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ORIGINAL RESEARCH

Physiological and biochemical markers of arterial stiffness fluctuate with age in apparently healthy people

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ABSTRACT

Objectives: Arterial stiffness develops with age and is an independent risk factor for cardiovascular disease. The brachial ankle pulse wave velocity (baPWV) and serum osteoprotegerin (OPG) are two new physiological and biochemical measures used to assess arterial stiffness. We looked at how age affects physiological and biochemical measures of arterial stiffness.

Materials and methods: It were a cross-sectional, observational study on 118 apparently healthy male and 114 female patients aged 30–>60 years who did not have any cardiovascular or peripheral vascular disease and were not on any antihypertensive or lipid-lowering medication. The following parameters were measured: brachial systolic blood pressure (bSBP), brachial diastolic blood pressure, central systolic blood pressure (cSBP), central diastolic blood pressure (cDBP), heart rate, augmentation index (AIx[percent]), and baPWV. The recorded data were used to calculate the mean arterial pressure (MAP), pulse pressure (PP), and PP ratio (PPR). Serum samples were analysed in order to determine the OPG level and lipid profile. The Kruskal–Wallis's test was used to compare the differences between the parameters.A Spearman correlation analysis was used to see if there was any relationship between baPWV and other parameters. To identify the factors linked with baPWV, multiple linear regression analysis was used. P 0.05 was deemed statistically significant.

Results: Males had significantly larger height, weight, and PPR values than females. Females exhibited considerably greater BMI, AIx (percentage), cSBP, cPP, and brachial PP values than males. In comparison to younger boys, older males showed considerably higher AIx (percent), cPP, and brachial PP. In compared to younger girls, older females had considerably greater AIx (percent), cPP, brachial PP, serum cholesterol, triglyceride (TG), low-density lipoprotein cholesterol (LDLc), and very LDLc (VLDLc). Serum OPG levels were discovered to be a primary factor influencing baPWV values in both males and females.Other cardiovascular measures such as cSBP, cDBP, cMAP, brachial SBP, and MAP influenced baPWV values in both genders, while serum cholesterol and LDLc influenced baPWV values in the male participants in the current study. Serum TG and OPG levels were found to be highly linked with baPWV in both genders, according to regression analysis.

Conclusion: Cardiovascular indices such as central blood pressure, peripheral blood pressure, and AIx (percent) increased with age in both genders, but PPR reduced in males. BaPWV readings also showed an increasing tendency with age. Females' serum cholesterol, TG, LDLc, and VLDLc levels increased with age. Serum OPG and serum TG levels were found to be key influencing factors of baPWV values in both genders, regardless of age.

Keywords: Arterial stiffness, Brachial-ankle pulse wave velocity, Serum osteoprotegerin

INTRODUCTION

The arterial system ages due to structural changes such as elastin fragmentation and degradation, an increase in collagen, thickening of the arterial wall, and increasing dilatation of arteries. [1] These modifications cause the vasculature to tighten gradually and the velocity of the pressure wave to increase as it travels down the aorta. During diastole, the pressure wave reflects from the periphery and returns to the heart in a normal elastic aorta. When coronary blood flow occurs during diastole, this reflected wave helps augment pressure. The velocity of the pressure wave increases as the aorta stiffens, and the reflected pressure wave eventually reaches the heart earlier, at systole.It raises systolic blood pressure (SBP) and increases cardiac afterload. The aortic stiffening, combined with the lack of diastolic augmentation from the reflected pressure wave, has the potential to limit coronary filling. [2]

Arterial stiffening is related with increased pulse pressure (PP), which eventually leads to isolated systolic hypertension, a disorder that affects 30% of adults by the age of 80. [3] Vascular calcification, which causes arterial stiffening, is an active process governed by complex enzymatic and cellular processes. [4] It mimics orthotopic or skeletal bone formation more. Before mineralisation, endochondral or intramembranous ossification occurs. In the absence of a collagen template, intramembranous ossification proceeds from osteoblast-induced calcification of collagen extracellular matrix [5, 6, 7].

Arterial stiffness is a major contributor to cardiovascular disease and is becoming a focal topic in efforts to detect and prevent cardiovascular disease at an early stage. To determine arterial stiffness, a number of physiological measures such as central blood pressure and the augmentation index (AIx (percent)) have been introduced [8, 9, 10]. Pulse wave velocity (PWV) is the most commonly used in clinical medicine because it can be measured simply and noninvasively. [11, 12] The carotid-femoral PWV (cfPWV) approach is used to assess arterial stiffness.It is precise and repeatable. However, in order to find carotid and femoral pulses, the procedure demands technical precision. To adopt arterial stiffness assessment in daily clinical practise, a reliable, reproducible, and simple technique that does not require technical skill is required. One such approach that has a good connection with cfPWV is brachial-ankle PWV (baPWV). [11]To that end, the current study was carried out to determine changes in physiological parameters such as baPWV, AIx (percent), central blood pressure, and biochemical parameters such as serum OPG, serum cholesterol, and triglyceride (TG) with increasing age in both genders, as well as the correlation of the other parameters with baPWV, which is one of the most important non-invasive parameters to ascertain arteria stiffness.

MATERIALS AND METHODS

SUBJECTS

Our investigation was a cross-sectional observational study that took place for two years. The study reportedly enrolled 118 healthy males and 114 females aged 30–>60 years who did not have any cardiovascular or peripheral vascular disease and were not on any antihypertensive or lipid-lowering therapy. The age-specific subgroups of the participants are shown in [Table 1].

Table 1: Age-specific subgroup distribution of the study participants

Age group	Male subjects (*n*=118)	Female subjects (*n*=114)
30–40 years	38	28
41–50 years	43	44
51–60 years	21	28
>60 years	16	14

PROCEDURE

The enrolled subjects were instructed to arrive at the Clinical Physiology Laboratory at 10–10:30 a.m. and to abstain from tea and coffee for 2–3 hours before the test. Following the participants' informed consent, the detailed medical, personal, nutritional, and family history relevant to the cardiovascular system were documented in the specified data pro forma. Anthropometric indicators were calculated. After a 10-minute rest, the individual was evaluated in a supine position. All measures were measured in the supine position in the Clinical Physiology Laboratory at 25°C.

The superficial length from the suprasternal notch to the brachium, where the pulse transducer was put, was noted for the calculation of Lb, and the superficial length from the suprasternal notch to the ankle, where the pulse transducer was placed, was noted for the calculation of La. As a result, the modified equation employed in this investigation is as follows: baPWV = (La-Lb)/ΔTba, where Lb = (0.2195 suprasternal notch to brachium [in cm] –2.0734) and La = (0.8129 suprasternal notch to ankle [in cm] +12.328) are distances and ΔTba is pulse transit time. [13]The coefficient of variation for these two measurements was calculated and found to be 0.05 percent. Mean arterial pressure (MAP) and PP ratio (PPR) were calculated from brachial and central blood pressure measurements in this study. PPR is defined as the ratio of peripheral to central PP. [Figure 1] depicts a representative record.

Under aseptic conditions, five millilitres of whole blood were drawn from the individuals' anterior cubital veins, and serum was separated according to usual protocol. The serum samples were separated and stored at 20°C. The serum was used to calculate the lipid profile. The colorimetric approach was used to estimate the coloured product. The serum was also used to estimate the OPG level. The enzyme immunoassay method was used to measure OPG in accordance with the manufacturer's protocol. The standard curve was plotted using the absorbance (A450) readings of the standards. This test detected OPG values ranging from 1.23 to 900 pg/ml. All of the samples were evaluated in a single run.

STATISTICAL ANALYSIS

The Shapiro–Wilk normality test was used to evaluate the data distribution pattern. The parameters were discovered to have a non-normal distribution. The information was given in the form of a median (Interquartile range). The Kruskal–Wallis test was used to assess the differences between variables, followed by post hoc analysis. To evaluate the relationship between baPWV and other parameters, Spearman correlation analysis was used. To identify the factors linked with baPWV, multiple linear regression analysis was used. $P < 0.05$ was regarded as statistically significant. An appropriate statistical tool was used to analyse the data (SPSS software, version 20 SPSS, IBM Inc., Chicago, IL).

RESULTS

The study included 232 seemingly healthy adults ranging in age from 30 to more than 60 years. There were 118 male individuals and 114 female ones among them. [Table 1] displays the data. Male respondents had a median age with an interquartile range of 45.5 (37–54)

years, while female patients had a median age with an interquartile range of 47 (40.8–53.3) years. Table 2 displays the individuals' anthropometric and clinical features.

Table 2: Anthropometric and clinical characteristics of male and female participants

Variables	Female subjects (n=114)	Male subjects (n=118)
Age (years)	47.0 (40.8–53.3)	45.5 (37.0–54.0)
Height (cm)	151.8 (147.0–155.0)	163.3 (159.0–168.3) ***
Weight (kg)	62.5 (55.0–70.0)	65.0 (56.0–72.0) *
BMI (kg/m^2)	27.1 (24.1–29.3) ***	24.4 (22.4–26.7)
baPWV (cm/s)	1289.6 (1073.8–1458.1)	1211.1 (1045.1–1477.4)
Augmentation index (%)	85.5 (69.0–105.3) ***	66.0 (52.0–81.3)
Central SBP (mmHg)	125.5 (113.8–138.0) *	117.5 (108.8–130.3)
Central DBP (mm Hg)	81.0 (72.0–89.0)	78.0 (73.5–89.0)
Central pulse pressure (mm Hg)	43.5 (38.0–53.0) **	39.0 (34.0–48.0)
Central MAP (mm Hg)	95.0 (86.2–105.3)	90.0 (85.6–103.3)
Brachial SBP (mm Hg)	133.0 (121.0–146.3)	128.5 (118.0–142.3)
Brachial DBP (mm Hg)	79.0 (72.0–87.3)	79.0 (73.0–90.0)
Brachial pulse pressure (mm Hg)	52.0 (45.0–64.0) *	49.0 (43.0–59.3)
Brachial MAP (mm Hg)	96.2 (89.0–106.1)	96.0 (87.8–104.9)
Pulse pressure ratio	1.2 (1.1–1.3)	1.3 (1.1–1.4) **
Heart rate (bpm)	78.0 (72.0–88.5)	78.0 (68.0–86.0)
Serum cholesterol (mg/dl)	191.0 (180.0–210.3)	190.0 (180.0–210.0)
Serum triglyceride (mg/dl)	148.5 (125.8–164.0)	142.0 (116.0–166.0)
Serum LDLc (mg/dl)	121.0 (112.0–137.3)	122.5 (109.0–137.5)
Serum HDLc (mg/dl)	41.0 (38.0–42.3)	40.0 (37.0–44.0)
Serum VLDLc (mg/dl)	29.7 (25.2–32.9)	28.4 (23.1–33.2)
Serum osteoprotegerin (pg/ml)	45.0 (28.0–90.0)	45.0 (28.0–90.0)

Data are represented as median (IQR), baPWV: Brachial ankle pulse wave velocity, $^{*}P<0.05$, $^{**}P<0.01$, $^{***}P<0.0005$. BMI: Body mass index, SBP: Systolic blood pressure, DBP: Diastolic blood pressure, MAP: Mean arterial pressure, LDLc: Low-density lipoprotein cholesterol, HDLc: High-density lipoprotein cholesterol, VLDLc: Very-density lipoprotein cholesterol

Males exhibited significantly higher values for height (P < 0.0005), weight (P 0.05), and PPR (P < 0.01) than females, according to the analyses. Females showed significantly greater BMI (P 0.0005), AIx (P < 0. 0005), central SBP (P < 0.05), central PP (P < 0.01), and brachial PP (P < 0.05) values than males. Other variables did not differ significantly across groups. Table 3 displays the anthropometric and clinical parameters of male patients of various ages.

Table 3: Anthropometric and clinical characteristics of male participants of different age groups

Variables	Group 1 (30–40 years) (*n*=38)	Group 2 (41–50 years) (*n*=43)	Group 3 (51–60 years) (*n*=21)	Group 4 (>60 years) (*n*=16)
Height (cm)	162.3 (159.0–165.3)	165.0 (160.0–170.0)	166.0 (161.5–169.0)	162.0 (151.0–168.8)
Weight (kg)	66.0 (60.0–73.0)	65.0 (56.0–72.0)	64.0 (53.0–72.5)	60.0 (53.5–71.5)
BMI (kg/m^2)	24.7 (23.1–27.1)	24.8 (22.0–26.8)	23.5 (21.6–25.4)	23.7 (21.5–27.0)
baPWV (cm/s)	1204.2 (1022.9–	1222.8 (1045.5–	1156.5 (1062.2–	1257.8 (1079.2–1473.8)

	1503.9)	1415.8)	1488.2)	
Augmentation index (%)	56.0 (46.0–68.0)	68.0 (52.0–82.0)	80.0 (57.5–97.5)**$^{(1,3)}$	81.5 (63.0–127.0)***$^{(1,4)}$
Central SBP (mmHg)	114.0 (107.0–126.8)	115.0 (110.0–-130.0)	124.0 (114.5–147.5)	132.0 (108.8–156.8)
Central DBP (mm Hg)	78.0 (71.8–86.0)	78.0 (74.0–89.0)	80.0 (76.0–89.0)	79.0 (69.0–96.0)
Central pulse pressure (mm Hg)	36.0 (31.3–40.3)	36.0 (32.0–48.0)	43.0 (35.5–53.0)	51.5 (41.0–62.5)***$^{(1,4)}$,*$^{(2,4)}$
Central MAP (mm Hg)	88.9 (83.7–98.8)	89.7 (86.3–103.3)	95.3 (89.3–106.4)	97.7 (81.4–117.6)
Brachial SBP (mm Hg)	126.5 (117.8–138.0)	127.0 (117.0-140.0)	132.0 (124.5-143.5)	141.5 (114.8-165.8)
Brachial DBP (mm Hg)	78.0 (71.0–88.0)	79.0 (73.0–90.0)	80.0 (74.5–89.0)	79.0 (68.0–94.0)
Brachial pulse pressure (mm Hg)	49.0 (42.8–55.0)	47.0 (42.0–59.0)	52.0 (44.5–62.0)	65.0 (47.0–72.0)*$^{(1,4)}$
Brachial MAP (mm Hg)	93.9 (86.9–104.3)	93.0 (88.7–104.7)	98.3 (90.9–106.2)	101.4 (83.3–118.2)
Pulse pressure ratio (PPR)	1.3 (1.2–1.5)*$^{(4,1)}$	1.3 (1.1–1.4)	1.2 (1.1–1.3)	1.2 (1.1–1.2)
Heart rate (bpm)	82.0 (75.8–88.3)	76.0 (68.0–84.0)	73.0 (65.0–82.5)	73.5 (68.0–85.8)
Serum cholesterol (mg/dl)	190.0 (180.0–206.3)	190.0 (176.0–210.0)	200.0 (177.0–218.5)	204.0 (178.5–218.5)
Serum triglyceride (mg/dl)	131.0 (117.0–158.5)	148.0 (112.0–166.0)	144.0 (116.0–165.0)	161.0 (121.0–195.3)
Serum LDLc (mg/dl)	124.5 (113.8–136.3)	121.0 (106.0–133.0)	125.0 (108.5–150.5)	121.5 (108.3–149.5)
Serum HDLc (mg/dl)	40.0 (38.0–44.0)	41.0 (38.0–44.0)	40.0 (37.0–44.5)	39.5 (33.3–43.5)
Serum VLDLc (mg/dl)	26.2 (23.4–31.7)	29.6 (22.4–33.2)	28.8 (23.2–33.0)	32.2 (23.0–39.1)
Serum osteoprotegerin (pg/ml)	45.0 (28.0–116.7)	45.0 (28.0–90.0)	45.0 (17.1–95.0)	45.0 (28.0–45.0)

Data are represented as median (IQR), baPWV: Brachial ankle pulse wave velocity, ****P<0.0005, ***P<0.001, *P<0.05. BMI: Body mass index, SBP: Systolic blood pressure, DBP: Diastolic blood pressure, MAP: Mean arterial pressure, LDLc: Low-density lipoprotein cholesterol, HDLc: High-density lipoprotein cholesterol, VLDLc: Very-density lipoprotein cholesterol

In compared to Group 1, females in Group 4 had significantly greater AIx (percent) ($p<0.05$), central PP ($P < 0.05$), brachial PP ($P < 0.05$), serum cholesterol ($P < 0.05$), serum TG ($P < 0.05$), serum low-density lipoprotein cholesterol (LDLc) ($P < 0.05$), and serum very LDLc (VLDLc) ($P < 0.05$). Other factors in different age groups of female participants did not differ significantly.

The blood OPG level ($r = 0.537$, $P < 0.0005$) was found to be a prominent factor influencing the levels of baPWV in male subjects by Spearman correlation analysis. However, central SBP ($r = 0.181$, $P < 0.05$), central DBP ($r = 0.249$, $P < 0.05$), central MAP ($r = 0.227$, P

< 0.05), brachial SBP (r = 0.219, P < 0.05), brachial DBP (r = 0.275, P < 0.01), brachial MAP (r = 0.261, P < 0.05), serum cholesterol level (r = 0.193, P < 0.05), and serum LDLc level (It should be mentioned that weight is adversely associated with baPWV values in male individuals (r = 0.216, P < 0.05).According to Spearman correlation analysis, serum OPG level (r = 0.499, P < 0.0005) was a substantial factor impacting the values of baPWV in female patients as well. Furthermore, central SBP (r = 0.268, P < 0.05), central DBP (r = 0.223, P < 0.05), central PP (r = 0.2, P < 0.05), cMAP (r = 0.245, P < 0.05), brachial SBP (r = 0.217, P < 0.05), and brachial MAP (r = 0.217, P < 0.05) were factors impacting baPWV values in female participants. Tables 1, 2, and 3 exhibit multiple regression analysis in male and female patients using baPWV as the dependent variable.

DISCUSSION

The current study included 232 apparently healthy people (30 to > 60 years of age) (118 men and 114 females). The participants in these various age groups are subjected to daily stress, which has an impact on their cardiovascular system. Aside from that, the ageing process leaves its natural imprint on the vessel wall's structure. Overall, it may have an effect on the functioning of the circulatory system, resulting in an increase in afterload on the heart. In the current investigation, various physiological and biochemical markers of arterial stiffness were used to determine the arterial stiffness in the participants. BaPWV was one of the physiological measures used.

Several studies have shown that PWV is an independent predictor of coronary heart disease and stroke in otherwise healthy people. [14,15] The measurement of baPWV shows the flexibility of the aorta and medium-sized arteries. Although there is a growing trend in baPWV values in both genders, it is not statistically significant. Although not statistically significant, baPWV is higher in postmenopausal females than in males of similar age. Previous research has shown that there is a correlation between baPWV and age. [16] However, no correlation was found between baPWV and age in the current investigation. It could be due to the smaller number of participants in the current study, particularly in the older age groups of both genders.

The current study found that, regardless of gender, AIx (percent) increased significantly with age. Furthermore, AIx (percent) in females was significantly higher than in males. This report backs up an earlier finding. [18] Females' blood vessels are narrower and stiffer than men', resulting in an earlier return of the reflected wave. It causes a considerable increase in AIx (percent) in females compared to males, regardless of age group. [19]

With increasing age, we found a considerable increase in central PP and brachial PP in both genders. It is consistent with current knowledge of the structural changes in the artery wall caused by ageing. [17] This biological change in the elastic artery wall is responsible for arterial stiffness, which induces early wave reflection during systole, resulting in a rise in central SBP. As a result, it is a fact that SBP and PP rise with age. The current study also found an increase in central and brachial systolic pressure with increasing age, regardless of gender [20].

In both male and female individuals, correlation analysis revealed that serum OPG levels were highly linked with baPWV. Furthermore, central SBP, DBP, and MAP were linked to baPWV, as were brachial SBP, DBP, and MAP [21, 22].

The current investigation found no age-related significant change in serum OPG levels in either gender. However, linear regression analysis demonstrated that serum OPG and TG levels were highly linked with baPWV in both males and females, regardless of age group. Serum VLDLc, on the other hand, was found to be inversely related to baPWV. High TG was found to be substantially linked with high baPWV values in the Japanese population. [23, 24]

LIMITATIONS

The current study has a small number of participants. To determine the cutoff value of baPWV in the given population, a large number of individuals from diverse age groups and both genders are necessary.

CONCLUSION

It is possible to conclude that as age progressed, cardiovascular indices such as central blood pressure, peripheral blood pressure, and AIx (percent) increased in both genders whereas PPR dropped in males. The levels of baPWV increased with age as well, albeit this was not statistically significant. Females' serum cholesterol, TG, LDLc, and VLDLc levels increased with age. Serum OPG and serum TG levels identified as key determinants influencing baPWV values in both genders, regardless of age.

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