Arterial Stiffness is Associated with Tissue Doppler Atrial Conduction Times and P Wave Dispersion in Hypertensive Patients

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Abstract

Background Arterial stiffness is strongly predictive for cardiovascular events in hypertensive individuals and it may increase the risk of stroke. This study was designed to evaluate the possible relationship between arterial stiffness and atrial electromechanical delay and P wave dispersion (PWD), as determinants of AF risk.

Materials and Methods The study included 75 hypertensive patients and 45 healthy control subjects. Atrial electromechanical coupling (time interval from the onset of P wave on ECG to the beginning of A wave with tissue Doppler echocardiography [PA]), intraatrial and interatrial electromechanical delay (EMD) and PWD were measured. Stiffness index β & PWV was measured to assess the arterial stiffness.

Results The interatrial EMD and PWD were prolonged in hypertensive patients compared to controls ($p < 0.01$ for both). There was increased arterial stiffness (PWV and stiffness index β) in hypertensive patients compared to controls (6.43 ± 1.73 vs. 4.8 ± 1.6 m/sec & 4.9 ± 2.8 vs. 2.63 ± 1.2 , $p < 0.01$ for both). By multivariate analysis; PWV and Stiffness index β were independently correlated with interatrial EMD ($B \pm SE = 0.42 \pm 1.87$, $B \pm SE = 0.39 \pm 0.21$ $p < 0.01$ for both) and PWD ($B \pm SE = 0.37 \pm 1.93$, $p < 0.01$, $B \pm SE = 0.25 \pm 0.18$, $p < 0.05$ respectively).

Conclusion In hypertensive patients arterial stiffness indexes increased and showed a significant correlation with interatrial EMD and PWD independent of other variables. Further research is needed to determine whether interventions that reduce arterial stiffness will limit the growing incidence of AF.

Key words: arterial stiffness, hypertension (HTN), interatrial EMD, P wave dispersion

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Introduction

Arterial stiffness is a strong independent predictive factor for stroke (1). Arterial stiffness involves collagen deposition, fragmentation of elastic tissue and calcifications (2). Aortic stiffening is associated with carotid intima-media thickening (3), atheroma formation (4) and plaque rupture (5). These “local” effects are likely to play a crucial role in the pathophysiology of stroke. Aortic stiffness also exerts an effect on left ventricular geometry and diastolic function (6). Ventricular remodeling is a powerful determinant of left atrial size (7). Recently, aortic stiffness was found to influ-

ence the diameter of the left atrium and expose the patient to embolic stroke by increasing their risk of atrial fibrillation (AF). This relationship is independent of other confounding factors, particularly cardiac remodeling (8). Elevated left atrial size and pressure may lead to fibrosis and electrical remodeling in the atrium, providing a substrate for the development of AF. Atrial fibrillation (AF) is one of the leading causes of stroke. The incidence of AF is increased in patients with hypertension compared with the normal population. This fact is attributed to elevated left atrial pressure and fibrosis secondary to pressure overload in the left atrium (9). Fibrosis and enlarged left atrial tissue prolong and divert the propagation of the action potential in left

atrial tissue and cause multiple micro reentries resulting in AF (10). The prolongation of intraatrial and interatrial electromechanical delays (EMD) and the inhomogeneous propagation of sinus impulses are well-known electrophysiologic characteristics of the atria prone to fibrillation (11). P wave dispersion is related to the inhomogeneous and interrupted conduction of sinus impulses, intraatrially and interatrially (12). Increases in the P-wave duration and P wave dispersion from standard ECGs with subsequent development of AF have been identified in patients with a wide range of cardiovascular disorders (10). Yet, to our knowledge, the relative contribution of arterial stiffness to the atrial electromechanical coupling in patients with hypertension as a risk of developing AF has not been evaluated.

The aim of our study was to investigate atrial electromechanical coupling noninvasively in patients with hypertension and determine its relation to arterial stiffness

Materials and Methods

The study included 75 hypertensive patients (45 males, 30 females; mean age, 59.7 ± 7.01 years) and 45 healthy volunteers (25 males, 20 females; mean age, 58.9 ± 4.46 years). Patients who had been diagnosed with hypertension for at least 4 years and whose blood pressure (BP) remained elevated despite salt restriction and lifestyle modifications were included. Whenever possible, any ongoing antihypertensive therapy was discontinued 1 week before the study and patients maintained their usual sodium regimens. The study included patients with moderate and severe hypertension. Patients with secondary hypertension with a history of coronary artery disease, left ventricular (LV) wall motion abnormality, LV ejection fraction (EF) less than 50%, primary cardiomyopathy, valvular heart disease, bundle branch block, atrioventricular conduction abnormalities on ECG, pericarditis, thyroid dysfunction, anemia, hypercholesterolemia, electrolyte imbalance, renal failure, pulmonary disease, poor echocardiographic image that was technically insufficient, were excluded from the study. The patients who had electrocardiographically documented AF episode or who underwent cardioversion to sinus rhythm pharmacologically and/or electrically and the patients who were taking antihypertensive drugs causing prolongation in PR duration (such as beta blocking agents, verapamil, and diltiazem) were also excluded. All patients were referred from a cardiology clinic and were taking their respective antihypertensive drugs. All of the patients were in sinus rhythm, and none of them were taking medications such as antiarrhythmics, tricyclic antidepressants, antihistamines, and antipsychotics. All patients had appropriate clinical and laboratory evaluations to exclude secondary hypertension.

Written informed consent was obtained from each subject. The institutional ethics committee approved the study protocol.

Echocardiography

A complete echocardiographic-Doppler examination was performed using (Hewlett Packard Sonos 5500 with 2.5 MHz transducer). Left ventricular (LV) end systolic diameter, LV end diastolic diameter, wall thickness, LV mass index (LVMI), relative wall thickness (RWT) = $2 \times \text{LV posterior wall thickness} / \text{LVEDD}$, LV end systolic volume (LVESV) & LV end diastolic volume (LVEDV) by 2-D & M-mode echocardiography according to the criteria of the American Society of Echocardiography (13). LV ejection fraction (LVEF) was measured by modified Simpson method. Early diastolic (E) wave velocity, late (A) wave velocity of mitral flow, E/A ratio, E wave deceleration time (DT) & isovolumic relaxation time (IVRT) were measured using pulsed wave Doppler flow.

The same echocardiographic machine was used to perform tissue Doppler echocardiography. The Nyquist limit was adjusted at 15 to 20 cm/s, and minimal optimal gain was used. The monitor sweep speed was set at 50 to 100 mm/s to optimize the spectral display of myocardial velocities. In an apical 4-chamber view, the pulsed Doppler sample volume was placed at the level of left ventricular lateral mitral annulus, septal mitral annulus, and right ventricular (RV) tricuspid annulus. The time interval from the onset of the atrial electrical activity (P wave on surface ECG) to the beginning of the mechanical atrial contraction (late diastolic A wave) was defined as atrial electromechanical coupling (PA). It was obtained from the lateral mitral annulus (lateral PA), septal mitral annulus (septal PA), and RV tricuspid annulus (RV PA), respectively. The difference between lateral PA and RV PA was defined as interatrial electromechanical delay (lateral PA-RV PA). The difference between septal PA and RV PA was defined as right-sided intra-atrial electromechanical delay (septal PA-RV PA). The difference between lateral PA and septal PA was defined as left-sided intra-atrial electromechanical delay (lateral PA-septal PA) (14). In atrial EMD measurements, intraobserver variability was assessed in 20 selected subjects at random from the patient study group by repeating the measurements under the same basal conditions. To test the interobserver variability, the measurements were performed offline from video recordings by a second observer. The intraobserver and interobserver variability for TDI calculated from 20 consecutive patients was 6.1% and 6.7% for PA lateral, 4.8% and 5.9% for PA Septum, 7.2% and 5.3% for RV PA, respectively.

Calculation of aortic root stiffness and distensibility

Aortic root systolic and diastolic diameters measured by 2D guided M-mode echocardiography 3 cm above the aortic valve in parasternal long axis view. Blood pressure (BP) was measured by arm sphygmomanometry. Two indices of aortic root mechanics were calculated blindly: 1) Distensibility (D) = $2 \times (\text{pulsatile change in aortic diameter}) / ([\text{diastolic aortic diameter}] \times [\text{pulse pressure}])$; 2) Stiffness index $\beta = [\ln(\text{systolic pressure}) / (\text{diastolic pressure})] \times \text{diastolic diameter} / \text{pulsatile}$

change in diameter (15).

Pulse-wave velocity

PWV is considered a good surrogate for arterial distensibility, being correlated with direct measurement of arterial stiffness (14). As stated by the Moens Koerteweg equation, PWV, which is proportional to the square root of Young's elastic modulus, travels faster in stiffer arteries. Pulsed Doppler was used to measure the time taken by the pulse wave to travel along the thoracic aorta. To measure the flow at the aortic arch, the transducer was placed at the suprasternal notch, and the sample volume was placed distally to the origin of the left subclavian artery. The distance (d_1) between the transducer and the sample volume was then measured in a 2D frame. The flow in the abdominal aorta was determined from the subcostal approach. The distance (d_2) from the Suprasternal notch to the position of the probe in the abdomen was then measured with a tape measure. The distance (d) between the 2 sample volumes was calculated as $d_2 - d_1$. The R wave of the QRS complex of a simultaneously recorded ECG was used as a fixed reference time point (16). The time (t) between the R wave on the ECG and the foot of each flow systolic wave was calculated, and PWV was then calculated as the distance traveled by the pulse wave divided by the time required, $PWV (m/s) = d/t$.

The P wave duration was measured from the onset to the offset of P wave. Maximum P wave duration (P max), defined as the longest P-wave duration in 12 lead surface ECG was determined. Also the minimum P wave duration (P min), defined as the shortest P wave duration in the 12 leads surface ECG was determined. All recordings were performed in the same quiet room during spontaneous breathing, following 10 minutes of adjustment in the supine position. P wave duration measurements were obtained manually by two of the investigators using calipers and magnifying lens for accurate definition of the electrocardiogram deflection. P wave dispersion (PWD) is calculated from the difference between maximum and minimum P wave durations (12).

In P max and PWD measurements, intraobserver variability was assessed in 20 subjects at random from the patient study group by repeating the measurements of the same ECG recordings. The intraobserver and interobserver variability for P max was 3.5% and 3.7%, respectively. To test the interobserver variability, the measurements were performed by a second observer in 20 selected subjects. The intraobserver and interobserver variability for PWD was 4.1% and 4.3%, respectively.

Statistical analysis

Continuous variables are expressed as mean $\pm$ SD and categorical variables are expressed as percentages. Comparison of variables between the two groups was performed using the χ^2 test and Student's t-test. The mean intraobserver and interobserver differences and interclass coefficients were used to evaluate intraobserver and interobserver variabilities.

The correlation was assessed by the Pearson correlation analysis. Multivariate linear regression analysis was used. Different variables of age; sex; body mass index; hemodynamic parameters including systolic and diastolic pressures; echocardiographic measurements including E/A, IVRT, and LVMI; and measured parameters of lateral PA, septal PA, RV PA, and interatrial and intra-atrial EMD, P max duration and PWD were added to the model. Finally backward stepwise analysis was used to determine the significant independent predictors of PWV and Stiffness index β that add significance to the model.

Results

Clinical data, echocardiographic parameters of left ventricular (LV) systolic, diastolic functions, EMD, ECG and arterial stiffness indexes are shown in Table 1: The values of IVS and RWT (relative wall thickness), left ventricular mass (LVMI), left atrial diameter (LAD), end systolic volume (ESV), end diastolic diameter (EDD), isovolumetric relaxation time (IVRT), were higher in hypertensive patients. E/A ratio was decreased in hypertensive patients. Lateral PA and septal PA values were higher in patients with hypertension when compared with controls. RV PA did not differ significantly between the 2 groups. The interatrial and intraatrial EMD were prolonged in patients with hypertension compared with controls. Maximum P wave duration and P wave dispersion were higher in patients with hypertension compared with controls. In correlation analysis, a positive correlation was detected between P wave dispersion and interatrial electromechanical delay ($r=0.44$, $p<0.01$) and there was a significant correlation between arterial stiffness indexes and age, E/A ratio, LVMI, LAD, interatrial EMD, left-sided intra-atrial EMD, right-sided intra-atrial EMD and P wave dispersion as shown in Table 2 and Fig. 1, 2.

By using backward stepwise analysis, PWV and Stiffness index β were independently correlated with interatrial EMD ($B \pm SE=0.42 \pm 1.87$, $p<0.01$, $B \pm SE=0.39 \pm 0.21$, $p<0.01$) and PWD ($B \pm SE=0.37 \pm 1.93$, $p<0.01$, $B \pm SE=0.25 \pm 0.18$ $p<0.05$).

Discussion

Atrial fibrillation is one of the leading causes of stroke. The incidence of AF is increased in hypertensive patients and particularly in elderly patients (17). In arterial hypertension, fibrosis develops in the left atrium and the left ventricle accounts for the development of LV diastolic dysfunction and AF (17). The present study showed that intraatrial and interatrial EMD were higher in patients with hypertension than in control subjects. It was shown that lateral (lateral PA), septal (septal PA) atrial electromechanical coupling times, were prolonged in patients with hypertension. RV PA, which reflects the right atrioventricular electromechanical coupling, was similar in patients and controls, this is because the right ventricle and pulmonary circulatory system

Table 1. Demographic, Clinical, Echocardiographic and ECG Criteria of the Studied Groups

	HTN patients (n = 75)	Normal (n = 45)	p
Age	59.7 ± 7.01	58.9 ± 4.46	> 0.05
Male (%)	45 (60%)	25 (55%)	> 0.05
Body surface area (m ²)	1.7 ± 0.5	1.5 ± 0.6	> 0.05
Heart rate	80 ± 14.4	78.8 ± 9.8	0.3
* Medication			
- Ca-antagonist (dihydropyridine)	45 (60%)	0 (0%)	< 0.01
-angiotensin II type 1 receptor blockers	30 (40%)	0 (0%)	< 0.01
- ACE-I	38 (51%)	0 (0%)	< 0.01
- Diuretics	29 (38%)	0 (0%)	< 0.01
Systolic blood pressure	193.2 ± 29.5	126 ± 20.1	< 0.01
Diastolic blood pressure	100.7 ± 12.3	79 ± 5.8	< 0.01
Mean arterial pressure (MAP)	113.3 ± 16.4	91 ± 14.6	< 0.01
Pulse pressure (PP)	94.7 ± 21.7	47.3 ± 11.8	< 0.01
End systolic volume (ESV) (mL)	56.9 ± 16.3	66.9 ± 19.3	0.02
End systolic diameter (ESD) (mm)	31.1 ± 5.8	37.9 ± 4.65	< 0.01
End diastolic diameter (EDD) (mm)	48.8 ± 6.3	50.8 ± 4.53	< 0.05
Ventricular septal thickness (mm)	13.6 ± 1.5	11.5 ± 1.0	< 0.01
Posterior wall thickness (mm)	12.7 ± 1.3	10.8 ± 1.3	< 0.01
Left ventricular mass (LVMI) (g/m ²)	135 ± 25	89 ± 22	< 0.01
RWT(relative wall thickness) (mm)	0.44 ± 0.07	0.4 ± 0.06	< 0.01
IVRT(isovolumic relaxation time) (ms)	137 ± 23	111 ± 15	< 0.01
E/A ratio	0.87 ± 0.27	1.0 ± 0.3	< 0.05
LV ejection fraction	64.2 ± 4.3	63.5 ± 4.57	0.59
LV fractional shortening	34.2 ± 4.38	34.1 ± 4.4	0.9
Midwall fractional shortening (mFS%)	15.4 ± 1.0	17.9 ± 0.9	< 0.01
Left atrial dimension(LAD) (mm)	39.1 ± 4.6	35.4 ± 2.9	< 0.05
E/A ratio	0.87 ± 0.27	1.0 ± 0.3	< 0.05
Distensibility (dynes-1.cm ²)	0.008 ± 0.005	0.019 ± 0.015	< 0.01
Stiffness index β	4.9 ± 2.8	2.63 ± 1.2	< 0.01
PWV(m/sec)	6.43 ± 1.73	4.8 ± 1.6	< 0.01
Max.P-wave duration (ms)	91.1 ± 11.5	88.2 ± 5.3	< 0.01
Min.P-wave duration (ms)	55.7 ± 4.7	57.1 ± 3.9	0.07
P-wave dispersion (ms)	44.4 ± 6.9	31.1 ± 4.1	< 0.01
Lateral PA (ms)	75.1 ± 10.5	55.1 ± 7.3	< 0.01
Septal PA (ms)	61.2 ± 7.1	45.6 ± 6.6	< 0.01
RV PA(ms)	45.3 ± 8.0	44.1 ± 7.7	> 0.05
Interatrial EMD (ms)	14.9 ± 9.2	10.6 ± 7.2	< 0.01
Left-sided intra-atrial EMD (ms)	29.7 ± 8.7	11.9 ± 9.5	< 0.01
Right-sided intra-atrial EMD (ms)	16.8 ± 9.2	2.5 ± 1.3	< 0.01

Table 2. Correlation of Arterial Stiffness Indexes and Other Parameters

	PWV		β stiffness index	
	r	p	r	p
Age (years)	0.42	< 0.01	0.39	< 0.01
E/A	-0.33	< 0.05	-0.3	< 0.05
Pulse pressure	0.42	< 0.01	0.58	< 0.01
ESV	0.39	< 0.01	0.34	< 0.05
LVMI	0.40	< 0.01	0.38	< 0.01
BMI	0.23	> 0.05	0.19	> 0.05
Heart rate	0.15	> 0.05	0.17	> 0.05
LAD	0.57	< 0.01	0.55	< 0.01
Max.P-wave duration (ms)	0.33	< 0.05	0.34	< 0.05
Min.P-wave duration (ms)	0.14	> 0.05	0.18	> 0.05
Interatrial EMD	0.6	< 0.01	0.63	< 0.01
Left-sided intra-atrial EMD (ms)	0.56	< 0.01	0.54	< 0.01
Right-sided intra-atrial EMD (ms)	0.35	< 0.05	0.33	< 0.05
P wave dispersion	0.54	< 0.01	0.47	< 0.01

are not primarily involved in essential hypertension. It was also shown that patients with hypertension had higher P max and P wave dispersion values. Interatrial electromechanical delay measured by TDI was well correlated with P dispersion calculated by surface ECG. These results are in accordance with Emiroglu et al. (18)

The prolongation of intraatrial and interatrial electromechanical delays and the inhomogeneous propagation of sinus

impulses are well-known electrophysiologic characteristics of the atria prone to fibrillation (11, 12). P wave dispersion is related to the inhomogenous and interrupted conduction of sinus impulses, intraatrially and interatrially (12). Increases in the P-wave duration and P wave dispersion from standard ECGs with subsequent development of AF have been identified in patients with a wide range of cardiovascular disorders (10).

Figure 1a. Correlation between stiffness index β and P dispersion.

Figure 2a. Correlation between stiffness index β and interatrial EMD.

Figure 1b. Correlation between PWV and P dispersion.

Figure 2b. Correlation between PWV and interatrial EMD.

The patients in the present study were asymptomatic and did not have a history of AF. Thus, increased P wave dispersion and P max in patients with hypertension probably indicate conduction system involvement, subsequent prolongation of intraatrial and interatrial conduction times, and the inhomogeneous propagation of sinus impulses. These results showed the prolonged duration between electrical stimulation and mechanical contraction. The mechanism of P wave dispersion prolongation in these patients is thought to be due to structural and electrophysiologic changes in the atrial myocardium. Chronic elevation of LV filling pressures may cause atrial fibrosis contributing to the prolongation of atrial activation time (19). The prolonged coupling time indicated a disorder in the mechanical properties of the myocardium in hypertensive patients.

The present study showed increased arterial stiffness indexes in hypertensive patients, with a significant relationship between the electromechanical properties (intraatrial and interatrial electromechanical delay) of the left atrium and aortic stiffness (estimated from PWV measurements and stiffness index). This relationship is independent from other confounding factors, particularly cardiac remodelling. Indeed, a rather extensive adjustment was performed to determine that aortic stiffness was independently associated with EMD & P dispersion. This included, as adjustment variables, left ventricular diameter, posterior wall thickness, and relative wall thickness (because of its important role in atrial remodel-

ing) (7), in addition to other variables (age, body mass index, etc).

This suggests that arterial stiffness *per se* may contribute to left atrium electromechanical dysfunction and thus, to the risk of AF and stroke in hypertensive patients.

Pulse wave velocity measurement (PWV) is the current “gold standard” for the assessment of aortic stiffness in hypertensive subjects (20). PWV is included amongst the risk factors for cardiovascular disease (21) and is strongly predictive for cardiovascular events in hypertensive individuals (22). An increase in aortic stiffness may increase the risk of stroke through several mechanisms such as an increase in central pulse pressure or an increase in carotid intima-media thickness, promoting the development of atherosclerotic lesions and thus the likelihood of plaque rupture (3-5). The present study proposed an exciting, alternative physiopathological approach. In agreement with the precedent hypothesis, aortic stiffness is able to influence the electromechanics of the left atrium and expose the patient to embolic stroke by increasing their risk of atrial fibrillation (AF). The interdependence between elastic aortic properties and the left ventricular mass is well established particularly with the relative wall thickness.

In this respect, the present study confirmed the relationship between parameters of left ventricular remodeling (LVESV, LVMI, RWT, LAD and E/A) and arterial stiffness. These findings are in line with previous reports (23).

As suggested by Gosse and Safar in view of a common embryological origin, the aorta may be considered, along with the left atrium and ventricle, as the third chamber of the left sided cardiac pump transforming the systolic output of the left ventricle into a continuous flow (24).

Other potential mechanisms include the possibility that increased arterial stiffness predisposes to neurohormonal activation (25) or a generalized cardiovascular inflammatory response (26), which, in turn may contribute to the development of AF (27). The study illustrates the importance of considering target organ damage at the sub-clinical stage in the hypertensive patient and reopens the question of a potential benefit of anti-hypertensive agents beyond reduction in arterial blood pressure (28). The favorable impact of antihypertensive treatment on aortic stiffness may contribute to the reduction of the extent of atherosclerosis, but also it may prevent the risk of the occurrence of AF (29). It is further supported by the capacity of an ACE-inhibitor to improve left atrial structural remodeling and vascular compliance in parallel (30). According to recent clinical trials, the blockade of the renin-angiotensin system (RAS) should be first-choice agents, whose efficacy remains to be established prospectively by targeting the relationship between aortic stiffness and the left atrium (30).

Limitations

Interatrial conduction time was not investigated by invasive electrophysiologic techniques. The present study did not support any cause-effect relationships between arterial stiffness and EMD or PWD. This study did not directly address the issue of a link between stiffness and AF and rather used EMD and P wave dispersion as surrogate markers of the risk of AF.

Conclusion

This study revealed that increased arterial stiffness is independently correlated with interatrial and intraatrial electromechanical delay and prolonged P wave dispersion in patients with hypertension. These results provide a possible new pathophysiological link between arterial stiffness and stroke, and consequently they may facilitate the design of a new approach to AF prevention.

The authors state that they have no Conflict of Interest (COI).

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