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ORIGINAL ARTICLE

The role of maximal inspiratory pressure on functional performance in adults with heart failure

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Abstract

Background Exercise intolerance is common among adults with heart failure (HF) and is a strong prognostic indicator. We examined maximal inspiratory pressure (MIP) as an indicator of maximal and submaximal exercise capacity in older HF patients.

Methods Fifty-one patients age $\geq$ 50 years with HF underwent MIP testing via the PrO_2 device. Peak oxygen uptake (VO_2), 6 min walk distance (6MWD), 30 s sit-to-stand test (STS), gait speed (GS), grip strength and lower extremity muscle strength [one-repetition maximum (1RM)] were measured. Correlation and exploratory multiple regression analyses investigated relationships between MIP, left ventricular ejection fraction (LVEF), age, body mass index (BMI) and physical function. MIP was then stratified by median (64 cm H_2O), and endpoints were compared between median groups.

Results The median age was 69 years [interquartile range (IQR): 66–73], and the median LVEF was 36.5% (IQR: 30%–45%). Regression identified MIP as an independent predictor for grip strength, 6MWD, 1RM weight and 30 s STS after adjustment for age, BMI and LVEF. MIP greater than the median (n = 25) independently predicted and reflected greater peak VO_2 [14.2 (12.8–18.1) vs. 11.5 (9.7–13.0) mL/kg/min; P = 0.0007] as well as 6MWD, 1RM, 30 s STS and GS (all $P < 0.05$).

Conclusion The analysis demonstrates that MIP is a novel biometric for exercise tolerance in adults with HF. Assessments of MIP are safe and convenient, with the potential to enhance routine HF surveillance and provide novel biometrics to guide HF therapeutics.

Keywords exercise intolerance; functional assessment; heart failure; inspiratory muscle performance; maximal inspiratory pressure; remote

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Introduction

The prevalence of heart failure (HF) increases with age. Exercise intolerance is a common symptom, with significant prognostic implications with respect to both mortality and quality of life (QoL). In addition to cardiac limitations, intrinsic disease-related diaphragmatic and skeletal muscle atrophy and weakening contribute to functional declines,[1,2] which are further compounded by sarcopenia and deconditioning.

Inspiratory muscle strength, particularly maximal inspiratory pressure (MIP), is a sensitive measure of respiratory muscle strength and has been studied extensively in various neuromuscular diseases, but it has also been a reliable marker predicting HF prognosis and QoL through its influence on ventilation, gas exchange and peripheral oxygenation.[3–7] However, the relationship between MIP and exercise tolerance has not been fully examined.

In a cross-sectional analysis of prospectively gathered data, we analysed the relationship between baseline inspiratory muscle performance (IMP) and exercise capacity in patients with HF. MIP was evaluated in relation to a broad composite of maximal and complementary submaximal functional

performance metrics. We hypothesized that greater MIP underlies greater functional performance and exercise tolerance and infer important clinical implications.

Methods

Study population

This study used baseline cross-sectional data from all eligible participants from a prospective trial of veterans (age $\geq$ 50 years) with HF with reduced ejection fraction (HFrEF) and preserved ejection fraction (HFpEF) (NCT03648762). An HF diagnosis was contingent on a previous hospitalization for HF or a physician assessment of HF. Each candidate was examined at the time of enrolment by a cardiologist to ensure that he or she had clinically stable HF without signs of symptoms of decompensation requiring hospitalization. Inclusion and exclusion criteria are outlined in *Table* S1.

HFrEF and HFpEF were differentiated by a left ventricular ejection fraction (LVEF) of $<$50% or $\geq$50%, respectively. LVEF was measured by echocardiogram or radionucleotide imaging study within 12 months of enrolment. All participants were not hospitalized but had mild–moderate symptoms [New York Heart Association (NYHA) class II or III] for the previous 3 months while on optimal guideline-directed medical therapy (GDMT), including beta-blockers, angiotensin II-converting enzyme inhibitors, angiotensin receptor blockers, angiotensin receptor/neprilysin inhibitors, vasodilators and/or aldosterone receptor antagonists, for the past 6 weeks.

Prospective data collection was conducted at Veterans Affairs Healthcare Systems at two sites from 2013 to 2019. The study was approved by the Institutional Review Board (IRB) at each site, and written informed consent was obtained from each participant at both sites before enrolment (IRB #1578178 in Boston, MA, USA, and #1617189 in Pittsburgh, PA, USA).

Maximal inspiratory pressure

The MIP is a measure of diaphragmatic strength and is assessed by the MIP generated during a sustained inspiratory effort for 1–2 s. While measurement of MIP can be performed both invasively and non-invasively, non-invasive measurements are more common due to their relative convenience.[8,9] A variety of handheld respiratory devices can provide assessments of MIP. The PrO_2 device (Smithfield, RI, USA) used in this study connects to a tablet computer to provide precise measures of MIP measured in centimetres of water (cm H_2O).

The MIP measures were performed three to five times with a 60 s rest period between trials according to standardized protocols.[9] The greatest MIP achieved was then recorded and used in the study analyses.

Pulmonary function testing (PFT)

Standard PFT and IMP both evaluate aspects of respiratory function.[10] PFTs were performed using a standardized protocol on a MedGraphics Ultima cart (MGC Diagnostics Corporation, Saint Paul, MN, USA). In this analysis, PFTs were assessed to exclude patients with severe chronic obstructive pulmonary disease (COPD) (*Table* S1) based on the forced expiratory volume in 1 s (FEV1) threshold of $<$50%.

Cardiopulmonary exercise testing (CPET)

Measurements of ventilatory gas exchange were assessed during symptom-limited exercise using a modified Balke protocol on a motor-driven treadmill.[11] As compared with bicycling exercise, walking treadmill exercise was felt to provide a more meaningful assessment of cardiorespiratory fitness and capacities for daily living among adults, both in respect to the greater familiarity of walking than cycling and its greater relatedness to everyday activity. The treadmill exercise was linked to ventilatory gas assessments on a MedGraphics Ultima CPET cart. A lightweight disposable pneumotach mouthpiece was positioned in participants' mouths during the exercise. Gas exchange metrics of peak oxygen uptake (VO_2), carbon dioxide output (VCO_2), minute ventilation (V_e), tidal volume (V_t), respiratory exchange ratio (RER) and Borg rate of perceived exertion (RPE) were all measured throughout the exercise test.[12] Ventilatory parameters were measured continuously during and after exercise. Peak performance was determined by achieving an RER $\geq$ 1.05 using 5 of 7 breath-by-breath measurements of VO_2 (to obtain optimal averaging) during symptom-limited exercise testing.

Six-minute walk test

A 6 min walk test was assessed using the standard methodology described by the American Thoracic Society. Participants were asked to walk back and forth along a 30 m course as quickly as possible for 6 min.[13] The test was scored as a 6 min walk distance (6MWD) in metres walked in 6 min and rounded to the nearest metre.

Gait speed (GS)

GS was assessed by asking participants to walk 5 m at a comfortable walking pace, starting from rest.[14] The test was performed three times, and the fastest time was recorded and used as the final GS.

Grip strength

Grip strength was assessed on both arms by asking participants to keep their arm at a right angle with the elbow next to their side while performing the test. Participants were instructed to squeeze a dynamometer with a maximum-effort isometric contraction that was maintained for 5 s. No other body parts were allowed to move.[15] The test was repeated three times, with a 60 s rest in between repetitions. The test was scored in pounds of pressure squeezed, and the maximum force attained in either arm was used as the performance measure in the calculations.

Lower extremity muscle strength and endurance

Lower extremity muscular strength and endurance were measured using a pneumatic resistance system (Keiser Corporation, Fresno, CA, USA) with computerized data acquisition of weight, power, force and fatigability of movement. To assess lower extremity muscle strength, maximum resistance was determined to measure the one-repetition maximum (1RM). To assess endurance, the resistance was set at 60% of the 1RM, and participants performed sequential submaximal repetitions until exhaustion. Endurance was measured as the number of repetitions recorded.

Thirty-second sit-to-stand test (STS)

A 30 s STS was assessed with participants seated in a straight-back chair without armrests. The evaluator asked participants to cross their arms in front of their chest and then sit and stand up as many times as they could in 30 s without using their arms. The test is a validated assessment of bilateral lower limb power and was scored by the number of stands in 30 s.[16]

Body composition assessment

Each participant underwent dual-energy X-ray absorptiometry (DXA) using a Lunar iDXA system (GE Healthcare GmbH, Vienna, Austria) after a cardiologist confirmed they were euvolaemic. Total body mass, fat mass, lean body mass, appendicular lean mass and bone mineral content were assessed. Body mass index (BMI), calculated from total body mass (kg) derived from DXA and then divided by the height in metres squared (kg/m^2), was used. The appendicular lean mass index (ALMI), also derived from DXA total lean body mass, was used in the sarcopenic assessment of this cohort.

Sarcopenia

Age-related sarcopenia was defined using the European Working Group on Sarcopenia in Older People (EWGSOP). This definition uses body composition as well as measures of GS and grip strength as part of the definition. ALMI of $<$7.0 kg/m^2 in men and 5.5 kg/m^2 in women are consistent with sarcopenia in association with GS $<$ 0.8 m/s and grip strength of $<$60 lbs for men and 35 lbs for women.[17,18] We further explored our data with the male MIP cut-off of 55 cm H_2O calculated as a biomarker of EWGSOP-defined sarcopenia, as calculated in Ohara *et al.*'s previously published study of MIP's role in sarcopenia.[19]

Statistical analyses

Non-parametric methods for statistical inference were used due to the non-normality of multiple variables within the dataset using D'Agostino–Pearson tests. Continuous variables were summarized as the median and interquartile range (IQR), and the Mann–Whitney test was used to measure the differences between MIP groups. Categorical variables were summarized as counts and percentages with χ^2 tests for comparison between MIP groups. The predicted MIP was calculated using previously published equations.[20]

Correlation analyses were performed with Spearman's rho. Univariable regression was conducted with each physical assessment as the dependent variable and MIP as the independent variable to assess the relationship of physical function with MIP. Multivariable regressions were conducted to explore the influence of MIP on physical function and exercise capacity in this veteran population with HF after adjusting for age, BMI and LVEF. All statistical analyses, including descriptive and regression analyses, were performed using MedCalc for Windows, Version 20.0.14 (MedCalc Software, Ostend, Belgium).

Results

Participant characteristics

Table 1 shows participant cross-sectional anthropometric and clinical characteristics. Fifty-one adults with HF underwent the assessments. The median age of the participants was 69 (IQR: 66–73), and the median LVEF was 36.5% (IQR: 30%–45%), with 77% diagnosed with HFrEF. Median MIP was 64

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Table 1 Clinical characteristics, inspiratory muscle performance and pulmonary function testing results between the median MIP cohorts.

	Total [*n* (%) or median (IQR)] (*N* = 51)	Less than median MIP [*n* (%) or median (IQR)] (*n* = 26)	Greater than median MIP [*n* (%) or median (IQR)] (*n* = 25)	*P*-value
Participant characteristics				
Age, years	69 (66–73)	72 (68–77)	67 (62–70)	0.004*
Sex (male, %)	49 (98%)	25 (100%)	24 (96%)	1.0[a]
BMI, kg/m^2	32.6 (29.0–37.2)	33.5 (29.2–40.1)	31.7 (28.4–34.9)	0.3
Ejection fraction, %	36.5 (30–45)	40 (29–55)	30 (30–40)	0.1
Inspiratory muscle performance				
Predicted maximal inspiratory pressure (cm H_2O)	105.1 (102.4–106.7)	103.4 (100.1–105.6)	106.2 (104.5–109.0)	0.003*
Measured maximal inspiratory pressure (cm H_2O)	64 (44–81)	44.5 (38–55)	81 (76–92)	<0.0001*
P-value comparing predicted vs. measured MIP	<0.0001	<0.0001	<0.0001	
Number of participants with measured MIP above predicted MIP (*n*)	3 (6%)	0 (0%)	3 (12%)	0.1[a]
Pulmonary function testing				
FEV1	2.3 (2.0–2.8)	2.1 (1.7–2.5)	2.6 (2.2–2.9)	0.01*
FEV1%, %	79 (68–90)	77 (67–89)	83 (69–90)	0.7
FVC	3.1 (2.7–3.4)	2.9 (2.4–3.1)	3.4 (2.9–3.5)	0.002*

Note: Statistical methods: data depicted as *N* (%) or median with interquartile range (IQR); comparisons done with χ^2 test or Mann–Whitney test as appropriate. A comparison between predicted maximal inspiratory pressure (MIP) and measured MIP was done with Wilcoxon's test of paired samples.
Abbreviations: BMI, body mass index; FEV1%, FEV1/FVC ratio; FEV1, forced expiratory volume in 1 s; FVC, forced vital capacity.
[a]Fisher's exact test was used if expected counts were <5.
*Statistically significant at $P < 0.05$.

(IQR: 44–81) cm H_2O, and median predicted MIP was 105.1 (IQR: 102.4–106.7), with only three participants having a measured MIP above their predicted MIP. The median BMI was 32.6 (IQR: 30–45). Fifty per cent of the participants or greater had hypertension, hyperlipidaemia and coronary artery disease. Thirty per cent of the participants also had arrhythmia, including rate-controlled atrial fibrillation. Consistent with GDMT, 90% of participants were on a beta-blocker, 81% of participants were taking an angiotensin-converting enzyme inhibitor, angiotensin receptor blocker or angiotensin receptor/neprilysin inhibitor, 44% were taking an aldosterone receptor antagonist and 73% were taking a statin (Table S2). No adverse events took place during the study measurements.

Exploratory correlation, regression and median stratification

Age correlated moderately with MIP ($r = -0.358$, $P = 0.01$). MIP also correlated moderately with peak VO_2 ($r = 0.430$, $P = 0.002$), FEV1 ($r = 0.494$, $P = 0.0003$), forced vital capacity (FVC) ($r = 0.541$, $P = 0.0001$), peak tidal volume during CPET ($r = 0.475$, $P = 0.0006$), peak minute ventilation during CPET ($r = 0.409$, $P = 0.0035$), lower extremity 1RM ($r = 0.520$, $P = 0.0002$), 6MWD ($r = 0.489$, $P = 0.0003$), GS ($r = 0.381$, $P = 0.006$) and grip strength ($r = 0.405$, $P = 0.0032$) (*Table* 2).

To clarify the relationship of MIP to previously established variables that affect VO_2, univariable and multivariable regression analyses were conducted using MIP, age, BMI and LVEF.[5,21,22] MIP was used as a continuous variable and as a binary categorical variable, characterized as above and below the median MIP (64 cm H_2O). In the univariable regression model (*Table* 3), MIP was a significant predictor of peak VO_2, maximum grip strength, GS, 6MWD, lower extremity 1RM and 30 s STS ($P < 0.05$ for all). However, MIP was not a significant predictor of lower extremity endurance as measured by the number of repetitions ($P = 0.4$). Similar results were seen when MIP was categorized as less than or greater than the median.

In a multivariable regression analysis controlling for age, ejection fraction and BMI, MIP's role was explored using both continuous and categorical variables above and below the median (*Table* 4). With MIP used as a continuous variable, MIP was a significant predictor of grip strength ($b = 0.15$, std. error = 0.06, $P = 0.02$), 6MWD ($b = 1.30$, std. error = 0.59, $P = 0.04$), lower extremity one-repetition weight ($b = 3.06$, std. error = 1.09, $P = 0.001$) and 30 s STS ($b = 0.08$, std. error = 0.02, $P = 0.0019$). With MIP used as a binary categorical variable of less than and greater than the median, MIP was again a significant predictor of 6MWD ($b = 67.08$, std. error = 29.37, $P = 0.03$) and 30 s STS ($b = 3.3$, std. error = 1.3, $P = 0.0150$) after adjustment for covariates. Additionally, categorical analysis added MIP as an independent predictor for peak VO_2 ($b = 3.5$, std. error = 1.5, $P = 0.03$), but no longer for grip strength ($b = 2.76$, std. error = 3.31, $P = 0.4$) or 1RM ($b = 80.9$, std. error = 59.8, $P = 0.2$).

MIP was not a significant predictor of GS or lower extremity endurance repetitions in either continuous or categorical multivariable analysis after adjusting for age, LVEF and BMI.

Table 2 Correlation matrix of maximal inspiratory pressure, functional performance measures and physiologic data.

		MIP	Predicted MIP	VO_2 peak (ml/kg/min)	Age	BMI	Ejection Fraction (%)	Total Lean Body Mass (kg)	FEV1	FVC	FEV1/FVC	Tidal Volume (mL)	Minute Ventilation (L/min)	Gait Speed (m/s)	One Repetition Weight (kg)	6 Minute walk test distance (m)	Grip Strength (lbs)
MIP	Correlation coefficient	1															
	Significance Level P																
Predicted MIP	Correlation coefficient	0.376	1														
	Significance Level P	0.007*															
VO_2 peak	Correlation coefficient	0.430	0.324	1													
(ml/kg/min)	Significance Level P	0.0019*	0.02*														
Age	Correlation coefficient	-0.358	-0.893	-0.219	1												
	Significance Level P	0.01*	<0.0001*	0.13													
BMI by DXA	Correlation coefficient	-0.086	0.018	-0.266	-0.085	1											
	Significance Level P	0.5833	0.9087	0.0890	0.5936												
Ejection Fraction	Correlation coefficient	-0.275	-0.223	-0.131	0.115	0.408	1										
(%)	Significance Level P	0.08	0.2	0.4	0.47	0.02*											
Total Lean	Correlation coefficient	0.114	0.245	-0.100	-0.146	0.664	0.196	1									
Body mass (kg)	Significance Level P	0.5	0.1	0.5	0.36	<0.0001*	0.2599										
FEV1	Correlation coefficient	0.494	0.295	0.496	-0.271	-0.088	-0.055	0.085	1								
	Significance Level P	0.0003*	0.04*	0.0003*	0.06	0.5784	0.7330	0.59									
FVC	Correlation coefficient	0.541	0.314	0.483	-0.290	-0.245	-0.133	-0.005	0.891	1							
	Significance Level P	0.0001*	0.03*	0.0004*	0.04*	0.1174	0.4069	0.98	<0.0001*								
FEV1/FVC	Correlation coefficient	0.228	0.197	0.321	-0.235	0.273	0.093	0.151	0.524	0.187	1						
	Significance Level P	0.11	0.2	0.02*	0.1	0.0807	0.5630	0.34	0.0001*	0.2							
Tidal Volume	Correlation coefficient	0.475	0.241	0.561	-0.141	0.070	-0.036	0.264	0.552	0.544	0.304	1					
(mL)	Significance Level P	0.0006*	1	<0.0001*	0.3	0.6627	0.8240	0.1	<0.0001*	0.0001*	0.04*						
Minute Ventilation	Correlation coefficient	0.409	0.326	0.593	-0.222	0.126	-0.133	0.363	0.454	0.478	0.311	0.701	1				
(L/min)	Significance Level P	0.004*	0.02*	<0.0001*	0.1	0.4320	0.4088	0.02*	0.0012*	0.0006*	0.03	<0.0001*					
Gait Speed (m/s)	Correlation coefficient	0.381	0.340	0.649	-0.297	-0.388	-0.105	0.024	0.330	0.407	0.111	0.420	0.413	1			
	Significance Level P	0.006*	0.02*	<0.0001*	0.04*	0.011*	0.5096	0.9	0.02*	0.004*	0.45	0.003*	0.003*				
One Repetition	Correlation coefficient	0.520	0.403	0.365	-0.384	0.061	-0.021	0.362	0.456	0.456	0.214	0.562	0.542	0.456	1		
Weight (kg)	Significance Level P	0.0002*	0.005*	0.01*	0.008*	0.7066	0.8982	0.02*	0.001*	0.0013*	0.15	<0.0001*	0.0001*	0.001*			
6 Minute walk test	Correlation coefficient	0.489	0.439	0.745	-0.422	-0.408	-0.227	-0.033	0.487	0.548	0.202	0.400	0.405	0.750	0.528	1	
distance (m)	Significance Level P	0.0003*	0.001*	<0.0001*	0.003*	0.007*	0.1537	0.8	0.0004*	<0.0001*	0.16	0.0049*	0.004*	<0.0001*	0.0001*		
Grip Strength (lbs)	Correlation coefficient	0.405	0.286	0.196	-0.266	0.157	0.065	0.417	0.454	0.416	0.254	0.497	0.461	0.300	0.681	0.301	1
	Significance Level P	0.003*	0.04*	0.2	0.06	0.3162	0.7	0.005*	0.0009*	0.003*	0.08	0.0003*	0.0009*	0.03*	<0.0001*	0.03*	

Note: Statistical method: Spearman's rank correlation coefficient.
Abbreviations: BMI, body mass index; DXA, dual-energy X-ray absorptiometry; FEV1, forced expiratory volume in 1 s; FVC, forced vital capacity; MIP, maximal inspiratory pressure; VO_2, oxygen consumption.
*Statistically significant at $P < 0.05$.

Table 3 Univariable unadjusted regression with MIP as a risk factor for physical performance.

Independent variable = MIP	Unadjusted (continuous)				Unadjusted (categorical, above and below the median)			
Dependent variable	*b*-value (std. error)	$R_{partial}$	R^2	*P*-value	*b*-value (std. error)	$R_{partial}$	R^2	*P*-value
Peak VO_2	0.06 (0.02)	0.37	0.13	0.0089*	3.8 (1.14)	0.44	0.19	0.0015*
Maximum grip strength (lbs)	0.15 (0.04)	0.43	0.19	0.0014*	4.8 (2.3)	0.28	0.08	0.0428*
Gait speed (m/s)	−0.02 (0.01)	−0.36	0.13	0.0099*	−0.87 (0.31)	0.37	0.14	0.0075*
6 min walk distance (m)	2.0 (0.59)	0.51	0.26	0.0002*	96.3 (24.4)	0.50	0.24	0.0003*
Lower extremity one-repetition weight (kg)	3.0	0.7	0.28	0.0001*	110.3 (38.3)	0.39	0.15	0.0060*
Lower extremity endurance strength testing (number of reps)	−0.08 (0.09)	−0.12	0.02	0.4	4.03 (4.8)	0.12	0.02	0.4
30 s sit-to-stand test (*n*)	0.08 (0.02)	0.51	0.26	0.0001*	3.6 (1.0)	0.46	0.21	0.0008*

Note: Test: univariable regression with maximal inspiratory pressure (MIP) as an independent variable.
Abbreviation: VO_2, oxygen consumption.
*Statistically significant at $P < 0.05$.

Effects of greater MIP on functional capacity

To further explore MIP and functional capacity, participants were stratified according to median MIP (64 cm H_2O), with $n = 26$ participants under the median and $n = 25$ participants over the median (*Table* 1). Participants with a higher MIP were younger [median age (IQR): 68 (66–73) vs. 72 (68–77) years, $P = 0.004$]. Participants with a higher MIP also had greater FEV1 and FVC on pulmonary functional testing ($P < 0.05$).

On maximal CPET testing, the participants with higher MIP exhibited a greater peak VO_2 [14.2 (12.8–18.1) vs. 11.5 (9.7–13.0) mL/kg/min]. In other functional assessments, subjects with greater MIP had greater 6MWD, lower extremity 1RM and endurance, a 30 s STS count and a faster GS ($P < 0.05$) (*Table* 5). Body composition analyses using DXA-derived measures showed no statistically significant differences in total mass, fat mass, bone mineral content, appendicular mass or total lean body mass ($P > 0.05$). Therefore, greater MIP in this cohort with HF was associated with higher submaximal and maximal functional performance, but not differences in body composition.

Seven total participants were considered sarcopenic by EWGSOP criteria, with no statistical difference in distribution between the two MIP cohorts (*Table* 6).[17] The MIP of the sarcopenic group and the non-sarcopenic group were not statistically different [median 56 (IQR: 43.5–78) cm H_2O vs. 68 (IQR: 45–90), $P = 0.5$], but there was a difference in BMI ($P < 0.0004$), likely as appendicular lean mass, a sub-measure of total body mass, is part of the definition. Only peak VO_2 showed a statistically significant difference between sarcopenic and non-sarcopenic ($P = 0.047$) (Table S3). When using the 55 cm H_2O cut-off from Ohara *et al*. in two-group comparisons in the current study's participant dataset, the cut-off can discriminate between higher and lower physical functions (Table S4).

Discussion

With the use of univariable and multivariable regression analyses, the current study shows that MIP is an independent predictor and a vital biomarker for exercise tolerance in adults with NYHA class II–III HF. MIP affects peak VO_2, a distinguishing assessment of cardiorespiratory fitness and prognosis, and complementary measures of submaximal aerobic capacity, strength, endurance and daily activity, all of which are pertinent to HF and its association with exercise intolerance.[23] Clinical implications are significant, as routine assessments of MIP at the point of care are convenient, safe and easily administered, implying opportunities for enhanced surveillance of functional performance that could be applied as part of routine management.

The results of the current study provide a comprehensive assessment of the relationship between inspiratory function and functional capacity in patients with a large range of comorbidities and HF severity. Additionally, the results are similar to those from other studies showing relationships between MIP and physical activity, with greater MIP being associated with greater functional capacity.[24,25] Moreover, our data are consistent with other studies that have found MIP to be significantly correlated with skeletal muscle mass index, dyspnoea, maximal oxygen consumption, oxidative stress and survival.[26–29] Notably, Ohara *et al*.'s MIP cut point of <55 cm H_2O for the presence of EWGSOP-defined sarcopenia in men without HF dichotomized the current cohort similarly to the stratification of the median MIP of 64 cm H_2O, despite many of this veteran population not meeting the criteria for EWGSOP-defined sarcopenia.[19] Data from the current study also align with recently published explorations of IMP and cardiovascular outcomes, illustrating a significant overlap between patients with physical frailty, respiratory muscle weakness and cardiovascular disease.[30] Notably, lower MIP was associated with higher LVEF, but LVEF

Table 4 Multivariable adjusted regression analysis of MIP, age, EF and BMI.

	MIP as a continuous variable				MIP as a categorical variable (median)			
	Maximal inspiratory pressure	Age	EF	BMI	Maximal inspiratory pressure	Age	EF	BMI
Peak oxygen consumption (VO_2)								
b-value (std. error)	0.06 (0.03)	−0.06 (0.10)	0.01 (0.06)	−0.09 (0.14)	3.5 (1.5)	−0.03 (0.10)	−0.01 (0.06)	−0.08 (0.13)
$R_{partial}$	0.33	−0.11	−0.03	−0.13	0.40	−0.06	−0.02	−0.11
P-value	0.07	0.6	0.9	0.5	0.03*	0.76	0.93	0.56
Maximum grip strength (lbs)								
b-value (std. error)	0.15 (0.06)	−0.10 (0.20)	0.02 (0.12)	0.48 (0.27)	2.76 (3.31)	−0.21 (0.22)	0.0001 (0.13)	0.41 (0.23)
$R_{partial}$	0.42	−0.10	0.02	0.30	0.15	−0.17	0.0001	0.24
P-value	0.02*	0.6	0.9	0.1	0.4	0.3	1.0	0.18
Gait speed (m/s)								
b-value (std. error)	0.002 (0.001)	−0.007 (0.005)	0.0008 (0.003)	−0.01 (0.01)	0.13 (0.07)	−0.01 (0.005)	0.001 (0.003)	−0.01 (0.01)
$R_{partial}$	0.29	−0.27	0.05	−0.31	0.32	−0.24	0.1	−0.30
P-value	0.1	0.1	0.8	0.09	0.07	0.18	0.76	0.1
6 min walk distance (m)								
b-value (std. error)	1.30 (0.59)	−4.48 (1.92)	0.52 (1.14)	−5.77 (2.66)	67.08 (29.37)	−4.22 (1.95)	0.58 (1.13)	−5.63 (2.66)
$R_{partial}$	0.37	−0.39	0.08	−0.37	0.39	−0.37	0.09	−0.36
P-value	0.04*	0.03*	0.65	0.04*	0.03*	0.04*	0.61	0.04*
Lower extremity one-repetition weight (kg)								
b-value (std. error)	3.06 (1.09)	−3.99 (3.50)	0.42 (2.04)	4.70 (4.80)	80.9 (59.8)	−5.62 (3.89)	0.30 (2.25)	3.51 (5.29)
$R_{partial}$	0.47	−0.21	0.04	0.18	0.25	−0.26	0.02	0.12
P-value	0.001*	0.3	0.8	0.3	0.2	0.2	0.9	0.5
Lower extremity endurance (number of reps)								
b-value (std. error)	−0.15 (0.08)	−0.47 (0.24)	0.02 (0.14)	0.35 (0.33)	−3.07 (3.97)	−0.37 (0.26)	0.03 (0.15)	0.42 (0.35)
$R_{partial}$	−0.35	−0.35	0.03	0.20	−0.14	−0.26	0.04	0.22
P-value	0.06	0.06	0.88	0.30	0.45	0.17	0.84	0.24
30 s sit-to-stand test (*n*)								
b-value (std. error)	0.08 (0.02)	−0.03 (0.08)	0.004 (0.05)	−0.14 (0.11)	3.3 (1.3)	−0.04 (0.09)	0.003 (0.05)	−0.14 (0.11)
$R_{partial}$	0.53	−0.07	0.01	−0.23	0.43	−0.09	0.01	−0.22
P-value	0.0019*	0.7	0.9	0.2	0.0150*	0.6	0.9	0.2

Note: Test: multivariable regression.
Abbreviations: BMI, body mass index; EF, ejection fraction; MIP, maximal inspiratory pressure.
*Statistically significant at $P < 0.05$.

Table 5 Functional assessment comparisons between the median MIP cohorts.

	Total [median (IQR)] ($N = 51$)	Less than median maximal inspiratory pressure [median (IQR)] ($n = 26$)	Greater than median maximal inspiratory pressure [median (IQR)] ($n = 25$)	*P*-value (Mann–Whitney)
Functional assessments				
Maximum grip strength (lbs)	34 (30–42)	32.5 (26–40)	36 (32–43)	0.06
Gait speed test (m/s)	1.0 (0.9–1.2)	0.9 (0.8–1.1)	1.1 (1.0–1.2)	0.007*
6 min walk distance (m)	360 (264–428)	298 (218–370)	415 (340–446)	0.0008*
Lower extremity one-repetition maximum (kg)	342 (300–450)	300 (275–350)	400 (330–463)	0.005*
Lower extremity endurance strength testing (number of reps)	24 (19–32)	20 (17–32)	25 (20–31)	0.4
Lower extremity endurance (kg)	206 (180–270)	180 (165–210)	240 (198–278)	0.004*
Total sit-to-stand test (*n*)	9 (7–12)	8 (5–9)	12 (9–13)	0.0005*
Maximal CPET assessments				
Peak VO_2 (mL/kg/min)	12.9 (10.8–16.2)	11.5 (9.7–13.0)	14.2 (12.8–18.1)	0.0007*
Peak VCO_2 (L/min)	1.4 (1.1–1.8)	1.3 (1.0–1.6)	1.6 (1.4–2.0)	0.006*
V_e (L/min)	51.9 (39.5–60.0)	46.5 (38.3–54.0)	57.3 (46.1–72.3)	0.005*
V_t (L)	1.6 (1.4–1.9)	1.4 (1.2–1.8)	1.9 (1.6–2.1)	0.001*
V_e/VCO_2 slope at peak	33.5 (28.8–37.6)	33.8 (28.1–37.8)	32.8 (30.4–37.6)	0.9
Respiratory exchange ratio (RER)	1.08 (1.02–1.14)	1.08 (1.02–1.12)	1.1 (1.06–1.17)	0.3
Body composition measures				
Body mass (kg)	94.3 (84.7–110.1)	94.5 (87.7–116.6)	94.3 (83.3–105.1)	0.5
Body mass index	30.7 (26.7–35.3)	31.6 (27.1–36.6)	29.9 (26.4–33.1)	0.6
Bone mineral content (kg)	3.0 (2.6–3.5)	3.0 (2.6–36.6)	3.2 (2.7–3.5)	0.5
Appendicular lean mass (kg)	25.4 (23.5–27.3)	24.6 (23.4–26.5)	25.9 (24.4–28.0)	0.2
Lean body mass (kg)	56.0 (51.9–59.8)	56.5 (51.4–64.0)	56.0 (54.1–59.5)	0.9
Lean body mass (%)	60.4 (55.0–64.6)	58.4 (54.3–64.2)	62.0 (56.9–65.0)	0.3
Fat mass (kg)	33.4 (26.4–44.9)	34.9 (27.3–47.8)	31.8 (26.0–41.6)	0.3
Fat mass (%)	36.3 (31.3–42.1)	38.7 (31.3–43.0)	34.4 (31.3–40.0)	0.4

Note: Statistical methods: data depicted as median with interquartile range (IQR); comparisons done with Mann–Whitney tests.
Abbreviations: CPET, cardiopulmonary exercise testing; MIP, maximal inspiratory pressure; VCO_2, volume of carbon dioxide; V_e, minute ventilation; V_e/VCO_2 slope, slope between minute ventilation and carbon dioxide production; VO_2, oxygen consumption; V_t, tidal volume.
*Statistically significant at $P < 0.05$.

Table 6 European Working Group on Sarcopenia in Older People criteria.

	Total [*n* (%)] ($N = 51$)	Less than median MIP [*n* (%)] ($n = 26$)	Greater than median MIP [*n* (%)] ($n = 25$)	*P*-value (Fisher's exact test)
Low gait speed[a]	9 (18)	7 (28)	2 (7)	0.14
Low grip strength[b]	51 (100)	26 (100)	25 (100)	n/a
Low appendicular lean mass index[c]	7 (16)	4 (18)	3 (14)	1.0
Sarcopenic per European Working Group on Sarcopenia in Older People criteria[d]	7 (16)	4 (18)	3 (14)	1.0

Note: Statistical methods: data depicted as *N* (% of the whole); comparisons done with Fisher's exact test due to expected counts being <5, *P*-value considered statistically significant if $P < 0.05$.
Abbreviations: MIP, maximal inspiratory pressure; n/a, not applicable.
[a]Gait speed < 0.8 m/s.
[b]Grip strength of <60 lbs (males) and <35 lbs (females).
[c]Appendicular lean mass index of <7.0 kg/m^2 (males) and 5.5 kg/m^2 (females).
[d]Sarcopenic if gait speed and muscle mass are low OR sarcopenic if gait speed is normal, and then grip strength and muscle mass are low.

did not correlate with any measure, nor was it an independent risk factor in any of the adjusted regressions predicting physical function; therefore, the entire spectrum of HF, regardless of LVEF, was shown to be associated with low exercise tolerance. This finding supports the importance of studying modifiable target biomarkers to bolster the treatment of HFrEF or HFpEF. Further study of IMP in this population is warranted to determine prognostic thresholds and treatment strategies. Considering that most of the current study's participants measured an MIP below their predicted MIP and that the categorical MIP above and below the median was independently predictive of peak oxygen consumption and exercise tolerance, the median MIP of 64 cm H_2O in this cohort can provide a benchmark for

further study into the stratification of MIP in the prognostication of HF (*Tables* 1 and 4).

MIP assessments using the portable system in the current study were performed in a clinical setting with consistent efficacy and safety without adverse events. This capability highlights the opportunity to apply remote MIP assessments, after proper training, to monitor IMP at home, in a nursing home or in other non-hospital clinical contexts as an effective and safely acquired metric of exercise capacity (e.g., in a patient's home or nursing home).[31,32] Further studies can focus on the potential use of this system to track a patient's IMP and functional stability over time and even to track the efficacy of therapeutics (e.g., exercise training) with the expectation that MIP will improve.

Reduced MIP, the proposed index for exercise intolerance and muscular inefficiency, is common in the adult population with HF. The respiratory metaboreflex is an important mechanism that may exacerbate exercise intolerance. This reflex is a hallmark of respiratory muscle weakness and is activated by the accumulation of metabolic byproducts (i.e., lactate and hydrogen ions) in the respiratory muscles, leading to increased sympathetic nerve activity and resulting in peripheral muscle vasoconstriction with decreased blood flow to exercising muscles.[33] HF can increase metabolic and respiratory demand and fatigue of the respiratory muscles and contribute to exercise intolerance. Although there was no significant difference in RER or V_e/VCO_2 slope differentiating MIP above and below the median in our cohort, our data show that greater MIP corresponded to greater exercise tolerance and greater peak VO_2. Thus, greater IMP appears to reflect an attenuation of the respiratory metaboreflex by reversal of respiratory muscle weakness and subsequent improvement in exercise performance (i.e., greater peak VO_2, GS and 6MWD).[34–37] Greater MIP was also associated with higher FEV1 and FVC, suggesting that the association of MIP with greater functional capacity in patients with HF is in part due to the impact of MIP on lung function and that the role of greater PFT results on functional performance as both were significantly correlated to all measures of functional performance and peak VO_2.

Curiously, only seven participants in our cohort met EWGSOP criteria for sarcopenia, but Ohara *et al.*'s discriminatory MIP cut-off dichotomized the current cohort similarly to the median (Table S4). Both the cut-off and the median were able to delineate decreased physical function to a greater extent than the EWGSOP cut-offs. The current cohort had a higher BMI and ALMI despite diminished physical and functional capacity. This suggests that the body composition parameters in the current sarcopenia-defining criteria may lead to an underestimation of sarcopenia in those with HF. The current analysis furthers this finding by noting that BMI only independently predicts 6MWD along with MIP and age in this population (*Table* 4). Additionally, a recent study suggested that the grip strength criteria from the EWGSOP may also be underestimating the prevalence of sarcopenia.[38] While the current study is small, it suggests that the incorporation of MIP may improve the identification of sarcopenia compared with current standards, which rely solely on grip strength and body composition (*Table* 6).

The present study has limitations that must be considered when interpreting the results. A small sample size restricts the power to detect significant effects and limits the generalizability of the findings. The study sample was also almost all male (98%) and all veterans from the United States, further limiting generalizability. Our study population also had multiple comorbidities that may have confounded HF evaluations. Finally, this study was conducted across multiple sites, which may have introduced additional sources of variability and heterogeneity.

In summary, our analysis demonstrates the clinical utility of MIP assessments in adults with class II–III HF on GDMT. Greater MIP was positively correlated with multiple indices of functional performance independent of age and body composition, with implicit value in discriminating clinical risk. Furthermore, technology-facilitated MIP assessments with PrO_2 can be measured remotely, highlighting the potential for MIP to be tracked from a distance for serial assessments and the potential to improve surveillance and therapeutic guidance. Further research exploring the application of IMP to HF management, the identification of sarcopenia and the utility of therapeutics to improve MIP is warranted.

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Conflict of interest statement

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Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1. Inclusion and Exclusion Criteria.
Table S2. Past Medical History and Medical Therapy in Total Cohort and cohorts stratified by Median MIP.
Table S3. Two-group comparison of MIP, BMI, and Age between Non-sarcopenic and Sarcopenic participants.
Table S4. Two-group comparison of Physical Function Assessments using MIP greater than or less than 55 cm H_2O.

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