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ORIGINAL RESEARCH

Percent Predicted Peak Exercise Oxygen Pulse Provides Insights Into Ventricular-Vascular Response and Prognosticates HFpEF

Jason P. Li, MD,[a,b] Charles Slocum, MD,[a] John Sbarbaro, BA,[a] Mark Schoenike, BS,[a] Joseph Campain, BS,[a] Cheshta Prasad, BA,[a] Matthew G. Nayor, MD, MPH,[c] Gregory D. Lewis, MD,[a] Rajeev Malhotra, MD, MS[a]

ABSTRACT

BACKGROUND Peak oxygen consumption and oxygen pulse along with their respective percent predicted measures are gold standards of exercise capacity. To date, no studies have investigated the relationship between percent predicted peak oxygen pulse (%PredO_2P) and ventricular-vascular response (VVR) and the association of %PredO_2P with all-cause mortality in heart failure with preserved ejection fraction (HFpEF) patients.

OBJECTIVES The authors investigated the association between: 1) CPET measures of %PredO_2P and VVR; and 2) %PredO_2P and all-cause mortality in HFpEF patients.

METHODS Our cohort of 154 HFpEF patients underwent invasive CPET and were grouped into %PredO_2P tertiles. The association between percent predicted Fick components and markers of VVR (ie, proportionate pulse pressure, effective arterial elastance) was determined with correlation analysis. The Cox proportional hazards model was used to identify predictors of mortality.

RESULTS The participants' mean age was 57 ± 15 years. Higher %PredO_2P correlated with higher exercise capacity. In terms of VVR, higher %PredO_2P correlated with a lower pressure for a given preload (effective arterial elastance $r = -0.45$, $P < 0.001$ and proportionate pulse pressure $r = -0.22$, $P = 0.008$). %PredO_2P distinguished normal and abnormal percent predicted peak stroke volume and correlated positively with %PredVO_2 ($r = 0.61$, $P < 0.001$). Participants had a median follow-up time of 5.6 years and 15% death. Adjusted for age and body mass index, there was a 5% relative reduction in mortality (HR: 0.95, 95% CI: 0.92-0.98, $P = 0.003$) for every percent increase in %PredO_2P.

CONCLUSIONS In HFpEF, %PredO_2P is a VVR marker that can stratify invasive parameters such as percent predicted peak stroke volume. %PredO_2P is an independent prognostic marker for all-cause mortality and those with higher %PredO_2P exhibited longer survival. (JACC Adv 2024;3:101101) © 2024 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

From the [a]Division of Cardiology, Department of Medicine, Massachusetts General Hospital, Boston, Massachusetts, USA; [b]Division of Cardiology, Department of Medicine, University of Washington School of Medicine, Seattle, Washington, USA; and the [c]Section of Cardiovascular Medicine and Preventive Medicine and Epidemiology, Department of Medicine, Boston University School of Medicine, Boston, Massachusetts, USA.

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ABBREVIATIONS AND ACRONYMS

%PredC$_{av}$O$_2$ = percent predicted peak arterio-mixed venous oxygen content difference

%PredO$_2$P = percent predicted peak oxygen pulse

%PredSV = percent predicted peak stroke volume

BMI = body mass index

C$_{av}$O$_2$ = arterio-mixed venous oxygen content difference

Ea = effective arterial elastance

HFpEF = heart failure with preserved ejection fraction

HR = heart rate

O$_2$P = oxygen pulse

PAP/CO = linear slope of pulmonary arterial pressure and cardiac output

PCWP = pulmonary capillary wedge pressure

PCWP/CO = linear slope of pulmonary capillary wedge pressure and cardiac output

PrPP = proportionate pulse pressure (at peak exercise)

PVR = pulmonary vascular resistance

RVSWI = right ventricular stroke work index

SVR = systemic vascular resistance

VE/VCO$_2$ = minute ventilation/carbon dioxide production

VVR = ventricular-vascular response

The heterogeneity of heart failure with preserved ejection fraction (HFpEF) pathophysiology, encompassing abnormalities of diastolic relaxation, peripheral oxygen uptake, and ventricular-vascular response (VVR), has resulted in therapeutic challenges.[1-3] Cardiopulmonary exercise testing (CPET) is an ideal approach to understand HFpEF physiology given that dynamic measurements often outperform resting measurements.[4-6] Peak oxygen uptake (VO_2) is the gold standard measure of functional capacity and is reduced in HFpEF patients compared to patients without heart failure.[7,8] Oxygen pulse (O_2P), a noninvasive CPET measure, represents the product of stroke volume (SV) and arterio-mixed venous oxygen content difference ($C_{av}O_2$).[9,10] HFpEF patients exhibit impaired augmentation of heart rate (HR), SV, and $C_{av}O_2$ during exercise.[2,6]

Both percent predicted models and peak values of exercise are predictors of adverse events.[10-12] Percent predicted values have the ability to adjust for age, body mass index (BMI), and sex.[11] Few studies have examined percent predicted peak O_2P (%PredO_2P) and its relationship with peak VO_2[10] and data are lacking on the relationship of %PredO_2P with peak HR, $C_{av}O_2$, and SV in HFpEF.

Previous studies have elucidated the synergistic dysfunction of the ventricles and arteries as playing a role in HFpEF pathophysiology.[7,13] Ventricular-vascular coupling can be assessed with echocardiography or invasive CPET and is an important determinant of exercise capacity, whereby the vasculature vasodilates to accommodate increased cardiac output, while blunting inappropriate increases in blood pressure.[14,15] Markers of ventricular-vascular coupling include systemic (SVR) and pulmonary (PVR) vascular resistance, effective arterial elastance (Ea), which is the ratio of end-systolic blood pressure to SV, and proportionate pulse pressure (PrPP), which is the ratio of pulse pressure to systolic blood pressure.[16,17] VVR is defined here as ventricular-vascular coupling during exercise and associated hemodynamic responses to exercise (ie, peak SV, peak right ventricular stroke work index, PAP/CO, PCWP/CO). PAP/CO is the slope of the linear relationship between pulmonary arterial pressure and cardiac output from rest to peak exercise, and PCWP/CO is the slope of the linear relationship of pulmonary capillary wedge pressure and cardiac output from rest to peak exercise.[18] The former examines the degree of right ventricular filling pressures relative to cardiac output, while the latter examines the degree of left ventricular filling pressures relative to cardiac output.[18]

We believe %PredO_2P would be an ideal noninvasive surrogate for measuring ventricular-vascular dysfunction because O_2P has long been thought of as a substitute for stroke volume.[19,20] We hypothesize that %PredO_2P should associate with markers of VVR and all-cause mortality in HFpEF.

In short, the role of %PredO_2P in determining VVR and survival of HFpEF patients remains incompletely understood. The objective of our study was to delineate %PredO_2P in a HFpEF cohort, demonstrate how %PredO_2P associates with ventricular-vascular decoupling, and explore the prognostic capabilities of %PredO_2P in HFpEF.

METHODS

PATIENT POPULATION AND STUDY DESIGN. Clinical assessment. A total of 663 consecutive patients who had dyspnea on exertion and left ventricular ejection fraction ≥50% underwent invasive CPET at our institution. Of those, 154 patients had HFpEF (defined as left ventricular ejection fraction ≥50% with resting supine pulmonary capillary wedge pressure [PCWP] ≥15 mm Hg and/or exercise PCWP/CO ≥2.0 mm Hg/L/min[18]), did not take atrioventricular nodal blocking agents, did not have atrial fibrillation, and were not paced by a pacemaker (Supplemental Figure 1). Excluding patients on atrioventricular nodal blocking agents, who were paced or had atrial fibrillation was done in order to assess unaffected intrinsic chronotropic responses to exercise.[8,21]

Cardiopulmonary exercise testing. All patients had Swan Ganz catheter placement via right internal jugular access and arterial line placement via radial artery access. First-pass radionuclide ventriculography was performed at rest and peak exercise. Patients underwent a maximum upright CPET via cycle ergometry, the start of which included a 3-minute resting period followed by 3 minutes of unloaded exercise. Subsequently, patients continued on an incremental exercise ramp protocol of 5 to 25 W/min, based on estimated exercise capacity. All patients surpassed their anaerobic threshold and had a respiratory exchange ratio in excess of 1.05. Right atrial pressure, mean pulmonary arterial pressure, PCWP, and systemic arterial pressures were measured minute-by-minute at end-expiration (Witt Biomedical). Fick-derived cardiac outputs were determined

at 1-minute intervals throughout exercise via simultaneous measurements of breath-by-breath VO_2 along with arterial and mixed venous O_2 content to derive $C_{av}O_2$ (MedGraphics). SV was calculated by dividing cardiac output by HR. Peak VO_2 was defined as the highest 30-second median VO_2 along the exercise ramp. The other components of peak values were chosen at the same minute measurement as peak VO_2 in order to accurately determine percent predicted. Percent predicted components were calculated using the Wasserman equation for maximal-predicted peak VO_2.[22] Age-predicted maximal HR was defined as 220 beats/min subtracted by age in years. Maximum-predicted peak O_2P was calculated by dividing Wasserman's predicted peak VO_2 by age-predicted maximal HR. Maximum $C_{av}O_2$ values for male and female were defined as 14.5 mL/dL and 13.0 mL/dL, respectively.[9,23] Percent predicted peak VO_2 (%PredVO_2), HR (%PredHR), and $C_{av}O_2$ (%Pred$C_{av}O_2$) were calculated from peak values divided by the theoretical maximum or normal values for each patient. Percent predicted peak stroke volume (%PredSV) was back calculated from Equation 1 below:

$$\%\text{PredSV} = \%\text{Pred}VO_2 / (\%\text{PredHR} \cdot \%\text{Pred}C_{av}O_2) \quad \text{(Eq. 1)}$$

%PredO_2P tertiles were formed for comparative analyses. We derived OUES using semilog transformation and VE/VCO_2 slope across time with linear regressions of minute-by-minute exercise measurements.[24]

Assessment of VVR. Linear regression of PCWP/CO and PAP/CO was determined through the least squares method.[18] Ea was calculated with the equation Ea = 0.9·SBP/SV.[16] SV and %PredSV were calculated as mentioned previously. Right ventricular stroke work index (RVSWI) was calculated with the equation RVSWI= SVI·(mPAP-mRAP)·0.0136.[25] PrPP was calculated as previously specified.[17] SVR and PVR were calculated as previously described.[26]

OUTCOMES. All-cause mortality was ascertained using the social security death index and electronic medical records.

STATISTICAL ANALYSIS. Statistical analysis was performed with Stata 16 (StataCorp) and GraphPad Prism 8 (GraphPad Software). The Shapiro-Wilk normality test was performed to assess for normality of distribution. Measurements are presented as mean ± SEM or median (IQR) for continuous variables, as appropriate, and as numbers and percentages for categorical variables. Groups were compared using the 1-way analysis of variance, Kruskal-Wallis test, or chi-square test, where appropriate. An extended Wilcoxon rank-sum test in Stata was used to assess the trend across ordered groups. Least square regressions were performed for %PredO_2P and the respective %Pred counterparts. Pearson correlation was calculated to assess linear relationships, and Spearman's rank-order correlation was assessed for monotonic relationships in nonparametric variables. Sensitivity and specificity analysis was used in stratifying %PredO_2P and %PredSV. A 2-sided *P* value of <0.05 was considered statistically significant, except when adjusting for multiple comparisons via Bonferroni correction, where indicated.

The Kaplan-Meier method was used to calculate cumulative survival rates. The log-rank test for trend was performed across tertiles. Unadjusted and adjusted Cox proportionality hazards modeling were performed using %PredO_2P as a covariate. The adjusted models included a combination of covariates including age, sex, BMI, peak VO_2, VE/VCO_2 slope, and %PredO_2P. The proportionality assumption was verified for all Cox regression models by Schoenfeld residual testing. The study was approved by the Mass General Brigham Institutional Review Board (2010P001704 and 2010P002423).

TABLE 1 Baseline Characteristics by Tertiles of Peak Oxygen Pulse

	%PredO_2P 42.1-139.2 Cohort (n = 154)	42.1-<76.2 Tertile 1 (n = 51)	%PredO_2P 76.2-<94.4 Tertile 2 (n = 51)	%PredO_2P 94.4-139.2 Tertile 3 (n = 52)	*P* Value
Age (y)	57 (1)	53 (2)	59 (2)	59 (2)	0.092
Female	66 (102)	57 (29)	71 (36)	71 (37)	0.223
BMI (kg/m^2)	29.9 (0.6)	27.8 (0.8)	29.5 (0.9)	32.5 (1.2)	0.014
LVEF (%)	66 (1)	66 (1)	67 (1)	65 (1)	0.404
Hypertension	46 (71)	35 (18)	53 (27)	50 (26)	0.159
Diabetes	12 (18)	10 (5)	14 (7)	12 (6)	0.846
HLD	36 (56)	25 (13)	43 (22)	40 (21)	0.137
ACEI or ARB	30 (46)	31 (16)	37 (19)	21 (11)	0.195
Diuretic	30 (46)	22 (11)	31 (16)	37 (19)	0.242
Statin	36 (55)	31 (16)	35 (18)	40 (21)	0.632

Values are mean (SEM), median (IQR) or % (n). *P* values of 1-way ANOVA, Kruskal-Wallis, or chi-square, as appropriate.

ACEI = angiotensin-converting-enzyme inhibitor; ARB = angiotensin receptor blockers; BMI = body mass index; HLD = hyperlipidemia; LVEF = left ventricular ejection fraction; O_2P = oxygen pulse.

RESULTS

BASELINE CHARACTERISTICS AND RESTING HEMODYNAMICS. With the exception of a trend towards higher BMI for higher %PredO_2P tertiles, the cohort's baseline characteristics, prevalence of comorbidities and medication usage did not differ across %PredO_2P tertiles, Table 1. Resting hemodynamic and ventilatory measures were similar across %PredO_2P tertiles except for HR ($P < 0.001$) and SV ($P = 0.001$ (Table 2).

TABLE 2 Resting and Peak Exercise Hemodynamic, Gas Exchange, and Metabolic Responses Across Percent Predicted Peak O_2P Tertiles

	Cohort	Tertile 1	Tertile 2	Tertile 3	*P* Value
Rest					
RA (mm Hg)	3 (0.2)	3 (0.5)	3 (0.3)	3 (0.3)	0.296
PAP (mm Hg)	17 (0.4)	18 (0.8)	17 (0.6)	17 (0.7)	0.171
Supine PCWP (mm Hg)	14 (0.5)	13 (1.0)	13 (0.8)	16 (0.8)	0.021
SBP (mm Hg)	148 (2)	145 (4)	151 (3)	149 (3)	0.185
DBP (mm Hg)	78 (1)	79 (2)	78 (2)	76 (2)	0.480
CO (L/min)	5.1 (0.1)	4.9 (0.2)	5.1 (0.2)	5.2 (0.2)	0.344
HR (beats/min)	81 (1)	89 (2)	80 (2)[a]	75 (1)[ab]	**<0.001**
SV (mL)	65 (2)	56 (3)	68 (4)[a]	71 (3)[a]	**0.001**
O_2P (mL/beat)	3.6 (0.1)	3.3 (0.1)	3.5 (0.2)	3.9 (0.1)	0.004
VO_2 (mL/min)	282 (6)	285 (11)	275 (9)	286 (10)	0.769
VO_2/kg (mL kg^{-1} min^{-1})	3.5 (0.1)	3.8 (0.1)	3.5 (0.1)	3.3 (0.1)	0.022
$C_{av}O_2$ (mL/dL)	5.6 (0.1)	5.6 (0.2)	5.6 (0.1)	5.7 (0.1)	0.511
C_aO_2 (mL/dL)	17.4 (0.2)	17.3 (0.3)	17.2 (0.3)	17.7 (0.3)	0.459
C_vO_2 (mL/dL)	11.8 (0.2)	11.7 (0.3)	11.7 (0.2)	12.0 (0.3)	0.842
$S_{av}O_2$ (%)	33 (1)	33 (1)	33 (1)	33 (1)	0.957
Hgb (g/dL)	12.8 (0.1)	12.8 (0.2)	12.7 (0.2)	13.0 (0.2)	0.611
Peak					
Work (W)	89 (3)	82 (5)	87 (4)	99 (5)	0.031
RER	1.19 (0.01)	1.22 (0.02)	1.18 (0.02)	1.17 (0.01)	0.040
RA (mm Hg)	11 (1.2)	11 (1.2)	13 (0.9)	11 (0.8)	0.168
PAP (mm Hg)	38 (1.5)	38 (1.5)	37 (1.3)	38 (1.2)	0.773
PCWP (mm Hg)	23 (1.5)	23 (1.5)	23 (1.0)	23 (1.1)	0.689
SBP (mm Hg)	186 (2)	188 (3)	188 (3)	181 (3)	0.226
DBP (mm Hg)	89 (1)	88 (2)	89 (2)	89 (2)	0.754
CO (L/min)	10.8 (0.2)	10.0 (0.4)	11.1 (0.3)	11.5 (0.5)	0.038
HR (beats/min)	134 (2)	143 (3)	135 (4)	123 (4)[ab]	**<0.001**
SV (mL)	82 (2)	71 (3)	83 (2)[a]	93 (3)[ab]	**<0.001**
O_2P (mL/beat)	9.2 (0.2)	7.6 (0.3)	8.8 (0.3)[a]	11.2 (0.4)[ab]	**<0.001**
VO_2 (mL/min)	1,208 (31)	1,069 (53)	1,181 (38)	1,369 (61)[ab]	**<0.001**
VO_2/kg (mL kg^{-1} min^{-1})	14.8 (0.3)	13.9 (0.5)	14.9 (0.5)	15.7 (0.7)	0.230
$C_{av}O_2$ (mL/dL)	11.1 (0.2)	10.7 (0.3)	10.7 (0.2)	11.9 (0.3)[ab]	**<0.001**
C_aO_2 (mL/dL)	18.2 (0.2)	18.1 (0.4)	17.9 (0.3)	18.5 (0.3)	0.405
C_vO_2 (mL/dL)	7.1 (0.1)	7.4 (0.3)	7.2 (0.2)	6.5 (0.2)	0.010
$S_{av}O_2$ (%)	61 (1)	59 (1)	59 (1)	65 (1)[ab]	**<0.001**
Hgb (g/dL)	13.6 (0.1)	13.6 (0.3)	13.5 (0.2)	13.7 (0.2)	0.715

Values are in mean (SEM) or median (IQR). *P* values of 1-way ANOVA, Kruskal-Wallis or chi-square when appropriate. Subgroup compariso *P* values of student t-test or Mann-Whitney U test as appropriate. Values in **bold** indicate statistically significant after adjusting for multiple comparisons. [a]$P < 0.0167$ vs tertile 1, Bonferroni adjusted. [b]$P < 0.0167$ vs tertile 2, Bonferroni adjusted.

C_aO_2 = arterial oxygen content; $C_{av}O_2$ = arterial-venous O_2 content difference; C_vO_2 = mixed venous oxygen content; CO = cardiac output; DBP = diastolic blood pressure; Hgb = hemoglobin; HR = heart rate; O_2P = oxygen pulse; PAP = pulmonary arterial pressure; PCWP = pulmonary capillary wedge pressure; RA = right atrial pressure; RER = respiratory exchange ratio; SBP = systolic blood pressure; SV = stroke volume; $S_{av}O_2$ = arterial-venous oxygen saturation; VO_2 = oxygen uptake; VO_2/kg = oxygen uptake per kilogram; Work = work load.

EXERCISE HEMODYNAMICS. HFpEF patients with higher %PredO$_2$P had higher peak O_2P, VO_2, $C_{av}O_2$, $S_{av}O_2$, SV and lower HR ($P < 0.001$ for all respective comparisons) (Table 2) compared to those with lower %PredO$_2$P. Tertile 3 had the lowest HR ($P < 0.0167$ compared to tertiles 1 and 2) and highest SV ($P < 0.0167$ compared to tertiles 1 and 2). Higher O_2P tertiles trended toward higher peak CO ($P = 0.038$) and maximum work ($P = 0.031$) that were not significant after adjusting for multiple comparisons.

Higher %PredO$_2$P tertile associated with more efficient oxygen utilization for a given ventilation as measured by OUES (trend $P = 0.010$) with a trend toward improved ventilatory efficiency as assessed by minute ventilation-to-CO_2 production ratio (VE/VCO_2 slope, trend $P = 0.098$ (Supplemental Table 1).

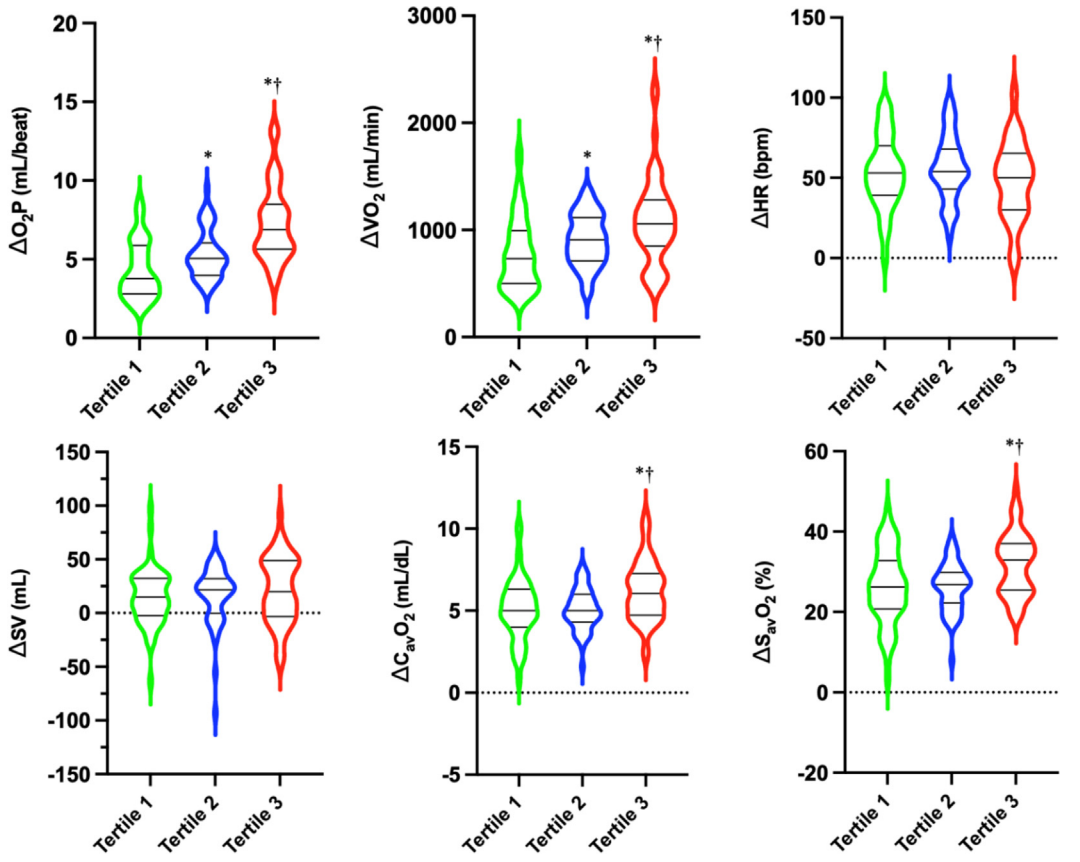
Participants with higher %PredO$_2$P had greater augmentation of O_2P, VO_2, and VO_2/kg than those in the lowest %PredO$_2$P tertile (Figure 1, Supplemental Table 1). We observed similar results for $C_{av}O_2$ and $S_{av}O_2$ in that those with the highest %PredO$_2$P tertile had improved augmentation compared to those in the lowest tertile (Figure 1). Notably, HR augmentation did not differ among the tertiles and SV augmentation did not have a statistical difference among groups despite a visible trend (Figure 1).

RELATIONSHIP OF PERCENT PREDICTED PEAK O_2P WITH OTHER PERCENT PREDICTED COMPONENTS. The relationships between the individual percent predicted components of the Fick equation with %PredO$_2$P are shown in Figure 2. %PredO$_2$P had positive correlations with %PredSV ($r = 0.66$, $P < 0.001$), %PredVO$_2$ ($r = 0.61$, $P < 0.001$), and %Pred$C_{av}O_2$ ($r = 0.41$, $P < 0.001$) and a negative correlation with %PredHR ($r = -0.37$, $P < 0.001$). Consistently, these same patterns were seen at corresponding peak absolute values of O_2P components (Supplemental Table 2). On average HFpEF patients with a lower %PredO$_2$P have relatively even contributions from %Pred$C_{av}O_2$ and %PredSV, whereas those with higher %PredO$_2$P have a pattern of relatively greater contribution from %PredSV than %Pred$C_{av}O_2$ (Figure 2). There was greater variability in %PredSV than %Pred$C_{av}O_2$ (Figure 2).

Because of the robust correlation of %PredO$_2$P with %PredSV, we performed sensitivity and specificity analyses of %PredO$_2$P in predicting %PredSV (Supplemental Figure 2). Using a common cutoff for CPET laboratory tests (≥80% %PredO$_2$P), we determined that all patients had ≥80% %PredSV. For %PredO$_2$P <80%, more than half (37/57) the patients had a %PredSV ≥80%. When we moved the threshold to ≥85% %PredO$_2$P, which is the value supported for heart failure patients,[10] all patients had a %PredSV ≥85%. These results indicate that a normal %PredO$_2$P is strongly tied with a normal %PredSV; however, an abnormal %PredO$_2$P is linked to an abnormal %PredSV only in a fraction of HFpEF patients due to the contribution from %Pred$C_{av}O_2$.

VENTRICULAR-VASCULAR RESPONSE. We observed a correlation between improved VVR and higher %PredO$_2$P (Table 3). Peak exercise SVR was negatively correlated with %PredO$_2$P (rho = −0.25, $P = 0.002$)

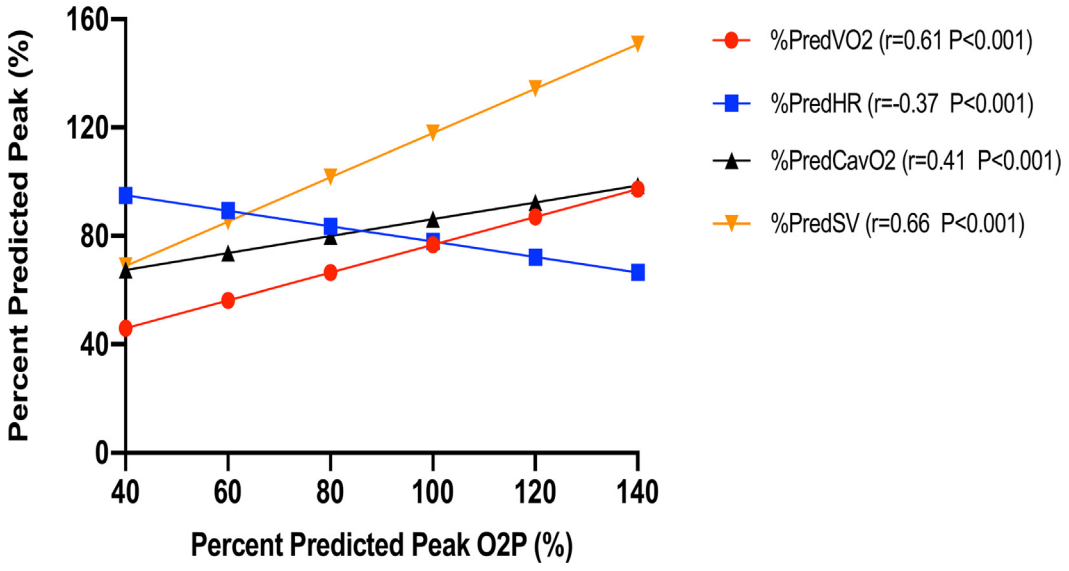
FIGURE 1 Augmentation of Fick Components During Exercise Across %PredO$_2$P Tertiles



During exercise, the highest tertile has improved augmentation of oxygen pulse, oxygen uptake, and $C_{av}O_2$ compared to the lower tertiles. Violin plots with first quartile, median and third quartile shown via horizontal black lines in ascending order. $\Delta C_{av}O_2$ = change in arterial-venous O_2 content difference from peak exercise to rest; ΔHR = change in heart rate from peak exercise to rest; ΔSV = change in stroke volume from peak exercise to rest; ΔO_2P = change in oxygen pulse from peak exercise to rest; $\Delta S_{av}O_2$ = change in arterial-venous oxygen saturation from peak exercise to rest; ΔVO_2 = change in oxygen uptake from peak exercise to rest. *$P < 0.0167$ vs tertile 1, Bonferroni adjusted. †$P < 0.0167$ vs tertile 2, Bonferroni adjusted. *P* values of student's *t*-test or Mann-Whitney *U* test as appropriate.

(Figure 3A), indicating that a higher vascular resistance is associated with lower %PredO$_2$P. Coupled with this vascular finding, %PredO$_2$P had positive correlations with peak SV (r = 0.48, $P < 0.001$) (Figure 3B) and %PredSV (r = 0.66, $P < 0.001$) (Figure 2). Furthermore, %PredO$_2$P had negative correlations with the established ventricular-vascular coupling measures of PrPP (r = −0.22, $P = 0.008$) (Figure 3C) and Ea at peak exercise (r = −0.45, $P < 0.001$) (Figure 3D). HFpEF patients associate with higher Ea,[27] and now we show that %PredO$_2$P can stratify impaired left ventricular and systemic vascular coupling within HFpEF. Similarly, for the right-sided circulation, there is some evidence of impaired right ventricular-pulmonary vascular coupling. Patients with lower %PredO$_2$P exhibited a trend toward higher peak PVR (r = −0.16, $P = 0.043$) (Figure 3E) and lower peak RVSWI (r = 0.21, $P = 0.010$; Figure 3F), though those trends were not statistically significant after adjusting for multiple comparisons. There was a relationship of lower PAP/CO slope (trend $P = 0.001$) (Figure 3G) and lower PCWP/CO slope (trend $P = 0.004$) (Figure 3H) across higher %PredO$_2$P tertiles, indicating that higher %PredO$_2$P is correlated with improved left-sided and right-sided hemodynamic responses to exercise. Overall, these results underscore the important insights that %PredO$_2$P can provide on VVR in HFpEF. When correlations of %PredO$_2$P with VVR variables were assessed across subsets of BMI <30 kg/m^2, BMI ≥30 kg/m^2, no diuretic use and diuretic use, those findings were similar to the whole cohort (Supplemental Table 3).

FIGURE 2 Percent Predicted Peak O_2P and Its Linear Relationships With %PredVO_2, %PredHR, %Pred$C_{av}O_2$, and %PredSV



%PredO_2P has positive correlations with %Pred$C_{av}O_2$, %PredSV, and %PredVO_2 and a negative correlation with %PredHR. Least square regressions were performed for %PredO_2P and the respective %Pred counterparts. The strength of the linear relationships was assessed via Pearson correlation. %Pred$C_{av}O_2$ = percent predicted peak arterio-mixed venous oxygen content difference; %PredHR = percent predicted peak heart rate; %PredO_2P = percent predicted peak oxygen pulse (O_2P); %PredSV = percent predicted peak stroke volume; %PredVO_2 = percent predicted peak oxygen uptake.

SURVIVAL OUTCOMES. The median follow-up time for the 154 patients was 5.6 years (IQR: 3.0-7.8 years) with 15% (n = 23) mortality. There was improved survival with increasing tertiles of %PredO_2P (**Figure 4**) (log-rank trend P = 0.0455). Cox proportional hazard modeling was performed with the restriction of having at most 2 to 3 covariates in order to maintain standard statistical etiquette.[28] Univariable analysis is presented in **Table 4**. When adjusted for age and BMI, there was a 5% reduction in risk of mortality (HR: 0.95, 95% CI: 0.92-0.98, P = 0.003) (**Table 5**) for every percent increase in %PredO_2P. For comparison, %PredO_2P performed as well if not better than traditional CPET prognostic markers such as peak VO_2 and VE/VCO_2 (Supplemental Table 4) and was an independent marker of all-cause mortality when adjusted for VE/VCO_2 slope and age or peak VO_2 and age (model 1 and model 2, respectively) (Supplemental Table 4).

DISCUSSION

In HFpEF patients, higher %PredO_2P correlated with higher maximal aerobic capacity, greater %PredSV

TABLE 3 Ventricular-Vascular Response Across Percent Predicted Peak O_2P Tertiles

	Cohort	Tertile 1	Tertile 2	Tertile 3	*P* Value
PCWP/CO (mm Hg*min/L)	3.0 (0.1)	3.5 (0.3)	2.9 (0.2)[a]	2.8 (0.3)[a]	**0.004**
PAP/CO (mm Hg*min/L)	3.8 (0.2)	4.5 (0.3)	3.6 (0.2)[a]	3.3 (0.2)[a]	**0.001**
Rest Ea (mm Hg/mL)	2.3 (0.1)	2.5 (0.1)	2.3 (0.1)	2.2 (0.1)	0.014
Peak Ea (mm Hg/mL)	2.2 (0.1)	2.6 (0.1)	2.1 (0.1)	1.9 (0.1)[ab]	**<0.001**
PrPP	0.52 (0.004)	0.53 (0.006)	0.53 (0.008)	0.51 (0.006)[a]	**<0.001**

Values are in mean (SEM) or median (IQR). Trend *P* values of an extended Wilcoxon rank-sum test above. Subgroup comparison *P* values of student t-test or Mann-Whitney U test when appropriate. Values in **bold** indicate statistically significant after adjusting for multiple comparisons. [a]$P < 0.0167$ vs tertile 1, Bonferroni adjusted. [b]$P < 0.0167$ vs tertile 2, Bonferroni adjusted.

Ea = effective arterial elastance; PAP/CO = linear slope of pulmonary arterial pressure and cardiac output; PCWP/CO = linear slope of pulmonary capillary wedge pressure and cardiac output; PrPP = proportionate pulse pressure (at peak exercise).

FIGURE 3 Correlations and Violin Plots of Ventricular-Vascular Response With %PredO$_2$P

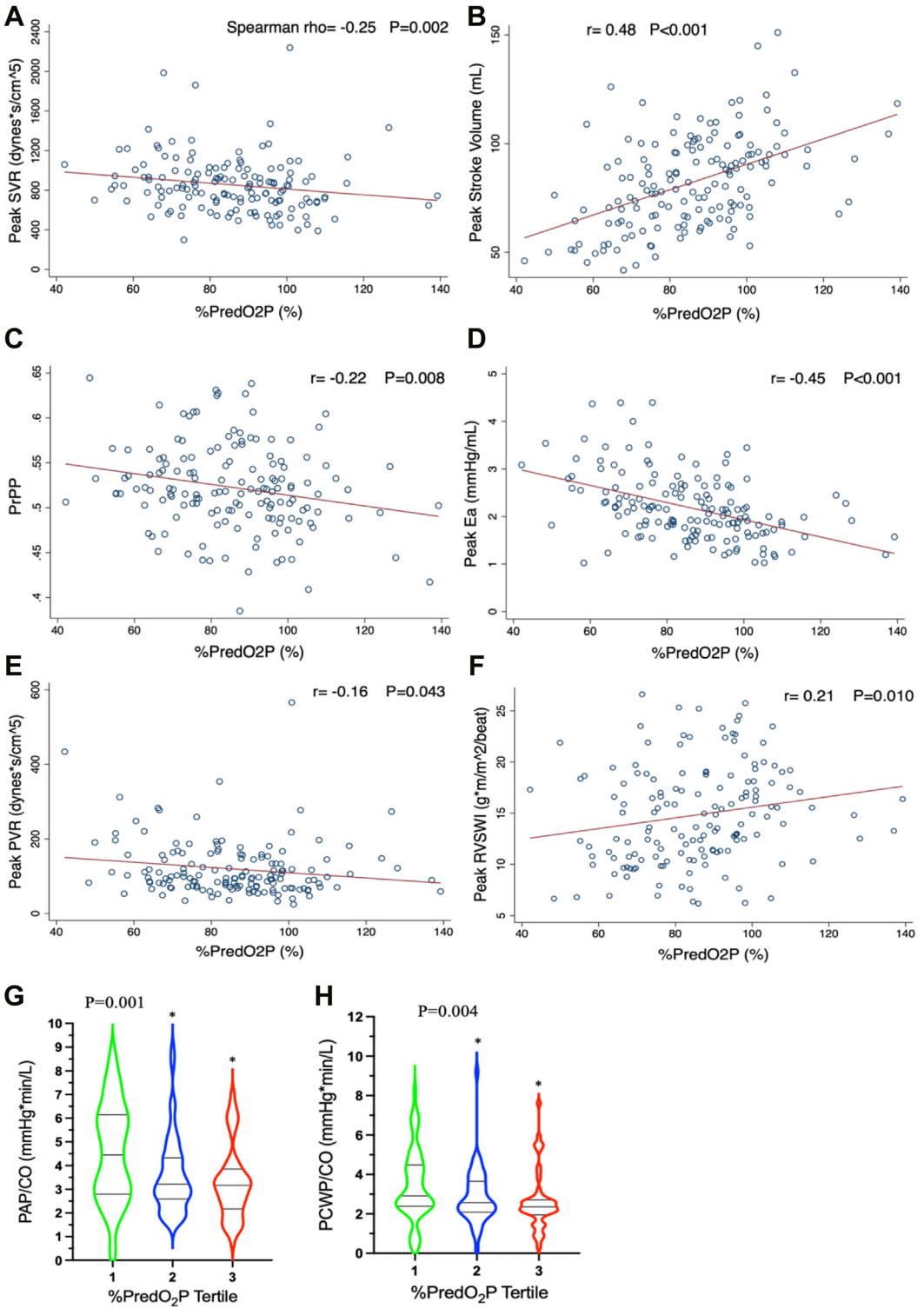


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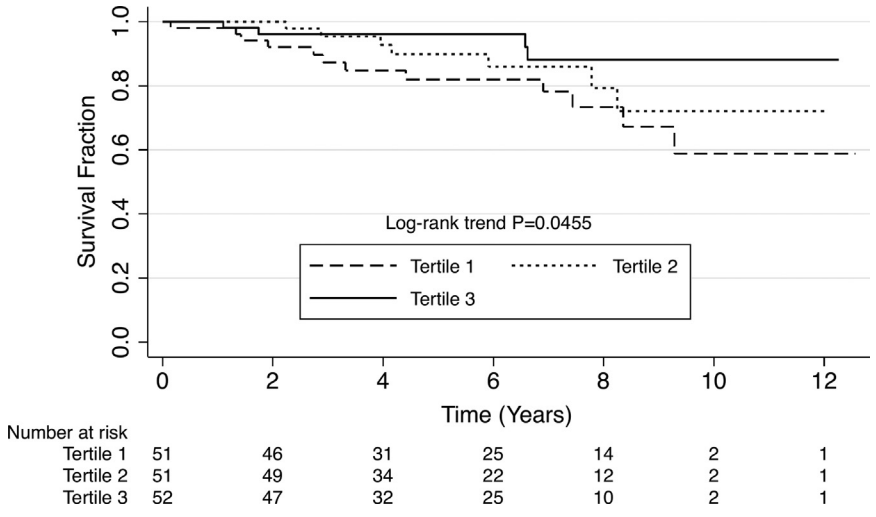
FIGURE 4 Kaplan-Meier Survival Outcomes Demonstrate Improved Survival Across Ascending %PredO$_2$P Tertiles



There was improved survival with increasing tertiles of %PredO$_2$P with a median follow-up of 5.6 years (IQR: 3.0-7.8 years). Log-rank trend $P = 0.0455$.

and %PredC$_{av}$O$_2$, and lower %PredHR. Those with lower %PredO$_2$P exhibited worse VVR (higher PAP/CO, PCWP/CO, Ea, PrPP, peak SVR, and lower peak SV). %PredO$_2$P was an independent predictor of all-cause mortality in HFpEF and those with higher %PredO$_2$P had higher survival (**Central Illustration**).

Ventricular-vascular coupling is a critical determinant of peak exercise capacity. Chen et al[15] showed evidence of ventricular-vascular decoupling in elderly patients. Borlaug et al[8] and Kawaguchi et al[13] carried that finding forward in HFpEF patients with the leading theory that a stiffer vasculature associates with a dampened stroke volume response to exercise. Lower exercise capacity in HFpEF associates with ventricular-vascular decoupling, a hallmark mechanism of diastolic dysfunction.[29,30] We observed a correlation of lower %PredO$_2$P with worse ventricular-vascular decoupling. Lower stroke volume response is correlated with a higher afterload in the systemic (higher SVR) and pulmonary (higher PVR) vascular systems—we see this with a correlation of lower peak SV and a trend of lower peak RVSWI in those with lower %PredO$_2$P. Furthermore, those with lower %PredO$_2$P had evidence of abnormal hemodynamic response to exercise with higher PrPP, PAP/CO and PCWP/CO (**Figure 3**). Previous studies have shown associations of lower stroke volume augmentation during exercise in HFpEF patients compared to normal or hypertensive controls.[31,32] Within our HFpEF population, we see a correlation of lower %PredO$_2$P with lower %PredSV (**Figure 2**). HFpEF patients have worse arterial stiffening compared to their

FIGURE 3 Continued

Patients with higher %PredO$_2$P correlated with improved left-sided and right-sided ventricular vascular response with exercise. %PredO$_2$P correlated with higher left ventricular stroke volume response (Peak SV), lower systemic vascular resistance (Peak SVR), and a more compliant vasculature (PrPP, PAP/CO, PCWP/CO) with exercise. There was a trend of higher right ventricular stroke volume response (peak RVSWI) and lower pulmonary vascular resistance (peak PVR) that was not statistically significant after Bonferroni correction. Violin plots with first quartile, median and third quartile shown via horizontal black lines in ascending order. (A) Spearman rank correlation of peak SVR vs %PredO$_2$P. (B) Peak stroke volume vs %PredO$_2$P. (C) PrPP vs %PredO$_2$P. (D) Peak Ea vs %PredO$_2$P. (E) Peak PVR vs %PredO$_2$P. (F) Peak RVSWI vs %PredO$_2$P. (G) PAP/CO across %PredO$_2$P tertiles. (H) PCWP/CO across %PredO$_2$P tertiles. *P*-values of Spearman rank-order correlation, Pearson correlation, or an extended Wilcoxon rank-sum test as appropriate. *$P < 0.0167$ vs tertile 1, Bonferroni adjusted. %PredO$_2$P = percent predicted peak oxygen pulse; CO = cardiac output; Ea = effective arterial elastance; PAP = pulmonary arterial pressure; PCWP = pulmonary capillary wedge pressure; PrPP = proportionate pulse pressure (at peak exercise); PVR = pulmonic vascular resistance; RVSWI = right ventricular systolic work index; SVR = systemic vascular resistance.

TABLE 4 Univariable Cox Proportional Hazards Regression Analysis for Mortality

	HR (95% CI)	*P* Value
Age	1.05 (1.02-1.08)	**0.001**
Sex	0.66 (0.29-1.52)	0.337
BMI	0.98 (0.92-1.04)	0.495
%PredO$_2$P	0.97 (0.95-0.99)	0.032
Peak VO$_2$	0.998 (0.997-0.999)	**0.004**
VE/VCO$_2$ slope	1.05 (1.01-1.08)	0.011

Values in **bold** indicate statistically significant after adjusting for multiple comparisons.
%PredO$_2$P = percent predicted peak oxygen pulse; BMI = body mass index; VE/VCO$_2$ = minute ventilation/carbon dioxide production slope; VO$_2$ = oxygen uptake.

TABLE 5 Multivariable Cox Proportional Hazards Regression Model Including %PredO$_2$P for Mortality

	HR (95% CI)	*P* Value
Age	1.06 (1.03-1.11)	**<0.001**
BMI	1.01 (0.94-1.09)	0.726
%PredO$_2$P	0.95 (0.92-0.98)	**0.003**

Values in **bold** indicate statistically significant after adjusting for multiple comparisons. Model includes covariates of age, BMI and %PredO$_2$P.
%PredO$_2$P = percent predicted peak oxygen pulse; BMI = body mass index.

hypertensive counterparts[33] and in particular arterial stiffening associate with higher exercise PCWP/CO.[34] When compared to healthy controls, HFpEF patients had a higher SVR response during exercise.[35] Here we show that in HFpEF patients, lower %PredO$_2$P is correlated with higher peak SVR.

Exercise capacity in HFpEF patients is in part limited by peripheral oxygen utilization,[2,36] and this finding is supported in our study. The highest %PredO$_2$P tertile is associated with higher tissue oxygen utilization. There is a positive correlation between %PredO$_2$P and %PredC$_{av}$O$_2$ (**Figure 2**) and between %PredO$_2$P and peak C$_{av}$O$_2$ (Supplemental Table 2), reaffirming the significance of peripheral oxygen utilization in HFpEF patients.[2]

Finally, the heart rate response plays a role in exercise capacity. HFpEF patients have reduced heart rate response compared to normal subjects.[7,8] Within HFpEF itself, the heart rate response to exercise especially in patients not on atrioventricular nodal blocking agents has not been thoroughly examined. Here we show that the heart rate response does not differ among the %PredO$_2$P tertiles. The lower %PredO$_2$P patients did not exhibit chronotropic incompetence during exercise.

Our findings support the robust correlation of %PredO$_2$P and %PredSV. Our sensitivity and specificity analysis underscores the stratification ability of %PredO$_2$P as a noninvasive marker for %PredSV, an invasive measurement.

Oliveira et al[10] showed the prognostic abilities of the synergistic use of peak VO$_2$ and %PredO$_2$P in heart failure patients. As for survival outcomes, our cohort was relatively healthy in that total mortality was low (15%, n = 23, with a median follow up time of 5.6 years) and the mean %PredVO$_2$ was greater than 50%.[12] When we compare this to the HFpEF population of Lam et al (mortality of 14% at the 2-year follow-up), the survival difference likely stems from differences in age (57 vs 72 years, respectively). In light of the younger and healthier population, we were still able to see a significant difference in survival among the %PredO$_2$P tertiles (**Figure 4**). In unadjusted Cox proportionality hazard modeling, for every percent increase in %PredO$_2$P there was a trend toward a 3% decrease in risk of mortality ($P = 0.032$) (**Table 4**) that was not significant after adjusting for multiple comparisons. Of note, Laukkanen et al[37] showed a higher relative risk of mortality in HFpEF patients with higher BMI despite similar peak O$_2$P. Indeed, when we adjusted for age and BMI in our model, %PredO$_2$P served as an independent marker of survival in HFpEF with every percent increase in %PredO$_2$P having a 5% reduction in risk of mortality ($P = 0.003$) (**Table 5**).

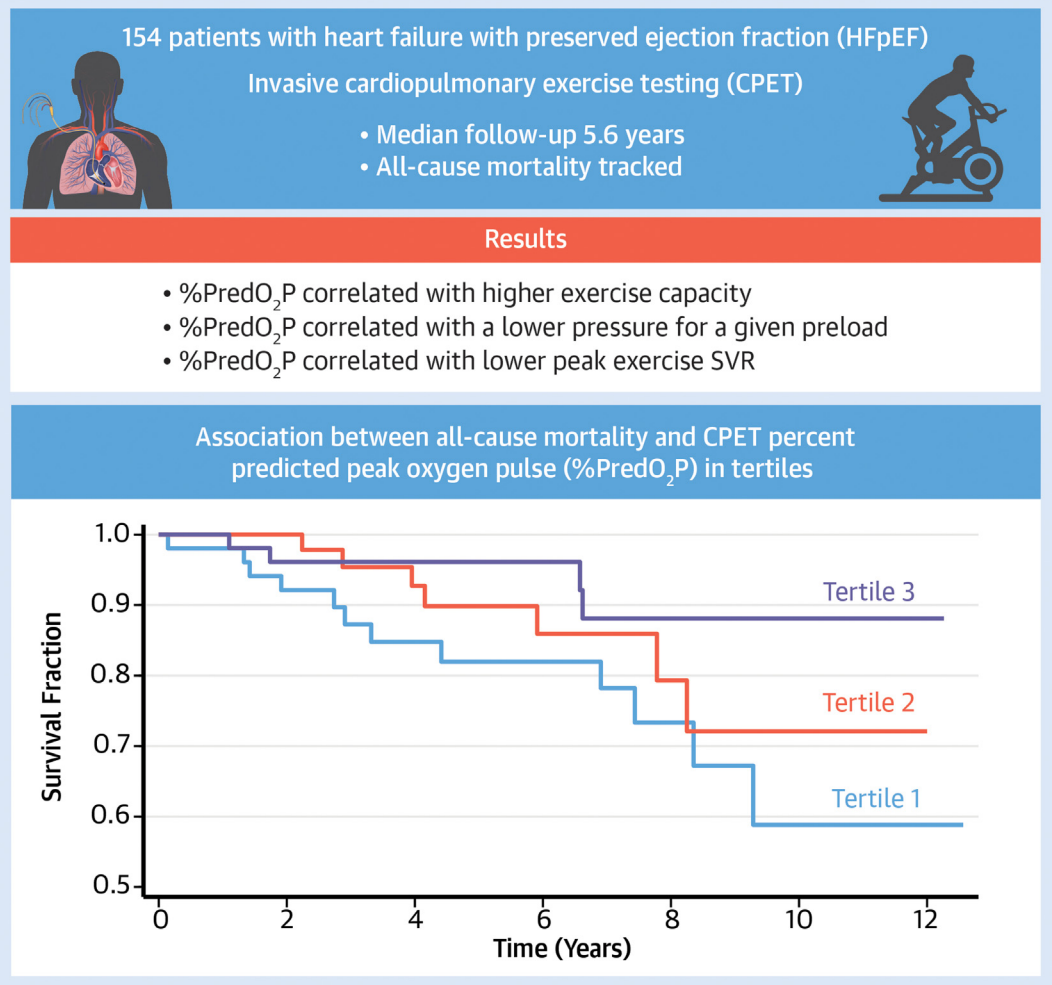
The ventricular-vascular decoupling pathophysiology of HFpEF is an avenue with potential therapies. Already there have been fruitful albeit smaller randomized studies. When HFpEF patients with elevated PVR were treated with albuterol their PVR decreased with improved cardiac output and pulmonary-ventricular coupling.[38] Inhaled sodium nitrite has been shown to decrease the rise in PCWP at peak exercise and overall decrease the resting PCWP.[39] %PredO$_2$P can potentially serve as a ventricular-vascular marker to stratify and to assess efficacy of therapeutic targets in HFpEF patients.

CONCLUSIONS

In our HFpEF cohort, higher %PredO$_2$P associates with higher maximal aerobic capacity, and %PredO$_2$P is a VVR marker that can stratify invasive parameters such as %PredSV. %PredO2P is an independent prognostic marker for all-cause mortality and those with higher %PredO$_2$P associated with higher survival.

STUDY LIMITATIONS. This study is a retrospective assessment of a prospectively enrolled cohort and based on a small number of patients, albeit with extensive physiologic phenotyping, and a relatively

CENTRAL ILLUSTRATION **CPET %PredO$_2$P: Association With Ventricular-Vascular Response and Survival in HFpEF**



Li JP, et al. JACC Adv. 2024;3(8):101101.

Created using a combination of Microsoft PowerPoint and BioRender. %PredC$_{av}$O$_2$ = percent predicted peak arterio-mixed venous oxygen content difference; %PredO$_2$P = percent predicted peak oxygen pulse; %PredSV = percent predicted peak stroke volume; C$_{av}$O$_2$ = arterio-mixed venous oxygen content difference; Ea = effective arterial elastance; HFpEF = heart failure with preserved ejection fraction; PAP/CO = linear slope of pulmonary arterial pressure and cardiac output; PCWP/CO = linear slope of pulmonary capillary wedge pressure and cardiac output; PrPP = proportionate pulse pressure (at peak exercise); PVR = pulmonary vascular resistance; SV = stroke volume; SVR = systemic vascular resistance; VVR = ventricular-vascular response.

small number of clinical endpoints. Because this study included patients not taking any atrioventricular nodal blocking agents, which is ideal for studying oxygen pulse because of its reliance on heart rate changes, the generalizability of the model may be limited in the general HFpEF population who are sometimes placed on atrioventricular nodal blocking agents. We acknowledge this is a proof-of-concept study.

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ADDRESS FOR CORRESPONDENCE: Dr Jason P. Li, University of Washington School of Medicine, 1959 NE Pacific Street, Box 356422, Seattle, Washington 98195-6422, USA. E-mail: jpli89@uw.edu.

PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: The synergistic dysfunction of the ventricles and arteries plays a role in HFpEF pathophysiology. Traditional measures of vascular resistance such as SVR and PVR and ventricular-vascular coupling terms such as PAP/CO are invasive and even Ea while can be obtained noninvasively remains difficult to measure. Oxygen pulse has long been thought of as a substitute for stroke volume.

TRANSLATIONAL OUTLOOK: %PredO_2P serves as a routinely measured, noninvasive ventricular-vascular marker that can potentially stratify and assess efficacy of therapeutic targets in HFpEF patients. %PredO_2P serves as an independent prognostic factor on survival in HFpEF.

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KEY WORDS CPET, HFpEF, peak oxygen pulse, ventricular-vascular response

APPENDIX For supplemental tables and figures, please see the online version of this paper.