Published in final edited form as:
Hypertension. 2022 September ; 79(9): 2042–2050. doi:10.1161/HYPERTENSIONAHA.121.18765.

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Association of Blood Pressure-Related Increase in Vascular Stiffness on Other Measures of Target Organ Damage in Youth

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Abstract

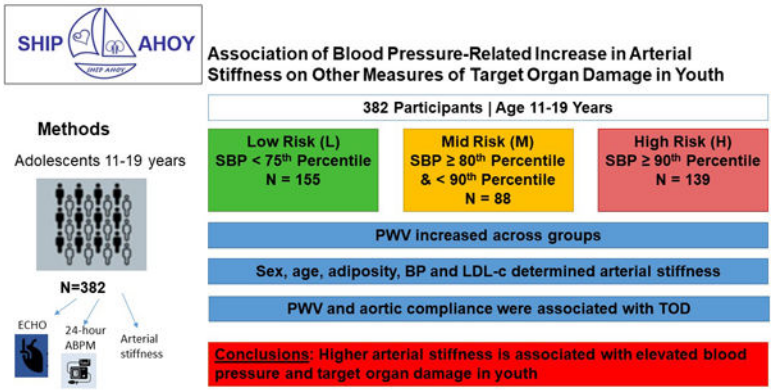
Background: Hypertension-related increased arterial stiffness predicts development of target organ damage (TOD) and cardiovascular disease (CVD. We hypothesized that BP-related increased arterial stiffness is present in youth with elevated BP and is associated with TOD.

Methods: Participants were stratified by systolic blood pressure (SBP) into low- (L = SBP <75th percentile, N= 155), mid- (M = SBP ≥80th and <90th percentile, N= 88), and high-risk BP categories (H ≥ 90th percentile, N= 139), based on age-, sex- and height-specific pediatric BP cut-points. Clinic BP, 24-hour ambulatory blood pressure monitoring (ABPM), anthropometrics and laboratory data were obtained. Arterial stiffness measures included carotid-femoral pulse wave velocity (PWV), and aortic stiffness. Left ventricular mass index (LVMi), LV systolic and diastolic function and urine albumin/creatinine were collected. ANOVA with Bonferroni correction was used to evaluate differences in CV risk factors, PWV, and cardiac function across groups. General linear models were used to examine factors associated with arterial stiffness, and to determine if arterial stiffness is associated with TOD after accounting for blood pressure.

Results: PWV increased across groups. Aortic distensibility, distensibility coefficient and compliance were greater in L than in M or H group. Significant determinants of arterial stiffness were sex, age, adiposity, BP and LDL-c. PWV and Aortic Compliance were significantly associated with TOD (systolic and diastolic cardiac function and urine albumin/creatinine ratio) after controlling for blood pressure.

Conclusions: Higher arterial stiffness is associated with elevated BP and TOD in youth emphasizing the need for primary prevention of CVD.

Graphical Abstract



Keywords

blood pressure; arterial stiffness; pediatrics; cardiac function; target organ damage; pulse wave velocity

Introduction:

Cardiovascular disease (CVD) is the world's leading cause of death.[1] Earlier onset of hypertension (HTN) is associated with greater risk for CVD,[2] which is concerning since the prevalence of elevated blood pressure (BP) in youth is near 15%.[3] Elevated BP and HTN lead to early vascular aging (EVA)[4, 5] which is associated with target organ damage (TOD) in adults[6] due to the transmission of high pressure pulsatile flow to delicate capillaries in important organs. Carotid-femoral pulse wave velocity (PWV), a measure of central arterial stiffness, is the gold standard assessment for EVA.[4] Measures of aortic stiffness and elasticity are additional measures that are also altered in pathophysiological conditions such as atherosclerosis, diabetes, and HTN.[7] Measurement of EVA is important as it is an independent predictor of CV events in adults.[8] Limited pediatric data show a similar relationship between EVA, BP and TOD but include few participants with elevated BP.[9, 10] We hypothesized that youth with elevated BP would have EVA[4] and that arterial stiffness would be related to TOD after controlling for BP.

Methods:

The study underwent institutional review board approval at each institution. Pparticipants and their parent/guardian provided written informed assent and consent. The data are available from the corresponding author upon reasonable request.

Population:

Participants in our multi-center study to evaluate the CV effects of elevated BP included 382 youth 60% male, 63% White and 16% Hispanic, age 11–19 years, mean = 15.6 ± 1.8 years, 35% of the participants were lean, 20% were overweight and 45% were obese [11]). Participants were stratified by systolic BP (SBP) into low-risk (L = SBP <75th percentile, N= 155), mid-risk (M = SBP ≥80th and <90th percentile, N= 88), and high-risk BP groups (H= SBP ≥ 90th percentile, N= 139) by the Fourth Report on High BP in Children,[12] since recruitment for the study started prior to release of the American Academy of Pediatrics Clinical Practice Guidelines.[13] For analyses, BP percentiles from the 2017 CPG on BP[13] were used. Exclusion criteria included current antihypertensive drug treatment or medications affecting BP, diabetes mellitus (type 1 or 2), chronic kidney disease, congenital heart disease, or secondary hypertension. Demographic, anthropometric data, vital signs, and lab values (fasting lipid panel, fasting glucose and insulin, creatinine, uric acid, C-reactive protein [CRP], urine Na/K ratio, urine albumin/creatinine ratio [ACR]) were obtained as previously described.[14]

Clinic BP Measurement:

Cuff size was based on arm circumference.[13] Blood pressures were obtained in the right arm by auscultation using an aneroid sphygmomanometer (Mabis MedicKit5; Mabis Healthcare, Waukegan, IL). Four BP measurements were obtained at 30-second intervals on each of 2 visits, with the average of the 2^{nd}, 3^{rd}, 4^{th} and 6^{th}, 7^{th}, 8^{th} BP measurements used.[15]

ABPM Measurement:

Ambulatory blood pressure was measured with the OnTrak 90227 (SpaceLabs, Snoqualmie, WA) according to pediatric ABPM guidelines.[16] ABP index was calculated as the mean measured BP divided by the 95^{th} percentile from the pediatric normative data for sex and height.[17]

Measures of CV TOD:

Cardiac images[14] were read using Cardiology Analysis System (Digisonics, Houston, TX). LV mass was calculated using the Deveraux equation[18–20] and indexed (LVMI) to $ht^{2.7}$[21]. Systolic function was evaluated with global longitudinal strain (GLS), strain rate, tine to peak longitudinal strain, time to peak longitudinal strain rate, LV ejection fraction (LVEF) and stroke volume (SV) (TOMTEC Corporation, Chicago, IL).[22] Cardiac output and systemic vascular resistance were calculated using standard formulas, with the assumption of 3 mmHg for CVP. Diastolic function was assessed using Doppler for mitral E/A and with tissue Doppler for average (septal/free wall) e'/a' and E/e'.

First morning urine albumin/creatinine (ACR) was obtained (microvascular dysfunction). [23, 24] Two individuals with extremely high ACR, had ACR set to missing.

Arterial Stiffness:

Pulse wave velocity: Carotid-femoral Pulse wave velocity (PWV) was measured using a SphygmoCor CPV (AtCor Medical, Sydney, Australia) [25, 26]. The pulse transit time (PTT) is the difference in time between the peak of the R-wave (from ECG leads) to the foot of the femoral pressure wave (obtained with a tonometer) minus the R-wave to foot of the carotid pressure wave time and PWV is distance/PTT. PWV is highly reproducible with coefficient of variation of 7%.[27]

Aortic Stiffness: Aortic stiffness was calculated using maximum diastolic and minimum systolic diameters of the ascending aorta 3–4 cm above the aortic valve in the parasternal long axis view.[28–31]

Aortic strain: $100(AoS - AoD)/AoD$

Aortic distensibility: $(2 \times \text{Ao strain})/ (SBP - DBP)$

Beta Stiffness index: $\beta = Ln(SBP/DBP)/\text{Ao strain}$

Distensibility coefficient: $[2 \times [(AoS - AoD)/AoD]/(SBP - DBP)]$

Aortic compliance: $\pi[(AoS^2\text{-}AoD^2)/4(SBP\text{-}DBP)]$

Peterson Elastic Modulus[32]: $E_p = (SBP\text{-}DBP)(AoD)/(AoS\text{-}AoD)$

Statistical Analysis:

Statistical Analysis Software (SAS Institute Inc., version 9.4, Cary, North Carolina, USA) was used. Means/frequencies were obtained by BP group. Variance stabilizing procedures were employed as needed. Differences between groups were analyzed using analysis of variance with Bonferroni correction for multiple compaisons or chi square.

Independent determinants of arterial stiffness were determined from a full linear model (age, sex, race, ethnicity, waist/height ratio, LDL-C, TG/HDL ratio, HOMA-IR, Creatinine, Uric Acid, CRP, MAP, daytime Ambulatory SBP and DBP indices) reduced until all parameters remaining were significant. Additional models were constructed to determine if arterial stiffness remained a significant determinant of TOD after adjustments (same variables omitting laboratory values). Correlations were higher between arterial stiffness and BP and TOD than Cardiac Index and SVR so only arterial stiffness was modeled. Mediation analysis was performed to evaluate whether BP was mediating the relationship between arterial stiffness and TOD.

Results:

CV Risk Factors by BP group Tables 1 and 2) showed more adverse profile at higher BP. The majority of participants were overweight (20%) or obese (45%). There were more participants with obesity in the H group compared to L group. There were no differences in lipid between groups except HDL was higher in the L compared to H group and glucose, HOMA-IR, insulin and CRP were significantly lower in the L group compared to the H group. Uric acid was lower in the L compared to the H group ($p<0.05$). There were no significant differences found in the urine sodium/potassium ratio. Both daytime and nighttime ambulatory systolic and mean diastolic BP and indexed DBP increased across groups. There were no significant differences in systolic or diastolic dipping among groups.

PWV was higher in H than in L group (L=4.83±0.69; M=5.08±0.76; H=5.35±0.92; $p\leq0.05$) (Figure 1, Table 3) although values are within normal limits.[33] The prevalence of abnormal PWV in this entire cohort (defined as PWV ≥ 5.93 m/sec from healthy lean youth) was 10%.[33] with most in H group (L=6.5%; M=10.2%; H=13.7%). H had higher percentage of abnormal PWV than L ($p = 0.039$). PWV was higher in males versus females (5.16 versus 4.95 m/sec; $P\leq 0.03$). Aortic distensibility, distensibility coefficient, and aortic compliance were greater in L than in M or H ($p\leq0.05$). There was no significant difference between groups in aortic strain, beta stiffness index or Peterson Elastic Modulus.

Left ventricular mass index was lower in L than in H group [LVMi ($g/m^{2.7}$): L=31.5; M=33.5; H=33.5]. LVEF was higher in the L group versus M group (Table 3, all $p\leq 0.05$). There was no difference in other systolic function measures. E/e' was higher in the H group, (worse diastolic function). Both E/A and e'/a' trended lower (adverse) in H versus L ($p =0.07$). The prevalence of elevated ACR was low (3.9% overall) and did not differ among groups but there was higher ACR in H vs L and M groups combined (9.3 versus 6.1; $p = 0.03$).

Significant determinants of PWV (Table 4) were age, waist/height ratio, MAP and ABPM nighttime diastolic index ($R^2 = 0.26$). Either clinic MAP and/or an ambulatory BP parameter was a major determinant of all measures of aortic stiffness. Male sex was a determinant for AD, Logβ stiffness index, DC and log[Peterson elastic pressure modulus]. LDL was associated with AS, DC, AC and log[Peterson elastic pressure modulus]. The amount of the variance in aortic stiffness explained by the models was low (R^2: AS=0.07, AD=0.12, Logβ=0.12, DC=0.11, AC=0.12, log[Peterson]=0.09). After adjustments. AC (Table 5) remained a determinant of E/e' and log[ACR]; PWV was a significant determinant of e'/a', and T2PLS4c.

In mediation analyses BP was either not significant in a model relating arterial stiffness to TOD (time to peak strain, Ualb/cr ratio), or did not change the beta estimate for arterial stiffness and (e'/a') indicating no mediation by BP. However BP was significant for the model of E/e' and the beta estimate for aortic compliance was reduced substantially indicating the BP mediated the relationship between AC and E/e'(data not shown).

Discussion:

We show that youth with elevated BP had adverse CV risk profile and increased arterial stiffness and BP (clinic or ambulatory BP) is a significant predictor of arterial stiffness. In turn, arterial stiffness predicts BP-related TOD (cardiac structure and function, microvascular dysfunction. Our data are the first to show that clinic BP and out of office BP related increases in arterial stiffness may be associated with cardiac TOD in youth. Longitudinal studies are needed to determine the time course for development of elevated BP and increased arterial stiffness and to make inferences on causality.

The association between elevated BP and arterial stiffness is well documented in adults.[5, 9, 34–44] Gedikli et al. demonstrated that arterial stiffness (measured by aortic PWV and AIx) was significantly higher in a group of prehypertensive adults compared to normotensive controls.[40] Similarly, in a longitudinal study of 777 adults followed over a 25 year period, participants with either prehypertension (SBP 120–139 mmHg) or hypertension (SBP > 140 mmHg) were found to have a steeper rate of PWV increase over the study period compared to normotensive controls.[38] In addition to clinic blood pressures, elevated BP measurements on ABPM were also found to correlate with PWV.[43, 45]

Similar findings have been noted in pediatric populations.[34, 46–54] In a study of 1171 children in Switzerland (average age of 7 years), participants with elevated BP (BP 90–95th %tile) or hypertension had higher PWV compared to their normotensive peers (PWV 4.44 vs 4.56 vs 4.29).[46] In 501 Spanish youth, a graded increase in PWV was present across BP strata.[55] A recent systematic review of carotid-femoral pulse wave velocity (PWV) in youth showed that cardiometabolic risk factors were positively associated with PWV, including positive associations with BP, impaired glucose metabolism, and metabolic syndrome.[56] Our study is the largest in the U.S. to show similar increase in PWV across BP groups, suggesting that elevation in BP prior to a clinical diagnosis of HTN is associated with vascular impairment even in youth.

Few studies have evaluated ABPM data and arterial stiffness in youth. Although Stabouli et al. found a significant correlation between PWV and many ABPM parameters, including mean BP, BP load, and variability, on analysis of covariance, only weighted 24-hr SBP variability and daytime SBP variability independently predicted PWV.[47] In contrast, our study found that only clinic MAP and ABPM nighttime diastolic index were independently associated with PWV. This difference may in part be due to differences in the population studied. While Stabouli's population consisted of a random sample of younger school aged children (average age 10 years), our study population primarily consisted of adolescents with increased BMI. Our study uniquely evaluated multiple aspects of arterial stiffness in youth and demonstrated that youth with normal BP have lower arterial stiffness by aortic distensibility, distensibility coefficient and aortic compliance compared to youth with elevated BP

The association between arterial stiffness and TOD has not been well explored. A study of 338 young adults found a linear relationship between 4-chamber global longitudinal strain and lower brachial distensibility, suggesting increased arterial stiffness was associated with

subclinical decline in systolic function.[57] In a study of adolescents and young adults with systemic lupus erythematosus (SLE), Chow et al. demonstrated that carotid arterial stiffness was a significant independent determinant of LV mass, early diastolic myocardial tissue velocity, and systolic strain rate of LV free wall.[58] Another pediatric study evaluated lean, obese and diabetic youth and found LVMi to be independently associated with higher global stiffness index calculated from 5 measurements of carotid artery stiffness, augmentation index, branchial distensibility and pulse wave velocity.[10] This study further demonstrates the association between arterial stiffness and CV TOD that persists after adjustment for BP, including a reduction in subclinical systolic and diastolic function and microvascular dysfunction (increased Ualb/cr ratio). However, our mediation analyses suggest that BP does mediate the relationship between aortic compliance and diastolic function.

Perspectives

These data demonstrate that cardiovascular risk profile and arterial stiffness worsens the higher the blood pressure category in adolescents without known preexisting conditions. Our data are the first to show that clinic BP and out of office BP related increases in arterial stiffness may be associated with cardiac TOD in youth. Longitudinal studies are needed to determine the time course for development of elevated BP and increased arterial stiffness and to make inferences on causality.

Limitations:

Due to the cross-sectional design of our study, causality and overall timeline for the development of TOD in our population cannot be determined. It is possible that some participants with WCH were included in the H group, however, in our modeling we included ABPM variables to correct for this. Whether a BP related increase in arterial stiffness or other factors (obesity related insulin resistance) cause increased stiffness resulting in elevated BP cannot be determined in our cross-sectional design. Our participants were oversampled toward the higher BP distribution (> 80%ile) and this may reduce generalizability to other populations. Finally, our study utilized a tonometric device for measuring PWV which, although is the gold standard, is not equivalent to oscillometric measures of PWV[59, 60] used in other studies.

Conclusion:

Youth with elevated BP have higher arterial stiffness which is associated with other preclinical measures of TOD. Early intervention in youth with high BP should be prioritized to prevent early cardiovascular disease.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Source of Funding:

American Heart Association (AHA) grant 15SFRN2368.

Abbreviations

ABP	Ambulatory blood pressure
ABPM	Ambulatory blood pressure monitor
AC	Aortic compliance
ACR	urine albumin/creatinine ratio
ANOVA	Analysis of variance
AoD	Aortic diameter in diastole
AoS	Aortic diameter in systole
AS	Aortic stiffness
BP	Blood pressure
CDC	Center for Disease Control
CPG	Clinical practice guidelines
CVD	Cardiovascular disease
CVP	Central venous pressure
DC	Distensibility coefficient
DBP	Diastolic blood pressure
EVA	Early vascular aging
GLS	Global longitudinal strain
HTN	Hypertension
LV	Left ventricle
LVEF	Left ventricular ejection fraction
LVMi	Left ventricular mass index
LVSF	Left ventricular shortening fraction
MAP	Mean arterial pressure
NHANES	National Health and Nutrition Examination Survey
PP	Pulse pressure
PWV	Pulse wave velocity
SBP	Systolic Blood Pressure
SV	Stroke volume

TDI	Tissue doppler imaging
TOD	Target Organ Damage

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Perspectives:

In the largest multi-center study of the effect of blood pressure on target organ damage in youth, we report the effect of elevated blood pressure on arterial stiffness. We also confirm the relationship between stiffer vessels and adverse cardiac structural and functional changes.

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Pathophysiological Novelty and Relevance

What is new?

- Clinic BP and out of office BP related increases in arterial stiffness may be associated with cardiac TOD in youth

What is relevant?

- Youth with elevated BP have higher arterial stiffness which is associated with other preclinical measures of TOD

Clinical/Pathophysiological Implications?

- Early intervention in youth with high BP should be prioritized to prevent early cardiovascular disease.

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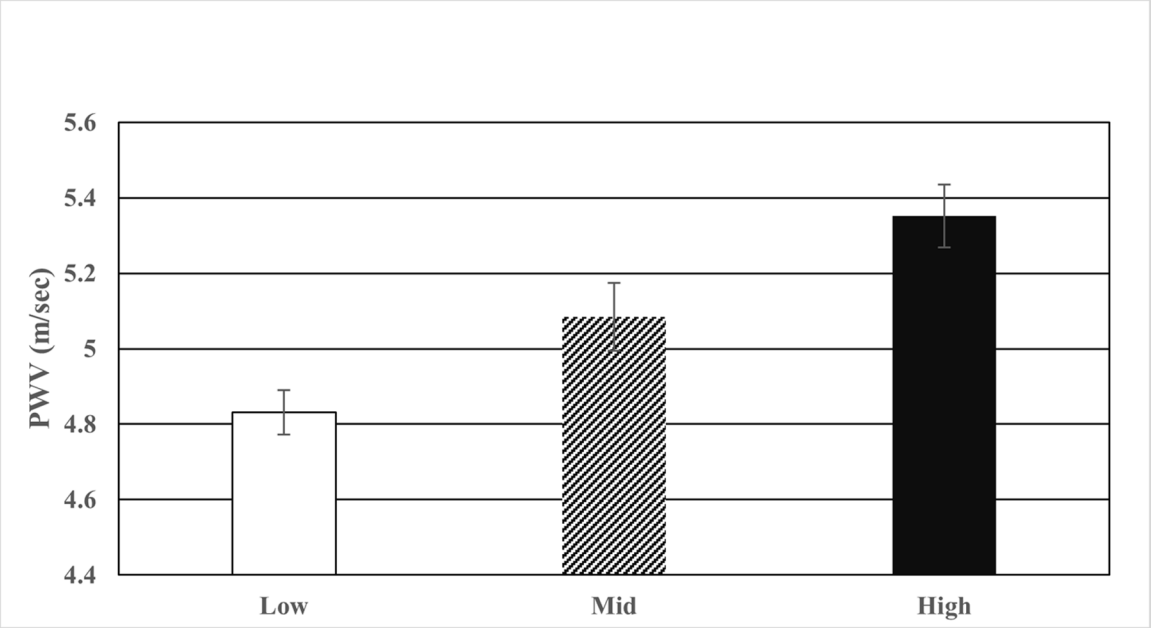

Figure 1.
PWV by BP group (Bonferroni corrected P≤0.0001 for low < high).

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Table 1.

Description of the study population (means, standard deviations or frequencies).

Characteristics	Low (L) N=155	Mid (M) N=88	High (H) N=139
Age (years)*	15.6 ± 1.6	15.9 ± 1.8	15.3 ± 1.9
Race (% non-White	25.0	37.9	37.1
Sex (% Male)†	52.3	71.6	61.2
Height (cm)*	168.7 ± 9.1	171.8 ± 10.9	168.5 ± 9.9
Weight (kg)‡	76.7 ± 23.3	85.6 ± 29.0	84.8 ± 25.0
BMI (kg/m2)§	26.7 ± 7.0	28.7 ± 8.6	29.7 ± 7.9
BMI percentile (%)§	78.0 ± 41.5	80.6 ± 20.9	86.4 ± 20.9
Obese (%)§	36.1	46.6	54.7
Waist (cm)§	86.1 ± 18.8	89.1 ± 19.5	93.5 ± 19.7
Waist/height ratio‖	0.5 ± 0.1	0.5 ± 0.1	0.6 ± 0.1
Total cholesterol (mg/dl)	152.0 ± 30.1	153.8 ±34.8	154.3 ± 33.2
LDL (mg/dl)	86.6 ± 26.9	90.7 ± 28.8	92.5 ± 28.4
HDL (mg/dl)#	47.4 ± 12.2	44.1 ± 11.5	43.3 ± 11.7
Triglycerides (mg/dl)	94.5 ± 62.2	99.4 ± 58.6	96.3 ± 48.8
Glucose (mg/dl)§	87.9 ± 8.0	89.5 ± 10.4	90.8 ± 8.2
Insulin (microIU/dl)§	17.9 ± 14.4	20.0 ± 14.4	23.8 ± 19.0
HOMA_IR§	3.98 ± 3.46	4.47 ± 3.31	5.48 ± 4.78
CRP (mg/dl)§	1.30 ± 1.69	1.39 ± 1.74	1.95 ± 2.16
Creatinine (mg/dl)**	0.72 ± 0.13	0.79 ± 0.18	0.72 ± 0.17
Uric acid (mg/dl)§	5.41 ± 1.63	5.81 ± 1.40	6.04 ± 1.52
Urine sodium/potassium ratio	4.09 ± 3.01	4.19 ± 3.16	3.99 ± 2.64

Bonferroni adjusted P≤0.04 for

*H<M

†M<L

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‡ L<M&H

§ L< H

// L&M<H

H<L

** L&H<M

BMI, body mass index; *CRP,* C-reactive protein*; DBP,* diastolic blood pressure; *HDL,* high density lipoprotein; *HR,* heart rate; *K1,* Korotkoff sound 1; *K5,* Korotkoff sound 5; *LDL,* low density lipoprotein; *MAP,* mean arterial pressure; *SBP,* systolic blood pressure.

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Hypertension. Author manuscript; available in PMC 2023 September 01.

Table 2.

Cardiovascular parameters stratified by BP group (means, standard deviations).

Characteristics	Low (L) N=155	Mid (M) N=88	High (H) N=139
K1 SBP (mmHg)*	111.5 ± 9.8	126.0 ± 5.6	132.7 ± 7.2
K4 DBP (mmHg)†	74.3 ± 13.1	82.9 ± 12.8	86.3 ± 13.4
K5 (mmHg)†	67.2 ± 9.9	73.3 ± 8.1	75.4 ± 10.5
MAP (mmHg)*	81.9 ± 8.7	90.9 ± 5.9	94.5 ± 7.6
SBP percentile (%)*	50.6 ± 27.1	86.1 ± 7.6	95.3 ± 3.3
DBP percentile (%)†	53.2 ± 29.1	69.1 ± 23.7	75.3 ± 26.0
HR (bpm)‡	72.0 ± 12.2	68.0 ± 11.6	73.6 ± 13.3
Ambulatory Daytime SBP (mmHg)*	117.9 ± 9.5	125.1 ± 9.0	130.5 ± 10.9
Ambulatory Daytime SBP Index*	0.88 ± 0.07	0.92 ± 0.07	0.97 ± 0.08
Ambulatory Nighttime SBP (mmHg)*	103.3 ± 9.2	110.0 ± 9.3	114.4 ± 10.6
Ambulatory Nighttime SBP Index*	0.88 ± 0.07	0.92 ± 0.08	0.97 ± 0.09
Ambulatory Daytime DBP (mmHg)*	69.0 ± 6.4	72.4 ± 6.8	75.0 ± 8.3
Ambulatory Daytime DBP Index*	0.84 ± 0.08	0.88 ± 0.08	0.91 ± 0.10
Ambulatory Nighttime DBP (mmHg)*	55.7 ± 5.7	58.1 ± 6.2	61.2 ± 8.6
Ambulatory Nighttime DBP Index*	0.84 ± 0.09	0.88 ± 0.10	0.92 ± 0.13
SBP dipping (%)	12.2 ± 6.1	11.9 ± 5.8	12.0 ± 5.9
DBP dipping (%)	19.0 ± 7.6	19.4 ± 7.8	18.1 ± 8.4
Cardiac Output (ml/min)§, #	3.2 ± 1.0	3.5 ± 1.3	3.9 ± 1.3
Cardiac Index (L/min/m2) ∥, #	1.7 ± 0.5	1.8 ± 0.5	2.0 ± 0.6
Systemic Vascular Resistance, metric (dynes*sec*cm^{-5}) #	2190.7 ± 738.3	2221.4 ± 780.0	2115.6 ± 749.4
Systemic Vascular Resistance (Wood units) #	27.4 ± 9.2	27.8 ± 9.7	26.4 ± 9.4

Bonferroni adjusted p ≤0.05 for

*L<M<H

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† L<M&L

‡ M<H

§ L<H

‖ L&M<H

n is different for these parameters (L = 123, M = 78, H = 112) due to inability to make these measurements on the full cohort.

Table 3.

Stiffness Parameters & Measures of TOD Parameters stratified by BP group (means, standard deviations).

Characteristics	Low (L) N=155	Mid (M) N=88	High (H) N=139
Pulse Wave Velocity (m/sec)*	4.83 ± 0.69	5.08 ± 0.76	5.35 ± 0.92
Aortic Strain (unitless)	17.9 ± 7.9	18.1 ± 6.7	19.0 ± 7.7
Beta Stiffness index (unitless)	3.58 ± 2.30	3.60 ± 2.38	4.82 ± 11.45
Peterson Elastic Modulus (mmHg)	72.0 ± 41.5	81.5 ± 43.5	113.8 ± 237.4
Aortic Distensibility (1/mmHg)†	0.0084 ± 0.0039	0.0071 ± 0.0027	0.0069 ± 0.0030
Distensibility Coefficient (1/mmHg)†	0.02 ± 0.01	0.01 ± 0.01	0.01 ± 0.01
Aortic Compliance (mm/mmHg)†	0.030 ± 0.013	0.025 ± 0.011	0.023 ± 0.010
LVM Index (g/m$^{2.7}$)*	31.5 ± 6.7	33.5 ± 6.8	33.5 ± 7.2
Shortening Fraction (%)	37.6 ± 4.4	36.7 ± 5.0	38.0 ± 5.0
Ejection Fraction (%)‡	58.0 ± 7.2	55.4 ± 6.7	56.3 ± 6.7
Peak Longitudinal Strain (%)§	−20.9 ± 3.5	−19.9 ± 3.2	−20.1 ± 3.4
Peak Longitudinal Strain Rate (/sec)	−1.03 ± 0.24	−1.02 ± 0.24	−1.03 ± 0.2
Time to peak longitudinal strain (msec)	37.2 ± 6.2	37.6 ± 6.1	38.8 ± 6.0
Time to peak longitudinal strain rate (msec)	22.9 ± 10.2	21.8 ± 9.5	22.8 ± 8.0
e'/a' ratio §	2.47 ± 0.79	2.38 ± 0.62	2.27 ± 0.67
E/A ratio §	2.35 ± 0.70	2.24 ± 0.66	2.16 ± 0.63
E/e' ratio‖	6.09 ± 1.38	5.88 ± 1.32	6.63 ± 1.60
Urine Albumin/Creatinine ratio	6.140 ± 7.500	6.040 ± 7.920	9.280 ± 20.250

Bonferroni adjusted P≤0.05 for

*L<H

†M&H< L

‡M<L

§model p <0.07

‖L&M<H. Higher values indicate worsening arterial stiffness for the following parameters: Pulse Wave Velocity, Aortic Strain, Beta Stiffness index, Peterson Elastic Modulus. Lower values indicate worsening arterial stiffness for the following parameters: Aortic distensibility, Distensibility Coefficient, Aortic Compliance.

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Table 4:

Determinants of Arterial Stiffness

	PWV	Aortic strain	Aortic distensibility	Log Beta Stiffness Index	Distensibility Coefficient	Aortic Compliance	Log Peterson elastic pressure modulus
Intercept	−0.5	24.6	0.01	1.8	0.03	0.05	3.7
Age	0.07					0.004	
Sex (male)			0.002	−0.1	0.003		−0.1
Waist/height	2.06						
LDL		−0.03			−0.00002	−0.00005	0.002
logCRP			−0.0004	0.05			
Creatinine				0.5			
Mean Arterial Pressure	0.01			−0.02		0.0002	−0.008
ABP daytime SBP index					−0.02	−0.05	1.4
ABP daytime DBP index	2.6			0.8			
ABP nighttime SBP index		16.0	−0.007				
ABP nighttime DBP index		−20.7					
R^2	0.26	0.07	0.12	0.12	0.11	0.12	0.09

Full model included: age, race, sex, waist-to-height ratio, LDL, Triglyceride, HDL, HOMA-IR, Creatinine, Urine acid, CRP, MAP, HR, Ambulatory SBP Index Daytime, Ambulatory DBP Index Daytime. All model p ≤0.0001 and all parameter estimates ≤0.05.

Table 5:

Association of Different Measures of Arterial Stiffness with Left Ventricular and Microvascular Dysfunction

	E/e'	e'/a'	Time to Peak Longitudinal strain	Log Urine Albumin/ Creatinine
Pulse Wave Velocity (femoral)		−0.05	0.91	
Aortic compliance	0.02			−13.09
Intercept	3.04	1.96	12.82	−5.54
Age	−0.14			
Sex (male)		0.08	1.83	0.23
Waist/height	2.54	−0.85		−2.22
Mean Arterial Pressure			0.08	
ABP daytime SBP index	6.89	0.48		0.81
ABP daytime DBP index	−3.04	−0.71		
Heart rate		−0.01	0.15	0.01
R^2	0.2	0.26	0.17	0.11

Full model included: age, race, sex, waist-to-height ratio, HR, Ambulatory SBP Index Daytime, Ambulatory DBP Index Daytime and one of the arterial stiffness variables. All model p ≤0.0001 and all parameter estimates ≤0.05. Increase in E/e' or decrease in e'/a' is consistent with worsening diastolic function. Increase in strain indicates worse systolic function.