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The Influence of Age on Hemodynamic Parameters During Rest and Exercise in Healthy Individuals

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ABSTRACT

OBJECTIVES In this study, the authors sought to obtain hemodynamic estimates across a wide age span and in both sexes for future reference and compare these estimates with current guideline diagnostic hemodynamic thresholds for abnormal filling pressure and pulmonary hypertension.

BACKGROUND At present, the influence of age on hemodynamic function is largely unknown. Because many diseases with proposed cardiac impact are more prevalent in the older population, it is pivotal to know how hemodynamic parameters are affected by age itself to discern the influence of disease from that of physiological aging.

METHODS Sixty-two healthy participants, evenly distributed with respect to age (20 to 80 years) and sex (32 women/30 men), were prospectively enrolled in the study. Participants were all deemed healthy by medical history, echocardiography, exercise test, spirometry, blood tests, and electrocardiogram. Participants had hemodynamic parameters measured using right heart catheterization during rest, passive leg raise, and incremental exercise.

RESULTS During rest, all hemodynamic parameters were similar between age groups, apart from blood pressure. During leg raise and incremental exercise, there was augmented filling pressure ($p < 0.0001$) and diminished cardiac output ($p = 0.001$) and hence a higher pressure:flow ratio (pulmonary artery pressure/capillary wedge pressure to cardiac output) with progressive age, evident from the earliest ages. All indexed hemodynamic measures were similar between sexes. The diagnostic threshold (pulmonary capillary wedge pressure ≥25 mm Hg) currently used during exercise testing to diagnose abnormal left ventricular filling pressure was measured in 30% of our healthy elderly participants.

CONCLUSIONS Cardiac aging was progressive without sex differences in healthy participants. The hemodynamic reference values obtained suggest that the diagnostic threshold for abnormal filling pressure should be individually determined according to age of the patient. (J Am Coll Cardiol HF 2017;5:337–46) © 2017 by the American College of Cardiology Foundation.

Cardiac function changes with age, but the extent and the time course of changes in healthy people are largely unknown. Because many diseases with proposed cardiac impact are more prevalent in the older population, it is pivotal to know how hemodynamic parameters are affected by increasing age in healthy people at rest and during exercise. Without this knowledge, it is

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ABBREVIATIONS AND ACRONYMS

AV = arteriovenous

BSA = body surface area

CI = cardiac index

CO = cardiac output

ECG = electrocardiogram

HFpEF = heart failure with preserved ejection fraction

LV = left ventricular

MAP = mean arterial pressure

mPAP = mean pulmonary artery pressure

PCWP = pulmonary capillary wedge pressure

PVR = pulmonary vascular resistance

RAP = right atrial pressure

SEM = standard error of the mean

SvO_2 = mixed venous oxygen saturation

SVR = systemic vascular resistance

VO_2-max = maximal volume of oxygen uptake (whole body)

difficult to discern the impact of disease from that of aging. The effect of aging on invasive hemodynamic parameters has previously been studied. As age progresses, maximal cardiac output (CO) diminishes during exercise, and changes in cardiac filling pressures are likely different from those of younger persons (1–5). However, most invasive studies included symptomatic individuals or elderly individuals with comorbidity referred for clinically indicated invasive hemodynamic evaluation (1,2), which may limit the interpretation when determining reference values and assessing the impact of age alone. From population studies using resting echocardiography, it is evident that proxy markers of ventricular relaxation change with age, with slowed diastolic ventricular suction and impaired contractility in longitudinally oriented myocardial fibers (6,7). However, invasive measurements in healthy participants have not provided convincing evidence that these changes lead to augmented filling pressures at rest (1,2,6). Recent studies have focused on exercise testing with simultaneous invasive hemodynamic measurements as a method to unmask pathological changes (8,9). Patients with heart failure and preserved ejection fraction (HFpEF) whose main clinical feature is exertional dyspnea, may have filling pressures comparable to age-matched peers at rest, but markedly elevated even at light exercise (10). Because this population is generally composed of the elderly, it is important to know what degree of change in filling pressures are due to normal aging and what are attributable to disease. Only scarce data on exercise testing with invasive measurements in healthy subjects free of comorbidity exist (3,9,11). Furthermore, in hemodynamic exercise studies across ages, the use of uniform exercise protocols make comparison of hemodynamic parameters across the age spectrum difficult owing to the decline in exercise capacity with age (1,8).

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The current study investigated the effects of aging on hemodynamic parameters in healthy men and women at rest and during exercise at equal relative workloads. The primary aim was to provide estimates of hemodynamic parameters over a wide age range in healthy individuals as a future reference against diseased populations and to determine if changes in hemodynamics display a linear correlation with age.

METHODS

Healthy subjects age 20 to 80 were enrolled in this prospective 2-center study. Subjects were recruited using advertisements to evenly represent sex and age when stratified into 6 decadal strata. Healthy subjects were deemed eligible if free from history of any acute or chronic cardiac or pulmonary disease; echocardiography without signs of chamber hypertrophy, reduced left ventricular (LV) ejection fraction or significant valvular disease (performed 0 to 2 weeks before experimental day); normal spirometry for their age; routine blood chemistry test with normal values (including estimated glomerular filtration rate, HbA1c, N-terminal pro B-type natriuretic peptide, thyroid-stimulating hormone, hemoglobin, C-reactive protein, white blood cell count, lipids); body mass index 20 to 30 kg/m^2; and an exercise test with electrocardiogram (ECG) without any pathological findings. Any medication with cardiovascular effects was paused 48 hours before the invasive tests. Active smoking was also an exclusion criterion (see the Online Appendix for all inclusion and exclusion criteria).

Participants provided oral and written informed consent before any testing. The protocol was approved by the regional ethical committee (Capital Region of Denmark; H-2-2013-072). The protocol was published on clinicaltrials.gov (NCT01974557).

ECHOCARDIOGRAPHY. Examinations were performed using a Philips iE33 (Philips Healthcare, Best, the Netherlands) or a Vivid 9 (General Electric, Horten, Norway) ultrasound system. LV volumes and LV ejection fraction were assessed with the Simpson modified biplane rule using apical 2- and 4-chamber views. LV mass was measured using LV wall thickness and LV end-diastolic diameter, as described by Devereux et al. (12). Maximal left atrial volume was measured using biplane planimetry.

RIGHT HEART CATHETERIZATION. Right heart catheterization was performed using a standard 7.5-F triple lumen Swan-Ganz catheter (Edwards Lifesciences, Irvine, California). Using the Seldinger technique and guided by ultrasound, the catheter was introduced under local anesthesia into the internal jugular vein and advanced to the pulmonary artery with the position of the catheter verified by identifying the signature pressure curves. Right atrial pressure (RAP); systolic, diastolic and mean pulmonary artery pressures (mPAP); and pulmonary capillary wedge pressure (PCWP) were measured. At rest, end-expiratory PCWP was measured and during exercise PCWP was averaged over 10 s. CO was measured using thermodilution as the average of

3 measurements with <10% variance and was indexed to body surface area (BSA) as cardiac index (CI). A maximum CO of 20 l/min was measureable. Caffeine or nicotine intake was not allowed on the trial day.

CALCULATIONS. BSA was estimated using the Dubois formula. Pulmonary vascular resistance (PVR) in Wood units was calculated as: (mean PAP - PCWP)/CO. Systemic vascular resistance (SVR) was calculated as: 80 × (mean arterial pressure [MAP] − RAP)/CO. Arteriovenous (AV) oxygen difference was calculated as: peripheral oxygen saturation (index finger) − mixed venous oxygen saturation (SvO_2).

EXERCISE PROTOCOL. One to 2 weeks before cardiac catheterization, standard cardiopulmonary exercise test with breath-by-breath gas analysis and measurement of heart rate were performed. All participants were subjected to an upright ergometer test that started at 25 W. Following this, the workload continually increased at increments of 25 W every 2 min until the maximal oxygen consumption (VO_2-max) was reached, preferably with a respiratory quotient (RQ) >1.12.

During the supine stress test with invasive measurements of hemodynamics, participants were challenged with workloads corresponding to those found at 25%, 50%, and 75% of the VO_2-max achieved during the upright cardiopulmonary exercise test. Hence, the graded workloads were relatively comparable between participants across ages.

PROTOCOL AND INTERVENTIONS. Participants were allowed to consume their normal diet; however, participants were asked to refrain from consuming products containing caffeine. After voiding, invasive and noninvasive equipment was placed (blood pressure, oxygen saturation, ECG, Swan-Ganz catheter).

After resting, examinations were made in the supine position with the legs resting flat (rest). The participants were then transferred to a reclining bike. In this position, the participants were supine, and both legs were raised perpendicular to the torso with a 70° to 80° bend in the knee joints with the feet strapped into the pedals (leg raise).

Following resting measurements participants were asked to exercise for 3 intervals (25%, 50%, and 75% of VO_2-max) that each lasted 4 min. Participants were asked to keep steady revolutions at 60 per min. All measurements were made 1 min into each interval for hemodynamic measurements to be at a reasonable steady state. Central venous blood samples for analyses of lactate concentrations and mixed SvO_2 were drawn at each sample time from the tip of the indwelling catheter.

TABLE 1 Baseline Characteristics

	All (n = 62)	Ages 20-39 Yrs (n = 20)	Ages 40-59 Yrs (n = 22)	Ages 60-80 Yrs (n = 20)
Age (yrs)	49 (45-54)	29 (27-33)	49 (47-52)	69 (66-71)
Female/male	32/30	10/10	12/10	10/10
Weight (kg)	75 (72-78)	72 (67-78)	77 (72-82)	75 (70-80)
BMI (kg/m^2)*	24 (24-25)	23 (21-24)	25 (24-27)	25 (24-26)
BSA (m^2)	1.9 (1.9-1.9)	1.9 (1.8-2.0)	1.9 (1.8-2.0)	1.9 (1.8-2.0)
Hemoglobin (mmol/l)	8.9 (8.7-9.1)	8.8 (8.4-9.2)	9.0 (8.7-9.3)	8.8 (8.4-9.2)
eGFR (ml/min/1.73 m^2)*	79 (76-83)	88 (83-93)	74 (67-81)	77 (72-82)
HbA1c (mmol/mol)*	35 (34-35)	33 (32-34)	34 (33-36)	36 (35-38)
CRP (mg/l)	1.9 (1.4-2.5)	1.9 (1.1-2.7)	1.9 (1.2-2.6)	2.1 (0.6-3.5)
TSH (10^3 × IU/l)	1.8 (1.6-2.0)	2.0 (1.6-2.4)	1.8 (1.5-2.1)	1.6 (1.2-2.1)
NT-proBNP (pmol/l)*	11 (8-14)	7 (6-8)	10 (7-13)	16 (7-24)
FEV_1 (l)*	3.4 (3.2-3.6)	3.9 (3.5-4.3)	3.4 (3.1-3.7)	3.0 (2.7-3.4)
FVC (l)*	4.5 (4.2-4.7)	4.9 (4.3-5.5)	4.5 (4.1-4.9)	4.0 (3.5-4.5)
VO_2-max (l/min)*	2.6 (2.4-2.8)	3.0 (2.6-3.3)	2.7 (2.4-3.0)	2.2 (1.9-2.5)
VO_2-max/weight (ml/min/kg)*	35 (33-37)	41 (38-45)	34 (31-37)	29 (26-32)
HR (beats/min)	63 (61-66)	63 (57-69)	64 (60-69)	62 (58-66)
SBP (mm Hg)*	132 (128-136)	119 (115-124)	133 (126-140)	143 (136-151)
DBP (mm Hg)*	75 (72-78)	65 (61-70)	81 (78-85)	77 (72-82)
MAP (mm Hg)*	89 (86-91)	79 (75-82)	94 (90-98)	92 (88-97)
LV mass index (g/m^2)	78 (73-83)	75 (65-84)	81 (71-92)	77 (68-86)
LVEDV (ml)	98 (91-105)	107 (90-123)	94 (84-105)	93 (83-104)
LVESV (ml)*	37 (34-41)	42 (34-50)	38 (32-43)	33 (28-37)
LVEF (%)	62 (60-63)	61 (58-63)	60 (58-63)	64 (61-67)
LA volume (ml/m^2)	24 (22-26)	24 (22-27)	23 (19-26)	26 (22-30)
E/A*	1.3 (1.2-1.4)	1.8 (1.6-2.1)	1.2 (1.2-1.3)	1.0 (0.9-1.1)
E/e′*	8.3 (7.5-9.0)	7.1 (5.0-9.1)	8.3 (7.3-9.3)	9.2 (8.2-10.2)

Values are mean (95% confidence interval) or n. Differences in age and LV mass index not tested. *$p < 0.05$, for difference across age categories.

BMI = body mass index; BSA = body surface area; CRP = C-reactive protein; DBP = diastolic blood pressure; eGFR = estimated glomerular filtration rate; FEV_1 = forced expiratory volume in 1 second; FVC = forced vital capacity; HR = heart rate; LA = left atrial; LV = left ventricular; LVEDV = left ventricular end-diastolic volume; LVESV = left ventricular end-systolic volume; MAP = mean arterial pressure; NT-proBNP = N-terminal pro B-type natriuretic peptide; SBP = systolic blood pressure; TSH = thyroid-stimulating hormone; VO_2-max = maximal oxygen consumption.

STATISTICAL ANALYSES. Estimates are summarized in 3 age categories (20 to 39 years, 40 to 59 years, 60 to 80 years) of comparable sex composition. All data were formally tested for normality using Shapiro-Wilk tests, histograms, and normal probability plots. Data were normally distributed. CO exceeding 20 l/min was imputed as 20 l/min (3 patients at 50% of VO_2-max, 10 patients at 75% of VO_2-max). To test differences between age groups and the effects of interventions a multivariate analysis of variance with repeated measures (Hotelling-Lawley trace) was applied to all the interventional sampling points (rest, leg raise, 25%, 50%, and 75% of VO_2-max). If statistical significant changes were evident ($p < 0.05$), a post hoc analyses with analysis of variance was used at single time points. No corrections were done for multiple testing, because the primary question was addressed using the multivariate analysis of variance test and analysis of variance was only repeated 5 times for variables

TABLE 2 Hemodynamic Measurements at Rest and During Interventions

	All	Ages 20–39 Years	Ages 40–59 Years	Ages 60–80 Years
Rest				
SBP (mm Hg)*	132 (128–136)	119 (115–124)	133 (126–140)	143 (136–151)
DBP (mm Hg)*	75 (72–78)	65 (61–70)	81 (78–85)	77 (72–82)
MAP (mm Hg)*	89 (86–91)	79 (75–82)	94 (90–98)	92 (88–97)
HR (beats/min)	63 (61–66)	63 (57–69)	64 (60–69)	62 (58–66)
CI (l/min/m^2)	2.7 (2.6–2.8)	2.9 (2.6–3.1)	2.8 (2.6–2.9)	2.6 (2.4–2.8)
SV (ml)	85 (79–91)	90 (77–103)	85 (74–95)	81 (73–89)
RAP (mm Hg)	5 (5–6)	5 (4–6)	6 (5–6)	5 (4–6)
mPAP (mm Hg)	14 (14–15)	13 (12–14)	15 (13–16)	15 (14–16)
PCWP (mm Hg)	9 (8–9)	9 (8–9)	9 (8–10)	8 (7–9)
SVR (dynes/s·cm^5)*	1,326 (1,246–1,406)	1,110 (993–1,227)	1,398 (1,273–1,524)	1,459 (1,319–1,598)
PVR (mm Hg/l/min^{-1})*	1.1 (1.0–1.2)	0.8 (0.7–1.0)	1.0 (0.8–1.2)	1.5 (1.2–1.7)
SvO_2 (%)	75 (74–76)	75 (73–77)	75 (72–78)	74 (73–76)
AV O_2 difference (%)	24 (23–25)	24 (23–26)	24 (22–27)	23 (21–25)
Lactate (mmol/l)	0.6 (0.6–0.7)	0.6 (0.5–0.7)	0.7 (0.6–0.8)	0.6 (0.5–0.7)
Leg raise				
SBP (mm Hg)*	136 (130–141)	122 (115–129)	133 (126–140)	152 (142–161)
DBP (mm Hg)*	76 (72–79)	65 (58–72)	78 (73–84)	83 (77–88)
MAP (mm Hg)*	89 (85–92)	78 (72–84)	91 (85–96)	97 (91–104)
HR (beats/min)	70 (67–73)	66 (60–72)	67 (61–72)	78 (73–82)
CI (l/min/m^2)*	3.2 (3.0–3.4)	3.1 (2.8–3.3)	3.0 (2.8–3.3)	3.5 (3.1–4.0)
SV (ml)	89 (84–94)	89 (80–99)	89 (80–98)	89 (78–99)
RAP (mm Hg)	9 (8–9)	8 (7–9)	9 (7–10)	9 (8–10)
mPAP (mm Hg)*	21 (19–22)	17 (15–19)	20 (18–22)	26 (24–28)
PCWP (mm Hg)*	14 (13–15)	12 (11–13)	13 (11–15)	16 (15–18)
SVR (dynes/s·cm^5)	1,101 (1,032–1,169)	992 (878–1,105)	1,159 (1,045–1,274)	1,141 (1,007–1,275)
PVR (mm Hg/l·min^{-1})*	1.2 (1.1–1.3)	0.9 (0.7–1.1)	1.2 (1.0–1.4)	1.5 (1.3–1.8)
SvO_2 (%)	69 (67–71)	72 (70–74)	70 (68–73)	65 (62–68)
AV O_2 difference* (%)	30 (28–31)	27 (24–30)	29 (27–30)	33 (30–37)
Lactate (mmol/l)	0.7 (0.6–0.7)	0.6 (0.5–0.7)	0.7 (0.6–0.8)	0.7 (0.6–0.8)

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significantly affected by age. Data summarized as pressure:flow ratio were tested for differences between age groups using linear regression. Values are tabulated as mean (95% confidence interval [CI]), and graphically as mean ± SEM, unless otherwise stated. All analyses were conducted using STATA version 13 (College Station, Texas).

RESULTS

BASELINE CHARACTERISTICS. A total of 62 Caucasians were enrolled in the study (32 women, 30 men). Baseline characteristics are summarized in **Table 1**. Body mass index and blood pressure increased with age, whereas the opposite relationship was true with age and lung function and exercise capacity (VO_2-max). Using the Wasserman-Hansen equation (13), the actual VO_2-max achieved by our participants was 28% above the predicted values.

RESTING HEMODYNAMICS. **Table 2** lists the hemodynamic values during supine rest. At rest, hemodynamic parameters were not different across age groups or between sexes (data grouped by sex shown in the Online Table 1), apart from increased PVR and SVR, which was reflected in the progressive increase in MAP with age ($p < 0.0001$). No differences were apparent in either lactate concentrations or SvO_2 between age groups during rest.

HEMODYNAMIC CHANGES DURING LEG RAISE AND EXERCISE. **Table 2** lists the hemodynamic responses to leg raise and incremental exercise (25%, 50%, and 75% of VO_2-max). There were no statistical differences between sexes, so all data were pooled for further analyses (data grouped by sex shown in the Online Table 1). CI was similar at baseline ($p = 0.19$) but, as expected from the VO_2-max trend, CI was higher in younger versus older participants across all exercise intensities and with leg raise ($p = 0.001$) (**Table 2**). During submaximal/maximal exercise (75% of VO_2-max), this relationship was best estimated by: cardiac index $= -0.05 \times \text{age (yrs)} + 11 \frac{\text{l}}{\text{min}}/\text{m}^2$ for patients age 20 to 80 years. Although there was no

TABLE 2 Continued

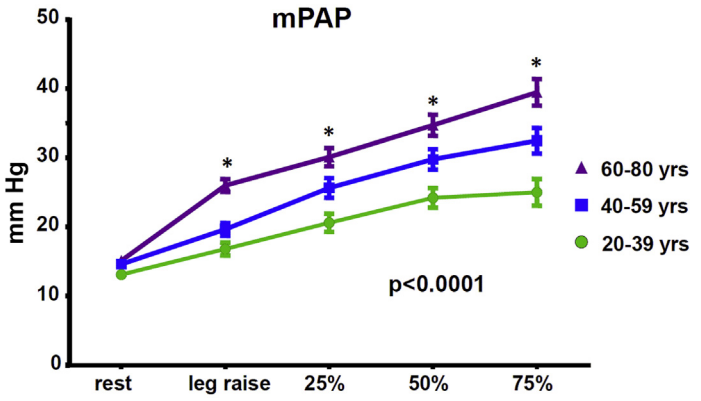
	All	Ages 20–39 Years	Ages 40–59 Years	Ages 60–80 Years
25% VO_2-max				
Workload (W)*	31 (29–34)	36 (30–42)	31 (26–35)	28 (24–31)
SBP (mm Hg)*	142 (138–149)	128 (121–135)	144 (134–153)	157 (149–166)
DBP (mm Hg)*	80 (77–83)	72 (68–77)	81 (74–88)	86 (80–91)
MAP (mm Hg)*	92 (89–96)	83 (79–87)	94 (87–101)	100 (95–105)
HR (bpm)	84 (81–88)	85 (78–92)	82 (75–89)	86 (80–91)
CI (l/min/m^2)*	5.2 (4.9–5.4)	5.6 (5.0–6.2)	5.0 (4.7–5.4)	4.8 (4.5–5.1)
SV (ml)	120 (110–129)	126 (105–146)	124 (107–141)	108 (95–121)
RAP (mm Hg)	9 (8–10)	7 (6–9)	10 (8–12)	10 (9–12)
mPAP (mm Hg)*	25 (24–27)	21 (18–23)	26 (22–29)	30 (27–33)
PCWP (mm Hg)*	16 (15–19)	13 (10–15)	17 (14–20)	19 (17–21)
SVR (dynes/s·cm^5)*	706 (653–759)	614 (526–701)	697 (616–788)	821 (725–918)
PVR (mm Hg/l/min^{-1})*	1.0 (0.9–1.1)	0.8 (0.6–0.9)	0.9 (0.7–1.1)	1.3 (1.1–1.5)
SvO_2 (%)	55 (53–56)	56 (54–59)	54 (51–56)	54 (51–57)
AV O_2 difference (%)	43 (42–45)	43 (40–45)	44 (42–47)	43 (40–46)
Lactate (mmol/l)	1.0 (0.9–1.1)	0.8 (0.6–1–0)	1.1 (0.9–1.4)	1.0 (0.8–1.1)
50% VO_2 max				
Workload (W)*	89 (82–96)	104 (90–118)	85 (74–96)	79 (68–90)
SBP (mm Hg)*	158 (152–164)	147 (137–157)	163 (152–174)	163 (154–171)
DBP (mm Hg)*	79 (75–84)	66 (59–73)	85 (80–91)	87 (82–92)
MAP (mm Hg)*	96 (91–100)	82 (75–89)	101 (93–109)	104 (99–109)
HR (beats/min)	105 (102–109)	110 (103–117)	104 (97–111)	102 (97–108)
CI (l/min/m^2)*	7.3 (7.0–7.7)	8.2 (7.6–8.9)	7.3 (6.8–7.8)	6.6 (5.9–7.2)
Stroke volume (mL)	132 (123–142)	138 (118–157)	136 (119–152)	123 (107–140)
RAP (mm Hg)	9 (8–10)	7 (6–9)	9 (7–11)	10 (8–12)
mPAP (mm Hg)*	30 (28–32)	24 (21–27)	30 (26–33)	35 (32–38)
PCWP (mm Hg)	17 (16–19)	15 (12–17)	18 (15–22)	19 (17–22)
SVR (dynes/s·cm^5)*	532 (484–581)	410 (353–468)	538 (480–596)	663 (556–771)
PVR (mm Hg/l/min^{-1})*	0.9 (0.8–1.0)	0.6 (0.5–0.8)	0.8 (0.7–1.0)	1.3 (1.0–1.5)
SvO_2 (%)	44 (42–45)	45 (43–48)	44 (41–46)	42 (39–45)
AV O_2 difference (%)*	54 (53–56)	53 (50–55)	53 (51–56)	56 (53–59)
Lactate (mmol/l)	2.0 (1.8–2.3)	2.0 (1.4–2.6)	2.2 (1.8–2.7)	1.9 (1.4–2.3)
75% VO_2 max				
Workload (W)*	149 (139–159)	174 (155–192)	144 (129–159)	130 (113–147)
SBP (mm Hg)*	173 (167–180)	159 (150–168)	172 (160–186)	188 (181–196)
DBP (mm Hg)*	88 (84–92)	82 (75–89)	89 (81–97)	93 (87–99)
MAP (mm Hg)*	107 (102–111)	98 (91–105)	107 (98–115)	116 (110–121)
HR (beats/min)*	132 (126–137)	141 (132–151)	126 (117–135)	128 (121–136)
CI (l/min/m^2)*	8.9 (8.6–9.3)	9.9 (9.6–10.4)	8.8 (8.4–9.3)	7.9 (7.2–8.6)
SV (ml)	129 (121–137)	130 (122–138)	139 (124–154)	115 (100–131)
RAP (mm Hg)*	9 (8–10)	7 (5–8)	9 (7–12)	11 (9–13)
mPAP (mm Hg)*	32 (30–34)	25 (22–28)	32 (27–38)	39 (36–43)
PCWP (mm Hg)*	18 (16–20)	13 (10–15)	19 (15–23)	23 (21–25)
SVR (dynes/s·cm^5)*	492 (451–534)	404 (364–444)	469 (424–513)	658 (555–761)
PVR (mm Hg/l/min^{-1})*	0.9 (0.8–1.0)	0.7 (0.6–0.8)	0.8 (0.6–1.0)	1.1 (0.9–1.4)
SvO_2 (%)	34 (32–35)	35 (32–37)	34 (31–36)	32 (29–35)
AV O_2 difference (%)	64 (62–65)	63 (60–66)	64 (61–66)	65 (62–68)
Lactate (mmoll)	5.9 (5.2–6.6)	6.0 (4.8–7.3)	6.3 (5.2–7.5)	5.3 (4.0–6.6)

Values are mean (95% confidence interval). *$p < 0.05$, for difference across age categories.

AV = arteriovenous; CI = cardiac index; mPAP = mean pulmonary artery pressure; PCWP = pulmonary capillary wedge pressure; PVR = pulmonary vascular resistance; RAP = right atrial pressure; SV = stroke volume; SvO_2 = mixed venous oxygen saturation; SVR = systemic vascular resistance; other abbreviations as in Table 1.

association between age and stroke volume at rest or during exercise, once adjusted for BSA, aging was associated with a significant decline in stroke volume at rest and during exercise. There was a consistent increase in MAP with increasing age ($p < 0.0001$) at rest and exercise. The MAP rose during exercise, but the magnitude of increase was equal between age groups ($p = 0.14$). The difference in A-V oxygen difference

FIGURE 1 mPAP Depicted During Rest and Interventions (Leg Raise: 25%, 50%, and 75% of Maximal Oxygen Consumption)



Participants were divided into 3 groups (20 to 39 years, 40 to 59 years, 60 to 80 years). Values are mean ± SEM. *p < 0.05 between age groups. mPAP = mean pulmonary artery pressure.

increased with progressive oxygen demand as well as with leg raise. The difference between age categories was mostly evident during the leg raise procedure (Table 2).

RAP. RAP increased in all age groups with exercise ($p < 0.0001$); however, there were no differences between age groups ($p = 0.19$). Depiction of RAP across all interventions grouped according to age category is presented in Online Figure 1.

PAP. mPAP was similar at rest ($p = 0.33$), but increased significantly with exercise ($p < 0.0001$). There was a significant incremental effect of age on mPAP ($p < 0.0001$) (Figure 1). During submaximal/maximal exercise (75% of VO_2-max), this relationship was best estimated by: mPAP = 0.33 × age + 16 mm Hg. Even though there were no significant differences in the response to exercise in the pulmonary pressure-flow relationship (ΔmPAP/ΔCO, $p = 0.22$), there was a significantly higher ratio in the older age groups seen across the spectrum of hemodynamic stress from leg raise to peak exercise (Figure 2) ($p < 0.003$). During rest, 10% of patients older than age 50 years had an mPAP = 21 mm Hg. No patients exceeded 21 mm Hg during rest.

Depiction of mPAP across all interventions grouped according to age category is presented the Online Figure 1.

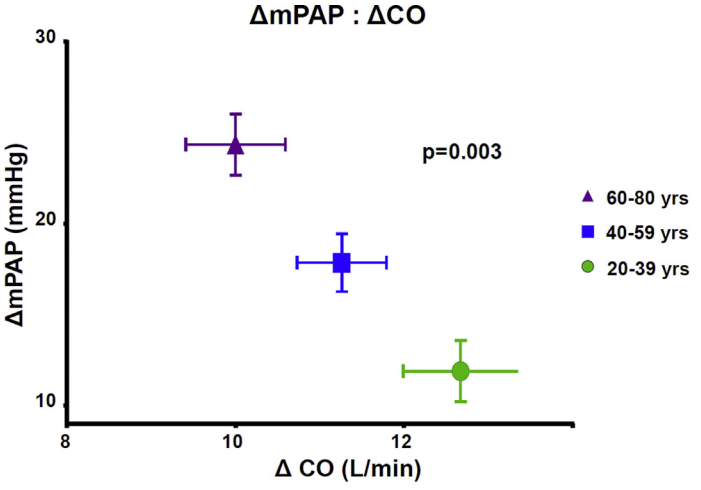
PULMONARY CAPILLARY ARTERY PRESSURE. PCWP increased in response to exercise ($p < 0.0001$), which was augmented with increasing age ($p < 0.0001$) (Figure 3). During submaximal/maximal exercise (75% of VO_2-max), this relationship was best estimated by: PCWP = 0.24 × age + 6 mm Hg. In participants age 20 to 39 years, no participants had a PCWP exceeding 25 mm Hg at highest intensity. In contrast, 6 participants (30%) age 60 to 79 years had a PCWP exceeding 25 mm Hg at highest intensity. When analyzing the exercise-induced changes in PCWP relative to CO (ΔPCWP/ΔCO), we observed a linear increase in the ratio with increasing age, which was not due to changes in stroke volume ($p = 0.001$) (Figure 4, Online Figure 2). Age also influenced PCWP observed in a post-hoc comparison of age groups at a workload of 25W, which was the case in 46 of 62 (74%) patients ($p = 0.004$, trend test) (Figure 5). At this workload, 4/46 (9%) had a PCWP ≥25 mm Hg.

Depiction of PCWP across all interventions grouped according to age category is present in the Online Figure 1.

VASCULAR RESISTANCES. SVR and PVR were lower in younger participants ($p < 0.006$ and $p < 0.0009$, respectively). However, the changes in SVR and PVR in response to exercise were comparable between age groups (SVR: $p = 0.41$; PVR: $p = 0.48$).

LACTATE AND CENTRAL SvO_2. Lactate increased in response to exercise ($p < 0.001$), but no differences were evident between the age categories ($p = 0.42$) or between age groups in response to increasing exercise intensity ($p = 0.07$).

FIGURE 2 Pressure Flow Relationship Depicted Between ΔmPAP and ΔCO From Baseline to 75% of VO_2-max in All Age Categories



Values are mean ± SEM. CO = cardiac output; other abbreviations as in Figure 1.

SvO_2 decreased as exercise intensity increased ($p < 0.0001$). There was no difference between age categories in response to exercise ($p = 0.08$).

DISCUSSION

The present study shows that during rest, ventricular filling pressures and CI do not differ between ages or sexes, but with increasing age, a lower CO during exercise is achieved despite higher LV filling pressure. This observation is likely from a physiological decrease in ventricular compliance and relaxation.

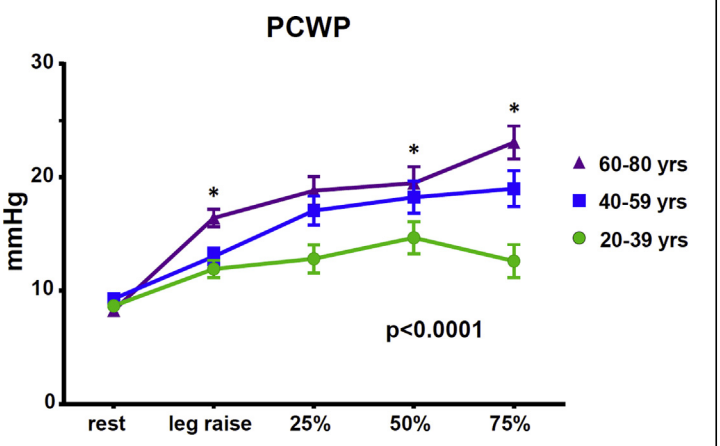
Not surprisingly, we found a positive relationship between age and MAP, which was caused by an increased systemic resistance with age. The similarities at rest across ages have been described in previous retrospective studies by van Empel et al. (1) and Ehrsam et al. (2). However, participants undergoing diagnostic cardiac catheterization were included in these studies and noncardiac comorbidities were present among included participants, which excluded definite conclusions on resting hemodynamics in healthy individuals. In a larger cohort, it was shown that the cumulative burden of noncardiac comorbidities attenuated cardiac function, assessed by echocardiography (14). This reiterates the importance of using a healthy population when examining the effects of age alone.

We used passive leg raise as a model to study increased preload. This simple intervention showed that passive leg raise increased CI, PCWP, and mPAP to different magnitudes between age categories, such that CI increased most in the youngest participant, whereas the opposite trend was evident with PCWP and mPAP. Interestingly, the modest increase in preload caused by passive leg raise was able to display age related differences in key hemodynamic parameters. Although leg raise has been shown to elicit significant differences between patients with HFpEF and individuals without cardiac disease (8), the diagnostic role of leg raise in identifying high filling pressures is still unsettled (10); currently, this maneuver is not included in major guidelines. Our data suggest that if leg raise is used in a diagnostic approach, hemodynamic variables should be interpreted according to the age of the patient.

In the 2016 European Society of Cardiology (ESC) heart failure guidelines, the diagnostic criteria for HFpEF are heart failure symptoms, LV ejection fraction 50%, and a resting mean PCWP of ≥15 mm Hg (15). However, resting PCWP measurements may not always provide prognostic information in this patient population, as shown by Dorf et al. (16). Using summarized data from all patients (**Table 2**), we confirmed that in healthy individuals, the resting mPAP was ≤15mm Hg and PCWP ≤9 mm Hg, irrespective of age or sex.

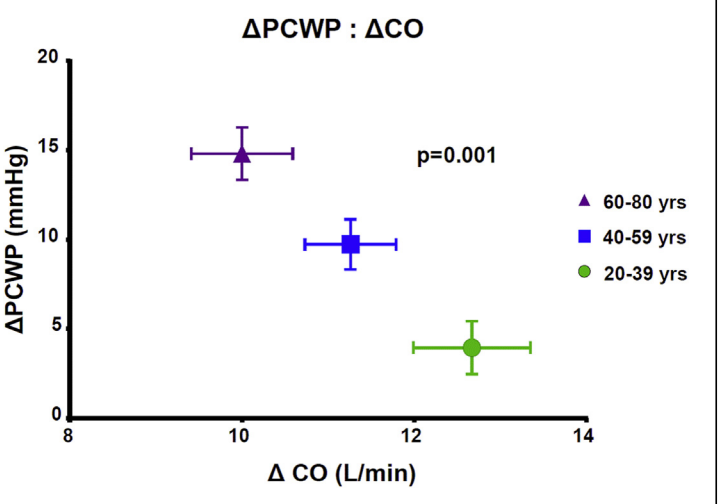
As suggested by the ESC heart failure guidelines, exercise testing is important in HFpEF diagnosis (15). Borlaug et al. (8) elegantly showed how exercise stress testing was able to unmask early signs of HFpEF, even in participants with normal resting

FIGURE 3 Mean PCWP Depicted During Rest and Interventions (Leg Raise: 25%, 50%, and 75% of VO_2-max)



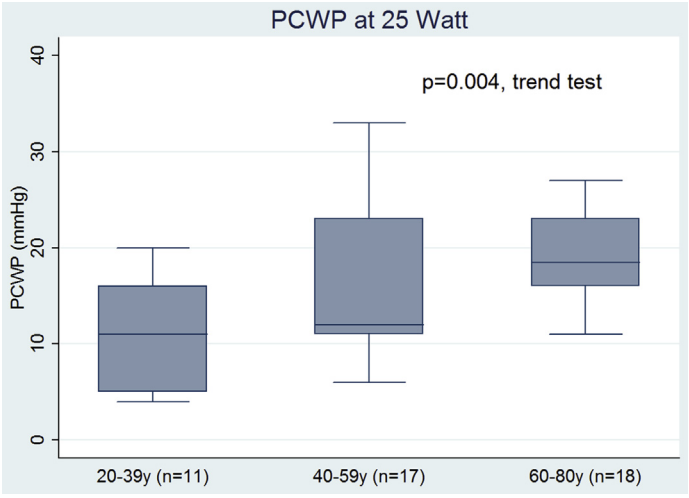
Participants were divided into 3 groups (20 to 39 years, 40 to 59 years, 60 to 80 years). Values are mean ± SEM. *$p < 0.05$ between age groups. PCWP = pulmonary capillary wedge pressure; other abbreviations as in Figure 1.

FIGURE 4 Pressure Flow Relationship Depicted Between ΔPCWP and ΔCO From Baseline to 75% of VO_2-max in All Age Categories



Values are mean ± SEM. Abbreviations as in Figures 1 and 2.

FIGURE 5 Box Plot of PCWP in Those Who Achieved a Workload of 25 W Across All Age Categories



Abbreviations as in Figure 2.

PCWP values (<15 mm Hg). In the Borlaug et al. (8) and other papers (9), diagnostic PCWP cutoff values for HFpEF were set at ≥15 and ≥25 mm Hg at rest and exercise, respectively. The reference values were based on studies with few participants without the possibility of sex- or age-matching (17,18). Using our healthy reference population, the PCWP diagnostic rule-out value of 15 during rest is well within our confidence intervals for all age groups (Table 2). During exercise, The PCWP diagnostic cutoff value during exercise of 25 mm Hg would include 4 of 10 in our 70- to 80-year age category, and 2 of 10 in our 60- to 69-year age category of healthy participants. Thus, when using exercise test to diagnose HFpEF, the diagnosing physician should be aware that 30% of healthy peers age ≥60 years in our study displayed values above 25 mm Hg in PCWP. This also suggests that diagnostic accuracy may be enhanced, if the PCWP diagnostic threshold was age adjusted.

The background for this observation is an inverse and linear relationship of the pressure flow relationship between mPAP, PCWP, and CI during exercise with age (Figures 3 and 4). The interrelationship between mPAP and PCWP with CO that we observed was a clear display of the attenuation of diastolic compliance with age, causing progressively higher intracardiac pressures at a given CO.

The age of the individual and the exercise intensity significantly influenced measurements. For future reference, the data presented in this study could aid in determining an age-corrected diagnostic threshold that would likely improve the diagnostic accuracy of invasive exercise tests (Table 2).

The 2015 ESC/European Respiratory Society (ERS) guidelines on pulmonary hypertension note that during rest, mPAP should not exceed 20 mm Hg (19), however a definite diagnosis requires mPAP of ≥25 mm Hg in addition to other criteria. Studies have been undertaken to examine the group of patients with pressures between 21 and 24 mm Hg (20,21), as "the clinical significance of a PAPm between 21 and 24 mm Hg is unclear [ESC/ERS guideline]." In our healthy cohort, 10% of patients older than age 50 years had an mPAP of 21 mm Hg during rest, which should lead to a conservative approach when dealing with patients with 21 mm Hg mPAP at rest, if other criteria are not clearly indicative of pulmonary hypertension. The ESC/ERS guidelines also state "Due to the lack of reliable data that define which levels of exercise-induced changes in mPAP or PVR have prognostic implications, a disease entity 'PH on exercise' cannot be defined" (19). Although our data do not provide prognostic information, it provides reference values for mPAP and PVR in healthy participants during exercise, which can be used for future determination of a diagnostic threshold for pulmonary hypertension.

A further aim of this study was to show if graded exercise would provide incremental information about filling pressures across ages. There were significant differences in PCWP between age groups when participants were subjected to the increasing grades of exercise (25% and 75% of VO_2-max). This highlights the importance of an exercise stress protocol with submaximal-maximal workloads to discern the effects of age on hemodynamic parameters (Table 2). Our study was not adequately powered to provide accurate estimates of which exercise loads would be sufficient to obtain maximal hemodynamic measures in every age group.

STUDY LIMITATIONS AND STRENGTHS. This study recruited 62 patients which is a moderate size sample, and, to our knowledge, exceeds other studies that prospectively recruited healthy participants (3,9-11,22,23). The sample size was based on power calculations and ethical considerations of exposing as few healthy participants as possible to this invasive protocol. With this sample size, the possibility of type II errors cannot be ignored. Whenever reporting reference values of healthy individuals, the obvious question is how to define healthy. Our intent was to get a selection of individuals with no major health issues and no obvious health problems at screening, while avoiding a selection of extremely

healthy individuals. Based on the baseline characteristics, especially the measures of pulmonary and cardiac function (**Table 1**), we believe our results are applicable as a general reference values. Because we only did resting echocardiogram, obtained medical history, and did an exercise ECG, we cannot definitely rule out that some patients could have had asymptomatic coronary disease.

When using our data as a reference, it should be noted that our population was Caucasian and age did not exceed age 80 years. In addition, patients had normal weight and had an exercise capacity above predicted values (+28%) for sedentary healthy people (13). Furthermore, exclusion criteria such as LV hypertrophy and left atrial enlargement may have selected participants in the more healthy spectrum across ages. Exercise has previously been shown to elicit hemodynamic changes of different magnitudes across ages, most notably in elderly participants (1,2). By using workloads relative to each individuals exercise capacity (25%, 50%, and 75% of VO_2-max), we believe our intervention posed a comparable hemodynamic stress on our participants regardless of their age, and hence allowed comparison between the age groups. Using comparable workloads across ages has not been reported earlier to our knowledge. We used 3 graded intensities of exercise during supine cycling (25%, 50%, and 75% of VO_2-max) determined from an upright ergometer VO_2-max test. We suspect from the level of exertion experienced by the participants, the lactate concentrations, and SVO_2 during the final increment that the effect of lying in a supine position may have posed a cardiopulmonary stress equaling that of submaximal/maximal work, but we did not have any way to quantify this. Of note, there was no difference in lactate levels or SvO_2 between age groups at any of the 3 workloads.

We report how the pressure-flow relationship is associated with age, as is the case for CO and age. In this study, we could only technically measure a CO of 20 l/min or less. This bias censored more measurements in the younger age groups, which most likely lead to more conservative estimates of these associations.

CONCLUSION

We provide estimates of hemodynamic properties in healthy individuals across all age groups—estimates that can be used as a reference against diseased populations (e.g., pulmonary hypertension) to discern the influence of any given disease on hemodynamics. It was evident that signs of cardiac aging were measureable even in the young participants and that the influence of aging on hemodynamics was progressive across all ages. Exercise was a valid method to unmask these changes because baseline measurements were equal across all ages and between sexes. Sex did not influence measurements at any time.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: The hemodynamic values summarized provide normative ranges that are applicable in daily clinical settings in which hemodynamic values are used for diagnostic purposes.

TRANSLATIONAL OUTLOOK: These hemodynamic values in healthy can serve as reference to discern the influence of disease from that of physiological aging. This enables a better understanding of the hemodynamic effects that various diseases—cardiac and noncardiac—pose on the heart.

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KEY WORDS aging, catheterization, exercise, sex, healthy, hemodynamics

APPENDIX For a supplemental table and figures, please see the online version of this article.