Echocardiographic Pulmonary Artery Systolic Pressure in the Coronary Artery Risk Development in Young Adults (CARDIA) Study: Associations With Race and Metabolic Dysregulation

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Background—The determinants of pulmonary artery systolic pressure (PASP) are not fully understood. It is unknown whether racial differences in PASP exist or if other population characteristics are associated with pulmonary pressure in humans. We examined echocardiographically estimated PASP in the Coronary Artery Risk Development in Young Adults (CARDIA) study, a middle-aged, biracial community-based cohort.

Methods and Results—At the CARDIA year-25 examination, 3469 participants underwent echocardiography, including measurement of tricuspid regurgitant jet velocity to estimate PASP. Clinical features, laboratory values, pulmonary function tests, and measurement of adipose depot volume were analyzed for association with PASP. PASP was estimated in 1311 individuals (61% female, 51% white). Older age, higher blood pressure, and higher body mass index were associated with higher PASP. Black race was associated with higher PASP after adjustment for demographics and left and right ventricular function (β 0.94, 95% CI 0.24-1.64; $P=0.009$), but this association was no longer significant after further adjustment for lung volume (β 0.42, 95% CI −0.68 to 0.96; $P=0.74$). Insulin resistance, inflammation (C-reactive protein and interleukin-6), and visceral adipose volume were independently associated with higher PASP after adjustment for relevant covariates. PASP rose with worsening diastolic function (ratio of early transmitral Doppler velocity to average mitral annular tissue Doppler velocity [E/e′] and left atrial volume index).

Conclusions—In a large biracial cohort of middle-aged adults, we identified associations among black race, insulin resistance, and diastolic dysfunction with higher echocardiographically estimated PASP. Further studies are needed to examine racial differences in PASP and whether insulin resistance directly contributes to pulmonary vascular disease in humans. (***J Am Heart Assoc***. 2017;6:e005111. DOI: 10.1161/JAHA.116.005111.)

Key Words: adipose tissue • echocardiography • inflammation • metabolic syndrome • pulmonary hypertension

Elevated pulmonary artery systolic pressure (PASP) is associated with increased mortality in individuals with and without prevalent cardiovascular disease.[1-4] Prior studies have established a relationship among PASP, older age, and left ventricular function.[1,3] The largest studies to date have been either retrospective in referral populations[1,3,5] or in racially homogeneous samples,[1,4] which may limit their generalizability. Black populations have a higher incidence of systemic hypertension, more advanced left ventricular (LV) remodeling, and lower lung volumes compared with whites.[6-10] It is unknown if these features are associated with higher pulmonary pressure in the black population.

The impact on PASP of variables not directly related to heart and lung function has not been described. Recent evidence in humans and experimental models suggests that metabolic traits such as insulin resistance and adiposity may directly contribute to pulmonary vascular disease.[11-14] We aimed to address important knowledge gaps with respect to

potential determinants of pulmonary artery pressure that have not been fully examined in humans.

The purpose of this study was to describe the relationship between race and cardiometabolic traits with PASP in the Coronary Artery Risk Development in Young Adults (CARDIA) study cohort, a middle-aged, biracial community-based population without prevalent cardiovascular disease.

Methods

Study Population

CARDIA is a prospective observational cohort study of the determinants of cardiovascular disease.[15] At the baseline examination (1985-1986), 5115 black or white men and women aged 18 to 30 years were enrolled from 4 sites in the United States. The design and study procedures for the CARDIA cohort have been described in detail.[15] Participants who underwent the year-25 (2010-2011) echocardiogram exam (n=3469) were included in this analysis. Institutional review boards from each site approved the study, and signed informed consent was obtained from all participants.

Clinical Covariates

Standard protocols were used at each study site for collection of all exam components.[15] Race and sex were self-reported. Systolic and diastolic blood pressures were averaged from the second and third readings measured using an automated, calibrated monitor. Pulmonary function testing was performed during the year-20 examination, as previously described.[16] Obesity was defined as a body mass index (BMI) of >30 kg/m^2. Physical activity was self-reported and quantified using a validated questionnaire.[15,17] Participants were asked about the frequency of engaging in 13 different categories of exercise and scored based on the duration and frequency of activity in each category. Exercise units were calculated based on the frequency and intensity of each activity. Laboratory data (glucose, lipids, insulin, creatinine, and C-reactive protein) were measured from fasting samples, processed centrally, and obtained on the same study visit as the echocardiogram. Interleukin-6 assays were performed during the year-20 examination; thus, analyses with this marker were exploratory, given the interval between measurement and PASP estimation. Prevalent diabetes was defined as a fasting glucose ≥126 mg/dL, a 2-hour postload glucose value

Table 1. Clinical Characteristics of CARDIA Participants With and Without a Measureable TR Jet

	No TR Jet (N=2159)	TR Jet (N=1311)	*P* Value
Age, y	51 (47, 53)	51 (47, 53)	0.41
Male	997 (46)	507 (51)	<0.001
White	1184 (55)	667 (51)	0.02
BMI, kg/m^2	29 (25, 35)	28 (25, 33)	<0.001
Hypertension	751 (35)	382 (29)	<0.001
SBP, mm Hg	118 (110, 129)	117 (108, 127)	<0.001
DBP, mm Hg	75 (67, 82)	74 (67, 81)	0.001
Diabetes mellitus	263 (12)	109 (8)	<0.001
Obesity	1001 (46)	510 (39)	<0.001
Hyperlipidemia	639 (31)	331 (26)	0.004
Metabolic syndrome	607 (28)	233 (18)	0.001
Glucose, mg/dL	94 (88, 103)	92 (86, 100)	<0.001
Insulin, mIU	9.3 (5.7, 15.2)	8.0 (5.0, 12.8)	<0.001
HOMA-IR	2.2 (1.3, 3.9)	1.8 (1.1, 3.1)	<0.001
Smoker, ever	467 (22)	277 (22)	0.59
FEV1, L	3.0 (2.5, 3.6)	2.9 (2.5, 3.5)	0.12
Physical activity, exercise units	271 (124, 478)	288 (138, 504)	0.82
eGFR, mL/(min·1.73 m^2)	94 (83, 108)	94 (83, 108)	0.73
Interleukin-6, ng/mL	1.7 (1.0, 3.0)	1.7 (1.0, 2.9)	0.035
C-reactive protein, mg/L	1.5 (0.6, 3.8)	1.3 (0.6, 3.0)	<0.001

Data are presented as median (25th, 75th percentiles) or counts (%). BMI indicates body mass index; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; FEV1, forced expiratory volume in 1 second; HOMA-IR, homeostatic model of insulin resistance; SBP, systolic blood pressure; TR, tricuspid regurgitant.

Table 2. Clinical Characteristics Stratified by Quartiles of Pulmonary Artery Systolic Pressure

	Pulmonary Artery Systolic Pressure, mm Hg				
	<27 (N=328)	27 to 31 (N=328)	31 to 34 (N=327)	>34 (N=328)	P Value
Age, y	50 (47, 53)	51 (47, 53)	50 (47, 53)	52 (48, 53)	0.006
Male	130 (40)	105 (32)	138 (42)	134 (41)	<0.035
Black	144 (43)	137 (42)	160 (49)	206 (63)	<0.001
BMI, kg/m^2	27 (24, 31)	28 (24, 32)	28 (25, 33)	31 (27, 35)	<0.001
Hypertension	68 (21)	88 (27)	97 (30)	129 (40)	<0.001
SBP, mm Hg	113 (105, 122)	116 (106, 126)	118 (107, 127)	122 (113, 132)	<0.001
DBP, mm Hg	72 (64, 78)	73 (66, 80)	74 (65, 80)	76 (70, 84)	<0.001
Diabetes mellitus	25 (8)	19 (6)	26 (8)	39 (12)	<0.001
Obesity	97 (30)	119 (36)	119 (37)	175 (54)	<0.001
Hyperlipidemia	82 (26)	80 (25)	78 (25)	91 (29)	0.67
Metabolic syndrome	30 (9)	45 (14)	49 (15)	66 (21)	<0.001
Glucose, mg/dL	91 (87, 99)	91 (85, 98)	93 (87, 100)	94 (87, 102)	0.019
Insulin, mIU	7.5 (4.8, 11.5)	7.6 (4.5, 12.2)	7.5 (4.8, 12.6)	9.7 (6.0, 14.5)	<0.001
HOMA-IR	1.7 (1.1, 2.9)	1.7 (1.0, 2.9)	1.8 (1.1, 2.8)	2.3 (1.3, 3.7)	<0.001
Smoker, ever	81 (25)	65 (20)	63 (20)	68 (21)	0.36
FEV1, L	3.1 (2.6, 3.6)	2.9 (2.5, 3.5)	3.0 (2.6, 3.6)	2.8 (2.3, 3.3)	<0.001
Physical activity, exercise units	312 (147, 516)	284 (156, 516)	303 (136, 548)	261 (104, 458)	<0.02
eGFR, mL/(min·1.73 m^2)	95 (83, 106)	94 (81, 107)	94 (82, 107)	96 (83, 108)	0.51
Interleukin-6, ng/mL	1.6 (0.9, 2.5)	1.5 (1.0, 2.6)	1.7 (1.0, 3.1)	1.9 (1.0, 3.3)	0.004
C-reactive protein, mg/L	0.9 (0.5, 2.1)	1.2 (0.5, 3.1)	1.3 (0.6, 2.7)	1.8 (0.7, 4.6)	<0.001

Data are presented as median (25th, 75th percentiles) or counts (%). BMI indicates body mass index; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; FEV1, forced expiratory volume in 1 second; HOMA-IR, homeostatic model of insulin resistance; SBP, systolic blood pressure.

≥200 mg/dL, hemoglobin A1c ≥6.5%, or the current use of antidiabetic medications. Prevalent hypertension was defined as self-report, systolic blood pressure ≥140 mm Hg, diastolic blood pressure ≥90 mm Hg, or use of antihypertensive medications. Estimated glomerular filtration rate was calculated from the chronic kidney disease epidemiology equation,[18] and the homeostatic model assessment of insulin resistance (HOMA-IR) was calculated according the formula (glucose [mg/dL]×insulin [mIU/mL])/405.[19] Metabolic syndrome was defined according to the third report of the National Cholesterol Education Program.[20]

Echocardiography

The CARDIA year-25 exam echocardiography protocol has been published previously[8] and was performed according to American Society of Echocardiography guidelines.[21-23] Transthoracic echocardiography was performed using an Artida cardiac ultrasound scanner (Toshiba Medical Systems, Otawara, Japan) by registered sonographers using a 1.8- to 4.2-MHz phased-array transducer according to a standard protocol. Experienced sonographers analyzed images offline using commercially available software (Digisonics Inc, Houston, TX). Experienced readers interpreted digitized images at a core reading center (Johns Hopkins University, Baltimore, MD). Wall motion 2-dimensional tracking software (Toshiba Medical Systems, Otawara, Japan) was used to perform speckle-tracking analysis to obtain longitudinal and circumferential left ventricular peak systolic strain. The tricuspid regurgitant (TR) jet velocity was measured in triplicate and averaged using continuous-wave Doppler echocardiography. PASP was estimated from the TR jet velocity and an assumed right atrial pressure of 10 mm Hg using the modified Bernoulli equation (PASP=4[TR jet velocity]^2+right atrial pressure). Our findings did not change in magnitude or significance when TR jet values were analyzed without an assumed right atrial pressure. Therefore, to provide better clinical context, we elected to report values as estimated PASP. Prior studies have made similar assumptions regarding right atrial pressure, which correlate well with invasive values.[1,3] Echocardiographic pulmonary hypertension (PH) was defined as PASP >40 mm Hg.[24,25]
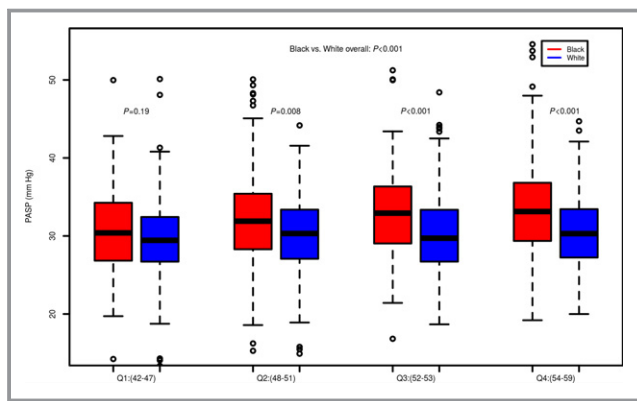
Figure 1. Comparison of pulmonary artery systolic pressure (PASP) in black and white CARDIA participants stratified by quartiles of age. PASP is significantly higher in black individuals (red bars) compared with whites (blue bars; *P*<0.001). This relationship was observed across each of the top 3 quartiles of age.

Computed Tomography

Returning participants at the year-25 exam were invited to undergo computed tomography of the chest and abdomen using 64-channel multidetector computed tomography scanners (GE Healthcare, Milwaukee, WI or Siemens, Erlangen, Germany).[26] Subcutaneous, visceral, and pericardial adipose depot volumes were quantified from computed tomography images (n=3174).[27] A Hounsfield unit range of −190 to −30 was used to identify adipose tissue in all depots. Pericardial adipose volume was quantified by summing the adipose-containing pixels in the axial slices within 15 mm above and 30 mm below the superior extent of the left main coronary artery.[28,29]

Statistical Analysis

Data are presented as median (interquartile range) or counts (percentage) for continuous and categorical variables, respectively. Comparisons between groups were performed using the Mann-Whitney U test or Kruskal-Wallis test, as appropriate. Categorical variables were compared using the chi-squared test. Correlation between continuous variables was measured using Spearman rank correlation. Multivariable linear regression models were used to examine the associations between PASP and clinical, echocardiographic, and adiposity variables. Covariates included in multivariable models were selected a priori based on clinical relevance. For the association between black race and PASP, we first adjusted for basic demographics (age, sex, BMI) and systolic blood pressure, which differs between races. We next built on this model by adding measures of LV and right ventricular (RV) structure and function, which were previously reported to differ by race in CARDIA.[8] Finally, we added forced expiratory

volume in 1 second (FEV1) given prior descriptions of racial differences in lung volume and function. In the model exploring HOMA-IR and PASP, we adjusted for basic demographics and diastolic function because of the association between diabetes and diastolic function.[30] For associations with visceral adipose, we adjusted for demographics, HOMA-IR, and C-reactive protein (CRP) to account for the possibility that insulin resistance and inflammation may mediate the relationship between adiposity and PASP. Nonlinear relationships between PASP and cardiometabolic variables were assessed using multivariable adjusted restricted cubic splines.

Results

Clinical Characteristics

In total, 3470 individuals participated in the year-25 echocardiography exam, of whom 1311 (38%) had a measureable TR jet, and these constituted the study cohort. No subject had severe TR or RV dysfunction. Characteristics of subjects with and without a measureable TR jet are presented in Table 1. Individuals without a measureable TR jet had more cardiovascular comorbidities and higher rates of diabetes, obesity, and metabolic syndrome. Clinical characteristics of the 1311 included study participants stratified by quartiles of PASP are shown in Table 2. Increasing PASP was associated with older age, higher systolic and diastolic blood pressure, and higher BMI. The prevalence of smoking was similar across PASP quartiles, but FEV1 and physical activity were lowest in the highest quartile of PASP (*P*<0.001 and *P*=0.02, respectively). There was no difference in the distribution of PASP between males and females (Table 2).

Black individuals accounted for 63% of the highest PASP quartile but only 49% of the study cohort. PASP was higher among black individuals (32±6 mm Hg vs 30±5 mm Hg in whites; *P*<0.001) overall and across the top 3 quartiles of age (Figure 1). A total of 86 individuals met an echocardiographic definition of PH, of whom 71% were black (Table 3). In general, subjects with PH were characterized by greater cardiometabolic dysfunction, including a higher prevalence of diabetes, obesity, hypertension, and hyperlipidemia and 21% lower reported physical activity (Table 3).

Cardiac Structure and Function

Although cardiac structure and function varied according to quartiles of PASP, most associations were nonlinear (Table 4). For example, LV end-diastolic volume index and end-systolic volume index were higher in the second and third PASP quartiles and declined in the highest quartile. Left atrial volume index and E/e′ increased across quartiles, indicative

Table 3. Clinical Characteristics Stratified by Presence or Absence of Echocardiographic Pulmonary Hypertension

	PASP>40 (N=86)	PASP<40 (N=1255)	*P* Value
PASP, mm Hg	42.1 (40.8, 47.2)	30.4 (27.1, 33.7)	<0.001
Age, y	52 (48, 54)	51 (47, 53)	0.024
Male	32 (37)	475 (39)	0.77
Black	61 (71)	583 (48)	<0.001
BMI, kg/m^2	32 (28, 37)	28 (24, 32)	<0.001
Hypertension	44 (51)	338 (28)	<0.001
SBP, mm Hg	124 (114, 136)	117 (107, 127)	<0.001
DBP, mm Hg	76 (71, 87)	73 (66, 80)	0.001
Diabetes mellitus	54 (64)	456 (37)	<0.001
Obesity	1010 (46)	510 (39)	<0.001
Hyperlipidemia	32 (38)	299 (25)	0.01
Metabolic syndrome	23 (28)	167 (14)	<0.001
Glucose, mg/dL	93 (88, 101)	92 (86, 100)	0.77
Insulin, mIU	10.08 (5.3, 15.7)	7.8 (5.0, 12.5)	0.076
HOMA-IR	2.4 (1.1, 3.8)	1.8 (1.1, 3.0)	0.095
Smoker, ever	16 (19)	261 (22)	0.24
FEV1, L	2.5 (2.1, 3.1)	3.0 (2.5, 3.5)	<0.001
Physical activity, exercise units	231 (61, 405)	292 (144, 510)	0.005
eGFR, mL/(min·1.73 m^2)	94 (84, 109)	94 (82, 108)	0.89
Interleukin-6, ng/mL	2.5 (1.2, 4.0)	1.6 (1.0, 2.8)	0.002
C-reactive protein, mg/L	2.2 (0.8, 7.1)	1.2 (0.6, 2.9)	<0.001

Data are presented as median (25th, 75th percentiles) or counts (%). BMI indicates body mass index; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; FEV1, forced expiratory volume in 1 second; HOMA-IR, homeostatic model of insulin resistance; PASP, pulmonary artery systolic pressure; SBP, systolic blood pressure.

of rising PASP with worse diastolic function. LV ejection fraction (LVEF) increased slightly with PASP, but there was no significant change in cardiac index or longitudinal or circumferential myocardial strain across quartiles. The association of PASP with RV function measurements was conflicting; we found no change in tricuspid annular plane systolic excursion (TAPSE) across quartiles but a significant increase in RV tricuspid annular tissue Doppler velocity (S′) in the highest quartile of PASP.

Determinants of PASP

Univariate and age- and sex-adjusted associations between clinical features and PASP are presented in Table 5. Multivariable models were created to specifically examine associations of PASP with race, metabolic features, and adiposity.

Black race was significantly associated with PASP after adjustment for age, sex, BMI, and systolic blood pressure (Table 6, Model 1; β 1.22, 95%CI 0.53-1.91; *P*<0.001). This relationship was attenuated but remained significant after LVEF, LA volume index, E/e′, and RV S′ were added to the model (Table 6, Model 2; β 0.94, 95%CI 0.24-1.64; *P*=0.009).

The association between black race and PASP was no longer significant after addition of FEV1 to the adjusted model (Table 6, Model 3; β 0.42, 95%CI −0.68 to 0.96; *P*=0.74). We found no significant interaction between race and BMI or race and sex for the association with PASP (*P*>0.05 for all).

Metabolism and Inflammation

The prevalence of diabetes and obesity increased across quartiles of PASP (Table 1). HOMA-IR increased across PASP quartiles and appeared to be driven by increased insulin levels, as fasting glucose was similar across groups. PASP increased with the number of components of the metabolic syndrome (*P*<0.001; Figure 2). The inflammation markers IL-6 and CRP increased with PASP, with CRP nearly doubling between the highest and lowest quartiles. The relationship between HOMA-IR and PASP was nonlinear when adjusted for age, sex, BMI, LA volume index, E/E′, and race (Table 7 and Figure 3; *P*=0.002). We observed an inflection point of rising PASP at HOMA-IR values consistent with the development of insulin resistance. PASP appeared to decline at higher HOMA-IR values; however, this is difficult to interpret given the wide

Table 4. Echocardiographic Characteristics Stratified by Quartiles of PASP

	PASP, mm Hg				
	<27 (N=328)	27 to 31 (N=328)	31 to 34 (N=327)	>34 (N=328)	P Value
LVEDVI, mL/m^2	52 (46, 61)	57 (49, 64)	57 (49, 63)	56 (48, 65)	<0.001
LVESVI, mL/m^2	20 (16, 25)	22 (18, 26)	22 (17, 26)	20 (16, 25)	<0.001
LVMI, g/m^2	78 (68, 93)	82 (69, 99)	80 (68, 97)	85 (70, 104)	0.049
LAVI, mL/m^2	23 (19, 28)	26 (21, 30)	26 (21, 30)	26 (22, 32)	<0.001
e′ avg, cm/s	10.6 (9.0, 12.0)	10.6 (9.2, 12.3)	10.7 (9.3, 12.1)	10.0 (8.6, 11.7)	0.018
E velocity, cm/s	76 (65, 86)	78 (68, 89)	80 (71, 91)	83 (74, 94)	<0.001
A velocity, cm/s	60 (49, 69)	61 (52, 72)	62 (51, 75)	68 (56, 80)	<0.001
E/A	1.3 (1.1, 1.5)	1.3 (1.1, 1.5)	1.3 (1.1, 1.5)	1.2 (1.1, 1.5)	0.09
Decel time, ms	178 (155, 206)	179 (149, 206)	178 (148, 201)	178 (146, 205)	0.60
E/e′	7.1 (6.1, 8.5)	7.5 (6.2, 8.7)	7.6 (6.4, 9.1)	8.3 (6.9, 10.1)	<0.001
LVEF, %	61 (57, 66)	61 (56, 65)	61 (57, 66)	63 (59, 68)	<0.001
CI, L/(min·m^2)	2.76 (2.32, 3.35)	2.84 (2.37, 3.45)	2.69 (2.30, 3.24)	2.90 (2.35, 3.45)	0.053
GLS, %	−15.2 (−16.6, −13.6)	−15.3 (−17.0, −13.7)	−15.1 (−16.9, −13.8)	−15.2 (−16.9, −13.7)	0.84
GCS, %	−15.1 (−16.8, −13.4)	−15.7 (−17.4, −13.6)	−15.2 (−17.1, −13.6)	−15.7 (−17.8, −13.5)	0.23
TAPSE, cm	2.5 (2.1, 2.8)	2.6 (2.2, 2.9)	2.5 (2.2, 2.9)	2.6 (2.3, 2.9)	0.37
RV S′, cm/s	12.9 (11.6, 14.3)	13.0 (11.7, 14.6)	13.3 (12.0, 15.1)	13.7 (12.4, 15.9)	<0.001

Data presented as median (25th, 75th percentiles). A indicates transmitral spectral Doppler late velocity; CI, cardiac index; Decel time, transmitral spectral E-wave deceleration time; E, transmitral spectral Doppler early velocity; e′ avg, average mitral annulus tissue Doppler early relaxation velocity; GCS, global circumferential systolic strain; GLS, global longitudinal systolic strain; LAVI, left atrial volume index; LVEDVI, left ventricular end-diastolic volume index; LVEF, left ventricular ejection fraction; LVESVI, left ventricular end-systolic volume index; LVMI, left ventricular mass index; PASP, Pulmonary Artery Systolic Pressure; S′, tricuspid annular tissue Doppler velocity; TAPSE, tricuspid annular plane systolic excursion.

confidence intervals. The association between CRP and increased PASP also remained significant, albeit modestly, after adjustment for age, sex, BMI, and race (β 0.09 per 1-unit increase, 95%CI 0.02-0.16; *P*=0.01). Models for these analyses are presented in Table 7.

Adiposity

Adipose volume quantification was performed in 91% (1195/1311) of participants with a measurable TR jet. Higher PASP was associated with greater subcutaneous, visceral, and pericardial adipose volume (Table 8; *P*<0.001 for all), although the correlation between PASP and each depot was modest (r_s=0.12-0.17; *P*<0.001 for all). The impact of visceral adiposity (the most metabolically active depot) on PASP was independent of age, sex, BMI, HOMA-IR, and CRP (Table 9; β 0.01 per cm^3, 95%CI 0.003-0.02; *P*=0.009). Of note, black race remained significantly associated with PASP in models adjusting for insulin resistance, CRP, and visceral adipose volume.

Discussion

We examined the clinical, physiologic, and biochemical correlates of PASP in 1311 participants in the CARDIA study,

a large biracial cohort of middle-aged individuals. In addition to confirming previously published relationships with age and LV function, we report newly recognized associations of higher PASP with black race and metabolic traits. Plasma markers of insulin resistance and inflammation and adipose volume were also associated with PASP.

Context With Existing Literature

Prior studies have examined the clinical and echocardiographic correlates of PASP.[1,3,5] In a large hospital-based referral cohort with normal echocardiograms, McQuillan et al found that higher age, male sex, BMI, and LVEF were associated with higher PASP.[3] Lam et al and Armstrong et al report similar findings with respect to age and BMI but did not find a difference in PASP between males and females,[1,5] as in CARDIA. Similar PASP between males and females does not appear to be related to the disproportionate number of females in CARDIA (61%), which is similar to those in other cohorts (57% to 67%).[1,4,5] As in other population-based studies, we found that LV diastolic function was a significant contributor to PASP.[1,5]

The CARDIA cohort builds on prior studies in this area with several strengths. The CARDIA study is prospective, and

Table 5. Univariate and Adjusted Associations of Clinical Features With PASP

Variable	β (95%CI)	*P* Value	β Adjusted for Age and Sex (95%CI)	*P* Value
Age, y	0.78 (0.25–1.32)	0.004	0.79 (0.26-1.32)	0.004
Male	0.39 (−0.28 to 1.06)	0.25	0.79 (0.26-1.32)	0.004
Black race	1.84 (1.20-2.49)	<0.001	1.12 (0.58-1.65)	<0.001
BMI, kg/m^2	1.46 (1.06-1.85)	<0.001	0.81 (0.29-1.33)	0.002
Hypertension	2.07 (1.36-2.78)	<0.001	0.69 (0.16-1.23)	0.01
SBP, mm Hg	1.38 (0.99-1.77)	<0.001	0.68 (0.15-1.21)	0.01
DBP, mm Hg	1.21 (0.80-1.61)	<0.001	0.82 (0.29-1.35)	0.002
Diabetes mellitus	1.74 (0.55-2.92)	0.004	0.75 (0.22-1.29)	0.006
Obesity	1.99 (1.33-2.65)	<0.001	0.81 (0.28-1.34)	0.003
Hyperlipidemia	0.56 (−0.20 to 1.32)	0.15	0.68 (0.13-1.23)	0.02
Metabolic syndrome	1.96 (1.07-2.86)	<0.001	0.71 (0.20-1.23)	0.007
Glucose, mg/dL	−0.03 (−0.21 to 0.16)	0.78	0.74 (0.21-1.27)	0.006
Insulin, mIU	0.61 (0.24-0.98)	0.001	0.76 (0.22-1.29)	0.005
HOMA-IR	0.28 (−0.01 to 0.57)	0.06	0.73 (0.20-1.27)	0.007
Smoker, ever	−0.48 (−1.28 to 0.33)	0.25	0.82 (0.28-1.37)	0.003
FEV1, L	−1.10 (−1.55 to −0.64)	<0.001	0.60 (0.04-1.17)	0.035
Physical activity, exercise units	−0.46 (−0.88 to −0.04)	0.03	0.82 (0.29-1.35)	0.003
eGFR, mL/(min·1.73 m^2)	−0.11 (−0.50 to 0.28)	0.59	0.74 (0.20-1.28)	0.007
Interleukin-6, ng/mL	0.45 (0.21-0.69)	<0.001	0.85 (0.28-1.42)	0.003
C-reactive protein, mg/L	0.41 (0.25-0.57)	<0.001	0.78 (0.26-1.31)	0.004

Beta coefficients (β) for continuous variables represent the effect of moving from a value at the 25th percentile to the 75th percentile. BMI indicates body mass index; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; FEV1, forced vital capacity in 1 second; HOMA-IR, homeostatic model of insulin resistance; PASP, pulmonary artery systolic pressure; SPB, systolic blood pressure.

echocardiogram interpretation was performed at a central core lab. No data have been published on PASP from a prospective cohort of middle-aged individuals. Prior reports have largely involved retrospective cohorts with clinical interpretations. The CARDIA cohort is 51% black, whereas race was not reported in prior reports or is assumed to be almost exclusively white or black. Finally, prior studies were limited to demographic and echocardiographic data. In contrast, the CARDIA study includes detailed information about comorbid conditions, plasma biomarkers, and adipose volume measurements.

Determinants of PASP

To our knowledge, this is the first large study to examine racial differences in PASP in a community-based population. Choudhary et al demonstrated that elevated PASP is associated with an increased risk of hospitalization for heart failure in the Jackson Heart Study, but this cohort does not include white individuals.[4] Ristow et al examined pulmonary pressure in the Heart and Soul Study, but racial differences were not compared directly, and only 105 black individuals were studied.[31] Khush et al found a similar TR gradient but higher PA diastolic pressure among black individuals (n=87 compared with 273 white) with coronary artery disease in the Heart and Soul Study.[32] In the CARDIA cohort, which is not selected for existing cardiovascular disease, black race was associated with higher PASP. This relationship did not appear to be mediated by BMI, prevalent hypertension, metabolic features, or LV/RV function. Rather, the relationship between race and PASP appeared to be most strongly influenced by lower FEV1 in black individuals. This finding is clinically relevant because even modest increases in PASP are associated with higher cardiovascular risk.[33] Data from the Multiethnic Study of Atherosclerosis suggest that there may be racial differences in RV adaptation to cardiopulmonary disease.[34] These findings warrant further investigation into racial differences in the development of pulmonary vascular disease, including at subclinical values of PASP.

Literature supporting a relationship between metabolic dysregulation and the development of pulmonary vascular

Table 6. Multivariate Associations of Black Race and PASP

	β (95%CI)	P Value
Model 1: age, sex, BMI, systolic blood pressure		
Black race	1.22 (0.53-1.91)	<0.001
Age, y	0.91 (0.38-1.43)	<0.001
Male	0.55 (−0.11 to 1.21)	0.10
BMI, kg/m^2	1.09 (0.69-1.50)	<0.001
SBP, mm Hg	0.91 (0.50-1.31)	<0.001
Model 2: age, sex, BMI, SBP, LVEF, LA volume index, RV S′		
Black race	0.94 (0.24-1.64)	0.009
Age, y	0.91 (0.38-1.44	<0.001
Male	0.59 (−0.08 to 1.26)	0.08
BMI, kg/m^2	0.79 (0.37-1.21)	<0.001
SBP, mm Hg	0.72 (0.29-1.14)	<0.001
LVEF, %	0.18 (−0.21 to 0.58)	0.36
LAVI, mL/m^2	0.96 (0.55-1.36)	<0.001
E/e′	0.57 (0.16-0.99)	0.007
RV S′, cm/s	0.99 (0.61-1.37)	<0.001
Model 3: age, sex, BMI, SBP, LVEF, LA volume index, RV S′, FEV1		
Black race	0.42 (−0.68 to 0.96)	0.74
Age, y	0.65 (0.07-1.22)	0.03
Male	1.89 (0.95-2.82)	<0.001
BMI, kg/m^2	0.81 (0.35-1.27)	<0.001
SBP, mm Hg	0.65 (0.19-1.10)	0.006
LVEF, %	0.23 (−0.20 to 0.66)	0.29
LAVI, mL/m^2	0.90 (0.47-1.34)	<0.001
E/e′	0.46 (0.02-0.96)	0.04
RV S′, cm/s	1.09 (0.69-1.50)	<0.001
FEV1, L	Nonlinear	0.02

Beta coefficients (β) for continuous variables represent the effect of moving from a value at the 25th percentile to the 75th percentile. BMI indicates body mass index; E, transmitral spectral Doppler early velocity; e′ avg, average mitral annulus tissue Doppler early relaxation velocity; FEV1, forced vital capacity in 1 second; LAVI, left atrial volume index; LVEF, left ventricular ejection fraction; PASP, pulmonary artery systolic pressure; RV S′, RV basal tissue Doppler myocardial velocity during systole; SPB, systolic blood pressure.
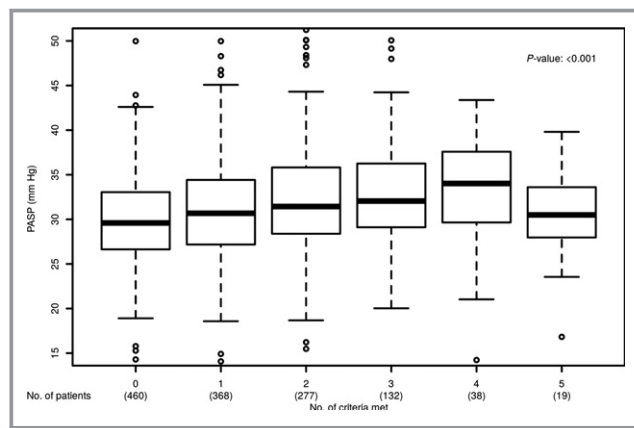

Figure 2. Pulmonary artery systolic pressure (PASP) according to number of prevalent components of the metabolic syndrome. CARDIA participants were categorized according to the number of metabolic syndrome components present. In general, we observed a stepwise increase in PASP as the number of metabolic syndrome components increased (*P*<0.001).

pulmonary pressure. For example, in wild-type mice, hyperinsulinemia, but not hyperglycemia, leads to an increase in systolic pulmonary artery pressure,[37] and reversal of insulin resistance with metformin in wild-type mice fed a high-fat diet leads to a reduction in pulmonary pressure.[38]

We found that HOMA-IR increased with PASP, including in the vast majority of participants whose PASP was within the

Table 7. Multivariate Associations of HOMA-IR and CRP With PASP

	β (95% CI)	P Value
HOMA-IR model		
HOMA-IR	Nonlinear	0.002
Age, y	0.87 (0.36-1.40)	<0.001
Male	0.83 (0.18-1.48)	0.01
BMI, kg/m^2	0.93 (0.46-1.41)	<0.001
LAVI, mL/m^2	0.92 (0.52-1.32)	<0.001
E/E′	0.83 (0.44-1.22)	<0.001
Black race	1.21 (0.55-1.87)	<0.001
CRP model		
CRP, mg/L	0.21 (0.04-0.39)	0.014
Age, y	1.00 (0.47-1.52)	<0.001
Male	0.87 (0.21-1.53)	0.009
BMI, kg/m^2	1.03 (0.61-1.46)	<0.001
Black race	1.45 (0.78-2.12)	<0.001

Beta coefficients (β) for continuous variables represent the effect of moving from a value at the 25th percentile to the 75th percentile. BMI indicates body mass index; CRP, C-reactive protein; E, transmitral spectral Doppler early velocity; HOMA-IR, homeostatic index of insulin resistance; LAVI, left atrial volume index; PASP, pulmonary artery systolic pressure.
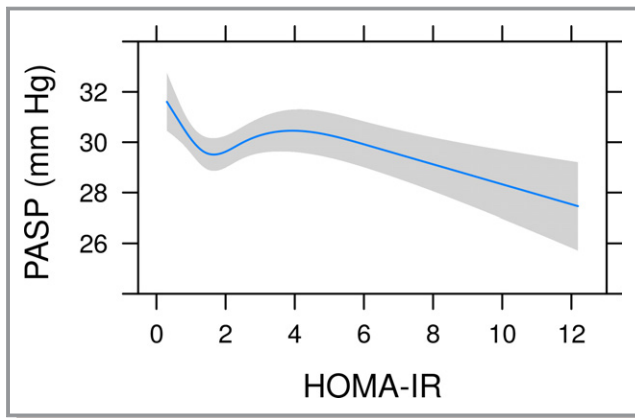
disease is growing. Robbins et al demonstrated that the prevalence of metabolic syndrome is increased in patients with pulmonary venous hypertension and pulmonary arterial hypertension.[13] In pulmonary arterial hypertension the prevalence of glucose intolerance approaches 50% and is independent of BMI, suggesting that obesity does not mediate the relationship.[35,36] Gopal et al recently demonstrated that pulmonary vascular disease and right ventricular dysfunction are worse in obese individuals with metabolic syndrome compared with those without metabolic syndrome.[14] Animal models support a direct contribution of insulin resistance to

Figure 3. Multivariable adjusted association between homeostatic model of insulin resistance (HOMA-IR) and pulmonary artery systolic pressure (PASP). When adjusted for age, sex, and BMI, the relationship between HOMA-IR and PASP in the CARDIA cohort was nonlinear. We observed an inflection point of increasing PASP at a HOMA-IR of ~2. Subsequent decline in PASP at high values of HOMA-IR may reflect reduced sample size at these values as suggested by the widening confidence interval.

Table 9. Multivariate Associations of Visceral Adiposity With PASP

	β (95%CI)	P Value
Visceral adipose, cm^3	1.32 (0.71-1.93)	<0.001
Age, y	0.92 (0.36-1.48)	0.001
Black race	2.23 (1.49-2.96)	<0.001
Male	0.46 (−0.28 to 1.21)	0.22
HOMA-IR	Nonlinear	0.01
CRP, mg/L	0.71 (−0.002 to 1.41)	0.03

Beta coefficients (β) for continuous variables represent the effect of moving from a value at the 25th percentile to the 75th percentile. CRP indicates C-reactive protein; HOMA-IR, homeostatic index of insulin resistance; PASP, pulmonary artery systolic pressure.

normal range. The relationship was nonlinear, with the greatest increase in PASP at values of HOMA-IR consistent with insulin resistance. The decline in PASP at very high values of HOMA-IR may reflect low sample size, which is supported by the wide confidence intervals. HOMA-IR was highest in those meeting an echocardiographic definition of PH (>40 mm Hg). Higher PASP also correlated with the number of prevalent components of the metabolic syndrome. These findings suggest that insulin resistance and related metabolic dysregulation may contribute to pulmonary vascular disease, including subclinical values of PASP. Mild elevation in invasive pulmonary pressure is associated with increased all-cause mortality and hospitalization, highlighting the potential clinical relevance of these findings.[33] Additional investigations are needed to better understand this relationship, ideally longitudinal studies that can examine the temporal relationship between insulin resistance and the response of pulmonary pressure.

A relationship between inflammatory markers and pulmonary vascular disease is well described.[39-42] Although observational, our findings appear to support such an association in a largely healthy cohort. As with HOMA-IR, both CRP and IL-6 were highest in the subset of individuals meeting an echocardiographic definition of PH; however, this observation could be related to uncaptured comorbid conditions that are associated with both inflammation and PH (eg, connective tissue disease).

Prior studies examining the echocardiographic correlates of PASP have not included quantitative measures of RV function. The relationship between RV function and PASP was conflicting in our study; RV S′ increased across quartiles of PASP whereas TAPSE did not change. A potential explanation for increased RV S′ with rising PASP is a compensatory increase in contractility in response to elevated afterload. RV S′ is a Doppler measurement of myocardial velocity, which may be more sensitive to subtle changes in RV function than TAPSE, a measure of displacement. Given the tight ranges of these parameters in this largely normal cohort, the clinical significance of a modest change in RV S′ is unknown. Of note, RV S′ and TAPSE were not statistically different in subjects with PASP >40 mm Hg, suggesting that increased contractility was not responsible for the increase in pressure.

Limitations

Our study has limitations, which should be considered when interpreting our findings. The CARDIA cohort is not as well

Table 8. Measures of Adiposity Stratified by Quartiles of PASP

	PASP, mm Hg				
	<27 (N=328)	27 to 31 (N=328)	31 to 34 (N=327)	>34 (N=328)	P Value
Total abdominal adipose, cm^3	392 (287, 501)	418 (288, 589)	423 (314, 589)	507 (373, 672)	<0.001
Subcutaneous adipose, cm^3	260 (186, 357)	281 (191, 412)	288 (204, 414)	343 (231, 484)	<0.001
Visceral adipose, cm^3	95 (62, 145)	102 (64, 158)	108 (74, 153)	124 (89, 183)	<0.001
Pericardial adipose, cm^3	42 (29, 60)	44 (30, 62)	41 (28, 62)	52 (35, 75)	<0.001

Data are presented as median (25th, 75th percentiles). PASP indicates pulmonary artery systolic pressure.

suited to evaluate the effects of age across a wide range compared with the studies by McQuillan and Lam; however, our study does fill an important gap in the literature regarding PASP in middle-aged adults. The cross-sectional design does not allow any determination regarding causality in the relationship between metabolic and inflammatory markers with PASP. Doppler-based estimations of PASP do not agree perfectly with invasive measurements and may over- or underestimate by up to 10 mm Hg in studies performed in clinical populations.[43] However, many studies show strong agreement between Doppler and invasive measurements, and echocardiography remains the mainstay in the evaluation of suspected pulmonary hypertension.[21] Right atrial pressure was not estimated based on inferior vena cava diameter and respiratory variation in the CARDIA cohort. We elected to add a constant 10 mm Hg to the TR gradient, an approach adopted by other studies of large cohorts.[1,3] Nonetheless, this approach may lead to over- or underestimation of PASP in some subjects. Finally, the prevalence of a measureable TR jet (38%) in CARDIA is lower than other published cohorts.[1,2,5] This may reflect differences in interpretation between clinical cohorts and centralized interpretation in the CARDIA echocardiography core lab. The high rate of obesity in CARDIA may also contribute to lack of a measureable TR jet.

Conclusions

In a large, prospective, and biracial cohort of middle-aged adults, we identified new associations between black race and metabolic dysregulation with higher echocardiographically estimated PASP. Further studies are needed to examine racial differences in PASP and whether metabolic dysfunction directly contributes to pulmonary vascular disease in humans.

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