Original

Are pulse wave velocity and arterial stiffness markers for early pre-clinical atherosclerosis detection in resistant hypertensive patients?

¿Son la velocidad de la onda del pulso y los marcadores de rigidez arterial para la detección precoz de la aterosclerosis preclínica en pacientes hipertensos resistentes?

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ABSTRACT

Pulse wave velocity and arterial stiffness are considered gold standard for assessing sub clinical target organ damage. Endothelial dysfunction is directly proportional to development of pre-clinical atherosclerosis. These above-mentionedsurrogate markers are relatively higher in patients with uncontrolled or resistant hypertension patients. The objective was to assess if arterial stiffness and pulse wave velocity are also surrogate markers for pre-clinical atherosclerosis development in patients with resistant hypertension. A total of 160 patients with resistant hypertension from Croatia and India were included in the study. Their central blood pressure and other clinical values were assessed using non-invasive device. With the results obtained can conclude that arterial stiffness is an independent marker which is directly proportional to endothelial dysfunction and development of pre-clinical atherosclerosis.

RESUMEN

La velocidad de la onda del pulso y la rigidez arterial se consideran el estándar de oro para evaluar el daño subclínico de órganos diana. La disfunción endotelial es directamente proporcional al desarrollo de la aterosclerosis preclínica. Estos marcadores sustitutos mencionados anteriormente son relativamente más altos en pacientes con hipertensión no controlada o resistente. El objetivo fue evaluar si la rigidez arterial y la velocidad de la onda del pulso también son marcadores sustitutos del desarrollo de la aterosclerosis preclínica en pacientes con hipertensión resistente. Un total de 160 pacientes con hipertensión resistente de Croacia e India fueron incluidos en el estudio. Su presión arterial central y otros valores clínicos se evaluaron utilizando un dispositivo no invasivo. Con los resultados obtenidos se puede concluir que la rigidez arterial es un marcador independiente que es directamente proporcional a la disfunción endotelial y al desarrollo de aterosclerosis preclínica.

Palabras clave: Aterosclerosis; Enfermedad Cardiovascular; Velocidad de la Onda del Pulso; Rigidez vascular; Presión Arterial Alta.

Keywords: Atherosclerosis; Cardiovascular Disease; Pulse Wave Velocity; Vascular Stiffness; High Blood Pressure.

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INTRODUCTION

Pulse wave velocity is the current gold standard of assessing arterial stiffness and vascular health. With the increasing age, it is well known that the vascular age also rises correspondingly. Normal biological changes within the arterial vessels due to the effects of oxidative stress, free radical particles and endothelial dysfunction. Endothelial dysfunction is the primitive stage for development of any vascular pathology according to Davignon et al.[1] The normal endothelium is regulated and controlled by the release of nitric oxide (NO). The NO is totally responsible for the normal vascular tonus maintenance, with the dilation and normalisation of the vessel wall.[2] The aortal (elastic type of artery) or central blood pressure is regarded the accurate measurement than the brachial artery (due to its muscular type) sensitive to several factors producing false positive result.[3] Arteriosclerosis along with endothelial dysfunction is the most common pathogenic mechanism for the progression of sub clinical atherosclerosis. The loss of distensability in the arteries or the cushioning effect increases the arterial stiffness and further degrades facilitating in the development of the development. Recently, non-invasive

central blood pressure measuring cuff devices have been developed for the assessment of arterial stiffness with the parameters like central blood pressure, pulse pressure, mean arterial pressure, augmentation index and pulse wave velocity.[4] These novel non invasive measurement techniques make it convenient to assess the above parameters and serve as novel vascular markers in determining early sub clinical atherosclerosis detection and further management by clinicians. Pulse pressure is the difference between systolic and diastolic blood pressure. Mean arterial pressure is defined as the average blood pressure in a single cardiac cycle. Pulse wave velocity is a diagnostic test at which the blood pressure pulse propagates through an artery or an arterial system.

The aim of this study isto assess and determine if arterial stiffness and pulse wave velocity are vascularbio-markers for earlypre-clinical atherosclerosis detection in resistant hypertension patients from Croatia and India.

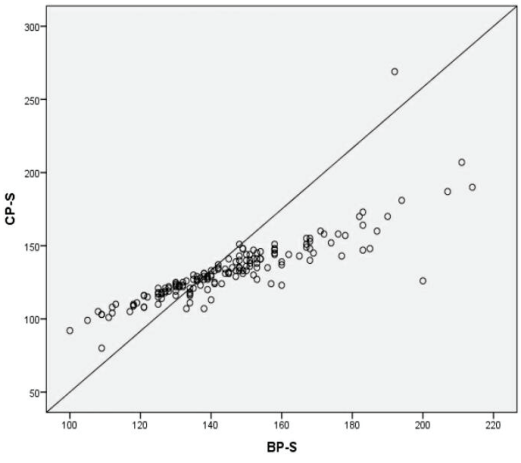
METHODS AND MATERIALS

We prospectively measured the blood pressure values at Merkur University Hospital, Zagreb, Croatia in January 2018 and Kasturba Medical college hospital, Mangalore, India in August 2018 was conducted. Our inclusion criteria were 160 patients (80 from each country) with Resistant hypertension (RH) (resistance to 3 or more drugs, one is diuretic) exclusion criteria being absence of chronic kidney disease, were analysed. The PWV, mean arterial pressure (MAP), pulse pressure (PP), CBP, brachial pressure (BP systolic and diastolic) were evaluated using the non-invasive Agedio B900 device (Germany).

The diagnosis of RH was made on the (basis of the ESH/ESC classification of resistant hypertension) inability to control the arterial pressure even after using three or more drugs. The drug combinations included angiotensin converting enzyme inhibitors (ACEI), angiotensin II receptor blockers (ARB), beta blockers (BB), calcium channel blockers (CCB) and diuretics (D). Combinations like ACEI+CCB+D and potassium sparing diuretic were preferred in 30% of the patients. We avoided an improper blood pressure measurement by using an suitable cuff size and informed the patients to avoid a heavy meal, exercise, smoking and alcohol and also allowing the patient to relax 5 minutes prior the assessment in our study following the new guidelines issued by the international society of hypertension in June 2020.An informed consent of the patients was obtained before participation. The study was approved by local institutional ethics committee. Statistical data was processed in SPSS software; significant differences were considered at p<0,01.The obtained data was interpreted in descriptive statistics and scattered plots.

RESULTS

Out of the total 160 patients, 80 (50%) were from India and 80 (50%) from Croatia. The total number of female subjects were 106 (53 were from each country) and males (27 from each country) were 54 respectively. The mean average age was 58.3±13.59; in females (F) 58.83±13.58and 57.58±13.5 in males (M). From the group statistics made gender wise, the values of BP-S, BP-D, MAP, CP-S, CP-D, cPP and PWV have been described in **TABLE NO 1**. The BP-S values in M/F were 147.26±22.12/144.10±21.29; the BP-D values in M/F were 94.98±13.36/88.57±12.25 respectively. The MAP values in M/F were122.67±14.12/116.23±15.15 and CP-S values were 134.94±25.49/131.33±19.14 respectively. The CP-D values in M/F were 96.80±14.15/90.25±12.41 and the cPP was 45.71±20.8/50.24±20.14 respectively.The values of PWV in M/F were 8.83±1.9/8.98±2.06 m/s. The BP-S values in Indian patients(I)/Croatian



Plot.1, *describes the correlation of central systolic pressure with brachial systolic pressure in patients from both the countries.*

Table 1. *describes the blood pressure values in both female and male subjects with resistant hypertension in both countries.*

	Gender	N	Mean	Std. Derivation	Std. Error Mean
BP-S	female	106	144.10	21.299	2.069
	male	54	147.26	22.126	3.011
BP-D	female	106	88.57	12.253	1.190
	male	54	94.98	13.361	1.818
MAP	female	80	116.23	15.158	1.695
	male	39	122.67	14.120	2.261
CP-S	female	106	131.33	19.148	1.860
	male	54	134.94	25.495	3.469
CP-D	female	106	90.25	12.411	1.205
	male	54	96.80	14.159	1.927
CENTRAL PULSE PRESSURE(cPP)	female	99	50.24	20.145	2.025
	male	52	45.71	20.813	2.886
PVW	female	105	8.98	2.061	.201
	male	53	8.83	1.959	.269

Table 2. *describes the blood pressure values in patients with resistant hypertension from both countries.*

	Gender	N	Mean	Std. Derivation	Std Error Mean
BP-S	Indian	80	144.50	21.958	2.455
	Croatian	80	145.84	21.280	2.379
BP-D	Indian	80	91.08	13.190	1.475
	Croatian	80	90.39	12.796	1.431
MAP	Indian	80	115.64	15.795	1.766
	Croatian	39	123.87	11.844	1.897
CP-S	Indian	80	132.74	23.409	2.617
	Croatian	80	132.36	19.526	2.183
CP-D	Indian	80	92.95	13.438	1.502
	Croatian	80	91.96	13.326	1.490
CENTRAL PULSE PRESSURE(cPP)	Indian	80	38.54	12.174	1.361
	Croatian	71	60.11	21.826	2.590
PVW	Indian	80	8.98	1.862	.208
	Croatian	78	8.88	2.186	.248

patients (C) were144.5±21.9/145.84±21.28; the BP-D values in I/C were 91.08±13.19/90.39±12.7 respectivelyand have been described in **TABLE NO 2**. The MAP values in I/C were115.64±15.7/123.87±11.8 and CP-S values were 132.36±23.4/132.36±19.5 respectively.The CP-D values in I/C were 92.95±13.4/91.96±13.3 and the cPP was 38.5±12.17/60.11±21.8 respectively. The values of PWV in I/C were8.98±1.8/8.88±2.1 m/s. The Pearson correlation between CP-S and BP-S was found to be statistically significant p=0.862(**see in figure n 1**). The difference between sexes was statistically significant for PWV (M/F: 8.8/8.9m/s p<0,01).

DISCUSSION

Varahabhatla et al in their prospective study on 80 patients described the effectiveness of PWV and CBP assessment in resistant hypertensive patients and the predictability of hypertension mediated target organ damage.[6]

Wilkinson et al, described the current possibilities of assessing vasomotor endothelial function. They tested the hypothesis of pulse-wave analysis (PWA) in combination with a provocative pharmacological test might provide an alternative method to assess endothelial dysfunction.[7]

Lane et al, described the non-invasive tools for establishing pre-clinical atherosclerosis in their review article. Brief data on PWV and pulse wave analysis was evident. Very little is known about the use of PWV in assessing the endothelial dysfunction.[8]

Sutton et al, in their study on 2488 participants reported that increased aortic pulse wave velocity and arterial stiffness were markers of cardiovascular events in well-functioning older population. Higher levels of arterial stiffness were associated with higher cardiovascular mortality rate and ischemic heart disease.[9]

Nichols in his review on clinical arterial stiffness assessment using non-invasive waveforms. Higher values of both systolic and pulse pressures resulting in elderly patients or hypertensive patients an increase in circumferential arterial wall stress is evident, which likely causes the breakdown of medial elastin, increasing the possibility of local vascular fatigue, endothelial dysfunction and development of atherosclerosis.[10]

Mori et al, in their cross-sectional study on 177 Latino and white hypertension population, reported that PWV was associated strongly with carotid intima thickness, proving that PWV assessment in hypertensive population irrespective of ethnicity is an adjunct and independent atherosclerotic marker.[11]

Terai et al in their longitudinal study on 813 patients described that increase in levels of arterial stiffness as assessed by PWV contributed to an increased incidence of stroke and heart disease, whereas higher reactive hyperaemia evaluation using strain gauge plethysmograph causes a reduced incidence of cardiovascular and cerebrovascular events. PWV is an independent predictor than strain gauge plethysmograph, which showed weak correlation and better outcome.[12]

Jadhav et al, in their study stated that pulse wave velocity along with flow mediated dilation were the best prediction markers for assessing pre-clinical atherosclerosis and endothelial dysfunction non-invasively. Their study included 102 patients with arterial hypertension and concomitant diabetes who were at high risk for atherosclerosis. High values of arterial stiffness and PWV followed by decreased flow mediated dilation of brachial artery were indicative of non-invasive PWV as a gold standard.[13]

Kim et al mentioned about the importance of pulse wave velocity and atherosclerosis in his review article. He discussed about the positives of pulse wave velocity inscreening pre-clinical atherosclerosis and cardiac disease prevention on a mass basis. Intensive lifestyle changes, optical risk stratification and therapeutic modulations are necessary for preventing preclinical atherosclerosis and cardiovascular event.[14]

McEniery et al, in their prospective study on 309 patients described the functioning of endothelium and large artery stiffness development. The results of their study described that even in healthy subjects, reduced endothelial function is strongly associated with not only higher PWV levels, but also pulse pressure and central blood pressure. The results obtained confirm the importance of endothelium dependant nitric oxide and its reduction strongly supporting development of pre-clinical atherosclerosis and increased vascular stiffness.[15]

CONCLUSIONS

Patients from both the countries did not show any statistical difference in the estimated values. With the non-invasive assessment of PWV and CBP, we can conclude that arterial stiffness is an independent marker which is directly proportional to endothelial dysfunction and development of pre-clinical atherosclerosis. The mechanism of this process is increased PWV and CBP and their contribution in elevating the risk for atherosclerosis development. The vascular age determined by PWV is of utmost importance in assessing the normal endothelial function. We can hypothesise that endothelial

dysfunction can be predicted non-invasively with the markers like CBP and PWV, despite of very less evidence. There is a high necessity for future longitudinal and higher population studies to describe the urgency of diagnosing pre-clinical atherosclerosis and validating the non-invasive devices for their regular use in the clinician's office.

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