

THE UTILITY OF PULSE PRESSURE MEASURED BY RADIAL ARTERIAL
TONOMETRY IN DETERMINING CARDIOVASCULAR DISEASE IN ADULTS

BY

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LIST OF ABBREVIATIONS

BP = Blood Pressure

CI = Confidence Interval

CHD = Coronary Heart Disease

CHF = Congestive Heart Failure

DBP = Diastolic Blood Pressure

HR = Hazard Ratio

HTN = Hypertension

LVH = Left Ventricular Hypertrophy

LVM = Left Ventricular Mass

MAP = Mean Arterial Pressure

MESA = Multi-Ethnic Study of Atherosclerosis

MI = Myocardial Infarction

PPb = Pulse Pressure measured by brachial blood-pressure cuff

PPr = Pulse Pressure measured from radial arterial tonometry

SBP = Systolic Blood Pressure

SD = Standard Deviation

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ABSTRACT

Darryl D. Prime

THE UTILITY OF PULSE PRESSURE MEASURED BY RADIAL ARTERIAL

TONOMETRY IN DETERMINING CARDIOVASCULAR DISEASE IN ADULTS

Thesis under the direction of David M. Herrington, M.D., M.H.S., Professor of Medicine

Elevated brachial PP is a surrogate measure for increased arterial stiffness and is associated with increased LVM and CHF. Pulse wave indices from radial arterial tonometry may be superior measures of arterial stiffness sequela compared to PPb. Relations of increased PPr with increased LVM in a cross-sectional was studied after adjustment for PPb. Second, relations of PPr with incident CHF over 4 years, was studied, after covariate adjustment in MESA. First, the multivariable models including PPb, PPr, and covariates for $LVM/h^2 (g/m^2)$ positively related PPb and PPr to LVM ($\beta = 0.14$, 95% CI 0.11-0.17 for $p < 0.0001$ for PPb; and $\beta = 0.13$, 95% CI 0.10-0.16, $p < 0.0001$ for PPr). Second, Cox proportional hazards models showed a 1-SD increase of PPr (HR 1.29, CI 1.02-1.63), but not of PPb, DBP or SBP, were significantly associated with CHF after adjusting for covariates excluding LVM, ECG LVH or incident MI. After adjusting for LVM or ECG LVH, the association between PPr and incident CHF was no longer significant. There is no additional benefit in measuring PPr over PPb in assessing the sequela of arterial stiffness. However, in addition to PPb, PPr may be a useful surrogate measure for arterial stiffness.

CHAPTER I

INTRODUCTION

Overview

The prevalence of cardiovascular disease in the United States is high, affecting 33% of the population¹. Cardiovascular disease was the underlying cause of death for 36% of all deaths in 2004, or 1 of every 2.8 deaths in the United States. The number of inpatient discharges from short-stay hospitals, from 1979 to 2004, with CVD listed as the first diagnosis increased 30% and in 2004 CVD ranked number one among all disease categories in hospital discharges. Detection and management of abnormalities of the vascular system before clinically overt CVD, therefore, will have a profound impact on population health. Arterial stiffness is a subclinical marker for CVD morbidity and mortality^{2, 3}. Therefore, a simple measure of arterial stiffness may be one method to identify asymptomatic individuals at risk for future CVD events.

Pulse pressure measured by arm cuff sphygmomanometer (PPb) is the difference between systolic (SBP) and DBP (DBP). PPb is an indirect measure of conduit arterial stiffness and has been associated with clinically adverse cardiovascular events⁴⁻¹⁰. Some studies suggest that PPb is a stronger predictor of cardiovascular events than MAP¹⁰, SBP^{6, 8, 10}, and DBP^{6, 8, 10}, particularly in individuals greater than the age of 60. Other studies have suggested that PPb can independently predict cardiovascular events after accounting for MAP^{9, 10}, SBP^{9, 10}, and DBP^{5, 10}. Many studies, however, have found that PPb is not an independent predictor of cardiovascular events after accounting for

conventional blood pressure measures (SBP and DBP), including events such as coronary heart disease¹¹⁻¹³, stroke¹¹⁻¹³ and coronary heart disease -related death¹².

Another method of estimating pulse pressure is by radial arterial tonometry (PPr). Measuring pulse pressure at the radial artery by tonometry has several advantages. PPr does not require the use of an occlusive cuff and therefore, does not significantly alter the hemodynamic status of the underlying artery. PPr, as opposed to PPb, does not depend upon the size of an individual's arm. Second, radial arterial tonometry allows for continuous monitoring of pulse pressure over time which can help account for pulse pressure variability. Third, PPr, compared to pulse pressure measured by tonometry at the brachial and carotid artery, is relatively unaffected by potent antihypertensive agents, including sublingual nitroglycerin, atenolol, diltiazem, captopril, and isradipine^{14, 15}. Fourth, since high resistance in small arteries and arterioles is the principal cause of the fall in mean pressure and pulse pressure, and abnormal small artery structure and resultant elevated small vessel resistance has been associated with cardiovascular events, the radial artery pulse pressure may provide useful prognostic information because it is located just proximal to these high resistance vessels^{16, 17}. Measuring pulse pressure at the level of the radial artery may be important because effective perfusion of tissues in areas of these high resistance vessels partly depends on the level of mean pressure and pulse pressure in arteries proximal to these vessel beds. Finally, the increase in the forward pulse wave propagation is associated with increasing arterial stiffness and is associated with higher pulse wave velocities. An increase in forward pulse wave propagation may also be related to higher pulse pressure amplitude measured in the peripheral circulation. If this is the case, increased PPr may also be strongly associated

with increased arterial stiffness. The radial pulse tonometer is comparatively costly and this must be considered when we compare the two measures.

PPb is associated with increased left ventricular mass¹⁸. This may be due to the fact that higher pulse pressures in the proximal arterial tree places increased workload on the heart. The heart muscle hypertrophies to compensate for this increased afterload¹⁹. Cardiac hypertrophy may then lead to subsequent congestive heart failure, coronary artery disease and stroke²⁰.

Despite its advantages, associations between PPr and clinical outcomes known to be associated with arterial stiffness have not been studied. Furthermore, the predictive value of PPr, compared to PPb, for incident cardiovascular events in population-based adults has not been studied. This chapter will provide a background on the subject of arterial stiffness and pulse pressure measures. Specifically the following themes will be discussed: (i) arterial hemodynamics, (ii) pathophysiology of arterial stiffness: reflected waves and aortic diameter (iii) measures of arterial stiffness and associated cardiovascular events, (iv) PPb and cardiovascular events and (v) therapeutic options for arterial stiffness.

In chapter II, the relationship between PPb and left ventricular mass and PPr and left ventricular mass will be examined in a cohort of population-based adults enrolled in the Multi-Ethnic Study of Atherosclerosis. In chapter III, the prognostic role of PPb and PPr for incident congestive heart failure will be examined. In addition, associations between pulse pressure derived from the two methods, left ventricular mass, and

congestive heart failure will be explored to determine if higher left ventricular mass mediates the association between pulse pressure and incident congestive heart failure.

Arterial hemodynamics

The purpose of the arterial circulation is to supply oxygen and nutrients to, and remove waste products from, the peripheral tissues. This can only be done well when blood flow is constant and steady as pulsatile flow in the capillaries of peripheral tissues will result in tissue death. The left ventricle of the heart, however, is a muscle and after contraction to eject blood to the periphery it must relax to receive its own blood flow and prevent fatigue. The arteries and arterioles connect the heart to the capillaries and thus their main purpose is to deliver blood to different tissues. There is also another important function of the vessels, however, and that is to even out the flow of blood from the left ventricle before it is delivered to the peripheral tissues. Dividing the arterial system into three anatomical and functional regions can help explain this important function.

The first arterial region consists of the aorta, the brachiocephalic arteries, and the carotid arteries. These arteries are relatively elastic because of the properties of their walls. They serve to store potential energy by storing blood during cardiac systole and releasing it to the peripheral circulation during diastole. The proximal aorta plays a key role in storing this potential energy. The aorta is composed of three layers: the thin inner layer called the intima, a thick middle layer called the media, and a thin outer layer called the adventitia. The media of the aorta is composed of multiple layers of coated, interwoven, helical sheets of elastic tissue arranged not only to provide maximal tensile strength, but also distensibility and elasticity. It is these properties of distensibility and

elasticity that allows the aorta to store potential energy. The velocity of intra-luminal blood is only 40 to 50 cm per second. The elastic properties of the aorta, however, when efficiently coupled with the pumping function of the heart, creates a milking effect that results in a pulse wave that is transmitted to the periphery at the speed of approximately 5 meters per second. The second arterial region consists of muscular vessels connecting the large arteries to the arterioles. They act not only as channels, distributing blood to the tissues, but these arteries can increase or decrease pulse wave propagation by changing their smooth muscle tone. Lastly, the arterioles, by changing their caliber, change peripheral resistance, and therefore are important in maintaining mean arterial blood pressure, and provide a steady and continuous flow of blood to the organs and tissues according to their metabolic demands²¹.

The first two portions of the arterial tree are felt to be responsible for the amplification of the amplitude of the pulse pressure wave that is normally seen in mammals as the wave travels from the aorta to the periphery. With aging, amplification of the pulse pressure wave decreases. The reasons for this have not yet been fully elucidated but a decrease in the pulse wave amplification has been associated with increased age²².

Arterial Stiffness- Pulse Wave Velocity

Historically, the consequences of a less compliant aorta (a stiffer aorta) has been described and explained as follows. Aortic stiffness results in an increase in aortic SBP as it is not able to cushion the ejected volume of blood from the heart. In addition, a stiff aorta is unable to augment DBP because it cannot store potential energy. This results in

an increase in SBP and a decrease in DBP, not only in the aorta but throughout the arterial tree. This increase in proximal SBP increases the afterload that the heart has to overcome in order to provide adequate stroke volume and puts increased workload on the heart leading to left ventricular hypertrophy²³. Second, since coronary blood flow occurs in diastole, the decrease in proximal DBP results in a decrease in coronary perfusion pressure and potentially lowers the threshold for cardiac ischemia²⁴. Third, measures of arterial stiffness are a major determinant of small-artery hypertrophy in rats, and increased strokes in adults^{25, 26}. Fourth, because arterial stiffness is the result of mechanical deterioration and fragmentation of the elastic fibers of the aorta, this leads to dilatation of the proximal aorta and the transfer of force to more inflexible components of the aortic wall such as collagen. According to this hypothesis, proximal arterial stiffness leads to an increased forward pulse wave velocity that reaches the major bifurcations of the arterial tree faster and there is premature arrival of the reflected pressure wave to the proximal aorta. Thus, the incident pressure wave produced by ejection of blood from the heart collides with the reflective pulse pressure wave from the periphery resulting in an augmentation of the proximal arterial pulse pressure^{21, 22}. Indeed, a recent expert consensus document on arterial stiffness suggests that carotid-femoral pulse wave velocity be the gold standard for measuring arterial stiffness²⁷.

Arterial Stiffness - Aortic Diameter

A recent study by Mitchell and colleagues calculated the aortic diameter in 128 hypertensive participants 40 to 75 years of age without diabetes mellitus, coronary artery disease, peripheral vascular disease or a smoking history and 30 normotensive controls of comparable age and gender. They found that pulse wave velocity, (PWV) was higher in

hypertensives compared to normotensives but the difference was not significant after adjustment for differences in mean arterial blood pressure. Using another method of measuring aortic stiffness, local impedance Z_e , and the water-hammer equation ($Z_e = \frac{4\rho PVV\omega}{\pi D^3}$), where ρ is the density of blood and D is the vessel diameter, they found that increased Z_e remained highly significant after accounting for MAP. Elevated PPb in the hypertensive group was explained primarily by Z_e and reduced effective diameter of the proximal aorta²⁸. They concluded that these findings did not support the hypothesis of secondary aortic degeneration, dilatation, and wall stiffening and suggested aortic function, in the absence of aortic structural deterioration, may play a role in the etiology of systolic hypertension. Indeed, the aorta is a dynamic organ and does remodel in response to changing demands dictated by blood flow, shear stress and tensile stress. This finding is supported by animal models. Placement of aortocaval shunts to produce systems of increased shear stress and aortic flow in rats resulted in a progressive increase in aortic diameter. The increase in aortic diameter resulted in the restoration of aortic shear stress to control levels. In the animals where aortic wall tensile stress was higher, medial cross-sectional area and the contents of elastin and collagen increased and were associated with an increase in smooth muscle cell hypertrophy, despite a decrease in arterial wall thickness. This suggests that compensatory aortic dilatation may be physiologic and not pathologic²⁹.

This study by Mitchell and colleagues was criticized for relying on calculated effective aortic diameter instead of using actual measurements of aortic root diameter. In a follow-up study by Mitchell and colleagues, aortic diameter was measured, and they

again found that characteristic impedance was elevated out of proportion to the increase in carotid femoral pulse wave velocity in individuals with systolic hypertension. They also reported lower measured aortic diameters, and higher aortic wall stiffness (using aortic elastance-wall thickness product (Eh), computed by rearranging the Moens–Korteweg equation to give: $Eh=c_0^2\rho D$, where c_0 is central aortic PWV, ρ is the density of blood, and D is measured aortic root diameter) in participants with increased pulse pressure³⁰. These findings were replicated by a study performed by Farasat and colleagues where aortic root diameter was measured in a population of 1256 healthy and untreated hypertensive individuals, aged 30 to 79 years. After adjusting for age, height, weight and MAP, aortic root diameter was independently and inversely associated with pulse pressure in both men and women. After additional adjustments for central arterial stiffness, central arterial wall thickness, reflected waves, and left ventricular geometry, aortic root diameter remained inversely associated with pulse pressure in both sexes. The authors concluded that an inappropriately small aortic diameter may contribute to the pathogenesis of systolic hypertension³¹.

Despite significant differences in schools of thought regarding the pathogenesis of arterial stiffness, there is a consistent increase in the forward wave propagation of the pulse pressure wave with increasing arterial stiffness. This increase in forward wave propagation may provide important prognostic information as it may be a more consistent measure of arterial stiffness.

Measures of Arterial Stiffness and Cardiovascular Events

Arterial stiffness is associated with many risk factors for cardiovascular disease including a high C-reactive protein level^{32, 33}, hyper-homocysteinemia³⁴, advanced glycation end-products in Type 1 diabetes mellitus³⁵, Type 2 diabetes mellitus³⁶, impaired glucose tolerance^{37, 38}, hypercholesterolemia^{39, 40}, hypertension⁴¹, tobacco smoking⁴², and obesity⁴³. These associations suggest that these risk factors may in part be a consequence of, or lead to, arterial stiffness. Measures of arterial stiffness have also been shown to be associated with coronary heart disease⁴⁴, congestive heart failure⁴⁵, fatal stroke⁴⁶, and chronic kidney disease⁴⁷.

Most investigators consider pulse pressure measured by blood pressure cuff a crude measure of arterial stiffness. As previously noted, pulse wave velocity is considered the gold standard for the measurement of arterial stiffness by the European Society of Cardiology. It is considered the most simple, noninvasive, robust, and reproducible method to determine arterial stiffness. Pulse wave velocity is usually obtained by comparing the velocity of pulse wave forms measured at various peripheral arterial sites on the body. The foot-to-foot velocity method is usually used, where the foot of the wave is defined at the end of diastole, when the steeper rise up the wave front begins. These are measured transcutaneously at the right common carotid artery and the right femoral artery, and the time delay (Δt or transit time) is measured between the feet of the two waveforms. A variety of characteristics of the waveforms can be used including Doppler, distention, and pressure. The distance (D) between the waves is usually added to the surface distance between the two recording sites. The pulse wave velocity is calculated as being equal to distance (D) in meters / (Δt) in seconds. Using this method, distance should be measured precisely because small inaccuracies may lead

to large errors in the absolute values of pulse wave velocity⁴⁸. Even though this measure is regarded as simple, there are significant limitations. First, in patients with obesity, diabetes, and peripheral artery disease the femoral pressure waveform may be difficult to record accurately⁴⁹. Second, large bust size in women can make distance measurements inaccurate. Third, abdominal obesity, especially in men, also make distance measures inaccurate⁴⁹. Lastly, the pressure wave may be attenuated and delayed in the presence of aortic, iliac or proximal femoral stenosis. With these limitations in mind, and the ongoing debate as to whether pulse wave velocity is within the pathologic pathway of arterial stiffness and cardiovascular events, more potentially reliable, noninvasive measure of arterial stiffness should be explored.

PPb and Cardiovascular Events

Many studies have shown that PPb is significantly associated with cardiovascular events, including new-onset atrial fibrillation⁵⁰, incident stroke⁵⁰, stroke mortality^{50, 51}, myocardial infarction^{6, 9, 10, 50}, new onset congestive heart failure^{5, 7, 10}, total cardiovascular disease mortality in patients with left ventricular dysfunction⁵², total mortality in patients undergoing hemodialysis^{53, 54}, and in elderly patients¹⁰. There are, however, almost an equal number of studies that have not found a significant association between PPb and cardiovascular events and/or mortality.

Most of the studies that demonstrate PPb as a significant predictor of CVD were performed in population cohorts whose participants were older or had significant comorbidities. Also, even when found to be a significant predictor of CVD, some of these studies found SBP to be a better predictor than PPb. Psaty and colleagues, analyzing the

Cardiovascular Health Study cohort, in which 5888 adults 65 years or older were enrolled and followed for 6.7 years, found that one standard deviation increase in PPb was associated with a 21% increased hazard for myocardial infarction and a 21% increased hazard for stroke after adjusting for age, sex, smoking, diabetes, clinical cardiovascular disease, and intimal medial wall thickness of the common carotid artery. PPb in this study was not associated with total mortality. A one standard deviation increase in SBP was associated with a 24% increased hazard for myocardial infarction and a 29% increased hazard for stroke. In the Cardiovascular Health Study, participants were on average 72 years of age, 11% had a history of cardiovascular disease and approximately 30% had either diabetes or impaired fasting glucose suggesting that this was an older and sicker population¹³.

A population with similar characteristics was studied by Chae and colleagues. They analyzed PPb in the community-based East Boston Health Project, using a total of 1621 men and women free of congestive heart failure at baseline. They were followed for up to 3.8 years. The main measure outcome was congestive heart failure incidence as ascertained by hospital discharge diagnosis and death certificates. The mean age of the cohort was 77.9 years, 10% had coronary heart disease, and 19% had diabetes. Pulse pressure measured by sphygmamometer was an independent predictor of congestive heart failure. For each 10 mm Hg elevation in pulse pressure, there was a 14% increased hazard for congestive heart failure (95% confidence interval, 1.05 -1.24; $P = 0.03$). In the highest tertile of pulse pressure (>67 mm Hg) there was a 55% increased odds for congestive heart failure ($P = 0.02$) compared with those in the lowest tertile. In this study, after excluding those with prevalent coronary heart disease at baseline, PPb was

associated with small numbers of incident myocardial infarction, but this finding was of borderline statistical significance after multivariate adjustment (hazard ratio (HR) per 10-mm Hg increase in PPb, 1.11; 95% CI, 0.99-1.24; P = 0.07). PPb was a significant independent predictor of total cardiovascular disease (a combined endpoint of congestive heart failure, myocardial infarction, or death due to cardiovascular disease) (HR/10 mm Hg, 1.12/10 mm Hg; 95% CI, 1.03-1.21; P = .006). Also, the association of PPb with incident congestive heart failure was independent of myocardial infarction and was observed in those without evidence of prevalent coronary heart disease⁵. Vaccarino and colleagues investigated PPb in predicting cardiovascular events in the elderly by analyzing participants in the Established Populations for Epidemiologic Study of the Elderly program. Participants (n = 2152) were followed for 10 years and included men and women aged 65 years or older free of coronary heart disease and congestive heart failure. After adjusting for cardiovascular-related covariates, a 10-mm Hg increment in PP was associated with a 12% increased hazard for coronary heart disease (CHD) (95% confidence interval [CI], 2% to 22%), a 14% increased hazard for CHF (95% CI, 5% to 24%), and a 6% increased hazard for overall mortality (95% CI, 0% to 12%). While SBP and MAP also showed positive associations with the end points, PPb yielded the highest likelihood ratio chi-square. When PPb was entered in the model with other blood pressure parameters (SBP, DBP, MAP or hypertension stage respectively), the association remained positive for PPb but became negative for the other blood pressure variables. The effect of PPb persisted after adjusting for current medication use and was present in normotensive individuals and individuals with isolated systolic hypertension but not in individuals with diastolic hypertension¹⁰.

In contrast, Haider and colleagues studied a relatively younger cohort of 2040 free-living Framingham Heart Study participants with a mean age of 61 years of age (with a range of 50 to 79 years). Seven percent of this population had diabetes mellitus. The mean follow-up for the outcome of new-onset heart failure was 17.4 years. SBP, DBP, and PPb were related to an increased hazard for CHF, but the relation was strongest for SBP and PPb. A 1-standard deviation (20 mm Hg) increment in SBP conferred a 56% increased hazard for congestive heart failure (HR, 1.56 [95% CI, 1.37 to 1.77]); similarly, a 1-standard deviation (16 mm Hg) increment in pulse pressure conferred a 55% increased hazard for CHF (HR, 1.55 [95% CI, 1.37 to 1.75]). These associations were unrelated to age, duration of follow-up, and initiation of treatment for hypertension during follow-up; they were also observed in patients with systolic hypertension (SBP \geq 140 mm Hg) at the baseline examination (HR, 1.41 [95% CI, 1.18 to 1.69] for PPb and 1.42 [CI, 1.14 to 1.76] for SBP)⁷. Taken together, these data suggest that in elderly populations with significant co-morbidities such as diabetes, PPb is a significant predictor for new-onset congestive heart failure, and possibly coronary heart disease even when accounting for SBP, and is a significant predictor for new-onset congestive heart failure in the middle-aged but SBP may be a sufficient measure in this population.

In patients with end-stage renal disease, PPb is a strong independent predictor of mortality. Klassen and colleagues studied 37,069 patients with end-stage renal disease for one year on maintenance hemodialysis in 782 centers across the United States retrospectively. By virtue of having end-stage renal disease, these patients were relatively sicker and represent a non-generalizable population. Also, in this population, moderately high blood pressures are associated with decreased mortality compared to having lower

blood pressures. The mean age was 60, and 47% were diabetics. The primary study outcome was death at one year. Mean PPb before dialysis was 75.0 mm Hg and after dialysis they it was 66.9 mm Hg, which is significantly higher than the general population. Approximately 19% of the population (n = 5731) died in one year, reflecting the poor prognosis of end-stage renal disease patients. In this study, multivariable Cox proportional hazards modeling showed a significant relationship between increasing PPb and increasing risk of death after adjusting for SBP. Each incremental elevation of 10 mm Hg in post-dialysis PPb was associated with a 12% increase in the hazard for death (HR, 1.12; 95% CI, 1.06-1.18). Post-dialysis SBP was inversely related to mortality with a 13% decreased hazard for death for each incremental elevation of 10 mm Hg (hazard ratio, 0.87; 95% confidence interval, 0.84-0.90). This finding highlights the importance of knowing the population characteristics and co-morbidities when studying pulse pressure. This measure, PPb, has not been associated with significant one-year mortality in younger populations without end-stage renal disease or congestive heart failure.

Tozawa and colleagues investigated PPb and the risk of cardiovascular events and total mortality in 1243 patients on chronic hemodialysis. The mean age of this cohort was 52.3 years, 17% were diabetics and 6 % had previous cardiovascular complications with the follow-up time being 9 years. After adjusting for age, sex, and other significant risk factors, the association with the risk of total mortality was positive for PPb (P=0.002) and SBP (P=0.04), but not significant for DBP (P=0.4), when they evaluated each pressure measure individually. Of the three measurements, PPb was the most significant. SBP and DBP were jointly entered into the Cox regression model (dual blood pressure component model, DPM), and the association with the risk of total mortality was positive for SBP

(HR, 1.083; 95% CI, 1.030 to 1.137) and negative for DBP (HR, 0.886; 0.808 to 0.970).

When diabetes mellitus was added as an adjusted variable to the model, PPb was no longer a significant predictor of total mortality; also PPb was a significant predictor for total mortality in the non-diabetic patients, but not in the diabetic patients. PPb was positively associated with the risk of stroke and acute myocardial infarction; however the predictive utility of PPb for each outcome was not superior to SBP and DBP when these blood pressure models were analyzed separately. In models where SBP and PPb were included in a single model, the association with the risk of stroke and acute myocardial infarction was positive for SBP ($P=0.01$) but not significant for PPb ($P=0.5$)⁵⁴. To summarize these data, PPb is a predictor of total mortality in patients undergoing chronic hemodialysis and may be a more potent predictor of total mortality than SBP or DBP but in this population SBP may be superior to PPb in predicting cardiovascular events.

In populations with left ventricular dysfunction or heart failure, compared to relatively healthy populations, PPb is more consistently predictive of cardiovascular events. Mitchell and colleagues studied 2231 participants enrolled in the SAVE (Survival and Ventricular Enlargement Trial). These participants aged 21 to 80 years of age had to have an ejection fraction less than or equal to 40% to be included in this trial.

Approximately a third of these participants had a previous myocardial infarction and 20% were diabetic. Pulse pressure was measured by sphygmomanometry 3-16 days after a myocardial infarction. After a follow up of 42 months, pulse pressure was a significant predictor of total mortality (relative risk, 1.08 per 10 mm Hg increment in pulse pressure; 95% CI, 1.00 to 1.17; $P<0.05$) and recurrent myocardial infarction (relative risk, 1.12; 95% CI, 1.01 to 1.23; $P<0.05$) after controlling for age, left ventricular ejection fraction,

MAP, sex, treatment arm (captopril or placebo), smoking history; history of prior myocardial infarction, diabetes, or hypertension; and treatment with β -blockers, calcium channel blockers, digoxin, aspirin, or thrombolytic therapy. Domanski and colleagues, in a study that supported these data, analyzed PPb and MAP for their effect on mortality in patients with left ventricular dysfunction. After adjusting for covariates related to cardiovascular disease in a multivariate analysis, higher pulse pressure remained an independent predictor of total and cardiovascular mortality (total mortality increased hazard, 1.05 per 10 mm Hg increment; 95% CI, 1.01 to 1.10; $p = 0.02$) while MAP was inversely related to total and cardiovascular mortality (total mortality relative risk, 0.89; 95% confidence interval, 0.85 to 0.94; $p < 0.0001$). In addition, PPb predicted total and cardiovascular mortality independent of MAP⁵². These data suggest a significant association of PPb and total and cardiovascular mortality in patients with left ventricular dysfunction.

In the Framingham Heart Study, Franklin and colleagues studied 1924 men and women with no clinical evidence of coronary heart disease who were not taking antihypertensive drug therapy. Members of the cohort with hypertension and taking antihypertensive therapy were excluded (30% of the cohort). In this study the cohort was relatively healthy. The average age of the participants was 61, 11% had glucose intolerance, and 7% of the participants smoked. After adjusting for age, sex, and other cardiovascular-related risk factors, PPb was found to be superior to both SBP and DBP as a predictor of coronary heart disease⁶. Strengths of this study included a long mean follow-up of 14.3 years. The participants in this study however were studied at a single center from a single geographic area (Framingham, Massachusetts) making

generalizability of these data difficult. Indeed, this level of superiority of PPb as a predictor for coronary heart disease over DBP and SBP has not been replicated in subsequent studies.

There are many studies that show that PPb does not provide any additional predictive information for cardiovascular events beyond that provided by SBP or MAP. Most of these studies included younger and healthier participants. Onat and colleagues evaluated the predictive value of DBP, SBP, and PPb for coronary heart disease morbidity and mortality in the Turkish Adult Risk Factor Study. Participants (n = 2601) were 20 years or older, were free of coronary heart disease at the baseline examination, and were followed up for a mean of 9.3 years. The mean age was 41 years, and 61% of the men and 17% of the women were smokers. In a logistic regression analysis for predictors of coronary mortality and morbidity, DBP was not significantly associated with the outcomes, while SBP was an independent risk predictor in both genders (odds ratio (OR) 1.016, 95% CI: 1.007-1.026). When two of three blood pressure components were entered jointly in the multivariable model, PPb had a value inferior to that of SBP among men and women. Thus, PPb was an important determinant of CHD risk in a population with a large age range but inferior in predictive power compared to SBP¹². This study population may not be representative of many US populations, however, as 60% of the men were current smokers¹².

Borghi and colleagues investigated the relative role of SBP, DBP, and PPb as risk factors for cardiovascular events in 2939 randomly selected residents free of cardiovascular disease in the Brisighella Heart Study. The average follow-up time was 23 years. In this study 6% of the participants were diabetics and the mean age was 45 years.

SBP was most strongly associated with coronary heart disease in multivariate adjusted analysis (SBP/10 mmHg; HR 1.32; 95% confidence interval 1.31-1.31), followed by PPb (PPb/10 mmHg; HR 1.24; 95% CI 1.23-1.25). Adjusted HRs for CHD events at SBP categories of 120–139, 140–159 and > 159 mmHg were 1.29 (95% CI, 0.85–1.97; P = 0.234), 1.69 (95% CI, 1.07–2.67; P = 0.025), and 2.04 (95% CI, 1.26–3.29; P = 0.004), respectively. The reference range for SBP was < 120 mmHg. For DBP ranges of 70–79, 80–89, and > 89, HRs for all categories were not significant. The reference range for DBP was < 70 mmHg. PPb ranges from 54–67 and > 67 mmHg were associated with HRs that were not statistically significant with the reference range of PPb being < 54. All three BP parameters demonstrated significant trends of HRs across BP categories (P < 0.001). Adjusted HRs for cardiovascular disease (CVD) events, which were defined as transient ischemic attack or stroke, at SBP categories of 120–139, 140–159 and > 159 mmHg were 1.85 (95% CI, 0.99–3.45; P = 0.521), 2.35 (95% CI, 1.23–4.50; P = 0.009), and 2.96 (95% CI, 1.52–5.77; P = 0.001), respectively. For DBP ranges of 70–79, 80–89 and > 89 mmHg, HRs not statistically significant. PPb ranges from 54–67 and > 67 mmHg were associated with HRs that were not statistically significant⁴.

Finally, Miura and colleagues compared PPb to other blood pressure measures for the prediction of 25-year CHD, CVD, and all-cause mortality rates in the Chicago Heart Association Detection Project in Industry Study. These participants were between the ages of 18 and 74, had no history of coronary heart disease, were not receiving antihypertensive treatment and did not have diabetes. Wald chi-square tests were used to compare the strength of relations. Associations of PPb were weaker than those for SBP for all end points in all age/gender groups. SBP or MAP showed the strongest relations to

all end points in all age/gender groups. The relations of SBP to death were stronger than were those of DBP, except for middle-aged men and for CVD in women. DBP showed significant positive associations with death, after controlling for SBP, in middle-aged participants. They concluded that the long-term risk of high blood pressure should be assessed mainly on the basis of SBP or of SBP and DBP together, not on the basis of PP, in apparently healthy adults. These data suggest that in a younger population without significant co-morbidities including congestive heart failure, diabetes mellitus, and end-stage renal disease, PPb may not be a significant predictor of coronary heart disease or cardiovascular events. It should be noted however that there may be many other explanations for the conflicting results reported. Other explanations include insufficient statistical power to observe an association, the varying methods of study design, and the varying methods of data analysis.

Potential Therapies for Arterial Stiffness

Many factors contribute to arterial stiffness including inappropriately low proximal arterial diameters, stroke volume from the heart, arterial architecture, MAP, and inappropriate vasoconstriction. Different diets and their relations to arterial stiffness have been studied, since diets high in cholesterol, salt and simple sugars have been associated with alterations in arterial vessel structure and function. When hypertensive adults are studied prospectively, increased salt intake not only increases BP but also decreases brachial artery diameter, suggesting a pressure -independent mechanism acting on the arterial wall. The antihypertensive effect of diuretics has minimal effect on this arterial geometry and stiffness⁵⁵. These data suggest that diets low in salt and their relation to arterial stiffness should be studied.

Tanaka and colleagues studied the effect of exercise on the age-related decrease in proximal arterial compliance. First, 151 healthy men aged 18 to 77 years were studied: 54 were sedentary, 45 were recreationally active, and 53 were endurance exercise-trained. Central arterial compliance (utilizing measures derived from simultaneous B-mode ultrasound and arterial applanation tonometry on the common carotid artery) was lower ($P < 0.05$) in middle-aged and older men than in young men in all 3 groups. There were no significant differences between sedentary and recreationally active men at any age. However, arterial compliance in the endurance-trained middle-aged and older men was 20% to 35% higher than in the 2 less active groups ($P < 0.01$). Age-related differences in central arterial compliance were smaller in the endurance-trained men than in the sedentary and recreationally active men. They also studied 20 middle-aged and older (53 ± 2 years) sedentary healthy men before and after a 3-month aerobic exercise intervention (primarily walking). Independent of changes in body mass, adiposity, arterial blood pressure, or maximal oxygen consumption, regular exercise increased central arterial compliance ($P < 0.01$) to levels similar to those of the middle-aged and older endurance-trained men. They concluded that the attenuation of the reduction in central arterial compliance by habitual exercise may be one mechanism by which the risk of cardiovascular disease is lowered in this population⁵⁶.

Weight loss due to modification in diet coupled with increased exercise⁵⁷ and weight loss after bariatric surgery⁵⁸ have also been shown to have beneficial effects on central arterial compliance.

Obstructive sleep apnea (OSA) is associated with hypertension, arterial stiffness and cardiovascular events⁵⁹. Phillips and colleagues investigated whether increased

arterial stiffness and elevated central BP (two important cardiovascular risk factors) would change, independent of peripheral blood pressure after either initiation or withdrawal from nasal continuous positive airway pressure (CPAP) treatment in subjects with OSA. In the intervention group there were reductions in arterial stiffness (aortic augmentation index changed by -2.5%) and central systolic BP (- 4.2 mmHg) without an associated reduction in peripheral BP. The change in arterial stiffness was associated with CPAP compliance. In a group from whom CPAP was withdrawn, there were no changes in arterial stiffness or BP on day 7 of follow-up. There was an early morning increase in DBP and heart rate relative to late evening. These data suggest that clinically important changes in arterial stiffness and central BP may occur following effective CPAP treatment of OSA without parallel changes in peripheral BP⁶⁰.

Since antihypertensive drugs decrease MAP and vessel vasoconstriction, studies investigating the effect of these drugs on arterial stiffness have been performed. In the Conduit Artery Function Evaluation (CAFE) study, a substudy of the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT) in which the impact of 2 different BP lowering-regimens (atenolol+/-thiazide-based versus amlodipine+/-perindopril-based therapy) on derived central aortic pressures and hemodynamics was examined, 2199 patients underwent radial artery applanation tonometry and pulse wave analysis. These measures were used to derive central aortic pressures and hemodynamic indexes on repeated visits for up to 4 years. Even though brachial systolic BPs were similar between treatment groups (delta 0.7 mm Hg; 95% CI, -0.4 to 1.7; P=0.2), there were substantial reductions in central aortic pressures only with the amlodipine-based regimen (central

aortic systolic BP, delta 4.3 mm Hg; 95% CI, 3.3 to 5.4; $P < 0.0001$; central aortic pulse pressure, Delta 3.0 mm Hg; 95% CI, 2.1 to 3.9; $P < 0.0001$)⁶¹.

Conclusions

Aortic stiffness is significantly associated with and may contribute to cardiovascular events and mortality. PPb is a surrogate, non-invasive measure of arterial stiffness and has been shown in some populations to be associated with cardiovascular events and mortality. Arterial stiffness can be treated. Thus methods that are better able to measure arterial stiffness non-invasively may be beneficial. The following hypotheses stated by the following manuscripts and the statistical analyses used to explore these hypotheses were originated by the submitter of the Master's thesis.

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Chapter II

Relationship between Increased Pulse Pressure, Measured by Radial Arterial Tonometry or by Brachial Cuff, and Increased Left Ventricular Mass: The Multi Ethnic Study of Atherosclerosis (MESA)

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Abstract

Elevated brachial pulse pressure is a surrogate measure for increased aortic stiffness and is associated with increased left ventricular mass (LVM) in the elderly. Measures derived from the pressure wave acquired from radial arterial tonometry have been suggested to be superior measures of arterial stiffness compared to pulse pressure by blood pressure cuff. Our goal was to determine if increased pulse pressure (PP), measured by radial arterial tonometry (PPr), is associated with increased LVM after adjustment for PP measured by brachial cuff (PPb) and traditional cardiovascular risk factors in a cross-sectional study. LVM, indexed to body size, and covariate data were available for 4147 men and women without clinically recognized cardiovascular disease, ages 45-84, enrolled in the Multi-Ethnic Study of Atherosclerosis (MESA). Results: Mean PPr was 58.1 ± 15.2 and mean PPb was 53.1 ± 16.7 mmHg, with a correlation coefficient of 0.73. The multivariable linear regression model including PPb, PPr, and covariates for $LVM/h^2 (g/m^2)$ positively related PPb and PPr to body size indexed-LVM ($\beta = 0.14$, 95% CI 0.11-0.17, $p < 0.0001$ for PPb; and $\beta = 0.13$, 95% CI 0.10-0.16, $p < 0.0001$ for PPr). These data suggest pulse pressure measured by radial arterial tonometry or by brachial cuff is associated with LVM indexed for body size after adjustment for each other and other traditional cardiovascular risk factors.

Introduction

Increased LVM is characterized by an increase in the size or number of sarcomeres in myocardial cells. It is a strong independent predictor for cardiovascular disease when measured by electrocardiogram or by echocardiography, and in

normotensive and hypertensive individuals^{1,2}. The prevalence of left ventricular hypertrophy, defined by an increase in LVM two standard deviations above a population mean, is 15-20% by echocardiography in a large free-living population of adults from the Framingham Heart Study³. Cardiovascular risk factors associated with increased LVM include increased systolic blood pressure, decreased diastolic blood pressure, diabetes mellitus, higher body mass index, active smoking, higher serum creatinine and higher urine albumin/creatinine levels^{4,6}. Increased LVM significantly increases the risk of stroke, coronary artery disease, congestive heart failure, ventricular arrhythmias, and sudden death^{2,7-9}. Arterial stiffness, if present in the proximal arterial beds, can place increased workload on the heart leading to increased LVM. Pulse pressure, measured by brachial blood pressure cuff (PPb) is the difference between systolic blood pressure and diastolic blood pressure. It is a surrogate measure of arterial stiffness and when elevated is strongly associated with increased LVM^{4,5}.

Measures obtained from aortic pulse pressure waveforms derived from radial arterial tonometry have been suggested to be superior measures of arterial stiffness compared to pulse pressure by blood pressure cuff. Specifically, one of the most common methods of estimating arterial stiffness is central artery pulse-wave analysis. Individual and generalized inverse transfer functions are used to recreate the aortic waveform from radial tonometry. This analysis has been validated with invasive and direct measurements of the aortic waveform¹⁰⁻¹² with the assumption that the aortic pressure waveform is a component of a forward pressure wave created by a ventricular contraction and a reflective wave returning from the periphery from distal branch sites. Many investigators have suggested that in the setting of arterial stiffness these reflected

waves arrive back faster to the aorta adding to the forward wave and augmenting the systolic pressure. This augmented aortic systolic pressure is felt to be a major pathologic feature in arterial stiffness and is defined as the difference between the second and the first systolic peaks ($P_2 - P_1$) expressed as a percentage of the PP (Figure 1). Previous studies have suggested that the forward pulse wave velocity can best represent the degree of circulatory arterial stiffness non-invasively but these findings have recently been questioned¹³⁻¹⁵. In addition, using measures from the radial arterial waveform without deriving an aortic pulse pressure waveform has recently been suggested¹⁶. Compared to PPb, radial arterial tonometry does not require the use of an occlusive cuff. Thus, it does not significantly alter the hemodynamic status of the underlying artery which may affect the pressure measures. Also, arterial tonometry allows for continuous monitoring of the pressure wave contour on a beat by beat basis over a period of time which may improve the precision of the sample. Many surrogate measures of arterial stiffness can be obtained from the radial arterial waveform to determine if they relate to increased LVM but, to our knowledge, the relationship between pulse pressure measured by radial arterial tonometry (PPr) and LVM has not been studied. We tested the hypothesis that PPr is associated with increased LVM after adjustment for PPb and traditional cardiovascular risk factors in the large multi-center, ethnically diverse Multi-Ethnic Study of Atherosclerosis study.

Methods:

Study Sample: This investigation utilized data from the Multi-Ethnic Study of Atherosclerosis (MESA). The aims and design of this observational study have been previously described¹⁷. Briefly, 6814 men and women, age 45-84 years were recruited between July 2000 and September 2002 from four self-reported race/ethnic groups:

White, African-American, Hispanic and Chinese-American. Participants were free of clinically evident cardiovascular disease, including congestive heart failure, myocardial infarction, coronary revascularization, stroke, atrial fibrillation, and peripheral vascular disease. Approval from the institutional review boards were obtained from the six MESA field centers and informed consent was obtained from all participants.

Baseline Data Collection: Medical history, physical measurements and laboratory data were derived from the initial examination of the MESA cohort which began in July 2000. Height and weight were measured. Participant age, gender, ethnicity, medical history, alcohol consumption, smoking, intentional exercise, current medications and medical diagnoses of diabetes and hypertension were obtained by questionnaire. History of hypertension and diabetes and the use of anti-hypertensive medications were also obtained from medical history¹⁷. Seated blood pressure (BP) was taken three times at rest with a Dinamap model Pro 100 oscillometric sphygmomanometer (Critikon, Tampa, Florida)¹⁸ with the average of the second and third measurements used in the analysis. Heart rate was acquired and computed from electrocardiographic analysis. High density lipoprotein (HDL) cholesterol was measured after a 12-hour fast and the Friedwald equation was used to calculate low-density lipoprotein (LDL) levels¹⁹. Kidney function was estimated with the Modification of Diet in Renal Disease formula, which calculates estimated glomerular filtration rate (eGFR) based on serum creatinine²⁰. Urine albumin and creatinine were measured by nephelometry and the rate-Jaffe reaction, respectively.

LV mass by Magnetic Resonance Imaging: The cardiac MRI scans were performed on voluntary consenting participants in MESA utilizing 1.5-T magnets, a median of 16 days after the baseline evaluation, as previously described²¹. Images were

obtained with a phased array, 4-element surface coil positioned anteriorly and posteriorly, while monitoring blood pressure and utilizing electrocardiographic gating. The left ventricle was imaged with fast gradient echo cine, with a time resolution of < 50 ms and mass was determined by volumetric imaging. Readers at a single reading center, blinded to participant risk factor data, read the imaging data utilizing MASS software (version 4.2, Medis, Leiden, Netherlands). Papillary muscles were excluded from LVM measurements. The high intra-class correlation for LVM in MESA has been previously reported⁵. LVM was indexed to the square of participant height in meters to account for differences in body size based on linear regression estimates for height predicting cardiac MRI-derived LV mass in a MESA reference sample free of significant risk factors²². LVM was also indexed to body surface area (BSA) using the Dubois and Dubois formula ($BSA = (W^{0.425} \times H^{0.725}) \times 0.007184$) since the most appropriate method of adjusting LVM for body size still remains controversial.

Pulse Pressure Measures: Pulse pressure was calculated from brachial artery pressure readings and by radial artery tonometry. Brachial artery pulse pressure (PPb) was calculated as the difference of the average verified systolic BP and diastolic BP measured by oscillometric sphygmomanometry. Arterial waveforms were measured with the HDI/Pulse Wave CR2000 (Hypertension Diagnostics, Inc., Eagan, Minnesota)²³. The pulse contour was recorded with a solid-state pressure transducer array (tonometer) after placing it over the radial artery of the dominant arm. An automated oscillatory blood pressure measurement supplied by the HDI/Pulse Wave CR2000 was performed in the contra-lateral arm to calibrate the device before, during and after the waveform assessment. A 30 second analog tracing of the radial waveform was digitized at 200

samples per second, excluding the dicrotic notch, once a calibrated measurement was obtained. A typical waveform for each participant was estimated by self-modeling regression. Self-modeling regression is a method for estimating functional data that arise when the ideal observation for each experimental unit is a curve or function, and the observed data consist of sets of noisy observations from each curve. This model is based on the relatively simple assumption that the x- and y- axes can be separately transformed, often in a parametric manner, for each curve so that the data from all curves lie approximately on one typical curve^{24, 25} (Figure 2). The radial pulse pressure (PPr), used in the analysis, was estimated by taking the difference between the maximum of the typical waveform and the first upward deflection of the typical waveform of all tracings within a 30 second period for each participant.

Statistical analysis: Variables previously reported to be associated with LVM were identified and included age, gender, race, cigarette use, hypertension, alcohol use, HDL, LDL, statin (HMG Co A reductase inhibitor) use, urine albumin/creatinine, glomerular filtration rate, angiotensin converting-enzyme inhibitor use, angiotensin receptor antagonist use, and glucose metabolism dysfunction status. Hypertension was defined as having a BP > 140/90 mm Hg or if participants took antihypertensive medications at the time of the baseline examination. Participant glucose metabolism status was categorized as (a) normal if fasting glucose was < 100 mg/dl, (b) impaired fasting glucose if participants were not on diabetic medications and fasting glucose was between 100 mg/dl and 125 mg/dl, (c) untreated diabetes if fasting glucose was 126 mg/dl or greater and insulin or oral hypoglycemic medications were not prescribed and (d) diabetes if fasting glucose was 126 mg/dl or greater or insulin/oral hypoglycemic

medications were prescribed^{4, 5, 26, 27}. Categorical data were reported as proportions and continuous data as mean values. The Pearson correlation coefficient between PPb and PPr was reported acknowledging the limited value in the comparison of closely related measurements. Variables that strongly correlated with PP such as SBP, DBP and hypertension, were not entered into the models. Multivariable linear regression models were constructed to determine whether pulse pressure measures were associated with body size indexed-LV mass after adjusting for age, gender, clinic site, ethnicity and covariates that have been shown to be associated with LVM. Body size indexed- LVM was the dependent variable and the independent variable(s) in the four linear regression models were 1) PPb; 2) PPr 3) PPb and PPr; and 4) PPb, PPr, age, gender, ethnicity, clinical site, and the other covariates. For graphical presentation, we subdivided PPb and PPr levels into quartiles and computed covariate-adjusted mean LVM/h^2 (g/m^2) in each level using analysis of variance (ANOVA) with adjustment for multiple comparisons by the Bonferroni method. Statistical analyses were performed using SAS version 9.1 software (SAS Institute Inc, Cary, NC) and statistical significance was declared at $p < 0.05$.

Results

Twenty-seven percent of the 6,814 MESA participants did not undergo cardiac MRI. Of these, 28% (out of 1810) could not complete cardiac MRI because of ineligibility mostly due to internal metal fragments or devices, 55% because of claustrophobia, 12% refused, 1.5% due to mechanical difficulties with the scanner, and 4% due to unknown reasons. Of the number of participants who completed cardiac MRI, 14% did not undergo radial arterial tonometry. Of these, 47% (out of 722) did not

complete radial tonometry for unknown reasons, 43% were missing due to poor segmentation (data inadequate for analysis), and 10% due to inability of the summary model to converge. Covariate data were missing for 134 participants and they were excluded. Compared to participants not included in the analysis (n = 2667), the 4147 participants that were included were younger (61 vs. 64 years), and had lower cuff (53 vs. 57 mmHg) and radial tonometry (58 vs. 60 mmHg) pulse pressures. Urine albumin/creatinine levels were lower (21 vs. 39 mg/g) in the included participants. Also, the included participants had a larger proportion of Chinese (14% vs. 8%), Hispanics (23% vs. 19%), a lower proportion of African Americans (25% vs. 33%), and a lower proportion of hypertensives (42% vs. 52%) (all differences between the included and excluded participants significant at a $p < 0.05$). The average age of the included participants was 61 (standard deviation (SD) = 10) and 52% were women (Table I). Thirty-eight % of the included participants were white, 25% African American, 14% Asian and 23% Hispanic. The proportion of included participants that used alcohol was 56%, 13% were diabetic and 12% were current smokers. Eight percent of the included participants had a glomerular filtration rate of less than 60 mL per minute/1.7 m² and 1% had a urinary albumin/creatinine greater than 300 mg per gram.

The LVM and the LVM indexed to body size for males and females included in the analysis are summarized in Table II. The mean and SD for demographic and historical cardiovascular risk factor variables by PPb and PPr; and the graphical representation of the correlation of PPb with PPr are shown in Table III and Figure 3 respectively. The mean (SD) of PPb was 53.1 ± 16.7 mmHg and the mean (SD) of PPr was 58.1 ± 15.2 , with the correlation coefficient being 0.73. The difference between

mean of PPb and the mean of PPr in the 45-54 age category was 6.8 mmHg, and this difference in the 75-84 age category was 3.8 mm Hg, possibly demonstrating the loss of amplification of the pulse pressure wave amplitude with age as it travels to the periphery. PPb and PPr were higher in females compared to males. In the race/ethnicity category, PPb and PPr were highest in African Americans and Hispanics and lowest in Asians. In the cigarette smoking category, PPb and PPr were lowest in current smokers and highest in never smokers. In the alcohol use category, PPb and PPr were lowest in current alcohol users and highest in participants who never drank alcohol. In participants with eGFR of less than 60 mg/dl, the mean (SD) of PPb and PPr were 63.5 (19.1) mm Hg and 66.3 (17.2) mmHg respectively, while for those with eGFR of greater or equal to 60 the mean (SD) of PPb and PPr were 52 (16.2) mm Hg and 57 (14.8) mm Hg respectively. PPb and PPr increased with increasing urinary albumin/creatinine.

Variables used in the model to predict LVM indexed to BSA and height-squared were age, gender, race, clinical site, urine albumin/creatinine, glomerular filtration rate, alcohol use, angiotensin receptor blocker use, angiotensin converting enzyme use, and cigarette smoking status. The results from the 4 multivariable statistical models for LVM are shown in the rows of Table IV. The slope, 95% confidence intervals (CI), and p-value are shown for test of the slope estimating body size-indexed LVM equal to zero, as a continuous variable, from linear regression analyses. When PPb alone was entered into the model for LVM/BSA (g/m^2) and separately for LVM/ $h^2(g/m^2)$, there were positive relations predicting both body-sized indexed LVM measures that were statistically significant ($p < 0.0001$) (Table IV, model 1). When PPr alone was entered into the model for LVM/BSA (g/m^2) and separately for LVM/ $h^2(g/m^2)$, there were positive relations

predicting both body-sized indexed LVM measures that were statistically significant ($p < 0.0001$ for both) (Table IV, model 2). When PPb and PPr were entered into the model for LVM/BSA (g/m^2) and separately for LVM/ h^2 (g/m^2), the positive relations between PPb and body size indexed-LVM measure remained significant ($p < 0.0001$ for both), as well as the positive relations between PPr and the body size indexed-LVM measure ($p < 0.0001$ for both) (Table IV, model 3). We then constructed models that included age, gender, race, clinical site, gender, urine albumin/creatinine, glomerular filtration rate, alcohol use, angiotensin receptor blocker use, angiotensin converting enzyme use, cigarette smoking status, PPb and PPr for LVM/BSA (g/m^2) and separately for LVM/ h^2 (g/m^2) (Table IV, model 4). In these models PPb was positively related to body size indexed-LVM after adjusting for PPr and the listed covariates, and PPr was positively related to body size indexed-LVM after adjusting for PPb ($p < 0.0001$ for both PP measures). What is important to note is that once PPb was in the model for predicting body size indexed-LVM (model 1), PPr contributed little to this prediction when added to that model (model 3). This was demonstrated by comparing the R^2 between model 1 (0.016) and model 3 (0.019).

Means of LVM/ h^2 (g/m^2) adjusted for age, gender, race, clinical site, gender, urine albumin/creatinine, glomerular filtration rate, alcohol use, angiotensin receptor blocker use, angiotensin converting enzyme use, and cigarette smoking status by quartiles of PPb or PPr with or without adjustment for each other are shown in Figure 4. The adjusted means for LVM/ h^2 (g/m^2) increased with increasing quartiles of PPb (Figure 4A), and the adjusted means for LVM/ h^2 (g/m^2) increased with increasing quartiles of PPr (Figure 4B). Also, the adjusted means of LVM/ h^2 (g/m^2) increased with increasing

quartiles of PPb after adjusting for PPr (Figure 4C), and the adjusted means of LVM/h^2 (g/m^2) increased with increasing quartiles of PPr after adjusting for PPb (Figure 4D).

Discussion

It is important to elucidate determinants of increased LVM since left ventricular hypertrophy is an important risk factor for further cardiovascular events. Elevated pulse pressure is a surrogate measure for increased proximal aortic arterial stiffness, a major component of cardiac pressure overload, when systolic blood pressure is accounted for, and is associated with increased LVM in the elderly in the Cardiovascular Health Study²⁸. We evaluated the cross-sectional associations between pulse pressure measures and LVM and demonstrate that pulse pressure is an independent predictor of LVM when measured by radial arterial tonometry or by brachial artery. These positive relations persisted after accounting for pulse pressures measured by blood pressure cuff or radial tonometry respectively. Investigators have reported that proximal arterial pulse pressure measures depend on five major factors, including the velocity of the ejection of blood from the left ventricle, the stroke volume of the heart, the elastic properties of the proximal arteries, the peripheral vascular resistance and the rapidity by which the reflected pulse pressure wave returns from the periphery^{29, 30}. Previous data suggest that the stiffness of the proximal aorta is responsible for the pathological increase in proximal pulse pressure seen in the middle-aged and elderly. Historically, the consequences of a less compliant aorta (a stiffer aorta) has been described and explained as follows. Aortic stiffness results in an increase in aortic and proximal systolic blood pressure as it is not able to cushion

the ejected volume of blood from the heart. In addition, a stiff aorta is unable to augment diastolic blood pressure because it cannot store potential energy. This results in an increase in systolic blood pressure and a decrease in diastolic blood pressure. This increase in proximal systolic blood pressure increases the afterload that the heart has to overcome in order to provide adequate stroke volume and puts an increased workload on the heart. Also, because arterial stiffness is the result of mechanical deterioration and fragmentation of the elastic fibers of the aorta, this leads to dilatation of the proximal aorta and the transfer of force to more inflexible components of the aortic wall such as collagen. According to this hypothesis, proximal arterial stiffness leads to an increased forward pulse wave velocity that reaches the major bifurcations of the arterial tree faster and there is premature arrival of the reflected pressure wave to the proximal aorta. Thus, the incident pressure wave produced by ejection of blood from the heart collides with the reflective pulse pressure wave from the periphery resulting in an augmentation of the proximal arterial systolic pressure^{31, 32}. Indeed, a recent expert consensus document on arterial stiffness suggests that carotid-femoral pulse wave velocity be the gold standard for measuring arterial stiffness¹³. Even though this measure is regarded as simple, there are significant limitations. First, in patients with obesity, diabetes and peripheral artery disease the femoral pressure waveform may be difficult to record accurately³³. Second, large bust size in women can make distance measurements inaccurate. Third, abdominal obesity, especially in men, also make these measures inaccurate³³. Lastly, the pressure wave may be attenuated and delayed in the presence of aortic, iliac, or proximal femoral stenosis.

A recent study by Mitchell and colleagues calculated the aortic diameter in hypertensive, middle-aged and elderly participants without diabetes mellitus, coronary artery disease, peripheral vascular disease or a smoking history and normotensive controls of comparable age and gender. They found that pulse wave velocity, (PWV) was higher in hypertensives compared to normotensives but the difference was not significant after adjustment for differences in mean arterial blood pressure. Using another method of measuring aortic stiffness, local impedance Z_e , they found that increased Z_e remained highly significant after accounting for mean arterial pressure. Elevated PP in the hypertensive group was explained primarily by Z_e and reduced effective diameter of the proximal aorta³⁴. They concluded that these findings did not support the hypothesis of secondary aortic degeneration, dilatation, and wall stiffening. They suggested that aortic function, in the absence of aortic structural deterioration, may play a role in the etiology of systolic hypertension. Indeed, the aorta is a dynamic organ and does remodel in response to changing demands dictated by blood flow, shear stress and tensile stress. In animal models placement of aortocaval shunts to produce systems of increased shear stress and aortic flow resulted in a progressive increase in aortic diameter. The increase in aortic diameter resulted in the restoration of aortic shear stress to control levels. In the animals where aortic wall tensile stress was higher, medial cross-sectional area and the contents of elastin and collagen increased and were associated with an increase in smooth muscle cell hypertrophy, despite a decrease in arterial wall thickness³⁵.

The study by Mitchell and colleagues was criticized for relying on calculated effective aortic diameter instead of using actual measurements of aortic root diameter. In a follow-up study by Mitchell and colleagues, aortic diameter was measured, and they

again found that characteristic impedance was elevated out of proportion to the increase in carotid femoral pulse wave velocity in individuals with systolic hypertension. They also reported lower measured aortic diameters, and higher aortic wall stiffness in participants with increased pulse pressure¹⁵. These findings were replicated by a study performed by Farasat and colleagues where aortic root diameter was measured in groups of healthy and untreated hypertensive middle-aged and elderly individuals. After adjusting for age, height, weight, and mean arterial pressure, aortic root diameter was independently and inversely associated with pulse pressure in both men and women. After additional adjustments for central arterial stiffness, central arterial wall thickness, reflected waves, and left ventricular geometry, aortic root diameter remained inversely associated with pulse pressure in both sexes. The authors concluded that a smaller aortic diameter may contribute to the pathogenesis of systolic hypertension³⁶. Despite the significant differences in schools of thought regarding the pathogenesis of arterial stiffness what is consistent is that there is an increase in the forward pulse wave propagation with increasing arterial stiffness. With these limitations in mind, and the ongoing debate as to whether pulse wave velocity is within the pathogenic pathway of arterial stiffness and cardiovascular events, a more potentially reliable, noninvasive measure of arterial stiffness should be considered.

The increase in the forward pulse wave propagation with increasing arterial stiffness may not only be associated with higher pulse wave velocity but may also be related to higher pulse pressure amplitude measured in the peripheral circulation. For this reason, elevated peripheral pulse pressures may also be a surrogate measure for increased arterial stiffness and this measure may then relate to higher LVM.

In addition, the decrease in amplification in pulse pressure as we age may also account for some of these findings. Amplification of the amplitude of the pulse pressure wave is normally seen in mammals as the wave travels from the aorta to the periphery. Acute elevations of blood pressure in young subjects (age <45) with vasopressors decreases pulse pressure amplification. However, peripheral and central pulse pressure in older individuals change in tandem allowing peripheral pulse pressure to be considered a reliable measure of central pulse pressure in this population³⁷. Finally, measuring pulse pressure at the radial artery by tonometry has several advantages over PPb as discussed in the introduction.

Our study has several limitations. Brachial cuff pressure was used both to calibrate the tonometer and to measure brachial pulse pressure. The calibration may have affected the absolute pulse pressure values measured by radial arterial tonometry. Second, MRI exams were only performed on 63% of the participants and this sub-group on average was healthier than the group who did not have an MRI performed. Third, the cross-sectional nature of this study prevents the temporal relationship between pulse pressure and the development of increased LV mass from being studied. Finally, the association between PPb or PPr and LV mass may have been confounded by unmeasured variables related to either pulse pressure measure and/or LV mass.

In summary we report significant associations between increased pulse pressure not only by brachial cuff but also by radial tonometry and increased LVM. Previous studies have suggested that increased pulse wave velocity and the consequent increased central pulse pressure are important determinants of increased LVM. The current study presents new data suggesting that increased amplitude of the pressure wave in the

periphery may have important associations with increased LVM. New insight into the development of increased LVM may be provided by better understanding the nature of the forward pressure waveform.

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Table I. Characteristics of 4147 Participants who Completed Cardiac MRI and were Included in the Analysis

	Women (n = 2161)	Men (n = 1986)
Age, yrs	61(10)	61(10)
Race/Ethnicity, %		
White	38.0	38.3
African American	25.4	23.8
Asian	14.0	14.0
Hispanic	22.5	23.9
Hypertension, %	42.3	39.7
Impaired Fasting Glucose, %	21.8	31.0
Diabetes, %	11.6	14.0
Current Alcohol Use, %	49.6	63.4
Current cigarette smoker, %	10.6	14.0
Angiotensin receptor antagonists, %	3.8	2.4
ACE Inhibitor Use, %	10.8	12.7
Systolic BP (mmHg)	125 (23.0)	125 (18.9)
Diastolic BP (mmHg)	69 (10.2)	75 (9.3)
HDL (mg/dl)	56.7 (15.2)	45.2 (11.4)
LDL (mg/dl)	117.5 (31.5)	117.0 (31.0)
HMG CoA reductase inhibitors, %	14.7	13.6
Glomerular filtration rate (mL/min/1.73 m ²)		
< 60	10.0	6.5
≥ 60	90.0	93.5
Urinary albumin/creatinine (mg/g)		
≤ 30	92.6	91.1
> 30 - 300	6.6	7.4
> 300	0.8	1.5
Exercise (per 1000 MET-min/week)		
< 19	61.3	52.6
19 - 30	14.2	14.5
> 30	24.5	32.9
Heart Rate (beats/min)	63.8 (9.0)	61.6 (9.6)

Values expressed as mean +/- standard deviation or percentage. BP = blood pressure; HDL = high-density lipoprotein; LDL = low-density lipoprotein; MRI = magnetic resonance imaging; MET = metabolic equivalents.

Table II. LV Mass and LV Mass Indexed to Body Size of Males and Females Included in the Analysis

	Women	Men
	(n = 2161)	(n = 1986)
LVM (g)	123	168
LVM/BSA (g/m^2)	70.6 \pm 12.4	85.6 \pm 16.1
LVM/ h^2 (g/m^2)	48.1 \pm 15	56.0 \pm 11.7

LVM = left ventricular mass, BSA = body surface area, h^2 = height squared in meters. Data are expressed as mean \pm standard deviation.

Table III. Covariates and Risk Factor Characteristics by PPb and PPr

	<i>PPb</i>	<i>PPr</i>
	Mean (SD)	Mean (SD)
Age Categories, yrs		
45-54	43.9 (10.6)	50.7 (10.5)
55-64	51.6 (14.8)	56.6 (13.5)
65-74	59.8 (17.3)	63.1 (15.5)
75-84	66.3 (18.0)	70.1 (17.5)
Gender		
Female	56.3 (17.9)	60.9 (15.7)
Male	49.8 (14.6)	55.1 (14.1)
Race/Ethnicity		
White	52.0 (16.0)	57.9 (14.4)
Asian	51.0 (16.1)	54.6 (15.0)
African American	55.4 (17.1)	59.8 (15.9)
Hispanic	54.0 (17.6)	58.9 (15.6)
Cigarette Smoking Status		
Never	53.6 (16.9)	58.5 (15.6)
Former	53.4 (16.7)	58.4 (15.1)
Current	50.2 (15.7)	55.8 (13.7)
Hypertension		
Yes	64.1 (17.8)	65.9 (16.6)
No	45.4 (10.5)	52.7 (11.4)
Alcohol Use		
Never	57.2 (18.4)	60.7 (16.3)
Former	53.6 (16.6)	58.8 (15.0)
Current	51.4 (15.8)	56.9 (14.8)
Angiotensin receptor antagonist use		
No	52.8 (16.5)	57.9 (15.0)
Yes	63.6 (20.8)	66.3 (18.9)
ACE inhibitor use		
No	52.1 (16.3)	57.3 (14.8)
Yes	60.8 (18.2)	64.4 (16.7)
Glomerular filtration rate (mg/dl)		
< 60	63.5 (19.1)	66.3 (17.2)
≥ 60	52.2 (16.2)	57.4 (14.8)
Urinary albumin/creatinine (mg/g)		
≤ 30	52.1 (16.0)	57.3 (14.8)
> 30 - 300	64.5 (18.9)	66.1 (16.7)
> 300	70.2 (20.8)	72.2 (21.0)

Values expressed as mean +/- standard deviation. PPb = pulse pressure measured by brachial blood pressure cuff, PPr = pulse pressure measured by radial arterial tonometry.

Table IV. Multivariable Analysis of Models Body Size-Indexed LV Mass Unadjusted and Adjusted for Risk Factors in Relation to PPb and/or PPr

	LVM/BSA (g/m^2)				LVM/ h^2 (g/m^2)			
	Slope	CI	P value	R ²	Slope	CI	P value	R ²
1: pp _b Unadjusted	0.12	0.09-0.15	<0.0001	0.016	0.13	0.11-0.16	<0.0001	0.038
2: pp _r Unadjusted	0.14	0.11-0.17	<0.0001	0.018	0.14	0.12-0.17	<0.0001	0.035
3: pp _b Adjusted for pp _r	0.06	0.02-0.10	<0.0001	0.019	0.09	0.06-0.12	<0.0001	0.042
3: pp _r Adjusted for pp _b	0.09	0.05-0.14	<0.0001	0.019	0.08	0.04-0.11	<0.0001	0.042
4: pp _b Adjusted for pp _r and other risk factors	0.14	0.10-0.18	<0.0001	0.326	0.14	0.11-0.17	<0.0001	0.284
4: pp _r Adjusted for pp _b and other risk factors	0.17	0.14-0.21	<0.0001	0.326	0.13	0.10-0.16	<0.0001	0.284

Indexed LVM is the dependent variable and the independent variable(s) in the 4 linear regression models are: 1) pp_b; 2) pp_r 3) pp_r and pp_b; and 4) pp_r, pp_b, and age, gender, race, clinical site, gender, urine albumin/creatinine, glomerular filtration rate, alcohol use, angiotensin receptor blocker use, angiotensin converting enzyme use, cigarette smoking status.

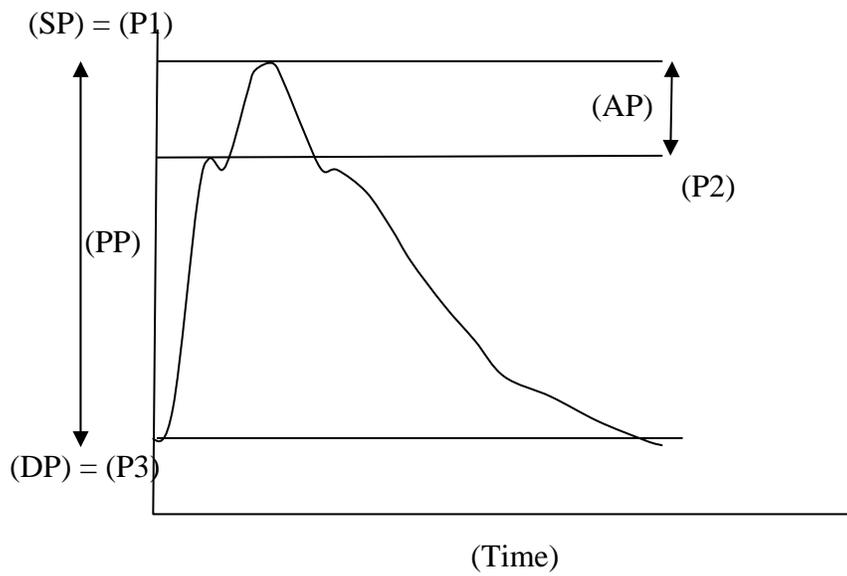


Figure 1. Aortic Pressure Waveform Derived from Radial Applanation Tonometry. The height of the late systolic peak (P1) above the inflection (P2) defines the augmentation pressure (AP), and the ratio of augmentation pressure to pulse pressure diastolic blood pressure is the augmentation index.

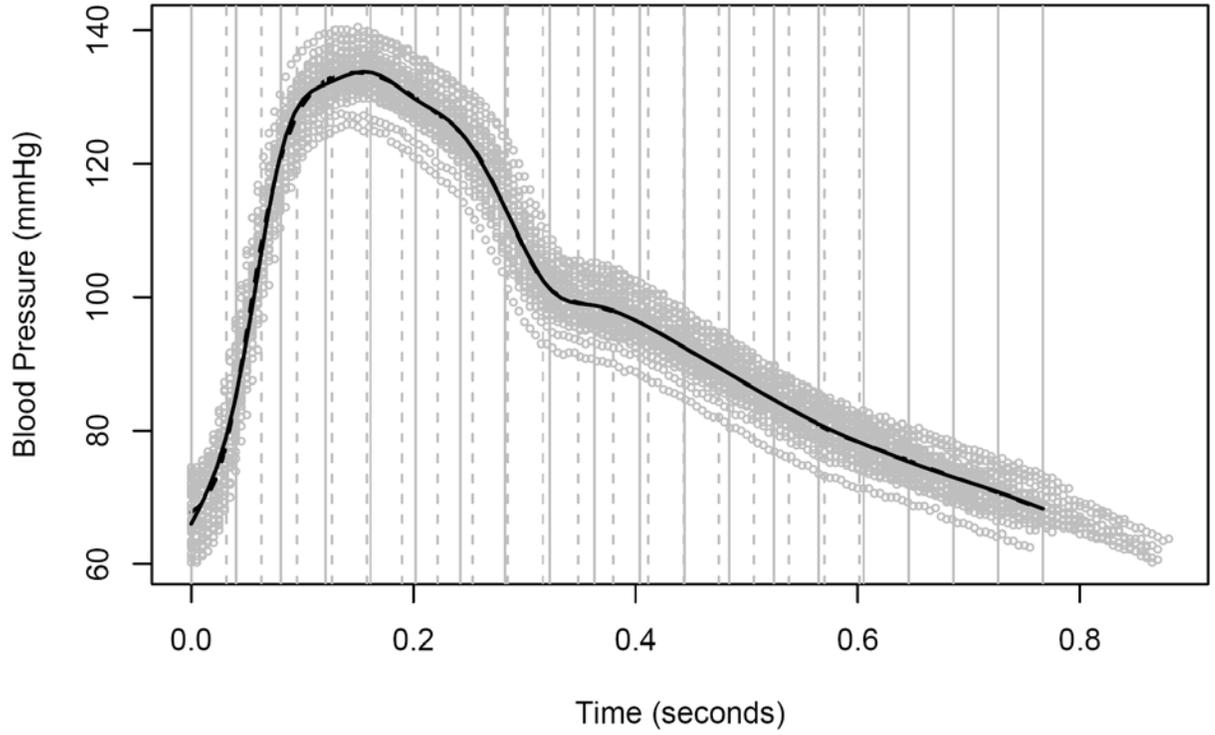


Figure 2 Typical Waveform Estimated by Self-Modeling Regression Summarizing Thirty Seconds of Digitized Radial Waveforms from One Participant.

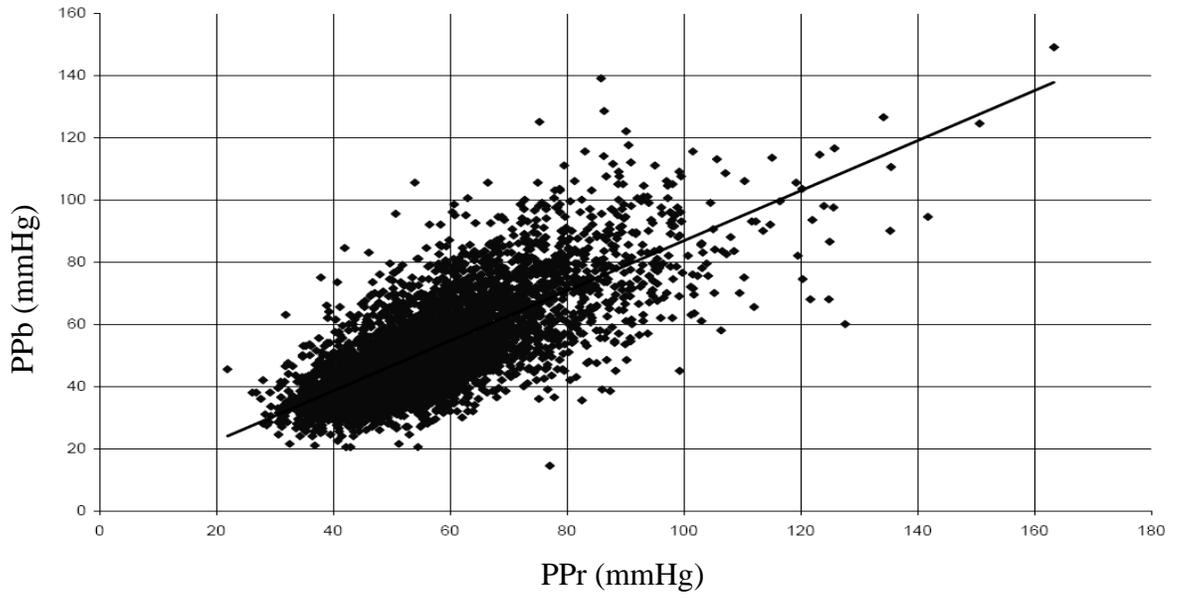


Figure 3. Correlation between PPb and PPr in mm Hg.

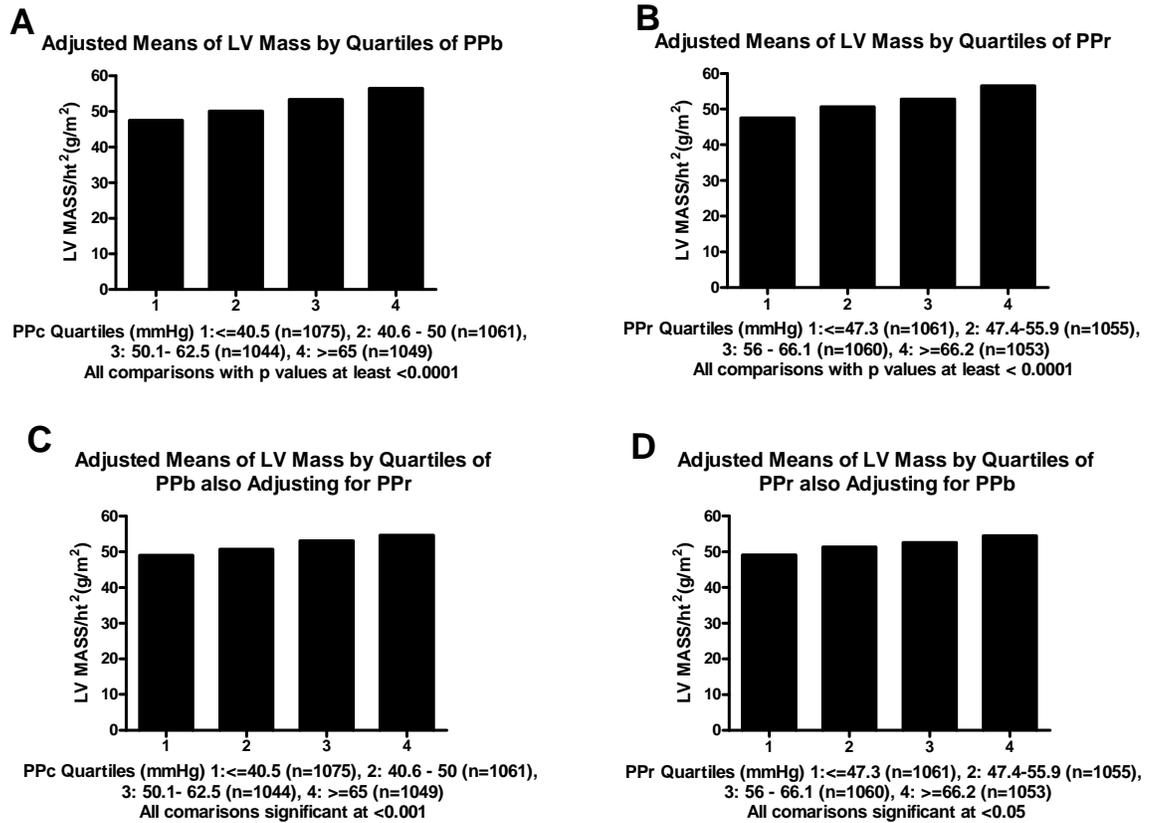


Figure 4. Means of LVM/h^2 (g/m^2) Adjusted for Covariates by Quartiles of PPb and PPr. Means of LVM/h^2 (g/m^2) adjusted for age, gender, race, clinical site, urine albumin/creatinine, glomerular filtration rate, alcohol use, angiotensin receptor blocker use, angiotensin converting enzyme use, and cigarette smoking status by quartiles of PPb or PPr. Analysis of variance (ANOVA) was used with adjustment for multiple comparisons by the Bonferroni method.

Chapter III

Pulse Pressure Determined by Radial Arterial Tonometry and Incident Congestive Heart Failure: The Multi Ethnic Study of Atherosclerosis (MESA)

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Abstract

Pulse wave velocity, a surrogate of arterial stiffness, is associated with cardiovascular events but is technically difficult to measure. Data on the relation between brachial pulse pressure (PPb) and cardiovascular events are inconsistent. Radial pulse pressure (PPr) may have several advantages in measuring arterial stiffness. In this study we examined the association between PPb, systolic blood pressure (SBP), diastolic blood pressure (DBP), and PPr with the incidence of congestive heart failure (CHF) in 5763 healthy men and women, aged 45-84 enrolled in the Multi-Ethnic Study of Atherosclerosis (MESA) during the 4 years of follow-up. Results: Increasing PPr hazard ratio (HR) 1.29/SD, 95% confidence interval (CI) 1.02-1.63), but not PPb (HR 1.17, 95% CI 0.91-1.52), DBP (HR 1.10/SD, CI 0.85-1.41) and SBP (HR 1.17/SD, CI 0.92-1.50), was significantly associated with CHF after adjusting for established risk factors excluding left ventricular mass or ECG left ventricular hypertrophy (SD = standard deviation). After adjusting for LV Mass or ECG LVH, the association between PPr and incident CHF was no longer significant. PPr, another measure of arterial stiffness, may be a significant clinical predictor of CHF. The association of PPr and CHF may be mediated by increasing LV mass or ECG LVH.

Introduction

Generally accepted knowledge of the role of hypertension as a major risk factor for cardiovascular diseases is derived mostly from studies focused on SBP and DBP levels, without taking into account their joint effects¹⁻³. Consequently, current guidelines for the classification and management of hypertension categorize hypertension related-

cardiovascular risk chiefly on SBP and DBP levels⁴. Blood pressure consists of steady and pulsatile components. The steady component is mainly a function of systemic vascular resistance and cardiac output, and the pulsatile component is determined by ejection of blood from the heart, large artery compliance, and the timing of pulse wave reflections from the periphery. In addition, the pulsatile component corresponds to the fluctuation of the pressure curve around the steady component^{5, 6}. The steady component can be estimated by calculating the mean arterial pressure (MAP), while the pulsatile component can be estimated by calculating pulse pressure. Both components can be estimated by using combined levels of SBP and DBP measured by blood pressure cuff.

Recent studies suggest that pulse pressure measured by blood pressure cuff (PPb), is a surrogate measure for proximal arterial stiffness. Higher pulse pressures in the proximal arterial tree places increased workload on the heart leading to systolic heart failure. Also, the heart muscle hypertrophies to compensate for this increased afterload⁷. This hypertrophy may then lead to CHF as a result of delayed relaxation⁸ or progressive LV dilatation. PPb is a strong predictor of incident cardiovascular events including atrial fibrillation⁹, coronary heart disease^{10, 11}, and CHF (CHF)¹¹⁻¹³. Some studies suggest that PPb is a stronger predictor of cardiovascular events than MAP, SBP, and DBP, particularly in individuals greater than the age of 60^{10, 11, 14}. Other studies have suggested that PPb can independently predict cardiovascular events after accounting for SBP, MAP and DBP^{6, 11, 15}. Many studies, however, have found that PPb does not provide additional predictive value for cardiovascular events after accounting for conventional blood pressure measures (SBP and DBP), including events such as coronary heart disease^{16, 17}, coronary heart disease -related death¹⁸, and CHF¹³.

Measuring pulse pressure at the radial artery by tonometry (PPr) is another method of indirectly estimating arterial stiffness and has several advantages. The main advantage is that PPr does not require the use of an occlusive cuff and therefore, does not significantly alter the hemodynamic status of the underlying artery. Previous studies have suggested that increased proximal arterial stiffness can be best represented by the velocity of the forward pulse wave as it travels down the periphery since stiffer arteries increase the propagation of the forward pulse wave¹⁹⁻²¹. We propose that increased amplitude of the forward pulse, as measured by PPr, may also measure increased forward pulse wave propagation and, consequently, be associated with incident CHF.

In this study we examined the association between PPb, SBP, DBP, and PPr with the incidence of CHF in participants enrolled in the Multi-Ethnic Study of Atherosclerosis (MESA) during the 4 years of follow-up. In addition, the association between PPb, SBP, DBP, and PPr with left ventricular mass was examined after accounting for baseline left ventricular mass by MRI or a diagnosis of left ventricular hypertrophy (LVH) by electrocardiogram to determine if elevated left ventricular mass mediated this association.

Methods

Study Sample: The Multi-Ethnic Study of Atherosclerosis (MESA) is a multicenter cohort study, the aims and design of which have been previously described²². Briefly, 6814 men and women, age 45-84 years were recruited between July 2000 and September 2002 from four self-reported race/ethnic groups: White, African-American, Hispanic and Chinese-American. Participants were recruited from six US communities in

Maryland, Illinois, North Carolina, California, New York, and Minnesota. Participants were free of clinically evident cardiovascular disease, including CHF, myocardial infarction, coronary revascularization, stroke, atrial fibrillation, and peripheral vascular disease. Approval from the institutional review boards were obtained from the six MESA field centers and informed consent was obtained from all participants.

Baseline Data Collection: Medical history, physical measurements, and laboratory data were derived from the initial examination of the MESA cohort which began in July 2000. Height and weight were measured. History of hypertension and diabetes and the use of anti-hypertensive medications were also obtained from medical history. Participant age, gender, ethnicity, medical history, alcohol consumption, smoking, intentional exercise, current medications, and medical diagnoses of diabetes and hypertension were obtained by questionnaire²². Seated blood pressure (BP) was taken three times at rest with a Dinamap model Pro 100 oscillometric sphygmomanometer (Critikon, Tampa, Florida)²³ with the average of the second and third measurements used in the analysis.

Kidney function was estimated with the Modification of Diet in Renal Disease formula, which calculates estimated glomerular filtration rate (eGFR) based on serum creatinine²⁴. Urine albumin and creatinine were measured by nephelometry and the rate-Jaffe reaction, respectively. Participants were categorized into 3 groups depending on their baseline urinary albumin (mg)/creatinine (g) ratio (UACR): 1) normal: UACR < 30; 2) micro-albuminuria: UACR 30 to 300; and 3) macro-albuminuria: UACR > 300. High density lipoprotein (HDL) cholesterol was measured after a 12-hour fast and the Friedwald equation was used to calculate low-density lipoprotein levels²⁵.

Hypertension was defined as having a BP > 140/90 mm Hg or if participants took antihypertensive medications at the time of the baseline examination. Participant glucose metabolism status was categorized as (a) normal if fasting glucose was < 100 mg/dl, (b) impaired fasting glucose if participants were not on diabetic medications and fasting glucose was between 100 mg/dl and 125 mg/dl, (c) untreated diabetes if fasting glucose was 126 mg/dl or greater and insulin or oral hypoglycemic medications were not prescribed, and (d) diabetes if fasting glucose was 126 mg/dl or greater or insulin/oral hypoglycemic medications were prescribed²⁶⁻²⁹. Body mass index (BMI) was calculated as $BMI = \text{weight (kg)} / \text{height}^2 (\text{m}^2)$ from weight measured to the nearest 0.5 kg and height to the nearest 0.1 cm. Obesity was defined as a BMI $\geq 30 \text{ kg/m}^2$ using the world health organization BMI classification system. Obese class I, II and III were defined as 30.00-34.99, 35.00-39.99, and $\geq 40 \text{ kg/m}^2$, respectively.

LV mass by Magnetic Resonance Imaging and LVH: The cardiac MRI scans were performed on 5004 (73.4%) participants with specific protocol and analysis methods in MESA utilizing 1.5-T magnets, a median of 16 days after the baseline evaluation, as previously described³⁰. The intra-class correlation for left ventricular (LV) mass in MESA has been previously reported²⁸.

Pulse Pressure Measures: Pulse pressure was calculated from brachial artery pressure readings and by radial artery tonometry. Brachial artery pulse pressure (PPb) was calculated as the difference of the average verified systolic BP and diastolic BP measured by oscillometric sphygmomanometry. Arterial waveforms were measured with the HDI/Pulse Wave CR2000 (Hypertension Diagnostics, Inc., Eagan, Minnesota)³¹. The pulse contour was recorded with a solid-state pressure transducer array (tonometer) after

placing it over the radial artery of the dominant arm. An automated oscillatory blood pressure measurement supplied by the HDI/Pulse Wave CR2000 was performed in the contra-lateral arm to calibrate the device before, during and after the waveform assessment. A 30 second analog tracing of the radial waveform was digitized at 200 samples per second, excluding the dicrotic notch, once a calibrated measurement was obtained. A typical waveform for each participant was estimated by self-modeling regression.^{32, 33} The radial pulse pressure (PPr), used in the analysis, was estimated by taking the difference between the maximum of the typical waveform and the first upward deflection of the typical waveform of all tracings within a 30 second period for each participant.

Study End Points: At intervals of 9 to 12 months, a telephone interviewer contacted each participant (or representative) to inquire about all interim hospital admissions, cardiovascular outpatient diagnoses, and deaths. In addition, MESA identified additional medical encounters through cohort visits, participant call-ins, medical record abstractions or obituaries. Next of kin interviews were also obtained for out of hospital cardiovascular deaths. Median follow-up time was 4.0 years (interquartile range: 3.1 to 4.2 years). Medical records and information were successively obtained on an estimated 98% of hospitalized cardiovascular events and 95% of outpatient cardiovascular diagnostic encounters. Two physicians reviewed all data independently for assignment of event dates and end point classification.

The outcome measure for this paper was clinical CHF which included patient complaints of shortness of breath or lower extremity edema. In addition to symptoms, clinical CHF required a diagnosis by a physician, and evidence that the patient received

medical treatment for CHF. Clinical CHF was also diagnosed with or without physician diagnosis but with appropriate patient symptoms when one or more of the following criteria were present: 1) pulmonary edema/congestion by chest X-ray 2) dilated ventricle or poor LV function by echocardiography or ventriculography; or 3) evidence of left ventricular diastolic dysfunction. Participants not meeting any criteria, including only a physician's diagnosis of CHF without any other evidence, were considered as having no CHF. The diagnosis of myocardial infarction required either abnormal cardiac biomarkers, CK-MB or troponin -I, (2 times the upper limit of normal) regardless of pain or ECG findings; evolving Q waves regardless of pain or biomarker findings; or a combination of chest pain, and ST-T evolution or new LBBB.

Statistical analysis: Data was presented as number (percentage) for categorical variables and mean +/- standard deviation (SD) for continuous variables. Fisher's exact tests were used and χ^2 tests were used for categorical variables. Two-sample t-tests were used for continuous variables. Participants that did not have radial arterial tonometry measured or SBP measured were excluded based on our a priori analysis plan. Also a priori, participants who had missing data on a variable needed for a particular model were excluded from the analysis.

Multivariable analyses were performed using Cox proportional hazards regression models. PPb, DBP, SBP, and PPr were included as continuous variables, and the hazard ratio (HR) and 95% CIs (CI) were calculated for each incremental standard deviation increase in these blood pressure measures. Four sets of models were used: model 1: unadjusted analyses; model 2: adjusted for established risk factors of CHF, which include age, gender, diabetes, BMI, low density lipoprotein, current cigarette smoking,

angiotensin converting enzyme (ACE) inhibitor use, angiotensin receptor blocker (ARB) use, glomerular filtration rate, and urine albumin/creatinine; model 3: adjusted for the established risk factors included in model 2 plus LV mass measured by MRI; and Model 4: adjusted for the established risk factors included in model 2 plus ECG LVH. To determine if PPb, PPr, DBP, or SBP predicted CHF independent of an interim MI during follow-up, additional analyses were performed adding interim MI as a time-varying covariate to model 2 (model 5). Variables that strongly correlated with each other such as PPb, PPr, SBP, DBP and hypertension, were not entered into these models simultaneously. Proportionality of hazards was evaluated visually by examining the linearity of $\log[-\log S(t)]$ versus $\log t$ plots. The 11 % of participants who were lost to follow up were censored at the time of last follow-up. To evaluate how much the association of BP measures with incident CHF was related to LV mass or LVH by ECG we compared the regression coefficient for these BP measures before and after adjusting for these variables (Model 3 and Model 4). Cumulative hazards of CHF by various BP measures split on their respective medians were illustrated and were compared using the log-rank test. Statistical analyses were performed using SAS version 9.1 software (SAS Institute Inc, Cary, NC) and statistical significance was declared at $p < 0.05$.

Results

Five thousand seven hundred and sixty-three participants completed radial arterial tonometry. Of the 6814 participants in MESA, 15.4% did not undergo radial arterial tonometry. Of these, 46% (out of 1051) did not complete radial tonometry for unknown reasons, 44% were missing due to poor segmentation (data inadequate for analysis), and 9.7 % due to inability of the summary model to converge. Compared to participants not

included in the analysis (n = 1051), the 5763 participants that were included were younger (62 vs. 65 years), and had lower cuff (54 vs. 57 mmHg). Also, the included participants had a larger proportion of Chinese (13% vs. 7%), Hispanics (23% vs. 16%), a lower proportion of African Americans (27% vs. 34%), and a lower proportion of hypertensives (44% vs. 51%) (all differences significant at a $p < 0.05$).

Baseline Characteristics. The distribution of baseline characteristics of the 5763 participants who completed radial tonometry by gender is shown in Table I. Reflecting the lack of clinically overt cardiovascular disease in this cohort at baseline, there was a relatively low prevalence of LVH by ECG, chronic kidney disease, diabetes, and albuminuria at baseline. Sixty-two out of 5,763 MESA participants with tonometry developed CHF during follow-up. Participants who developed CHF were more likely to have been older, male, hypertensive, obese, diabetic, current smokers, diagnosed with LVH on ECG, have increased left ventricular mass, an elevated urine albumin/creatinine, or have a decreased GFR. (Table II). At the end of follow-up 26 % of the participants who had a myocardial infarction developed CHF. During this time, only 0.7% of the participants who did not have a myocardial infarction developed CHF. Of the participants that completed an MRI exam at baseline (74.2%), 98.4% had an LVEF of \geq 50% and this proportion was 85.7% among the 42 participants who developed CHF and had an MRI performed at baseline.

The association of blood pressure parameters and incident CHF. The cumulative hazard of CHF by the various blood pressure parameters are shown in Figure 1. Higher PPb, SBP, and PPr, but not DBP were associated with incident CHF. Compared to the plots of SBP, DBP and PPb, there was an early and consistent separation of CHF

risk for > 50 percentile vs. ≤ 50 percentile PPr. The results of the multivariable Cox proportional hazards models are shown in Table III. Increasing PPb, SBP and PPr but not DBP were significant predictors of CHF in the unadjusted model (Table III, model 1). Increasing PPb and SBP were not significantly associated with CHF, (Table III, model 2) after adjusting for established risk factors. Increasing PPr remained a significant predictor for CHF after adjustment for established risk factors (model 2). After adjusting for increasing LV mass or a diagnosis of ECG LVH in addition to established risk factors (model 3 and 4), the association between increasing PPr and CHF was no longer present (model 3) or significant (model 4). Interim MI during follow up was associated with a significant increase in incident CHF (HR 37.8; 95% CI 21.9-65.6). After adding interim MI to model 2 (model 5), PPr was no longer a significant predictor for CHF.

Discussion

This study shows associations between various blood pressure measures including a novel measure of PP at the radial artery using tonometry. We demonstrate that PP measured by radial arterial tonometry, but not brachial cuff PP, SBP, or DBP, is a significant predictor of incident CHF after adjustment for established CHF-related risk factors excluding measures of LV mass or hypertrophy and incident MI. We also demonstrate that baseline LV mass or ECG LVH attenuates the association between increasing PPr and CHF suggesting increasing LV mass or LVH may be in the causal pathway between PPr and CHF.

Surrogate Measures of Arterial Stiffness

Pulse pressure, measured by brachial blood pressure cuff is a surrogate measure of proximal arterial stiffness. This can place increased workload on the heart leading to increased LVM^{28, 34}. Measures obtained from aortic pulse pressure waveforms derived from radial arterial tonometry have been suggested to be superior measures of arterial stiffness compared to pulse pressure by blood pressure cuff. Specifically, one of the most common methods of estimating arterial stiffness is proximal pulse-wave analysis. Individual and generalized inverse transfer functions are used to recreate the aortic waveform from radial tonometry. This analysis has been validated with invasive and direct measurements of the aortic waveform³⁵⁻³⁷ with the assumption that the aortic pressure waveform is a component of a forward pressure wave created by a ventricular contraction and a reflective wave returning from the periphery from branch sites in the periphery. Many investigators have suggested that in the setting of arterial stiffness these reflected waves arrive back faster to the aorta adding to the forward wave and augmenting the systolic pressure. This augmented aortic systolic pressure is felt to be a major pathologic feature in arterial stiffness and is defined as the difference between the second and the first systolic peaks of the waveform expressed as a percentage of the pulse pressure. Previous studies have suggested that the best non-invasive measure of circulatory arterial stiffness is forward pulse wave velocity but these findings have recently been questioned¹⁹⁻²¹. In addition, using measures from the radial arterial waveform without deriving an aortic pulse pressure waveform has recently been suggested³⁸. Compared to PPb, radial arterial tonometry does not require the use of an occlusive cuff and thus does not significantly alter the hemodynamic status of the underlying artery. Also, arterial tonometry allows for continuous monitoring of the

pressure wave contour on a beat by beat basis over a period of time which may improve the precision of the sample.

Arterial Stiffness Measures and Cardiovascular Events

Aortic pulse wave velocity is generally considered to be the gold standard non-invasive measure for arterial stiffness but its prognostic significance and the difficulties with its precision has questioned this position. For example, Hansen and colleagues investigated the prognostic significance of aortic pulse wave velocity (APWV) compared to office PP and 24 –hr ambulatory PP in a general Danish population, aged 40 - 70 years, (n = 1678), in the Monitoring Trends and Determinants in Cardiovascular Disease (MONICA) health survey over a median follow-up of 9.4 years. After adjusting for age, sex, BMI, MAP, smoking, and alcohol intake; APWV was significantly related to a composite of cardiovascular endpoints including cardiovascular mortality, coronary artery disease, and stroke, whereas office and 24-hour PP lost their predictive value. However, after risk factor adjustment, office PP related more strongly to coronary heart disease (HR 1.30, CI 1.04-1.61) compared to APWV (HR 1.16, CI 1.00-1.35) for every SD increase in these measures. Also, even though this measure is regarded by some as the gold standard for measuring arterial stiffness, there are significant limitations. First, in patients with obesity, diabetes and peripheral artery disease the femoral pressure waveform may be difficult to record accurately³⁹. Second, large bust size in women can make distance measurements inaccurate. Third, abdominal obesity, especially in men, also make distance measures inaccurate³⁹. Lastly, the pressure wave may be attenuated and delayed in the presence of aortic, iliac, or proximal femoral stenosis. With these limitations in mind, in addition to an ongoing debate as to whether pulse wave velocity is

within the pathologic pathway of arterial stiffness and cardiovascular events, a more potentially reliable, noninvasive measure of arterial stiffness should be considered^{21, 40, 41}.

Intra-arterial PP, Target End-Organ Damage, and Cardiovascular Events

Animal and clinical studies have suggested that elevated PP strongly predicts significant changes in small vessel arterial structure, which may explain its predictive value for cardiovascular events. Rizzoni and colleagues demonstrated that higher media to lumen ratio of small resistance arteries, an index of structural alteration in the microcirculation, was one of the strongest predictors of cardiovascular events in a selected high-risk population after adjusting for cardiovascular risk factors⁴². In addition, in this study, only brachial pulse pressure provided additional predictive value for cardiovascular events. De Ciuceis and colleagues demonstrated that a higher media to lumen ratio predicted fatal cardio-cerebrovascular events and nonfatal cardiovascular events after adjusting for known cardiovascular risk factors in a medium –risk patient population⁴³. Further, James and colleagues investigated the relation between blood pressure measures and media to lumen ratio in a population of adults older than 60 years of age. They found that clinic and ambulatory PP were the only significant predictors of media to lumen ratio independent of age, other parameters of clinic blood pressure including brachial MAP, SBP, DBP, and blood pressure variability⁴⁴. Christensen and colleagues measured intra-arterial blood pressures measures in spontaneously hypertensive rates at the level of the infra-renal abdominal aorta and found that 81% of the variation in media to lumen ratio could be accounted for by intra-arterial 24-hour PP, 24-hour MAP, and 24-hour heart rate. In addition, intra-arterial PP was the major associated factor with media to lumen ratio and intra-arterial PP was the only significant

correlate to media thickness⁴⁵. Khattar and colleagues in a retrospective study of hypertension clinic patients followed for 9.4 years, showed similar findings. They showed that 24-hours brachial intra-arterial PP compared to intra-arterial SBP and intra-arterial DBP was the strongest hemodynamic determinant of increased intima-media thickness of the carotid artery, and increased LV Mass index. They suggested that PP may be a strong determinant of small and large vessel smooth muscle growth; and left ventricular hypertrophy⁴⁶. Clinical use of arterial tonometer at the radial site has been validated in humans studies with intra-arterial radial pulse measures in a heterogeneous group, aged 17 to 79 years with excellent amplitude correlations⁴⁷.

Strengths and Limitations

Major strengths of this study include the sample size, detailed documentation of imaging and clinical measures, and the higher percentage of follow-up data obtained. There are, however, several limitations to this study. Brachial cuff pressure was used both to calibrate the tonometer and to measure brachial pulse pressure. The calibration may have affected the absolute pulse pressure values measured by radial arterial tonometry. Second, radial tonometry was only performed on 84.6% of the participants and this subgroup was healthier than the group who did not have radial tonometry performed. Third, because BP measures, LV mass and LVH were measured at relatively the same time, the conclusions regarding the possible mechanistic role higher LV mass/LVH has in the association of PPr with CHF should be interpreted cautiously.

Conclusions

Higher pulse pressures measured by radial arterial tonometry are independently associated with incident CHF in this cohort compared to SBP, DBP or pulse pressure measured by brachial blood pressure cuff when the distribution of baseline MRI LV Mass/ECG LVH and incident MI are not considered. This association between increasing radial pulse pressure and incident CHF is attenuated by LV mass and LVH suggesting their importance in the causal pathway of this association. Further studies in other populations are needed to determine the importance of radial arterial pulse waveform measures including pulse pressure in the prognosis of cardiovascular events.

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Table I. Distribution of Baseline Characteristics of 5763 Participants who Completed Radial Tonometry by Gender

	Women (n = 3032)	Men (n = 2731)
Age, yrs	62.3(10.2)	62.2(10.2)
Ethnicity, n (%)		
African American	848 (28.0)	696(25.5)
Hispanics	688(22.7)	635(23.3)
Caucasians	1117 (36.8)	1053(38.6)
Chinese Americans	379(12.5)	347(12.7)
Diabetes classification, n (%)		
Normal	1939(64.0)	1424(52.1)
IFG	701(23.1)	885(32.4)
Diabetes	392(12.9)	422(15.5)
Hypertension, n (%)	1396(46.0)	1165(42.7)
Systolic blood pressure (mm Hg)	126.7(23.1)	125.7(19.0)
Mean arterial pressure (mm Hg)	88.4(13.1)	92(11.4)
Diastolic blood pressure (mm Hg)	69.2(10.2)	75.2(9.3)
Cigarette smoking, n (%)		
Never	1813(60.0)	1140(41.8)
Former	870(28.8)	1200(44.0)
Current	341(11.3)	385(14.1)
LVH by electrocardiography, n (%)	18(0.6)	39(1.4)
LV Mass (g)	123.2(27.1)	168.4(36.9)
Body Mass Index (kg/m ²)		
Normal	929(30.6)	733(26.8)
Class 1 Overweight	1035(34.1)	1239(45.4)
Class 2 Overweight	906(29.9)	716(26.2)
Class 3 Overweight	162(5.3)	43(1.57)
LDL (mg/dl)	118(32.0)	117(31.0)
ACE inhibitor use	359 (11.8)	387(14.2)
ARB use	185(6.1)	108(3.95)
Glomerular filtration rate (mL/min/1.73 m ²)		
< 60	327(10.8)	204(7.5)
≥ 60	2705(89.2)	2527(92.53)
Urinary albumin/creatinine (mg/g)		
≤ 30	2766(91.2)	2466(90.3)
> 30 - 300	227(7.5)	220(8.1)
> 300	39(1.3)	45(1.7)
Myocardial Infarction during follow-up, n (%)	13(0.43)	54(2.0)
Incident Symptomatic CHF, n (%)	24(0.79)	38(1.39)

For continuous variables, mean values +/- standard errors are shown. Percentages for continuous variables are shown in parentheses. All the participants with symptomatic CHF or any other kind of cardiovascular disease at baseline were excluded from the study. Impaired fasting glucose (IFG) was defined as fasting glucose of 100 to 125 mg/dl. Mean arterial pressure (MAP) = 2/3 x diastolic blood pressure + 1/3 x systolic blood pressure. LV mass was measured by MRI

Table II. Univariate Analyses with Means and Proportions of Covariates by Congestive Heart Failure Status at the End of Follow-up

	No CHF (n=5696)	CHF (n=62)	P value	Unadjusted Odds Ratio	Confidence Intervals (95%)
Age, yrs	62.2 (10.1)	69.4 (8.9)	<0.0001		
Gender					
Female	3006/3030 (99.21)	24/3030 (0.79)	0.0274	1.77	1.06 – 2.96
Male	2690/2728 (98.61)	38/2728 (1.39)			
LV Mass (g)	144.3 (38.8)	188.6 (60.0)	<0.0001		
Ethnicity, n (%)					
Hispanics	1304/1322 (98.64)	18/1322 (1.36)	0.2185	1.0	
African American	1524/1543 (98.77)	19/1543 (1.23)		0.903	0.470 – 1.741
Caucasians	2145/2167 (98.98)	22/2167 (1.02)		0.743	0.397 – 1.391
Chinese Americans	723/726 (99.59)	3/726 (0.41)		0.301	0.070 – 0.892
Diabetes classification, n (%)					
Normal	3336/3361 (99.26)	25/336 (0.74)	0.0004	1	
IFG	1568/1586 (99.87)	18/1586 (1.13)		1.532	0.833 – 2.816
Diabetes	792/811 (97.66)	19/811 (2.34)		3.201	1.754 – 5.842
Hypertension					
No	3183/3199 (99.5)	16/3199 (0.50)	<0.0001	3.64	2.06 – 6.45
Yes	2513/2559 (98.20)	46/2559 (1.80)			
Cigarette smoking, n (%)					
Never	2931/2951 (99.32)	20/2951 (0.68)	0.0045	1	
Former	2039/2067 (98.65)	28/2067 (1.35)		2.012	1.131 – 3.582
Current	712/726 (98.07)	14/726 (1.93)		2.882	1.449 – 5.734
LVH by ECG, n (%)					
No	5616/5670 (99.05)	54/5670 (0.95)	<0.0001	14.86	6.43 – 34.3
Yes	49/56 (87.50)	7/56 (12.5)			
Body Mass Index (kg/m²)					
Normal	1646/1661 (99.10)	15/1661 (0.90)	0.0472	1	
Class 1 Overweight	2253/2274 (99.08)	21/2274 (0.92)		1.023	0.526 – 1.990
Class 2 Overweight	1598/1618 (98.76)	20/1618 (1.24)		1.373	0.701 – 2.692
Class 3 Overweight	199/205 (97.07)	6/205 (2.93)		3.309	1.269 – 8.625
LDL (mg/dl)	117.3 (31.5)	117.4 (30.6)	0.9890		
Glomerular filtration rate (mL/min/1.73 m²)					
< 60	515/530 (97.17)	15/530 (2.83)	<0.0001	3.14	1.77 – 5.59
≥ 60	5181/5228 (99.10)	47/5228 (0.90)			
Urinary albumin/creatinine (mg/g)					
≤ 30	5181/5227 (99.12)	46/5227 (0.88)	<0.0001	1	
> 30 - 300	435/4471 (97.32)	12/447 (2.68)		3.107	1.634 – 5.909
> 300	80/84 (95.24)	4/84 (4.76)		5.632	1.98 – 16.02
Myocardial Infarction during follow-up, n (%)					
No	5646/5690 (99.23)	44/5690 (0.77)	<0.0001	46.2	25.0 – 85.4
Yes	50/68 (75.53)	18/68 (26.47)			

Categorical data were reported as proportions (%) and continuous data as mean values with standard deviation (SD). CHF = congestive heart failure, IFG = impaired fasting glucose, LV = left ventricular, LVH = left ventricular hypertrophy, ECG = electrocardiogram. P values represent tests by Chi-square or Fisher exact test for categorical variables and test for means between groups by independent t-tests for continuous variables. Odds ratio were calculated using the Mantel-Haenszel method.

Table III. Unadjusted and Adjusted Hazard Ratios for Symptomatic CHF in relation to Blood Pressure Measures in the MESA study (n = 5763)

BP Measures (mm Hg) scaled to SD	Hazard Ratios (95% Confidence Interval)				
	Model 1: Unadjusted	Model 2: Adjusted for established risk factors*	Model 3: Model 2 + adjustment for LV Mass	Model 4: Model 2 + adjustment for EKG LVH	Model 5: Model 2 + adjustment for MI (time-dependent)
PPb	1.627 (1.333-1.986)	1.172 (0.906-1.516)	1.047 (0.771-1.422)	1.116 (0.858-1.453)	1.132 (0.857-1.495)
DBP	1.197 (0.938-1.527)	1.096 (0.852-1.410)	0.891 (0.652-1.218)	1.025 (0.795-1.321)	1.099 (0.846-1.428)
SBP	1.627 (1.319-2.007)	1.173 (0.917-1.502)	0.983 (0.730-1.324)	1.096 (0.852-1.410)	1.141 (0.880-1.479)
PPr	1.634 (1.362-1.961)	1.289 (1.020-1.628)	0.999 (0.722-1.381)	1.240 (0.979-1.570)	1.172 (0.920-1.493)

Hazard ratios were calculated for one standard deviation increase in blood pressure measures. *Age, gender, BMI, cigarette smoking status (2 degrees of freedom), LDL, angiotensin receptor blockade use, angiotensin converting enzyme inhibitor use, GFR, urine albumin/creatinine, diabetes mellitus. PPb = pulse pressure measured by blood pressure cuff, BP = blood pressure, DBP = diastolic blood pressure, SBP = systolic blood pressure, PPr = pulse pressure measured by radial arterial tonometry. NS = not significant.

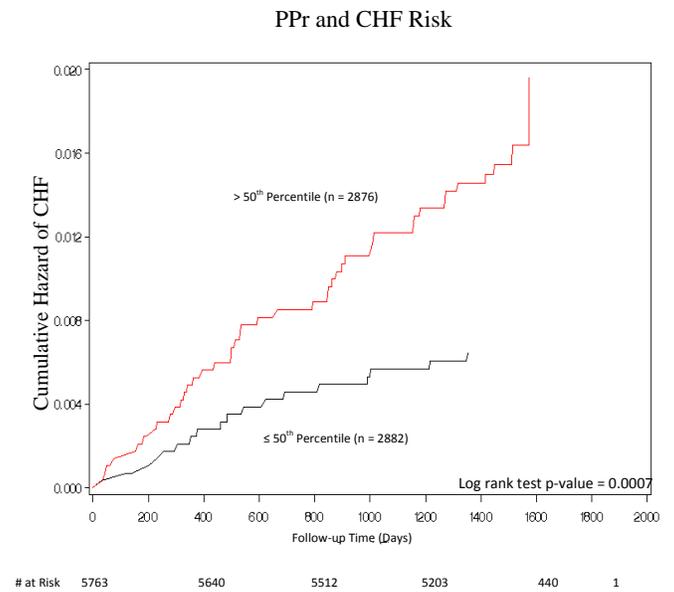
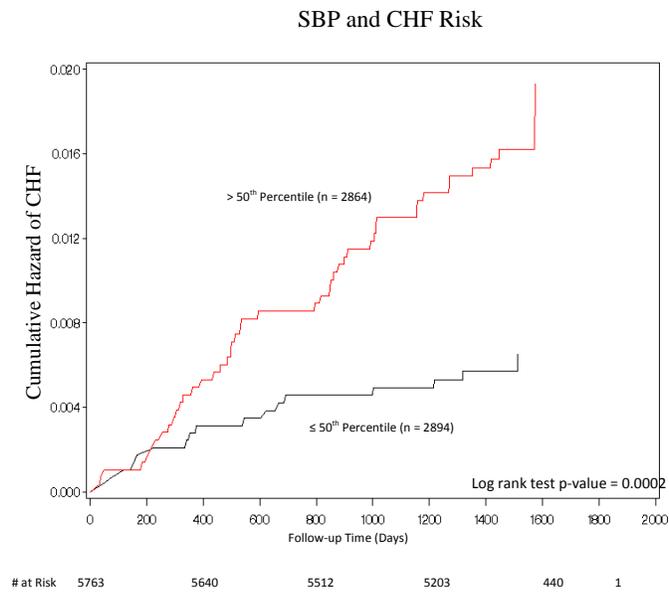
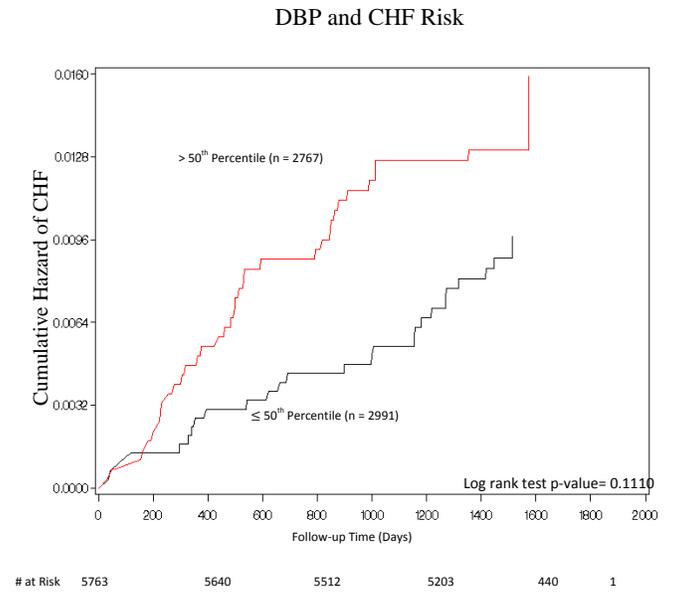
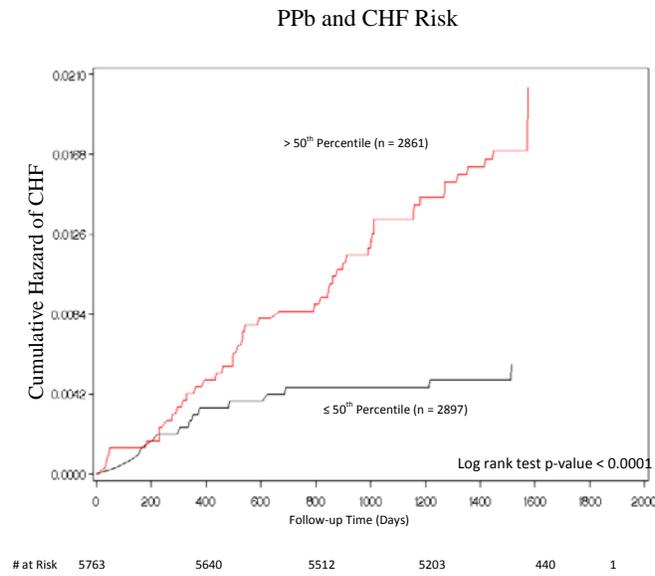


Figure 1. Cumulative Hazard of CHF by Categories of Blood Pressure Measures in the MESA (Multi-Ethnic Study of Atherosclerosis). The 50th percentiles for PPc, DBP, SBP, PPr were 50.00, 72.00, 123.00, 56.45 mmHg, respectively.

CHAPTER IV

Discussion of one of the Methods used to Summarize Participant Pulse Waveforms: Regression Splines to Summarize Arterial Pulse Pressure Waveforms

The arterial pulse is any cyclic ebb and flow generated by the heart with its frequency being the same as the heartbeat. During systole, left ventricular contraction pushes blood into the ascending aorta. Properties of the arterial pulse can be summarized well by describing the flow of the arterial pulse, the pressure pulsations, and the diameter changes caused by the pulsations in the arteries throughout the body. As blood flows from the heart into the descending aorta, a pressure wave is generated. This pressure wave is then propagated distally to arterial branches throughout the body. The lower and upper limits of the pulsatile pressure fluctuations of a peripheral artery are usually between 40 to 80% of the mean pressure within that artery, respectively. The arterial pulse pressure waveform is an uninterrupted measure of blood pressure throughout the entire cardiac cycle or over multiple cycles. The contour of this waveform is best appreciated when plotted over time. When the arterial pulse is measured in this way, it provides information not only on the pressure wave initiated by the ejection of blood from the heart, but also measures the pressure waves reflected from multiple branch sites in the arterial system. In our studies, the pulse pressure waveform was measured by radial arterial tonometry as described in the Introduction. Previous summary methods of peripheral pulse pressure waveforms have concentrated on reconstructing the aortic pulse pressure waveform, but these

methods have been heavily criticized with the most important criticism being the relatively poor correlation of values during validation^{1,2}.

Investigators in the Multi-Ethnic Study of Atherosclerosis (MESA), a prospective multi-center study, used a method called self modeling regression (SEMOR) to summarize these pulse pressure waveforms^{3,4}. The SEMOR model has some important assumptions. First, it is assumed that all the curves from an experimental unit, for example 30 of the observed curves measured for a single participant over 30 seconds at a heart rate of 60 beats per minute, have the same typical shape. Second, the observed curves have a typical shape only after separately transforming the x and y axes for the observed curves in a parametric manner (curve-specific transformation modeled as random) and then modeling these values with a non-parametric function. Third, the non-parametric function most suitable for a curve is a cubic regression spline.

The Regression Spline

Regression analysis has many forms. One of these is spline regression which is comprised of a family of methods. These methods include dummy variable analysis, time counters, intervention analysis, interrupted time series, and piecewise linear models. The notion of the spline originated from the drafting technique of using a thin, flexible strip called a spline to draw smooth curves through a set of points. To explain how spline regression can be useful consider the following. Let us assume that a continuous variable, Y , appears to change its course over time due to some event. For example, Y (the daily Dow Jones

industrial average index price) can demonstrate a steady rise over many days and then drop because of the announcement by the Federal Reserve Bank of a change in interest rates. If the price drop is abrupt then it may be appropriate to use the interrupted time series spline model, which is efficient in accounting for intercept shifts. However, if the price drops gradually with time, a “smoothing” spline model is more appropriate because it is able to capture the slope change smoothly when it connects two regression lines without interruption. If we define our variable, $Y = a + bT + cD(T - T_1) + e$, (Equation 1) where Y is the daily Dow Jones industrial average index price, T is the time counter across days in the series, $1, 2, \dots, N$; and D is a dummy scored 0 in the days before the interest rate change and 1 for the days afterward. T_1 is the count corresponding to the day of the interest rate change so that $D(T - T_1) = 1, 2, 3, \dots$ is a count of the number of days since the rate change. If, for example, the “spline knot,” the time when interest rates are changed, was October, 12th, 2007; then the estimation of the model, would yield two regression lines, one before, r_1 , and one after, r_2 , October, 12th, 2007, with no jump or break in the trend. Thus, spline regression is a family dummy variable models with a few basic restrictions placed on them. For the example above, if the dummy variable model was unrestricted, the slopes and the intercepts of the Dow Jones industrial index, before and after the interest rate change, would be very different. The restrictions avoid the inappropriate break seen when joining the 2 regression lines, r_1 and r_2 , in a time trend. This type of spline model is called a piecewise linear regression. Piecewise linear spline regression will be discussed in further detail as it highlights a major technique

used in spline regression. Pindyck and Rubinfeld described splines as a piecing together of two or more linear regressions.⁵ These regressions are composed of a continuous explanatory variable defined over specified segments of the domain of that variable and a dependent variable that is a continuous function of that explanatory variable over all segments, but with different slopes in each of the separate segments. The regression line slopes in the different segments are discontinuous even though the function is continuous. The point of discontinuity describes the knot locations which are breaks in the continuous function. Thus spline regression models are used when a regression line is broken into a number of line segments separated by knots. The assumed true regression line changes direction at these join points, but does not break like the raw data at these points. These techniques will work well for functions that do not instantaneously increase or decrease with time but that increase or decrease gradually. So splines are used to demand continuity restrictions at the join points so that the regression line can change direction without inappropriate breaks in the line at those join points. Depending on the shape of certain regression curves, piecewise linear spline regression models can have a much better fit than linear regression models or polynomial regression models.

In general, spline regression models are simpler when the spline knots are few and known in advance. For our purposes, the pulse wave has relatively few knots of known number because the pulse wave has a typical shape. They are, however, in unknown locations. When the knot locations are unknown they have to be estimated from the data. Indeed, estimating the location of a spline knot can

be very useful. For example, the location of a spline knot may be able to forecast when a bull stock market becomes a bear stock market. The regression model must take on nonlinear parameters when knot locations are unknown and nonlinear estimation methods such as nonlinear least squares must be used. In an example given by Marsh and Cormier, strength of commitment to religion is the continuous explanatory variable and a person's age is used instead of time, which is the dependent variable⁶. They tried to determine whether or not the importance of religion in daily life changes over a lifecycle. That is, does a person's age affect the importance of religion to him or her? They assumed that this relation was best described by a regression spline and that there were three points in a person's life when the emphasis on the importance of religion took place. They then formulated an appropriate continuous, interval data measure of the importance of religion in a person's life. Specifically, they used data from the 1996 American National Election Survey and started with a binary response to a survey question that asked if religion is an important part of their lives. A total of 1178 respondents replied important, whereas 319 said not important. Logistic regression was performed of this binary response on the responses from a set of other questions (eight of them) that measured religious involvement and commitment. They then used the predictive value of estimated probability of answering "important" to this question as a continuous, interval measure. The predicted values from this logistic regression demonstrated that the eight questions did a good job of explaining the importance of religion in people's lives. This enabled them to use the predicted values from this logistic regression as a

continuous interval measure of the importance of religion and its association with a person's age in a spline regression model. Hints on the location of the spline knots and the shape of the curve can be found using the predicted values from this logistic regression. A more detailed explanation of spline knot location is as follows⁶. Estimation of a spline regression with unknown knot location involves estimating not only the usual regression coefficients, but also the knots, K_1, K_2, \dots, K_N . This must be performed using the nonlinear least squares regression, because there will be terms in the model that involve the product of these spline knot parameters and the usual regression coefficients. These terms can be regarded as cross-product terms from the interaction between spline knot parameters and the regression coefficients. This model can be estimated as follows: $Y_i = a + b_0 * \text{age}_i + b_1 * D_{1i} * (\text{age}_i - K_1) + b_2 * D_{2i} * (\text{age}_i - K_2) + b_3 * D_{3i} * (\text{age}_i - K_3) + e_i$, (Equation 2), where Y_i is your measure of the importance of religion, a and b are regression coefficients, e_i is the error term for the i th individual. D is previously defined after Equation 1. In order to highlight the cross-product terms, the above equation can be rewritten as follows: $Y_i = a + b_0 * \text{age}_i + b_1 * D_{1i} * \text{age}_i - b_1 * K_1 * D_{1i} + b_2 * D_{2i} * \text{age}_i - b_2 * K_2 * D_{2i} + b_3 * D_{3i} * \text{age}_i - b_3 * K_3 * D_{3i} + e_i$. The three cross product terms $b_1 * K_1, b_2 * K_2$, and $b_3 * K_3$ demand that we use nonlinear regression methods to estimate the eight regression parameters $a, b_0, b_1, K_1, b_2, K_2, b_3$, and K_3 . Marsh and Cormier then saw the nonlinear least squares procedure successfully converge after eight iterations using SAS software (SAS Institute Inc, Cary, NC). Their residuals were 1341.427, which was significant, although an F distribution could not be inferred since the

model was not linear. The asymptomatic 95% confidence intervals showed that six of the estimated regression parameters were statistically significant (a , b_0 , b_3 , K_1 , K_2 , K_3) asymptotically at the 5% level of significance or better. Also, their original spline knot locations for age at which the importance of a religion was emphasized changed from 35, 55, and 75 to approximately 30, 45, and 71.

In MESA, a cubic spline regression model was used as the basis of estimating the shape of the radial pulse wave curve. Whether one should use a third-order polynomial or a cubic spline, a second-order polynomial or a quadratic spline depends on the trajectory of the data point curvature. Qingzhi and colleagues give a good description of the construction of this model. First, they describe a procedure called cubic spline interpolation as follows. They note that in performing spline interpolation, the desire is to connect m experimental data points, (x_1, y_1) , (x_2, y_2) , ..., and (x_m, y_m) , by a smooth curve and then divide the curve by those points into $m - 1$ intervals. They then assume, in each interval, that the data points can be represented by a third-order polynomial, $g = a_i + b_i x + c_i x^2 + d_i x^3$, (Equation 3) (where x is the independent variable, g is the dependent variable, and a_i , b_i , c_i , and d_i are parameters for the i th interval. To define $m - 1$ intervals completely, a set number of parameters (a_i , b_i , c_i , and d_i) have to be determined, the amount of which is dependent by the number of experimental data points, m . Specifically the number of parameters is given by $4 \times (m - 1)$. Therefore, $4 \times (m - 1)$ equations are required. The $2 \times m$ equations can be designated by assuming that the above equation is valid for all the data points. The $2 \times (m - 2)$ equation can be designated by assuming that both the first and the

second derivatives of the dependent variable with respect to the independent variable are continuous at each internal data point. One can specify the other two equations by assuming that the second derivative of the dependent variable is zero at two end points, (x_1, y_1) and (x_m, y_m) . After all the $4 \times (m - 1)$ parameters are determined, Equation 3 is used to interpolate any point within an interval.

Despite its usefulness, in general, in describing certain data, cubic spline modeling is useful only when the number of data points is small. If there are many data points and the data points are dense, spline interpolation cannot be used. Cubic spline regression is similar to cubic spline interpolation. The difference between cubic spline regression and cubic spline interpolation is that only a small number of knots are used in cubic spline regression based on the change in the curve of the data point path. In a cubic spline regression model, Equation 3 is replaced by the general equation $g = a + bx + cx^2 + dx^3 + \sum_{i=1}^K D_i a_i (x - x_i)^3$, (Equation 4) where a_i , b_i , c_i , and d_i are parameters, x_i is the location of the i th knot, K is the number of knots (K knots define $K + 1$ regression intervals as end data points are not used as knots), and D_i is the dummy (or indicator) variable defined to be one in a particular range of x and to be zero otherwise. The model equations used for any two adjacent intervals differ only by one term, thus the slight difference in model equations for two adjacent intervals is created. This allows the curve predicted by the cubic spline regression model to be very smooth⁷.

There are many advantages to modeling curves in this manner. Regression splines, their summary measures, derivatives and integrals are simple to compute.

In the case of pulse waveforms, the intercept, or first upward deflection, of the typical shape is an estimation of minimum diastolic blood pressure. The integral function of the curve is an estimate of mean arterial pressure. Also, this method is also able to capture the variance components of the pulse waveforms which may represent the short-term amplitude variability of systolic blood pressure, a novel measure that should be studied for prognostic significance^{8,9}. In the MESA cohort 5,866 of the 6,814 participants underwent radial arterial tonometry (see results of paper in chapter 2). Of these, the summary SEMOR model failed to converge in 102 participants (1.7%). This occurred when the waveforms over 30 seconds were very unstable.

In conclusion, self modeling regression with regression splines and random curve-specific parameters was applied for the analysis of the arterial pulse pressure waveforms in MESA to capture the variability contained in 30-40 seconds of measuring time and also helped to summarize each participant's waveform on one typical curve.

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PUBLICATIONS:

1. CME questions for select chapters of ACP Medicine 2006 (Dale D et al. ACP Medicine, 2006 Edition).
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