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## Is There an Association Between Carotid-Femoral Pulse Wave Velocity and Coronary Heart Disease in Patients with Coronary Artery Disease: A Pilot Study

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**Abstract:** Arterial stiffness has been shown to predict cardiovascular morbidity and mortality. Carotid-femoral pulse wave velocity (cfPWV) is regarded the gold standard marker of arterial stiffness. In previous studies, cfPWV was associated with the presence of coronary heart disease (CHD). However, with regard to CHD severity as assessed by the Syntax Score, only brachial-ankle PWV was reported to correlate with Syntax Score; no data exist for cfPWV.

In this pilot study, we evaluated the possible associations between cfPWV, CHD and Syntax Score in 62 consecutive patients (49 males; mean age: 64±12years) with chest pain undergoing scheduled coronary angiography. cfPWV was significantly higher in CHD patients than in non-CHD individuals (10 vs. 8.4 m/s;  $p = 0.003$ ). No significant association was found between cfPWV and CHD severity as assessed by Syntax Score. A cut-off point of 12.3 m/s was considered as diagnostic for abnormally increased cfPWV (specificity: 97%; sensitivity: 12%; positive likelihood ratio: 3.558). Further research is needed to establish the relationship between cfPWV and Syntax Score.

**Keywords:** Arterial stiffness, coronary angiography, coronary heart disease, pulse wave velocity, syntax score.

### INTRODUCTION

Arterial stiffness represents an early manifestation of atherosclerosis characterized by adverse structural and functional alterations within the vessel wall. Markers of arterial stiffness include pulse pressure, augmentation index (AIx) and pulse-wave velocity (PWV), the latter being the most widely used index; carotid-femoral PWV (cfPWV) is regarded the gold standard for the measurement of arterial stiffness [1]. These markers have been related to increased risk for fatal and non-fatal cardiovascular disease (CVD) events [2].

Arterial stiffness has been associated with several CVD risk factors such as increasing age, obesity, dyslipidemia, diabetes mellitus (DM), smoking and hypertension [3 - 9]. Other metabolic disorders related to increased CVD morbidity and/or mortality such as metabolic syndrome (MetS), non-alcoholic fatty liver disease (NAFLD), hyperuricemia, obstructive sleep apnea (OSAS) and chronic kidney disease (CKD), have also been linked to abnormal arterial stiffness [10 - 14].

Arterial stiffness (assessed by cfPWV) has been previously linked to the presence of coronary heart disease (CHD) [15 - 17]. Syntax score (SYnergy between percutaneous coronary intervention with TAXus and cardiac surgery) may

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be used to evaluate CHD complexity, severity and clinical prognosis in various patient subgroups undergoing percutaneous coronary interventions (PCIs) [18]. Only 2 studies evaluated the association between Syntax Score (as a marker of CHD severity) and brachial-ankle PWV (baPWV) [19, 20] reporting significant correlations between the 2 variables. However, no data exist with regard to cfPWV and Syntax score.

We evaluated the possible associations between cfPWV, CHD and Syntax Score in patients with stable angina undergoing scheduled coronary angiography.

## PATIENTS AND METHODS

A total of 62 consecutive patients with chest pain (49 males; mean age:64, SD: 12 years) undergoing a scheduled coronary angiography at the Cardiology Department of Agios Loukas Hospital, Thessaloniki, Greece, were included in the present pilot study. The study was approved by the local ethics committee and informed consent was obtained from all participants.

Prior to coronary angiography, a detailed individual and family history was recorded and physical examinations including weight, height, heart rate and blood pressure measurements, as well as laboratory analyses serum creatinine, total cholesterol, triglycerides, high density lipoprotein cholesterol (HDL-C) and low density lipoprotein cholesterol (LDL-C) were performed in all patients. Furthermore, arterial stiffness was assessed by the measurement of cfPWV with an automated applanation tonometry device *i.e.* Spymocor (AtCor Medical, Sydney, Australia). AIx75 (AIx adjusted to a standard heart rate of 75bpm) was also recorded. Glomerular filtration rate (GFR) was calculated based on the Modification of Diet in Renal Disease (MDRD) formula  $186.3 \times (\text{serum creatinine in mg/dl} - 1.154) \times (\text{age in years} - 0.203) \times 1.212$  (if black)  $\times 0.742$  (if female).

Syntax score is calculated based on angiographical findings; an online calculator was used to generate Syntax score (<http://www.syntaxscore.com>).

Exclusion criteria were acute or chronic infections, non-cardiac chest pain, cancer, systematic diseases, major surgical procedures during the last 3 months, history of acute myocardial infarction, cardiac arrhythmias, cardiomyopathies, carotid sinus syndrome, previous percutaneous coronary intervention (PCI), severe carotid stenosis and peripheral arterial disease.

Following coronary angiography, the study population was divided into 2 groups: patients with angiographically proven CHD *i.e.* those with >50% stenosis (n = 33) and non-CHD individuals (n = 29).

## Statistical Analysis

Statistical analyses were performed using the SPSS version 23.0 software package (SPSS Inc., Chicago, USA). Normally distributed continuous variables were expressed as mean and standard deviation (SD), whereas non-normally distributed ones were expressed as median and interquartile range (IQR); categorical values were presented as frequencies with percentages. Differences between the 2 study groups as well as other subgroups (*i.e.* diabetic, dyslipidemic and hypertensive patients) were evaluated by Student's t- test, or the Mann Whitney U test, whenever more appropriate. The association between categorical variables was assessed with the chi-square test or the Fisher's exact test whenever more appropriate. Correlations between continuous variables were examined by Pearson r or Spearman Rho correlation coefficients. Logistic regression analysis was performed and odds ratios were presented with the corresponding 95% confidence intervals (OR, 95% CI). A multivariable model was built with backward elimination based on likelihood ratio criteria, where univariate predictors with P-values lower than 0.05 were considered for inclusion. The model fit was evaluated with the Hosmer-Lemeshow test. Discrimination performance of the multivariable model was evaluated with the C-index. Furthermore, receiver operating characteristic (ROC) curves analysis was used to determine the cut-off point for the diagnosis of abnormally increased cfPWV. A 2-tailed  $p < 0.05$  was considered as significant.

## RESULTS

Table 1 summarizes the differences between CHD and non-CHD patients in all studied variables. There were significantly more males in the CHD group compared with the non-CHD group (91 vs. 65%;  $p = 0.014$ ) as well as patients with a history of dyslipidemia (91 vs 69%, respectively;  $p = 0.029$ ). Triglycerides levels were also greater in the CHD group compared with the non-CHD group [137 (94 - = 0.044)]. Similarly, cfPWV was significantly higher in CHD patients than in non-CHD individuals (10 vs 8.4 m/s;  $p = 0.003$ ), whereas AIx75 did not differ between the 2 groups. No

significant association was observed between cfPWV and CHD severity as assessed by Syntax Score ( $r = 0.038$ ;  $p = 0.833$ ). Furthermore, CHD patients were more likely to receive a statin than non-CHD individuals (66.7 vs 41.4 %;  $p = 0.046$ ).

In multivariable analysis, only cfPWV remained significantly different between the 2 groups (Table 2). The Hosmer and Lemeshow test indicated a good fit of the data ( $p = 0.585$ ) and the discriminative performance of the model was good (C-index=0.81) The model fit was assessed with the Hosmer and Lemeshow test ( $p = 0.585$ ) with a C-index of 0.81, indicating a good power and fit of the model.

**Table 1. Differences between patient groups in all studied variables.**

	CHD n = 33	Non CHD n = 29	P
Gender, male, n(%)	30(91)	19(65)	<b>0.014</b>
Mean height, meters (SD)	1.72 ( 0.8)	1.70 (0.8)	0.539
Mean weight in kg (SD)	85.1 (14.8)	91.7 (18.1)	0.123
Mean age in years (SD)	64 (12)	63 (11)	0.569
History of Hypertension, n(%)	22(66)	23(79)	0.265
Current Smokers, n (%)	13(39)	6(20)	0.111
History of Diabetes, n (%)	10(30)	4(14)	0.121
History of Dyslipidemia, n (%)	30(91)	20(69)	<b>0.029</b>
Family history of CHD, n (%)	15(45)	7(24)	0.080
Median GFR mL/min/1.73 m <sup>2</sup> (IQR)	87.5 (67-94)	81.2 (68-96)	0.849
Median Total cholesterol, mg/dL (IQR)	162(147-209)	180 (158-203)	0.476
Median LDL-C, mg/dL (IQR)	101 (81-145)	110(93-135)	0.631
Median HDL-C, mg/dL (IQR)	44(36-53)	52(39-57)	0.156
Median Triglycerides, mg/dL (IQR)	137(94-179)	106(87-142)	<b>0.044</b>
Mean Heart rate, bpm (SD)	68 (10)	66 (9)	0.598
Median SBP, mmHg (IQR)	120(110-140)	125(110-135)	0.679
Median DBP, mmHg (IQR)	80(70-83)	80(70-90)	0.878
Mean AIx75 (SD)	21.1(10.6)	21.8(10.7)	0.796
Median cfPWV, m/s (SD)	10(9-11)	8.4(7.6-9.8)	<b>0.003</b>
LVH, n (%)	17(51)	9(31)	0.103
Nitrates, n (%)	9 (27.3)	3(10.3)	0.092
β-Blockers, n(%)	21(63.6)	16 (55.2)	0.498
ACE inhibitors, n (%)	4(12.1)	5(17.2)	0.568
Angiotensin receptor blockers, n (%)	18(54.5)	10(34.5)	0.113
Calcium channel blockers, n (%)	12(36.4)	7(24.1)	0.297
Diuretics, n (%)	16(48.5)	8(27.6)	0.092
Statins, n (%)	22(66.7)	12(41.4)	<b>0.046</b>
Aldactone, n (%)	2(6.9)	1(3)	0.595

CHD: coronary heart disease; GFR: glomerular filtration rate; LDL-C: low density lipoprotein cholesterol; HDL-C: high density lipoprotein cholesterol; SBP: systolic blood pressure; DBP: diastolic blood pressure; AIx75: augmentation index adjusted to a standard heart rate of 75bpm; cfPWV: carotid-femoral pulse wave velocity; LVH: left ventricular hypertrophy; ACE:angiotensinconvertingenzyme; SD:Standard deviation; IQR: Interquartile range

## DISCUSSION

We evaluated the associations between cfPWV, CHD and Syntax Score in patients with chest pain undergoing a scheduled coronary angiography. Significantly more males and patients with a history of dyslipidemia were observed in the CHD group than the non-CHD group, as expected. CHD patients were more likely to receive a statin and had higher triglycerides levels compared with non-CHD individuals.

With regard to arterial stiffness, cfPWV was independently associated with CHD prevalence (but not AIx75). These findings are in agreement with previous studies [15 - 17]. However, a link between AIx75 and a composite endpoint of myocardial infarction, stroke, cardiac, cerebrovascular, and peripheral revascularization as well as total mortality has been reported in Austrian males (n = 520) undergoing coronary angiography [21].

We found no significant association between cfPWV and CHD severity as assessed by Syntax Score. To our knowledge, this is the first study to estimate the relationship between cfPWV and Syntax Score. In contrast, Syntax Score has been previously related to baPWV [19, 20].

In this study, the value of 12.3 m/s was characterized as the cut-off point for the diagnosis of abnormally increased cfPWV in this patient population (specificity: 97%; sensitivity: 12%). This is similar to the cut-off point for cfPWV (*i.e.*

12 m/s) suggested by the Task Force for the Management of Arterial Hypertension of the European Society of Hypertension (ESH) and the European Society of Cardiology (ESC) in 2007 to estimate subclinical atherosclerosis [22]. However, in the more recent 2013 ESH/ESC guidelines for the management of arterial hypertension, the cfPWV cut-off point for asymptomatic organ damage was 10 m/s [23].

**Table 2. Factors associated with CHD.**

	OR	95% CI	p
Gender	4.9	0.9 - 26.5	0.065
History of dyslipidemia	0.45	0.09 - 2.4	0.347
cfPWV	1.38	1.04 - 1.85	0.026

OR: odds ratio; CI: confidence intervals; CHD: coronary heart disease; cfPWV: carotid-femoral pulse wave velocity

Antihypertensive drugs have been consistently shown to improve arterial stiffness [24 - 26]. Similar beneficial effects may be exerted by statins [27]. Of note, antihypertensive therapy did not differ between groups in the present study, whereas patients with CHD were more likely to use statin with a marginal *p* value ( $p = 0.046$ ).

Our study has limitations including the small sample size, recruitment of patients from one clinical center and its cross-sectional design. However, this is a pilot study and to our knowledge the first to evaluate the association between cfPWV and Syntax Score.

## CONCLUSION

cfPWV was independently associated with CHD prevalence in patients with chest pain undergoing scheduled coronary angiography. Patients with DM or dyslipidemia had higher cfPWV values than individuals without these metabolic disorders. However, no significant association was observed between cfPWV and CHD severity as assessed by SyntaxScore. A cut-off point of 12.3 m/s for the diagnosis of abnormally increased cfPWV may be used in this patient population. Further research is needed to establish the relationship between cfPWV and Syntax Score.

## CONFLICT OF INTEREST

This original study was conducted independently. The authors did not receive financial or professional help with the preparation of the manuscript. The authors have given talks, attended conferences and participated in advisory boards and trials sponsored by various pharmaceutical companies.

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