Early Contribution of Arterial Wave Reflection to Left Ventricular Relaxation Abnormalities in a Community-dwelling Population of Normotensive and Untreated Hypertensive Men and Women

Marco Canepa, MD[1,2,3,*], **Majd AlGhatrif, MD**[1,4,*], **James B. Strait, MD, PhD**[1,2], **Hao-Min Cheng, MD**[5,6], **Shao-Yuan Chuang, PhD**[7], **Chen-Huan Chen, MD**[5,6], **Claudio Brunelli, MD**[3], **Luigi Ferrucci, MD, PhD**[2], and **Edward G. Lakatta, MD.**[1]

[1]Laboratory of Cardiovascular Sciences, Human Cardiovascular Studies Unit, National Institute on Aging, NIH, Baltimore, MD, USA

[2]Longitudinal Studies Section, Translational Gerontology Branch, National Institute on Aging, NIH, Baltimore, MD, USA

[3]Division of Cardiology, Research Center of Cardiovascular Biology, University of Genova, Genova, Italy

[4]Department of Medicine, Johns Hopkins Bayview Medical Center, Johns Hopkins School of Medicine, Baltimore, MD, USA

[5]Department of Medical Research and Education, Taipei Veterans General Hospital, Taipei, Taiwan

[6]Department of Medicine, National Yang-Ming University, Taipei, Taiwan

[7]Division of Preventive Medicine and Health Service, Research Institute of Population Health Sciences, National Health Research Institutes, Miaoli, Taiwan

Abstract

We examined the contribution of arterial wave reflection to early abnormalities in left ventricular relaxation, whether this association was modified by gender or hypertension, and the role of reflected wave timing and amplitude. We studied a cohort of normotensive and untreated essential hypertensive Taiwanese participants (675 men, 601 women, mean age 52 years). Doppler flow and applanation tonometry were performed to assess carotid-femoral pulse wave velocity (PWV) and augmentation index (AI). Diastolic parameters including transmitral E/A, E-deceleration time, and left atrial diameter were measured by echocardiography. In multivariate models predicting E/A, women were more likely to have lower E/A than men (β −0.08, p<.001). AI was significantly

Corresponding author: Marco Canepa, MD Longitudinal Studies Section, Translational Gerontology Branch, National Institute on Aging, NIH. Harbor Hospital Center-Room NM524, 3001 S. Hanover Street, Baltimore, MD 21225 Tel: (410) 350-7340 Fax: (410) 350-7304 drcanepamarco@gmail.com, marco.canepa@nih.gov.
*These Authors contributed equally to the present work.

associated with lower E/A in both men (β −0.09, p=0.005) and women (β −0.12, p<.001) independent of PWV. Inclusion of AI in the overall model reduced the gender difference in E/A by 61% and rendered it non-significant. There was a significant interaction between AI and hypertension (p=0.02). The inverse association between AI and E/A was significant only in normotensive men and women, and only for the amplitude but not timing of the reflected wave. In conclusion, the contribution of wave reflection to left ventricular diastolic dysfunction was independent of arterial stiffness, more pronounced in normotensive individuals, and explained a significant portion of the gender difference in diastolic function.

Keywords

wave reflection; arterial stiffness; augmentation index; pulse wave velocity; diastolic function; hypertension

INTRODUCTION

Aging is associated with a progressive decline in left ventricular (LV) diastolic function that can be detected as early as the third decade of life [1]. The natural history of LV diastolic dysfunction is characterized initially by a progressive impairment in LV relaxation, followed by a superimposed decline in LV compliance that results in the need for increased atrial pressures to maintain LV filling and cardiac output. Recent studies emphasize the importance of asymptomatic LV diastolic dysfunction as an early stage in the progression to clinically overt heart failure with preserved ejection fraction[2], a clinical condition that accounts for 50% of patients with heart failure and is more prevalent in women [3].

Several studies have linked LV diastolic dysfunction with indexes of arterial stiffness and wave reflection [4–10]. Augmentation index (AI) is regarded as a global, integrated measure of wave reflection, and aortic pulse wave velocity (PWV) as the reference method for assessment of arterial stiffness[11]. With arterial stiffening, both the amplitude and timing of the arterial pressure wave changes such that a larger amplitude reflected wave returns to the heart before the closure of the aorta, thereby increasing LV systolic load [12] and impairing diastolic relaxation [13, 14]. Compared to markers of global arterial stiffness, however, community-based studies have shown only a small association between LV diastolic function and markers of wave reflection [8, 9].

Considering that arterial stiffness and subsequent increases in wave reflection precede hypertension [15, 16], it is plausible that the effect of wave reflection on early stages of LV diastolic dysfunction begins prior to the development of hypertension. The relatively larger hemodynamic burden of hypertension compared to wave reflection might even mask effects of wave reflection as hypertension evolves. Indeed, the conflicting results regarding the effect of wave reflection on LV diastolic dysfunction might be due to different distributions of hypertension, use of antihypertensive medications, and other cardiovascular risk factors in previous studies [4, 5, 7–9], which could alter LV diastolic properties and augmentation pressures.

Using echocardiographic and vascular measures acquired from a middle-age population of normotensive and untreated hypertensive Taiwanese men and women free from cardiovascular disease, we tested the following hypotheses: i) wave reflection contributes to LV diastolic dysfunction beyond the effect of arterial stiffness, and more in non-hypertensive than hypertensive individuals; ii) higher indices of wave reflection explain, in part, the higher prevalence of LV diastolic dysfunction seen in women; iii) in normotensive individuals, the amplitude of the reflected wave rather than the timing of its arrival is associated with more pronounced LV diastolic function. The composition and characteristics of this study population make it the ideal setting to study these earliest associations of arterial mechanisms with LV diastolic dysfunction.

METHODS

Study Population

The final study cohort of 1276 normotensive and untreated essential hypertensive Taiwanese (675 men, 601 women) was drawn from a previous community-based survey conducted in 1992–1993 [17]. Forty-eight participants from the original cohort were excluded because of significant valve disease (more than mild) and systolic dysfunction (LV ejection fraction<50%). None of the subjects was on antihypertensive therapy, and none had a history of angina pectoris, peripheral vascular disease, or diabetes mellitus. Each participant underwent a 2-hour cardiovascular study including a complete medical history, anthropometric measurements, physical examination, carotid applanation tonometry, Doppler flow examination, and echocardiography.

Definition of Variables

Clinical Variables—Anthropometric measurements included height, weight and waist circumference, which was measured at the minimum circumference between the iliac crest and the rib cage. Body mass index was calculated as weight in kilograms divided by the square of height in meters. Measurements of brachial systolic blood pressure (SBP) and diastolic blood pressure (DBP) were taken manually with a mercury sphygmomanometer using an appropriately sized cuff by senior cardiologists. Two or more measurements separated by at least 5 minutes were taken from the right arm of participants after they were seated for at least 5 min. Reported blood pressures represent the average of at least two consecutive measurements. Hypertension was defined as a value of SBP 140 mm Hg or DBP 90 mmHg. Participants were categorized as ever vs. never smokers. Blood lipids were assayed by standard laboratory techniques[18].

Arterial Parameters—Carotid-femoral PWV was measured by recording sequential non-directional Doppler flow velocity signals at the right common carotid artery and right femoral artery and a simultaneous ECG [19]. Carotid artery pressure waveforms were registered noninvasively with applanation tonometry and calibrated using brachial mean blood pressure and DBP. The calibrated pressure waveforms were analyzed using custom-designed software to identify the inflection point resulting from the wave reflection and the incisura resulting from the aortic valve closure, and central pulse pressure (cPP), augmented pressure (Pa), augmentation index (AI, defined as Pa divided by cPP and expressed as a

percentage), systolic ejection period (SEP), reflected wave transit time (RWTT), and the backward time-independent pressure component of the reflected wave (Pb) were calculated as previously described and validated [19].

Cardiac Variables—Echocardiography was performed in all subjects by the same experienced sonographer using a Hewlett-Packard Sonos 500U system equipped with a 2.5-MHz transducer. Left ventricular wall thicknesses and internal dimensions were measured from 2D guided M-mode echocardiograms, and LV mass and end-systolic wall stress (an index of LV contractility) were calculated as previously described [17]. Mitral inflow was assessed with pulsed-wave Doppler echocardiography from the apical 4-chamber view. The Doppler beam was aligned parallel to the direction of flow, and a 1- to 2-mm sample volume was placed between the tips of mitral leaflets during diastole.

From the mitral inflow profile, the E- and A-wave velocity, E-deceleration time (DT), and E/A velocity ratio were measured [20]. The left atrial (LA) diameter was measured as the longest systolic dimension on recordings taken through the aortic root and left atrium using M-mode in the parasternal long axis view. Both LV mass and LA diameter were indexed to body surface area.

Statistical Analysis

Data are presented as percent or mean±SD. Student's t test and chi-squared test were used for between-group comparisons when appropriate. Simple correlations between age, LV diastolic and arterial parameters were assessed with Pearson's correlation coefficients. Stepwise multivariate regression analyses were used to assess the independent determinants of LV relaxation (E/A). Independent variables were selected based on their known or expected association with E/A, and included age, heart rate, height, waist circumference, triglycerides, smoking, LV mass index, end-systolic wall stress, and hypertension. Regression β-coefficients were expressed in units of SD from the mean for each parameter (z-standardized) to allow for comparison of the magnitude of each relationship.

First, PWV and AI were successively added to gender-specific models to examine their contribution to LV diastolic dysfunction (decreasing E/A) and to test for the independent association of AI with E/A controlling for PWV. Second, to test whether the difference in AI would explain differences in LV diastolic function between men and women, the same analysis was conducted in the overall sample; the gender difference explained by AI was estimated as the reduction in β-coefficient for gender term (female=1) after adding AI to the model [21]. Third, to test whether the effect of AI differs in non-hypertensive vs. hypertensive subjects, the interaction between AI and hypertension was tested, and multivariate models were stratified by hypertension. Finally, univariate and multivariate analyses were conducted in normotensive individuals to evaluate the association of reflected wave amplitude (Pb) vs. arrival timing (log-transformed RWTT) with diastolic parameters. Collinearity was assessed in each model calculating the variance inflation factor, that was considered acceptable when 2. Accordingly, height was removed from models that included a gender term, and the variable hypertension was preferred over continuous values

of SBP. All analyses were performed using the SAS package (version 9.3, SAS Institute Inc., Cary, NC). Statistical significance was set at p<0.05.

RESULTS

Characteristics of the study population and univariate associations

Table 1 summarizes the clinical, arterial and cardiac characteristics of the study cohort by gender. Mean age was not significantly different between men and women. Men were significantly taller, had larger waist circumference, lower BMI, and were more frequently smokers (all p<.0001). Brachial SBP was significantly higher in women (p=0.01), but there was no significant difference in DBP or in prevalence of hypertension between genders (p=0.55). Women had significantly higher AI, cPP, Pa, and Pb (all p<.0001), shorter RWTT (p<.0001) and longer SEP (p=0.03), while no difference was observed in PWV between genders (p=0.87). Women had significantly larger LA diameter index (p<.0001) and apparently comparable DT and E/A. However, lower E/A was noticed in women (1.05±0.01 vs. 1.01±0.01, p=0.02) after simple adjustments for an individual's age and HR [22].

Table 2 summarizes the univariate associations between age, PWV, AI and diastolic parameters in the two genders. As expected, PWV, AI, DT and LA diameter index significantly increased with age in both men and women, while E/A decreased with age (all p<.0001). AI and PWV were significantly correlated in both genders (p<.0001). Increased PWV and AI were both negatively correlated with E/A and positively with DT and LA diameter index (p<.001). We focused our multivariate analysis on E/A because it displayed higher correlations with PWV and AI in both genders, and its decrease represents an early marker of impaired LV relaxation that has been shown as an independent predictor of subsequent cardiovascular events (including heart failure) in a population of untreated hypertensive individuals comparable to ours [22].

Arterial stiffness, wave reflection and LV diastolic function

In multivariate analyses (Table 3), a significant negative association was firstly confirmed between PWV and E/A in both men (β −0.06, p=0.05, Model 1) and women (β −0.10, p=0.005, Model 1). In order to evaluate the effect of wave reflection beyond arterial stiffness, AI was then added to the models, and found to significantly decrease E/A in both men (β −0.09, p=0.005, Model 2) and women (β −0.12, p<.001, Model 2). Most of the terms in the models had a significant association with E/A. As expected, age and heart rate were the principal contributors in both genders, followed by waist circumference and AI in men and by LV mass index and AI in women (Table 3, Model 2). These results remained substantially unchanged when SBP was substituted for hypertension, except there was a slight increase in collinearity (variance inflation factor for SBP in men=2.1, in women=2.8, Supplemental Table S1).

Wave reflection explains a significant portion of gender differences in LV diastolic function

The significance of gender differences was then tested by running the model in the pooled data for men and women. In a multivariate model including a gender term (Supplemental

Table 2S), female gender was associated with significantly worse LV relaxation (β for women vs. men −0.08, p<.001). However, the addition of AI substantially reduced (by about 61%) the difference in LV diastolic function between women and men and rendered it non-significant (β for women vs. men −0.03, p=0.20, Supplemental Table 2S).

Contribution of wave reflection to LV diastolic dysfunction is more pronounced in non-hypertensive subjects

Approximately half of the study cohort (48%) was diagnosed with untreated essential hypertension, without significant differences between men and women (47% vs. 49% respectively, p=0.55). A detailed table listing clinical, arterial and cardiac characteristics of the study cohort by both gender and hypertension is provided in the online supplemental materials (Supplemental Table S3). The high percentage of untreated hypertensive participants allowed us to perform separate multivariate analyses initially for normotensive and hypertensive individuals, with subsequent stratification by gender. Initially, contribution of AI to the decrease in E/A appeared significantly stronger in normotensive (β −0.17, p<. 0001) compared to hypertensive individuals (β −0.08, p=0.03), and there was a significant interaction between AI and hypertension (p=0.02). After further stratifying the analysis by gender, a significant negative association between AI and E/A was found in both normotensive men (β −0.13, p=0.005) and women (β −0.15, p=0.001), but not in their hypertensive counterparts (see Supplemental Table S4 for details). In addition, there was no significant interaction between AI and gender in the overall model (p=0.45), confirming the interpretation that the strength of the association between AI and E/A was substantially similar in both sexes. When Pa (the pressure added to the incident wave by the reflected one) was substituted for AI in multivariate models, the results did not substantially change, and Pa also showed significant interaction with hypertension (p<.001) and negative association with E/A only in normotensive men (β −0.13, p=0.005) and women (β −0.15, p=0.001), but not in those with hypertension (men β −0.00, p=0.96; women β −0.01, p=0.76).

Association of amplitude and timing of the reflected wave with LV diastolic dysfunction in normotensive individuals

In separate univariate analysis of the relationships of Pa and its two main components (Pb and RWTT) with diastolic parameters in normotensive individuals, the amplitude (Pb) but not the timing (RWTT) of the reflected wave was significantly associated with E/A, DT and LA diameter index in both genders (Table 4). After adjusting for multiple potential confounders, these relationships were no longer statistically significant.

DISCUSSION

The main findings of the present study are: (1) increased wave reflection, independent of arterial stiffness, is associated with decreased LV diastolic function and explains gender difference in LV relaxation in a middle-age population of normotensive and untreated hypertensive Taiwanese individuals and (2) wave reflection contribution to LV diastolic dysfunction is more pronounced in normotensive individuals, and in this group is driven by the amplitude rather than the timing of the reflected wave.

Wave reflection contributes to LV diastolic dysfunction beyond arterial stiffness

In both men and women AI was significantly associated with decreased E/A independently of PWV. This important relationship has been investigated in prior experimental and clinical studies, which have shown the profound effects of an increase in late-systolic load on diastole [6, 23]. At the myocardial level, the transition from LV contraction to LV relaxation occurs in mid-to-late systole before the closure of the aortic valve, and increases in LV pressure load during this phase may lead to LV diastolic dysfunction [13, 14]. Both wave reflection and arterial stiffening are important determinants of systolic arterial LV loading[11]. Our findings differ from those in two previous population studies, where the strength of the association between arterial stiffness and LV diastolic dysfunction appeared to be greater than that of wave reflection [8, 9]. Possible explanations include mean age of the study samples, prevalence of cardiovascular diseases and use of medications. Indeed, compared with previous studies [8, 9], our population was 10 to 20 years younger, and this might be relevant since AI is considered a preferred marker of vascular stiffness before the sixth decade of life when compared to PWV[24]. In addition, more than 80% of the patients in previous studies were on regular antihypertensive medications, and also, patients with diabetes, hypercholesterolemia, atrial fibrillation, valvular disease, coronary artery disease and LV systolic dysfunction were included in the analysis [8, 9]. The presence of so many confounders firstly decreases the reliability of the measures themselves (especially when considering the effect of medications on vascular parameters [25] and that of atrial fibrillation, valvular diseases and systolic dysfunction on diastolic parameters [20]). Secondly, it increases the possibility of shared underlying pathways that lead to stiffening of both arterial and LV walls (e.g. deposition of advanced glycation end products and fibrosis in diabetes) being more likely than a potential causal relationship between the two in the aforementioned studies. In contrast, our population was free from diabetes, cardiovascular diseases and cardiovascular medications. Because our study was also of a younger age and had fewer confounders (principally smoking in men and untreated hypertension in about half of the sample), it provided an opportunity to demonstrate the contribution of wave reflection to early abnormalities in LV relaxation, before aging and age-related cardiovascular diseases exert their own deleterious effects on LV diastolic function.

Wave reflection explains gender differences in LV diastolic function

As expected on the basis of the age of our cohort, wave reflection parameters were greater in women than in men, while mean PWV was not significantly different [19, 24]. In univariate and multivariate analysis, no gender differences existed in the strength of the association of AI with diastolic parameters. In contrast to these findings, Shim and colleagues found that after appropriate matching for age the association between AI and LV diastolic dysfunction was restricted to women [26]. Other studies have generally shown more significant correlations in women than men [9, 10, 27]. Nevertheless, none of these prior studies clearly determined whether arterial stiffness or wave reflection or both are implicated in the higher frequency of LV diastolic dysfunction in women than men [3]. We used a different approach to this issue. After adjusting for potential confounders including age, heart rate, hypertension, waist circumference, triglycerides, smoking, LV mass, end-systolic wall stress and PWV, we found that female sex was associated with a more pronounced reduction in LV relaxation (lower E/A). However, accounting for AI did explain a significant portion of

the gender differences in LV relaxation. In other words, as suggested in a recent editorial [27], after accounting for all other potential confounders, "matching" men and women for vascular properties removed their difference in LV diastolic dysfunction in our study.

Contribution of wave reflection to LV diastolic dysfunction is more pronounced in normotensive individuals

It is well known that once hypertension develops, it results in significant structural changes in both the cardiac and arterial walls, that include LV hypertrophy [28] and arterial stiffness[29], which in turn worsen LV diastolic function. Indeed, longitudinal studies of selected normotensive individuals have recently shown that increased AI [16] and PWV [15, 16] are likely precursors of hypertension. Since we [19] and others [24] have previously shown that AI rises steeply with age before the 6th decade and then plateaus, we hypothesized that increased AI could significantly augment cardiac afterload in individuals without hypertension and thereby potentially contribute to the development of early abnormalities in LV relaxation independent of PWV. Our study of a large group of men and women is the first to evaluate whether the independent association between AI and LV diastolic function differs between normotensive and hypertensive individuals. We observed a significant interaction between AI and hypertension and indeed, in subgroup analysis the association between AI and E/A was significant only in normotensive but not in hypertensive men and women. A more pronounced effect of the reflected wave in normotensive subjects suggests that it imposes hemodynamic burden on the left ventricle and contribute to early manifestation of LV diastolic function prior to the occurrence of hypertension. That the association between reflected wave and LV diastolic function becomes weaker once hypertension evolves might indicate that the relatively larger hemodynamic burden of hypertension overwhelms that of reflected wave.

Amplitude but not timing of wave reflection is associated with LV diastolic dysfunction in normotensive individuals

The variable "Pa" is the pressure added to the incident wave by the reflected one, and represents the pressure boost that is caused by wave reflection and with which the left ventricle must cope. Our multivariate analysis in normotensive individuals demonstrated a significant negative association between Pa and E/A. A high Pa may result from either an increased amplitude or an earlier return of the reflected wave, or both. In our analysis, however, only "Pb", the absolute amplitude of the reflected wave, independent of wave reflection timing, was significantly correlated with diastolic parameters in normotensive men and women.

Previous studies in animal models have shown that the cardiac muscle is capable of matching an early-systolic overload by increasing the number of interacting cross-bridges and prolonging contraction[23]. In contrast, this cooperative activity is lost when the increased load occurs in mid-to-late systole, thereby slowing LV relaxation[23]. This is supported by findings in humans, where an increase in late-systolic afterload was shown to have the greatest impact on LV diastolic dysfunction[4, 6]. In our study, as in previous ones [12, 30], RWTT duration was consistently lower than the time to the end of systole, and the ratio between RWTT and SEP corresponded to approximately the first third of systole [12, 30], with

women displaying significantly lower values possibly because of their smaller arterial diameter, shorter height and closer physical proximity between heart and reflecting sites [19, 30, 31]. Thus, the early return of the reflected wave in our population may explain why we found no significant association between RWTT and LV diastolic function in normotensive individuals, but instead only observed an effect from the backward time-independent pressure component of the reflected wave.

Study Limitations

The cross-sectional nature of this study limits causal interpretations and all results should be confirmed by prospective longitudinal studies. Second, tissue Doppler (which represents the best current technique to evaluate LV diastolic function [20]) was not available at the time when the present study was conducted, and LA volume measurement was not yet routinely performed. Therefore, we used E/A, DT and LA diameter as continuous parameters for LV diastolic function, and selected E/A as dependent variable in our multivariate models. E/A has a U-shaped relation with LV diastolic function, with high E/A values seen in healthy normal subjects as well as in patients with cardiac disease and restrictive LV filling pattern [20]. However, a restrictive LV filling pattern is a very uncommon finding in hypertensive patients without heart disease, and only 14 individuals were found with an E/A >2 and a DT < 150 ms (the thresholds proposed for identifying patients with increased LA pressure[32]). Thus, restrictive physiology is unlikely to explain the normal to high E/A pattern observed in the present study.

Perspective

A decrease in E/A has been consistently associated with increased undesirable cardiovascular outcomes in different population [33, 34], including middle-age untreated hypertensive individuals similar to those in the present study, in whom an E/A lower than 0.96 was shown as an independent predictor of subsequent cardiovascular events including heart failure [22]. Thus, while lower E/A cut offs have been generally proposed to identify the presence of first degree LV diastolic dysfunction [35], evidence suggests that in a healthy middle-age population even smaller decrease in E/A should be regarded as an indication of worse cardiovascular prognosis [22]. The association between higher AI and lower E/A demonstrated in our study should be considered with respect to this perspective. Thus the potential clinical implications of our findings are echoed in a recent study, demonstrating that normotensive individuals with high wave reflection have the same risk of incident heart failure of those with hypertension and low wave reflection [36].

Conclusion

In summary, our study of a large middle-age population of normotensive and untreated hypertensive Taiwanese individuals demonstrated a significant association between increased wave reflection and decreased LV diastolic function that was independent of arterial stiffness. The contribution of wave reflection to LV diastolic dysfunction was more pronounced in normotensive individuals, and appeared to be driven by the amplitude rather than the timing of the reflected wave. Further accounting for the gender difference in wave reflection explained a significant portion of the gender difference in LV relaxation. Future longitudinal studies are warranted to prove a causal relationship between wave reflection

and early LV relaxation abnormalities and whether targeting wave reflection could delay the progression of LV diastolic dysfunction associated with aging and the development of hypertension.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Summary table

What is known about this topic

- Previous community-based studies conducted in older population with higher prevalence of cardiovascular diseases and medications showed only a small contribution of wave reflection to left ventricular (LV) diastolic dysfunction [8, 9].

- None of these prior studies clearly determined whether arterial stiffness or wave reflection or both are implicated in the higher frequency of LV diastolic dysfunction in women than men [3].

- Considering that arterial stiffness and subsequent increases in wave reflection precede hypertension [15, 16], it is plausible that the effect of wave reflection on early stages of LV diastolic dysfunction begins prior to the development of hypertension.

What this Study adds

- Our middle-aged population of normotensive and untreated hypertensive individuals free from cardiovascular diseases and medications provided an exceptional opportunity to study the contribution of wave reflection to early abnormalities in LV relaxation, before aging and age-related cardiovascular diseases exert their own deleterious effects on LV diastolic function.

- In this population, increased wave reflection, independent of arterial stiffness, was associated with decreased LV diastolic function and it explained a significant portion of gender differences in LV relaxation.

- Wave reflection contribution to LV diastolic dysfunction was more pronounced in normotensive individuals, and appeared to be driven by the amplitude rather than the timing of the reflected wave.

Table 1

Characteristics of the study population by gender.

	Men (n=675)	Women (n=601)	P
Clinical Variables			
Age, y	52.4 ±12.9	51.9 ±12.6	0.51
Height, cm	164.8 ±6.6	153.3 ±5.9	<.0001
Body mass index, Kg/m^2	24.3 ±3.2	25.3 ±4	<.0001
Waist circumference, cm	86.4 ±8.8	82.5 ±10.3	<.0001
Smoking, %	55	3	<.0001
Untreated essential hypertension, %	47	49	0.55
Low-density lipoprotein cholesterol, mg/dL	120.9 ±33.8	123.2 ±34.9	0.24
Triglycerides, mg/dL	118.8 ±65.4	109.6 ±57.4	<.01
Heart rate, beats/min	73.4 ±10.4	73.7 ±9.5	0.66
Brachial systolic blood pressure, mmHg	134.9 ±22.1	138.4 ±27.1	0.01
Brachial diastolic blood pressure, mmHg	85.1 ±13.7	84 ±14.3	0.18
Arterial Variables			
Pulse wave velocity (PWV, m/s)	9.4 ±2.1	9.4 ±2.4	0.87
Augmentation index (AI, %)	7.3 ±14.4	19.6 ±13.9	<.0001
Central pulse pressure (mmHg)	39.9 ±13.9	44.1 ±16.9	<.0001
Augmented pressure (Pa, mmHg)	3.7 ±7.1	9.8 ±9	<.0001
Backward pressure (Pb, mmHg)	16 ±6	18 ±7	<.0001
Systolic ejection period (SEP, ms)	299 ±55	304 ±28	0.03
Reflected wave transit time (RWTT, ms)	74.6 ±43.9	55.9 ±26.6	<.0001
RWTT/SEP	0.26 ±0.16	0.19 ±0.10	<.0001
Cardiac Variables			
E/A ratio	1.04±0.34	1.02±0.34	0.25
Deceleration time, ms	182 ±43	181 ±38	0.82
Left atrial diameter index, cm/m^2	2 ±0.3	2.2 ±0.3	<.0001
Left ventricular mass index, g/m^2	101 ±23	99 ±27	0.13
End-systolic wall stress, mmHg/mL	12.4 ±4.7	14.8 ±5.5	<.0001

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Table 2

Gender-specific univariate associations between age, diastolic parameters, PWV and AI.

	Age		PWV		AI	
	Men	**Women**	**Men**	**Women**	**Men**	**Women**
PWV	0.40*	0.47*				
AI	0.39*	0.35*	0.28*	0.30*		
E/A	−0.63*	−0.66*	−0.39*	−0.49*	−0.34*	−0.40*
Deceleration Time	0.24*	0.39*	0.19*	0.33*	0.15*	0.20*
LA diameter index	0.24*	0.46*	0.18*	0.16*	0.20*	0.26*

LA=left atrial; other abbreviations as in Table 1;

*
p<.001.

Table 3

Multivariate analyses of relationships between E/A, PWV and AI in men and women.

| | Model 1 | | | | Model 2 | | | |
| | Men | | Women | | Men | | Women | |
	β	P	β	P	β	P	β	P
Age	−0.55	<.0001	−0.42	<.0001	−0.51	<.0001	−0.41	<.0001
Heart Rate	−0.19	<.0001	−0.15	<.0001	−0.20	<.0001	−0.18	<.0001
Height	0.07	0.02	0.12	<.001	0.05	0.08	0.10	0.002
Waist Circumference	−0.16	<.0001	−0.08	0.01	−0.16	<.0001	−0.07	0.03
Triglycerides	−0.06	0.04	−0.08	0.006	−0.06	0.06	−0.08	0.01
Smoking	−0.05	0.06	−0.02	0.45	−0.05	0.06	−0.02	0.37
LV mass index	−0.08	0.02	−0.17	<.0001	−0.07	0.03	−0.15	<.0001
End-systolic wall stress	−0.08	0.02	−0.06	0.08	−0.08	0.02	−0.04	0.17
Hypertension	−0.10	0.003	−0.12	<.001	−0.07	0.05	−0.09	0.02
PWV	−0.06	0.05	−0.10	0.005	−0.06	0.08	−0.10	0.005
AI					−0.09	0.005	−0.12	<.001

All measures were standardized to a mean of 0 and a SD of 1 to facilitate comparison of regression coefficients between different variables. β= standardized coefficients. Variance inflation factor was 2 in all models. LV=left ventricular; other abbreviations as in Table 1.

Men: 1-SD change in age (12.9 years), heart rate (10.4 beats/min), height (6.6 cm), waist circumference (8.8 cm), triglycerides (65 mg/dL), LV mass index (23 g/m2), ESSV (4.7 mmHg/mL), PWV (2.1 m/s), AI (14.4 %).

Women: 1-SD change in age (12.6 years), heart rate (9.5 beats/min), height (5.9 cm), waist circumference (10.3 cm), triglycerides (57 mg/dL), LV mass index (27 g/m2), ESSV (5.5 mmHg/mL), PWV (2.4 m/s), AI (13.9 %).

Table 4

Univariate association of amplitude and timing of the reflected wave with diastolic parameters in normotensive men and women.

	Pa		Pb		Log RWTT	
	Men	Women	Men	Women	Men	Women
E/A	-0.28^{*}	-0.39^{*}	-0.19	-0.32^{*}	0.01	0.01
Deceleration Time	$0.11^{\dagger}$	0.25^{*}	$0.10^{\dagger}$	0.24^{*}	-0.05	0.02
LA diameter index	0.22^{*}	0.32^{*}	0.27^{*}	0.34^{*}	-0.04	-0.04

LA=left atrial; log RWTT=log transformed reflected wave transit time; other abbreviations as in Table 1;

*
p<.001

† p<.05.