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Pulse Pressure Relation to Aortic and Left Ventricular Structure in Older People in the AGES-Reykjavik Study

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Abstract

High pulse pressure, a major cardiovascular risk factor, has been attributed to medial elastic fiber degeneration and aortic dilation, which transfers hemodynamic load to stiffer collagen. However, recent studies suggest higher pulse pressure is instead associated with smaller aortic diameter. Thus, we sought to elucidate relations of pulse pressure with aortic stiffness and aortic and cardiac dimensions. We used magnetic resonance imaging to examine relations of pulse pressure with lumen area and wall stiffness and thickness in the thoracic aorta and left ventricular structure in 526 participants (72 to 94 years of age, 295 women) in the community-based Age, Gene/Environment Susceptibility-Reykjavik Study. In a multivariable model that adjusted for age, sex, height, weight, and standard vascular risk factors, central pulse pressure had a negative relation with aortic lumen area (all effects expressed as mm Hg/SD; $B = -8.1 \pm 1.2$, $P < 0.001$) and positive relations with left ventricular end-diastolic volume ($B = 3.8 \pm 1.0$, $P < 0.001$), carotid-femoral pulse wave velocity ($B = 3.6 \pm 1.0$, $P < 0.001$), and aortic wall area ($B = 3.0 \pm 1.2$, $P = 0.015$). Higher pulse pressure in older people is associated with smaller aortic lumen area and greater aortic wall stiffness and thickness and left ventricular volume. Relations of larger ventricular volume and smaller aortic lumen with higher pulse pressure suggest mismatch in hemodynamic load accommodation by the heart and aorta in older people.

Keywords

aortic stiffness; hypertension; pulse wave velocity; pulse pressure; magnetic resonance imaging

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Conflicts of Interest

Dr. Mitchell is the owner of Cardiovascular Engineering, Inc., a company that develops and manufactures devices to measure vascular stiffness, serves as a consultant to and receives honoraria from Novartis and Merck, and is funded by research grants HL094898, DK082447, HL107385 and HL104184 from the National Institutes of Health. Ms. Torjesen, Mr. Gotal and Ms. Bell are employees of Cardiovascular Engineering, Inc.

Introduction

Increased pulse pressure (PP) is associated with increased characteristic impedance (Z_c) of the aorta and increased load on the heart, leading to susceptibility to ischemia,¹ diastolic dysfunction² and adverse clinical events.^{3–6} Previous studies have shown that PP increases markedly after mid-life when Z_c increases rapidly and aortic diameter, which increases steadily throughout early- and mid-life,^{7;8} begins to plateau.⁹ Z_c , which interacts with peak flow to produce the forward traveling pressure wave, has a strong negative relation with aortic lumen area¹⁰ and positive relations with aortic stiffness and wall thickness. The relation between pulse wave velocity (PWV) and aortic lumen dimensions is complex. According to both the Moens-Korteweg and Bramwell-Hill equations, PWV is inversely associated with aortic lumen size. However, aortic wall stiffening as a result of elastin fragmentation and aortic dilation can transfer load to substantially stiffer collagen, resulting in an increase in PWV despite the increase in diameter.¹¹ Thus, higher PP in late life could be associated with variable contributions from a smaller aortic lumen area, greater aortic wall stiffness, and higher flow. An inverse relation between proximal aortic lumen area and PP has been demonstrated in prior studies using echocardiographic imaging,^{10;12;13} although this relation has not been tested along the length of the aorta. Smaller aortic lumen area associated with higher PP could represent inward encroachment on the lumen due to aortic wall thickening or insufficient remodeling of the aorta across the life course to match hemodynamic demand. Dart et al showed that PP was inversely associated with aortic dimensions and suggested that increased PP implies a mismatch in stroke volume, aortic diameter or PWV.¹⁴ We hypothesize that higher PP is associated with 1) smaller aortic lumen dimensions along the entire thoracic aorta, 2) a smaller lumen area that is attributable to an intrinsically smaller aorta rather than lumen encroachment by wall thickening, and 3) greater hemodynamic demand compared to individuals with lower PP, as evidenced by higher resting flow and larger left ventricular (LV) size, resulting in mismatch between LV size, aortic flow and lumen area. In the present study, MRI was used to examine relations of PP with aortic lumen area, wall area and stiffness and LV structure, in a community-based sample of older people.

Methods

Study participants

The rationale and design of the Age, Gene/Environment Susceptibility—Reykjavik Study (AGES-Reykjavik) have been presented.¹⁵ AGES-Reykjavik originates from the Reykjavik Study, a community-based cohort established in 1967 to prospectively study cardiovascular disease in Iceland. Between 2008 and 2011 a second AGES-Reykjavik exam (AGES-II) was conducted in which a total of 3,411 men and women participated in detailed evaluations of cardiovascular, neurocognitive, musculoskeletal and metabolic phenotypes. A random subset of the AGES-II cohort was recruited to participate in an MRI evaluation of aortic and cardiac structure and function. After excluding participants due to inability to participate in the MRI examination, 602 of the 633 participants initially recruited into the MRI study had images acquired and represent the base sample for this analysis.

AGES-II was approved by the National Bioethics Committee in Iceland, which acts as the institutional review board for the Icelandic Heart Association, and by the National Institute on Aging Intramural Institutional Review Board. All participants gave written informed consent.

Data Acquisition

Arterial tonometry data and auscultatory blood pressure were acquired as described in the online Data Supplement (please see <http://hyper.ahajournals.org>). MRI was acquired using a 1.5 T scanner (Signa Excite, GE Medical Systems, Waukesha, WI). Fast imaging employing steady state acquisition (FIESTA) cine sequences of the LV were acquired in the 2- and 4-chamber views (Supplemental Figure S1).

Measurements of lumen area and wall thickness were acquired at three levels in the thoracic aorta (Supplemental Figure S2). Level 1 was near the root of the aorta, 1 cm distal to the sinotubular junction; level 2 was in the descending arch at the level of intersection with the level 1 plane; and level 3 was located at the upper edge of the T12 vertebral body (Supplemental Figure S2). At each aortic level, FIESTA cine sequences were acquired to measure lumen dimensions, double inversion recovery (DIR) images were acquired to measure wall dimensions, and phase-contrast (PC-MRI) images were acquired to measure flow. MRI acquisition parameters are detailed in the online Data Supplement (please see <http://hyper.ahajournals.org>).

Data Analysis

Tonometry and MRI data were transferred to the core laboratory (Cardiovascular Engineering, Inc., Norwood, MA) for analysis. Tonometry waveforms were signal-averaged with the ECG used as a fiducial point. Blood pressures were over-read in the core laboratory. Systolic and diastolic cuff pressures were used to calibrate the peak and trough of the signal-averaged brachial pressure waveform. Diastolic and integrated mean brachial pressures were then used to calibrate carotid, radial, and femoral pressure tracings.¹⁶ Additional tonometric measurements were calculated as described in the online Data Supplement (please see <http://hyper.ahajournals.org>).

Custom macros and plugins (Image J version 1.44p, National Institutes of Health, USA) were used to quantify aortic lumen and wall dimensions, aortic length, flow, and LV dimensions. LV epicardial and endocardial volumes were calculated using a biplane area-length calculation.¹⁷ LV mass and volume were measured at end-diastole, and stroke volume was defined as the difference in chamber volume at end-diastole and chamber volume at end-systole. The online data supplement contains detailed descriptions of MRI analyses (please see <http://hyper.ahajournals.org>). All MRI modes were tested for inter-analyst reproducibility (Supplemental Table S1).

Statistical Analyses

Aortic lumen area, aortic wall area, LV end-diastolic volume (LVEDV) and LV mass were natural log transformed, and carotid-femoral pulse wave velocity (CFPWV) was inverse transformed, to normalize their distributions and minimize heteroskedasticity. Sex-specific

z-scores were used for all continuous, independent variables in multivariable models. Minimally adjusted (age and sex) models examined individual relations of central and peripheral PP with aortic lumen area, wall area, wall thickness, and flow, and CFPWV, LVEDV and LV mass.

Multivariable linear regression models were used to examine the relations of central PP with aortic and ventricular measures, while adjusting for additional risk factors. The following vascular risk factors were first entered into each of the models and remained in the models regardless of significance level: age, sex, height, weight, heart rate, mean arterial pressure, total cholesterol, high density lipoprotein cholesterol, triglycerides, prevalence of diabetes, fasting glucose, hemoglobin A1_c, hematocrit, prevalence of cardiovascular disease, use of hypertension drugs, statin use and current tobacco use. Triglycerides, glucose, and hemoglobin A1_c were natural log transformed. The primary model then offered the following variables stepwise: LVEDV, CFPWV and the averages of the level 1 through level 3 diastolic aortic lumen areas and wall areas.

In secondary analyses, we re-estimated the primary models with the spatially averaged aortic variables replaced by values measured individually at each level. Next, we estimated models using peripheral PP as the dependent variable and entered the same covariates as in the primary models. We reassessed the primary model after replacing average diastolic aortic lumen areas with average systolic aortic lumen areas at levels 1 through 3. Next, we estimated the primary model using the mean of the diastolic outer aortic areas at levels 1 through 3, rather than lumen area, to further assess the role of aortic wall thickness. We reassessed the primary model with augmentation index as an additional covariate, then reassessed the primary model again including LV mass. Finally, we estimated the primary model after replacing LVEDV with various measures of flow entered separately: stroke volume, peak flow volume at level 1, and peak flow velocity at level 1. For all PP models, effects are expressed as mm Hg difference in PP per 1 SD difference in the independent variable. A two-tailed P-value of <0.05 was considered significant.

Results

Of the 602 participants who underwent any component of the MRI imaging protocol, 39 had unusable tonometry, 12 had unusable LV images, 28 had unusable aortic wall images at one or more aortic levels, 18 had unusable diastolic aortic lumen images at one or more aortic levels, and 3 had missing covariates, resulting in a sample size of 526 participants for primary statistical models. Subgroup analyses that included either systolic aortic lumen area or level 1 aortic flow were subject to additional exclusions (62 unusable systolic lumen area images and 21 unusable aortic flow images), resulting in sample sizes of 464 and 505, respectively. Characteristics of the sample are presented in Table 1 and a summary of structural aortic variables is presented in Table 2.

Individual relations between central and peripheral PP and key aortic and LV variables are presented in Supplemental Table S2. Central PP had negative relations with aortic lumen area, positive relations with LV dimensions, CFPWV, augmentation index and flow variables, and no relation with aortic wall area (Table S2). Individual relations for peripheral

PP had the same directional associations as those for central PP. The primary multivariable models for central PP are presented in Table 3. Central PP had a negative relation with diastolic aortic lumen area and a positive relation with LVEDV, CFPWV, and aortic wall area.

In secondary analyses, models that offered aortic variables individually at each of the 3 aortic levels (Supplemental Table S3), revealed associations comparable to those in the primary model except that aortic wall area was only significant at level 2. Models for peripheral PP demonstrated relations similar to those in the primary central PP models (Supplemental Table S4). A model using the average of the systolic, rather than diastolic, aortic lumen areas at each level had similar relations with central PP ($B=-8.3\pm1.3$, $P<0.001$, $n=464$) as those in the primary model. When diastolic aortic outer area was offered instead of diastolic aortic lumen area, a negative relation with central PP persisted ($B=-5.6\pm0.9$, $P<0.001$), while all other variables maintained the same directional relations with central PP as in the primary model. Aortic wall area was not included in the model that used outer aortic area because of collinearity between wall area and outer aortic area. Augmentation index was not significant when offered as an additional covariate in the primary model. When LV mass was included in the model, it had a positive relation with central PP ($B=4.6\pm1.0$, $P<0.001$), and there were similar associations among the remaining variables as in the primary model. In a model that entered stroke volume instead of LVEDV, stroke volume had a positive relation with central PP ($B=5.9\pm1.0$, $P<0.001$), and diastolic aortic lumen area maintained its negative relation with central PP ($B=-8.2\pm1.2$, $P<0.001$). Peak flow volume ($B=6.9\pm1.0$, $P<0.001$) and peak flow velocity ($B=4.5\pm1.1$, $P<0.001$) at level 1 each had positive relations with central PP ($n=505$), while the other independent variables maintained the same directional relations with central PP as in the primary models.

Discussion

We examined relations of central PP with aortic lumen area, wall thickness and stiffness and LV characteristics measured by MRI in models that adjusted for body size and standard vascular risk factors in a community-based sample of older people. We found that higher central PP was associated with smaller aortic lumen and outer area, greater aortic stiffness, higher LV mass and volume, and greater aortic wall area. This study provides a number of novel insights into the pathogenesis of elevated PP, specifically 1) that the known inverse relation between aortic root diameter and PP^{10;12–14} pertains along the length of the thoracic aorta and can be verified by MRI, 2) that the association of elevated PP with a smaller aortic lumen area is attributable to an overall smaller aortic cross section, whether measured at the endothelium or adventitia and whether measured in systole or diastole, as opposed to encroachment of a thicker aortic wall on the lumen area, and 3) that elevated PP is associated with dissociation between a smaller aortic lumen and a larger LVEDV. Some have speculated that in an older cohort, elevated PP should be associated with aortic medial degeneration and elastin fragmentation leading to lumen dilation and transfer of load to collagen, which is several orders of magnitude stiffer than elastin.¹¹ However, PP represents combined effects of aortic stiffness, lumen area, and flow; in our older community-based cohort, the strongest correlate of PP among these variables was aortic lumen area, which was inversely related to PP in risk factor-adjusted multivariable models.

Aortic structure and remodeling capacity

The aorta normally remodels to accommodate increased resting flow.^{18;19} Within and across species, aortic lumen area increases proportionally with flow volume in order to maintain a relatively constant flow velocity across several orders of magnitude of aortic flow volume and body size.^{20;21} Prior studies have shown that aortic remodeling to a larger diameter may offset the effects of wall stiffening on functional measures that are heavily dependent on lumen area, such as Z_c and compliance.^{22;23} In our cohort, peak flow *velocity* was higher and aortic lumen area was smaller in participants with higher PP, suggesting that aortic remodeling may be insufficient to accommodate ambient resting flow *volume* in some individuals, resulting in higher PP. Furthermore, the observation that smaller inner and outer aortic dimensions were associated with elevated PP suggests that higher PP was primarily attributable to an overall smaller aorta, consistent with insufficient aortic remodeling rather than wall thickening.

Impaired aortic remodeling may be associated with failure to sense higher flows because of endothelial dysfunction as suggested by findings of a previous study that found that an atherogenic lipid profile is associated with a smaller diameter of the ascending aorta.²⁴ Alternatively, the extent to which an individual aorta can remodel may depend on the pool of elastic fibers available, which may be determined early in life. Elastic fiber production occurs rapidly during gestation and the postnatal period and decreases thereafter.²⁵ Throughout adulthood, the aorta has little elastic fiber turnover,²⁶ as the gene program responsible for fiber production is down-regulated.²⁷ Therefore, the amount of elastin available presumably represents the result of interplay among genetic, epigenetic and environmental factors present at a young age. Aortic diameter is a highly heritable trait with a higher heritability (52%) than LV end-diastolic dimension (38%),²⁸ suggesting that the aorta may be more limited than the LV in its ability to remodel in response to environmental stimuli.

Ventricular-aortic coupling

Our observation that participants with higher PP have a larger LVEDV, but a smaller aortic lumen area (Table 3), suggests that higher PP is associated with suboptimal coupling between the LV and aorta in this cohort. Elevated PP is associated with a level of ambient cardiac output—whether assessed by LVEDV, peak volumetric flow, or stroke volume—that is too great to be accommodated by the aortic lumen area.

In light of the fact that stroke volume does not increase with advancing age in adults,²⁹ one might question the importance of matching between flow and aortic lumen area in this cohort. However, it is important to note that we are examining cross-sectional relations between PP and various hemodynamic measures at one point in time in older individuals. At that point in time, individuals with higher PP have smaller inner and outer aortic area, larger LVEDV, higher aortic flow volume and velocity, and greater aortic wall stiffness and thickness. It is important to underscore that we are not proposing that the aorta has remodeled to a smaller aortic lumen area in those with higher PP. A progressive increase in aortic lumen area with age, starting soon after birth and continuing throughout life, has been well documented.^{7–9} We are rather proposing that the lifelong process of aortic remodeling

to a larger diameter in response to somatic growth, midlife weight gain and other factors may be impaired in those individuals that develop a wider PP. Whether PP will continue to increase with age in older cohorts such as ours and the correlates of that change will require additional longitudinal follow-up.

Limitations

Our study has a number of important limitations. This community-based study included only participants older than 70 years of age. Survivor bias is an important concern in such a cohort. However, prior studies have found negative relations between aortic diameter and PP in younger cohorts.^{10;12–14} Nevertheless, it may be informative to study relations between PP and detailed MRI-based aortic measures in a younger and broader cohort with greater variation in age, PP and aortic diameter. Our cross-sectional study allows us to examine associations but does not permit us to draw causal inferences. Our cohort was drawn from an isolated population of European descent; therefore, our observations may not apply to other races or ethnicities. For logistical reasons, blood pressure, tonometry and MRI measures were obtained sequentially rather than simultaneously. We expect that a sequential approach may have weakened relations between aortic structure and PP. To minimize the confounding effects of time delay between tonometry and MRI, participants were placed in the body coil on the detachable MRI gurney and allowed to accommodate before blood pressure and tonometry were assessed. They were then transferred directly into the MRI magnet with no further change in posture. Our study reports minimal differences in central and peripheral PP values compared to some previous studies;³⁰ however, it is likely that the transfer function employed in those studies overestimates aorta-brachial pressure amplification.³¹ In our cohort of older people employing direct carotid tonometry calibrated to measured brachial mean and diastolic pressure, central and peripheral pressures were quite similar, as has been reported previously.¹⁴

Perspectives

Our study demonstrates that higher PP in older people is associated with higher wall stiffness, smaller aortic lumen area and dissociation between aortic and cardiac adaptations to resting hemodynamic state. There are several important implications of our findings. If smaller aortic lumen area is a manifestation of inappropriate aortic remodeling, for example, as a result of impaired endothelial transduction of flow, it may be possible to restore relations between aortic flow and aortic lumen area by addressing risk factors for endothelial dysfunction. Reducing hemodynamic demand on the aorta, for example, through weight loss, may also be beneficial. The presence of mismatch between LV structure and aortic geometry may predispose affected older individuals to dramatic increases in PP during typical daily activities, which in extreme cases may lead to ventricular overload and symptoms of heart failure despite preserved systolic function. Additionally, our results suggest that therapies that reduce aortic wall stiffness and modestly increase aortic lumen area may be particularly effective at reducing PP and potentially mitigating the associated high risk for adverse events.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Novelty and Significance

What is new?

- Detailed MRI analysis shows that elevated PP is associated with smaller aortic lumen area at three aortic locations.
- Elevated PP is directly related to LVEDV, yet inversely related to aortic lumen area, suggesting dissociation of aortic and ventricular adaptations to hemodynamic demand.

What is relevant?

- Elevated PP is associated with mismatch between aortic lumen diameter, wall stiffness and flow.
- Interventions that reduce or prevent dissociation between aortic and ventricular dimensions, while also reducing aortic wall stiffness, may be optimal for reducing PP.

Summary

Higher PP is a strong predictor of cardiovascular risk and is associated with smaller aortic dimensions and larger LV dimensions. Small aortic size relative to heart size may be indicative of hemodynamic demand that exceeds the remodeling capacity of the aorta but not the heart, resulting in mismatch between aortic diameter and flow.

Table 1

Characteristics of the sample.

	Men (n=231)	Women (n=295)
Age, years	73 to 88	72 to 94
Height, cm	177±6	162±5
Weight, kg	83±12	71±12
Body mass index, kg/m ²	26.5±3.6	27.1±4.2
Heart Rate, min ⁻¹	62±10	65±10
Central blood pressure, mm Hg		
Systolic	139±25	145±24
Pulse pressure	74±24	81±25
Peripheral blood pressure, mm Hg		
Systolic	140±21	143±18
Diastolic	65±10	64±9
Pulse pressure	75±19	79±18
Mean	93±13	95±11
Carotid-femoral pulse wave velocity, m/s	14.3±4.8	12.9±4.6
Augmentation index	6.2±11.3	10.5±14.9
Peak flow volume, mL	374±68	286±53
Peak flow velocity, mL/s	45±12	42±11
LV end-diastolic volume, mL	117±33	92±20
LV end-diastolic mass, g	166±34	119±22
Glucose, mmol/L	5.7±0.9	5.5±0.8
HbA1c, %	5.7±0.6	5.7±0.5
Total Cholesterol, mmol/L	4.9±1.0	5.7±1.1
HDL Cholesterol, mmol/L	1.4±0.4	1.8±0.4
Triglycerides, mmol/L	1.1±0.5	1.2±0.5
Medical history, n (%)		
Diabetes	25 (11)	22 (7)
Treated hypertension	157 (68)	225 (76)
Statin use	106 (46)	101 (34)
Cardiovascular disease	87 (38)	42 (14)
Current tobacco use	20 (9)	17 (6)

CFPWV, carotid-femoral pulse wave velocity; LV, left ventricular; HDL, high density lipoprotein. Values are mean ± 1 standard deviation, unless otherwise noted.

* Sample size for flow variables is 223 men and 282 women.

Table 2

Structural aortic variables.

Variable	Men			Women		
	Level 1	Level 2	Level 3	Level 1	Level 2	Level 3
Diastolic lumen area, mm ²	865±203	596±121	466±99	709±148	458±111	353±83
Diastolic outer area, mm ²	1251±261	887±161	680±125	1053±197	720±145	539±106
Systolic lumen area, mm ²	974±232	660±120	512±98	815±156	509±106	386±86
Wall area, mm ²	385±79	291±52	214±34	345±68	262±48	186±33
Mean wall thickness, mm	3.3±0.5	3.0±0.4	2.5±0.3	3.2±0.4	3.0±0.4	2.4±0.3

Values are mean ± 1 standard deviation.

* Sample size for systolic values is 201 men and 263 women.

Table 3

Multivariable correlates of central pulse pressure.

Model	Variable	B±SE	P	VIF	Model R ²
0	Vascular Risk Factors	--	--		0.37
1	Aortic lumen area	-4.8±0.9	<0.001	1.1	0.40
2	Aortic lumen area	-5.5±0.9	<0.001	1.2	0.42
	LVEDV	3.7±1.0	<0.001	1.4	
3	Aortic lumen area	-5.9±0.9	<0.001	1.2	0.43
	LVEDV	3.9±1.0	<0.001	1.4	
	CFPWV	3.7±1.0	<0.001	1.5	
4	Aortic lumen area	-8.1±1.2	<0.001	2.4	0.44
	LVEDV	3.8±1.0	<0.001	1.4	
	CFPWV	3.6±1.0	<0.001	1.5	
	Aortic wall area	3.0±1.2	0.015	2.3	

LVEDV, left ventricular end-diastolic volume; CFPWV, carotid-femoral pulse wave velocity; VIF, variance inflation factor. Model adjusts for age, sex, height, weight, heart rate, mean arterial pressure, total and high density lipoprotein cholesterol, triglycerides, diabetes, glucose, hemoglobin A1c, hematocrit, cardiovascular disease, treated hypertension, statin use and current tobacco use. Model 0 includes only the abovementioned risk factors. The mean across the first three aortic levels in diastole was used for aortic lumen area and aortic wall area. All continuous variables were converted to sex-specific Z-scores and entered individually in order of significance; thus, B represents the difference in pulse pressure in mm Hg per 1 SD difference in the independent variable.