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Central Blood Pressure and Subclinical Atherosclerotic Risk in Young Hispanic American Women

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Background: The incidence of younger women being hospitalized from cardiovascular disease (CVD) events is on the rise. Hispanic women are generally thought to have higher CVD risk factor burden than non-Hispanic White (NHW) women yet Hispanic Americans have lower mortality from CVD. Traditional measures of CVD may not accurately capture CVD risk in Hispanic Americans. Hence, the purpose of this study was to assess the impact of ethnicity on vascular reactivity and central hemodynamic load to gain insight into subclinical CVD risk in young women.

Methods: Brachial flow-mediated dilation (FMD), low-flow mediated constriction (L-FMC), carotid-femoral pulse wave velocity (cfPWV), and pulse wave analysis (from synthesized aortic pressure waveforms) were measured in 25 Hispanic women and 31 NHW women aged between 18-35 years. FMD and L-FMC were combined to provide an index of total vessel reactivity.

Results: NHW and Hispanic women did not differ in age or traditional CVD risk factors (P>.05 for all). Compared with NHW women, Hispanic women had greater vascular reactivity (8.7±4.1 vs 11.7±4.1 %, P=.011), lower central pulse pressure (28±5 vs 24±3 mm Hg, P=.001) and lower pressure from wave reflections (12±2 vs 10±1 mm Hg, P=.001). There were no differences in cfPWV between NHW women and Hispanic women (5.4±0.7 vs 5.3±0.7 m/s, P=.73).

Conclusion: Young Hispanic women have greater vascular reactivity and lower central pulsatile hemodynamic load compared with NHW women, suggesting lower subclinical CVD risk. *Ethn Dis*. 2021;31(4):489-500; doi:10.18865/ed.31.4.489

Introduction

Cardiovascular disease (CVD) accounts for 1 in every 4 deaths in the general population, and may be more prevalent in women, accounting for 1 in every 3 female deaths.[1] While CVD is traditionally considered a disease of aging, the incidence of younger women being hospitalized with and experiencing premature mortality from CVD events is on the rise.[2,3] There are disparities in CVD, based on race and ethnicity. Hispanic American women generally have higher prevalence of diabetes, obesity, and hypercholesterolemia compared with non-Hispanic White (NHW) women. Despite higher CVD risk factor burden, prevalence of ischemic heart disease, peripheral artery disease and stroke is lower in Hispanic Americans compared with NHW Americans.[4] Moreover, incidence of sudden cardiac death and mortality from CVD is lower in Hispanic Americans compared with NHWs, an observation often referred to as the Hispanic Paradox in CVD.[5] Whether traditional CVD risk factors are representative of actual risk in Hispanic Americans has been challenged.[6] Six studies encapsulating findings from >23,000 participants suggest that with use of traditional risk factors, CVD risk prediction for Hispanic Americans remains "modest at best."[7] Given that the Hispanic population is the fastest-growing ethnic group in the United States and CVD risk is increasing in young women, a greater understanding of CVD risk in Hispanic American women is needed.[8]

Measures of subclinical atherosclerosis and central hemodynamic load may offer novel insight into CVD risk in Hispanic Americans.[9,10] Brachial artery flow-mediated dilation (FMD, a measure of peripheral vascular endothelial function) and carotid-femoral pulse wave velocity (cfPWV, a measure of aortic stiffness)

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have been shown to predict cardiovascular mortality in the general population and specifically in Hispanic Americans.[11,12] Select studies note ethnic differences in aortic stiffness in older adults, with Hispanic Americans having greater subclinical CVD burden and hastened vascular aging compared with NHW Americans.[13] Middle-aged and older Hispanic adults also have higher aortic augmentation index (AIx) compared with NHW adults suggesting increased pressure from global wave reflections and central hemodynamic burden.[10] Increased augmentation index is associated with an increased risk of CVD mortality in the general population and increased target organ damage in Hispanic Americans.[14-16] Less is known regarding subclinical CVD risk in younger Hispanic adults and specifically younger Hispanic American women. As we shift toward a paradigm of primordial prevention as a means of abrogating disparities in CVD across race and sex, examining subclinical CVD risk in younger multi-ethnic groups of women will become increasingly important.[17,18]

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Our overarching purpose was to examine measures of subclinical atherosclerosis and central hemodynamic load in young Hispanic American and NHW women to gain insight into underlying physiological origins of the Hispanic Paradox. The primary aim was to assess and compare peripheral vascular reactivity (measured as brachial FMD and low-flow mediated constriction [L-FMC]) and aortic stiffness (measured as cfPWV) in young Hispanic American and NHW women. A secondary aim was to explore and compare central pulsatile hemodynamic burden in young Hispanic American and NHW women assessed as aortic pulse pressure (PP) and pressure from wave reflections (augmentation index and backward wave pressure [Pb] derived from wave separation analysis). We hypothesized that young Hispanic American women would have lower subclinical atherosclerotic risk (higher brachial FMD and L-FMC and lower carotid-femoral pulse wave velocity) compared with NHW women. We further hypothesized that young Hispanic American women would have lower central pulse pressure and lower pressure from wave reflections (augmentation index and Pb) compared with NHW women.

Methods

Participants

Fifty-six women (25 Hispanic and 31 NHW) between the ages of 18-35 were recruited from the greater Syracuse community to participate in this research study. Exclusion criteria for participants consisted of self-reported (from a health history questionnaire) hypertension, peripheral artery disease, hyperlipidemia, diabetes mellitus, pulmonary disease, or renal disease. Recruitment efforts included placement of flyers around the Syracuse community, word of mouth, emails and endorsements from various Hispanic community associations in the area (eg, La Casita Cultural Center). All women self-reported regular menstrual cycles (mean 11±2 cycles/year); none were amenorrheic and none were smokers. Following approval by the Institutional Review Board for Research at Syracuse University, written informed consent was obtained from all participants before testing.

Visit 1

Body mass and height were measured using an electronic scale and stadiometer (Sonaris, Detecto, USA) and used to calculate body mass index (BMI) as weight/height^2. Body surface area (BSA) was calculated using the Mosteller formula as: $\sqrt{}$(weight/height/3600). Body composition was estimated using air displacement plethysmography (BodPod, COSMED, Italy). Following anthropometrics, participants were familiarized with vascular-hemodynamic procedures that would be performed on visit 2. Participants completed a series of questionnaires (online via REDcap) that surveyed health history and socioeconomic status (SES). An SES score was derived from the sum of questions pertaining to participants' years of education, ownership of material goods (eg, car,

smartphone, computer), parental ownership of similar items (eg, car, smartphone, computer), as well as owning a home vs renting a home/apartment. Participants were then fitted with an accelerometer (GT3X+ version 6.13, ActiGraph LLC) and instructed to wear the device for 7 consecutive days. Data from the device were downloaded using the low-frequency filter and analyses carried out as previously described.[19] A complete day of acclerometer use was defined as at least 10 hours of wear time while awake, which is consistent with the minimum set by the NHANES[20] and a minimum of 4 days of wear data were necessary in order for participants to be included in data analysis. A cut point of 2020 activity counts/min was used to determine the amount of time in minutes spent at a physical activity level of moderate-to-vigorous intensity (MVPA).[20]

Visit 2

Participants were asked to arrive for the lab visit after an overnight fast (no food or sugar containing drinks for at least 12 hours), and to refrain from exercise, alcohol, and caffeine consumption for at least 24 hours. This visit was scheduled in the early follicular phase of the participant's menstrual cycle (within the first 5 days of the onset of menses) to standardize the vascular measures across potential shifts in female sex hormones.

A finger stick blood sample was obtained and a validated point-of-care device (Cholestech LDX, Abbott, Abbott Park, IL, USA) was used to analyze fasting blood glucose (GLU), total cholesterol (TC), high-density lipoprotein (HDL) cholesterol, low density lipoprotein (LDL) cholesterol, and triglycerides (TG).

An automated oscillometric blood pressure cuff (Omron, Kyoto, Japan) was used to take brachial systolic (SBP) and diastolic blood pressure (DBP) measurements. Measures were taken in duplicate and if values deviated by >5 mm Hg, additional measures were taken. The average of the two closest measures <5 mm Hg was used for subsequent analyses. Mean arterial pressure (MAP) was calculated as 1/3 SBP + 2/3 DBP. Pulse pressure (PP) was calculated as SBP-DBP.

Applanation tonometry (SphygmoCor, AtCor Medical) was used to measure blood pressure waveforms in the carotid, radial, and femoral arteries. Aortic stiffness was measured using carotid-femoral pulse wave velocity following established guidelines.[21] The distance between the carotid and femoral pulse sites was calculated by subtracting the distance between the supra-sternal notch and the carotid pulse-site from the distance between the supra-sternal notch and the femoral pulse-site. The equation used to determine pulse wave velocity was: Δ distance (m) / Δ time (s). Pulse wave velocity is expressed in absolute values as well as relative to MAP (*100). Aortic pressure waves were synthesized from radial pressure waveforms using a generalized transfer function and calibrated against brachial MAP and DBP. Augmentation index was calculated as the difference between the early- and late-systolic peaks of the pressure waveforms relative to the total pulse pressure and expressed as a percentage and standardized to a heart rate of 75 beats per min (AIx75). Pressure waveforms were also separated into forward (Pf) and backward/reflected (Pb) components using a modified average-flow waveform based on the original flow triangulation method of Westerhof et al and has been described previously in detail.[22,23]

Ultrasound (Prosound α7, Aloka, Tokyo, Japan) was used to assess brachial flow-mediated dilation (FMD) and low-flow mediated constriction (L-FMC) as we have previously described.[24] The brachial artery was longitudinally imaged 2 cm distal to the antecubital fossa using a 13.0-4.0 MHz linear array probe. Baseline diameters were measured during end-diastole (determined by simultaneous ECG R-wave gating) using ultrasonic calipers. Following baseline brachial artery diameter measurements, a narrow tourniquet-style blood pressure cuff (Hokanson, Bellevue, WA) was placed around the lower arm and inflated to a supra-systolic pressure (200 mm Hg) for 5 min. Brachial diameters were measured at 150 s and 210 s into the occlusion period. L-FMC was calculated as the percentage diameter change: (baseline diameter – minimum occlusion diameter)/(baseline diameter) × 100. Following the 5 min occlusion period, the cuff was released resulting in reactive hyperemia.

Beat-to-beat mean velocity (MnV) and peak systolic velocity (PSV) were recorded during a 30 s post occlusion epoch and values entered into a software program (Graphpad, Prism, 3.0) to calculate the area under the curve (AUC) of the reactive hyperemic response to

cuff deflation as an estimate of the shear stress stimulus.[25] Following this initial 30 s post cuff release measurement, brachial diameters were semi-continuously measured for an additional 60 s (one still frame captured every 10 s from 30 s post cuff release to 90 s post cuff release) to capture an estimate of peak diameter, which was used for subsequent calculations. FMD was expressed in absolute terms (peak – baseline) as well as a percentage and calculated as: (peak diastolic diameter – baseline diameter)/(baseline diameter) × 100. FMD was adjusted for both the MnV AUC and PSV AUC to adjust for the shear stimulus.[26] The vasoactive range ([VAR] ie, total vessel reactivity) was additionally calculated as (peak diastolic diameter post cuff release – minimum diastolic diameter during cuff occlusion)/(baseline diameter) × 100 and taken as a measure of global vascular reactivity.[27]

All data are reported as mean ± SD. The normality of distribution was confirmed using Kolmogorov-Smirnov and Shapiro-Wilk tests as well as via visual inspection of Q-Q plots and histograms. A χ^2 test was used to test differences in categorical variables between groups. Analysis of variance (ANOVA) was used to assess group differences in continuous outcome variables. Analysis of covariance (ANCOVA) was used to: 1) co-vary for the shear stimulus when comparing brachial FMD; 2) co-vary for contraceptive medication use. All analyses were performed using SPSS v 24 (SPSS Inc, Chicago, Illinois) with significance set a priori as P<.05.

Table 1. Descriptive characteristics

Variable	Hispanic, n=25	NHW, n=31	P
Age, years	22±4	22±4	.82
Body mass index, kg/m^2	24±3	24±5	.74
Body surface area, m^2	1.67±0.17	1.74±0.14	.08
Body fat, %	32±7	29±7	.11
Total cholesterol, mg/dL	172±31	165±36	.42
Low density lipoprotein cholesterol, mg/dL	98±30	90±33	.40
High density lipoprotein cholesterol, mg/dL	60±15	63±18	.60
Triglycerides, mg/dL	86±32	88±38	.81
Glucose, mg/dL	86±7	90±9	.08
Moderate-to-vigorous physical activity, min/day	50±21	51±20	.85
Socioeconomic status, index	20±2	19±2	.29
Oral contraceptive use, n, %	7, 28	12, 39	.19
Family history cardiovascular disease, n, %	2, 8	4, 13	.45

kg, kilograms; m, meters; mg, milligrams; dL, deciliters; n, number; NHW, non-Hispanic White

Results

Participant descriptive characteristics are displayed in Table 1. There were no significant group differences in mean age, body surface area, body mass index, body fat percentage, fasting blood lipids, glucose, MVPA, family history of CVD, socioeconomic status or contraceptive use (all P>.05).

Hispanic American women had significantly lower mean brachial pulse pressure (P=.009) and aortic pulse pressure (P=.001) compared with NHW women (Figure 1). After adjusting for contraceptive medication use with ANCOVA, group differences in mean brachial pulse pressure remained significant (adjusted means: 37 vs 41 mm Hg, P=.011) as did group differences in aortic pulse pressure (adjusted means: 24 vs 28 mm Hg, P=.001).

Hispanic American women also had significantly lower mean aortic Pf (P=.016) and Pb (P=.001) compared with NHW women (Figure 2). After adjusting for contraceptive medication use with ANCOVA group differences in mean Pf remained (adjusted means: 22 vs 25 mm Hg, P=.017) as did group differences in mean Pb (adjusted means: 10 vs 12 mm Hg, P=.001). In general, when comparing women taking contraceptive medication vs not taking contraceptive medication, there were no group differences in mean brachial pulse pressure (P=.50), aortic pulse pressure (P=.70), Pf (P=.89), Pb (P=.42), or vasoactive range (P=.99) (data not shown).

There were no group differences in mean carotid-femoral pulse wave velocity or MAP in NHW and Hispanic American women (Table 2, P>.05). Compared with NHW women, Hispanic American women had significantly smaller brachial artery diameters and larger shear stress stimulus during reactive hyperemia (PSV AUC) following cuff release (Table 3, P<.05). There was a trend for Hispanic American women to have higher FMD compared with NHW women although this was largely abrogated with expressing FMD relative to PSV AUC (or MnV AUC) or co-varying for PSV

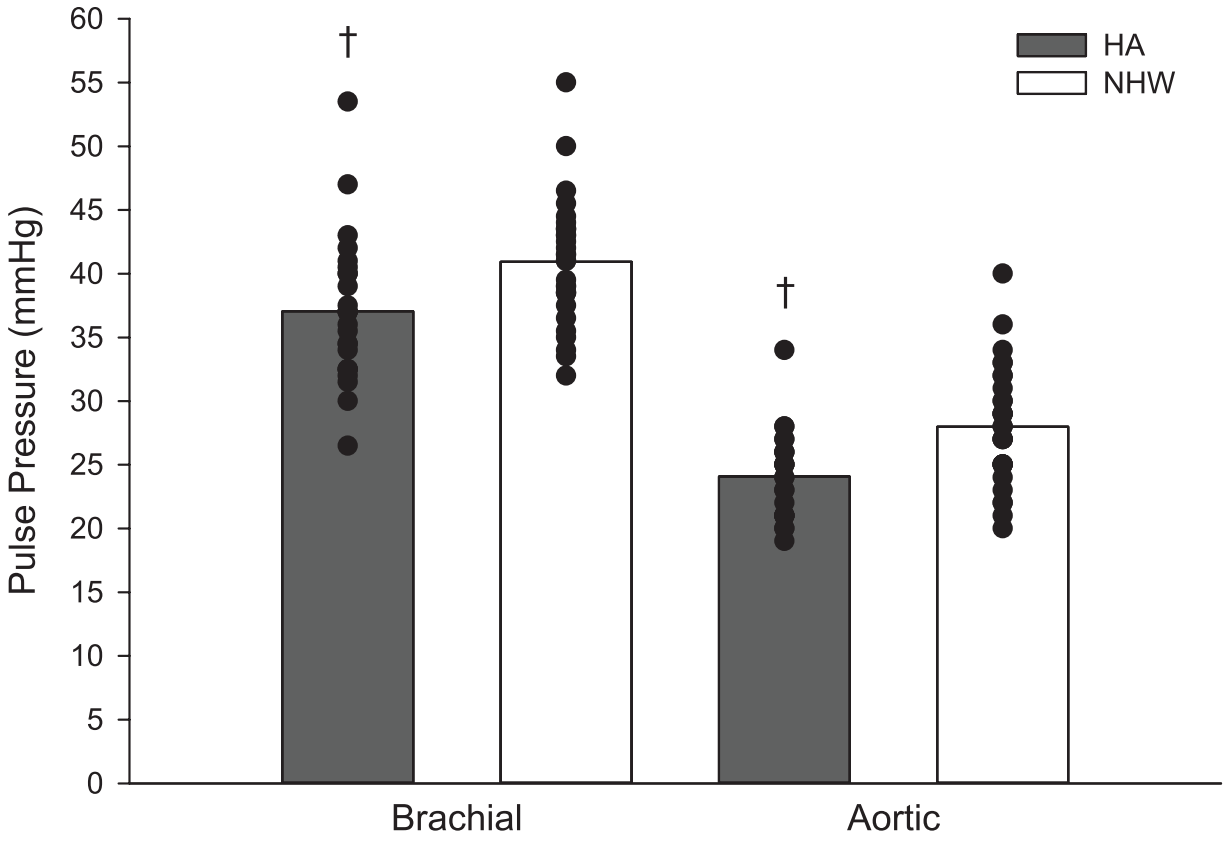

Figure 1. Brachial and aortic pulse pressure in Hispanic American (HA) and non-Hispanic White (NHW) women.
† Significant group difference (P<.05)

AUC (or MnV AUC) with ANCOVA.

Compared with NHW women, Hispanic American women had an overall larger mean vasoactive range (Figure 3, P=.011). Significant group differences remained after additional adjustment for contraceptive use with ANCOVA (adjusted means: 8.7 vs 11.7%, P = .011).

Discussion

The overarching purpose of this study was to examine and compare measures of subclinical atherosclerosis and central hemodynamic burden in young Hispanic American and NHW women. While Hispanic American and NHW women had similar traditional CVD risk factor profiles (brachial blood pressure, blood lipids, fasting glucose, body mass index, body fat, socioeconomic status, MVPA, and family history of CVD), Hispanic American women had greater peripheral vascular reactivity and lower pulse pressure. Thus, our findings suggest that young Hispanic American women have lower subclinical CVD risk compared with NHW women.

Hispanic American women had slightly higher brachial FMD and slightly greater L-FMC compared with NHW women, resulting in an overall greater total vessel reactivity. Relying solely on FMD to assess vasomotor function may lead to clinical misinterpretation of overall subclinical CVD risk.[28] Baseline vascular tone is such that the artery is in a state of vasoconstriction. Thus, historically, physiologists would often refer to smooth muscle relaxation as a state of "less constriction" and not "dilation" per se. A vessel with higher baseline tone resulting

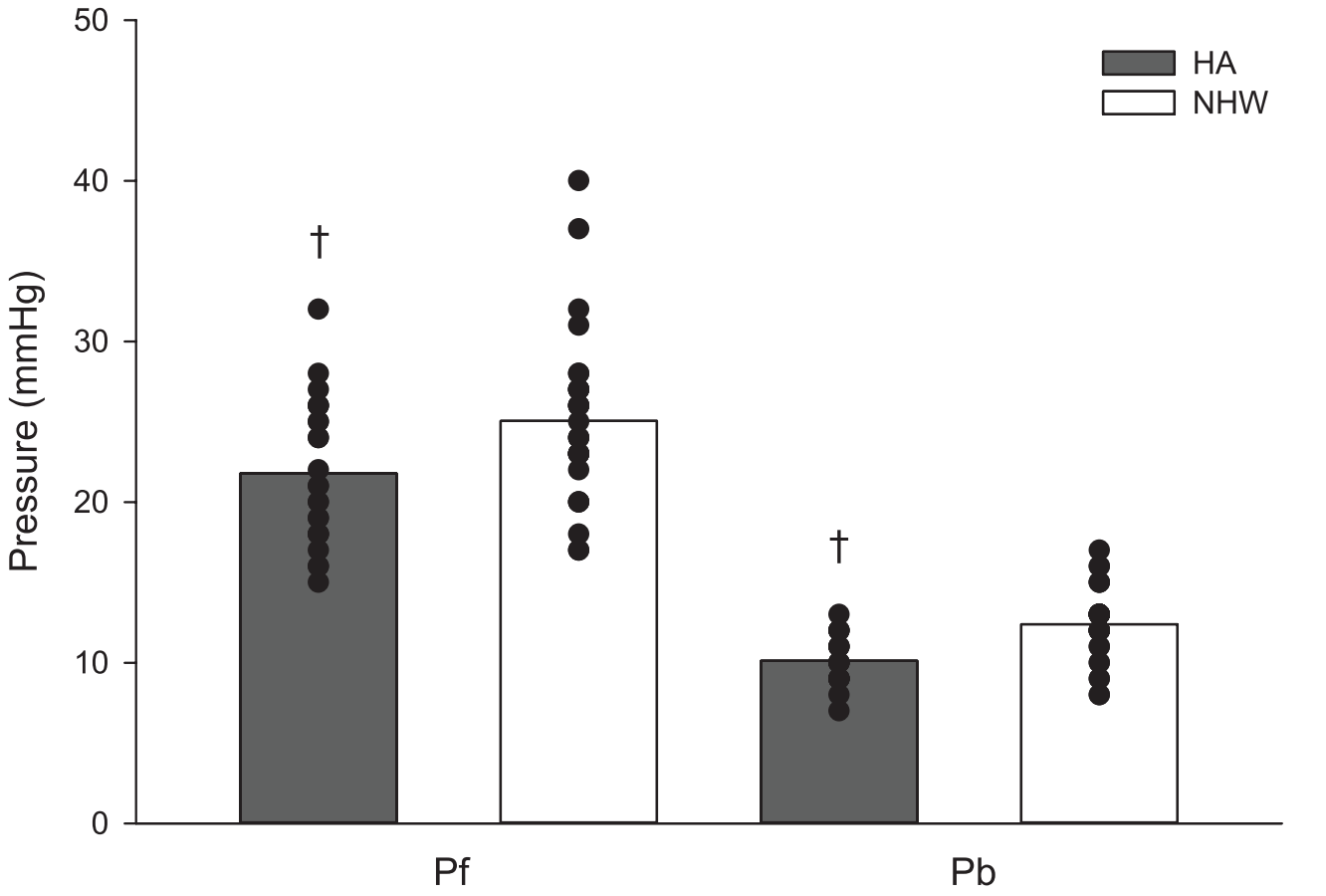

Figure 2. Forward wave pressure (Pf) and backward/reflected wave pressure (Pb) in Hispanic American (HA) and non-Hispanic White (NHW) women.
† Significant group difference (P<.05)

in an excessively preconstructed state might have a normal FMD despite underlying endothelial dysfunction.[28] FMD does not offer insight into resting vascular tone nor vasoconstrictor responsiveness to states of low shear, hence the origins of the assessment of L-FMC. Individuals with higher CVD risk factor burden may have blunted vasoconstrictor tone to acute reductions in shear stress.[29] Thus the combination of FMD and L-FMC may offer insight into both basal endothelial activity as well as overall endothelial recruitability and thus be used as a measure of total vessel reactivity or endothelial reserve.[30]

While FMD and L-FMC are each clinically relevant and physiologically important, a composite score encapsulating both FMD and L-FMC may provide additive insight into overall vascular endothelial health.[29] Gori et al noted that, when compared with either FMD or L-FMC alone, a composite endpoint resulted in better discrimination of patients diagnosed with hypertension, congestive heart failure and coronary artery disease from healthy volunteers.[30] In a recent study from Königstein et al, compared with FMD and L-FMC, the vasoactive range showed the highest ability to discriminate CVD risk in a sample of apparently healthy men and women across a wide age range.[28] Using this composite endpoint, we noted a greater vasoactive range in the Hispanic American women compared with the NHW women suggesting greater overall endothelial function in Hispanic American women.

Although FMD and L-FMC are somewhat related constructs, they each capture a unique aspect of vascular

function.[29,31] Both FMD and L-FMC are endothelium-dependent processes[31] with FMD being partially driven by nitric oxide (NO) and L-FMC being partially driven by endothelin-1 (ET-1) and endothelium-derived hyperpolarizing factor (EDHF).[27,29] More research will be needed to elucidate the mechanisms responsible for differences in vasoactive range in NHW and Hispanic women.

Some of the noted ethnic differences in vascular endothelial function may have been related to underlying differences in vascular geometry. Hispanic American women had smaller brachial artery diameters compared with NHW women. Smaller vessel diameters likely contributed to a greater shear stress stimulus during reactive hyperemia.[32] Smaller vessels may also be hyper-responsive to vasoactive agents.[32] It should be noted that there were no ethnic differences in body surface area and adjusting for body surface area had no effect on the ethnic differences in vessel diameter (adjusted means: 2.8±0.4 in HA vs 3.1±0.4 in NHW, P=.02) suggesting that ethnic differences in vessel size were not due to possible differences in stature.

There were no group differences in global measures of vascular aging (ie, carotid-femoral pulse wave velocity and augmentation index) concomitant with differences in forward wave pressure (Pf) and reflected wave pressure (Pb) suggesting that measures derived from wave separation may offer additional insight into subclinical CVD risk in young, otherwise apparently healthy adults. The augmentation index is often used as a measure of central hemodynamic burden attributable to increased pressure from wave reflections. Wave reflections arise when the incident wave generated by left ventricular contraction encounters bifurcations or arterial-arteriolar impedance mismatches producing backward traveling waves varying in speed and magnitude. The augmentation index as a measure solely attributable to wave reflections has been challenged because this parameter can be influenced by other hemodynamic factors extending beyond wave reflections.[33] It must also be underscored that the augmentation index should not be used interchangeably with other measures of arterial stiffness.[21] As eloquently discussed by Mitchell, when augmentation index is >0, augmented pressure from the pressure waveform alone represents just the "tip of the iceberg" because the majority of the reflected wave may be masked by the falling edge of the forward pressure wave.[34]

Conversely, when augmentation index <0 as is common in young, healthy adults, augmentation index provides virtually little insight into wave reflection magnitude because calculated values are negative. Backward wave pressure (Pb) decomposed

Table 2. Brachial and aortic hemodynamics

Variable	Hispanic, n=25	NHW, n=31	P
Brachial systolic blood pressure, mm Hg	109±9	112±9	.34
Brachial diastolic blood pressure, mm Hg	72±7	71±7	.40
Mean arterial pressure, mm Hg	85±7	85±7	.85
Heart rate, bpm	61±8	58±7	.09
Aortic systolic blood pressure, mm Hg	98±8	100±8	.33
Aortic diastolic blood pressure, mm Hg	73±7	72±7	.34
Aortic augmentation index, %	2±4	3±3	.51
Aortic augmentation index x@75, %	1±3	1±3	.85
Aortic pulse wave velocity, $m \bullet s^{-1}$	5.2±0.7	5.4±0.7	.52
Aortic PWV /MAP, $m \bullet s^{-1}$/MAP	6.3±0.7	6.3±0.7	.76

bpm, beats per minute; mm Hg; millimeters of mercury; $m \bullet s^{-1}$, meters per second; PWV, pulse wave velocity; MAP, mean arterial pressure.

Table 3. Brachial endothelial function

Variable	Hispanic, n=25	NHW, n=31	P
Brachial diameter, mm	2.8±0.4	3.1±.4	.006
Absolute flow mediated dilation, mm	.19±.12	.17±.12	.59
Relative flow mediated dilation, %	7.8±4.1	5.6±4.2	.058
Low-flow mediated constriction, %	-4.1±3.0	-3.1±1.9	.15
Peak systolic velocity, AUC	1955±640	1608±399	.016
Mean velocity, AUC	924±372	765±253	.06
FMD/PSV_{AUC}	.43±.25	.35±.25	.28
FMD/MnV_{AUC}	.94±.55	.80±.66	.41
FMD/PSV_{AUC} [a]	7.5±4.0	5.8±4.1	.15
FMD/MnV_{AUC} [a]	7.6±4.0	5.7±4.1	.10

FMD, flow-mediated dilation; AUC, area under the curve; PSV, peak systolic velocity; MnV, mean velocity.
a. ANCOVA adjusted means.

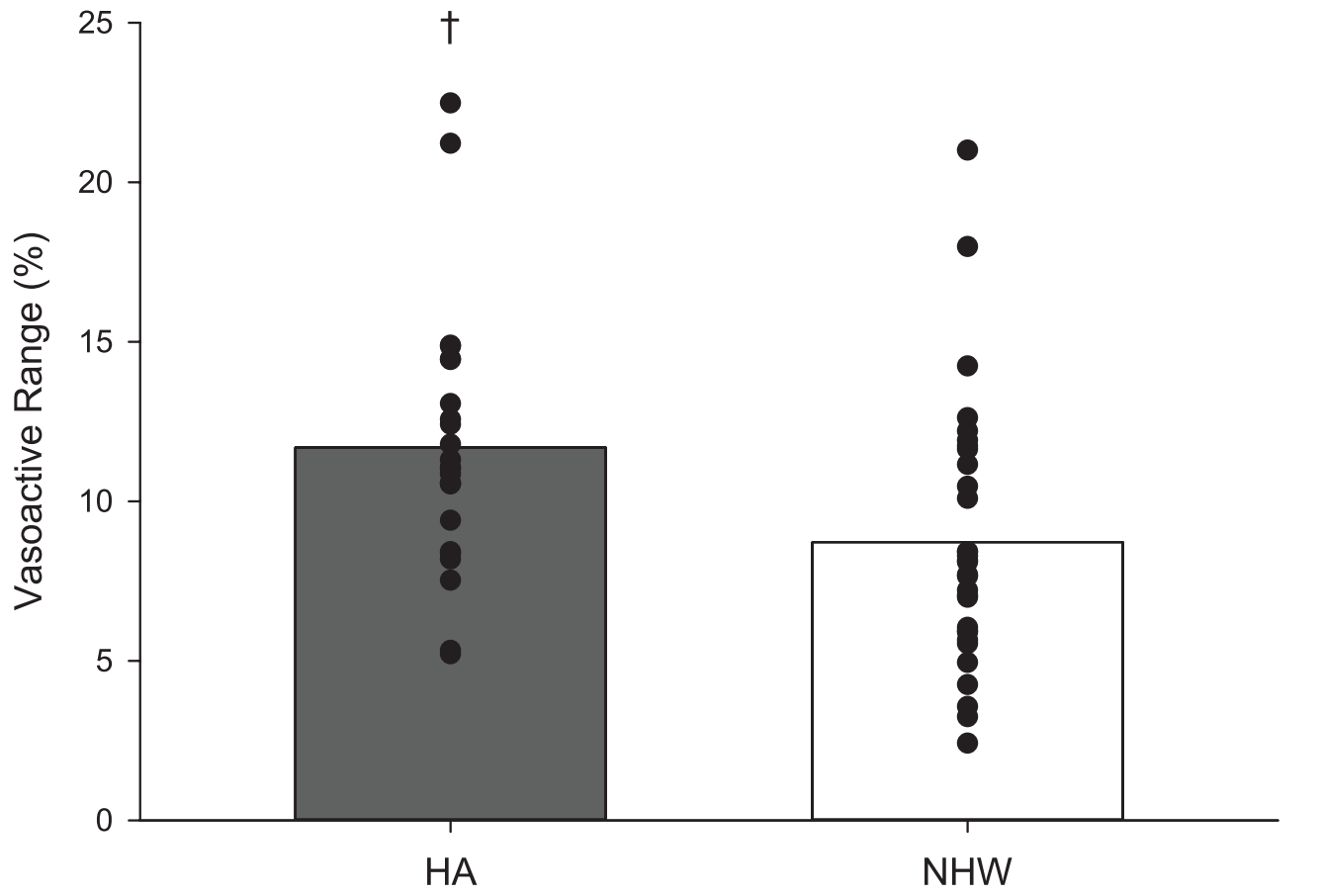

Figure 3. Brachial vasoactive range (total vessel reactivity) in Hispanic American (HA) and non-Hispanic White (NHW) women.
† Significant group difference (P<.05)

from wave separation analysis has been suggested by some, including the American Heart Association,[21] to be the preferred measure of wave reflection magnitude because it is less sensitive to timing of wave travel and encapsulates even those aspects "hidden" by the forward wave or occurring within diastole. Pb from wave separation analysis has been shown to be an independent predictor of end-organ damage, coronary perfusion, clinical outcomes (renal function, LV mass, diastolic function, and heart failure) and cardiovascular mortality.[35,36] In the Framingham Heart Study, forward wave pressure (Pf) was shown to contribute to age-associated increases in pulse pressure.[37] These and our findings suggest lower central hemodynamic burden in young Hispanic women compared with NHW women. Ethnic differences in Pf and Pb may also have important implications for differences in endothelial function and pulse pressure, discussed next.

Hispanic American women had lower brachial and central pulse pressure compared with NHW women. Elevated pulse pressure is an established CVD risk factor associated with target organ damage and incident cardiovascular events.[38] Age-associated widening of pulse pressure is thought to be driven by increases in large artery stiffness.[21] Ethnic differences in large artery stiffness have been noted in middle-age and older adults.[13,39] However, we noted no differences in aortic stiffness between young Hispanic American and NHW women and this is novel. Our findings suggest other hemodynamic factors[40] may be responsible for ethnic differences in pulse pressure in young women. As

Hispanic American women had lower forward (Pf) and reflected (Pb) wave pressure compared with NHW women, these observations might suggest an important role for characteristic input impedance (as it relates to the genesis of Pf) and terminal impedance (as it relates to Pb) in modulating pulsatile hemodynamics in young women.[41] Increased endothelial function and peripheral vasodilatory capacity may enhance forward wave transmission and dispersion into the periphery while also reducing pressure from wave reflections, contributing to lower pulse pressure. However, given the cross-sectional nature of this study, our findings cannot be used to infer directionality of associations.

Pulse pressure itself has been shown to cause endothelial damage and reduce peripheral vascular reactivity.[44] Elevated pulse pressure may increase oxidative stress in turn reducing NO bioavailability and increasing ET-1 levels.[42] Endothelial damage may subsequently alter peripheral vascular tone (affecting vascular wall capacitance, compliance, and resistance),[43] increasing the magnitude of pressure from wave reflections and augmenting pulse pressure. Indeed, manipulating both NO and ET-1 via blockade of NO synthase or ET-1 receptors has been shown to alter pressure from wave reflections and pulse pressure.[44-46]

Study Limitations

An important limitation of our study was the exclusion of individuals with a history of CVD. Although there were no differences in traditional risk factors between our groups, our results may differ in individuals with greater prevalence of traditional risk factors. Presence of CVD risk factors in childhood and adolescence increases risk for adulthood CVD.[47] Moreover, CVD risk factors in young adulthood are associated with a hastening of vascular aging manifesting as increases in arterial stiffness and endothelial dysfunction in middle age.[48] A recent study from Horvath et al suggests that Hispanics in the United States (and women in general) have lower intrinsic epigenetic aging rates.[49] Thus, young Hispanic American women may also have attenuated vascular aging compared with young NHW women.

Of interest and relevant to this study, intrinsic epigenetic aging rates tend to have insignificant associations with traditional CVD risk factors.[49] Acculturation and ethnic differences in external epigenetic aging rates (inflammation and cardiometabolic risk) may change across the lifespan and alter the trajectory of vascular aging, offering insight into potentially greater vascular dysfunction with advancing age in Hispanic Americans.[41] Numerous reasons have been put forth to explain this Hispanic Paradox, although most of the hypotheses focus on older adults and none fully explain the paradox.[5] With respect to younger adults, several psycho-social factors may confer vascular resiliency including: familism (*familismo* and social support), greater social support and lower social isolation (*personalismo*), faith/spirituality, and dispositional optimism; all of these may act as stress buffers and protect the vasculature from heightened allostatic load introduced by traditional CVD risk factors.[8]

There is also heterogeneity in culture across Hispanics in the United States with 10 Hispanic subgroups comprising 92% of the total US Hispanic American population.[8] There may be differences in CVD risk based on Hispanic/Latinx background.[8] Owing to the small sample size of this study, we were not able to perform sub-group comparisons within the Hispanic American women based on familial ethnic origin. More research will be needed to examine mechanisms of ethnic differences in endothelial function and pulsatile hemodynamics.

Our findings suggest that young Hispanic American women have lower subclinical CVD risk compared with NHW women.

Additional limitations should be noted. We measured the shear stimulus for FMD as AUC for the first 30 s following release of occlusion and did not measure the shear stimulus in its entirety (ie, AUC time to peak dilation) as is currently recommended.[50] It should be noted that only 30 s of reactive hyperemia shear is needed to elicit a "maximal" FMD response as originally shown by Pkye and Tschakovsky[25] and confirmed by others.[51] We also measured FMD through

90 s post cuff release and not 180 s. Peak dilation in young, healthy adults typically occurs within 50-60 s post cuff release with 100% achieving maximal dilation within 90 s[51] and all participants herein had peak dilation occur within this time frame with subsequent measures demonstrating return toward baseline values. Thus, we believe we were able to capture a good estimate of a maximal dilatory response in the time frame appraised.

Conclusion

Young Hispanic American women may have lower subclinical CVD risk compared with young NHW women as evidenced by greater peripheral vascular reactivity and lower central pulsatile hemodynamics. Our findings offer novel insight into possible physiological origins of the Hispanic Paradox.

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Conflict of Interest

No conflicts of interest to report.

Author Contributions

Research concept and design: Pagan Lasalle, Heffernan; Acquisition of data: Lasalle, DeBlois, Keller, Heffernan; Data analysis and interpretation: Lasalle, DeBlois, Stoner, Heffernan; Manuscript draft: Lasalle, DeBlois, Keller, Stoner, Heffernan; Statistical expertise: Stoner, Heffernan; Acquisition of funding: Heffernan; Supervision: Stoner, Heffernan

References

1. Garcia M, Mulvagh SL, Merz CN, Buring JE, Manson JE. Cardiovascular disease in women: clinical perspectives. *Circ Res*. 2016;118(8):1273-1293. https://doi.org/10.1161/CIRCRESAHA.116.307547 PMID:27081110
2. Arora S, Stouffer GA, Kucharska-Newton AM, et al. Twenty Year Trends and Sex Differences in Young Adults Hospitalized With Acute Myocardial Infarction. *Circulation*. 2019;139(8):1047-1056. https://doi.org/10.1161/CIRCULATIONAHA.118.037137 PMID:30586725
3. Khan SU, Yedlapati SH, Lone AN, et al. A comparative analysis of premature heart disease- and cancer-related mortality in women in the USA, 1999-2018. *Eur Heart J Qual Care Clin Outcomes*. 2021;qcaa099. https://doi.org/10.1093/ehjqcco/qcaa099 PMID:33555018
4. Willey JZ, Rodriguez CJ, Moon YP, et al. Coronary death and myocardial infarction among Hispanics in the Northern Manhattan Study: exploring the Hispanic paradox. *Ann Epidemiol*. 2012;22(5):303-309. https://doi.org/10.1016/j.annepidem.2012.02.014 PMID:22424967
5. Cortes-Bergoderi M, Goel K, Murad MH, et al. Cardiovascular mortality in Hispanics compared to non-Hispanic whites: a systematic review and meta-analysis of the Hispanic paradox. *Eur J Intern Med*. 2013;24(8):791-799. https://doi.org/10.1016/j.ejim.2013.09.003 PMID:24095273
6. D'Agostino RB Sr, Grundy S, Sullivan LM, Wilson P; CHD Risk Prediction Group. Validation of the Framingham coronary heart disease prediction scores: results of a multiple ethnic groups investigation. *JAMA*. 2001;286(2):180-187. https://doi.org/10.1001/jama.286.2.180 PMID:11448281
7. Cortes-Bergoderi M, Thomas RJ, Albuquerque FN, et al. Validity of cardiovascular risk prediction models in Latin America and among Hispanics in the United States of America: a systematic review. *Rev Panam Salud Publica*. 2012;32(2):131-139. https://doi.org/10.1590/S1020-49892012000800007 PMID:23099874
8. Rodriguez CJ, Allison M, Daviglus ML, et al; American Heart Association Council on Epidemiology and Prevention; American Heart Association Council on Clinical Cardiology; American Heart Association Council on Cardiovascular and Stroke Nursing. Status of cardiovascular disease and stroke in Hispanics/Latinos in the United States: a science advisory from the American Heart Association. *Circulation*. 2014;130(7):593-625. https://doi.org/10.1161/CIR.0000000000000071 PMID:25098323
9. Sharman JE, Boutouyrie P, Laurent S. Sharpening the focus on causes of ethnic differences in aortic stiffness. *JACC Cardiovasc Imaging*. 2017;10(1):62-64. https://doi.org/10.1016/j.jcmg.2016.09.005 PMID:27838308
10. Chirinos JA, Kips JG, Roman MJ, et al. Ethnic differences in arterial wave reflections and normative equations for augmentation index. *Hypertension*. 2011;57(6):1108-1116. https://doi.org/10.1161/HYPERTENSIONAHA.110.166348 PMID: 21536986
11. Yeboah J, Folsom AR, Burke GL, et al. Predictive value of brachial flow-mediated dilation for incident cardiovascular events in a population-based study: the multi-ethnic study of atherosclerosis. *Circulation*. 2009;120(6):502-509. https://doi.org/10.1161/CIRCULATIONAHA.109.864801 PMID:19635967
12. Pflederer MC, Long CS, Beaty B, et al. Longitudinal changes in vascular risk markers and mortality rates among a Latino population with hypertension. *Tex Heart Inst J*. 2016;43(2):131-136. https://doi.org/10.14503/THIJ-15-5053 PMID:27127427
13. Goel A, Maroules CD, Mitchell GF, et al. Ethnic difference in proximal aortic stiffness: an observation from the Dallas Heart Study. *JACC Cardiovasc Imaging*. 2017;10(1):54-61. https://doi.org/10.1016/j.jcmg.2016.07.012 PMID:27838302
14. Krantz MJ, Long CS, Hosokawa P, et al. Pulse wave velocity and carotid atherosclerosis in white and Latino patients with hypertension. *BMC Cardiovasc Disord*. 2011;11(1):15. https://doi.org/10.1186/1471-2261-11-15 PMID:21481252
15. Vlachopoulos C, Aznaouridis K, O'Rourke MF, Safar ME, Baou K, Stefanadis C. Prediction of cardiovascular events and all-cause mortality with central haemodynamics: a systematic review and meta-analysis. *Eur Heart J*. 2010;31(15):1865-1871. https://doi.org/10.1093/eurheartj/ehq024 PMID:20197424
16. Townsend RR, Rosendorff C, Nichols WW, et al. American Society of Hypertension position paper: central blood pressure waveforms in health and disease. *J Am Soc Hypertens*. 2016;10(1):22-33. https://doi.org/10.1016/j.jash.2015.10.012 PMID:26612106
17. Arnett DK, Blumenthal RS, Albert MA, et al. 2019 ACC/AHA Guideline on the Primary Prevention of Cardiovascular Disease: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Circulation*. 2019;140(11):e596-e646. https://doi.org/10.1161/CIR.0000000000000678 PMID:30879355
18. Cho L, Davis M, Elgendy I, et al; ACC CVD Womens Committee Members. Summary of Updated Recommendations for Primary Prevention of Cardiovascular Disease in Women: JACC State-of-the-Art Review. *J Am Coll Cardiol*. 2020;75(20):2602-2618. https://doi.org/10.1016/j.jacc.2020.03.060 PMID:32439010

19. Barreira TV, Redmond JG, Brutsaert TD, et al. Can an automated sleep detection algorithm for waist-worn accelerometry replace sleep logs? *Appl Physiol Nutr Metab*. 2018;43(10):1027-1032. https://doi.org/10.1139/apnm-2017-0860 PMID:29701486
20. Troiano RP, Berrigan D, Dodd KW, Mâsse LC, Tilert T, McDowell M. Physical activity in the United States measured by accelerometer. *Med Sci Sports Exerc*. 2008;40(1):181-188. https://doi.org/10.1249/mss.0b013e31815a51b3 PMID:18091006
21. Townsend RR, Wilkinson IB, Schiffrin EL, et al. Recommendations for improving and standardizing vascular research on arterial stiffness: a scientific statement from the American Heart Association. *Hypertension.*2015;66(3):698-722. https://doi.org/10.1161/HYP.0000000000000033 PMID: 26160955
22. Kips JG, Rietzschel ER, De Buyzere ML, et al. Evaluation of noninvasive methods to assess wave reflection and pulse transit time from the pressure waveform alone. *Hypertension.* 2009;53(2):142-149. https://doi.org/10.1161/HYPERTENSIONAHA.108.123109 PMID: 19075098
23. Westerhof BE, Guelen I, Westerhof N, Karemaker JM, Avolio A. Quantification of wave reflection in the human aorta from pressure alone: a proof of principle. *Hypertension.* 2006;48(4):595-601. https://doi.org/10.1161/01.HYP.0000238330.08894.17 PMID: 16940207
24. Augustine JA, Lefferts WK, Dowthwaite JN, Brann LS, Brutsaert TD, Heffernan KS. Subclinical atherosclerotic risk in endurance-trained premenopausal amenorrheic women. *Atherosclerosis*. 2016;244:157-164. https://doi.org/10.1016/j.atherosclerosis.2015.11.011 PMID:26647371
25. Pyke KE, Tschakovsky ME. Peak vs. total reactive hyperemia: which determines the magnitude of flow-mediated dilation? *J Appl Physiol.* 2007;102(4):1510-1519. W https://doi.org/10.1152/japplphysiol.01024.2006 PMID: 17170205
26. Stoner L, McCully KK. Peak and time-integrated shear rates independently predict flow-mediated dilation. *J Clin Ultrasound*. 2012;40(6):341-351. https://doi.org/10.1002/jcu.21900 PMID:22407951
27. Humphreys RE, Green DJ, Cable NT, Thijssen DH, Dawson EA. Low-flow mediated constriction: the yin to FMD's yang? *Expert Rev Cardiovasc Ther*. 2014;12(5):557-564. https://doi.org/10.1586/14779072.2014.909728 PMID:24745959
28. Königstein K, Wagner J, Frei M, et al. Endothelial function of healthy adults from 20 to 91 years of age: prediction of cardiovascular risk by vasoactive range. *J Hypertens.* 2021;39(7):1361-1369. https://doi.org/10.1097/HJH.0000000000002798 PMID:33470736
29. Gori T, Dragoni S, Lisi M, et al. Conduit artery constriction mediated by low flow a novel noninvasive method for the assessment of vascular function. *J Am Coll Cardiol*. 2008;51(20):1953-1958. https://doi.org/10.1016/j.jacc.2008.01.049 PMID:18482663
30. Gori T, Grotti S, Dragoni S, et al. Assessment of vascular function: flow-mediated constriction complements the information of flow-mediated dilatation. *Heart*. 2010;96(2):141-147. https://doi.org/10.1136/hrt.2009.167213 PMID:19858140
31. Dawson EA, Alkarmi A, Thijssen DH, et al. Low-flow mediated constriction is endothelium-dependent: effects of exercise training after radial artery catheterization. *Circ Cardiovasc Interv*. 2012;5(5):713-719. https://doi.org/10.1161/CIRCINTERVENTIONS.112.971556 PMID:23011264
32. Thijssen DH, Dawson EA, Black MA, Hopman MT, Cable NT, Green DJ. Heterogeneity in conduit artery function in humans: impact of arterial size. *Am J Physiol Heart Circ Physiol*. 2008;295(5):H1927-H1934. https://doi.org/10.1152/ajpheart.00405.2008 PMID:18775852
33. Sharman JE, Davies JE, Jenkins C, Marwick TH. Augmentation index, left ventricular contractility, and wave reflection. *Hypertension.* 2009;54(5):1099-1105. https://doi.org/10.1161/HYPERTENSIONAHA.109.133066 PMID: 19720955
34. Mitchell GF. Triangulating the peaks of arterial pressure. *Hypertension* . 2006;48(4):543-545. https://doi.org/10.1161/01.HYP.0000238325.41764.41 PMID: 16940226
35. Chirinos JA, Kips JG, Jacobs DR Jr, et al. Arterial wave reflections and incident cardiovascular events and heart failure: MESA (Multiethnic Study of Atherosclerosis). *J Am Coll Cardiol*. 2012;60(21):2170-2177. https://doi.org/10.1016/j.jacc.2012.07.054 PMID:23103044
36. Wang KL, Cheng HM, Sung SH, et al. Wave reflection and arterial stiffness in the prediction of 15-year all-cause and cardiovascular mortalities: a community-based study. *Hypertension.* 2010;55(3):799-805. https://doi.org/10.1161/HYPERTENSIONAHA.109.139964 PMID: 20065155
37. Mitchell GF, Wang N, Palmisano JN, et al. Hemodynamic correlates of blood pressure across the adult age spectrum: noninvasive evaluation in the Framingham Heart Study. *Circulation*. 2010;122(14):1379-1386. https://doi.org/10.1161/CIRCULATIONAHA.109.914507 PMID:20855656
38. Winston GJ, Palmas W, Lima J, et al. Pulse pressure and subclinical cardiovascular disease in the multi-ethnic study of atherosclerosis. *Am J Hypertens*. 2013;26(5):636-642. https://doi.org/10.1093/ajh/hps092 PMID:23388832
39. Markert MS, Della-Morte D, Cabral D, et al. Ethnic differences in carotid artery diameter and stiffness: the Northern Manhattan Study. *Atherosclerosis*. 2011;219(2):827-832. https://doi.org/10.1016/j.atherosclerosis.2011.08.028 PMID:21906739
40. Mitchell GF, Gudnason V, Launer LJ, Aspelund T, Harris TB. Hemodynamics of increased pulse pressure in older women in the community-based Age, Gene/Environment Susceptibility-Reykjavik Study. *Hypertension.* 2008;51(4):1123-1128. https://doi.org/10.1161/HYPERTENSIONAHA.107.108175 PMID: 18259005
41. Segers P, Rietzschel ER, De Buyzere ML, et al. Noninvasive (input) impedance, pulse wave velocity, and wave reflection in healthy middle-aged men and women. *Hypertension.* 2007;49(6):1248-1255. https://doi.org/10.1161/HYPERTENSIONAHA.106.085480 PMID: 17404183
42. Kuvin JT, Sidhu M, Patel AR, Sliney KA, Pandian NG, Karas RH. Pulse pressure and peripheral arterial vasoreactivity. *J Hum Hypertens*. 2005;19(6):501-502. https://doi.org/10.1038/sj.jhh.1001844 PMID:15729377
43. Chamiot-Clerc P, Renaud JF, Safar ME. Pulse pressure, aortic reactivity, and endothelium dysfunction in old hypertensive rats. *Hypertension.* 2001;37(2):313-321. https://doi.org/10.1161/01.hyp.37.2.313. PMID: 11230291
44. Vuurmans TJ, Boer P, Koomans HA. Effects of endothelin-1 and endothelin-1 receptor blockade on cardiac output, aortic pressure, and pulse wave velocity in humans. *Hypertension.* 2003;41(6):1253-1258. https://doi.org/10.1161/01.HYP.0000072982.70666.E8 PMID: 12743011
45. Hu CT, Chang KC, Wu CY, Chen HI. Acute effects of nitric oxide blockade with L-NAME on arterial haemodynamics in the rat. *Br J Pharmacol*. 1997;122(6):1237-1243. https://doi.org/10.1038/sj.bjp.0701496 PMID:9401792
46. Stewart AD, Millasseau SC, Kearney MT, Ritter JM, Chowienczyk PJ. Effects of inhibition of basal nitric oxide synthesis on carotid-femoral pulse wave velocity and augmentation index in humans. *Hypertension.* 2003;42(5):915-918. https://doi.org/10.1161/01.HYP.0000092882.65699.19 PMID: 12975386
47. Pool LR, Aguayo L, Brzezinski M, et al. Childhood risk factors and adulthood cardiovascular disease: a systematic review. *J Pediatr*. 2021;232:118-126.e23. https://doi.org/10.1016/j.jpeds.2021.01.053 PMID:33516680
48. Nilsson PM. Early vascular aging (EVA):

consequences and prevention. *Vasc Health Risk Manag*. 2008;4(3):547-552. https://doi.org/10.2147/VHRM.S1094 PMID:18827905

49. Horvath S, Gurven M, Levine ME, et al. An epigenetic clock analysis of race/ethnicity, sex, and coronary heart disease. *Genome Biol*. 2016;17(1):171. https://doi.org/10.1186/s13059-016-1030-0 PMID:27511193
50. Harris RA, Nishiyama SK, Wray DW, Richardson RS. Ultrasound assessment of flow-mediated dilation. *Hypertension.* 2010;55(5):1075-1085. https://doi.org/10.1161/HYPERTENSIONAHA.110.150821 PMID: 20351340
51. Black MA, Cable NT, Thijssen DH, Green DJ. Importance of measuring the time course of flow-mediated dilatation in humans. *Hypertension.* 2008;51(2):203-210. https://doi.org/10.1161/HYPERTENSIONAHA.107.101014 PMID: 18086954