Original Research Article

Age-associated changes in physiological and biochemical arterial stiffness markers in apparently healthy

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Abstract

Introduction: Cardiovascular (CV) disease is the first cause of mortality and morbidity worldwide.1 Prevention of this condition, which is responsible of more than 2,200 deaths per day only in the United States, is a public health priority.**Materials and Methods:** This was an observational, cross-sectional study conducted between conducted over a period of 6 months. Apparently, healthy 70 males and 60 females of age group 30–>60 years without any cardiovascular or peripheral vascular disease or on any antihypertensive and lipid-lowering therapy were recruited in the study. **Results:** A total of 130 apparently healthy subjects in the age group of 30 to more than 60 years participated in the study. Out of them, 70 were male and 60 were female subjects. The analysis revealed that males had significantly higher values with respect to height ($P < 0.0005$), weight ($P < 0.05$) and PPR ($P < 0.01$) than females. Females had significantly higher values with respect to BMI ($P < 0.0005$), AIx ($P < 0.0005$), central SBP ($P < 0.05$), central PP ($P < 0.01$) and brachial PP ($P < 0.05$) than males. There was no significant difference in other variables between the groups. Significant difference in other variables in different age groups of male participants.**Conclusion:** The present analysis demonstrated a direct relationship of inflammation and hemostasis with SI measured by digital photo plethysmography, which was modulated by the extent of arterial stiffening.

Keywords: Arterial stiffness markers, Cardiovascular disease, Digital photo plethysmography

Introduction

Cardiovascular (CV) disease is the first cause of mortality and morbidity worldwide.[1] Prevention of this condition, which is responsible of more than 2,200 deaths per day only in the United States, is a public health priority[2]. Thus, in the last decades, great efforts have been made in the search of non-invasive biomarkers, able to identify the individual at risk for CV events in the asymptomatic, subclinical stage[3]. Some biomarkers are currently recommended in order to improve stratification of CV risk, whereas others are considered useful only for research purposes[4,5]. Increasing evidence points out at vascular stiffness as a reliable biomarker of vascular aging, able to represent an integrated marker of the overall burden of CV risk factors on the vasculature over time; furthermore, it may be perse a mechanism of disease, by inducing cardiac, renal, and brain microcirculatory damage and favoring CV events. Increased aortic stiffness has been shown to predict future CV events[6] and improve risk reclassification in those at intermediate risk[7]. However, several questions in this field are still open, limiting the wide use of these tools in the clinical practice. This article will review the basic aspects of physiology of large artery stiffness, as well as current evidence about its possible clinical applications.

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Materials and Methods

This was an observational, cross-sectional study conducted between conducted overaperiod of 6 months. Apparently, healthy 70 males and 60 females of age group 30–>60 years without any cardiovascular or peripheral vascular disease or on any antihypertensive and lipid-lowering therapy were recruited in the study. [Table 1] shows the age-specific subgroups of the participants.

Procedure

The subject was examined in a supine position after resting for 10 min. All parameters were recorded at 25°C in Clinical Physiology Laboratory in supine position. Peripheral (brachial artery) diastolic blood pressure (DBP), SBP, Central BP and AIx (%) were using USCOM BP+ (USCOM Ltd., Sydney, Australia). USCOM BP+ equipment employs supra systolic oscillometric technology to compute central blood pressure. For the recording of baPWV, pulse waveform of brachial artery and posterior tibial artery was recorded simultaneously with pulse transducers for 5 min using Powerlab TM 4/35 hardware and Labchart TM 8 reader software was used to analyse the data (AD Instruments, Sydney, Australia). The sample acquisition frequency was set at 1000 Hz. The components below 50 Hz were stored using a low pass filter and the wavefront was determined. The time interval between the foot of the wave front of brachial and ankle waveform was designated as Δ Tba. The distance between the sampling points of baPWV was calculated in earlier

report as follows: baPWV=(La-Lb)/ΔTba where, Lb = (0.2195 × height of the patient [in cm] –2.0734) and La = (0.8129 × height of the patient [in cm]+12.328), La and Lb are distances and ΔTba is pulse transit time.[12] However, in the present study, a minor modification was done in the equation. For calculation of Lb, superficial length from suprasternal notch to brachium, where pulse transducer was placed, was noted and for calculation of La, superficial length from suprasternal notch to ankle, where pulse transducer was placed, was noted. Therefore, the modified equation used in the present study 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), La and Lb are distances and ΔTba is pulse transit time. [13] Moreover, the coefficient of variation was calculated for these two measurements and was found to be 0.05%. In the present study, mean arterial pressure (MAP) and PP ratio (PPR) were derived from recorded brachial and central blood pressure. PPR is the ratio of peripheral PP to central PP. Five milliliters of whole blood were collected from anterior cubital vein of the participants under aseptic precautions and serum was separated following standard protocol. The separated serum samples were stored at −20°C. The serum was utilized for the estimation of lipid profile. The colored product was estimated by colorimetric method (Erba Diagnostics, Germany). The serum was utilized for estimation of OPG level as well. OPG was measured by enzyme immunoassay method as per the manufacturer's protocol (Sigma Chemical, St Louis, USA). The absorbance (A450) reading of the standards was used to plot the standard curve. The range of detectable concentrations of OPG by this assay was 1.23–900 pg/ml. All samples were tested in one single run.

Results

A total of 130 apparently healthy subjects in the age group of 30 to more than 60 years participated in the study. Out of them, 70 were male and 60 were female subjects. The data are shown in [Table 1]. The median age with an interquartile range of male subjects was 44.4 (36.0–53.0) years and that of female subjects was 48 (39.9–54.4) years. Anthropometric and clinical characteristics of the subjects are shown in [Table 1].

The analysis revealed that males had significantly higher values with respect to height ($P < 0.0005$), weight ($P < 0.05$) and PPR ($P < 0.01$) than females. Females had significantly higher values with respect to BMI ($P < 0.0005$), AIx ($P < 0.0005$), central SBP ($P < 0.05$), central PP ($P < 0.01$) and brachial PP ($P < 0.05$) than males. There was no significant difference in other variables between the groups. [Table 1] shows the anthropometric and clinical characteristics of male subjects in different age groups.

Table 1: Anthropometric and clinical characteristics of male and female participants

Variables	Males Subjects (n=70)	Females Subjects (n=60)
Age (years)	44.4 (36.0–53.0)	48.0 (39.9–54.4)
Height (cm)	162.1 (158.0–169.2)***	152.7 (146.0–156.0)
Weight (kg)	64.9 (55.9–71.9)*	63.4 (56.0–71.0)
BMI (kg/m^2)	25.1 (21.3–25.9)	26.9 (23.9–28.4)***
baPWV (cm/s)	1223.2 (1039.8–1480.1)	1290.1 (1072.9–1460.0)
Augmentation index (%)	65.9 (51.8–82.1)	84.9 (701.–106.1)***
Central SBP (mmHg)	121.1 (109.1–129.8)	126.1 (114.1–139.1)*
Central DBP (mm Hg)	77.0 (72.4–90.1)	79.9 (71.8–90.1)
Central pulse pressure (mm Hg)	38.9 (33.8–49.1)	42.8 (37.9–54.1)**
Central MAP (mm Hg)	89.9 (84.8–104.1)	94.8 (85.8–106.1)
Brachial SBP (mm Hg)	126.7 (116.3–145.4)	131.6 (120.6–147.4)
Brachial DBP (mm Hg)	78.8 (72.9–91.1)	78.9 (71.6–88.1)
Brachial pulse pressure (mm Hg)	48.7 (42.2–60.2)	51.0 (44.7–65.1)*
Brachial MAP (mm Hg)	94.0 (86.1–105.2)	95.7 (86.7–107.2)
Pulse pressure ratio	1.2 (1.0–1.5)**	1.1 (1.0–1.4)
Heart rate (bpm)	77.8 (67.8–87.8)	77.9 (71.8–89.6)
Serum cholesterol (mg/dl)	189.8 (179.8–211.1)	19.6 (179.7–211.1)
Serum triglyceride (mg/dl)	141.6 (115.8–167.1)	147.2 (124.9–165.1)
Serum LDLc (mg/dl)	121.7 (108.3–138.1)	120.8 (111.6–138.2)
Serum HDLc (mg/dl)	39.8 (36.9–45.2)	42.1 (37.8–43.0)
Serum VLDLc (mg/dl)	27.9 (22.8–34.0)	28.9 (24.1–33.2)
Serum osteoprotegerin (pg/ml)	44.6 (27.3–91.2)	44.7 (27.3–91.2)

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

Significant difference in other variables in different age groups of male participants. [Table 3] shows the anthropometric and clinical characteristics of female subjects in various age groups.

Table 2: Anthropometric and clinical characteristics of male participants of different age groups

Variables	Group 1 (29–39 years) (*n*=20)	Group 2 (40–49 years) (*n*=26)	Group 3 (50–59 years) (*n*=14)	Group 4 (>59 years) (*n*=10)
Height (cm)	161.7 (158.8–166.1)	164.7 (159.8–171.1)	165.8 (160.2–170.1)	161.6 (150.8–169.3)
Weight (kg)	65.8 (59.8–74.1)	64.7 (55.0–72.0)	63.7 (52.8–73.1)	59.6 (52.9–72.2)
BMI (kg/m2)	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 (1022.9–1503.9)	1222.8 (1045.5–1415.8)	1156.5 (1062.2–1488.2)	1257.8 (1079.2–1473.8)
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	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)

Hg)				
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)	123.7 (112.7–136.3)	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

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

Variables	30–40 years (*n*=26)	41–50 years (*n*=22)	51–60 years (*n*=8)	>60 years (*n*=4)
Height (cm)	150.5 (143.6–158.0)	151.9 (144.1–158.2)	150.0 (149.0–152.8)	150.2 (143.7–157.2)
Weight (kg)	57.3 (52.8–66.1)	64.0 (54.8–74.1)	59.7 (54.2–66.7)	64.8 (53.3–71.1)
BMI (kg/m2)	24.7 (21.8–29.3)	27.8 (22.7–31.)	25.7 (23.2–29.1)	27.8 (22.9–33.2)
baPWV (cm/s)	1307.8 (1086.8–1513.1)	1263.9 (1013.9–1453.0)	1220.9 (1008.9–1424.0)	1413.7 (1197.9–1692.0)
Augmentation index (%)	74.9 (60.9–89.0)	84.9 (72.4–108.2)	88.9 (66.9–108.0)	93.9 (68.9-130.0)*(1,4)
Central SBP (mmHg)	117.9 (107.0–132.0)	131.5 (114.7–143.8)	123.0 (109.0–139.0)	124.9 (116.0–143.6)
Central DBP (mm Hg)	76.9 (70.6–91.0)	84.9 (74.7–95.3)	77.9 (66.8–91.0)	74.9 (65.3–85.0)
Central pulse pressure (mm Hg)	38.6 (34.5–47.0)	42.9 (35.2–56.7)	42.0 (38.7–57.3)	48.2 (40.3–57.0)*(1,4)
Central MAP (mm Hg)	90.9 (83.0–104.6)	98.7 (86.5–110.0)	91.6 (83.6–105.7)	92.8 (83.6–102.0)
Brachial SBP (mm Hg)	127.8 (119.7–138.2)	136.8 (121.9–149.2)	132.8 (118.7–146.1)	128.5 (124.9–151.4)
Brachial DBP (mm Hg)	76.7 (71.1–86.2)	80.3 (73.7–93.1)	75.1 (68.8–88.3)	73.6 (64.7–84.1)
Brachial pulse pressure (mm Hg)	47.7 (39.2–59.7)	50.1 (43.3–68.3)	51.7 (45.9–65.4)	60.7 (49.4–70.2)*(1,4)
Brachial MAP (mm Hg)	93.3 (88.6–105.2)	97.6 (88.9–111.1)	92.1 (85.1–107.2)	92.6 (83.1–106.4)
Pulse pressure ratio	1.0 (0.9–1.3)	1.0 (0.9–1.1)	1.0 (0.9–1.2)	1.0 (0.9–1.3)
Heart rate (bpm)	78.8 (72.7–93.2)	79.3 (70.7–91.7)	74.7 (69.7–88.2)	70.9 (62.9–88.6)
Serum cholesterol (mg/dl)	185.0 (173.9–197.1)	190.9 (177.9–213.3)	194.7 (180.1–209.8)	209.7 (184.7–233.6)*(1,4)
Serum triglyceride (mg/dl)	138.7 (116.0–159.1)	143.9 (116.9–168.3)	148.8 (138.8–163.7)	163.7 (141.8–187.2)*(1,4)
Serum LDLc (mg/dl)	112.7 (106.1–126.2)	120.8 (110.9–132.1)	120.3 (110.7–138.2)	135.4 (113.4–152.7)*(1,4)
Serum HDLc (mg/dl)	38.9 (34.1–47.9)	38.6 (36.8–5.1)	39.9 (36.7–42.1)	41.9 (39.9–45.1)
Serum VLDLc (mg/dl)	27.8 (22.1–32.4)	28.7 (22.9–33.1)	29.7 (27.8–34.2)	32.7 (28.8–38.2)*(1,4)
Serum osteoprotegerin (pg/ml)	43.9 (27.8–99.1)	44.7 (5.9–91.2)	43.9 (44.9–91.1)	44.7 (29.7–191.2)

Data are represented as median (IQR), baPWV: Brachial ankle pulse wave velocity, *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

We observed that females of Group 4 had significantly higher AIx (%) (p<0.05), central PP (cPP) ($P < 0.05$), 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) in comparison to Group 1. There was no significant difference in other variables in different age groups of female participants.Spearman correlation analysis showed that serum OPG level ($r = 0.537$, $P < 0.0005$) was major factor influencing the values of baPWV in male subjects. However, central SBP ($r = 0.181$, $P < 0.05$), central DBP ($r = 0.249$, $P < 0.01$), central MAP (cMAP) ($r = 0.227$, $P < 0.05$), brachial SBP ($r = 0.219$, $P < 0.05$), brachial DBP ($r = 0.275$, $P < 0.01$), brachial MAP ($r = 0.261$, $P < 0.01$), serum cholesterol level ($r = 0.193$, $P < 0.05$) and serum LDLc level ($r = 0.188$, $P = 0.05$) were also other factors influencing the values of baPWV in male subjects. It is to be noted that weight is negatively associated ($r = −0.216$, $P < 0.05$) with baPWV values in male subjects. In the female subjects also, serum OPG level ($r = 0.499$, $P < 0.0005$) was major factor influencing the values of baPWV as per Spearman correlation analysis. Moreover, central SBP ($r = 0.268$, $P < 0.01$), central DBP ($r = 0.223$, $P < 0.05$), central PP ($r = 0.2$, $P < 0.05$), cMAP ($r = 0.245$, $P < 0.01$), brachial SBP ($r = 0.217$, $P < 0.05$) and brachial MAP ($r = 0.217$, $P < 0.05$) were other factors influencing the values of baPWV in female subjects. shows multiple regression analysis using baPWV as the dependent variable in male and female subjects.The results of multiple regression analysis revealed that both in males and females, serum TG and OPG levels were strongly associated with baPWV. However, serum VLDLc was negatively associated with baPWV.The predictive regression equations for serum TG, VLDLc and OPG considering baPWV as the dependent variable were calculated as follows.

Discussion

Within the present analysis, the clinical relevance of inflammation and hemostasis for AS has been evaluated in the largest population-based investigation to date. To the best of our knowledge this is the first study demonstrating the relation between a panel of biomarkers reflecting these processes and SI derived from digital photo plethysmography.Strong and independent associations of hematocrit,

WBCC and IL-1RA with SI were found among both men and women. Fibrinogen was also related with AS in females.

Interestingly, associations between inflammatory and hemostatic markers with SI were significantly influenced by CVRFs, especially by smoking and hypertension. This supports their pathophysiological effects on the arterial tree in cardiovascular or arteriosclerotic disease.C-reactive protein represents the best studied biomarker of cardio metabolic disorders so far[3,4]The most pronounced change was seen for CRP, where the significant association with SI disappeared in the fully adjusted model in men (remaining borderline in women). Functionally, CRP was proposed to have effects that may influence initiation and progression of vascular disease, including mediation of vascular dysfunction, induction of a pro-thrombotic state and cytokine release, activation of the complement system and facilitation of extracellular matrix remodelling[11-15]. Though, epidemiological data on a cross-sectional relationship between CRP and measures of AS from the literature are controversial[8-10]. Remarkably, CRP was a strong predictor of PWV in a prospective setting within longer follow-up periods of 16 or 20 years, whereas the investigation with a shorter follow-up time[13,14] revealed no meaningful relationship of CRP to stiffness measures. This rather suggests a long-term effect of inflammation on AS.Hematocrit, a well-known predictor of future cardiovascular events[16-18] demonstrated the strongest association with SI in all subsamples with measurable stiffness. It was the only marker associated with SI in the physiological state of presumably healthy males. Its important role as determinant of SI is not surprising, since AS is highly related to mechanical property of blood flow. The fact that the well-known correlates of hematocrit such as male sex, smoking and blood pressure were also major determinants of SI in our previous analysis, supports a possible synergistical effect of this "risk marker - risk factor" clustering.While the association between fibrinogen and SI found in the present analysis is expected, due to close relation between hematocrit and fibrinogen, the sex difference in this association is remarkable. It was found in females only and remained also after adjusting for hormonal influence, which possibly implies an important role of other conventional CVRFs in vascular stiffening among women. Current published data on the association between fibrinogen and AS are contradictory: no association between fibrinogen and PWV was reported from participants from the Framingham Offspring Study[10], 429 apparently healthy middle-aged women[15]or patients with end-stage renal disease[16]. In contrast,a positive association between increased fibrinogen concentrations and cf-PVW was found in 229 hypertensive and 159 age-matched normotensive individuals[17].IL-1RA was strongly positively related with SI in both sexes even after adjustment for traditional CVRFs and various medications within the present analysis. This naturally occurring anti-inflammatory antagonist of the interleukin-1 family of pro-inflammatory cytokines is currently also applied in the treatment of various inflammatory conditions. Increased IL-1RA concentrations at baseline were found to be associated with an increased risk for incident CVD and type 2 diabetes mellitus. Only one study has evaluated the role of IL-1RA in decreased arterial compliance so far and identified IL-1RA as a strong predictor of aortic PWV over 16 years[11]. The non-inverse association between IL-1RA and SI supports the idea of understanding this marker as counter-regulated response to interleukin 1β (IL-1β)-mediated pro-inflammatory stimuli. Currently, IL-1β represents one of the substantive upstream inflammatory cytokine and major target for immunomodulation, since its inhibition has already been linked to the reduction in IL-6, CRP and fibrinogen concentration in the high vascular risk patients.Interestingly, although IL-1β and IL-18 belong to the same IL-1 family of cytokines and shear similar regulation by NLRP3 inflammasome they seem have differential impact on vasculature within the present analysis. IL-18 is considered as a potent inducer of interferon-γ (INF-γ) production, thereby resulting in the enhanced expression of matrix metalloproteinase, and subsequent degeneration of compliant elastin fibers. Several differences in IL-1β and IL-18 signaling have been already reported, with a potent activation of nuclear factor-kappa B by IL-1β and only weak or even null effects on it in case of IL-18. In distinction, IL-18/IFN-γ effects are mediated mainly through activation of JAK-STAT pathway. Moreover, to ensure adequate cell activation, IL-18 requires a co-stimulant (most commonly IL-12) as well as the much higher concentration than IL-1β, which, in contrast, is already active in the low picomol range. Other potential mechanism for the observed discrepancies might include induction of cyclooxygenase-2 expression by IL-1β with subsequent production of prostaglandin E_2, as a key mediator of vascular remodeling and negative regulator of IFN-γ-mediated response. On the contrary, neither cyclooxygenase-2 nor other acute phase proteins such as e.g. IL-6 could be sufficiently induced by IL-18. Thus, one might speculate that other than IFN-γ-mediated effects might be detrimental for the relationship between inflammation and AS. Further indirect confirmation of this represents a fact, that neopterin, as a protein releasing upon stimulation with IFN-γ, was also not associated with SI in the current study. In addition to being a marker of IFN-γ inducible inflammation, neopterin possesses potent pro-oxidative properties that might be responsible for destabilization and vulnerability of the arterial wall. Despite their hypothetical crucial role in AS, neither IL-18 nor neopterin presented as independent determinant of SI.Interestingly, the patterns of association between circulating biomarkers and AS were varying from low to higher cardiovascular risk profiles. The differential associations with SI in the range from presumably cardiovascular healthy individuals, via those with CVRFs or established disease to individuals with severe AS (i.e. "very stiff" status) indicate a variable significance of biomarkers in the development and progression of AS and the state, where arterial compliance is completely lost[19-22]

Limitations

All biomarkers were measured only once in this large sample; therefore, data could include a regression dilution bias. Although biomarker concentrations mediated the relation between SI with future cardiovascular risk as indicated by risk scores, no direct evidence was investigated for this effect. Currently published evidences on SI (clinical, epidemiological etc.) are not as widely available compared to the methods, assessing e.g. stiffness of the large arteries, such as carotid-femoral pulse wave velocity (cf-PWV). Finally, results may not be extrapolated to other populations, ethnicities or age groups.The strengths of this study are the investigated well-characterized, population-representative, large-scale cohort sample with sufficient enough power to assess associations sex-specifically. Various traditional CVRFs were carefully assessed by measurements and not based on self-reported data only, which minimizes a possible misclassification. In contrast to other studies, several inflammatory and hemostatic markers were analyzed simultaneously.

Conclusion

The present analysis demonstrated a direct relationship of inflammation and hemostasis with SI measured by digital photo plethysmography, which was modulated by the extent of arterial stiffening. Simultaneous evaluation of biomarkers and SI improved the assessment of the risk for future CV events or mortality. The mediation of the relation between chronic low-grade inflammation and SI by smoking and arterial hypertension supports the idea of nonpharmacological (e.g. smoking cessation) or pharmacological (e.g. appropriate antihypertensive treatment or hypothetically even anti-inflammatory agents, such as e.g. canakinumab) interventions for improvement of arterial compliance.

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