Original Article
Relationship between global pulse wave velocity and diastolic dysfunction in postmenopausal women

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Abstract: Objective: Global aortic pulse wave velocity (PWVg) is a simple, accurate, and noninvasive method to determine large artery stiffness. The goal of our study was to investigate the relationship between PWVg, LV mass, and diastolic function in postmenopausal women. Patients and method: We screened 321 consecutive women with echocardiographic examination to determine PWVg. LV diastolic dysfunction (LVDD) and LV hypertrophy (LVH) were diagnosed according to ASE (American Society Echocardiography) Guidelines. Results: The mean age of the 321 women studied was 59.9 years of age with 20 percent of the women menstruate and 80 percent post-menopausal. Amongst the post-menopausal women, 168 patients had LVDD (66.7%), 127 had mild diastolic dysfunction, 40 had moderate diastolic dysfunction, and 1had severe diastolic dysfunction. In these post-menopausal patients with diastolic dysfunction, 89.3% had an increased PWVg while 10.7% had a normal PWVg which was highly statistically significant (p < 0.001). The patients with a normal PWVg all had mild diastolic dysfunction. Increased left atrial volume indexed for body surface area was present in only 19 women, 12 of whom had LVDD and 14 increased PWVg, but statistical analysis was not performed due to the low number of women affected. There was no statistically significant difference in age between postmenopausal women with and without increased PWVg. Conclusion: In our population of postmenopausal women, we observed a strong relationship between LVDD and LVH with PWVg. Our study supports the usefulness of assessment of aortic stiffness as a marker of cardiovascular disease.

Keywords: Aortic stiffness, pulse wave velocity, global pulse wave velocity, postmenopausal women, left ventricular mass, left ventricular dysfunction

Introduction

Aortic stiffness has been shown to be a valuable early indicator of future cardiovascular disease and mortality among the general population and hypertensive patients [1-3]. Risk scores calculated using traditional methods are not reliable in predicting cardiovascular events in individuals deemed suitable for early prevention. Asymptomatic patients with hypertension can be erroneously labeled as low or moderate risk to develop cardiovascular disease. Arterial stiffness has an incremental value over that provided by traditional risk factors for predicting cardiovascular events and target organ damage [4].

Increased arterial stiffness is the major cause of increased systolic pressure and increased pulse pressure in the older patients which has been shown to correlate with myocardial infarction and stroke [4]. The increase in pulse pressure results in an increased left ventricular workload and reduced perfusion of the coronary arteries during diastole [2]. More recent studies have begun to show an association between aortic stiffness and diastolic dysfunction [5].

Carotid femoral pulse wave velocity (PWVc) is an independent predictor of cardiovascular (CV) events, but global PWV (PWVg) seems to be more accurate than PWVc for determining aortic stiffness as assessed in our prior study [6]. PWVg is a simple, accurate, and noninvasive method to determine large artery stiffness. The determination of PWVg does not require dedicated equipment because it can be performed
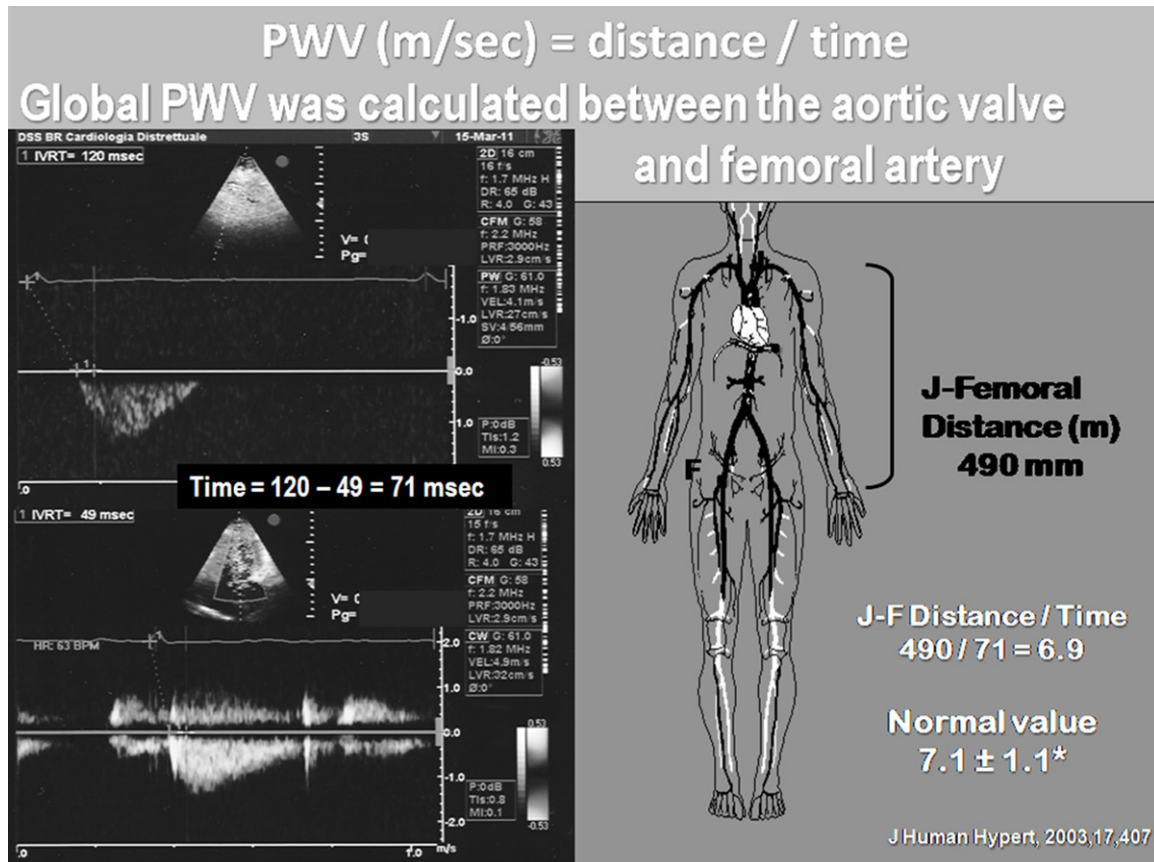
Figure 1. Illustrates the method to calculate global pulse wave velocity (PWV) between the left ventricular (LV) out-flow tract and femoral artery.

by a common echocardiographic machine, does not require extensive training of echocardiographers, and it is not time consuming [6]. Aortic PWV is considered an intrinsic measure of arterial stiffness according to the Moens-Korteweg equation where PWV is proportional to the square root of the incremental elastic modulus of the vessel wall (given there is a constant ratio of wall thickness to vessel radius and blood density and assuming that the artery wall is isotropic and experiences isovolumetric change with pulse pressure) [7]. Therefore PWV is related to the pulsatile component of left ventricular (LV) afterload and is linked to prognostically adverse cardiac phenotypes, including depressed LV systolic function [8, 9].

If the initial speed of the pressure wave is mainly determined by the velocity of myocardial shortening [11] and LV ejection time is related to shortening velocity [12], the relationship between myocardial function and pulse pressure can be assessed. Currently, the associa-tion between aortic PWV and LV mass and function is understudied, but it may support a better comprehension of the mechanism of heart failure with preserved ejection fraction (HFpEF). HFpEFis a condition associated with high morbidity and mortality, has an increasing prevalence, and is common among postmenopausal women [1]. Women display increased arterial stiffening, increased ventricular stiffening, and increased rates of left ventricular diastolic dysfunction (LVDD) with aging [13, 14]. In addition, the association of increased arterial stiffness with mortality is twice as high in women than men [9]. The goal of our study is to investigate the relationship between PWVg, LV mass, and diastolic function in postmenopausal women.

Patients and methods

We screened 321 consecutive women at our heart station that were referred by their general practitioners for baseline evaluation. 257 were

post-menopausal (80%), either natural or surgical, and 64 were menstruate (20%). The mean age of the patients was 59.9 ± 12 years. All of the patients underwent clinical examination, M-mode and two-dimensional echocardiographic examination, pulsed wave and continuous wave Doppler examination, and determination of PWVg by methods listed below. Exclusion criteria were: diagnosis of LV ejection fraction < 50%, wall motion abnormalities, coronary artery disease, severe valvular disease, previous cardiac valvular surgery, atrial fibrillation, pulmonary hypertension estimated by Doppler interrogation of tricuspid regurgitation, serum creatinine > 1.2 mg, and major non-cardiovascular disease.

Aortic stiffness was assessed by PWVg measured in a partially supine position with the head of the examining table elevated by 30° after resting for at least 10 minutes. The examination was performed with pulsed Doppler (3.5 MHz probe) using two-dimensional (2D) echocardiographic guidance and ECG trigger. GE Vivid 3 Expert HealthCare from Galeno 126, Miland (Italy) was used which is an echo-Doppler system equipped with a multi-frequency transducer. The interval between the beginning of the QRS complex and the foot of the systolic upstroke in the Doppler spectral envelope was calculated. The Doppler spectral envelopes were obtained from the apical 5 chamber view by placing the pulsed Doppler sample volume in the LV outflow tract just below the flow acceleration identified by color Doppler and by directly placing the probe over the right common femoral artery (**Figure 1**). These were averaged over five consecutive cycles, none simultaneously (but at the same heart rate) at the LV outflow tract and at the right common femoral artery.

The PWVg was calculated between the LV outflow tract and right common femoral artery by dividing the straight line distance between suprasternal notch and right common femoral artery by the transit time. The distance was assessed using a tape measure located at the same place as the ultrasound probe. The transit time was defined as the difference between two intervals of time using the Doppler method. This method has just been previously validated [6, 15]. The Doppler images were recorded on hard disks to be analyzed later using the calipers of the echo machine. In all of the patients, intra-observer variation in PWVg was studied

and inter-observer reproducibility was analyzed independently by two trained ultrasonographers. The ultrasonographic study of the left ventricle was performed by 2 investigators who were unaware of patients' clinical data. Linear measurements were made according to the American Society of Echocardiography [16]. LV mass was calculated according to Devereux et al as follows: $0.832 \times [(EDD + IVSd + PWd) \times 3 - (EDD) \times 3] + 0.6)$ where EDD is LV end diastolic diameter, IVS is diastolic interventricular septal thickness, and PWd is the end diastolic posterior wall thickness. This was corrected by height in meters at the power of 2.719 to account for the effect of the patient being overweight [17, 18].

Pulsed-wave Doppler examination of mitral inflow as well as tissue Doppler imaging of the mitral annulus at the lateral wall of LV was performed in each subject to determine LV diastolic function and its grading according to the Recommendations for the Evaluation of Left Ventricular Diastolic Function by ASE [19]. LA volume was calculated using an ellipsoid model that assumes that the LA can be represented as a prolate ellipse with a volume of $4\pi/3$ (L/2) (D1/2) (D2/2) where L is the long axis and D1 and D2 are orthogonal short-axis dimensions. According to the American Society of Echocardiography recommendations, LA volume can be estimated using this biplane dimension length formula by substituting the LA antero-posterior diameter acquired from the parasternal long axis as D1, LA medial-lateral dimension can be estimated from the parasternal short-axis as D2, and the LA long-axis can be estimated from the apical 4-chamber for L.

Statistical analysis

Data on PWVgs were available for all women. The general characteristics of the study population were described by the mean and standard deviation. The association between PWVg measurements, menopausal status, LV mass, and function parameters was evaluated using a Student's t-test for continuous variables and Chi-square test for categorical variables. A P value < 0.05 was considered significant. Women were compared according to post-menopausal status and PWVg. The cut off value for a normal PWVg has been previously reported to be 7.1 ± 1.1 m/sec [15]. Values greater were considered to have an increased PWVg.

Table 1. Results of our study

		Number	Mean Age (years)
Total women studied		321	59.9
Postmenopausal women mean PWVg 8.5 m/s		257 (80%)	64.1
Menstruate women mean PWVg 6.4 m/s		64 (20%)	43.2
Postmenopausal women			
with increased PWVg	normal 7.1 ± 1 m/s	212 (82.5%)**	64.6*
with normal PWVg		45 (17.5%)**	61.7*
with LVDD	(mild 127, moderate 40, severe 1)	168 (66.7%)	64.9
- and increased PWVg		150 (89.3%)**	65.2*
- and normal PWVg		18 (10.7%)**	63.6*
with LVH		71 (28.1)	64.4
- and increased PWVg		62 (87%)***	64.8*
- and normal PWVg		9 (13%)***	63.2*
with increased LAV		19 (7.4%)§	
- and increased PWVg		14	
- and normal PWVg		5	
Menstruate women			
with increased PWVg	normal 7.1 ± 1 m/s	40 (62.5%)**	
with normal PWVg		24 (37.5%)**	
with LVDD	(all mild)	14 (21.8%)	
- and increased PWVg		10 (71.4%)§	
- and normal PWVg		4 (28.6%)§	
with LVH		7 (10.9%)	
- and increased PWVg		4 (57%)§	
- and normal PWVg		3 (43%)§	

PWVg = global pulse wave velocity, LVDD = left ventricular diastolic dysfunction, LVH = left ventricular hypertrophy, LAV = left atrial volume. Values are expressed as mean (SD) in the case of continuous variables, and as percentages for categorical variables. *= p insignificant, **= p significant, < 0.01, ***= p significant, < 0.05, §number too small for statistical analysis.

Results

The results of our study are described in **Table 1**. The mean age of the 321 women studied was 59.9 years of age with 20 percent of the women menstruate and 80 percent post-menopausal. The mean PWVg of the entire population was 8.2 m/sec. 257 women were post-menopausal (80%) with a mean age of 65.1 years and a mean PWVg of 8.5 m/sec while 64 were menstruate with a mean age of 43.2 years a mean PWVg of 6.4 m/sec.

Amongst the post-menopausal women, 168 patients had LVDD (66.7%); 127 had mild diastolic dysfunction, 40 had moderate diastolic dysfunction, and 1had severe diastolic dysfunction. In the post-menopausal patients with diastolic dysfunction, 89.3% had an increased PWVg while 10.7% had a normal PWVg which

was highly statistically significant (p < 0.001). The patients with a normal PWVg all had mild diastolic dysfunction. There was no significant difference in age in women with LVDD in relation to increased or normal PWVg but the age range was narrow. Increased left atrial volume indexed for body surface area was present in only 19 women of these women, 12 of whom had LVDD and 14 had increased PWVg, but statistical analysis was not performed due to the low number of women affected. LVH was present in 71 of these patients (28.1%). 62 of these 71 patients had an increased PWVg (87.4%) while 9 (12.6%) had a normal PWVg. There was no significant difference in age between women with LVH with or without increased PWVg but the age range of the women was narrow.

Amongst the menstruate women, only 14 patients had diastolic dysfunction all of which

was graded as mild. In the patients with diastolic dysfunction, 10 (71.4%) had an increased PWVg while 4 (28.6%) had a normal PWVg. No patients had an increased left atrial size and only 4 patients had LVH (3 of who had an elevated PWVg).

Discussion

The main finding of our study is a strong relationship between PVWg and both LV mass and LVDD. Aortic stiffness is partly determined by an increased velocity of myocardial shortening in young people. With increasing age, arterial stiffness increases causing increased afterload which leads to LV hypertrophy and subsequent diastolic dysfunction [1-3]. Aortic PWVg is widely used to estimate arterial stiffness asan indicator of the elastic properties of the arterial tree and it is a strong predictor of cardiovascular complications inessential hypertension [13, 21]. The cardiovascular risk of increased aortic stiffness has been shown to have important gender differences [13, 22]. In our previous study, menopausal status was shown to influence PWVg and blood pressure independently of age [6].

This study supports previous work which has shown that large artery stiffness portends multiple alterations in the structure and function of the LV including a significant increase in mass [23, 24]. In agreement with previous studies [8, 9, 25, 26], our findings suggest that elevated aortic impedance is a major stimulus for the development of unfavorable LV changes in function and a significant increase in LV mass. More importantly, this is the first study to show that these changes are clearly evident in postmenopausal and/or hypertensive women. The relationship between aortic stiffness and LV mass and function was independent of age which has been shown by other authors [27].

Many studies have looked at PWV as a major determinant of the vascular load imposed on the LV but no distinction was made between men and women [8, 9, 28]. The impact of PWVg, which has been shown to be more accurate, on postmenopausal women is first shown here. There is little data in humans concerning the relationship between aortic PWV and LV myocardial function.

In healthy subjects, changes in pulse transit time follow changes in heart rate. This indirectly suggests that PWV may be affected by myocardial function [29]. Furthermore, it has been shown that aortic PWV has an inverse relationship with LV ejection time in young healthy men [10]. These two previous studies point to presence of a relationship between myocardial function and aortic PWV in humans. No data has been published on the relationship between myocardial function and aortic PWV at different ages, sexes, or in postmenopausal women.

Our data about PWVg and LV function in postmenopausal women illustrates the clinical implications of aortic PWV. In young people with elastic arteries and low peripheral resistance, aortic PWV is highly influenced by the velocity of LV chamber shrinking. In our population of postmenopausal women, PWV is determined primarily by large artery stiffness and is strongly associated with LV diastolic dysfunction and LV mass increase.

Our data is supported by the observation that heart failure with normal EF is associated with impaired LV diastolic function and significant ventricular and aortic stiffening diagnosed by magnetic resonance [30]. An increase in aortic stiffness is also independently correlated with reduced LV longitudinal function, increased LV filling pressures, and high BNP levels [31]. An important relationship has been observed between aortic elastic properties and arteriograph derived PWV in patients affected by hypertrophic cardiomyopathy [32].

A complex interaction exists between aortic PWVg and the left ventricle in postmenopausal, hypertensive women. PWVg is primarily determined by aortic stiffness and in our population the associated increase in vascular load superimposed on the left ventricle is not associated with depressed systolic function, but it is associated with an increase in LV mass. The interactions of PWVg with LV mass and function imply that aortic PWVg might have a different clinical and prognostic impact on populations of patients based on gender and age. Prospective studies with a much larger number of patients need to be done to assess this hypothesis. However our study supports the usefulness of the assessment of aortic stiffness as a marker of cardiovascular disease to identify women at major risk to develop LVDD and LVH at an early stage.

Conclusion

In our population of postmenopausal women, we observed a strong relationship LVDD and LVH with PWVg. Our study supports other studies published in the literature regarding the usefulness of the assessment of aortic stiffness as a marker of cardiovascular disease. Prospective studies are needed to determine if the measurement of PVWg is able to identify women at risk to develop LVDD and LVH early enough to intervene.

Acknowledgements

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