Clinical Investigation

Pulmonary Arterial Wedge Pressure at Rest and During Exercise in Healthy Adults: A Systematic Review and Meta-analysis

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ABSTRACT

Background: The pulmonary arterial wedge pressure (PAWP) response to exercise may unmask latent heart failure with preserved ejection fraction. There remains a lack of consensus over threshold values for PAWP during exercise. A systematic review of studies examining PAWP by means of right heart catheterization at rest and during exercise in healthy individuals was performed.

Methods and Results: Relevant data derived from healthy volunteers were stratified by age (older than 40 years vs 40 years or younger) and sex. Three exercise intensities were predefined: light, moderate, and strenuous. Weighted means and weighted 95% confidence intervals (CIs) for the aggregate data were calculated. A total of 424 individuals from 32 unique studies were included, of which 19% (n = 82) were female. PAWP reached weighted mean and 95% CI values of 19 (17−21) and 17 (16−18) mm Hg at light and moderate exercise, respectively. The PAWP response to exercise was similar between men and women >40 years of age. However, exercise intensities were lower in women.

Conclusions: PAWP increases during exercise, reaching up to 20 mm Hg in adults >40 years of age. Older women achieve PAWP values similar to those of older men, but at lower intensities. Findings support a threshold of at least 25 mm Hg as an absolute cutoff value for "normal" PAWP response to exercise in individuals >40 years old. (*J Cardiac Fail 2019;25:114−122*)

Key Words: Hemodynamics, pulmonary artery wedge pressure, pulmonary pressure, exercise, healthy, right heart catheterization.

Heart failure with preserved ejection fraction (HFpEF) is considered to be in the differential diagnosis of older adults presenting with exertional dyspnea.[1] The spectrum of HFpEF includes patients with minimal evidence of congestion and signs and symptoms that can overlap with other cardiac and noncardiac conditions.[1] Increasingly, exercise during right heart catheterization (RHC) is used as a clinical maneuver to unmask evidence of LV diastolic impairment that may explain symptoms of dyspnea.[1−6] An "exaggerated" pulmonary arterial wedge pressure (PAWP) response in relation to exercise-associated increases in cardiac output (CO) is of interest as a measure that may indicate the presence of HFpEF pathophysiology.[1]

Current guidelines support the potential clinical utility of invasive exercise hemodynamics for diagnosis of HFpEF, but without fully endorsing this practice as a recommendation. An important limitation is the relative paucity of data from healthy subjects from which to select an appropriate reference range.[6] Age and female sex may be important considerations[7,8] because it is well understood that both factors are associated with progressive left ventricular (LV) stiffening,[9] a process that likely predisposes to the development of HFpEF. Diagnostic thresholds should allow adequate discrimination of abnormal responses from those of healthy older men and women.

The published experience including RHC during exercise in healthy individuals dates back to the 1940s. Despite this

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long history, it is unclear whether existing knowledge is directly relevant to the older, sedentary, predominantly female population most likely to be referred for exercise hemodynamics testing currently. Therefore, our purpose here was to systematically review the characteristics of inclusion cohorts and methodologies for exercise interventions from studies reporting PAWP data during exercise in healthy volunteers. We further aimed to refine the quantitative description of the PAWP response to exercise by calculating weighted means and 95% confidence intervals (CIs), particularly in healthy older men and women over the age of 40 years.

Methods

Search Strategy and Data Sources

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Review and Meta-analysis (PRISMA) guidelines and was registered on PROSPERO (registration no. 42017070702). Peer-reviewed publications evaluating hemodynamics during rest and exercise in healthy volunteers were identified from comprehensive literature searches of Pubmed/Medline and Embase databases from database inception to June 2017. A secondary search of reference lists of key studies and reviews was also conducted. Examples of key word headings used were "pulmonary arterial pressure and exercise," "pulmonary wedge pressure and exercise," "right heart catheterization and exercise," "right heart catheter and exercise," "pulmonary arterial pressure and exercise and healthy," "pulmonary wedge pressure and exercise and healthy," "right heart catheterization and exercise and healthy," and "right heart catheter and exercise and healthy." The search was restricted to publications available in English.

Study Selection: Inclusion and Exclusion Criteria

Two reviewers (D.G. and L.A.) independently undertook the systematic search of the key words and identified eligible studies, verified independently by a third reviewer (S.E.). Any discrepancy was resolved by consensus of 2 senior reviewers (S.E. and S.M.). Studies were included in the review based on the following criteria: 1) original prospective investigations; 2) hemodynamics measured by RHC; 3) sample population consisting of men or women defined as "healthy" if the methods indicated that subjects were asymptomatic, recruited from their local communities to participate on a voluntary basis, and screened to exclude chronic or acute medical conditions; and 4) use of dynamic aerobic exercise modalities, including treadmill or cycle ergometry, and including symptom-limited peak exercise and 1- or multistage steady-state submaximal exercise. Studies were excluded based on the following criteria: 1) meta-analyses, systematic reviews, editorials, comments, case reports, conference abstracts, and dissertations; 2) the sample population was labeled "normal" but consisted of patients with medical conditions or referred for diagnostic RHC for evaluation of cardiovascular symptoms, such as dyspnea or chest pain; 3) exercise performed at high altitude or under hypoxic conditions (the study was retained in the analysis if data from sea level or at normal oxygen tension were reported separately); 4) exercise protocols including upper body, 1-legged, water, handgrip, extension, and isometric exercise; and 5) studies reporting duplicate cohorts (from which a single publication was selected based on the most relevant data pertaining to objectives of this study).

Full-Text Review, Quality Assessment, and Data Extraction

To organize variability, a data filter was applied to extract relevant information on demographic characteristics, exercise protocol, and hemodynamic measurements from every study included in this analysis. Age, sex ratio, training status, exercise type, and exercise protocol were independently extracted.

To organize information regarding the exercise stimulus, the following variables were extracted if possible: exercise modality, exercise position (supine, upright or semiupright, standing), and work rate (WR) stages. Hemodynamic variables extracted were resting and exercise PAWP, mean pulmonary arterial pressure (mPAP), heart rate (HR), and cardiac index (CI).

Data Stratification

Data were stratified on predefined criteria for age, sex, exercise modality, body position, training level, and exercise intensity. The "younger" cohort included subjects $\leq$40 years of age, the "older" group $>$40 years. Sex was stratified as male or female. Exercise modality was stratified as cycling or treadmill exercise. Body position was identified as supine, upright, semiupright for cycling, and standing (walking) for treadmill exercise. Training level was defined as untrained, recreationally active, and trained. "Trained" was defined according to assessment of the authors, self-reported history, or evaluation of peak aerobic capacity. Finally, 3 exercise intensities were predefined (Light, moderate, and strenuous exercise), and data were assigned to these categories according to the following hierarchic criteria: 1) percentage of HR reserve (light $<$40%, moderate 40%$-$59%, strenuous $\geq$60%); 2) WR (light $<$50 W, moderate 50$-$119 W, strenuous $\geq$120 W); 3) HR achieved (light 90$-$119 beats/min, moderate 120$-$139 beats/min, strenuous $\geq$140 beats/min); and 4) CI (light: 4$-$6 $L \cdot min^{-1} \cdot m^{-2}$, moderate 6.1$-$8 $L \cdot min^{-1} \cdot m^{-2}$, strenuous $>$8 $L \cdot min^{-1} \cdot m^{-2}$). Owing to variations between study protocols, not all subjects were examined at all stages of exercise.

Data Analysis

The weighted means and the weighted 95% CIs for the whole population reviewed were calculated (Revman 5.3; Cochrane Collaboration, Oxford, United Kingdom) with

the use of the generic inverse variance method and random-effects model. To examine the effect of sex and age, subgroup analysis was performed with those studies in which the results were provided according to these variables. An alpha of $P < .05$ was considered to be significant. The recorded data were not reported uniformly in the original publications. The majority of the studies summarized data without presenting individual data. In studies where individual data were presented, the group mean values and SDs were calculated and reported in the present analysis.

Results

Figure 1 illustrates the results of the systematic search and stratification of studies based on inclusion and exclusion criteria. Our search strategy identified 5,714 publications. Of these, 599 described RHC with exercise as an intervention and were further evaluated for eligibility. Reasons for study exclusion are detailed in Fig. 1. The main reason for exclusion was a population that did not meet criteria for "healthy." Thirty-nine studies were determined to be eligible for analysis, 7 of which included data from the same cohort of subjects published in different journals by the same research group. As such, the final analysis included 32 unique studies. Supplemental Table 1 lists the relevant extracted data from the 32 included studies according to age groups.[7,8,10–39] One study presented data for 3 age groups separately,[8] and another investigation reported data for different training levels (recreationally active and trained).[10] Therefore, these 2 studies appear more than once in Supplemental Table 1 as groups were sorted for data extraction. The total population of this systematic review included 424 individuals, of which 19% (n = 82) were women. The population >40 years of age included 176 subjects (31% [n = 55] women); the population ≤40 years of age included 248 subjects (11% [n = 27] women). The majority of studies (56%) were conducted in untrained individuals.

Subject Characteristics Stratified by Age

Supplemental Table 2 shows general characteristics and baseline hemodynamics (supine) of the included subjects stratified by age. At rest, baseline hemodynamics were similar except for CI, which was significantly higher in ≤40 years compared with >40 years ($P = .01$). Baseline PAWP in the supine position was similar for both age groups.

Hemodynamic Response to Exercise Stratified by Age

Table 1 and Fig. 2 present the weighted means (95% CIs) for PAWP, mPAP, CI, and WR compared between groups of subjects ≤40 and >40 years exercising at 3 predefined exercise intensities. HR was not statistically different between the 2 age groups across all exercise intensities. At light or moderate exercise intensities, PAWP was significantly higher in subjects >40 years old, reaching weighted mean values 95% CIs) of 19 (17−21) and 17 (16−18) mm Hg, respectively. Similarly, mPAP was significantly higher in subjects >40 years old exercising at light or moderate intensities. At light or moderate exercise intensities, CI was similar between younger and older subjects. There were fewer subjects >40 years studied at strenuous exercise intensities. For older subjects studied at this level of exercise, PAWP was 15 (8−22) mm Hg and not statistically different compared with younger subjects. At strenuous exercise intensity however, CI was significantly lower for the older cohort. WRs at each exercise intensity were significantly higher for subjects ≤40 years compared with >40 years of age ($P < .001$).

Subject Characteristics Stratified by Age and Sex

Supplemental Table 3 shows subjects characteristics in subjects ≤40 years and >40 years of age stratified by sex. In both cohorts, baseline hemodynamics were similar between men and women. This subgroup analysis of sex could be performed only with studies in which the results for men and women were provided separately. Therefore, the sample size for this analysis was smaller and does not include all unique patients identified in this systematic review.

Hemodynamic Response to Exercise in Men and Women >40 Years of Age

The weighted means (95% CIs) for the exercise hemodynamic variables in subjects aged >40 years stratified by sex are presented in Table 2 and Fig. 3. At light and moderate exercise intensities, the absolute PAWP responses were similar between men and women >40 years of age. Similar to the overall cohort aged >40 years, the means (95% CIs) for PAWP were 19 (16−21) mm Hg for men and 17 (15−19) mm Hg for women at light exercise and 17 (15−19) mm Hg at moderate exercise for both men and women. There were no significant sex differences in the mPAP or CI response in subjects aged >40 years. WR was significantly higher in men compared with women at light and moderate exercise ($P < .001$). There were only 3 studies[8,20,23] that included a stage meeting our criteria for strenuous exercise intensity. One of those studies did not report PAWP,[20] and only 1 study provided data for its 10 women separately.[8] As such, we observed PAWP that exceeded 20 mm Hg at strenuous exercise in both men and women, higher than what was observed in the entire cohort aged >40 years.

Hemodynamic Response to Exercise in Men and Women ≤40 Years

Supplemental Fig. 1 shows the weighted means (95% CIs) for the hemodynamic outcome variables during exercise in men and women aged ≤40 years. There were very little data available from women aged ≤40 years. The PAWP data during exercise were available from only

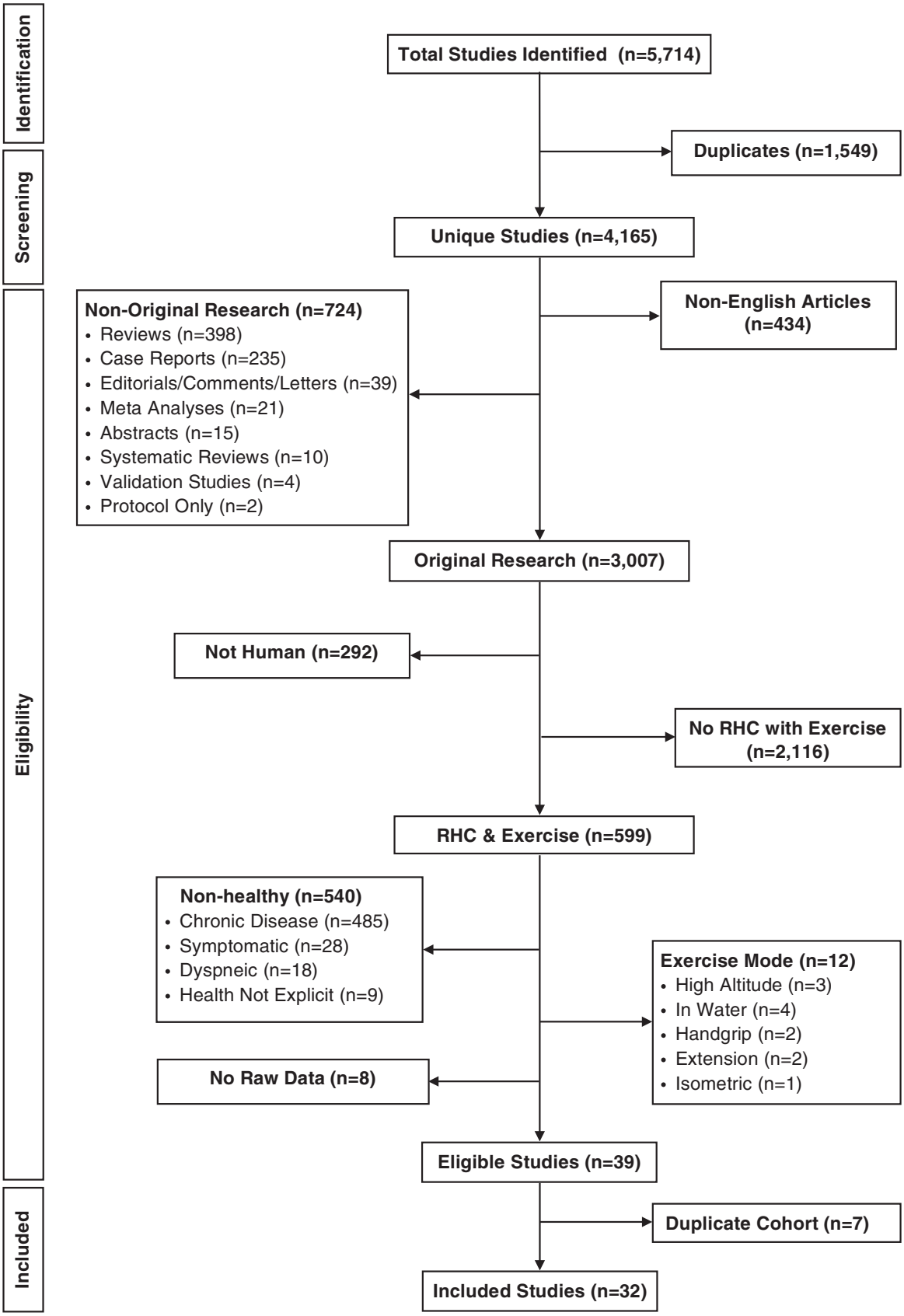

Fig. 1. CONSORT diagram of study search, selection, and stratification process. RHC, right heart catheterization.

Table 1. Weighted Means (95% Confidence Intervals) for Hemodynamics and Work Rate Data in Healthy Humans ≤40 years and >40 Years of Age Across Exercise Intensities

	≤40 y			>40 y		
Variable	Light	Moderate	Strenuous	Light	Moderate	Strenuous
PAWP, mm Hg	11 (9–13)	13 (10–15)	13 (10–16)	19 (17–21)*	17 (16–18)*	15 (8–22)
mPAP, mm Hg	20 (19–22)	22 (20–24)	28 (25–30)	28 (22–33)*	29 (24–34)*	29 (22–35)
CI, $L \cdot min^{-1} \cdot m^{-2}$	5.3 (3.8–6.8)	7.3 (5.8–8.7)	9.2 (8.8–9.7)	5.4 (5.2–5.6)	7.7 (7.5–7.9)	7.4 (7.2–7.6)*
HR, beats/min	106 (102–109)	137 (130–144)	158 (95–222)	100 (95–106)	119 (112–126)	137 (122–152)
WR, W	98 (49–146)	134 (104–164)	223 (182–265)	46 (33–59)*	72 (46–98)*	116 (93–140)*

See Fig. 2 for sample sizes. CI, cardiac index; HR, heart rate; mPAP, mean pulmonary arterial pressure; PAWP, pulmonary arterial wedge pressure; WR, work rate.
*$P < .05$ vs ≤40 years.

20 women reported by 2 studies[8,33] and from only 10 women at strenuous exercise.[33]

Heterogeneity for Hemodynamic Response to Exercise

Heterogeneity (I^2) values for hemodynamic and work rate data in healthy humans ≤40 years and >40 years of age and in healthy men and women >40 years of age across exercise intensities are presented in Tables 3 and 4, respectively.

Discussion

In this systematic review and meta-analysis, we aimed to improve the quantitative understanding of the PAWP

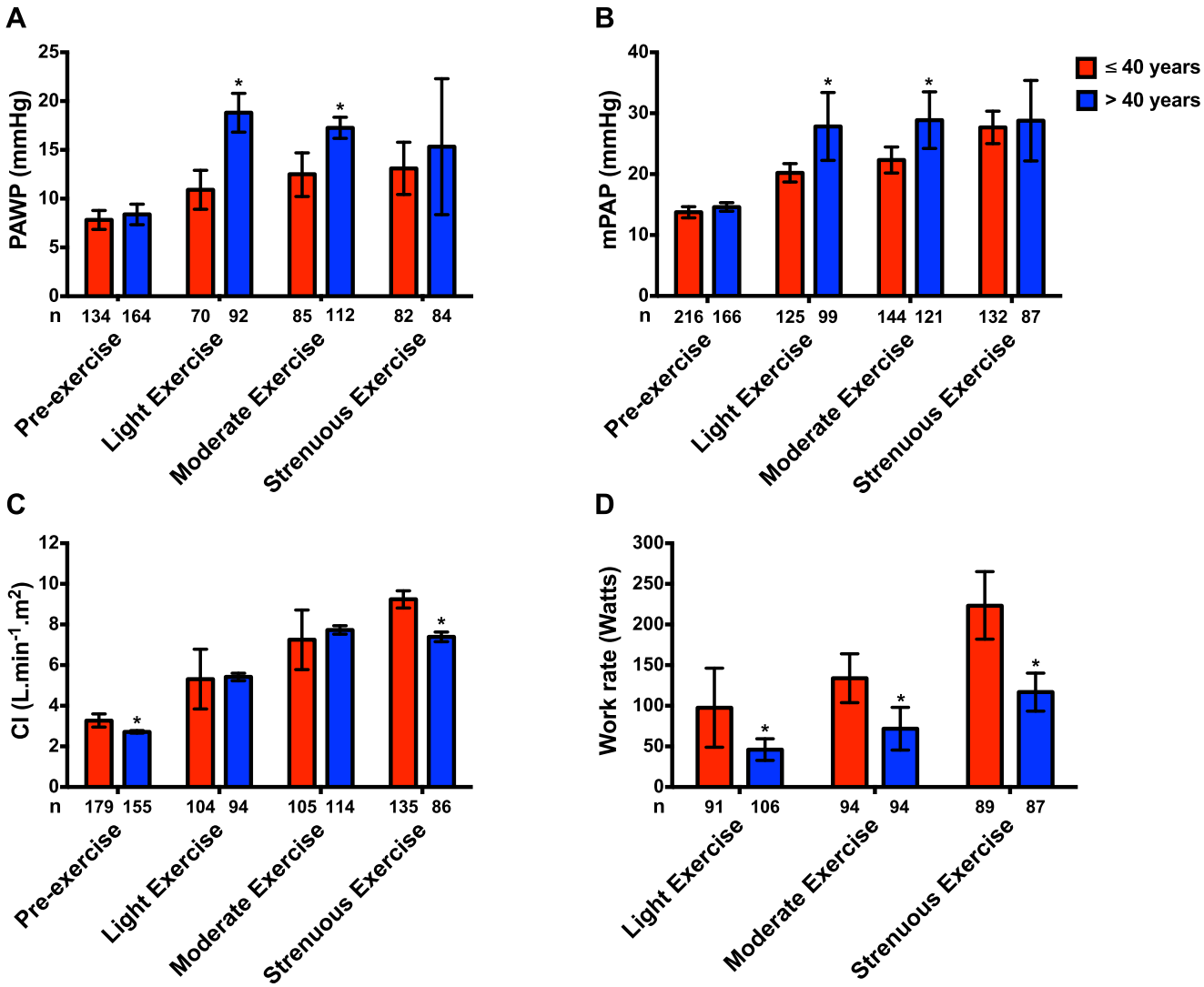

Fig. 2. Weighted means (95% confidence intervals) for (A) pulmonary arterial wedge pressure (PAWP), (B) mean pulmonary arterial pressure (mPAP), (C) cardiac index (CI), and (D) work rate in healthy humans aged ≤40 years and >40 years across exercise intensities. *$P < .05$ vs ≤40 years. Pre-exercise values represent data obtained in the same position as exercise and are different from baseline supine hemodynamics.

Table 2. Weighted Means (95% Confidence Intervals) for Hemodynamics and Work Rate Data in Healthy Men and Women >40 Years of Age Across Exercise Intensities

	Men			Women		
Variable	Light	Moderate	Strenuous	Light	Moderate	Strenuous
PAWP, mm Hg	19 (16–21)	17 (15–19)	22 (19–25)	19 (17–20)	17 (15–19)	23 (21–26)
mPAP, mm Hg	26 (21–32)	29 (23–34)	30 (19–40)	29 (26–32)	32 (25–39)	41 (37–45)
CI, $L \cdot min^{-1} \cdot m^{-2}$	5.5 (5.3–5.8)	7.2 (6.9–7.5)	7.1 (6.7–7.4)	5.4 (5.1–5.7)	7.2 (6.7–7.7)	7.9 (7.0–8.8)
HR, beats/min	99 (93–105)	118 (109–127)	112 (86–139)	100 (92–108)	118 (107–129)	108 (95–121)
WR, W	72 (48–97)	106 (82–130)	129 (123–136)	55 (31–79)*	81 (41–120)*	134 (123–145)

See Fig. 3 for sample sizes. Abbreviations as in Table 1.
*$P < .05$ vs men.

response to exercise in healthy asymptomatic men and women, particularly over the age of 40 years. In a previous systematic review, Kovacs et al[40] evaluated the mPAP response to exercise as the primary variable of interest in otherwise healthy adults, although PAWP was also reported. These authors had broader inclusion criteria for health and also stratified the cohort by age. Interestingly, in that review, older adults demonstrated a strikingly elevated PAP response to "slight" exercise, but the sample size of older adults was relatively small. The present analysis was performed because further data have emerged. Moreover, there is an evolving clinical practice to objectively phenotype the extent of ventricular chamber dysfunction in response to physiologic exercise stress.[3,6] There is

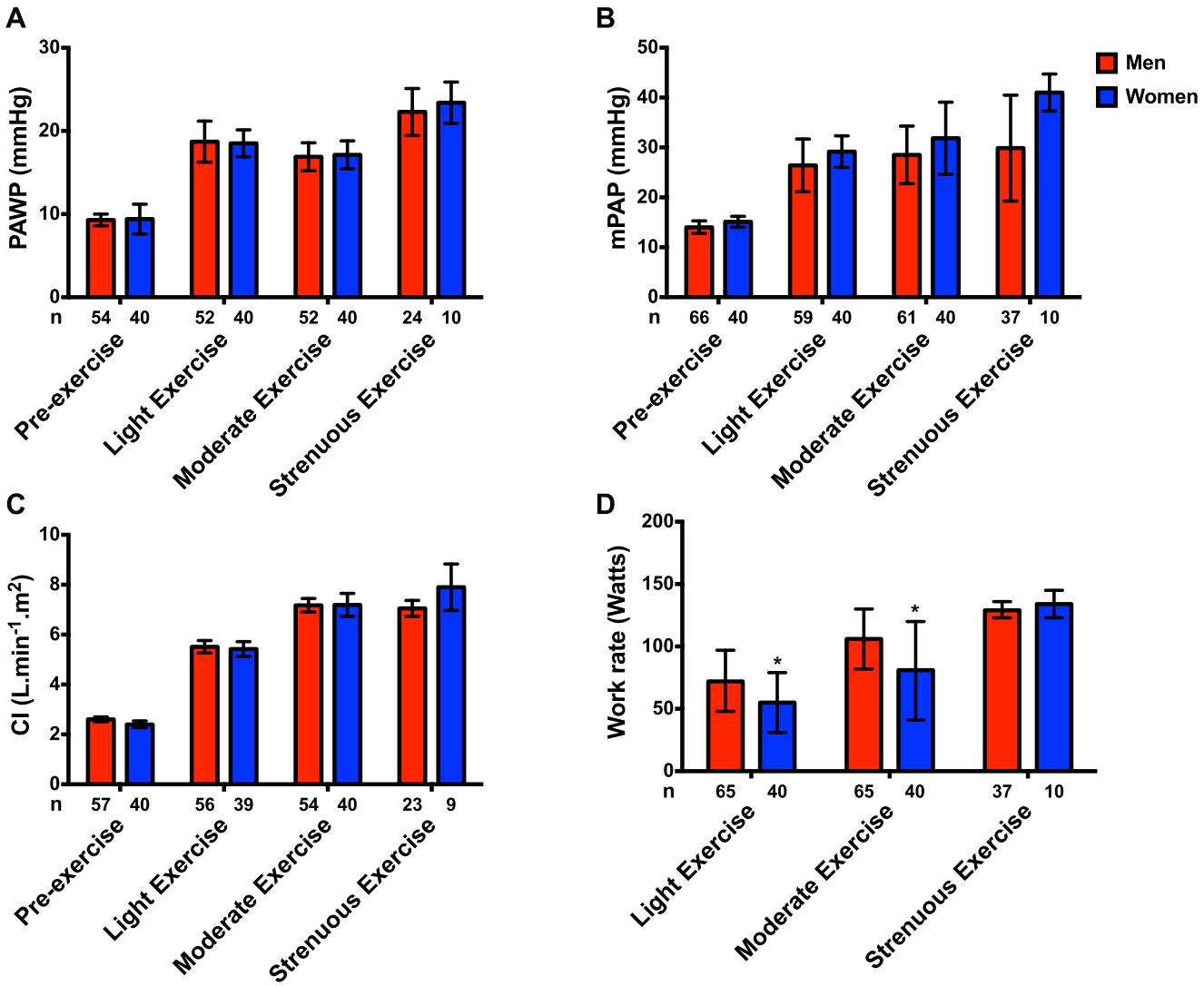

Fig. 3. Weighted means (95% confidence intervals) for (A) PAWP, (B) mPAP, (C) CI, and (D) work rate in healthy men and women aged >40 years across exercise intensities. *$P < .05$ vs men. Abbreviations as in as in Fig. 2.

Table 3. Heterogeneity (I^2, %) Values for Hemodynamics and Work Rate Data in Healthy Humans ≤40 Years and >40 Years of Age Across Exercise Intensities

	≤40 y			>40 y		
Variable	Light	Moderate	Strenuous	Light	Moderate	Strenuous
PAWP	86	83	88	67	71	98
mPAP	85	86	95	95	92	96
CI	98	98	37	96	96	87
HR	67	90	100	87	92	95
WR	99	94	98	95	97	90

Abbreviations as in Table 1.

Table 4. Heterogeneity (I^2, %) Values for Hemodynamics and Work Rate Data in Healthy Men and Women >40 Years of Age Across Exercise Intensities

	Men			Women		
Variable	Light	Moderate	Strenuous	Light	Moderate	Strenuous*
PAWP	60	73	0	0	74	N/A
mPAP	93	93	96	67	87	N/A
CI	92	87	81	95	93	N/A
HR	89	93	42	86	91	N/A
WR	96	94	93	97	98	N/A

Abbreviations as in Table 1.
*I^2 values at strenuous exercise in women were not applicable, because data at this stage were derived from a single study.

particular interest in the PAWP response to exercise as a means of quantitatively describing the pathophysiologic spectrum associated with HFpEF and dyspnea.

Recently, Wolsk et al[8] demonstrated that invasively measured PAWP responses to exercise were successively higher across 3 groups of otherwise healthy adults divided by increasing age. In that study, the cohort included participants with an exercise capacity above age-predicted values. The present analysis sought to expand on the works of Kovacs et al and Wolsk et al in several respects. We aimed to assemble a sample truly inclusive of healthy, asymptomatic, and untrained adults in the general population with the intent of stratifying by age and sex. Furthermore, we aimed to analyze the aggregated data and improve the quantitative description of the normal exercise hemodynamics phenotype, particularly in men and women over the age of 40 years. Our primary end point was the PAWP response, and, if possible, we aimed to stratify exercise intensities.

Our review demonstrates that the pool of available exercise hemodynamics data obtained from healthy older volunteers remains small. Despite renewed interest in exercise hemodynamics evaluation, we identified a total of 9 studies that had recruited completely healthy volunteers over the age of 40 years. Six studies have been published since 2012 and include 87% of the entire cohort of women >40 years ever studied. The sample of healthy women in the younger cohort was surprisingly even smaller, with a total of 23 ≤40 years of age. From a clinical perspective, an older cohort is most relevant to the age of onset of cardiovascular disease. Although Kovacs et al[40] predefined an older group as ≥50 years, Redfield et al[9] employed a cutoff of 45 years to define an older cohort in a large community-based echocardiography study. Our rationale for stratifying the age based on the cutoff value of 40 years was to remove the very youthful, thus enriching the older cohort in our analysis.

We observed that the mean PAWP at supine rest in healthy adults is ~8 mm Hg, regardless of age and sex. Compared with younger adults, older adults demonstrated elevated PAWP responses consistently during lighter intensities of exercise, which is in line with the findings of Wolsk et al[8] and Kovacs et al[40] showing PAWP is higher in older adults even at low exercise intensity. In the present analysis, the 95% CIs demonstrated that the upper range of PAWP values are proximate to and can exceed 20 mm Hg in older adults during all intensities of exercise. This was not observed in the cohort <40 years of age, in which the upper limit of the 95% CI did not exceed 16 mm Hg across all exercise intensities studied. Increases in both CI and HR were similar between older and younger groups, generally rising with escalation of intensity. As such, in the younger cohort the data are consistent with the notion that pulmonary arterial and wedge pressures have a linear relationship with increases in CO. The physiology appears possibly more complex in the older cohort, for whom, particularly at lower-intensity early exercise, increases in flow do not likely fully explain the increase in pressures.[41]

For subjects >40 years of age, the present review demonstrated that values for PAWP at rest and during exercise are similar between men and women. Furthermore, CI also was similar; however, WRs at all intensities of exercise were lower in women. These data suggest that when adjusted for WR, PAWP may be consistently higher for older women than for men across exercise intensities.[7] In patients with

dyspnea of unknown origin, it has been demonstrated that higher values for PAWP adjusted for WR and body weight are an independent predictor of poor prognosis.[42] In the present review, it was not possible to further adjust WR for body size based on the data extracted. Interestingly, the majority of patients referred for diagnostic hemodynamic exercise evaluation of dyspnea of unknown origin and potential HFpEF are women. The PAWP response to exercise in the context of WR may be complex and may be affected by both central cardiac responses and peripheral mechanisms of skeletal muscle function and oxygen extraction.[43] It may then be useful to explore sex differences in these component physiologies that may predispose women to developing pathologic syndromes of breathlessness.

Although not embraced as standard practice, the growing uptake of exercise hemodynamics testing has been reflected in contemporary clinical trials, which have used exercise PAWP responses as an inclusion criterion objectively defining the presence of HFpEF. For example, the Reduce Elevated Left Atrial Pressure in Patients With Heart Failure (REDUCE LAP-HF) trial used age >40 years and exercise PAWP as enrollment criteria to test a novel interatrial shunt device therapy.[44] There has been uncertainty regarding the upper threshold for the PAWP response, which has been variably defined as an exercise PAWP >20 mm Hg[2] up to 25 mm Hg.[1,43,44] As discussed, our findings support the notion that age-specific cutoff points may require consideration. The data presented in the present review would suggest that between these 2 proposed thresholds, the upper limit of >20 mm Hg is too low in a population older than 40 years of age. Our findings favor selection of an upper reference value of at least 25 mm Hg in both men and women to optimize specificity for identifying abnormal PAWP responses to exercise.

Study Limitations

There were limitations to our study. There remains opportunity to improve standardization in the performance of exercise hemodynamics assessment. Our findings were limited by heterogeneity among the studies. Although exercise intensities were stratified based on criteria defined a priori, the process was still limited by variability of criteria used to define effort during exercise. Another important consideration in exercise hemodynamics evaluation is body position, which ranged from supine to upright. As such, comparisons may be challenging because mechanical efficiency and relative effort of exercise is affected by body position.[40] The methods for hemodynamic analysis of the PAWP may also vary, because some studies presented automated digitally reported mean values, whereas others reported values at end-expiration. Our search was restricted to studies in English, because we were not able to interpret studies published in other languages.[40] The approach to handling data also introduced some limitations as stratification of data introduced a loss of sample size and statistical power, particularly at strenuous exercise intensity.

Conclusion

Data from RHC in healthy individuals suggest a normal mean PAWP of 8 mm Hg at rest that increases during exercise, reaching in excess of 20 mm Hg in some adults aged >40 years even at light intensity. Our analysis favors selection of at least 25 mm Hg as an upper cutoff value for the "normal" PAWP response to exercise in men and women >40 years of age, and it highlights the opportunity to expand the pool of data available in healthy older subjects with the use of systematic methodology.

Disclosures

None.

Supplementary Data

Supplementary data related to this article can be found at doi:10.1016/j.cardfail.2018.10.009.

References

1. Borlaug BA, Nishimura RA, Sorajja P, Lam CS, Redfield MM. Exercise hemodynamics enhance diagnosis of early heart failure with preserved ejection fraction. Circ Heart Fail 2010;3:588–95.
2. Berry NC, Manyoo A, Oldham WM, Stephens TE, Goldstein RH, Waxman AB, et al. Protocol for exercise hemodynamic assessment: performing an invasive cardiopulmonary exercise test in clinical practice. Pulm Circ 2015;5:610–8.
3. Galie N, Humbert M, Vachiery JL, Gibbs S, Lang I, Torbicki A, et al. 2015 ESC/ERS guidelines for the diagnosis and treatment of pulmonary hypertension: the Joint Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS): endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC), International Society for Heart and Lung Transplantation (ISHLT). Eur Heart J 2016;37:67–119.
4. Givertz MM, Fang JC, Sorajja P, Dimas V, Forfia PR, Kapur NK, et al. Executive summary of the SCAI/HFSA clinical expert consensus document on the use of invasive hemodynamics for the diagnosis and management of cardiovascular disease. J Card Fail 2017;23:487–91.
5. Maron BA, Cockrill BA, Waxman AB, Systrom DM. The invasive cardiopulmonary exercise test. Circulation 2013;127:1157–64.
6. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JG, Coats AJ, et al. 2016 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure: the Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure of the European Society of Cardiology (ESC). Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. Eur J Heart Fail 2016;18:891–975.
7. Esfandiari S, Wright SP, Goodman JM, Sasson Z, Mak S. Pulmonary artery wedge pressure relative to exercise work rate in older men and women. Med Sci Sport Exerc 2017;49:1297–304.
8. Wolsk E, Bakkestrom R, Thomsen JH, Balling L, Andersen MJ, Dahl JS, et al. The influence of age on hemodynamic parameters during rest and exercise in healthy individuals. JACC Heart Fail 2017;5:337–46.
9. Redfield MM, Jacobsen SJ, Borlaug BA, Rodeheffer RJ, Kass DA. Age- and gender-related ventricular-vascular stiffening: a community-based study. Circulation 2005;112:2254–62.
10. Alexander JK, Hartley LH, Modelski M, Grover RF. Reduction of stroke volume during exercise in man following ascent to 3,100 m altitude. J Appl Physiol. 1967;23(6):849–58.

11. Andersen MJ, Ersboll M, Bro-Jeppesen J, Gustafsson F, Hassager C, Kober L, et al. Exercise hemodynamics in patients with and without diastolic dysfunction and preserved ejection fraction after myocardial infarction. Circulation Heart failure. 2012;5(4):444–51.
12. Banchero N, Sime F, Penaloza D, Cruz J, Gamboa R, Marticorena E. Pulmonary pressure, cardiac output, and arterial oxygen saturation during exercise at high altitude and at sea level. Circulation. 1966;33(2):249–62.
13. Bevegard S, Holmgren A, Jonsson B. The effect of body position on the circulation at rest and during exercise, with special reference to the influence on the stroke volume. Acta physiologica Scandinavica. 1960;49:279–98.
14. Bevegard S, Holmgren A, Jonsson B. Circulatory studies in well trained athletes at rest and during heavy exercise. With special reference to stroke volume and the influence of body position. Acta physiologica Scandinavica. 1963;57:26–50.
15. Binak K, Sirmaci N, Ucak D, Harmanci N. Circulatory changes in acute glomerulonephritis at rest and during exercise. British heart journal. 1975;37(8):833–9.
16. Blumchen G, Valdivieso E, Jette M, Landry F. Filling pressures in post-myocardial infarction patients: comparison between isometric and dynamic exercise. European heart journal. 1987;8(Suppl G):39–42.
17. Christie JL, Sheldahl LM, Tristani FE, Wann LS, Sagar KB, Levandoski SG, et al. Cardiovascular regulation during head-out water immersion exercise. Journal of applied physiology. 1990;69(2):657–64.
18. Claessen G, La Gerche A, Dymarkowski S, Claus P, Delcroix M, Heidbuchel H. Pulmonary vascular and right ventricular reserve in patients with normalized resting hemodynamics after pulmonary endarterectomy. Journal of the American Heart Association. 2015;4(3):e001602.
19. Damato AN, Galante JG, Smith WM. Hemodynamic response to treadmill exercise in normal subjects. J Appl Physiol. 1966;21(3):959–66.
20. Degre S, de Coster A, Messin R, Denolin H. Normal pulmonary pressure-flow relationship during exercise in the sitting position. Internationale Zeitschrift fur angewandte Physiologie, einschliesslich Arbeitsphysiologie. 1972;31(1):53–9.
21. Ekelund LG. Circulatory and respiratory adaptation during prolonged exercise of moderate intensity in the sitting position. Acta physiologica Scandinavica. 1967;69(4):327–40.
22. Epstein SE, Beiser GD, Stampfer M, Robinson BF, Braunwald E. Characterization of the circulatory response to maximal upright exercise in normal subjects and patients with heart disease. Circulation. 1967;35(6):1049–62.
23. Granath A, Jonsson B, Strandell T. Circulation in Healthy Old Men, Studied by Right Heart Catheterization at Rest and during Exercise in Supine and Sitting Position. Acta medica Scandinavica. 1964;176:425–46.
24. Higginbotham MB, Morris KG, Williams RS, McHale PA, Coleman RE, Cobb FR. Regulation of stroke volume during submaximal and maximal upright exercise in normal man. Circulation research. 1986;58(2):281–91.
25. Holmgren A, Jonsson B, Sjostrand T. Circulatory data in normal subjects at rest and during exercise in recumbent position, with special reference to the stroke volume at different work intensities. Acta physiologica Scandinavica. 1960;49:343–63.
26. Hossack KF, Adair OV, Crowley ST. Atrial natriuretic factor production during upright exercise. Cardiology. 1990;77(6):433–42.
27. Kao AC, Van Trigt 3rd P, Shaeffer-McCall GS, Shaw JP, Kuzil BB, Page RD, et al. Central and peripheral limitations to upright exercise in untrained cardiac transplant recipients. Circulation. 1994;89(6):2605–15.
28. Kitzman DW, Higginbotham MB, Cobb FR, Sheikh KH, Sullivan MJ. Exercise intolerance in patients with heart failure and preserved left ventricular systolic function: failure of the Frank-Starling mechanism. Journal of the American College of Cardiology. 1991;17(5):1065–72.
29. Kubicek F, Gaul G. Comparison of supine and sitting body position during a triangular exercise test. I. Experiences in healthy subjects. European journal of applied physiology and occupational physiology. 1977;36(4):275–83.
30. Lonsdorfer-Wolf E, Richard R, Doutreleau S, Billat VL, Oswald-Mammosser M, Lonsdorfer J. Pulmonary hemodynamics during a strenuous intermittent exercise in healthy subjects. Medicine and science in sports and exercise. 2003;35(11):1866–74.
31. Maeder MT, Thompson BR, Htun N, Kaye DM. Hemodynamic determinants of the abnormal cardiopulmonary exercise response in heart failure with preserved left ventricular ejection fraction. Journal of cardiac failure. 2012;18(9):702–10.
32. Reeves JT, Groves BM, Sutton JR, Wagner PD, Cymerman A, Malconian MK, et al. Operation Everest II: preservation of cardiac function at extreme altitude. Journal of applied physiology. 1987;63(2):531–9.
33. Regensteiner JG, Bauer TA, Reusch JE, Quaife RA, Chen MY, Smith SC, et al. Cardiac dysfunction during exercise in uncomplicated type 2 diabetes. Medicine and science in sports and exercise. 2009;41(5):977–84.
34. Riley RL, Himmelstein A, et al. Studies of the pulmonary circulation at rest and during exercise in normal individuals and in patients with chronic pulmonary disease. The American journal of physiology. 1948;152(2):372–82.
35. Slonim NB, Ravin A, Balchum OJ, Dressler SH. The effect of mild exercise in the supine position on the pulmonary arterial pressure of five normal human subjects. The Journal of clinical investigation. 1954;33(7):1022–30.
36. Stickland MK, Welsh RC, Petersen SR, Tyberg JV, Anderson WD, Jones RL, et al. Does fitness level modulate the cardiovascular hemodynamic response to exercise? Journal of applied physiology. 2006;100(6):1895–901.
37. van Empel VP, Mariani J, Borlaug BA, Kaye DM. Impaired myocardial oxygen availability contributes to abnormal exercise hemodynamics in heart failure with preserved ejection fraction. Journal of the American Heart Association. 2014;3(6):e001293.
38. Wagner PD, Gale GE, Moon RE, Torre-Bueno JR, Stolp BW, Saltzman HA. Pulmonary gas exchange in humans exercising at sea level and simulated altitude. Journal of applied physiology. 1986;61(1):260–70.
39. Widimsky J, Berglund E, Malmberg R. Effect of Repeated Exercise on the Lesser Circulation. J Appl Physiol. 1963;18:983–6.
40. Kovacs G, Berghold A, Scheidl S, Olschewski H. Pulmonary arterial pressure during rest and exercise in healthy subjects: a systematic review. Eur Respir J 2009;34:888–94.
41. Wright SP, Esfandiari S, Gray T, Fuchs FC, Chelvanathan A, Chan W, et al. The pulmonary artery wedge pressure response to sustained exercise is time-variant in healthy adults. Heart 2016;102:438–43.
42. Dorfs S, Zeh W, Hochholzer W, Jander N, Kienzle RP, Pieske B, et al. Pulmonary capillary wedge pressure during exercise and long-term mortality in patients with suspected heart failure with preserved ejection fraction. Eur Heart J 2014;35:3103–12.
43. Houstis NE, Eisman AS, Pappagianopoulos PP, Wooster L, Bailey CS, Wagner PD, et al. Exercise intolerance in HFpEF: diagnosing and ranking its causes using personalized o2 pathway analysis. Circulation 2018;137:148–61.
44. Feldman T, Mauri L, Kahwash R, Litwin S, Ricciardi MJ, van der Harst P, et al. A transcatheter interatrial shunt device for the treatment of heart failure with preserved ejection fraction (REDUCE LAP-HF I): a phase 2, randomized, sham-controlled trial. Circulation 2018;137:364–75.