ORIGINAL RESEARCH

Hemodynamic Profile of Patients With Heart Failure and Preserved Ejection Fraction Vary by Age

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***Background*—**Patients with heart failure with preserved ejection fraction (HFpEF) exhibit a range of cardiovascular phenotypic profiles modified by several common comorbidities. In particular, patients with HFpEF tend to be older; however, it is unclear whether the effects of cardiovascular aging per se modify the expression of HFpEF. We therefore sought to investigate the interaction between age and physiologic profile in patients with HFpEF.

***Methods and Results*—**We assessed the hemodynamic and metabolic profile of 40 patients with HFpEF. Patients underwent right heart catheterization at rest and during supine cycle ergometry, and were segregated into 2 groups by the median age of the cohort. Older patients with HFpEF demonstrated reduced resting cardiac output (4.8±1.2 L/min versus 5.7±1.1 L/min). With exercise, older patients demonstrated a marked rise in arteriovenous oxygen content difference (10.8±1.8 versus 7.9±2.4 mL, $P \leq 0.001$), driven by enhanced oxygen extraction. There was no significant difference in peak pulmonary capillary wedge pressure (30±7 mm Hg versus 27±6, $P=0.135$), including when indexed to workload (pulmonary capillary wedge pressure/W, 0.88 mm Hg/W versus 0.92; $P=0.83$).

***Conclusions*—**Older patients with HFpEF display a different physiological phenotype compared with younger patients, with enhanced oxygen extraction and lower increment in cardiac output to increase oxygen consumption from rest to peak supine exercise. This finding highlights the importance in considering age when considering therapeutic options in patients with HFpEF. **(*J Am Heart Assoc*. 2017;6:e005434. DOI: 10.1161/JAHA.116.005434.)**

Key Words: aging • geriatrics • heart failure with preserved ejection fraction • hemodynamics • oxygen extraction

Heart failure with preserved ejection fraction (HFpEF) contributes to half of all cases of heart failure. Patients with HFpEF are typically older, hypertensive, and female,[1] and share multiple comorbidities including obesity, renal dysfunction, and diabetes mellitus.[2] As the population continues to age, the prevalence of HFpEF is expected to rise and become the dominant form of heart failure.[3] Although the pathophysiology of HFpEF is complex, diastolic dysfunction is considered to be a key contributing abnormality. Epidemiologic studies confirm that there is a substantial conversion from asymptomatic diastolic dysfunction to overt heart failure.[4,5]

As the physiology of HFpEF is incrementally understood, it has become evident that considerable phenotypic variation exists.[6,7] Exercise intolerance in patients with HFpEF is the result of central hemodynamic and peripheral mechanisms; however, the influence of age is not certain. While it is known that aging may influence diastolic relaxation[8] and passive myocardial stiffness together with effects on peripheral arterial endothelial and skeletal muscle function.[9,10] the precise impact of aging on HFpEF physiology is not well known. Therefore, the present study sought to identify the dominant limitation to exercise across the spectrum of age in patients with HFpEF.

Methods and Results

Forty patients undergoing detailed hemodynamic evaluation for HFpEF contributed to the study. Patients enrolled in previous studies assessing exercise hemodynamics in HFpEF

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Clinical Perspective

What Is New?

- Heart failure with preserved ejection fraction accounts for half of all cases of heart failure and predominantly occurs in the older population.
- There is significant heterogeneity in patients with heart failure with preserved ejection fraction.
- This exercise hemodynamic study demonstrates that older patients with heart failure with preserved ejection fraction have a different physiological phenotype compared with younger patients.

What Are the Clinical Implications?

- Understanding subtypes of heart failure with preserved ejection fraction is critical to appropriately targeting therapy.
- The differing physiological limitation to exercise across the spectrum of age may lead to different foci of therapy, such as exercise therapy for the periphery versus pharmacological therapy targeting filling pressures or cardiac output.

who satisfied criteria outlined by the European Society of Cardiology guidelines for the diagnosis of HFpEF[11] were included. Study protocols were approved by human research ethics committee of The Alfred Hospital and informed written consent was obtained from all participants.

Catheterization and Exercise Protocol

Following informed consent, patients underwent standard right heart catheterization using a 7F sheath from the brachial or jugular venous approach. A 3F arterial sheath was inserted into the radial artery for arterial blood sampling. No medication changes were made before catheterization and tests were performed in the unfasted state. At rest, end-expiratory measurements were taken from the right atrium, right ventricle, pulmonary artery, and pulmonary capillary wedge position. Symptom-limited (leg fatigue and/or dyspnea) exercise was performed using supine cycle ergometry at a cadence of 60 revolutions per minute, with a graded increase in resistance every 3 minutes to a maximum of 1.5 W/kg. Repeated hemodynamic measurements were taken at peak exercise from the wedge position and pulmonary artery. During exercise, pressures were recorded at the end of expiration. Mixed venous blood gas samples were taken at rest and at peak exercise from the pulmonary artery following discarding of 5 mL of blood. Arterial blood pressure (BP) was obtained by direct measurement via the radial arterial sheath. Cardiac output (CO) at rest was measured via thermodilution as an average of ≥3 measurements at rest and a single measurement was taken at each stage of exercise and indexed to body surface area (cardiac index). Oxygen consumption (VO_2) was calculated using the Fick equation based on arterial and mixed venous samples at rest and during exercise and hemoglobin and CO at rest and during exercise. Oxygen delivery was calculated as the product of the arterial oxygen content and CO. The oxygen extraction ratio (O_2ER) is the quotient of VO_2 divided by the oxygen delivery, presented as a percentage.

Statistical Analysis

Continuous variables are reported as mean±SD. Between-group differences were compared by Student *t* test. The correlation between age and hemodynamic and metabolic variables was analyzed using the Pearson correlation coefficient. Statistical analysis was performed with SPSS 23 (IBM Corp). Missing data were excluded from analysis (<5% of overall data, from specific subanalyses only).

Patient Characteristics

The mean age of the study cohort was 68 years. To compare the rest and exercise hemodynamic profiles of younger and older patients with HFpEF, the study group was separated by the group median. The younger group (n=21) had a mean age of 62±8 years and the older group (n=19) had a mean age of 75±5 years. The baseline demographics and resting hemodynamics of the study population are presented in Table 1. Body mass index was slightly higher in the younger age group; however, this was not statistically significant (32.1±6.3 versus 29.5±3.8, P=0.14). There were more women within the younger group, but there was no significant difference in mean age between sexes.

Resting Hemodynamics

Resting heart rate, mean pulmonary artery pressure, and mean pulmonary capillary wedge pressure were similar between groups (Table 1). Systolic BP was significantly higher in the older patients while the mean arterial BP was similar between the 2 groups. Cardiac index was significantly lower at baseline in older patients with HFpEF.

Exercise Hemodynamics

Peak power output, VO_2, heart rate, systolic BP, mean pulmonary artery pressure, pulmonary capillary wedge position, and systemic vascular resistance were not significantly different between groups. Peak arterial venous oxygen difference (AVO_2Diff) and O_2ER were significantly higher, while venous O_2 saturation was significantly lower in older compared with younger patients with HFpEF (Table 2).

Table 1. Baseline Demographics

Variable	Group 1 (n=21) Younger	Group 2 (n=19) Older	*P* Value
Median age, y	62±7.5	75±4.6	
Men, %	43%	58%	0.355
Weight, kg	89.7±21.6	83.2±16.8	0.301
BMI, kg/m^2	32.1±6.3	29.5±3.8	0.141
Resting hemodynamics			
HR, beats/min	69.3±14.2	65.7±8.6	0.338
Systolic BP, mm Hg	145±15	157±13	0.012*
Mean PAP, mm Hg	20±6	22±9	0.449
PCWP, mm Hg	12±5	13±5	0.408
Cardiac output, L/min	5.7±1.1	4.8±1.2	0.019*
Cardiac index, L/min per m^2	2.9±0.5	2.5±0.4	0.015*
Indexed stroke volume, mL/m^2	43±10	38±7	0.111
SVR, mm Hg/min per mL^{-1}	17±5	21±6	0.064
LVSWI, g/m^2 per beat	97.7±22.3	87.5±22.7	0.161
Hemoglobin, g/L	129.8±17.9	135.8±15.3	0.970
Mixed venous oxygen saturation, %	72.8±6.8	69.2±6.3	0.096
Arteriovenous oxygen difference, mL	4.5±1.4	5.1±1.0	0.126
VO_2, mL/min	264.0±93.6	245.5±76.6	0.511
VO_2, mL/kg per min	3.13±1.53	3.00±0.89	0.756
Oxygen delivery	1033.1±240.6	857.2±275.1	0.043*
Oxygen extraction ratio, %	25.1±7.4	29.4±6.3	0.065

Continuous variables are presented as mean±SD. **P* value reflects comparative *t* test, with significance defined as <0.05. BMI indicates body mass index; BP, blood pressure; HR, heart rate; LVSWI, left ventricular stroke work index; PAP, pulmonary artery pressure; PCWP, pulmonary capillary wedge pressure; SVR, systemic vascular resistance; VO_2, oxygen consumption.

Table 2. Hemodynamic Parameters With Exercise

Exercise Hemodynamics			
Variable	Group 1 (n=21) Younger	Group 2 (n=19) Older	*P* Value
Peak workload, W	42±28	44±24	0.803
Indexed workload, W/kg	0.46±0.26	0.53±0.28	0.361
Exercise time, min	5.2±3.4	5.2±2.7	0.970
Systolic BP, mm Hg	188±25	196±24	0.316
Heart rate, beats/min	105±20	98±20	0.314
Mean PAP, mm Hg	40±9	42±9	0.427
PCWP, mm Hg	27±6	30±7	0.135
Cardiac output, L/min	10.1±3.3	8.5±3.0	0.127
Cardiac index, L/min per m^2	5.0±1.4	4.4±1.6	0.212
SVR, mm Hg/min per mL^{-1}	13.1±6.1	14.8±5.9	0.360
Mixed venous oxygen saturation, %	53.3±12.0	38.8±9.6	<0.001*
Hemoglobin, g/L	135.8±15.3	133.8±13.8	0.689
Arterial oxygen saturation, %	96.4±2.8	96.1±2.6	0.73
Arteriovenous oxygen difference	7.9±2.4	10.8±1.8	<0.001*
VO_2, mL/min	824.4±356.0	929.6±394.4	0.399
VO_2, mL/kg per min	9.1±3.4	11.3±5.4	0.139
Oxygen delivery	1849.0±662.9	1628.7±707.3	0.329
Oxygen extraction ratio, %	44±12.1%	60.3±9.1%	<0.001*

Continuous variables are presented as mean±SD. **P* value comparative *t* test with significance defined as <0.05. BP indicates blood pressure; PAP, pulmonary artery pressure; PCWP, pulmonary capillary wedge pressure; SVR, systemic vascular resistance; VO_2, oxygen consumption.

The results of Pearson correlation between age and hemodynamic and metabolic variables are shown in Table 3. There was a modest relationship with decreasing body mass index (r=0.39, P=0.01). At rest, systolic BP, systemic vascular resistance, AVO_2Diff, and O_2ER were all positively correlated, while there was an inverse association with CO. With exercise, there was an increase in mean exercise pulmonary capillary wedge position with increasing age (r=0.35, P=0.03), with a stronger relationship with AVO_2Diff (r=0.44, P=0.006) and O_2ER (r=0.48, P=0.002). There was no significant correlation with CO (r=−0.25, P=0.12).

The major new finding of this study is that the determinants of physical limitation in patients with HFpEF differ according to age. This finding has important implications for the development of targeted therapies. Specifically, while younger and older patients with HFpEF increased their VO_2 to similar degrees during exertion, the physiologic determinants were different across the groups. In particular, older patients with HFpEF were reliant upon O_2ER to a greater degree.

Adequate delivery of oxygen to the active muscles is essential for aerobic activity. Convective O_2 delivery is dependent on multiple factors, including adequate pulmonary oxygenation, normal oxygen-carrying capacity, hemoglobin, and CO.[12] Peripheral O_2 extraction is directly proportionate to delivery and inversely related to muscle blood flow.[13,14] Moreover, abnormal skeletal morphology (decreased oxidative muscle fibers, capillarity[15] oxidative metabolism,[16] and mitochondrial function[17]) may also play an important role in

Table 3. Bivariate Correlation With Age

Correlation		
Variable	Correlation	Significance
Weight, kg	−0.37	0.02*
BMI, kg/m^2	−0.39	0.01*
Resting		
Systolic BP, mm Hg	0.38	0.02*
Cardiac output, L/min	−0.50	0.001*
SVR, mm Hg/min per mL^{-1}	0.36	0.022*
Mixed venous O_2 saturation, %	−0.39	0.02*
Arteriovenous oxygen difference	0.40	0.013*
O_2 delivery	−0.48	0.002*
O_2 extraction ratio, %	0.42	0.009*
Exercise		
Exercise duration, min	0.07	0.66
Mean PAP, mm Hg	0.30	0.063
Mean PCWP, mm Hg	0.35	0.03*
Cardiac output, L/min	−0.25	0.12
SVR, mm Hg/min per mL^{-1}	0.18	0.269
Mixed venous O_2 saturation, %	−0.46	0.004*
Arteriovenous oxygen difference	0.44	0.006*
Oxygen extraction ratio, %	0.484	0.002*

Statistical significance was determined at *P<0.05. BMI indicates; BP, blood pressure; O_2, oxygen; PAP, pulmonary artery pressure; PCWP, pulmonary capillary wedge pressure; SVR, systemic vascular resistance.

limiting exercise tolerance. Abnormalities in each of these parameters have been seen in patients with HFpEF compared with healthy controls; however, the ability to modulate these parameters, through blood flow redistribution, skeletal muscle vasodilation, and microvascular control mechanisms may vary across age groups to attain the same VO_2 during peak exercise.

Haykowsky et al[18] reported that AVO_2Diff reserve (peak exercise minus rest) was the strongest independent predictor of peak VO_2 during upright exercise in older patients (mean age 69 years) with HFpEF and age-matched healthy controls. Bhella and colleagues[16] found that the lower VO_2 during peak treadmill exercise in older patients with HFpEF compared with age-matched healthy controls was primarily the result of a significantly lower AVO_2Diff, as peak CO (and cardiac index) were not significantly different between groups. Finally, Dhakal and colleagues[19] demonstrated that peak AVO_2Diff and peak heart rate were the leading predictors of peak VO_2 using invasive hemodynamics and cardiopulmonary exercise testing. In 104 patients with HFpEF (mean age 63±12), peak AVO_2Diff was lower in HFpEF compared with heart failure with reduced ejection fraction and was a primary predictor of peak VO_2. In 40% of patients, impaired peripheral extraction was the predominant limiting factor to exercise capacity.

We confirm and extend these findings by demonstrating that the increased VO_2 from rest to peak supine exercise in older patients (mean age 75 years) with HFpEF is caused by increased oxygen delivery and concomitant increase in O_2ER (decreased mixed venous O_2 saturation). The mechanisms responsible for the increased O_2ER were not examined in this study; however, they may be caused by a greater transit time for O_2 to be extracted by the active muscles as a result of a lower CO (and muscle blood flow) compared with younger patients with HFpEF. The ability to augment CO did not differ between groups, which may suggest that VO_2 is dependent on factors not dependent on flow, such as muscle wasting. That DO_2 was 40% higher in older compared with younger patients with HFpEF may suggest differences in capillarity, and diffusion distance may differ between groups, although we cannot definitively prove these findings.[20]

Studies have identified a range of abnormalities in parameters of both central cardiovascular performance and peripherally in relation to vascular and skeletal muscle structure and function. Central hemodynamic limitations include impaired diastolic function, chronotropic incompetence, abnormal right ventricular-pulmonary artery coupling,[21] and vasodilator reserve. Age is a powerful nonmodifiable risk factor for the development of HFpEF and plays a fundamental role in passive and active relaxation properties. Aging is associated with myocardial fibrosis, transforming growth factor-β activation, myocardial stiffness through hypophosphorylation of titin, and impaired calcium signaling.[8] Population-based studies demonstrate that age is a significant predictive factor of the development of diastolic dysfunction, even in individuals without apparent cardiovascular disease. Similarly, age was predictive of the development of incident heart failure.[5,22] These changes with increasing age may reduce CO, particularly with exertion, and compensatory mechanisms develop to enhance oxygen extraction to maintain the same VO_2. Indeed, we found that AVO_2Diff was positively related (r=0.44, P=0.006) and mixed venous O_2 saturation was inversely related to age in patients with HFpEF.

Previous studies have examined CO response to exercise in patients with HFpEF. Currently, only one invasive study has measured AVO_2Diff during maximal exercise with a similar power output to our study (40 W) in older patients with HFpEF (mean age 67 years). Abudiab et al[23] performed symptom-limited exercise hemodynamic assessment in 109 patients with HFpEF compared with controls, and determined that CO reserve limitation was the primary limitation to exercise; however, AVO_2Diff indexed to VO_2 was higher in patients with HFpEF, again supporting peripheral adaptation to the impairment in oxygen delivery. Notably, the peak AVO_2Diff of the patients with HFpEF and controls were not significantly

different (9.9 and 10.1 mL/dL, respectively), similar to the value we found in our older patients with HFpEF. Moreover, our rest-to-peak exercise change in AVO_2Diff (5.7 mL/dL) is similar to that reported by Abudiab et al (5.2 mL/dL).

The failure of previous trials of therapy in HFpEF to produce positive results has been attributed to the heterogeneity of the population and as such phenotypic classification has been developed to target therapy more effectively.[6] Such models have included variables such as hypertension, obesity, coronary artery disease, and renal dysfunction. Shah et al[24] prospectively analyzed 397 patients with HFpEF for phenotype classification using clinical characteristics, natriuretic peptide values, and echocardiographic data. Using cluster analysis, 3 groups were identified, with the oldest group at highest risk for adverse outcomes, with the highest pulmonary pressures (both mean pulmonary artery pressure and pulmonary capillary wedge position) and worst right ventricular function. This novel study did not include exercise hemodynamics, however, and no physiological parameters of oxygen extraction were assessed. Including these parameters may lead to an improved understanding of the physiologic separation between these subtypes, or identify new phenotypes, permitting the use of targeted therapy. Importantly, the study highlights the concept that HFpEF describes a collection of disease pathologies culminating in the syndrome of heart failure, and careful dissection of the various contributing components is critical to offering the appropriate therapy. Exercise testing may be useful to phenotype the predominant limitation to exercise to guide future trials and treatment. Given that older individuals have reduced muscle mass, coupled with the finding that resistance can increase muscle mass and capillarity,[25] we believe that older patients with HFpEF may benefit from resistance training. Consistent with this finding, Pu et al[26] found that resistance training increases aerobic endurance, type I (oxidative) myosin heavy chain, and citrate synthase activity in older patients (77 years) with heart failure with reduced ejection fraction. In this study, we demonstrate that across age groups, exercise testing in patients with HFpEF demonstrates different mechanisms to attain the same VO_2. Future therapies will need to take into account age and exercise hemodynamic parameters to target therapy appropriately.

Strengths and Limitations

This study differs from previous trials in several ways. First, VO_2 was calculated rather than using expired gas analysis. Second, the analysis was performed between patients with HFpEF, rather than comparing physiology with that of healthy controls. Objective quantification of physiologic peak using peak respiratory exchange ratio or lactate was not recorded, and patients exercised to symptom-limited maximum. The small group sizes increase the chance of type II error, and larger group sizes may yield a difference in CO. Echocardiographic data during rest and exercise were not available for all participants, and, as such, accurate quantification of left ventricular end-diastolic volume through direct visualization and echocardiographic parameters of diastolic dysfunction such as E/e′ were not available. Similarly, left ventricular wall thickness and left ventricular mass were not recorded at the time of cardiac catheterization. As a retrospective study, further delineation of the relative contributions to exercise of both CO and peripheral oxygen extraction could not be performed, and although workload matching was not part of the initial protocol, all groups performed a similar level of exercise. Notably, the youngest cohort of patients attained a lower peak VO_2, perhaps limited by volitional exhaustion, although this could not be analyzed retrospectively. Finally, the study did not directly assess peripheral blood flow or arterial endothelial dysfunction, which have been implicated in the pathogenesis of HFpEF[13,27] and may be responsible for the impaired peripheral reserve in younger patients.

Conclusions

With increasing age, patients with HFpEF demonstrate evidence of enhanced peripheral oxygen extraction. Older patients improve arteriovenous oxygen difference through enhanced peripheral oxygen extraction to maintain equivalent peak VO_2 to younger patients. This study highlights the difference in central versus peripheral factors across the spectrum of age in patients with HFpEF.

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Disclosures

None.

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