Published in final edited form as:

Am Heart J. 2010 June ; 159(6): 1081–1088. doi:10.1016/j.ahj.2010.02.024.

Central Aortic Pressure is Independently Associated With Diastolic Function

Sumeet Subherwal, MD, MBA¹, Lisa de las Fuentes, MD², Alan D. Waggoner, MHS², Sharon Heuerman, RN², Karen E. Spence, MS², and Victor G. Davila-Roman, MD, FACC, FASE²

¹Duke University, Durham, NC

²Cardiovascular Imaging and Clinical Research Core Laboratory and Cardiovascular Division, Department of Medicine, Washington University, St Louis, MO

Abstract

Background—Studies investigating the association between central aortic pressures and diastolic function have been limited.

Methods—Consecutive ambulatory patients (n=281, mean age 49±13 yrs, 49% male) with normal LV systolic function were included. LV filling pressure (E/Em) was estimated by Doppler-derived ratio of mitral inflow velocity [E] to septal [Em] by tissue Doppler, LV relaxation by Em, central aortic pressures by radial tonometry. Central aortic systolic (cSBP), diastolic (cDBP), mean (cMAP), and pulse pressure (cPP) were entered individually into stepwise linear regression models to determine their association with E/Em or Em.

Results—In univariate analysis, cPP correlated most strongly with E/Em (Spearman's rho=0.45, p<0.001), while cSBP correlated most strongly with Em (Spearman's rho=−0.51, p<0.001). Multivariate analysis demonstrated that the pulsatile component of afterload, cPP, contributed most to E/Em (partial r²=23%); meanwhile the nonpulsatile components (cDBP and cMAP), were significant but small contributors (partial r² of 6% and 5% respectively) of LV relaxation (Em).

Conclusion—The nonpulsatile components of aortic afterload (central mean aortic pressure (cMAP) and central aortic diastolic blood pressure cDBP), exhibited a weak but significant association with LV relaxation, while the pulsatile component of afterload, central aortic pulse pressure (cPP), exhibited strong association with LV filling pressure.

Keywords

diastolic function; pulse pressure; aortic blood pressures

Introduction

Population-based studies demonstrate a strong association between peripheral artery pulse pressure and cardiovascular morbidity, including an increased risk of heart failure, recurrent

Correspondence: Victor G. Davila-Roman, MD, FACC, FASE, Professor of Medicine, Anesthesiology, and Radiology, Director, Cardiovascular Imaging and Clinical Research Core Laboratory, Washington University School of Medicine, Cardiovascular Division, Box 8086, 660 South Euclid Avenue, St. Louis, Missouri 63110, Tel: (314) 362-4748, Fax: (314) 747-8170, vdavila@wustl.edu.

Conflict of Interest. Mr. Waggoner is a consultant for St. Jude Medical and Boston Scientific. Dr. Davila-Roman is a consultant for St. Jude Medical, AGA Medical, Arbor Surgical Technologies, Inc., Boston Scientific, CoreValve Inc., Medtronic, and AtriCure, Inc.; however, such relationships present no conflicts related to the present work. All other authors have no conflicts of interest to declare related to this manuscript.

myocardial infarction, and cardiovascular mortality ¹⁻⁵. Recently, it has been suggested that the central aortic blood pressure exhibits higher predictive risk for cardiovascular disease than peripheral brachial artery blood pressure, since the left ventricle (LV) pumps directly against the afterload in the central arteries ⁶⁻¹⁰.

Central aortic blood pressure is characterized by two main components: a pulsatile and a “steady” nonpulsatile component (Figure 1) ¹¹. The nonpulsatile component is determined by mean aortic pressure (cMAP) and central aortic diastolic blood pressure (cDBP), while the pulsatile component of central aortic blood pressure, the pulse pressure (cPP), is itself determined by two complementary systems: the 2-element Windkessel model ¹² and the propagative properties of the arterial circulation that result in wave reflection (Figure 1) ^{13, 14}. The 2-element Windkessel model describes cPP as being determined by a pulsatile component (i.e. arterial compliance) and partly by a nonpulsatile component (i.e. total peripheral resistance, TPR).

Studies in animal models have shown that increased aortic afterload results in LV diastolic dysfunction, characterized by impaired LV relaxation and increased LV end-diastolic pressure ^{15, 16}. Consequently, elevated central aortic blood pressure may contribute to LV diastolic dysfunction in humans as well. This becomes clinically significant given the high prevalence of LV diastolic dysfunction in patients with hypertension, type 2 diabetes mellitus, obesity, and others diseases ¹⁷. However, studies investigating the association between central aortic pressures and diastolic function have been limited. The present study was designed to test the hypothesis that the pulsatile component of central aortic pressure significantly contributes to left ventricular diastolic function.

Methods

Study Population

Subjects enrolled in this study consisted of 281 consecutive ambulatory subjects aged 21 years and older who volunteered to participate in a phenotype-genotype study of hypertensive heart disease at Washington University School of Medicine. Subjects were recruited through the volunteer research office, flyers posted throughout the medical center, or through word of mouth. Furthermore, subjects are representative of the demographics of the St. Louis Metropolitan area, including proportional representation of race and gender.

All study subjects underwent a complete cardiovascular evaluation after an 8 hour fast, including: 1) history and physical examination; 2) heart rate and blood pressure (obtained after 10 min of rest in the supine position and expressed as the average of three consecutive measurements in each arm); 3) measurements of fasting serum glucose and insulin (for those not receiving insulin and/or oral hypoglycemic agents); 4) comprehensive echocardiogram to assess cardiac structure and function; and 5) analysis of central aortic blood pressure and pressure waveform using pulse wave analysis by radial tonometry. Exclusion criteria included: 1) history or findings of cardiovascular disease including heart failure symptoms or systolic dysfunction (LV ejection fraction $\leq 50\%$), significant valvular heart disease (i.e. greater than mild valvular insufficiency or stenosis), hypertrophic cardiomyopathy, evidence of coronary artery disease (defined as history and/or treatment for angina and/or myocardial infarction, history of coronary artery revascularization procedures and/or coronary angiography with $>50\%$ stenosis in one or more of the major coronary arteries, and/or regional wall motion abnormalities on rest echocardiography); 2) serum creatinine >1.4 mg/dL; 3) pregnancy or lactating; 4) major systemic illness (i.e. chronic inflammatory disease, active malignancy, etc.); and 5) current atrial fibrillation (since radial tonometry is not accurate in these patients). The protocol was approved by the Human Research Protection Office at Washington University, St. Louis, Missouri. All subjects provided written

informed consent prior to study enrollment. The authors are solely responsible for the design and conduct of the study, including all study analyses, the drafting and editing of the paper and its final contents.

Systemic hypertension was defined according to Joint National Committee VII (JNC VII) criteria, as a BP $\geq 140/\geq 90$ mmHg and/or current antihypertensive therapy¹⁸. Diabetes was defined according to revised American Diabetes Association criteria, as: a) fasting serum glucose level ≥ 126 mg/dL and/or b) current medical therapy with an oral hypoglycemic agent and/or insulin¹⁹.

Cardiac Structure and Function Analysis

Echocardiographic examination was performed with a commercially available ultrasound system (Acuson Sequoia System C512, Mountain View, CA). LV internal dimensions at end-diastole and end-systole were measured from two-dimensional (2D) guided M-mode images determined in the cross-sectional view. LV end-diastolic and end-systolic volumes were obtained from the apical four and two chamber views to calculate the LV ejection fraction (LVEF)²⁰. Normal LV systolic function was defined as an LVEF $>50\%$ and without evidence of segmental wall-motion abnormalities. LV mass was determined by the 2D area-length method and indexed to the body surface area to derive the LV mass index (LVMI)²⁰. Stroke volume was determined as the product of the LV outflow tract area and the velocity time integral; cardiac output was derived as the product of heart rate and stroke volume²¹. Pulsed-wave Doppler (PWD)-derived transmitral flow indices included the early diastolic (E) velocity²¹. Tissue Doppler imaging (TDI)-derived early diastolic (E_m) myocardial velocities were obtained at the septal mitral annulus from the apical four-chamber view²². All reported echocardiographic measurements represent the average of three consecutive cardiac cycles.

Diastolic Function

The two major components of diastolic function, LV relaxation and LV filling pressures, were derived by echocardiography. TDI-derived E_m is a well-validated measure of LV relaxation^{22–24}, and the ratio of PWD-derived transmitral E-wave velocity to the TDI-derived mitral annular velocity (i.e. E/E_m) provides an estimate of mean LV filling pressure^{23, 25}.

Central Aortic Blood Pressure and Pressure Waveforms

Central aortic pressure waveforms were determined by use of applanation tonometry of the radial artery (SphygmoCor, AtCor Medical, Australia) as previously described and validated^{26–30}. Briefly, subjects were placed in the supine position and after 10 minutes of rest, three brachial artery blood pressure measurements were obtained in each arm using a noninvasive manual sphygmomanometer. The high-fidelity transducer was then placed on the subject's left radial artery and the recorded pressure waveforms were calibrated using an average of the peripheral brachial artery blood pressure. The average of at least two separate tonometric measurements was used for analysis. The applanation tonometry measurements were performed by a research nurse who was blinded to all other results including clinical and echocardiographic information.

The central aortic pressure waveforms were derived using a validated mathematic transformation of the radial pressure waveform^{31, 32}. The central aortic pressure waveforms were used to calculate the various components of aortic blood pressure; cPP was calculated as the difference between the peak central aortic systolic pressure (cSBP) and diastolic pressure (cDBP) (Figure 2), while cMAP was determined by the equation: $cMAP = 2/3 * cDBP + 1/3 * cSBP$.

The association between diastolic function and the three components that make up pulse pressure (e.g. the 2-element Windkessel model and wave reflection, Figure 1) were investigated to determine which components of pulse pressure specifically contributed most to diastolic function 12, 13. Arterial compliance, the pulsatile component of the Windkessel model, was estimated by the ratio of stroke volume to central pulse pressure (SV/cPP) 33, 34. Total peripheral resistance (TPR), the nonpulsatile component of the Windkessel model, was estimated as the central mean aortic pressure divided by cardiac output (cMAP/CO). Central augmented pressure (cAP), which represents the reflective component of the central pressure waveform, was calculated as the difference between the peak pressure and the foot of the reflected wave form (Figure 2). The non-reflected pulse pressure (NRPP) was calculated as the difference between the foot of the reflected wave form and cDBP. The NRPP represents the pulsatile portion of the initial pressure wave that is independent of the reflected wave (i.e. before the reflected wave merges with the forward wave).

Statistical Analysis

Variables were expressed as mean $\pm$ standard deviation. Variables not normally distributed were logarithmically transformed for analysis (i.e., LVMI, E/Em, cPP, and NRPP). Spearman's Rank test was used to test the correlation between indices of afterload with the two major determinants of LV diastolic function, LV filling pressure (E/Em) and LV relaxation (Em). Multivariate linear regression was then used to determine the independent contribution of blood pressure parameters to LV filling pressure and LV relaxation. Central aortic systolic (cSBP), cDBP, cMAP, and cPP were entered individually into stepwise linear regression models that included potential confounding covariates of LV diastolic function (age, sex, BMI, creatinine, LVMI, history of diabetes, smoking, and hypertension). Similarly, the various components that determine pulse pressure (i.e., arterial compliance, TPR, cAP, and NRPP) were then entered into the multivariate regression models individually to determine which of these determinants of pulse pressure were most strongly associated with LV filling pressure or LV relaxation. To test for the effects of collinearity of variables, a VIF analysis was performed; values >10 were considered indicative of collinearity. Statistical analysis was performed using SAS version 9.2 (SAS Inc., Gary, NC). All tests were 2-tailed. P-values for comparisons of variables in univariate analysis and in each regression model were adjusted for multiple comparisons using a Bonferroni adjustment; an adjusted p-value <0.05 was considered significant.

Sources of Funding

This work was supported in part by NIH grants R01HL71782 (V.G.D.-R.), S10RR14778 (V.G.D.-R.), K12RR023249, KL2RR024994, and UL1RR024992 (L.d.l.F.), M01RR00036 (General Clinical Research Center to Washington University) and from the Robert Wood Johnson Foundation (L.d.l.F.) and The Barnes-Jewish Hospital Foundation.

Results

Study Population

The study population consisted of 281 subjects (49% male); a significant percentage of the subjects were hypertensive and/or had type 2 diabetes mellitus (Table 1). The population was relatively overweight, with 72% having a BMI >25 kg/m². As per inclusion criteria, LV systolic function was normal in all.

Correlations of Hemodynamic Parameters with LV Diastolic Function

Central blood pressure parameters (cPP, cSBP, cDBP, cMAP) showed significant correlations with mean LV filling pressures and LV relaxation (Table 2). cPP correlated

most strongly with E/Em (Spearman's $\rho=0.45$, $p<0.001$), while cSBP correlated most significantly with Em (Spearman's $\rho=-0.51$, $p<0.001$). Mean LV filling pressure (E/Em) exhibited positive correlation with the central aortic blood pressure parameters, and inverse correlation with aortic compliance. Conversely, LV relaxation (Em) exhibited inverse correlation with the blood pressure parameters (i.e. cSBP, cDBP, cPP, cMAP) and a positive correlation with aortic compliance.

Independent Contributors of LV Relaxation (Em)

The association between the nonpulsatile components of central aortic blood pressure (i.e., cDBP and cMAP) and LV relaxation (Em) were weak but statistically significant (Table 3); no significant associations were found between the pulsatile components (i.e., cPP and cSBP) and LV relaxation.

Independent Contributors to Mean LV Filling Pressures (E/Em)

Among the central aortic blood pressure parameters, only the pulsatile components of blood pressure (i.e., cPP and cSBP) contributed independently to mean LV filling pressures (E/Em) in multivariate analysis (Table 4); cPP was most strongly associated with E/Em (partial $r^2=23\%$) in multivariate analysis.

In analyses of the association between diastolic function and the various components that make up pulse pressure (e.g. the 2-element Windkessel model and wave reflection, Figure 1), the pulsatile components of the 2-element Windkessel model (i.e., compliance) and the pulsatile components of the central pressure waveform (i.e., cAP, NRPP) were independently associated with LV filling pressures (Table 5). However, the nonpulsatile component of pulse pressure, TPR, was not associated with LV filling pressure in multivariate analysis. The association between the various pulsatile elements of afterload (i.e., cPP, compliance, cAP, NRPP) and LV filling pressure remained statistically significant even after limiting analysis to non-diabetic subjects ($n=219$) (data not shown). To determine whether adjustment for antihypertensive drug therapy weakened the association between indices of central aortic pressures and LV diastolic function, the stepwise linear regression models were repeated to include classes of antihypertensive medication use. The model remained largely unchanged with the hemodynamic parameter remaining significant in all models, even after Bonferroni-adjustment for multiple testing (data not shown).

Discussion

In this ambulatory population with normal LV systolic function, a significant association was found between LV diastolic function and central aortic pressures. The associations between the nonpulsatile components of afterload (represented by cMAP and cDBP) and measures of LV relaxation were weak but significant. The associations between the pulsatile components of afterload (represented by cPP and cSBP), with the more clinically relevant E/Em, a marker of mean LV filling pressure, were modest yet significant. In fact, cPP was noted to be the most significant contributor of LV filling pressure in the multivariate analysis ($r^2=23\%$). The clinical importance of this finding rests in the potential for improving diastolic function (both LV relaxation and LV filling pressures) by lowering central blood pressure, an untested hypothesis that requires further study.

The pulsatile component of central aortic blood pressure (cPP) is determined the 2-element Windkessel model¹² and the propagative properties of the arterial circulation that result in wave reflection (Figure 1) 13, 14. The interaction between these two complementary systems is seen as the left ventricle contracts generating a forward propagating pressure wave that travels through the aorta and arterial tree until partially reflected by the resistance arteries

(small muscular arteries and arterioles). The wave speed is partly influenced by TPR and arterial compliance (the two components of the Windkessel model). In healthy compliant vessels, the reflected wave merges with the next forward wave during diastole. However, in less compliant vessels, such as those found in the elderly, and those with hypertension and/or diabetes, the reflected waves merge earlier with the next forward wave in late systole, thereby augmenting cPP by a value equal to cAP^{35, 36}. It is cPP that the present study found to be the variable that contributed most strongly to mean LV filling pressure.

These findings are further supported by the fact that only the pulsatile components of cPP (i.e. the reflective component of the central pressure waveform [cAP], NRPP, and arterial compliance) contribute independently to LV filling pressure. As expected, the nonpulsatile component of cPP (i.e., TPR) was not an independent contributor to LV filling pressure. The results of the present study may provide mechanistic insight regarding the association between pulse pressure and end-organ damage, particularly diastolic heart failure^{1, 4}.

It has been previously shown that increased afterload and central artery reflected waves contribute to LV hypertrophy. LV hypertrophy is itself strongly associated with LV diastolic filling pressures^{7, 37}. The results of the present study extend upon these findings by demonstrating that the pulsatile components of afterload contribute to LV filling pressure independent of LV mass.

Sharman et. al., investigated the relation between arterial wave properties and diastolic function and found an association between central aortic pulse pressure and diastolic function³⁸. However, this analysis was limited to a diabetic cohort and found that the partial contribution of cPP to E/Em in multivariate analysis was rather small, partial $r^2=3\%$ compared to the partial $r^2=23\%$ found in the present study; these differences may be explained by the different study populations and/or different statistical modeling. The present study not only validated the finding that cPP contributes to E/Em after limiting analysis to the non-diabetic subjects, but in addition expanded upon the work of prior investigators by demonstrating a significant association between the individual components of pulse pressure (i.e. compliance, cAP, NRPP) with LV diastolic function in a heterogeneous patient cohort that included not only diabetics and non-diabetics, but also included subjects with other comorbidities such as hypertension, dyslipidemia, and obesity.

Similar to the study of Borlaug et al., the present study shows that aortic compliance, but not TPR, is associated with LV filling pressure³⁹. However, the present study differed from that of Borlaug et al. in several ways. First, the present study focused primarily on the association of the pulsatile and/or nonpulsatile components of afterload on diastolic function while Bourlaug's study investigated loading sequence and other arterial properties. Second, the present study enrolled a larger study population (281 in present versus 48 in Borlaug). Third, diastolic function was assessed by spectral TDI in the present study rather than by color-coded tissue Doppler as assessed by Borlaug. Also consistent with prior studies in animal models, the present study also found an association between afterload and LV relaxation and demonstrated that the nonpulsatile component of afterload contributes significantly to LV relaxation¹⁶.

Limitations

The present study was observational and cross-sectional, and thus causality cannot be determined; furthermore, long-term clinical events and outcomes were not collected. LV diastolic function (LV filling pressure and LV relaxation) was assessed by echocardiography rather than by invasive measurements, however the noninvasive methods used in the present study have been shown to provide robust assessment of LV diastolic function. Similarly, central pressures were measured using validated noninvasive methods rather than direct

invasive measurement of central aortic pressures. The study population comprised of relatively healthy ambulatory subjects with normal systolic function and thus the findings may not be applicable to other groups, particularly those with systolic and/or diastolic heart failure. The mean BMI in the present study ($29.5 \pm 6.3 \text{ kg/m}^2$) suggests that a large number of subjects were overweight and/or obese, and thus some may have sleep apnea, which has been associated with increased aortic stiffness and diastolic dysfunction^{40, 41}.

Perspectives

The present study shows that the pulsatile component of afterload (cPP) was strongly associated with LV filling pressures in multivariate modeling, and thus provides mechanistic insight explaining the association between pulse pressure and diastolic function. To further confirm the findings of the present study, large clinical trials are needed to test the hypothesis that a reduction in pulsatile blood pressure improves LV filling pressure and thus LV diastolic function independent of LV mass.

Abbreviations and Acronyms

cPP	Central Aortic Pulse Pressure
cSBP	Central Aortic Systolic Blood Pressure
cDBP	Central Aortic Diastolic Blood Pressure
cMAP	Central Aortic Mean Arterial Blood Pressure
cAP	Central Augmented Pressure
NRPP	Nonreflected Pulse Pressure
TPR	Total Peripheral Resistance
LVMI	Left Ventricular Mass Index

References

1. Franklin SS, Khan SA, Wong ND, Larson MG, Levy D. The Framingham Heart Study. Is Pulse Pressure Useful in Predicting Risk for Coronary Heart Disease? *Circulation* 1999;100(4):354–360. [PubMed: 10421594]
2. Sesso HD, Stampfer MJ, Rosner B, Hennekens CH, Gaziano JM, Manson JE, et al. Systolic and Diastolic Blood Pressure, Pulse Pressure, and Mean Arterial Pressure as Predictors of Cardiovascular Disease Risk in Men. *Hypertension* 2000;36(5):801–807. [PubMed: 11082146]
3. Benetos A, Safar M, Rudnicki A, Smulyan H, Richard J-L, Ducimetiere P, et al. Pulse Pressure : A Predictor of Long-term Cardiovascular Mortality in a French Male Population. *Hypertension* 1997;30(6):1410–1415. [PubMed: 9403561]
4. Chae CU, Pfeffer MA, Glynn RJ, Mitchell GF, Taylor JO, Hennekens CH. Increased Pulse Pressure and Risk of Heart Failure in the Elderly. *JAMA* 1999;281(7):634–643. [PubMed: 10029125]
5. Mitchell GF, Moye LA, Braunwald E, Rouleau J-L, Bernstein V, Geltman EM, et al. Sphygmomanometrically Determined Pulse Pressure Is a Powerful Independent Predictor of Recurrent Events After Myocardial Infarction in Patients With Impaired Left Ventricular Function. *Circulation* 1997;96(12):4254–4260. [PubMed: 9416890]
6. Saba PS, Roman MJ, Pini R, Spitzer M, Ganau A, Devereux RB. Relation of arterial pressure waveform to left ventricular and carotid anatomy in normotensive subjects. *Journal of the American College of Cardiology* 1993;22(7):1873–1880. [PubMed: 8245342]
7. Roman MJ, Ganau A, Saba PS, Pini R, Pickering TG, Devereux RB. Impact of arterial stiffening on left ventricular structure. *Hypertension* 2000;36(4):489–494. [PubMed: 11040224]
8. Safar ME, Smulyan H. Coronary ischemic disease, arterial stiffness, and pulse pressure. *American Journal of Hypertension* 2004;17(8):724–726. [PubMed: 15323069]

9. Williams B, Lacy PS, Thom SM, et al. The CI, for the Anglo-Scandinavian Cardiac Outcomes Trial I, Committee CSCaW. Differential Impact of Blood Pressure-Lowering Drugs on Central Aortic Pressure and Clinical Outcomes: Principal Results of the Conduit Artery Function Evaluation (CAFE) Study. *Circulation* 2006;113(9):1213–1225. [PubMed: 16476843]
10. Roman MJ, Devereux RB, Kizer JR, Lee ET, Galloway JM, Ali T, et al. Central pressure more strongly relates to vascular disease and outcome than does brachial pressure: the Strong Heart Study. *Hypertension* 2007;50(1):197–203. [PubMed: 17485598]
11. Jankowski P, Bilo G, Kawecka-Jaszcz K. The pulsatile component of blood pressure: its role in the pathogenesis of atherosclerosis. *Blood Press* 2007;16(4):238–245. [PubMed: 17852092]
12. Stergiopulos N, Westerhof N. Determinants of Pulse Pressure. *Hypertension* 1998;32(3):556–559. [PubMed: 9740625]
13. Dart AM, Kingwell BA. Pulse pressure--a review of mechanisms and clinical relevance. *J Am Coll Cardiol* 2001;37(4):975–984. [PubMed: 11263624]
14. Safar ME, Levy BI, Struijker-Boudier H. Current perspectives on arterial stiffness and pulse pressure in hypertension and cardiovascular diseases. *Circulation* 2003;107(22):2864–2869. [PubMed: 12796414]
15. Gillebert TC, Leite-Moreira AF, De Hert SG. Load Dependent Diastolic Dysfunction in Heart Failure. *Heart Failure Reviews* 2000;5(4):345–355. [PubMed: 11498648]
16. Leite-Moreira AF, Correia-Pinto J, Gillebert TC. Afterload induced changes in myocardial relaxation: A mechanism for diastolic dysfunction. *Cardiovascular Research* 1999;43(2):344–353. [PubMed: 10536664]
17. Fischer M, Baessler A, Hense HW, Hengstenberg C, Muscholl M, Holmer S, et al. Prevalence of left ventricular diastolic dysfunction in the community. Results from a Doppler echocardiographic-based survey of a population sample. *Eur Heart J* 2003;24(4):320–328. [PubMed: 12581679]
18. Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo JL Jr, et al. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: the JNC 7 report. *Jama* 2003;289(19):2560–2572. [PubMed: 12748199]
19. Genuth S, Alberti KG, Bennett P, Buse J, DeFronzo R, Kahn R, et al. Follow-up report on the diagnosis of diabetes mellitus. *Diabetes Care* 2003;26(11):3160–3167. [PubMed: 14578255]
20. Schiller NB, Shah PM, Crawford M, DeMaria A, Devereux R, Feigenbaum H, et al. Recommendations for quantitation of the left ventricle by two-dimensional echocardiography. American Society of Echocardiography Committee on Standards, Subcommittee on Quantitation of Two-Dimensional Echocardiograms. *J Am Soc Echocardiogr* 1989;2(5):358–367. [PubMed: 2698218]
21. Quinones MA, Otto CM, Stoddard M, Waggoner A, Zoghbi WA. Recommendations for quantification of Doppler echocardiography: a report from the Doppler Quantification Task Force of the Nomenclature and Standards Committee of the American Society of Echocardiography. *J Am Soc Echocardiogr* 2002;15(2):167–184. [PubMed: 11836492]
22. Nagueh SF, Middleton KJ, Kopelen HA, Zoghbi WA, Quinones MA. Doppler Tissue Imaging: A Noninvasive Technique for Evaluation of Left Ventricular Relaxation and Estimation of Filling Pressures. *Journal of the American College of Cardiology* 1997;30(6):1527–1533. [PubMed: 9362412]
23. Ommen SR, Nishimura RA, Appleton CP, Miller FA, Oh JK, Redfield MM, et al. Clinical Utility of Doppler Echocardiography and Tissue Doppler Imaging in the Estimation of Left Ventricular Filling Pressures : A Comparative Simultaneous Doppler-Catheterization Study. *Circulation* 2000;102(15):1788–1794. [PubMed: 11023933]
24. Sohn DW, Chai IH, Lee DJ, Kim HC, Kim HS, Oh BH, et al. Assessment of mitral annulus velocity by Doppler tissue imaging in the evaluation of left ventricular diastolic function. *J Am Coll Cardiol* 1997;30(2):474–480. [PubMed: 9247521]
25. Rivas-Gotz C, Khoury DS, Manolios M, Rao L, Kopelen HA, Nagueh SF. Time interval between onset of mitral inflow and onset of early diastolic velocity by tissue Doppler: a novel index of left ventricular relaxation: Experimental studies and clinical application. *Journal of the American College of Cardiology* 2003;42(8):1463–1470. [PubMed: 14563593]

26. Pauca AL, O'Rourke MF, Kon ND. Prospective evaluation of a method for estimating ascending aortic pressure from the radial artery pressure waveform. *Hypertension* 2001;38(4):932–937. [PubMed: 11641312]
27. Van Bortel LM, Balkestein EJ, van der Heijden-Spek JJ, Vanmolkot FH, Staessen JA, Kragten JA, et al. Non-invasive assessment of local arterial pulse pressure: comparison of applanation tonometry and echo-tracking. *J Hypertens* 2001;19(6):1037–1044. [PubMed: 11403351]
28. O'Rourke MF, Adji A. An updated clinical primer on large artery mechanics: implications of pulse waveform analysis and arterial tonometry. *Curr Opin Cardiol* 2005;20(4):275–281. [PubMed: 15956823]
29. O'Rourke MF, Pauca A, Jiang XJ. Pulse wave analysis. *Br J Clin Pharmacol* 2001;51(6):507–522. [PubMed: 11422010]
30. Wilkinson IB, Fuchs SA, Jansen IM, Spratt JC, Murray GD, Cockcroft JR, et al. Reproducibility of pulse wave velocity and augmentation index measured by pulse wave analysis. *J Hypertens* 1998;16(12 Pt 2):2079–2084. [PubMed: 9886900]
31. Chen CH, Nevo E, Fetets B, Pak PH, Yin FC, Maughan WL, et al. Estimation of central aortic pressure waveform by mathematical transformation of radial tonometry pressure. Validation of generalized transfer function. *Circulation* 1997;95(7):1827–1836. [PubMed: 9107170]
32. Cameron JD, McGrath BP, Dart AM. Use of radial artery applanation tonometry and a generalized transfer function to determine aortic pressure augmentation in subjects with treated hypertension. *J Am Coll Cardiol* 1998;32(5):1214–1220. [PubMed: 9809928]
33. Remington JW, Noback CR, Hamilton WF, Gold JJ. Volume elasticity characteristics of the human aorta and prediction of the stroke volume from the pressure pulse. *Am J Physiol* 1948;153(2):298–308. [PubMed: 18872643]
34. Chemla D, Hebert J-L, Coirault C, Zamani K, Suard I, Colin P, et al. Total arterial compliance estimated by stroke volume-to-aortic pulse pressure ratio in humans. *Am J Physiol Heart Circ Physiol* 1998;274(2):H500–H505.
35. Agabiti-Rosei E, Mancia G, O'Rourke MF, Roman MJ, Safar ME, Smulyan H, et al. Central Blood Pressure Measurements and Antihypertensive Therapy: A Consensus Document. [Miscellaneous Article].
36. O'Rourke MF, Adji A. An updated clinical primer on large artery mechanics: Implications of pulse waveform analysis and arterial tonometry. *Current Opinion in Cardiology* 2005;20(4):275–281. [PubMed: 15956823]
37. Wachtell K, Smith G, Gerds E, Dahlöf B, Nieminen MS, Papademetriou V, et al. Left ventricular filling patterns in patients with systemic hypertension and left ventricular hypertrophy (the LIFE study). *Losartan Intervention For Endpoint*. *Am J Cardiol* 2000;85(4):466–472. [PubMed: 10728952]
38. Sharman JE, Haluska BA, Fang ZY, Prins JB, Marwick TH. Association of arterial wave properties and diastolic dysfunction in patients with type 2 diabetes mellitus. *Am J Cardiol* 2007;99(6):844–848. [PubMed: 17350379]
39. Borlaug BA, Melenovsky V, Redfield MM, Kessler K, Chang HJ, Abraham TP, et al. Impact of arterial load and loading sequence on left ventricular tissue velocities in humans. *J Am Coll Cardiol* 2007;50(16):1570–1577. [PubMed: 17936156]
40. Fung J, Li T, Choy D, Yip G, Ko F, Sanderson J, et al. Severe Obstructive Sleep Apnea Is Associated With Left Ventricular Diastolic Dysfunction*. *Chest* 2002;121(2):422. [PubMed: 11834652]
41. Kasikcioglu H, Karasulu L, Durgun E, Oflaz H, Kasikcioglu E, Cuhadaroglu C. Aortic elastic properties and left ventricular diastolic dysfunction in patients with obstructive sleep apnea. *Heart and Vessels* 2005;20(6):239–244. [PubMed: 16314904]

Figure 1.
Working Model of the Pulsatile and Nonpulsatile Components of Central Aortic Blood Pressure. **Pulsatile elements, ++ Nonpulsatile elements.

Aortic Pressure Waveform

Figure 2.
Components of the Central Aortic Pressure Waveform. cAP=Central Augmented Pressure,
NRPP=Non-reflected Pulse Pressure, cPP=Central Aortic Pulse Pressure.

Table 1

Baseline Characteristics of the Study Population (n=281).

Baseline Characteristics	
<i>Demographics:</i>	
Age (yrs)	49 ± 13
Gender (% Male)	49%
Race:	
Caucasian	61%
African American	32%
Asian	5%
Other	2%
History of hypertension	47%
History of Diabetes	22%
Tobacco use	49%
Body Mass Index (kg/m ²)	29.5 ± 6.3
Serum Creatinine (mg/dL)	0.9 ± 0.2
<i>Use of Antihypertensive Agents By Drug Class(%)</i>	
Beta Blockers	7%
ACE Inhibitors	15%
Angiotensin Receptor Blockers (ARB's)	8%
Calcium Channel Blockers	11%
Diuretics	23%
<i>Cardiac Function:</i>	
Ejection Fraction (%)	63 ± 6
Em (cm/s)	13.4 ± 5.7
E/Em	5.7 ± 1.8
Cardiac Output (L/min)	4.6 ± 0.1
LVMI (g/m ²)	86.0 ± 18.0
<i>Vascular Function:</i>	
Central SBP (mm Hg)	115 ± 15
Central DBP (mm Hg)	80 ± 8
Central PP (mm Hg)	34 ± 11
Central MAP (mm Hg)	92 ± 10
Central Augmented Pressure (mm Hg)	9 ± 7
Compliance (mL/mm Hg)	2.3 ± 0.9
Total Peripheral Resistance (dynes•sec/cm ⁵)	1684 ± 27

Values presented as mean ± standard deviation for continuous variables or percentage for categorical. Abbreviations: BSA, body surface area.

Table 2

Correlations between LV diastolic function and hemodynamic load parameters.

Variable	LV Filling Pressure (E/Em)		LV relaxation (Em)	
	Spearman's rho	p-value*	Spearman's rho	p-value*
<i>Blood Pressure Parameters:</i>				
Central SBP (mm Hg)	0.39	<0.001	−0.51	<0.001
Central DBP (mm Hg)	0.12	<0.001	−0.32	<0.001
Central PP (mm Hg)	0.45	<0.001	−0.42	<0.001
Central MAP (mm Hg)	0.27	<0.001	−0.45	<0.001
<i>Components of Pulse Pressure:</i>				
Central Augmented Pressure (mm Hg)	0.36	<0.001	−0.35	<0.001
NRPP (mm Hg)	0.43	<0.001	−0.36	<0.001
Compliance (mL/mm Hg)	−0.30	<0.001	0.30	<0.001
Total Peripheral Resistance (dynes•sec ² /cm ⁵)	0.04	0.50	−0.10	0.08

* P-value adjusted for multiple comparisons using a Bonferroni adjustment.

Abbreviations: NRPP, nonreflected pulse pressure.

Table 3
Multivariate linear regression assessing the association between LV relaxation (Em) and nonpulsatile load parameters.

Variable	<i>cDBP</i> [†]			<i>cMAP</i> [†]		
	Beta Coefficient	p-value	partial r ²	Beta Coefficient	p-value	partial r ²
Age	-0.58	<0.001	0.42	-0.54	<0.001	0.42
LVMI	-0.18	<0.001	0.03	-0.18	<0.001	0.03
DM	-0.14	0.001	0.02	-0.14	0.001	0.02
Hemodynamic Load Parameter[‡]	-0.19	<0.001*	0.06	-0.18	0.005*	0.05

Each hemodynamic load parameter was entered into a multivariate linear regression that included the following covariates: age, sex, BMI, creatinine, LV mass index, history of diabetes, smoking, and hypertension.

* P-value adjusted for multiple comparisons using a Bonferroni adjustment

Abbreviations: LVMI, left ventricular mass index; DM, diabetes mellitus.

Table 4
Multivariate linear regression assessing the association between LV filling pressure (E/Em) and pulsatile load parameters.

Variable	Pulsatile Load Parameters			
	cPP**		cSBP**	
	Beta Coeff.	p-value *	Beta Coeff.	p-value *
BMI	0.28	<0.001	0.27	<0.001
Age	0.17	0.008	0.27	<0.001
Male	-	-	-0.14	0.006
Hemodynamic Load Parameter**	0.35	<0.001 ⁺	0.20	<0.001 ⁺
				0.17

Each hemodynamic load parameter was entered individually into a multivariate linear regression that included the following covariates: age, sex, BMI, creatinine, LV mass index, history of diabetes, smoking, and hypertension.

* P-value adjusted for multiple comparisons using a Bonferroni method.

Table 5

Multivariate linear regression assessing the association between LV filling pressure (E/Em) and the individual components of central aortic pulse pressure

	<i>Individual Components of Central Aortic Pulse Pressure</i>				<i>Compliance**</i>			
	<i>NRPP**</i>		<i>cAP**</i>					
	Beta Coeff.	p- value	partial r ²	Beta Coeff.	p- value	partial r ²	Beta Coeff.	p- value
BMI	0.25	<0.001	0.05	0.29	0.003	0.10	0.34	<0.001
Age	0.25	<0.001	0.05	0.20	<0.001	0.15	0.29	<0.001
Male	-0.16	0.001	0.03	-	-	-	-	-
Hemodynamic Load Parameter**	0.29	<0.001⁺	0.20	0.27	0.003⁺	0.04	-0.20	0.03⁺
Diabetes Mellitus	-	-	-	0.12	0.03	0.01	-	-

Each hemodynamic load parameter was entered individually into a multivariate linear regression that included the following covariates: age, sex, BMI, creatinine, LV mass index, history of diabetes, smoking, and hypertension.

* P-value adjusted for multiple comparisons using a Bonferroni method.