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

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ABSTRACT

OBJECTIVES 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 $\geq$ 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 2016;■:■–■) © 2016 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 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

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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)

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).

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 seconds. 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).