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Association of blood pressure and aortic distensibility with P wave indices and PR interval: the Multi-Ethnic Study of Atherosclerosis (MESA)

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Abstract

Introduction—Hypertension is an established risk factor for atrial fibrillation. Understanding the association of blood pressure (BP) levels and aortic distensibility with P wave indices (PWIs) and PR interval, intermediate phenotypes of atrial fibrillation, could provide insights into underlying mechanisms.

Methods—This analysis included 3180 men and women aged 45–84 participating in the Multi-Ethnic Study of Atherosclerosis, a community-based cohort in the United States. Aortic distensibility was evaluated in 2243 of these individuals using cardiac magnetic resonance imaging. PWIs and PR interval were automatically measured in standard 12-lead ECGs. Sitting BP and other cardiovascular risk factors were assessed using standardized protocols. Left ventricular mass was measured by magnetic resonance imaging.

Results—Higher systolic and diastolic BP, and greater pulse pressure were associated with a significantly greater P wave terminal force. These associations, however, were markedly attenuated or disappeared after adjustment for left ventricular mass. Systolic BP, diastolic BP, and pulse pressure were not strongly associated with PR interval or maximum P wave duration. Reduced aortic distensibility was associated with a longer PR interval but not with PWIs: compared with individuals in the top quartile of aortic distensibility, participants in the lowest

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quartile had on average a 3.7 ms longer PR interval (95% CI: 0.7, 6.7, $p=0.02$), after multivariable adjustment.

Conclusion—In this large community-based sample, associations of BP and aortic distensibility with PWIs and PR interval differed. These results suggest that processes linking hypertension with the electrical substrate of atrial fibrillation, as characterized by these intermediate phenotypes, are diverse.

Keywords

aorta; blood pressure; electrocardiography; epidemiology

INTRODUCTION

Atrial fibrillation (AF), the most common sustained arrhythmia in clinical practice, is expected to affect almost 6 million Americans by 2050.¹ AF increases the risk of stroke,² heart failure,³ and mortality,⁴ and is associated with a decreased quality of life,⁵ making it a major public health problem. Several variables in the 12-lead resting electrocardiogram (ECG), including the PR interval and P wave indices (PWIs) (e.g. duration, amplitude and dispersion of the P wave), have been identified as predictors of the future risk of AF.⁶⁻⁹ The P wave and the PR interval reflect atrial depolarization and atrioventricular conduction, and can be affected by the presence of atrial fibrosis, a major electrophysiological and structural substrate for the development of AF.¹⁰ Thus, these ECG measures have been proposed as endophenotypes (i.e. intermediate phenotypes) of AF.¹¹ Studying predictors of PR interval and PWIs might provide valuable insights into the pathophysiology of AF and could offer the opportunity to intervene before the development of clinical AF, thus potentially preventing this arrhythmia.

High blood pressure (BP) and hypertension have been consistently associated with a higher risk of developing AF,¹²⁻¹⁵ and with alterations in PWIs.¹⁶⁻¹⁸ In an analysis of the Framingham Heart Study, pulse pressure was identified as a better predictor of the future risk of AF than mean BP,¹⁹ suggesting that aortic stiffness, manifested as increased pulse pressure, might be responsible for this increased risk. Aortic stiffness—lack of aortic distensibility—causes ventricular overload²⁰ and this, in turn, could lead to diastolic dysfunction and left atrial enlargement, an established risk factor of AF.²¹ No information exists, however, on the association of directly-measured aortic stiffness with AF or with its endophenotypes.

Therefore, we explored whether aortic distensibility, measured with magnetic resonance imaging (MRI), and blood pressure were associated with several AF endophenotypes (PR interval and PWIs) in the Multi-Ethnic Study of Atherosclerosis (MESA). We hypothesized that lower aortic distensibility and higher BP would be associated with longer PR interval and higher PWIs, independently of other cardiovascular risk factors.

METHODS

Study population

The MESA study sample has been previously described in detail.²² Briefly, between July 2000 and August 2002, 6814 men and women (2622 whites, 1893 African-Americans, 1496 Hispanics, 803 Chinese-Americans), aged 45-84, without clinical cardiovascular disease were recruited from 6 United States (US) communities: Baltimore City and Baltimore County, MD; Chicago, IL; Forsyth County, NC; Los Angeles County, CA; New York, NY;

and St. Paul, MN. The institutional review boards at all participating centers approved the study, and all participants gave informed consent.

At baseline, all MESA participants underwent a detailed physical examination and provided information on sociodemographic characteristics, lifestyles, and clinical variables using standardized questionnaires (protocols, manuals, and forms are available in the MESA website, www.mesa-nhlbi.org). Consenting participants with no contraindications underwent cardiac MRI (n=5004) which included assessment of the ascending aorta in 3541 of them.

For the present analysis, we included individuals with information on left ventricular mass from cardiac MRI and ECG-based measurements (n=4964). We excluded individuals taking type 1 or 3 anti-arrhythmic drugs, digoxin, calcium channel blockers, beta blockers, or any other antihypertensive medication (n=1767), those with PR interval <80 or >320 ms, Wolff-Parkinson-White syndrome, or advanced atrioventricular block (n=2), and those with missing information on any of the covariates (n=31). The final sample included 3180 eligible individuals; of these, 2243 had information on aortic distensibility. Atrial fibrillation at baseline was an exclusion criterion for participation in MESA.

Cardiac MRI measurements

MRI was performed using 1.5-T whole-body MRI systems, Signa CV/I or Signa LX (General Electric Medical Systems). The receiver coil used was a 4-element phased-array coil placed on the anterior and posterior surfaces of the chest. For evaluation of aortic distensibility, MRI scans of the aorta were obtained using gradient echo phase-contrast cine MRI with ECG gating. Images of the ascending and descending aorta were obtained in the transverse plane at the level of the right pulmonary artery perpendicular to the aortic lumen. Imaging parameters were as follows: repetition time: 10 ms; echo time, 1.9 ms; field of view, 34 cm; slice thickness, 8 mm; matrix size: 256 × 224; 2 signal averages; temporal resolution, 20 ms; velocity encoding gradient, 150 cm/s; and receiver bandwidth, ±32 kHz. Minimum and maximum cross-sectional areas (with respect to the cardiac cycle) of the ascending aorta were determined using an automated contour routine with the software FLOW (MEDIS Medical Imaging Systems, Leiden, the Netherlands). Aortic distensibility was calculated as (maximum area – minimum area)/[(minimum area) × PP] × 1000, where PP is the pulse pressure in millimeters of mercury. PP is defined as the difference between systolic and diastolic BP measured immediately before and after the MRI aortic measurements, averaging both measures. These measurements were taken while the patient was in the supine position on the MRI scanner gantry.

MRI-based left ventricular (LV) mass was calculated as the difference between the epicardial and endocardial areas multiplied by the slice thickness and section gap, and then multiplied by the specific gravity of the myocardium (1.05 g/ml). LV mass was adjusted for body size by dividing $100 \times \text{LV mass}$ by the predicted LV mass based on height, weight, and sex, as: $100 \times \text{LV mass} / (a \times \text{height}^{0.54} \times \text{weight}^{0.61})$, where $a = 6.82$ for women and 8.25 for men with mass in grams, height in meters, weight in kilograms, as described elsewhere.²³

ECG measures

Three sequential 10-second resting 12-lead ECG were recorded in all participants using a Marquette MAC- 1200 electrocardiograph (GE Medical). The ECG digital signal was transmitted over analogue phone lines to a central ECG reading center (EPICARE, Wake Forest University) blinded to all clinical details of the participants. P wave durations and amplitudes needed to calculate PWIs (P wave duration and P wave terminal force) were automatically measured with the GE Marquette 12-SL program 2001 version (GE

Marquette, Milwaukee, WI) from the first of these ECGs. Global PR interval was defined as the duration from the earliest onset of P wave to the earliest onset of QRS complex. Maximum P wave duration was the longest P wave duration (the sum of P and P prime) across the 12 leads. Finally, P wave terminal force was defined as the duration in seconds of the terminal part (negative) of the P wave in lead V1 multiplied by its depth in microvolts.²⁴ Because of the automatic measurement, the repeatability of all ECG measures was 100%.⁶

Assessment of other covariates

Three seated BP measurements were taken 5 minutes apart using an automated device (Dinamap Pro 100). The mean of the last 2 measurements was considered for analysis. Trained technicians measured height, weight, and waist circumference following a standardized protocol. Diabetes was defined as current use of glucose-lowering medications, fasting glucose ≥ 126 mg/dL, or nonfasting glucose ≥ 200 mg/dL. Use of medication, current smoking, ethanol intake, income, and education were ascertained from standardized questionnaires. Physical activity was assessed at baseline using an activity questionnaire adapted from the Cross-Cultural Activity Participation Study.²⁵

Statistical analysis

The cross-sectional association of blood pressure and aortic distensibility with PR interval and PWIs was calculated using multivariable general linear regression models, with the different ECG phenotypes as dependent variables. Separate models were fit for systolic BP, diastolic BP, pulse pressure, and aortic distensibility, considered as continuous variables (in standard deviation units) and categorized in quartiles. In initial models, we adjusted for age, gender, race/ethnicity, and heart rate. In subsequent models, we included the following variables: study site, income (3 levels), education (3 levels), height (cm), body mass index (kg/m^2), total cholesterol (mg/dL), HDL-cholesterol (mg/dL), serum creatinine (mg/dL), physical activity (MET-min/week), cigarette smoking (never, former, current smoker), pack-years of smoking, diabetes (yes/no), use of lipid lowering medications (yes/no), and alcohol intake (grams/week). We explored the presence of non-linear associations by categorizing blood pressure variables in quartiles and by using polynomial functions. Additional models were run log-transforming P wave terminal force. None of these analyses provided strong evidence for departures from linearity, and a simpler model with blood pressure measurements modeled as linear continuous variables is reported. Overall model performance was evaluated with the r^2 statistic. No evidence of collinearity between predictors was observed as assessed through the variance inflation factor. Finally, because a potential association of blood pressure or aortic distensibility with PR interval or PWIs might be mediated through LV hypertrophy, we ran an additional analysis adjusting for body size-adjusted LV mass. Interpretation of results are based on estimates of association and their confidence intervals, and not on p-values obtained from significance testing.²⁶

RESULTS

Table 1 reports selected characteristics of the 3180 eligible MESA participants overall and by race/ethnicity. PR interval and PWIs had higher values in African Americans compared to other ethnic/racial groups. Similarly, African Americans had the highest average systolic and diastolic BP and lowest aortic distensibility.

Higher systolic and diastolic BP, and pulse pressure were associated with higher P wave terminal force, though these associations were markedly attenuated or disappeared after adjustment for left ventricular mass (table 2). A 1-standard deviation (19.3 mmHg) difference in systolic BP was associated with $0.13 \mu\text{V} \cdot \text{s}$ (95% CI 0.07, 0.19) larger P wave terminal force after adjustment for multiple confounders, while the increase was only 0.06

$\mu\text{V} \cdot \text{s}$ (95% CI $-0.01, 0.12$) after LV mass adjustment. Corresponding differences (95% CI) in P wave terminal force were $0.16 \mu\text{V} \cdot \text{s}$ (0.10, 0.22) and $0.11 \mu\text{V} \cdot \text{s}$ (0.05, 0.18) for 1-standard deviation (9.9 mmHg) of diastolic BP, and $0.07 \mu\text{V} \cdot \text{s}$ (0.00, 0.14) and $0.00 \mu\text{V} \cdot \text{s}$ ($-0.07, 0.07$) for 1-standard deviation (14.8 mmHg) of pulse pressure. Systolic BP, diastolic BP, and pulse pressure were not strongly or consistently associated with PR interval or maximum P wave duration.

Lower levels of aortic distensibility were associated with a longer PR interval both before and after adjustment for multiple potential confounders and left ventricular mass. PR interval was 1.06 ms longer (95% CI 0.04, 2.07) for each 1-standard deviation decrease (1.32 mmHg^{-1}) in aortic distensibility in multivariable models not adjusted for LV mass, with a slight attenuation after LV mass adjustment (table 2). In an analysis categorizing aortic distensibility in quartiles, those in the lowest quartile had a PR interval 3.8 ms longer (95% CI 0.9, 6.8; $p=0.01$) than those in the upper quartile. After additional adjustment for left ventricular mass, this difference was similar (3.7 ms, 95% CI 0.7, 6.7; $p=0.02$) (table 3). Aortic distensibility was not associated with maximum P wave duration or P wave terminal force (table 2).

Results were mostly unchanged after including 795 individuals using anti-hypertensive medications and adjusting for this variable, after exclusion of 113 participants with QRS interval ≥ 120 ms, or when we used average P wave duration or P wave duration in lead II instead of maximum P wave duration (data not shown). Sex modified the association of aortic distensibility and pulse pressure with maximum P wave duration. In women, lower aortic distensibility was associated with longer P wave duration, while no clear association was observed in men (p for interaction $=0.01$). Similar results were observed for pulse pressure (p for interaction $=0.02$) (Figure 1). No other interactions were observed between sex and blood pressure or aortic distensibility. Associations were not significantly different across racial/ethnic groups.

DISCUSSION

In this large, community-based study, we found that higher systolic BP, diastolic BP, and pulse pressure were associated with greater P wave terminal force, but not with PR interval or P wave duration. As expected, these associations were mostly attenuated after adjustment for left ventricular mass. Lower aortic distensibility, a marker of aortic stiffness, was associated with a longer PR interval duration, but not with PWIs. Results were not significantly different across racial/ethnic groups; however, sex modified the association of aortic distensibility and pulse pressure with maximum P wave duration.

Changes in cardiac structure could mediate the observed association between elevated BP and PWIs. Increased systemic BP leads to hemodynamic overload resulting in left ventricular hypertrophy,²⁷ and left atrial enlargement.²⁸ Also, increased cardiac afterload has been associated with left atrial remodeling involving conduction abnormalities in animal experiments.²⁹ Our results suggest that PWIs such as the P wave terminal force, as markers of interatrial conduction delay, could be more appropriate electrocardiographic markers of these morphological and functional changes than the PR interval. Finally, we observed that lower aortic distensibility was associated with longer P wave duration in women, but not in men. The significance of this observation and any potential underlying mechanisms are unclear.

The association of aortic distensibility with PR interval but not with PWIs suggests a link with the atrioventricular conduction system rather than the atrial substrate. Aging-related fibrosis is known to lead to slower atrioventricular conduction and prolongation of the PR

interval.³⁰ A similar process could be responsible for a loss of arterial distensibility. In fact, a parallel stiffening of the aorta and cardiac conduction system has been observed in an aging rabbit model.³¹

Our results have potential implications for the clinical use of PWIs and the PR interval. Both PWIs and PR interval are predictors of mortality and AF incidence in the general population,^{9, 32, 33} but their role as risk markers could be different across diverse cardiovascular outcomes given the observed distinct relationship with BP and aortic distensibility. For example, P wave duration was better than PR interval at predicting AF in an analysis of the Framingham Heart Study,⁹ while a different analysis in the same cohort found PR interval to better predict pacemaker implantation than AF incidence or mortality.³² Additional analyses in other cohorts should explore these associations.

Strengths of our analysis include the large sample size, the diversity of the study population, and the availability of information on confounders and potential mediators, including left ventricular mass measured by cardiac magnetic resonance. Limitations of the present study are the cross-sectional design, which does not provide information on the temporality of associations, and potential for measurement error in the different variables. Specifically, ECG measurements were based on a standard 10-second 12-lead ECG. Other methods, such as signal-averaged ECG for the measurement of P wave duration, could have eased this limitation. However, signal-averaged ECG is a time-consuming technique of difficult implementation in large community-based studies. Finally, some of the observed associations might be due to chance.

In conclusion, we observed that BP and arterial distensibility were differently associated with ECG-based measurements of atrial and atrioventricular function and morphology. Future research should explore the implications of these results in the use of PWIs and PR interval as risk markers of cardiovascular outcomes.

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Figure 1.

Adjusted average maximum P wave duration by quartiles of aortic distensibility and pulse pressure, in men (light blue) and women (dark blue), Multi-Ethnic Study of Atherosclerosis, 2000-2002. Bars represent 95% confidence intervals. Results from general linear model including age, sex, race/ethnicity, study site, income, education, heart rate, height, body mass index, total cholesterol, HDL-c, creatinine, physical activity, smoking status, pack-years of smoking, alcohol intake, diabetes, use of lipid lowering medications, left ventricular mass, aortic distensibility or pulse pressure quartile, and an interaction term for sex and aortic distensibility or pulse pressure quartiles.

Table 1

Selected characteristics of participants included in the analysis, Multi-Ethnic Study of Atherosclerosis, 2000-2002

N	3180
Age, years	59.4 (9.9)
Gender, % female	51.4
Race/ethnicity, %	
White	41.1
African-American	20.5
Hispanic	23.9
Chinese-American	14.5
Education, % completed high school	83.7
Smoking, % current	14.1
Alcohol use, drinks/week	4.0 (8.2)
Exercise, MET-min/wk	1636 (2348)
BMI, kg/m ²	27.1 (4.8)
Height, cm	167 (10)
SBP, mmHg	121 (19)
DBP, mmHg	71 (10)
Pulse pressure, mmHg	50 (15)
Aortic distensibility, mmHg ⁻¹ [†]	2.02 (1.32)
Body size-adjusted left ventricular mass, %	102 (18)
Diabetes, %	6.7
Heart rate, bpm	62.8 (9.0)
PR interval, ms	162.4 (23.0)
P wave duration (maximum), ms	103.9 (12.4)
P wave terminal force, $\mu\text{V}\cdot\text{s}$	1.93 (1.68)

Values correspond to mean (standard deviation) or percentages.

[†] Available in 2243 participants.

Table 2

Difference (Δ) in PR interval and P wave indices associated with 1-standard deviation increment in systolic and diastolic blood pressure, pulse pressure, and aortic distensibility, MESA, 2000-2002

	PR interval, ms		P wave duration (maximum), ms		P wave terminal force, $\mu V \cdot s$	
	Δ (95% CI)	P-value	Δ (95% CI)	P-value	Δ (95% CI)	P-value
Systolic BP (SD=19.3 mmHg)						
Model 1	0.39 (-0.45, 1.24)	0.36	0.46 (0.02, 0.90)	0.04	0.15 (0.09, 0.21)	<0.0001
Model 2	0.07 (-0.80, 0.94)	0.88	0.19 (-0.26, 0.64)	0.41	0.13 (0.07, 0.19)	0.0003
Model 3	-0.28 (-1.20, 0.64)	0.55	-0.14 (-0.62, 0.33)	0.56	0.06 (-0.01, 0.12)	0.08
Diastolic BP (SD=9.9 mmHg)						
Model 1	0.59 (-0.27, 1.45)	0.18	0.69 (0.24, 1.14)	0.003	0.16 (0.10, 0.23)	<0.0001
Model 2	0.30 (-0.57, 1.17)	0.50	0.46 (0.01, 0.91)	0.05	0.16 (0.10, 0.22)	<0.0001
Model 3	0.07 (-0.82, 0.97)	0.87	0.24 (-0.22, 0.71)	0.30	0.11 (0.05, 0.18)	0.0007
Pulse Pressure (SD=14.8)						
Model 1	0.15 (-0.75, 1.05)	0.74	0.17 (-0.30, 0.64)	0.64	0.11 (0.04, 0.17)	0.002
Model 2	-0.13 (-1.06, 0.81)	0.79	-0.07 (-0.55, 0.41)	0.77	0.07 (0.00, 0.14)	0.04
Model 3	-0.47 (-1.44, 0.51)	0.35	-0.40 (-0.90, 0.10)	0.12	0.00 (-0.07, 0.07)	0.92
Aortic distensibility (SD=1.32 mmHg ⁻¹)						
Model 1	-0.99 (-2.01, 0.02)	0.08	-0.37 (-0.90, 0.15)	0.16	-0.04 (-0.11, 0.03)	0.27
Model 2	-1.06 (-2.07, -0.04)	0.04	-0.41 (-0.93, 0.10)	0.12	-0.04 (-0.11, 0.04)	0.32
Model 3	-1.00 (-2.03, 0.02)	0.06	-0.31 (-0.83, 0.21)	0.24	0.00 (-0.07, 0.07)	0.98

SD: standard deviation. Model 1: multivariable linear model adjusted for age, gender, race, and heart rate; model 2: adjusted additionally for study site, income, education, height, body mass index, total cholesterol, HDL-cholesterol, creatinine, physical activity, cigarette smoking status, pack-years of smoking, diabetes, use of lipid lowering medications, and grams of alcohol week; model 3: adjusted additionally for left ventricular mass

Table 3

Difference (95% confidence interval) in PR interval, in milliseconds, by quartiles of aortic distensibility, MESA, 2000-2002

	Q1	Q2	Q3	Q4
Aortic distensibility, mmHg ⁻¹ , range	<1.188	1.188-1.763	1.764-2.565	2.566
N	561	561	561	560
Model 1	3.94 (0.95, 6.93)	3.70 (0.88, 6.53)	1.93 (−0.74, 4.60)	Ref.
Model 2	3.84 (0.86, 6.83)	3.31 (0.49, 6.14)	1.21 (−1.45, 3.87)	Ref.
Model 3	3.71 (0.69, 6.73)	3.21 (0.36, 6.05)	1.13 (−1.54, 3.81)	Ref.

Model 1: multivariate linear model adjusted for age, gender, race, and heart rate; model 2: adjusted additionally for study site, income, education, height, body mass index, total cholesterol, HDL-cholesterol, creatinine, physical activity, cigarette smoking status, pack-years of smoking, diabetes, use of lipid lowering medications, and grams of alcohol week; model 3: adjusted additionally for left ventricular mass