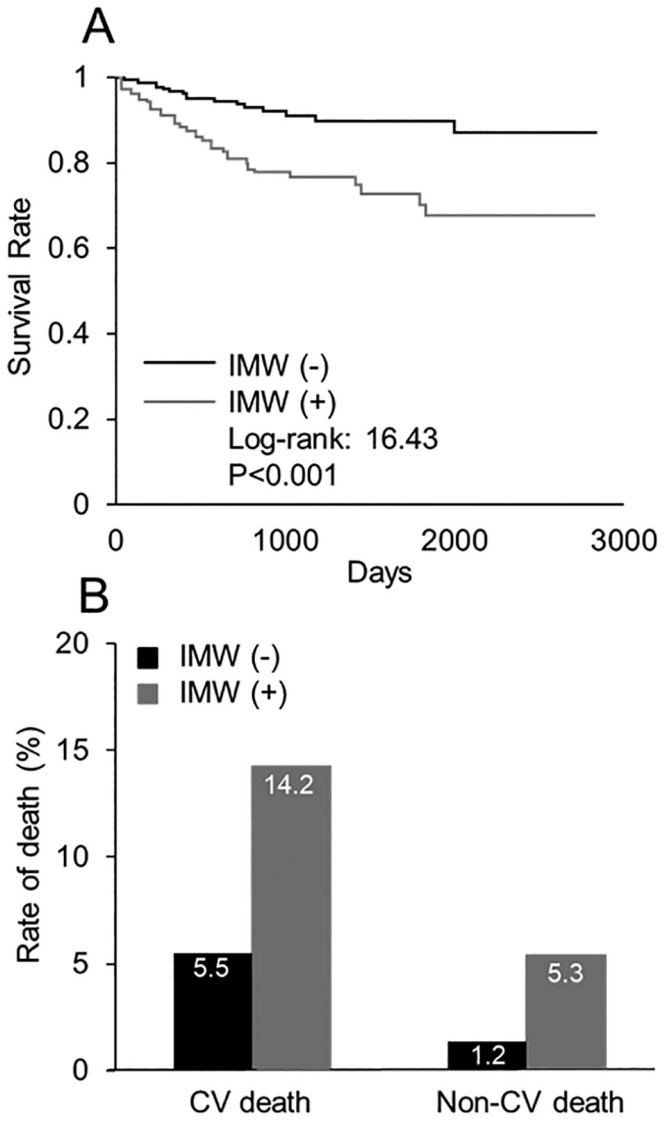

Fig. 1. Kaplan-Meier survival curve of the association between inspiratory muscle weakness and all-cause mortality in HFrEF (A) and rates of CV and non-CV mortality in HFrEF with (+) and without (−) inspiratory muscle weakness (IMW) (B). Patients with HFrEF and inspiratory muscle weakness had lower survival rates than patients with HFrEF without inspiratory muscle weakness (log-rank: 16.43, $p < 0.001$; adjusted HR: 2.13, 95%CI: 1.17–3.88). Patients with HFrEF and inspiratory muscle weakness had higher rates of CV ($p = 0.026$) and non-CV mortality ($p = 0.012$) compared to patients with HFrEF without inspiratory muscle weakness. Data from[15] used with permission.

disease when medical therapy has not halted the underlying pathology. Although survival rates at one-year post-surgery are approaching ~85%, recovery following HTxp remains complicated by factors such as primary graft dysfunction, allograft vasculopathy, and immunorejection of the new heart. It is becoming increasingly clear that prompt adoption of exercise-based CR is not only safe but may beneficially reverse the pathophysiological consequences of cardiac denervation and prevent immunosuppression-induced adverse effects following HTxp.[39–41] However, it appears that several other patient-related 'risk factors' adversely affect the postoperative clinical course in HTxp recipients, including inspiratory muscle weakness. In addition to 'global' dysfunction of skeletal muscle mass and strength (e.g., reduced handgrip strength), patients awaiting HTxp exhibit poor inspiratory muscle strength, as evidenced by a MIP of ~51–60 cmH_2O or ~ 48–55% predicted, and endurance, often quantified as a reduced time to task failure while breathing against an incrementing or constant inspiratory resistance.[42–44] Importantly, it appears that increased inspiratory muscle strength may enhance postoperative recovery following HTxp, whereas inspiratory muscle weakness may be related to poor short-term outcomes in HTxp recipients. For example, 1–3 weeks of preoperative IMT was shown to improve group mean MIP by ~37% in patients awaiting HTxp.[45] Interestingly, patients exhibiting substantial postoperative complications (i.e. pneumonia, atelectasis, and/or hypoventilation during recovery) had a significantly lower MIP at baseline and did not respond positively to IMT, while those patients that did not have substantial postoperative complications exhibited a 40% increase in MIP with IMT.[45] Moreover, lower absolute and percent predicted MIP were associated with prolonged mechanical ventilation and longer ICU stay during recovery from HTxp.[46] From the aforementioned evidence, it appears that inspiratory muscle strength may be an important preoperative clinical marker of postoperative recovery and outcomes in patients undergoing HTxp. Given that greater inspiratory muscle strength *before* HTxp and other cardiac surgeries (e.g., coronory artery bypass graft surgery[47]) has been associated with a reduced incidence of postoperative complications and length of hospital stay, then further exploration of increasing inspiratory muscle strength in the preoperative phase as an intervention to improve early postoperative outcomes in patients undergoing HTxp is warranted.

Stable angina and acute MI with intervention

Preliminary data suggests that reduced inspiratory muscle strength is present in patients with stable angina and acute MI.[48–50] Specifically, in a study of nearly 1900 participants, Hamilton et al., found that inspiratory muscle strength (i.e. MIP) was lower in patients with stable angina ($n = 977$) compared to healthy controls ($n = 919$) and found that inspiratory muscle strength was lower in patients with stable angina than controls [MIP: 78 cmH_2O (89% predicted) vs. 85 cmH_2O (100% predicted)].[48] Further, patients with acute MI following revascularization have also been reported to exhibit reduced inspiratory muscle strength compared to controls [MIP: 83–89 cmH_2O (78–85% predicted) vs. 109 cmH_2O (108% predicted)].[50] Future studies are warranted to determine the true prevalence of inspiratory muscle weakness in these patients as well as acute MI patients without revascularization.

Coronary Artery Bypass Graft (CABG) and valve replacement

Patients referred to CR for CABG or valve replacement surgery also often exhibit inspiratory muscle dysfunction. Specifically, it has been often shown that inspiratory muscle strength is reduced relative to normative values in patients referred for CABG or heart valve repair/replacement *prior* to the intervention.[51–55] For example, Stein et al., reported reduced inspiratory muscle strength compared to normative values preoperatively in patients with coronary artery disease undergoing CABG (MIP: 65–72 cmH_2O; 60–68% predicted).[55] Similarly, Palaniswamy et al., found that patients with rheumatic mitral valve stenosis have lower inspiratory muscle strength prior to balloon valvotomy than normative values (MIP: 52 cmH_2O; 49% predicted).[54] In terms of inspiratory muscle dysfunction post-intervention, it is important to recognize that the surgical procedures associated with CABG and valve replacement can themselves result in diaphragm dysfunction and weakness. Indeed, although the reported incidence varies considerably between studies, postoperative diaphragmatic paralysis can occur in up to 60% of patients following cardiac surgery.[56] This diaphragmatic paralysis occurs secondary to phrenic nerve injury, which can be the consequence of freezing injury from saline slush for hypothermic myocardial protection, mechanical injury to the phrenic nerve during internal mammary artery harvesting for CABG, and indirect injury (e.g., stretching by the sternal retractor).[56] As a result, CABG and heart valve surgeries are associated with ~17–36% reduction in inspiratory muscle strength from the pre- to postoperative state, and this reduction can persist for several weeks or months.[51,53,55,57] In a similar manner to HTxp, preoperative inspiratory muscle weakness and 'global'

respiratory muscle dysfunction, the latter characterized by inspiratory and expiratory muscle weakness combined with elevated resting breathing frequency, is associated with a higher incidence of pulmonary complications in the postoperative period following CABG and heart valve repair/replacement surgery, respectively.[47,58] Lower inspiratory muscle strength is directly related to impaired functional capacity in patients following these cardiac surgeries.[51,55] In addition, CABG and heart valve surgeries are associated with decreases in lung function, atelectasis, and impairments in gas exchange and respiratory mechanics.[51,53,55,57,59] Taken together, it is crucial for future studies to understand the temporality of the development of inspiratory muscle weakness in these patients specifically in the preoperative period as well as to investigate the impact of IMT performed in the pre and/or postoperative period on long-term patient oriented outcomes in patients following CABG and heart valve surgeries.

Impact of pulmonary comorbidities

It is important to note that many pulmonary diseases, including chronic obstructive pulmonary disease (COPD), are *themselves* associated with significant inspiratory muscle weakness and often coexist with CVD. For example, COPD is prevalent in patients with HF (~13 to 39%) and those with ischemic heart disease (~3 to 64%).[60] Like CVD, many patients with COPD have significantly lower MIP compared to normative values,[61] which is of major clinical relevance. Whether due to mechanical weakening of the diaphragm secondary to lung hyperinflation-related muscle shortening and/or reduced diaphragm muscle force generating capacity resultant of loss of myosin content and sarcomeric injury,[62] loss in inspiratory muscle strength is an independent determinant of survival in people with COPD[63]. Thus, while the presence of comorbid pulmonary disease is certainly not prerequisite for inspiratory muscle weakness in patients with CVD, it is worth noting that coexisting conditions may, in concert, be responsible for inspiratory muscle weakness in patients undergoing phase II CR.

Impact of CR on inspiratory muscle function

Structured exercise training is a core component of CR that facilitates advantageous health benefits across multiple organ-systems with resultant improvements in clinical and physiological outcomes. The impact of exercise training in the CR setting on inspiratory muscle function has been investigated primarily in HFrEF and following CABG, with some[50,64–68] but not all[69,70] reporting a beneficial effect on inspiratory muscle strength. For example, Adamopoulos et al., reported that 12 weeks of exercise-based CR (30–45 min of cycle exercise at 70–80% maximum heart rate, 3 days a week for 12 weeks) combined with SHAM IMT (10% sustained MIP performed 30 min as the sham arm) elicited a 7% increase in inspiratory muscle strength in patients with HFrEF.[64] Conversely, Vibarel et al., found that exercise training consisting of 3 sets of 10 min at 70–80% peak heart rate interspersed with 5 min of active recovery, 3 days a week for 8 weeks did not improve inspiratory muscle strength in patients with HFrEF.[69] A possible reason for the divergent findings regarding the positive impact of exercise training on inspiratory muscle strength in HFrEF is the presence or absence of baseline inspiratory muscle weakness (i.e. pre-CR). To this point, it was shown that 20–45 min of cycle exercise at ~75% maximum oxygen uptake, 3 days a week for 12 weeks resulted in a ~ 72% increase in MIP in patients with HFrEF and inspiratory muscle weakness was present (baseline MIP: 56 cmH_2O; 61% predicted).[71] It is important to acknowledge that this degree of inspiratory muscle strength improvement (~72%) with exercise training is 'atypically' large (other studies have found inspiratory muscle strength improvements of 7–14% following exercise training in patients with HFrEF), reasons for which are unclear. A recent study reported that 5 months of exercise-based CR (phase I and phase II) was associated with a 14% increase in MIP in 456 patients with HF[72]. Interestingly, however, this improvement in inspiratory muscle strength was not a universal finding with an increase in MIP observed in only 326 (72%) of the patients studied. The authors noted that, compared to patients in which there was an increase in MIP following CR, the 'non-responding' group (i.e. those in whom MIP did not increase) had a higher MIP and a lower prevalence of inspiratory muscle weakness at baseline (MIP: 67.5 ± 27.0 vs. 54.9 ± 26.4 cmH_2O; prevalence of inspiratory muscle weakness: 20 vs. 38%); that is, those patients with inspiratory muscle weakness at baseline were more likely to exhibit improvements in MIP following CR.[72] Strikingly, it has been reported that *any* CR-induced increase in MIP (i.e. ≥0 cmH_2O) is associated with lower rates of all-cause (log-rank: $p = 0.021$; adjusted IRR: 0.70, 95% IC: 0.52–0.93) and CV events (log-rank: $p = 0.003$; adjusted IRR: 0.52, 95% IC: 0.36–0.75) (see Fig. 2).[72] In combination, the aforementioned evidence suggests that baseline inspiratory muscle weakness itself may be an important modulator of the effect of exercise-based CR on inspiratory muscle strength.

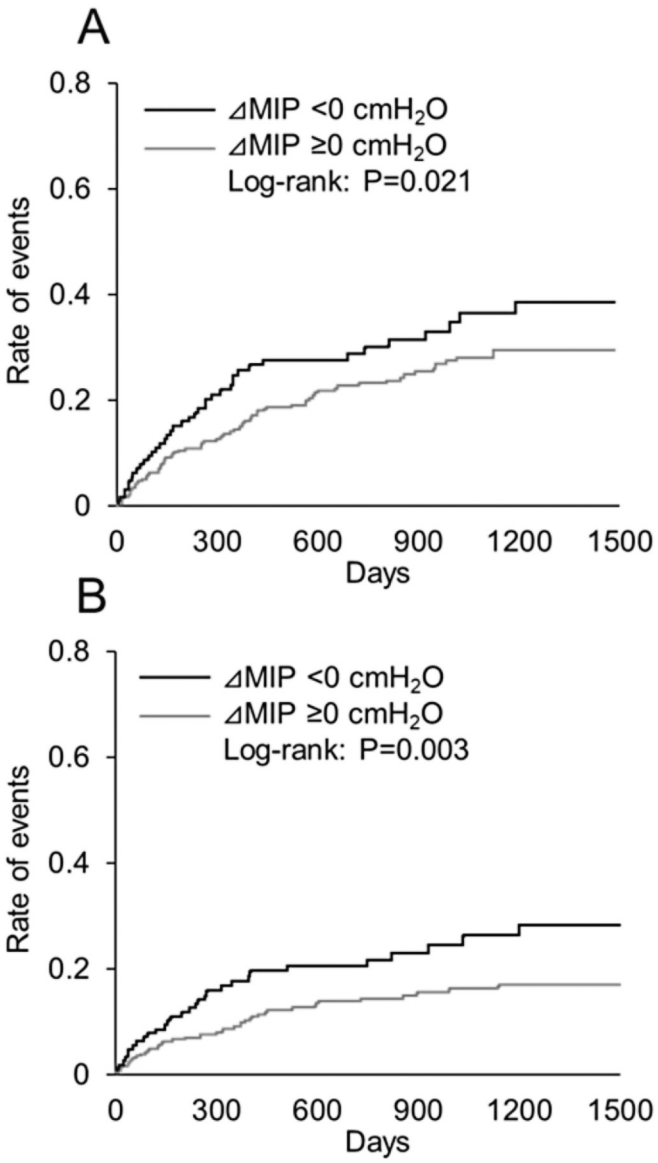

Fig. 2. Kaplan-Meier survival curve of the association between changes in inspiratory muscle strength (MIP) and all-cause clinical events (A) and CV events (B). Patients with HFrEF with an ≥0 MIP increase from pre to post-CR was associated with lower rates of all-cause clinical events (log-rank: $p = 0.021$; adjusted IRR: 0.70, 95% IC: 0.52–0.93) and CV events (log-rank: $p = 0.003$; adjusted IRR: 0.52, 95% IC: 0.36–0.75). Data from[72] used with permission.

Consistent with the evidence in HFrEF, exercise training in the CR setting (30 min of cycle exercise at 50–80% heart rate reserve, 2–3 days a week for 12 weeks) resulted in 4–20% improvement in inspiratory muscle strength in patients who had undergone CABG.[66–68] In addition, the impact of an outpatient home-based walking program prescribed 4 days a week for ~8 weeks on respiratory muscle strength was recently investigated in patients following MI in which the majority exhibited inspiratory muscle weakness.[50] In this study, the outpatient home-based walking program resulted in 41% improvement in inspiratory muscle strength. Taken together, these data provide evidence that exercise training performed in the CR setting elicits improvements in inspiratory muscle function in HFrEF, CABG, and MI with those patients exhibiting inspiratory muscle weakness appearing to exhibit the greatest increases in inspiratory muscle strength. Future studies are necessary to determine the role that exercise intensity prescribed in the CR setting plays in improving inspiratory muscle strength and function as high-intensity interval training, compared to moderate-intensity training, elicits greater increases in MIP in healthy adults.[73]

Concurrent inspiratory muscle training and CR

Recent studies have suggested that IMT performed concurrently with exercise training in the CR setting is a viable interventional strategy to optimize inspiratory muscle strength gains as well as other physiological and clinical outcomes in patients exhibiting inspiratory muscle weakness with a clinical indication to CR. Specifically, in patients with HFrEF and inspiratory muscle weakness, Winkelmann and colleagues found that concurrent IMT (30% MIP with a breathing frequency of 15–20 breaths per minute for 30 min, 7 days a week for 12 weeks) and exercise training in the CR setting elicited greater improvements in MIP, peak exercise capacity, and ventilatory efficiency (i.e. decreased $\dot{V}_E/\dot{V}CO_2$ slope) than exercise training alone.[71] In contrast, other studies in patients with HFrEF, but without inspiratory muscle weakness have found no further improvement in inspiratory muscle strength and exercise capacity with concurrent IMT (36 inspiratory efforts at 60% sustained MIP, 3 days a week for 12 weeks) and exercise training than with exercise training alone.[64,65] However, these latter studies did report greater improvements in inspiratory muscle endurance (indicative of greater inspiratory muscle fatigue resistance), quality of life, and dyspnea with concurrent IMT and exercise training compared to exercise training alone.[64,65] Like the benefits of exercise training on MIP improvements, inspiratory muscle weakness appears to modulate MIP improvements with concurrent IMT and exercise training in patients with HFrEF.

In patients who had undergone CABG, IMT (3–5 sets of 10 inspiratory efforts at 30–80% MIP, 2 days a week for 12 weeks) performed in combination with exercise training in the CR setting has resulted in greater improvements in MIP, peak exercise capacity, functional capacity, and quality of life compared to exercise training alone.[66,67] In contrast, a recent study has also found that concurrent high-intensity IMT (5 sets of 10–12 inspiratory efforts at 50–80% MIP, 3 days a week for 12 weeks) did not confer additional physiological benefits in these patients compared to exercise training.[68] Again, a likely explanation for these inconsistent findings is differences in baseline MIP (i.e. pre-CR) as the former studies reporting potentiated benefit with concurrent IMT and exercise training included patients who had undergone CABG with baseline MIP that were $< 20\%$ lower (and many with inspiratory muscle weakness) compared to the latter study demonstrating no additional benefit with IMT.

Lastly, Laoutaris and colleagues investigated the impact of exercise training (prescribed for 45 min at a moderate intensity) combined with IMT (prescribed at 60% sustained MIP) on exercise capacity and other physiological outcomes in patients with LVAD[74]. They found that exercise training combined with IMT elicited improvements in exercise capacity, ventilatory efficiency, and quality of life, while the control group (who did not perform exercise training or IMT) exhibited no changes. Future studies are warranted to elucidate if IMT potentiated these beneficial physiological responses compared to exercise training alone in patients with LVAD.

Summary

Collectively, the studies outlined above provide a framework supporting inspiratory muscle impairment in patients typically referred to and/or undergoing CR, which is associated with negative clinical outcomes (e.g., greater mortality risk). To date, there is evidence that inspiratory muscle weakness is prevalent in HFrEF, while larger cohort studies are needed to determine the prevalence of inspiratory muscle weakness in other indications to CR (e.g., stable angina and acute MI with and without revascularization). Exercise training performed in the CR setting appears to elicit beneficial inspiratory muscle strength responses for patients with HFrEF and those who had undergone CABG. Importantly, there is preliminary evidence in patients with HFrEF and those who had undergone CABG indicating that IMT performed concurrently with exercise training results in greater improvements in inspiratory muscle strength as well as other physiological responses (e.g., exercise capacity) in those patients with inspiratory muscle weakness. Taken together, these data provide a foundation for future studies to investigate the clinical outcomes associated with inspiratory muscle weakness in CR patients as well as develop evidence-based CR prescription to ameliorate these pathological responses.

Proposed changes to CR programming: Incorporating assessment and specific training of the inspiratory muscles in clinical practice

Maximal inspiratory pressure strength measurements at CR entry

Given its functional significance and prognostic importance, we pose the question: should inspiratory muscle dysfunction and/or weakness be assessed *as standard* clinical routine in all patients at the initiation of phase II CR programming? When addressing this question, it is important to consider the practical-, time-, and cost-implications of introducing such measures as part of the phase II CR patient evaluation. We propose that inspiratory muscle strength assessments should be performed at CR entry in all patients which will allow for the identification of those patients with inspiratory muscle weakness. It should be noted that assessing inspiratory muscle strength at CR entry may result in underestimation of MIP in some patients for a variety of factors such as the length of time following cardiac surgery as an improvement in inspiratory muscle strength has been reported during the recovery period (however, inspiratory muscle strength levels generally remain suboptimal in these patients). However, the determination of these factors and the optimal timing of the maximal inspiratory strength test to establish the most appropriate baseline test would also incur a higher time commitment by the CR staff. As stated above, diaphragm and/or global inspiratory muscle size and function can be assessed using a variety of different techniques, including lung function testing, magnetically or electrically evoked muscle pressure(s), and ultrasound or CT imaging.[13] For example, proposing that ultrasound-derived diaphragm thickness at total lung capacity ("DT-insp") reflects both muscle mass and contractility (i.e. *a comprehensive indicator of diaphragm function*), Miyagi et al. reported that 44% of patients hospitalized with HF had impaired diaphragm muscle function.[75] However, based on our experience, it is likely that using ultrasound to assess diaphragm function would prove unsuitable for standard practice in most CR centers. Indeed, the examination of diaphragm muscle thickness using ultrasound requires expert training, is time consuming, and relies upon specialized (*and typically expensive*) equipment. Similarly, assessing inspiratory muscle function using CT imaging, artificial nerve stimulation techniques, or newer advents such as optoelectronic plethysmography can be invasive in nature, extremely time-consuming and costly, and require expert user

knowledge and training, making them not well suited for routine clinical implementation.

By contrast, the measurement of MIP (and maximal expiratory pressure; MEP) provides a simple, non-invasive, quick, and cost-effective assessment of respiratory muscle strength (see Fig. 3 for an illustrative example of an mouth pressure meter used to measure MIP).[13] Although dependent upon patient voluntary effort, MIP can provide an accurate indication of the presence and severity of inspiratory muscle weakness when expressed relative to normative values.[14,76] However, to ensure its clinical utility and to optimize the identification of inspiratory muscle weakness, it is of crucial importance that MIP is assessed in line with current recommendations.[13] First, due primarily to the length-pressure relationship of the respiratory muscles, MIP varies considerably with lung volume. Thus, it is generally recommended that MIP is measured close to residual volume where *relatively* large changes in lung volume have a *relatively* minimal effect on MIP.[14,77] Second, due to the volitional nature of the technique, it is important that patients are strongly urged to make maximal inspiratory efforts during the assessment of MIP. The patient should ideally be seated and the operator administering the test should ensure that there are no air leaks around the mouthpiece. Based on current guidelines, the patient should be coached to maintain the maximal effort for at least 1.5 s; this is because MIP is reported as the maximum pressure sustained for 1 s. However, in our experience, encouraging patients to maintain the maximal effort for 3 to 4 s results in greater and more reproducible MIP values. Third, reproducibility of MIP is of paramount importance. Clearly, if there are concerns regarding a patient's ability to consistently perform the MIP maneuver then any definitive identification of inspiratory muscle weakness and/or improvements in inspiratory muscle strength post-intervention are questionable. Having a patient 'practice' and learn the correct MIP technique and how to give a maximal effort is important. Indeed, reliability of MIP is better after an initial warm-up of the inspiratory muscles and if at least 5 attempts are performed.[14] Once the operator is satisfied that the patient is performing the maximal maneuver correctly, then MIP is typically recorded as the highest value of three efforts that vary by less than 10%. In our experience, the assessment of MIP according to the aforementioned procedures typically takes ~10–15 min in each patient.

Another important consideration in determining if CR patients exhibit inspiratory muscle weakness is to ask the question, 'what is normal'? That is, what MIP cut-off values should be used to make the determination of inspiratory muscle weakness? In the absence of clearly defined lower limits of normal, clinically significant inspiratory muscle weakness has been proposed to be present when MIP is <80 cmH_2O or < 70 cmH_2O for men and women, respectively.[13,14] As MIP is dependent on age and sex,[76,78] identifying inspiratory muscle weakness as a percent of a normative value (e.g., <70% of the predicted value) may be more appropriate. However, caution is also urged here as the choice of MIP reference values strongly impacts the prevalence of inspiratory muscle weakness. Indeed, in a sample of 1729 subjects who underwent clinical determination of MIP, the prevalence of inspiratory weakness ranged from 33 to 67% depending on which of the six commonly cited reference values for MIP were used.[78] It should be emphasized that the goal herein is not to redefine the clinical diagnosis of inspiratory muscle weakness but rather to identify CR patients who may exhibit inspiratory muscle weakness as they are the most likely to benefit with concurrent IMT and CR.

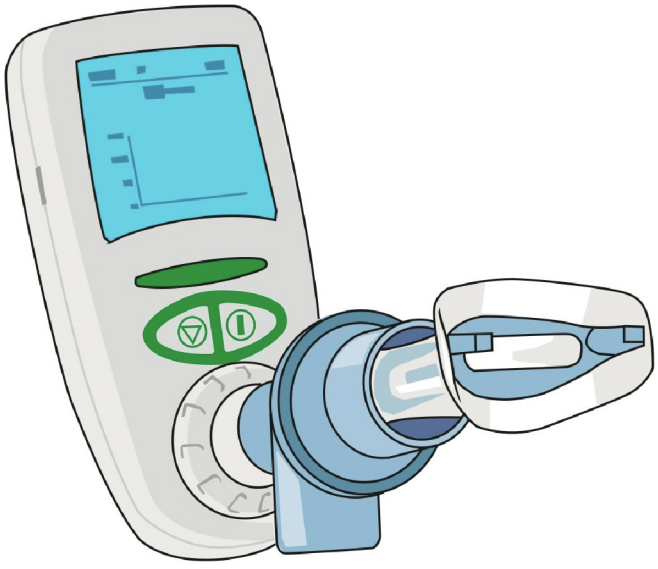

Fig. 3. Illustrative example of a handheld mouth pressure meter used to measure maximal inspiratory pressure.

Practical guidance for implementing IMT during CR enrollment

Based on the evidence that we have presented in this review, IMT may be considered an adjunct therapy that efficaciously improves inspiratory muscle function and alleviates some of the burden associated with inspiratory muscle weakness in patients undergoing phase II CR, especially in those who present with low baseline MIP (i.e. <60 cmH_2O). While voluntary hyperpnea and resistive loading techniques have been used to train the inspiratory muscles, "pressure-threshold loading" is by far the most utilized technique. Commercially available pressure-threshold loading devices typically incorporate a spring-loaded valve; this requires the patient to generate sufficient negative inspiratory pressure to overcome the load and initiate inspiration with each 'breath' (see Fig. 4 for an illustrative example of such an inspiratory muscle trainer). Such loading allows quantifiable targeting of IMT 'intensity' (i.e. percent of MIP) by providing quasi-flow independent resistance to inspiration.

We are unaware of any standardized IMT prescription. Indeed, the optimal training frequency, intensity, and duration remain relatively unknown. A series of placebo-controlled studies across the early-to-late 2000's suggested that 30 dynamic efforts performed twice daily, 6-to-7 days per week, and for 4-to-9 weeks against a pressure-threshold load equivalent to ~50% MIP can significantly improve maximal inspiratory muscle strength and exercise capacity, and attenuate the magnitude of exercise-induced inspiratory muscle fatigue in healthy individuals.[79–81] In this IMT model, training progression is ensured by instructing patients to periodically increase the resistive load such that the completion of 30 breaths approximates the limit of inspiratory muscle tolerance. Similarly, such threshold-loading IMT has been shown to increase MIP, alleviate dyspnea, and improve multiple measures of exercise capacity, including six-minute walk test distance and peak oxygen uptake ($\dot{V}O_{2peak}$), in patients with heart disease and heart failure.[31,43,82–88] However, the IMT parameters used varied considerably across these studies; indeed, target load ranged between 30 and 60% of MIP, training frequency varied from 2-to-3 times per day and 3-to-7 times per week, with total training duration ranging from 6-to-12 weeks. In patients with COPD, IMT can improve inspiratory muscle strength and endurance with those with inspiratory muscle weakness appearing to exhibit the greatest improvements.[89–91] While improvements in exercise capacity following IMT in patients with COPD have been documented, this is not a universal finding.[89] Interestingly, 'high-intensity' IMT has been shown to increase MIP by ~29% and six-minute walk test distance by 27 m and improve dyspnea and fatigue (via Chronic Respiratory Disease Questionnaire) by 1.4 and 0.9 points per item, respectively, in those with COPD[92]. For this IMT protocol, training is typically performed 3-to-5 days per week for ~8 weeks.[93] Each training session is comprised of 2-min of loaded inspirations followed by 1-min of unloaded recovery

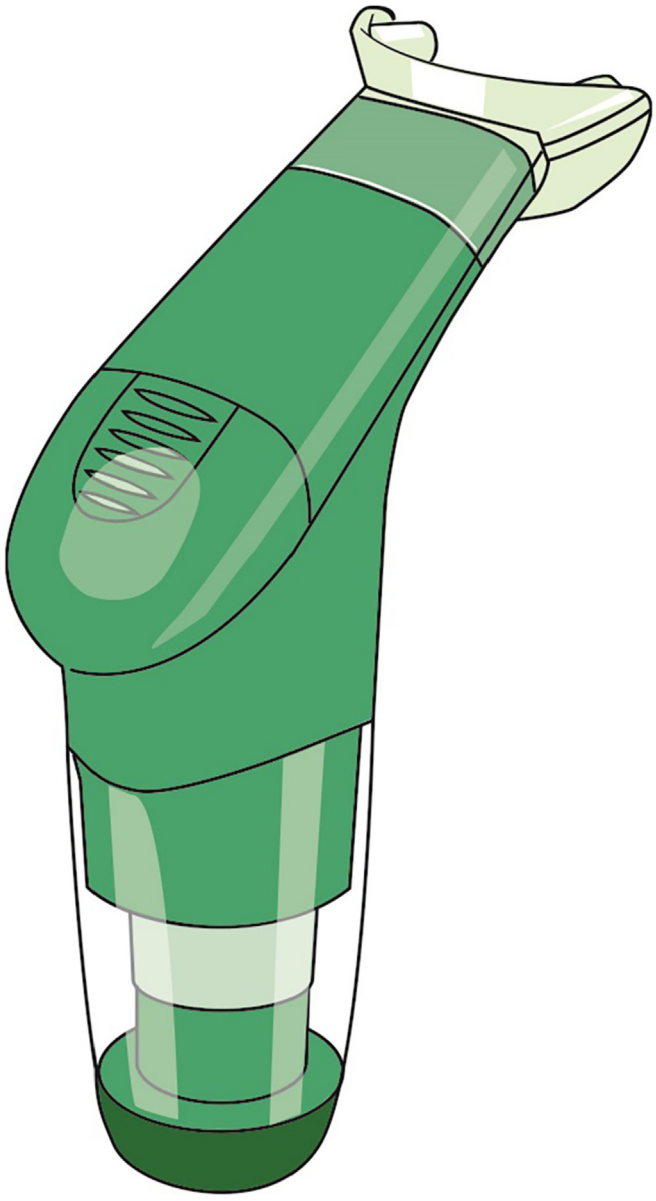

Fig. 4. Illustrative example of a threshold inspiratory muscle trainer.

breathing repeated seven times such that total loaded and unloaded breathing time are 14-min and 6-min, respectively. A relatively low threshold-load is applied at the first training session (~20–30% of baseline MIP), with the load progressively increased so that patients are generating ~70% of baseline MIP during the third or fourth training sessions. The load is then further increased over the remainder of the training period to a level whereby patients are only just able to complete the final 2-min loaded interval.[93]

While no definitive guidance can be given on the optimal IMT protocol, it is generally recommended that the initial training threshold-load should be set at ≥30% baseline MIP and that total time spent doing IMT should be ~15–20 min per day; this can be split up into two or three separate smaller time periods throughout the day. Based on the available literature, IMT should be performed ≥5 days per week for at least 4 weeks to engender measurable clinical and physiological benefits. We advocate that a patient's first 3-to-5 IMT sessions are done under the direct supervision of the CR (or pulmonary/PR) staff. This is to ensure correct patient use of the training device, the optimal setting of the initial threshold load, and to guide the patient on how to appropriately up-titrate the threshold load. Once the CR/PR staff are satisfied that the patient is performing IMT correctly and understands how to progress the training load, then patients can transition to performing IMT in their own time at home. As such, addition of IMT to a patient's standard CR care will have negligible impact on the time available for center-based aerobic and strength exercise training. General guidance for the implementation of IMT is given in Table 1.

Knowledge gaps and areas worthy of future investigation

There are numerous future lines of research that need to be addressed to better understand how inspiratory muscle weakness impacts clinical outcomes as well as strategies to mitigate these adverse outcomes. First, studies investigating the prognostic utility of MIP in predicting mortality and CVD events in CR patients following MI, stable angina, and valve surgery are warranted. The proposed change to CR programming elaborated above would assist in addressing this topic. These studies will be critical to provide additional evidence for intervening on inspiratory muscle weakness in these patients in the CR setting as well as determining specific differences across CR indications. Second, by what magnitude would inspiratory muscle strength and/or measures of exercise capacity and dyspnea have to improve to consider IMT as 'successful'? Do longer-term impacts (e.g., lower hospital readmission and/or mortality) have to be evidenced to consider IMT as clinically beneficial? These are difficult questions to answer. In a study discussed above, it was found that any increase in MIP during CR was associated with improved survival rates in patients with HF[72]; however, numerous questions remain. For example, is this association between increases in MIP and mortality consistent across other indications to CR? Should practitioners strive for changes in MIP or a specific value (absolute or relative of a predictive normal value)? These are important gaps that need to be addressed by using both clinical and physiological outcomes. Third, a major gap in knowledge is the determination of the optimal IMT exercise prescription. Previous studies investigating IMT in patients with CVD as well as those investigating concurrent IMT with exercise training in the CR setting have used multiple IMT prescription strategies. As such, future studies are necessary to determine the optimal intensity (high versus low), frequency (2–3 days versus 7 days per week), and duration for IMT prescription to be performed in combination with CR. Fourth, it is unclear if concurrent IMT and exercise training is more advantageous for inspiratory muscle strength and other physiological outcomes (e.g., exercise capacity) than exercise training alone for patients with other CR indications such as stable angina and MI with inspiratory muscle weakness.

Table 1
Practical guidance for IMT prescription in the CR setting.

	"Traditional"	*"High-intensity"*
Mode	Pressure-threshold loading device	Pressure-threshold loading device
Intensity	≥30% baseline MIP	Start at 20% baseline MIP. Following the 3rd IMT session, increase to the maximal inspiratory load (% of baseline MIP) tolerable
Duration	2 sets of 30 inspiratory efforts	7 sets of 2 min of inhaling against the inspiratory load with 1 min recovery between each set
Frequency	≥5 days per week for >4 weeks	3 days per week for 8 weeks

The total time for a IMT session for both the 'traditional' and 'high-intensity' IMT prescriptions is ~15–20 min. It is important to note that a standardized IMT prescription does not currently exist. The IMT prescription strategies outlined above are based on previous studies implementing 'traditional'[31,66,67,71,82–84,86–88,91] and 'high-intensity'[92] IMT prescription strategies in patients with COPD and CVD. IMT, inspiratory muscle training; MIP, maximal inspiratory pressure.

Funding

This work was supported by the National Institutes of Health (K12 HD065987 to JRS). This publication was also made possible through the support of the Mary Kathryn and Michael B. Panitch Career Development Award in Hypertension Research Honoring Gary Schwartz, M.D. (JRS).

Author contributions

JRS and BJT contributed to the conception, drafting and critical review of the manuscript. All authors gave final approval and agree to be accountable for all aspects of work ensuring integrity and accuracy.

Declaration of Competing interest

The authors declare no competing interests.

References

1. Virani SS, Alonso A, Aparicio HJ, et al. Heart disease and stroke statistics-2021 update: a report from the American Heart Association. Circulation 2021;143:e254-e743.
2. Dalal HM, Doherty P, Taylor RS. Cardiac rehabilitation. BMJ 2015;351:h5000.
3. Anderson L, Oldridge N, Thompson DR, et al. Exercise-based cardiac rehabilitation for coronary heart disease: Cochrane systematic review and Meta-analysis. J Am Coll Cardiol 2016;67:1-12.
4. Berry JD, Pandey A, Gao A, et al. Physical fitness and risk for heart failure and coronary artery disease. Circ Heart Fail 2013;6:627-634.
5. Mancini DM, Eisen H, Kussmaul W, Mull R, Edmunds Jr LH, Wilson JR. Value of peak exercise oxygen consumption for optimal timing of cardiac transplantation in ambulatory patients with heart failure. Circulation 1991;83:778-786.
6. Jones NL, Killian KJ. Exercise limitation in health and disease. N Engl J Med 2000;343:632-641.
7. Fletcher GF, Ades PA, Kligfield P, et al. Exercise standards for testing and training: a scientific statement from the American Heart Association. Circulation 2013;128:873-934.
8. Mancini DM, Henson D, LaManca J, Levine S. Respiratory muscle function and dyspnea in patients with chronic congestive heart failure. Circulation 1992;86:909-918.
9. McParland C, Krishnan B, Wang Y, Gallagher CG. Inspiratory muscle weakness and dyspnea in chronic heart failure. Am Rev Respir Dis 1992;146:467-472.
10. Meyer FJ, Borst MM, Zugck C, et al. Respiratory muscle dysfunction in congestive heart failure: clinical correlation and prognostic significance. Circulation 2001;103:2153-2158.
11. Ambrosino N, Opasich C, Crotti P, Cobelli F, Tavazzi L, Rampulla C. Breathing pattern, ventilatory drive and respiratory muscle strength in patients with chronic heart failure. Eur Respir J 1994;7:17-22.
12. Ribeiro JP, Chiappa GR, Neder JA, Frankenstein L. Respiratory muscle function and exercise intolerance in heart failure. Curr Heart Fail Rep 2009;6:95-101.
13. Laveneziana P, Albuquerque A, Aliverti A, et al. ERS statement on respiratory muscle testing at rest and during exercise. Eur Respir J 2019;53.
14. American Thoracic Society/European Respiratory S. ATS/ERS statement on respiratory muscle testing. Am J Respir Crit Care Med 2002;166:518-624.
15. Hamazaki N, Kamiya K, Matsuzawa R, et al. Prevalence and prognosis of respiratory muscle weakness in heart failure patients with preserved ejection fraction. Respir Med 2020;161:105834.
16. Vaz Fragoso CA, Beavers DP, Hankinson JL, et al. Respiratory impairment and dyspnea and their associations with physical inactivity and mobility in sedentary community-dwelling older persons. J Am Geriatr Soc 2014;62:622-628.
17. Buchman AS, Boyle PA, Wilson RS, Gu L, Bienias JL, Bennett DA. Pulmonary function, muscle strength and mortality in old age. Mech Ageing Dev 2008;129:625-631.
18. Buchman AS, Boyle PA, Wilson RS, Leurgans S, Shah RC, Bennett DA. Respiratory muscle strength predicts decline in mobility in older persons. Neuroepidemiology 2008;31:174-180.
19. van der Palen J, Rea TD, Manolio TA, et al. Respiratory muscle strength and the risk of incident cardiovascular events. Thorax 2004;59:1063-1067.
20. Schunemann HJ, Dorn J, Grant BJ, Winkelstein Jr W, Trevisan M. Pulmonary function is a long-term predictor of mortality in the general population: 29-year follow-up of the Buffalo Health Study. Chest 2000;118:656-664.
21. Lee HM, Liu MA, Barrett-Connor E, Wong ND. Association of lung function with coronary heart disease and cardiovascular disease outcomes in elderly: the Rancho Bernardo study. Respir Med 2014;108:1779-1785.
22. Arcari A, Magnacca S, Bracone F, et al. Relation between pulmonary function and 10-year risk for cardiovascular disease among healthy men and women in Italy: the Moli-sani Project. Eur J Prev Cardiol 2013;20:862-871.
23. Agarwal SK, Heiss G, Barr RG, et al. Airflow obstruction, lung function, and risk of incident heart failure: the atherosclerosis risk in communities (ARIC) study. Eur J Heart Fail 2012;14:414-422.
24. Killian KJ, Jones NL. Respiratory muscles and dyspnea. Clin Chest Med 1988;9:237-248.
25. Nakagawa NK, Diz MA, Kawauchi TS, et al. Risk factors for inspiratory muscle weakness in chronic heart failure. Respir Care 2020;65:507-516.
26. Walsh JT, Andrews R, Johnson P, Phillips L, Cowley AJ, Kinnear WJ. Inspiratory muscle endurance in patients with chronic heart failure. Heart 1996;76:332-336.
27. Chiappa GR, Roseguini BT, Vieira PJ, et al. Inspiratory muscle training improves blood flow to resting and exercising limbs in patients with chronic heart failure. J Am Coll Cardiol 2008;51:1663-1671.
28. Chua TP, Anker SD, Harrington D, Coats AJ. Inspiratory muscle strength is a determinant of maximum oxygen consumption in chronic heart failure. Br Heart J 1995;74:381-385.
29. Nishimura Y, Maeda H, Tanaka K, Nakamura H, Hashimoto Y, Yokoyama M. Respiratory muscle strength and hemodynamics in chronic heart failure. Chest 1994;105:355-359.
30. Frankenstein L, Nelles M, Meyer FJ, et al. Validity, prognostic value and optimal cutoff of respiratory muscle strength in patients with chronic heart failure changes with beta-blocker treatment. Eur J Cardiovasc Prev Rehabil 2009;16:424-429.
31. Dall'Ago P, Chiappa GR, Guths H, Stein R, Ribeiro JP. Inspiratory muscle training in patients with heart failure and inspiratory muscle weakness: a randomized trial. J Am Coll Cardiol 2006;47:757-763.
32. Hamazaki N, Masuda T, Kamiya K, et al. Respiratory muscle weakness increases dead-space ventilation ratio aggravating ventilation-perfusion mismatch during exercise in patients with chronic heart failure. Respirology 2019;24:154-161.
33. Arena R, Myers J, Hsu L, et al. The minute ventilation/carbon dioxide production slope is prognostically superior to the oxygen uptake efficiency slope. J Card Fail 2007;13:462-469.
34. Smith JR, Hageman KS, Harms CA, Poole DC, Musch TI. Effect of chronic heart failure in older rats on respiratory muscle and hindlimb blood flow during submaximal exercise. Respir Physiol Neurobiol 2017;243:20-26.
35. Smith JR, Ferguson SK, Hageman KS, Harms CA, Poole DC, Musch TI. Dietary nitrate supplementation opposes the elevated diaphragm blood flow in chronic heart failure during submaximal exercise. Respir Physiol Neurobiol 2018;247:140-145.
36. Borghi-Silva A, Carrascosa C, Oliveira CC, et al. Effects of respiratory muscle unloading on leg muscle oxygenation and blood volume during high-intensity exercise in chronic heart failure. Am J Physiol Heart Circ Physiol 2008;294:H2465-H2472.
37. Olson TP, Joyner MJ, Dietz NM, Eisenach JH, Curry TB, Johnson BD. Effects of respiratory muscle work on blood flow distribution during exercise in heart failure. J Physiol 2010;588:2487-2501.
38. Smith JR, Berg JD, Curry TB, Joyner MJ, Olson TP. Respiratory muscle work influences locomotor convective and diffusive oxygen transport in human heart failure during exercise. Phys Rep 2020;8, e14484.
39. Uithoven KE, Smith JR, Medina-Inojosa JR, Squires RW, Olson TP. The role of cardiac rehabilitation in reducing major adverse cardiac events in heart transplant patients. J Card Fail 2020;26:645-651.
40. Haykowsky M, Taylor D, Kim D, Tymchak W. Exercise training improves aerobic capacity and skeletal muscle function in heart transplant recipients. Am J Transplant 2009;9:734-739.
41. Anderson L, Nguyen TT, Dall CH, Burgess L, Bridges C, Taylor RS. Exercise-based cardiac rehabilitation in heart transplant recipients. Cochrane Database Syst Rev 2017;4, CD012264.
42. Ambrosino N, Bruschi C, Callegari G, et al. Time course of exercise capacity, skeletal and respiratory muscle performance after heart-lung transplantation. Eur Respir J 1996;9:1508-1514.
43. Cahalin LP, Semigran MJ, Dec GW. Inspiratory muscle training in patients with chronic heart failure awaiting cardiac transplantation: results of a pilot clinical trial. Phys Ther 1997;77:830-838.
44. Fernandes L, de Oliveira IM, Fernandes P, et al. Impact of heart transplantation on the recovery of peripheral and respiratory muscle mass and strength in patients with chronic heart failure. Transplant Direct 2018;4, e395.
45. Nomori H, Kobayashi R, Fuyuno G, Morinaga S, Yashima H. Preoperative respiratory muscle training. Assessment in thoracic surgery patients with special reference to postoperative pulmonary complications. Chest 1994;105:1782-1788.
46. Begot I, Gomes WJ, Rocco IS, et al. Inspiratory muscle weakness is related to poor short-term outcomes for heart transplantation. Braz J Cardiovasc Surg 2021;36:308-317.
47. Hulzebos EH, Helders PJ, Favie NJ, De Bie RA, Brutel De La Riviere A, Van Meeteren NL. Preoperative intensive inspiratory muscle training to prevent postoperative pulmonary complications in high-risk patients undergoing CABG surgery: a randomized clinical trial. Jama 2006;296:1851-1857.
48. Hamilton AL, Killian KJ, Summers E, Jones NL. Muscle strength, symptom intensity, and exercise capacity in patients with cardiorespiratory disorders. Am J Respir Crit Care Med 1995;152:2021-2031.
49. Huzmeli I, Ozer AY, Akkus O, et al. Comparison of functional exercise capacity, quality of life and respiratory and peripheral muscle strength between patients with stable angina and healthy controls. J Int Med Res 2020;48.300060520979211.
50. Matos-Garcia BC, Rocco IS, Maiorano LD, et al. A home-based walking program improves respiratory endurance in patients with acute myocardial infarction: a randomized controlled trial. Can J Cardiol 2017;33:785-791.
51. Cargnin C, Karsten M, Guaragna J, Dal Lago P. Inspiratory muscle training after heart valve replacement surgery improves inspiratory muscle strength, lung function, and functional capacity: a randomized controlled trial. J Cardiopulm Rehabil Prev 2019;39:E1-E7.
52. De Troyer A, Estenne M, Yernault JC. Disturbance of respiratory muscle function in patients with mitral valve disease. Am J Med 1980;69:867-873.
53. Morsch KT, Leguisamo CP, Camargo MD, et al. Ventilatory profile of patients undergoing CABG surgery. Rev Bras Cir Cardiovasc 2009;24:180-187.

54. Palaniswamy C, Selvaraj DR, Guleria R, et al. Respiratory muscle strength in rheumatic mitral stenosis improves after balloon valvotomy. J Cardiovasc Med (Hagerstown) 2010;11:440-443.
55. Stein R, Maia CP, Silveira AD, Chiappa GR, Myers J, Ribeiro JP. Inspiratory muscle strength as a determinant of functional capacity early after coronary artery bypass graft surgery. Arch Phys Med Rehabil 2009;90:1685-1691.
56. Aguirre VJ, Sinha P, Zimmet A, Lee GA, Kwa L, Rosenfeldt F. Phrenic nerve injury during cardiac surgery: mechanisms, management and prevention. Heart Lung Circ 2013;22:895-902.
57. Savci S, Degirmenci B, Saglam M, et al. Short-term effects of inspiratory muscle training in coronary artery bypass graft surgery: a randomized controlled trial. Scand Cardiovasc J 2011;45:286-293.
58. Rodrigues AJ, Mendes V, Ferreira PE, et al. Preoperative respiratory muscle dysfunction is a predictor of prolonged invasive mechanical ventilation in cardiorespiratory complications after heart valve surgery. Eur J Cardiothorac Surg 2011;39:662-666.
59. Westerdahl E, Lindmark B, Bryngelsson I, Tenling A. Pulmonary function 4 months after coronary artery bypass graft surgery. Respir Med 2003;97:317-322.
60. Roversi S, Fabbri LM, Sin DD, Hawkins NM, Agusti A. Chronic obstructive pulmonary disease and cardiac diseases. An urgent need for integrated care. Am J Respir Crit Care Med 2016;194:1319-1336.
61. Kofod LM, Hage T, Christiansen LH, et al. Inspiratory muscle strength and walking capacity in patients with COPD. Eur Clin Respir J 2020;7:1700086.
62. Ottenheijm CA, Heunks LM, Dekhuijzen RP. Diaphragm adaptations in patients with COPD. Respir Res 2008;9:12.
63. Gray-Donald K, Gibbons L, Shapiro SH, Macklem PT, Martin JG. Nutritional status and mortality in chronic obstructive pulmonary disease. Am J Respir Crit Care Med 1996;153:961-966.
64. Adamopoulos S, Schmid JP, Dendale P, et al. Combined aerobic/inspiratory muscle training vs. aerobic training in patients with chronic heart failure: the vent-HeFT trial: a European prospective multicentre randomized trial. Eur J Heart Fail 2014;16:574-582.
65. Laoutaris ID, Adamopoulos S, Manginas A, et al. Benefits of combined aerobic/resistance/inspiratory training in patients with chronic heart failure. A complete exercise model? A prospective randomised study. Int J Cardiol 2013;167:1967-1972.
66. Dos Santos TD, Pereira SN, Portela LOC, et al. Moderate-to-high intensity inspiratory muscle training improves the effects of combined training on exercise capacity in patients after coronary artery bypass graft surgery: a randomized clinical trial. Int J Cardiol 2019;279:40-46.
67. Hermes BM, Cardoso DM, Gomes TJ, et al. Short-term inspiratory muscle training potentiates the benefits of aerobic and resistance training in patients undergoing CABG in phase II cardiac rehabilitation program. Rev Bras Cir Cardiovasc 2015;30:474-481.
68. Miozzo AP, Stein C, Marcolino MZ, et al. Effects of high-intensity inspiratory muscle training associated with aerobic exercise in patients undergoing CABG: randomized clinical trial. Braz J Cardiovasc Surg 2018;33:376-383.
69. Vibarel N, Hayot M, Ledermann B, Messner Pellenc P, Ramonatxo M, Prefaut C. Effect of aerobic exercise training on inspiratory muscle performance and dyspnoea in patients with chronic heart failure. Eur J Heart Fail 2002;4:745-751.
70. Trevizan PF, Antunes-Correa LM, DML Lobo, et al. Effects of inspiratory muscle training combined with aerobic exercise training on neurovascular control in chronic heart failure patients. ESC Heart Fail 2021;8:3845-3854.
71. Winkelmann ER, Chiappa GR, Lima CO, Viecili PR, Stein R, Ribeiro JP. Addition of inspiratory muscle training to aerobic training improves cardiorespiratory responses to exercise in patients with heart failure and inspiratory muscle weakness. Am Heart J 2009;158:768.e761–767.
72. Hamazaki N, Kamiya K, Yamamoto S, et al. Changes in respiratory muscle strength following cardiac rehabilitation for prognosis in patients with heart failure. J Clin Med 2020;9.
73. Dunham C, Harms CA. Effects of high-intensity interval training on pulmonary function. Eur J Appl Physiol 2012;112:3061-3068.
74. Laoutaris ID, Dritsas A, Adamopoulos S, et al. Benefits of physical training on exercise capacity, inspiratory muscle function, and quality of life in patients with ventricular assist devices long-term postimplantation. Eur J Cardiovasc Prev Rehabil 2011;18:33-40.
75. Miyagi M, Kinugasa Y, Sota T, et al. Diaphragm muscle dysfunction in patients with heart failure. J Card Fail 2018;24:209-216.
76. Sclauser Pessoa IM, Franco Parreira V, Fregonezi GA, Sheel AW, Chung F, Reid WD. Reference values for maximal inspiratory pressure: a systematic review. Can Respir J 2014;21:43-50.
77. Rochester DF. Tests of respiratory muscle function. Clin Chest Med 1988;9:249-261.
78. Rodrigues A, Da Silva ML, Berton DC, et al. Maximal inspiratory pressure: does the choice of reference values actually matter? Chest 2017;152:32-39.
79. Volianitis S, McConnell AK, Koutedakis Y, McNaughton L, Backx K, Jones DA. Inspiratory muscle training improves rowing performance. Med Sci Sports Exerc 2001;33:803-809.
80. Romer LM, McConnell AK. Specificity and reversibility of inspiratory muscle training. Med Sci Sports Exerc 2003;35:237-244.
81. Romer LM, McConnell AK, Jones DA. Inspiratory muscle fatigue in trained cyclists: effects of inspiratory muscle training. Med Sci Sports Exerc 2002;34:785-792.
82. Mancini DM, Henson D, La Manca J, Donchez L, Levine S. Benefit of selective respiratory muscle training on exercise capacity in patients with chronic congestive heart failure. Circulation 1995;91:320-329.
83. Johnson PH, Cowley AJ, Kinnear WJ. A randomized controlled trial of inspiratory muscle training in stable chronic heart failure. Eur Heart J 1998;19:1249-1253.
84. Weiner P, Waizman J, Magadle R, Berar-Yanay N, Pelled B. The effect of specific inspiratory muscle training on the sensation of dyspnea and exercise tolerance in patients with congestive heart failure. Clin Cardiol 1999;22:727-732.
85. Cahalin LP, Arena R, Guazzi M, et al. Inspiratory muscle training in heart disease and heart failure: a review of the literature with a focus on method of training and outcomes. Expert Rev Cardiovasc Ther 2013;11:161-177.
86. Padula CA, Yeaw E, Mistry S. A home-based nurse-coached inspiratory muscle training intervention in heart failure. Appl Nurs Res 2009;22:18-25.
87. Stein R, Chiappa GR, Guths H, Dall'Ago P, Ribeiro JP. Inspiratory muscle training improves oxygen uptake efficiency slope in patients with chronic heart failure. J Cardiopulm Rehabil Prev 2009;29:392-395.
88. Mello PR, Guerra GM, Borile S, et al. Inspiratory muscle training reduces sympathetic nervous activity and improves inspiratory muscle weakness and quality of life in patients with chronic heart failure: a clinical trial. J Cardiopulm Rehabil Prev 2012;32:255-261.
89. Gosselink R, De Vos J, van den Heuvel SP, Segers J, Decramer M, Kwakkel G. Impact of inspiratory muscle training in patients with COPD: what is the evidence? Eur Respir J 2011;37:416-425.
90. Lotters F, van Tol B, Kwakkel G, Gosselink R. Effects of controlled inspiratory muscle training in patients with COPD: a meta-analysis. Eur Respir J 2002;20:570-576.
91. Gloeckl R, Marinov B, Pitta F. Practical recommendations for exercise training in patients with COPD. Eur Respir Rev 2013;22:178-186.
92. Hill K, Jenkins SC, Philippe DL, et al. High-intensity inspiratory muscle training in COPD. Eur Respir J 2006;27:1119-1128.
93. Sturdy G, Hillman D, Green D, Jenkins S, Cecins N, Eastwood P. Feasibility of high-intensity, interval-based respiratory muscle training in COPD. Chest 2003;123:142-150.