

# Markers of arterial stiffness in a sample of Lebanese subjects with Grade I essential hypertension

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## Abstract

**Objectives:** Arterial stiffness is becoming a major global condition associated with an increased risk of cardiovascular problems and death. Several markers have been linked to arterial stiffness.

**Methods:** To determine and evaluate these relations, anthropometric parameters (weight, height, and pulse rate), biochemical profile, and central and peripheral indices of arterial function were measured in 114 Lebanese subjects with Grade I essential hypertension.

**Results:** Age was associated with a higher pulse wave velocity ( $p=.001$ ), central systolic blood pressure ( $p=.013$ ), central pulse pressure ( $p=.028$ ), central augmentation index ( $p\leq.0001$ ) with a lower heart rate ( $p=.08$ ), and glomerular filtration rate ( $p=.019$ ). Pulse wave velocity was found to be higher in older subjects ( $>65$  years) and correlated with higher body mass index ( $r=.85$ ) independent of age. Aging also correlated with higher plasma glucose and alterations in calcium–phosphorus metabolism.

**Conclusion:** Aging is associated with increased arterial stiffness which is reflected by an increase in the pulse wave velocity, augmentation index, central pulse pressure, and central systolic blood pressure with a reduction in heart rate. Also, a higher body mass index and a lower estimated glomerular filtration rate ( $< 60$  mL/min/1.73 m<sup>2</sup>) are associated with increased arterial stiffness while calcium and phosphorus metabolism may play a role by promoting vascular calcification.

## Keywords

Arterial stiffness, hypertension, pulse wave velocity, aging, Lebanon

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## Introduction

Cardiovascular disease has become a major global health problem, and arterial stiffness was found to be one of its highest contributors.<sup>1</sup> Several predictors of arterial stiffness were identified, among which, the most important is the carotid-femoral pulse wave velocity (PWV).<sup>2–4</sup> Other predictors include central pulse pressure (CPP) and augmentation index (AI), usually found elevated in patients with end-stage renal disease, and constitute strong independent predictors of all-cause mortality including cardiovascular mortality.<sup>5–8</sup>

Many studies reported that arterial stiffness increases with age,<sup>9</sup> hypertension,<sup>10</sup> obesity,<sup>11,12</sup> smoking,<sup>13</sup> diastolic heart failure,<sup>14</sup> diabetes,<sup>15</sup> coronary artery disease,<sup>16</sup> peripheral arterial disease,<sup>17</sup> dyslipidemia,<sup>18</sup> and end-stage renal disease.<sup>19</sup>

While many studies explored the relation of age to PWV and various sphygmocardiographic parameters, few have focused on the relations between the PWV and biochemical parameters. In these studies, PWV was increased in patients

who had an altered renal function or elevated total/low-density lipoprotein (LDL) cholesterol and glucose levels. Furthermore, serum phosphorus level, even within the normal reference range, can be associated with an increased risk of cardiovascular diseases in patients with chronic kidney disease and even in healthy subjects.<sup>20–22</sup> The underlying mechanism is still not

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**Table 1.** Parameters according to age category in years.

Parameters (units)	10–29 (n=3)	30–39 (n=11)	40–49 (n=23)	50–59 (n=32)	60–69 (n=25)	>70 (n=20)	r	p-value
Gender (male/female)	0/3	8/3	16/7	17/15	8/17	11/9	.09/.7	.88/.11
BMI	23±2	28±3	28±4	28±3	26±4	28±4	.58	.253
PWV	5.4±.4	6.5±.8	7±1.2	7.9±1.5	8±1.5	9.8±2.3	.98	.001
Central SBP (mmHg)	98±14	106±7	107±13	111±12	109±12	124±21	.90	.013
Central DBP (mmHg)	69±10	79±7	77±11	76±10	72±8	70±12	.17	.741
Central PP (mmHg)	29±7	27±5	30±6	36±8	37±9	54±17	.86	.028
Peripheral SBP (mmHg)	113±12	118±7	118±14	120±11	117±13	133±21	.76	.076
Peripheral DBP (mmHg)	68±11	78±7	76±11	75±10	71±8	70±12	.15	.768
Peripheral PP (mmHg)	45±11	40±8	42±9	46±9	46±11	64±19	.69	.127
Central AI (%)	11±15	14±10	19±11	28±13	33±11	36±6	.98	<.0001
Peripheral AI (%)	45±24	34±13	29±16	15±18	13±18	8±12	.98	<.0001
Heart rate (per min)	73±12	70±11	70±11	70±13	67±8	64±7	-.92	.008
Time to reflection (ms)	139±6	153±17	145±18	137±14	135±11	133±8	.63	.182
GFR (60 mL/min/1.73 m <sup>2</sup> )	101±25	85±13	94±20	84±23	82±20	61±28	.88	.019
Glucose (mg/dL)	86±3	94±6	112±17	102±14	100±12	119±34	.78	.067
LDL cholesterol (mg/dL)	NA	122±35	114±21	111±36	116±36	99±32	.81	.092
Calcium (mg/dL)	9.35±.2	9.52±.4	9.43±.4	9.51±.5	9.34±.4	9.72±.4	.55	.253
Phosphorus (mg/dL)	NA	3.4±.5	3.54±.5	3.52±.8	3.45±.5	3.64±.6	.67	.210
Spot urine creatinine (mg/dL)	NA	216±85	121±46	124±64	95±50	65±40	.94	.004

BMI: body mass index; PWV: pulse wave velocity; SBP: systolic blood pressure; DBP: diastolic blood pressure; AI: augmentation index; GFR: glomerular filtration rate; LDL: low-density lipoprotein; NA: not available.

clearly understood. It is believed that phosphorus may stimulate the vascular smooth muscle leading to endothelial changes and medial calcification. Consequently, arterial stiffness arises with an increased CPP and PWV.<sup>23–25</sup>

The objective of this study is to evaluate the existing relations between PWV and biochemical parameters in addition to the central and peripheral sphygmocardiographic parameters in a sample of Lebanese patients with Grade I essential hypertension.

## Materials and methods

### Subjects

All subjects (total of 114) with Grade I essential hypertension (systolic blood pressure (SBP)=140–159 mmHg or diastolic blood pressure (DBP)=90–99 mmHg) who underwent carotid-femoral PWV measurement in our clinics at the American University of Beirut Medical Center between 2014 and 2015 were included in this retrospective study. After reviewing all patients' medical files, there were 60 males and 54 females with a mean age of 55±14 years and a range between 12 and 82 years. In total, 22 patients had diabetes and 56 dyslipidemia. Height and weight, and central and peripheral sphygmocardiographic parameters were measured simultaneously with the carotid-femoral PWV. Body mass index (BMI) was calculated using the following equation: weight/(height)<sup>2</sup>, and hemodynamic parameters were recorded using sphygmocor (Atcor): brachial systolic and DBP (mmHg), pulse pressure (mmHg), stroke pressure

(mmHg), augmentation and AI (%), time to reflection (ms), heart rate (per min), and amplification ratio.

### Laboratory measurements

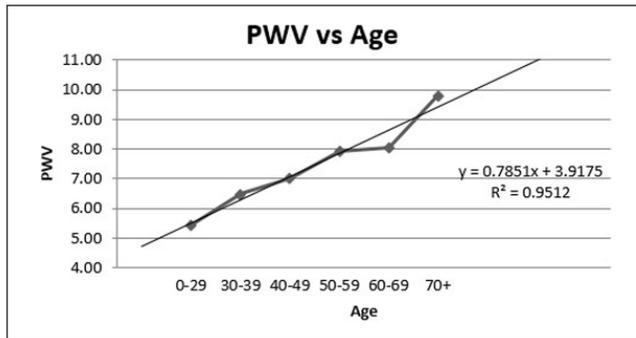
Serum levels for LDL cholesterol (mg/dL), total cholesterol (mg/dL), glucose (mg/dL), creatinine (mg/dL), calcium (mg/dL), phosphorus (mg/dL), and spot urine for creatinine (mg/dL) were measured during the same week of PWV measurement. Estimated glomerular filtration rate (eGFR) was calculated using the modification of diet in renal disease (MDRD) equation which takes into account the gender, age, race, and creatinine. According to this equation, an eGFR above 60 mL/min/1.73 m<sup>2</sup> is considered as normal, while lower than 60 mL/min/1.73 m<sup>2</sup> is taken as abnormal.

**Statistics.** Data for every parameter and within each category were presented as mean±standard deviation (Tables 1 and 2). Our analysis was conducted in two steps. In the first model, subjects were subdivided according to age categories: 10–29, 30–39, 40–49, 50–59, 60–69, and >70 years. PWV, central, peripheral, and biological parameters were compared against age followed by calculation of Pearson's correlation levels. In the second model, patients were subdivided according to their PWV levels into six categories: 5–5.9, 6–6.9, 7–7.9, 8–8.9, 9–9.9, and >10. Pearson's correlation levels between PWV and both sphygmocardiographic and biological parameters were calculated. Analysis was done using SPSS software version 20.0 (SPSS, Inc.), p-values were calculated, and the level of statistical significance was set to .05.

**Table 2.** Parameters in subjects older than 70 years.

eGFR (mL/min/1.73 m <sup>2</sup> )	PWV	CPP (mmHg)	BMI	Calcium (mg/dL)	Phosphorus (mg/dL)	Glucose (mg/dL)
<60	9.83	56.1	28.36	9.53	3.64	130.4
>60	10.06	51.56	27.87	9.46	3.43	107.5

eGFR: estimated glomerular filtration rate; PWV: pulse wave velocity; CPP: central pulse pressure; BMI: body mass index.

**Figure 1.** Relation of pulse wave velocity with age.

## Results

All sphygmocardiographic and biological parameters are summarized in Tables 1 and 2. As expected, PWV increased gradually with age; a sharp increase was noted in the 70s age group with a milder increase in the 50s age group (Figure 1).

Aging had obvious multiple effects on arterial stiffness. With age, there was a marked increase in PWV ( $r=.98$ ,  $p=.001$ ), central SBP ( $r=.90$ ,  $p=.013$ ), CPP ( $r=.86$ ,  $p=.028$ ), and central AI ( $r=.98$ ,  $p\leq.0001$ ) but with a decrease in heart rate ( $r=.92$ ,  $p=.08$ ). A trend toward a shorter time to reflection was noted but it was not statistically significant (Table 1). There was also a significant decrease in amplification ratio ( $r=.99$ ,  $p<.0001$ ), but no changes in central or peripheral DBP. The 70s age group had the most significant changes in all parameters ( $n=20$  out of 114).

Data showed that increased PWV with age was associated with a significant decrease in GFR and spot creatinine ( $p=.019$  and  $.004$ , respectively). Although there was a moderate correlation with BMI, calcium and phosphorus levels, and a strong correlation with glucose and LDL cholesterol, however, all these changes were not statistically significant (Table 1).

However, a subanalysis of the 70s age group subjects was done according to their GFR. We noted that the lower eGFR group ( $<60$  mL/min/1.73 m<sup>2</sup>) had a slightly lower mean PWV compared to the normal eGFR group, higher BMI, higher calcium and phosphorus levels, markedly higher glucose levels, and a higher CPP (Table 2).

In the second model, the analysis was conducted independently of age and the subjects were classified according to their PWV levels. There were strong correlation levels between PWV and various sphygmocardiographic parameters.

PWV strongly correlated with central SBP ( $r=.90$ ,  $p=.013$ ), CPP ( $r=.94$ ,  $p=.005$ ), central augmentation index (CAI;  $r=.87$ ,  $p=.023$ ), and the time to reflection ( $r=.91$ ,  $p=.011$ ). However, there was no correlation between PWV and the heart rate ( $r=-.22$ ) (Table 3). Increased PWV was associated with a decrease in central DBP and peripheral DBP, and an increase in peripheral SBP ( $r=.91$ ,  $p=.11$ ).

Moreover, there were substantial changes in the highest PWV level group ( $\geq 10$ ) when compared to the group of PWV between 9 and 9.9. Central SBP, CPP, and central AI increased greatly in this group (Table 3).

Similar changes were also noted in the PWV group between 8 and 8.9 when compared to the group of PWV between 7 and 7.9. Unlike the group of PWV  $>10$ , the time to reflection was greatly reduced (from 141.34 to 135.06 ms, respectively) (Table 3).

It would be also important to note that the increasing PWV was associated with a higher BMI ( $r=.85$ ,  $p=.034$ ) and a lower spot urine creatinine ( $r=.84$ ,  $p=.036$ ). Correlation levels were strong for GFR, LDL cholesterol, and glucose ( $r=.71$ ,  $.74$ , and  $.77$ , respectively) and moderate for calcium and phosphorus levels ( $r=.62$  and  $.63$ , respectively). However, none of these correlations were statistically significant.

## Discussion

In this study, we found several statistically significant correlations between age and markers of arterial stiffness. When the analysis was conducted independently of age, PWV correlated well with the BMI and central and peripheral sphygmocardiographic parameters. There was an age-related increase in aortic PWV with the sharpest increase occurring in the elderly group ( $>70$  years).

Similar to the Anglo-Cardiff Collaborative Trial (ACCT) trial, PWV was more affected in the elderly group, while in younger individuals, the AIs were noted.<sup>6</sup>

When the  $\geq 70$ s age group was divided into two groups according to their GFR, we noted a markedly elevated CPP in the lower GFR group. However, the PWV did not significantly differ which could be explained by the fact that PWV measurement is not very accurate. In fact, we have to measure the exact distance between the carotid and femoral artery which can be difficult to perform especially in obese individuals. That is why CPP measurement is considered a more important and more reliable marker. An unexpected

**Table 3.** Parameters studied according to PWV category.

Parameters (units)	5–5.9 (n=17)	6–6.9 (n=20)	7–7.9 (n=32)	8–8.9 (n=18)	9–9.9 (n=13)	>10 (n=14)	r	p-value
Gender (male/female)	8/9	10/10	19/13	5/13	9/4	9/5	.15/.55	.77/.26
Age (years)	47 ± 14	47 ± 11	56 ± 12	63 ± 12	56 ± 7	70 ± 8	.92	.009
BMI	26 ± 4	27 ± 4	27 ± 3	27 ± 4	28 ± 5	29 ± 4	.85	.034
Central SBP (mmHg)	106 ± 13	102 ± 11	110 ± 13	117 ± 13	113 ± 9	124 ± 22	.90	.013
Central DBP (mmHg)	77 ± 10	74 ± 11	75 ± 10	74 ± 10	75 ± 8	70 ± 12	.86	.028
Central PP (mmHg)	30 ± 5	28 ± 5	35 ± 9	43 ± 11	38 ± 10	54 ± 20	.94	.005
Peripheral SBP (mmHg)	116 ± 13	113 ± 12	120 ± 13	126 ± 14	122 ± 8	134 ± 21	.91	.011
Peripheral DBP (mmHg)	76 ± 10	73 ± 10	74 ± 10	73 ± 10	73 ± 8	69 ± 12	.88	.019
Peripheral PP (mmHg)	40 ± 7	40 ± 8	46 ± 10	53 ± 11	48 ± 11	65 ± 21	.95	.004
Central AI (%)	23 ± 16	21 ± 11	25 ± 14	32 ± 11	30 ± 12	33 ± 7	.87	.023
Peripheral AI (%)	23 ± 23	26 ± 14	21 ± 19	11 ± 15	9 ± 16	15 ± 18	.68	.136
Heart rate (/min)	66 ± 9	71 ± 10	68 ± 9	67 ± 8	73 ± 18	65 ± 10	.22	.665
Time to reflection (ms)	143 ± 28	143 ± 14	141 ± 11	135 ± 9	132 ± 11	132 ± 8	.91	.011
GFR (60 mL/min/1.73 m <sup>2</sup> )	81 ± 18	88 ± 18	85 ± 24	84 ± 28	84 ± 21	65 ± 28	.71	.112
Glucose (mg/dL)	98 ± 9	103 ± 24	99 ± 13	100 ± 12	100 ± 14	125 ± 38	.77	.069
LDL cholesterol (mg/dL)	115 ± 32	113 ± 22	112 ± 36	120 ± 38	105 ± 33	98 ± 29	-.74	.091
Calcium (mg/dL)	9.46 ± .4	9.44 ± .4	9.51 ± .5	9.29 ± .4	9.54 ± .3	9.74 ± .4	.62	.187
Phosphorus (mg/dL)	3.44 ± .5	3.55 ± .5	3.52 ± .7	3.5 ± .5	3.45 ± .6	3.65 ± .6	.63	.183
Spot creatinine (mg/dL)	205 ± 80	118 ± 47	124 ± 64	79 ± 45	119 ± 47	52 ± 29	.84	.036

BMI: body mass index; SBP: systolic blood pressure; DBP: diastolic blood pressure; AI: augmentation index; GFR: glomerular filtration rate; LDL: low-density lipoprotein.

finding in this group was a higher calcium level, which could be explained by the relatively low sample size.

According to McEniery et al.,<sup>7</sup> AI increases with age until it reaches a plateau around 60 years. In addition, Redheuil et al.<sup>26</sup> reported a significant change in the AI in the 50s age group and remained stable after that. However, in our study, the AI kept increasing after the age of 60 years to reach a peak in the elderly group (>70 years).

Moreover, independent of age, a PWV higher than 10 was associated with a sharp increase in several central and peripheral sphygmocardiographic parameters. According to Lantelme et al.,<sup>27</sup> heart rate is influenced by PWV. However, this was not observed in our study.

BMI, similar to other studies, was the only statistically significant biochemical parameter associated with arterial stiffness. Rider et al.<sup>11</sup> showed that obese individuals had a significantly higher PWV, and C-reactive protein (CRP) and leptin levels compared to normal weighed individuals.

According to Ix et al.,<sup>22</sup> a high-serum phosphorus level is associated with a statistically significant increase in ankle brachial index. It appeared to be associated with high pulse pressure and reduced arterial elasticity if unadjusted, but when adjusted to age, race, lipid panel, BMI, GFR, and CRP, it lost its significance. Our study showed a moderate association between the phosphorus level and the PWV, but with a p-value of .183.

A high calcium and phosphorus level may promote arterial stiffness. One possible explanation is that any abnormalities in the calcium–phosphorus metabolism favor precipitation

and vascular calcification that, in turn, increases arterial stiffness. The non-significant results for calcium and phosphorus may probably be attributed to the relatively small number of subjects. It would be of interest to look for the parathyroid hormone (PTH) value for these subjects or for fibroblast growth factor 23 (FGF23) in the subgroup of patients with eGFR <60 cc/mn, but this was not done in our study. Future studies need to be conducted to accurately assess the relation of arterial stiffness to the calcium and phosphorus levels.

The relation between LDL cholesterol and arterial stiffness is still unclear. Some studies demonstrated that a high LDL cholesterol is associated with an increase in pulse pressure and AI while others could not find any relation.<sup>28,29</sup> Also, a lower HDL cholesterol may contribute to arterial stiffness.<sup>30</sup> The use of statins may improve arterial stiffness and atherogenesis by reducing the activity of RhoA and promoting endothelial membrane cytoskeletal reorganisation.<sup>31</sup>

However, our study has several limitations. The small sample size and the fact that it was conducted in a single institution make our result possibly not representative of the Lebanese population. In addition, as with any retrospective study, there are several biases in our study such as information bias. Some of the data contained in the patients' medical files were missing or not collected. A third limitation is the fact that we did not measure the levels of PTH or ionized calcium which could have further clarified the contribution of the calcium–phosphorus metabolism toward promoting arterial stiffness. Finally, most of the patients were already on antihypertensive medications when they presented to our

clinics. That is why they had central and peripheral blood pressures lower than expected and hence our results could have been possibly altered.

## Conclusion

Aging is associated with an increased arterial stiffness reflected by an increase in the PWV, AI, CPP, and central SBP with a reduction in heart rate. Also, a higher BMI and a lower eGFR ( $<60\text{ mL/min/1.73 m}^2$ ) are associated with increased arterial stiffness while calcium and phosphorus metabolism may play a role by promoting vascular calcification. However, further studies are needed to define the precise role of calcium, phosphorus, and LDL cholesterol in promoting arterial stiffness.

## Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

## Ethical approval

Ethical approval was not sought for this study because this was a retrospective study.

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## Informed consent

Informed consent was not sought for this study because this was a retrospective study.

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