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Arterial stiffness measured by carotid femoral pulse wave velocity is associated with disease severity in chronic obstructive pulmonary disease

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Authors role in the study:

All authors contributed to conception and design of the study and acquisition, analysis and interpretation of data. Servet Kayhan also contributed to English editing of the manuscript and drafted the article. Aziz Gumus also contributed to statistical analysis, assembling tables and figures.

ABSTRACT

Background and objective: Patients with chronic obstructive pulmonary disease (COPD) face an increased risk of cardiovascular disease and increased cardiac mortality. Carotid femoral pulse wave velocity (cf-PWV) is a validated measure of arterial stiffness, a well-recognized predictor of adverse cardiovascular outcomes, and offers higher predictive value than classical cardiovascular risk factors. In this study, we investigated the association between COPD and arterial stiffness using cf-PWV as a non-invasive technique.

Methods: This clinical study was prospective, observational and cross-sectional. Sixty-two patients with stable COPD and 22 healthy controls were enrolled. Physical examinations, chest x-rays, pulmonary function tests, arterial blood gas analysis and 6 minute walking test

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were performed on each participant, and cf-PWV was measured via a validated tonometry system.

Results: Patients with COPD exhibited increased arterial stiffness as compared to the control subjects. These differences were associated with decreases in forced expiratory volume in 1 second (FEV_1), partial pressure of oxygen in arterial blood, and oxygen saturation during the 6 minute walking test. We observed higher cf-PWV values in COPD patients with more severe disease forms as compared to patients with mild and moderate disease forms. According to linear regression analyses, only FEV_1 was an independent predictor of cf-PWV in our study population.

Conclusion: Our results suggest that cf-PWV, a measure of arterial stiffness, is increased in patients with more severe and advanced COPD as compared to those with mild and moderate forms. Airflow limitation and hypoxemia may induce increased arterial stiffness in COPD patients.

Key Words: cardiovascular disease, clinical respiratory medicine, COPD, inflammation, respiratory function test

Short title: Carotid femoral pulse wave velocity in COPD

INTRODUCTION

Patients with chronic obstructive pulmonary disease (COPD) face an increased risk of cardiovascular disease as compared to the normal population; moreover, cardiac disease is among the leading causes of death in these patients.[1-3] Increased evidence suggests that COPD is associated with systemic inflammation, which could also initiate the development of comorbid diseases.[1, 4] Additionally, airflow obstruction profoundly affects cardiac function and gas exchange, leading to systemic consequences. An increased prevalence of ischemic

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heart disease and hypertension is seen in COPD patients, and these conditions are often linked to poor prognoses.[3]

Carotid-femoral pulse wave velocity (cf-PWV) is the gold standard measure for arterial stiffness.[5-7] Previous studies have documented the importance of arterial stiffness as a prognostic factor and an independent predictor of all-cause and cardiovascular mortality.[1] Due to decreased arterial compliance, arterial stiffness is a well-known predictor of cardiovascular risk and can be assessed by measuring radial artery tonometry, aortic PWV or cf-PWV.[8]

As a response to the systemic inflammation associated with COPD, arterial stiffness and cardiovascular risk may also increase in this disease.[9] Due to this increased systemic inflammation and impaired endothelial nitric oxide production, COPD patients also frequently exhibit endothelial dysfunction.[10] The aim of our study is to define the relationship, if any, between arterial stiffness and airflow limitations in COPD.

METHODS

Study design and patients:

This is a prospective, observational, and descriptive type study. The study was approved by the ethics committee of Recep Tayyip Erdogan University and was designed in accordance with the Declaration of Helsinki. The study was conducted between 01 September 2012 and 31 December 2012 in the pulmonology clinic including 62 consecutive patients with stable COPD and 22 healthy subjects. COPD patients with history of any cardiovascular disease, hypertension and diabetes mellitus were excluded. The study and control groups were examined physically by a cardiologist. Furtherly, electrocardiographic and echocardiographic examimations were also performed to rule out any cardiac disease. The study population (i.e., the COPD patients) and the control population (i.e., the healthy subjects) shared similar gender properties. All participants provided informed consent to participate in the study.

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Physical examinations, chest x-rays, pulmonary function tests, arterial blood gas analysis and 6 minute walking test were performed on each subject. As a marker of systemic inflammation serum CRP levels are also measured. The spirometric classification of COPD is divided into four groups based on post-bronchodilator forced expiratory volume in 1 second (FEV_1) levels. These are mild (GOLD-1, $FEV_1 \geq 80\%$ of predicted), moderate (GOLD-2, $50\% \leq FEV_1 < 80\%$ of predicted), severe (GOLD-3, $30\% \leq FEV_1 < 50\%$ of predicted) and very severe (GOLD-4, $FEV_1 < 30\%$ of predicted) according to the Global Initiative against Chronic Obstructive Lung Disease (GOLD).[11]

Pulmonary function tests:

Pulmonary function tests were measured using a spirometer (nSpire Health, Inc., Germany). Forced vital capacity (FVC) (% of predicted), FEV_1 (% of predicted), FEV_1/FVC (%), mean 25-75% of forced expiratory flow (FEF_{25-75})and peak expiratory flow rates (PEF) (l/s) were measured. Spirometric tests were performed while the patients were sitting and repeated at least three times. ~~in.~~ The best test was selected and used for analysis. The functional data were expressed as absolute values and as percentages of predicted values generated by the European Respiratory Society according to the demographic characteristics of the adult population of Europe.[12]

COPD exacerbations

All the patients were questionned for COPD exacerbation which is a, sustained and acute worsening of the patient's condition from the stable state that required additional treatments.[36] COPD patients were classified according to number of exacerbation which they had in the last one year. And the cf-PWV levels were matched between the groups.

Arterial blood gas analysis:

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Arterial blood samples were taken from radial arteries while the patients were breathing room air after a resting 15 minutes. Blood gas analysis was performed immediately by using a gas analyser (RAPIDLab 248/348 Systems, Siemens AG healthcare, Germany). We determined the pH, oxygen saturation level, the partial pressure of carbon dioxide and oxygen of the arterial blood. We measured oxygen saturation levels of control group by pulse oximetry (BCI 3303, BCI International, Wisconsin USA). Only the individuals with normoxemia, having oxygen saturation level in 95% or greater values, were included to study. Actually, we did not perform an arterial blood gas analysis in healthy and normoxemic control group.

Six minute walking test:

The 6 minute walking test was performed in our pulmonology clinic and we used a corridor with a 30 m in length. The test was completed according to the standards the ATS guidelines.[35] The pulse rates, systolic and diastolic blood pressures of the subjects were measured before and after the test. The parameters including the oxygen saturation levels before and after the 6 minute walking test, the distance that the patients walked over 6 minutes, and the lowest and the highest oxygen saturation levels during the test were recorded. A pulse oximeter device (Choicemmed MD300C12, South Korea) was used to measure the blood oxygen levels. During the test, a decrease in oxygen saturation level of equal or more than 4% from the initial level of the patient was accepted as desaturation.

Pulse wave velocity:

An experienced cardiologist who was blinded to patient data performed vascular assessments in the morning after an overnight fast from food and cigarette smoking (i.e., for at least 8 h). cf-PWV was calculated by a validated non-invasive device (SphygmoCor, AtCor

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Medical, Sydney, Australia) from the pulse transmit time and the distance between two recording sites. The distance travelled by the pulse wave over the surface of the body was measured with a tape measure (i.e., from sternal notch to right carotid artery and from sternal notch to right femoral artery) and was divided by the transit time. The final result was recorded and expressed as meters/second (m/s). The expert consensus document advises on the cf-PWV measurement procedures in general and provides arguments for the use of 80% of the direct carotid-femoral distance as the most accurate distance estimate.[20] We used the following formula for cf-PWV measurements: [cfPWV= (estimated direct distance = 0.45 x subtracted distance + 0.21 x height + 0.08) x 0.8].

Statistical analysis:

We used SPSS (SPSS version 15; SPSS Inc., Chicago, IL, USA), a statistical programme, to analyse the data. Continuous variables are presented as the mean ± standard deviation, and categorical variables are expressed as a percentage. The Kolmogorov Smirnov test was used to analyse the normally distributed data. The Mann-Whitney U test and the Kruskal-Wallis test were used for the nonparametric variables. Logistic regression was used for the multivariate analysis of the independent variable. Student's t-test and ANOVA were used for the comparison of averages for the parametric variables. P values lower than 0.05 was accepted as statistically significant.

RESULTS

The study group included 32 patients with $FEV_1 \geq 50\%$ of the predicted (i.e., classified as GOLD 1 and 2), 30 patients with $FEV_1 < 50\%$ of the predicted (i.e., classified as GOLD 3 and 4). The demographic characteristics of the study groups are presented in Table 1. Our patients were mainly male, and the patient group was on average older as compared to the

mean age of the controls. Moreover, although the patients with $FEV_1 \geq 50\%$ of the predicted had similar smoking habits as compared to that of the controls, patients with $FEV_1 < 50\%$ of the predicted had more intense smoking habits as compared to both the controls and the patients classified as GOLD 1 and 2. We revealed an increased PWV in both of the patient groups as compared to that of the healthy controls. Additionally, patients with $FEV_1 < 50\%$ of the predicted had even higher PWV values as compared to either that of the controls or patients with $FEV_1 \geq 50\%$ of the predicted.

The results from the arterial blood gas analysis, pulmonary function tests, and 6 min walking test results in COPD patients were analysed using Student's t- test and are summarised in Table 2. The performance of the 6 minute walking test was recorded with a mean distance of 360±69 meters in COPD patients and 427±64 meters in control group. As expected blood gas values, pulmonary function tests, and the 6 minute walking test parameters were significantly worse in patients classified at the GOLD 3 and 4 stages than that of patients classified at the GOLD 1 and 2 stages. We found that cf-PWV levels in COPD patients were independent of age and BMI in a univariate analysis of covariance and that cf-PWV values increased with disease severity or decrease in FEV_1 (p: .018).

The mean cf-PWV levels were found to be higher in COPD patients (10.95±3.74 m/s, n=62), than the healthy controls (7.32±1.88 m/s, n=22), but the difference was significant (p: .003). The Pearson correlations comparing these variables are presented in Table 3. cf-PWV showed a weak correlation with the age (p: .049) and cf-PWV did not change with smoking habits (pack/year) and BMI ($p< .05$). We found weak and negative correlations between cf-PWV (m/s) and the partial pressure of oxygen in arterial blood (p: .007, r: -.341) (Fig.1), and also between cf-PWV (m/s) and FEV_1 levels (p: .001, r: -.408) (Fig.2). The other spirometric parameter FVC showed weak and negative correlation with cf-PWV (p: .008, r: -.333) where the FEF_{25-75} showed a moderate and negative correlation ($p< .001$, r: -.511). We did not find a

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correlation between cf-PWV and serum CRP levels in this study (p: .826, r: .025), and between cf-PWV and smoking degree (pack-year), (p: .429, r: .102)

We observed higher cf-PWV values in COPD patients with greater disease severity as compared to that of patients with mild and moderate disease forms. The linear regression analysis identified that only FEV1 was an independent predictor of cf-PWV (p: .043) in our study population. The mean cf-PWV levels were found to be higher in the patients who had one or more exacerbations in the last one year (12.23±4.09 m/s, n=14), than the patients without any exacerbation during same period (11.01±3.81 m/s, n=48), and the difference was not significant (p: .331).

DISCUSSION

Arterial stiffness is mainly associated with aging and hypertension and it shows the structural and functional changes within the arterial wall .[13, 14] Previous research has shown that PWV is an independent predictor of mortality and stroke in the general population and in patients with end-stage renal disease, hypertension, and diabetes.[8, 15-17] Therefore, European guidelines on cardiovascular disease prevention considered the PWV as a test of target organ damage in hypertensive patients .[18, 19] In a cohort consisting primarily of treated hypertensive participants, aortic-PWV was associated with target organ damage in coronary, cerebral, and peripheral arterial beds.[19] PWV is a surrogate marker for vascular stiffness.[20] The present study was conducted to investigate the role of airflow limitation and hypoxemic parameters on PWV in subjects with COPD; interestingly, an increased cf-PWV was indeed observed in COPD patients. We also documented that a decline in pulmonary function tests and the partial pressure of oxygen in arterial blood is mainly associated with cf-PWV.

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Measures of arterial stiffness has been used to predict adverse cardiovascular events in different populations.[3, 5, 21, 22] In fact, a recent meta-analysis including individuals at high and low risk of cardiovascular events showed that aortic-PWV was associated with an increased risk of adverse cardiovascular events and cardiovascular and all-cause mortality.[22] In the offspring cohort of the Framingham Heart Study, aortic-PWV was independently associated with cardiovascular events.[5] Similarly, Terai et al.[21] demonstrated that aortic-PWV predicted myocardial infarction or stroke in a cohort of 676 patients with essential hypertension during a mean follow-up of 57 months.

COPD and coronary artery disease are both highly prevalent disease in the world and they share common risk factors, including smoking cigarettes, being elderly, and having a sedentary type lifestyle. It was well documented that the patients with severe and very severe forms of COPD had a greater risk of cardiovascular disease.[23] The patients with severe airflow limitations have a significantly higher risk of death from coronary artery disease , and this higher risk is independent of smoking behaviour, age and sex [24] In the Lung Health Trial, approxiametly 6,000 patients were followed for 14 years, FEV_1 was found to be an independent predictor of the probability of mortality from myocardial infarction.[25] The results of our study revealed that arterial stiffness increases with disease severity in COPD. Our findings could offer evidence as to why the risk of heart disease is higher for COPD patients. Indeed, arterial stiffness as a result of vascular disease is a good predictor of cardiovascular events and can be assessed noninvasively by measuring cf-PWV .[26] Age, smoking habits, body mass index, pulmonary function test levels, and the results of the arterial blood gas analysis may affect the cf-PWV. Our study population included COPD patients who smoked more heavily as compared to control group, but the PWV results in this study were not associated with the smoking habits of the individuals. Our results showed a weak correlation

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between age and cf-PWV (p=0.049, r=0.251) and did not show any correlation between body mass index and cf-PWV (p >0.05).

Another study [28] has also confirmed that arterial stiffness is increased in patients with COPD as compared to the arterial stiffness of normal smokers and non-smokers, which is in accordance with our results; however, the authors showed that arterial stiffness is unrelated to disease severity measured by circulating C-reactive protein concentrations, which is not in accordance with our findings based on spirometric results. Sabit et al.[29] included patients with stable COPD representing GOLD stages 1 through 4, and healthy smokers and ex-smokers were used as control subjects. They observed greater mean aortic-PWV in the COPD patients as compared to control subjects. Furthermore, much like our results, aortic-PWV was correlated to the GOLD stage, thereby indicating that the more severe airflow limitations are associated with higher PWV values.[27-29] Ultimately, COPD and hypoxemia may induce increased arterial stiffness, which may promote thickening of arterial walls, atherosclerotic plaque formation and vascular remodelling. The sequences of this process may start in the early stages of COPD and get worsen with the decline in lung function.

We thought that the systemic inflammation related to smoking may cause an increase in arterial stiffness in COPD patients. To find out the association between the systemic inflammation and smoking, we measured serum CRP levels in COPD patients. But we did not found any statistical significance between these parameters. The other confounders other than systemic inflammation, such as impaired microcirculation related to hypoxemia and increased local inflammatory reactions related to smoking in target organs (lungs, heart and arteries) may cause arterial stiffness.

The existence of systemic inflammation in COPD patients has been implicated in the pathogenesis cardiovascular comorbidities such as ischaemic heart disease and

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atherosclerosis.[30] The number of macrophages and interferon-c secreting Th1 lymphocytes increase in atherosclerotic plaques as well as in the peripheric regions of the lungs of COPD patients.[31, 32] The increased arterial stiffness may predispose to systemic hypertension and an increased risk of cardiovascular disease in COPD patients.[30] At the same time, arterial stiffness may reflect some pathological mechanisms, such as systemic inflammation, connective tissue abnormalities, impairment in endothelial function, and impairment of nitric oxide production which are associated with pathogenesis of COPD.[33] These results might lead to the conclusion that arterial stiffness increases in the latter stages of COPD.

Castagna et al. assessed the prevalence of peripheral arterial disease and its implications for exercise limitation in COPD patients.[34] In this study, the authors stated that there is a considerable effect of peripheral arterial disease on exercise intolerance, and it should be taken into account in the multidisciplinary treatments including pulmonary rehabilitation programmes in COPD.

Smoking induced systemic inflammation may cause an inflammatory response resulting in damage in several organs and structures. The repair of the damage in the lungs triggered by smoking and noxious gases results in COPD while the repair of the damage in systemic arteries results in atherosclerosis and increased arterial stiffness. Severe inflammatory reactions and pathologic structural changes ocur in the lungs and the vessels, particularly in genetically predisposed individuals. And this link may explain why COPD and arterial stiffness did not existed in all of the smokers. To explain how arterial stiffness occurs in other groups of patients who do not have COPD or hypoxemia and are non-smokers some other factors also should be detected. The other risk factors also play an important role on the mechanism of arterial stiffness other than smoking include obesity, diabetes mellitus, age, sex, hyperlipidemia, life style, genetic factors. As a result, to implicate COPD as a causative mechanism in the development of atherosclerosis, more elaborate investigations are required.

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Our study has several limitations. First, a cascade of events starting by hypoxemia and leading to arterial stiffness in smoking-associated COPD concomitant with airflow limitation could not be clarified. Second, the association between arterial stiffness and the other states of chronic airway obstruction with airway limitation and hypoxemia, such as alpha-1 anti-trypsin deficiency, bullous emphysema, and chronic persistent asthma could not be investigated in the absence of cardiovascular disease. Third, other confounders such as impaired microcirculation and increased local inflammation could not be identified. Fourth, the main limitation of this study is the small sample size. Fifth, our study is cross-sectional in nature; therefore, the study results cannot be used to implicate causality.

Conclusions

Despite these limitations, we used validated endpoints to strengthen our results. Based on these findings, we believe that hypoxemia affects arterial stiffness and vice versa in a vicious cycle, and they can lead to more rapid clinical deterioration. Moreover, cf-PWV is increased in COPD patients, and arterial stiffness is more prominent in patients with severe forms of COPD as compared to patients with mild and moderate forms.

Conflicts of interest

The authors declare that there are no conflicts of interest.

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Figure Legends:

Figure 1: Negative correlation between carotid-femoral pulse wave velocity (m/s) and PaO_2 (mmHg)

Figure 2: Negative correlation between carotid-femoral pulse wave velocity (m/s) and FEV_1 (% of predicted)

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Table 1: Demographic characteristics of the study groups

Parameters	**GOLD I and II ($FEV_1 \geq 50$ % of predicted, n=32), mean ± SD**	**GOLD III and IV ($FEV_1 <50$ % of predicted, n=30), mean ± SD**	**Control (n:22), mean ± SD**	**p value**
Male/female	1/31	1/29	1/21	
Age (year)	59.2 ± 10.2	65.2 ± 8.6	57.4 ± 7.6	.029* .739† .008‡
BMI (kg/m²)	27.2 ± 5.9	26.8 ± 5.4	26.7 ± 3.0	.933* .934† .998‡
Smoking (pack-year)	33.2 ± 11.8	41.6 ± 10.9	31.1 ± 12.6	.017* .791† .006‡
PWV	9.9 ± 3.3	12.7 ± 3.9	7.3 ± 2.9	.004* .013† < .001‡

Values are presented as mean (±SD). GOLD I and GOLD II (mild and moderate COPD having FEV_1> %50 of predicted), GOLD III and GOLD IV (severe and very severe COPD having FEV_1<%50 of predicted). The mean and standart deviation of the groups were analysed by using Anova variance test Tukey post hoc tests were used in binary. *: comparison of GOLD I and GOLD II (mild and moderate) patients with GOLD III and GOLD IV (severe and very severe) COPD patients, †:comparison of GOLD I and GOLD II (mild and moderate) patients with control groups, ‡ : comparison of GOLD III and GOLD IV (severe and very severe) COPD patients with control groups. BMI: body mass index, PWV: pulse wave velocity.

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Table 2: Analysis of arterial blood gas analysis, pulmonary function test and 6 min walk test results in COPD patients by Student's t- test

Parameters	**GOLD I and GOLD II (n=32), mean ± SD**	**GOLD III and GOLD IV (n=30), mean ± SD**	**p value**
Arterial blood gas analysis			
pH	7.41 ± 0.03	7.40 ± 0.02	.55
PaO_2 (mmHg)	77.1 ± 7.0	67.2 ± 7.5	< .001
$PaCO_2$ (mmHg)	38.3 ± 2.9	40.7 ± 5.1	.027
SaO_2	96.4 ± 1.3	94.2 ± 2.2	< .001
Pulmonary function tests			
FEV_1 (% of predicted)	64 ± 9	38 ± 8	< .001
FVC (% of predicted)	83 ± 11	55 ± 11	< .001
FEV_1/FVC	61 ± 4	54 ± 7	< .001
FEF_{25-75} (% of predicted)	36 ± 10	20 ± 8	< .001
PEF (% of predicted)	54 ± 13	38 ± 12	< .001
6 min walk test			
6MWT (meter)	427 ± 64	360 ± 69	< .001
The highest SaO_2 (%)	97.4 ± 0.9	95.2 ± 2.4	< .001
The lowest SaO_2 (%)	94.4 ± 3.3	90.3 ± 5.2	.001
Desaturation rate	3.1 ± 3.2	4.9 ± 3.6	.032

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Table 3: Pearson correlation analysis between parameters of the patients and carotid-femoral pulse wave velocity in COPD

Parameters	**Pulse wave velocity**	
	r value	**p value**
Age (year)	.251	.049
Smoking (pack-year)	.102	.429
BMI (kg/m²)	.080	.535
Pulmonary function tests		
FEV_1 (% of predicted)	-.408	.001
FVC (% of predicted)	-.333	.008
FEF_{25-75} (% of predicted)	-.511	< .001
PEF (% of predicted)	-.228	.075
Arterial blood gas analysis		
pH	-.012	.925
PaO_2 (mmHg)	-.341	.007
$PaCO_2$ (mmHg)	.147	.254
SaO_2	-.275	.030
6 min walk test		
6MWT (meter)	-.359	.004
Desaturation rate	.443	< .001

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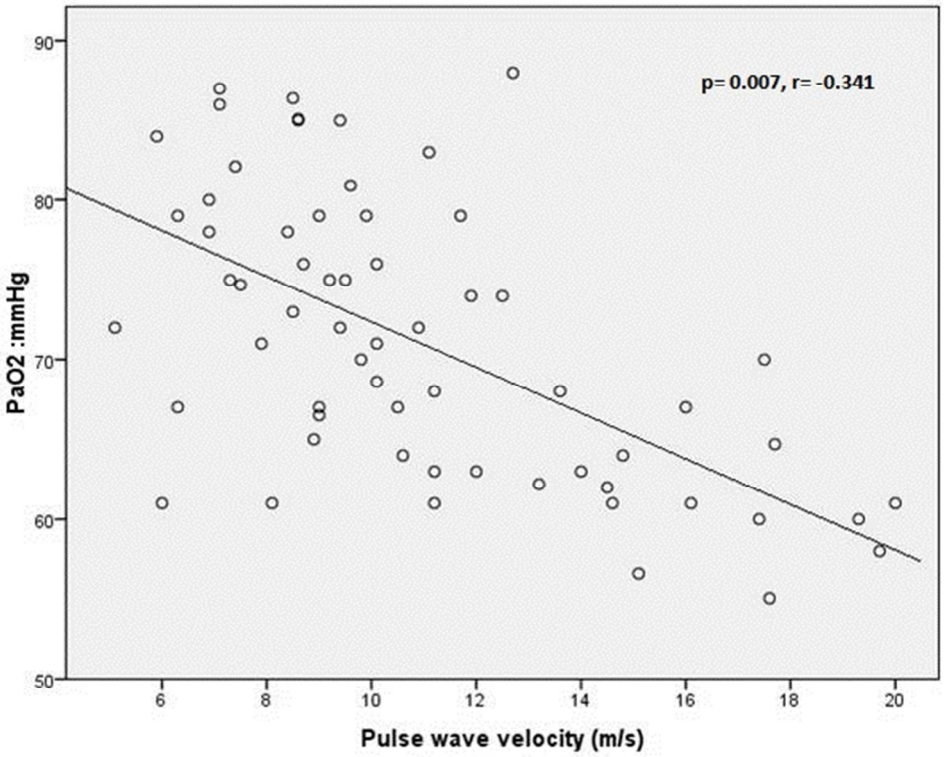

Negative correlation between carotid-femoral pulse wave velocity (m/s) and PaO2 (mmHg)
53x42mm (300 x 300 DPI)

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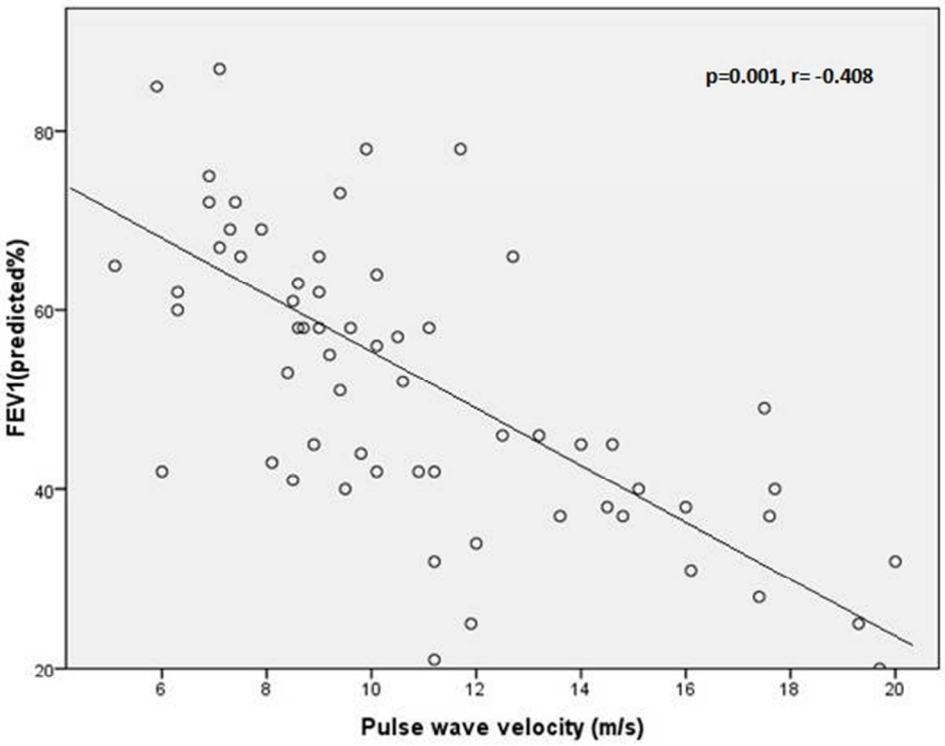

Negative correlation between carotid-femoral pulse wave velocity (m/s) and FEV1 (% of predicted)
53x42mm (300 x 300 DPI)