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Non-invasive evaluation of arterial stiffness in patients with increased risk of cardiovascular morbidity: A cross-sectional study

Yashmaina Sridhar, M.U.R. Naidu, P. Usharani, Y.S.N. Raju¹

Departments of Clinical Pharmacology and ¹General Medicine, Nizam's Institute of Medical Sciences, Hyderabad -500 082, Andhra Pradesh, India

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Correspondence to: Dr. M. U. R. Naidu E-mail: murnaidu@yahoo.com

ABSTRACT

Objectives: Cardiovascular disease (CVD) is associated with a generalized atherosclerotic process that begins in the large arteries, representing vascular pathology leading to increased cardiovascular morbidity and mortality. Pulse wave velocity (PWV) is a simple, accurate, reproducible and a good prognostic marker of arterial stiffness. Testing arterial stiffness with non-invasive techniques provides an opportunity to evaluate large patient populations with cardiovascular risk. Therefore, the aim of the present study was to evaluate non-invasively the arterial stiffness (AS) in patients with high cardiovascular risk.

Materials and Methods: Totally 3969 subjects [CAD - 845, DM - 973, ESRD - 942, RA - 221 and 988 age-matched healthy controls] were enrolled in the study approved by the IEC, NIMS; and all the subjects gave written informed consent to participate. Pulse wave velocity was determined non-invasively by PeriScope (M/S Genesis Medical Systems, Hyderabad, India).

Results: In patients with CAD, DM, ESRD and RA, heart rate (HR), blood pressure (BP) and PP were significantly more than healthy controls. Peripheral and central arteries' PWVs were higher in these patients' group. The mean HR was maximum in RA patient, while systolic blood pressure (SBP) was highest in ESRD patient. There was a good correlation between ba PWV and PP in all patients' group and healthy controls except RA patients. **Conclusion:** Our study findings emphasize the importance of the PWV in identifying the vascular damage in patients with high CV risk. Increased PWV was found to be a good independent predictor of cardiovascular morbidity.

KEY WORDS: Arterial stiffness, cardiovascular risk, pulse wave velocity

Cardiovascular (CV) morbidity and mortality is the leading cause of all deaths as per WHO's recent projection and is predicted to increase in future years.^[1] The stiffness of aorta and other arteries is a potential risk factor for increased CV morbidity and mortality, representing vascular pathology.^[2] Arterial stiffness (AS) increases with age and other concomitant cardiovascular risk factors like coronary artery disease (CAD), diabetes mellitus (DM) and end-stage renal disease (ESRD).^[3,4] Rheumatoid arthritis (RA) is associated with increased central blood pressure (BP) and AS, independent of clinically manifested cardiovascular disease or risk factor.^[5]

Pulse wave velocity (PWV) is now recognized as a standard method for the measurement of AS. Determination of PWV is the most reliable and reproducible method among the various indices of AS.^[3-5] In a cohort of elderly patients, PWV was the strongest predictor of cardiovascular mortality.^[6] Several non-invasive methods have been developed for quantitatively evaluating arterial wall distensibility using the pulse wave analysis. AS may be measured using a variety of different techniques, which measure either carotid-femoral PWV (assess central arteries) or brachial ankle PWV (assess peripheral arteries).^[7] However,

the majority of measurements are made for experimental and physiological studies rather than in clinical settings. Now, the most important task is to assess the CV risk.

Therefore, the present study was aimed to evaluate the PWV in various groups of patients, known to have increased risk of cardiovascular morbidity, using oscillometric technique, which measures carotid-femoral and brachial ankle PWVs simultaneously.^[7]

Materials and Methods

The present study was conducted in the department of Clinical Pharmacology and Therapeutics. The study protocol, informed consents and other trial-related documents received the written approval of Institutional Ethics Committee (IEC) of the institution. Patients attending the outpatient department of Cardiology, Diabetology, Nephrology, Rheumatology and Internal Medicine were invited to participate in the study. Participants, after understanding the study protocol and procedures, gave their written informed consent for the study. Patients of CAD had atherosclerotic arterial disease on angiogram, confirmed by the cardiologist, WHO diagnostic criteria was used for recruiting DM patients,^[8] RA patients met 1987 American College of Rheumatology (ACR) criteria,^[9] ESRD patients had creatinine clearance <10 ml/min, while the control group consisted of normal, healthy individuals with no atherosclerotic risk factors. Patients with severe CAD, congestive heart failure (CHF), hypertension, patients on insulin, diabetic neuropathy, ketosis or stroke and peripheral arterial disorder were excluded from the study. Before the determination of PWV, recording of complete medical history including details of drug regimen and clinical examination was performed by the clinician.

Pulse wave velocity was determined by PeriScope (M/S Genesis Medical Systems, Hyderabad, India) in an 8-channel realtime PC-based simultaneous acquisition and analysis system. The acquisition rate is 200 samples per second, which is sufficient because the significant frequency content of the pressure as well as ECG waveform is not more than 40 Hz. According to Nyquist's criteria, the minimum sampling rate should be 80 samples per second. Hence, a sampling rate of 200 Hz/s is optimum. It supports a sophisticated digital signal-processing algorithm to calculate all the results. System has dedicated hardware module connected to 4 ECG electrodes and 4 blood pressure measuring cuffs. It is very user-friendly and fully automatic. Once started, the test recording completes itself by displaying results directly. The report contains 8-second traces of Lead I and II ECG, all pressure pulse waveforms and all calculated results. Device has a built-in database that can be used to store patient folders for further referrals at any point of time. PeriScope is a PC-based low-cost instrument. When used with a laptop, it can be carried to remote locations. It uses ECG as a marker. It does not use phonocardiogram. PeriScope thus facilitates use in epidemiological studies, which has been validated and has had good interday and interobserver reproducibility (r = 0.88-0.90) for various estimated central and peripheral arterial velocities, according to the procedure described earlier.^[7]

In brief, PWV was determined by a non-invasive pulse wave analyzing device. Participants were asked to refrain

Table 1

Clinical characteristics of all subjects

from smoking and drinking caffeine-containing beverages 12 h before the test. They were also advised not to take their morning dose of medicine on the day of procedure, before completing the test. Procedure was performed always by the same operator in the morning hours between 8 and 10 a.m. with subject resting in supine position at least for 10 min before the recording. Electrodes for electrocardiogram were placed on ventral surface of both wrists and medial side of ankles, and BP cuffs were wrapped on both upper arm brachial artery and tibial artery above ankles. The cuffs were connected to a plethysmographic sensor, which determines volume pulse form and an oscillometric pressure sensor, which measures blood pressure volume waveforms from the brachial and tibial arteries. All the pressure recordings were done for about 10 s and data were stored in the computer for analysis. Software was applied to calculate the following parameters from the waveforms, which were stored in the computer for analysis like - systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP), pulse pressure (PP), heart rate (HR), heart brachial (hb) PWV, heart ankle (ha) PWV, brachial ankle (ba) PWV, carotid-femoral (C-F) PWV and ankle brachial index (ABI).

Data are expressed as mean \pm SD. Statistical analysis was performed using the Graph pad PRISM software version 4 (Graph pad software Inc., San Diego, California, USA). Difference between all the groups was evaluated by unpaired Student's 't' test and ANOVA. Linear regression analysis and Pearson's correlation analysis were performed to evaluate the association between ba PWV and pulse pressure. Probability values of P < 0.05 were considered to indicate statistical significance.

Results

Including healthy controls, totally 3969 subjects were recruited for the determination of PWVs in the present study. The clinical characteristics of all the patient groups and healthy controls are presented in Table 1. Pulse wave velocity was determined in 988 healthy controls (612 males, 376 females),

	Healthy subjects	CAD patients	DM patients	ESRD patients	RA patients
Number	988	845	973	942	221
Gender (M/F)	612/376	594/251	678/295	636/306	49/172
Age (years)	47 ± 7	48 ± 8	49 ± 7	46 ± 9	46 ± 10
Weight (kg)	57.61 ± 10.04	67.06 ± 11.06	65.98 ± 9.99	61.35 ± 11.76	59.56 ± 12.56
Height (cm)	165.9 ± 7.77	161.5 ± 9.40	161.1 ± 10.69	164 ± 9.99	158.6 ± 8.4
BMI (kg/m ²)	20.98 ± 3.58	25.63 ± 4.78	25.43 ± 3.29	23.89 ± 3.73	23.72 ± 5.07
Heart rate (bpm)	72.32 ± 5.6	$81.26 \pm 5.3^{*}$	$82\pm6.2^{\ast}$	80 ± 6.34*	$86.3 \pm 7.37^{*}$
Systolic BP (mmHg)	122.8 ± 9.4	146.7 ± 10.37*	141.2 ± 11.8*	$149.8 \pm 8.31^{*}$	130.8 ± 9.4*
Diastolic BP (mmHg)	80.67 ± 5.02	$90.7\pm3.3^{\ast}$	$104.8 \pm 6.9^{*}$	$102.3 \pm 8.1^{*}$	$98.8\pm8.5^{\ast}$
MAP (mmHg)	69.73 ± 9.95	$81.58 \pm 10.75^*$	$80.45 \pm 9.78^{*}$	89.3 ± 8.19*	$81.25 \pm 10.35^{*}$
Pulse pressure (mmHg)	48.35 ± 10.02	$60.52 \pm 9.32^*$	60.52 ± 8.45	$55.07 \pm 9.34^*$	50.53 ± 10.90*
TC (mg/dl)	150.53 ± 28.5	$220.43 \pm 30.8^{*}$	$244.35 \pm 26.4^{*}$	$188.06 \pm 25.8^*$	$186.3 \pm 28.1^{*}$
HDL (mg/dl)	57.8 ± 11.25	$37.38 \pm 9.54^{*}$	$38.57 \pm 8.26^*$	$42.21 \pm 10.46^*$	$40.16 \pm 10.65^{*}$
TG (mg/dl)	116 ± 18. 97	310 ± 38.27*	$298.43 \pm 42.12^*$	$219.26 \pm 22.45^*$	189.9 ± 23.5*
FBS (mg/dl)	95.4 ± 15.3	$136.32 \pm 18.7^{*}$	$158.8 \pm 14.4^{*}$	111 ± 11.28*	$106 \pm 10.64^{*}$

CAD - Coronary artery disease, DM - Diabetes mellitus, ESRD - End-stage renal disease, RA - Rheumatoid arthritis, TC - Total cholesterol, HDL - High density lipoprotein, TG - Triglycerides, FBS - Fasting blood glucose. Values are expressed as mean ± SD. *P < 0.0001 vs healthy subjects

845 CAD patients (594 males, 251 females), 973 Diabetic patients (678 males, 295 females), 942 ESRD patients (636 males, 306 females) and 221 RA patients (49 males, 172 females). The mean BMI, HR, SBP, DBP, MAP and PP were found to be significantly higher in CAD, DM, ESRD and RA patients than in control group.

The maximum SBP 149.8 \pm 8.31 mmHg was found in ESRD patients, while the HR was maximum 86.3 \pm 7.37 bpm in RA patients. Table 2 shows the mean values of hb PWV, ha PWV, ba PWV and ankle brachial index (ABI). As seen from the table, all the PWVs mentioned were found to be significantly higher in CAD, DM, ESRD and RA patients' group than in healthy control (P < 0.0001). Brachial ankle PWV was maximum 1679 \pm 151.2 cm/s in CAD patients than 1620 \pm 132.7 cm/s in DM patients, 1631 \pm 140.4 cm/s in ESRD and 1515 \pm 198.8 cm/s in RA patients. The ba PWV in healthy controls was 1284 \pm 117.2 cm/s.

Similar to be PWV, the C-F PWV was also found to be significantly higher in all patients groups than healthy control [Figure 1]. There was a good correlation (P < 0.0001) between be PWV and pulse pressure in all the patient groups including healthy control (P < 0.0001), except the RA patients [Table 3].

Discussion

In recent years, much interest has been developed to study the inter-relationship between AS and CV Disease. Pulse pressure and PWV, both, are good surrogate measures of AS. Patients with certain disease states that are associated with increased cardiovascular risk including hypertension, DM, hypercholesterolaemia, ESRD and RA are found to have increased AS.^[3] Using different techniques, AS may be measured in patients. Both invasive and non-invasive methods have been used for determination of PWV, which utilize either flow

Table 2

Pulse wave velocity and ankle brachial index

Figure 1: Carotid-femoral PWV in healthy controls and patient groups



or pressure wave recordings. The technique of PWV is valid and reproducible and has been widely applied in both healthy, normal volunteers and patients. $^{[10]}$

In our study, we have used a non-invasive device, PeriScope, which simultaneously records pressure wave from four limbs to calculate PWVs. The device was validated and found to have good reproducibility in PWV measurement in healthy and CAD patients.^[7] Recently, a method which uses magnetic resonance imaging technique has been described.^[11] Although it allows assessment of accurate path length and measurements from less inaccessible arteries, is expensive, time consuming and needs skilled, trained persons. Problems with the use of ultrasound to assess AS, include the limited resolution, reproducibility and experienced operator. We estimated AS from oscillometric blood pressure measurement. The pattern of oscillations depends on AS; therefore, by coupling this to a computer algorithm, an index of AS can be calculated. This

	Healthy subjects	CAD patients	DM patients	ESRD patients	RA patients
Heart brachial PWV (cm/s)	$\textbf{284.8} \pm \textbf{42.12}$	$312.3 \pm 39.4^{*}$	$323.8 \pm 57.43^{*}$	$312.4 \pm 49.92^{*}$	317.3 ± 55.10*
Heart ankle PWV (cm/s)	458.1 ± 51.50	$545.7\pm48.5^{\ast}$	$561.8 \pm 45.1^{*}$	$542.7 \pm 56.46^{\ast}$	$521.7 \pm 49.77^*$
Brachial ankle PWV (cm/s)	1284 ± 117.2	$1679 \pm 151.2^{*}$	$1620 \pm 132.7^{*}$	$1631 \pm 140.4^{*}$	$1515 \pm 198.8^{*}$
ABI	1.13 ± 0.07	1.16 ± 0.10	1.12 ± 0.08	1.16 ± 0.11	1.12 ± 0.13

CAD - Coronary artery disease, DM - Diabetes mellitus, ESRD - End-stage renal disease, RA - Rheumatoid arthritis. Values are expressed as Mean ± SD. *P < 0.0001 vs healthy subjects

Table 3

Means and correlational analysis (Pearson r value) of pulse wave velocity and pulse pressure in healthy and patient groups

	Healthy subjects	CAD patients	DM patients	ESRD patients	RA patients
Brachial ankle PWV	1284 ± 117.2	1679 ± 115.2	1620 ± 132.7	1631 ± 140.4	1515 ± 198.8
Pulse pressure	48.35 ± 10.02	60.52 ± 9.32	60.52 ± 8.45	55.07 ± 9.34	50.53 ± 10.90
Pearson (r)	0.2621	0.2723	0.2990	0.3068	0.07862
95% Confidence interval	0.1671 to 0.3522	0.1402 to 0.3950	0.2001 to 0.3918	0.1087 to 0.4814	-0.1705 to 0.3183
P-value	<0.001	<0.001	<0.001	<0.003	ns
CAD - Coronary artery disease, DM - Diabetes mellitus, ESRD - End-stage renal disease, RA - Rheumatoid arthritis. Values are expressed as mean ± SD					

method has been shown to be reproducible and is currently being evaluated in outcome studies and clinical practice.^[7]

Arterial stiffness assessed by PWV correlates to the number of treated and non-treated cardiovascular risk factor, atherosclerotic events and cardiovascular risk as predicted by the Framingham risk equations.^[11] PWV is also positively correlated with carotid media thickness, a marker of atherosclerotic burden in the coronary arteries.^[12] Both intimamedia thickness and PWV increase with risk factors for CVD. We have found that in CAD patients, there was a significant increase in ba PWV and C-F PWV. Several previous studies have also shown usefulness of ba PWV in estimating AS,^[13] aortic damage.^[14] Recently, the clinical application of ba PWV in CAD patients has been evaluated and high ba PWV was shown to predict the presence of CAD.^[15]

Lehmann *et al.* have studied the arterial compliance in type 2 DM patients using measurements of PWV and reported that as compared to age- and sex-matched non-diabetic controls, patients have significantly stiffer aorta.^[16] Our finding of increased ba PWV and C-F PWV in DM patients is in accordance with other studies. Woolam *et al.* found that carotid to radial PWV is increased in DM patients.^[17] Studies have shown that PWVs other than C-F are also clinically useful.^[18] Brachial ankle PWV principally reflects the stiffness of elastic vessels and may differ from that of carotid PWV and aortic PWV. In DM, PWV of lower limb is predominantly affected than upper limb vessels.^[19] Patients with DM in our study had increased ba PWV than control subjects.

In a Indian population study, mean ba PWV in DM patients was found to be more than 1600 cm/s;^[20] in our patients, the mean ba PWV was 1620 cm/s. Value beyond 1400 cm/s of ba PWV was considered abnormal.^[20] Between ba PWV and PWV from aorta, there is very good correlation.^[21] We also got good correlation between ba PWV and C-F PWV in our patient population. Aortic PWV of 900 cm/s is suggested as a threshold value for high risk of CV disease in clinical studies and has excellent co-relation with ba PWV value of 1400 cm/s.^[22] Except in healthy controls, in all our patients' groups, the C-F PWV and ba PWVs were more than 900 and 1400 cm/s, respectively.

Compared to age- and mean BP-matched non-uremic patients, the AS is greater in ESRD, especially in younger uremic subjects. Aortic stiffness was an independent risk factor for total mortality and cardiovascular morbidity and mortality in ESRD patients.^[4] In ESRD patients, the augmentation index and PWV are independent predictors of mortality and have a greater predictive power, than pulse pressure. Arterial wall stiffness assessed by aortic PWV in pre-dialysis and haemodialysis patients was found to be significantly greater than the healthy subject. The mean aortic PWV of the predialysis group was higher than that of the haemodialysis group.^[23] Large arteries, like aorta or common carotid artery, are enlarged in ESRD patients in comparison to age-, sex- and pressure-matched control subject.^[4,23]

Rheumatoid arthritis is associated with excess cardiovascular mortality, which is not explained by systemic vasculitis or traditional cardiovascular risk factors.^[24] Pulse wave analysis appears to be a more sensitive measure of vascular dysfunctions in RA and may be a preferred surrogate marker.^[5] The large artery compliance in RA patients was significantly reduced compared to healthy controls.^[5] In our RA patient group, the ba PWV was significantly higher than in control, but it was apparently less than CAD, DM and ESRD groups.

First preliminary evidence of increase in AS in RA patients, assessed by PWA was shown by Klocke *et al.*^[5] We assessed the function of large arteries in subjects with RA using pulse wave analysis. In RA patients, both ba PWV and C-F PWV were significantly higher than healthy controls. Quantitative analysis of arterial pressure waveform is now possible using non-invasive technique or pulse wave analysis.

Increased resting HR has also been identified as a risk factor for cardiovascular and all-cause mortality in population studies.^[25] The mean HR was highest in RA patients in our study than other risk groups. The higher resting heart rate in these RA patients had also been reported, earlier^[5] and can be attributed to anaemia.

There was good correlation between pulse pressure and ba PWV in patients with CAD, DM, ESRD and healthy control. For a given ventricular ejection, large arterial stiffness is a major determinant of pulse pressure, a clinical marker of which is PWV.

Conclusion

Our study findings emphasize the importance of the PWV in identifying the vascular damage in patients with high CV risk. Increased PWV was found to be a good independent predictor of cardiovascular morbidity. This technique may prove useful to evaluate the impact of interventions, especially drug treatment, to evaluation of arterial stiffness.

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