High C reactive protein associated with increased pulse wave velocity among urban men with metabolic syndrome in Malaysia

Amilia Aminuddin, MD, MMedSc, Zaiton Zakaria, MBBS, PhD, Ahmad F. Fuad, BSc, Jaarin Kamsiah, MD, MSc, Faizah Othman, MD, PhD, Srijit Das, MBBS, MSc, Yusof Kamisah, BSc, PhD, Haji S. Qodriyah, MBBS, PhD, Zakiah Jubri, BBiomedSc, PhD, Nor Anita M. Nordin, MSc, PhD, Wan Z. Ngah, BSc, PhD.

ABSTRACT

الأهداف: دراسة الأثر العرقي في سرعة موجة النبض الفخذي ومؤشر الزيادة وتحديد العلاقة بين ارتفاع كمية البروتين عالي الحساسية وارتفاع سرعة موجة النبض الفخذي ومؤشر الزيادة عند متلازمة الأيض.

الطريقة: أجريت دراسة مقطعية على 380 رجل صيني وماليزي خلال الفترة من سبتمبر 2009م حتى 2011م في واد كلان، ماليزيا. تم قياس مؤشر الزيادة وسرعة موجة النبض الفخذي باستخدام المسجل. تم قياس مستويات البروتين شديد الحساسية وقياس متلازمة الأيض باستخدام مؤشر الاتحاد الدولي للسكر والطريقة المنسقة.

النتائج: كان مؤشر الزيادة لدى الماليزيين أعلى من الصينيين. كان مؤشر سرعة موجة النبض الفخذي عالياً لدى المصابين بمتلازمة الأيض 8.5 [8.3–8.7] بالمقابل 8.2 [8.0–8.4] p=0.03، الطريقة المرتبة 8.5 [8.4–8.7] بالمقابل 8.2 [8.0–8.4]، p=0.007، الطريقة المرتبة 1.9±0.8 بالمقابل 1.1±0.4 ملغ/لتر p=0.002 بالمقارنة مع عدم ظهور متلازمة الأيض. كما أظهرت الدراسة أيضاً أن الأشخاص بمتلازمة الأيض لديهم ارتفاع كمية البروتين عالي الحساسية 3< وارتفاع سرعة موجة النبض الفخذي.

خاتمة: أظهرت الدراسة أن الأشخاص الماليزيين لديهم ارتفاع في مؤشر الزيادة بالمقارنة مع الأشخاص الماليزيين الصينيين. ارتبطت متلازمة الأيض مع ارتفاع سرعة موجة النبض الفخذي وارتفاع كمية البروتين عالي الحساسية. من بين المصابين بمتلازمة الأيض ارتبط ارتفاع مستويات البروتين شديد الحساسية مع ارتفاع سرعة موجة النبض الفخذي. قد يعكس قياس كمية البروتين عالي الحساسية مدى الضرر الوعائي في متلازمة الأيض.

Objectives: To determine the association between carotid femoral pulse wave velocity (PWV_{CF}); augmentation index (AI); and high-sensitivity C reactive protein (hs-CRP) with metabolic syndrome (MetS), and to determine the influence of ethnicity on PWV_{CF} and AI, and the association between high hs-CRP and increased PWV, and AI in MetS.

Methods: A cross-sectional study was conducted at Universiti Kebangsaan Malaysia Medical Center, Kuala Lumpur, Malaysia from September 2009 to September 2011. Three hundred and eighty men (Chinese and Malays) were recruited from the study. The PWV_{CF} and AI were measured by Vicorder (SMT Medical, Wuerzburg, Germany). The hs-CRP level was also determined. We defined MetS using the International Diabetes Federation (IDF) and harmonized criteria.

Results: Malays had higher AI compared to the Malaysian Chinese. Patients with MetS had higher PWV_{CF} (IDF criteria: 8.5 [8.3-8.7] versus 8.2 [8.0-8.4] m/s, p=0.03; harmonized criteria: 8.5 [8.4-8.7] versus 8.2 [8.0-8.4] m/s, p=0.007) and hs-CRP (IDF criteria: 0.9±2.0 versus 0.4±1.1 mg/L, p=0.0007; harmonized criteria: 0.8±1.9 versus 0.4±1.1 mg/L, p=0.002) compared to non-MetS. In subjects with MetS, those with high hs-CRP (>3mg/L) had higher PWV_{CF}.

Conclusions: Augmentation index values were significantly higher in Malays compared with Malaysian Chinese. Metabolic syndrome was associated with increased PWV_{CF} and hs-CRP. Patients with MetS and high hs-CRP were associated with higher PWV_{CF}. The measurement of hs-CRP reflects the degree of subclinical vascular damage in MetS.

Saudi Med J 2013; Vol. 34 (3): 266-275

From the Department of Physiology (Aminuddin, Zakaria, Fuad, Nordin), Department of Pharmacology (Kamsiah J, Kamisah Y, Qodriyah), Department of Anatomy (Othman, Das), and the Department of Biochemistry (Jubri, Ngah), Universiti Kebangsaan Malaysia Medical Center, Jalan Raja Muda Abdul Aziz, Kuala Lumpur, Malaysia.

Received 7th November 2012. Accepted 16th January 2013.

Address correspondence and reprint request to: Dr. Zaiton Zakaria, Physiology Department, Universiti Kebangsaan Malaysia Medical Center, Jalan Raja Muda Abdul Aziz, 50300 Kuala Lumpur, Malaysia. Tel. +60 (3) 92897577. Fax. +60 (3) 26939687. E-mail: amyyra1234@yahoo.com.my

Metabolic syndrome (MetS), which is highly prevalent worldwide, has increased risk of progression to diabetes and cardiovascular disease (CVD).[1,2] Arterial stiffness (AS) is one of the underlying mechanisms.[3] Metabolic syndrome is also associated with increased C-reactive protein (CRP), which is a marker of inflammation.[4,5] Furthermore, previous studies showed that CRP increased the risk prediction of CVD and diabetes in MetS.[5,6] However, the association between high CRP level with increased AS in MetS among Asian population are lacking.[7,8] The presence of various definitions of MetS may also complicate the results. Recently, a meeting by several expert groups has standardized the definition of MetS, under 'harmonized' criteria.[9] These criteria include the presence of at least 3 out of 5 risk factors as MetS; raised blood pressure (BP), raised triglycerides (TG), low high density lipoprotein (HDL), and raised fasting blood glucose or central obesity (ethnic specific). In Malaysia, the harmonized criteria have identified more individuals with MetS, compared to other definitions (National Cholesterol Education Program [NCEP], World Health Organization [WHO], and International Diabetes Federation [IDF]).[10] This will target more people who are at risk of developing diabetes and CVD so that early preventive measures may be taken. Harmonized criteria differed slightly from IDF classification, whereby in the latter the presence of central obesity is a pre-requisite plus 2 other risk factors.[11] With reference to AS, previous study found that the IDF criteria has identified more patients with increased AS compared to that using the NCEP classification.[12] For the measurement of AS, carotid femoral pulse wave velocity (PWV_{CF}) is accepted as the gold standard.[3] It reflects the speed of the wave that travels along the aorto-iliac pathway, and it is a direct measure of the AS. Another surrogate measure of AS is augmentation index (AI), which actually represents a wave reflection that arrives back to the aorta after the forward wave, hits the peripheral artery.[3] Both PWV_{CF} and AI are established predictors of CVD.[13,14] Previous researches showed that ethnicity influenced PWV and AI, with many studies focused on African-American, Caucasian, and Hispanic ethnicity.[15,16] Malaysia is a multi-ethnic country whereby the 2012 census showed that it is dominated by Malays (67.4%), followed by Chinese (24.6%), Indians (7.3%), and other minorities (0.7%)[17] and so far, no study was carried out to determine the influence of ethnicity on AI and PWV in Malaysia. The present study aimed to look into 3 main objectives. Firstly, we aimed to determine the association between PWV, AI, and inflammatory marker with MetS since there is a paucity of data on these topics in Malaysia. Secondly, this study aimed to investigate whether there is a difference in PWV and AI in 2 major races in Malaysia, namely Malays and Chinese. Lastly, to investigate whether high CRP in those with MetS was associated with increased PWV and AI. The results may be used as references to other researchers in Malaysia and may expand the role of high-sensitivity CRP (hs-CRP) in the clinical setting.

Disclosure. Authors have no conflict of interests, and the work was not supported or funded by any drug company. This study was funded by the Universiti Kebangsaan Malaysia (UKM-AP-TKP-09-2009).

Methods. The search of previous studies was carried out via internet search engine such as Google scholar, PubMed, and Ovid. This study was a cross-sectional study and was part of the aging male study, which obtained ethical approval from the university (UKM-AP-TKP-09-2009) prior to the subjects' recruitment. The aging male study was conducted in order to determine the effect of aging on hormonal, oxidative, nutritional, physical activity, bone health and cardiovascular health of men more than 20 years of age residing the Klang Valley, Malaysia.[18] Klang valley is an urbanized area, which include the capital city of Kuala Lumpur and adjoining cities in the Selangor area. The main study area was at Universiti Kebangsaan Malaysia Medical Center, Kuala Lumpur. Non-randomized purposive sampling technique was adopted, with carefully selected volunteers. The minimum sample size required for this study was 200 subjects and was based on hs-CRP since this parameter needed the largest number of subjects compared to PWV_{CF} and AI. The mean value of hs-CRP and their standard deviations (SD) in MetS (2.99±3.90) and non-MetS subjects (1.46±3.42) were used based on the previous research, with 80% power, 95% confidence interval, and 4 groups of subjects.[19] The calculation was carried out manually based on a published formula.[20]

The subjects were recruited via advertisements in major newspapers, radio broadcastings, flyers, and public announcements through local community centers and mosques. Recruitment was carried out from September 2009 to September 2011. Subjects were given detailed information pertaining to the study and all subjects were requested for written consent. This study followed the principles of Helsinki Declaration. All subjects were asked to fast at least 8 hours prior to the measurements being taken. Every subject was also

requested to filled up the questionnaires. The 2 major components of these questionnaires were declaration of medical condition and basic demographic data. These questionnaires were adapted from a screening questionnaire used by the Medical Molecular Biology Institute, Universiti Kebangsaan Malaysia (UMBI, UKM) (unpublished). This was followed by a detailed medical history and physical examination by a qualified physician. Inclusion criteria were male, aged ≥39 years, who were healthy or have cardiovascular risk factors (obesity, hypertension, smoking, dyslipidemia, and diabetes). Exclusion criteria were those with past medical history (self-reported) of ischemic heart disease, renal disease, chronic lung disease, liver disease, cancer, and chronic arthritis. At the end of the study, 380 participants were recruited. The subjects consisted of 28% Malays and 72% Chinese men. Other races were not recruited due to logistic problems. The higher percentage of Chinese that participated was due to more volunteers from this ethnic group.

Metabolic syndrome definition. The clinical definition of MetS based on the IDF criteria include central obesity (waist circumference >90 cm for Asians) as a pre-requisite plus any 2 of the followings: raised TG (>1.7 mmol/L) or specific treatment for this, reduced HDL-cholesterol (<1.03 mmol/L) or specific treatment for this, raised BP (systolic BP >130 mm Hg or diastolic BP >85 mm Hg) or on antihypertensive medication and raised fasting blood glucose (>5.6 mmol/L) or previously diagnosed diabetes mellitus.[11] For harmonized criteria definition, the subjects needed to have at least 3 out of 5 risk factors mentioned above, while central obesity was not considered as a pre-requisite.[9]

Anthropometry measurement. Height was measured without shoes by using a wall-mounted stadiometer (SECA, Hamburg, Germany). Weight was measured by using digital scale (SECA, Hamburg, Germany). Body mass index (BMI) was calculated by dividing weight with height^2 (kg/m^2). Waist circumference (WC) was measured on bare midriff at horizontal plane, midway between the lowest rib and the superior border of iliac crest at the end of normal expiration.[11]

Measurement of arterial stiffness, brachial and aortic BP. Carotid femoral pulse wave velocity was measured via Vicorder (SMT medical, Wuerzburg, Germany) according to the standard protocol outlined by the manufacturer. Subjects were asked to lie supine for 5 minutes prior to testing, with shoulders raised at 30 degrees. The cuffs were placed on the right arm, right thigh and around the neck. The neck cuff contains a pad sensing pressure from the right carotid artery. Both femoral and carotid cuffs were inflated to 65 mm Hg to get the corresponding oscillometric signals from both cuffs. The signals were then digitally analyzed for measurement of transit time (TT), which is the delay berween the recorded pulse waves. The distance travelled by the pulse wave (DPW) was measured as distance from suprasternal notch to mid thigh cuff. DPW was entered to the computer and the Vicorder computed PWV_{CF} as DPW/TT (m/s). The device also recorded brachial BP pressure waveform from the right arm and aortic pressure waveform was derived by using brachial-to-aortic mathematical transfer function.[21] This method provides the measurement of the brachial and aortic BP. Another parameter that could be obtained with this device is augmentation index (AI), which is a measure of wave reflection. It was calculated from aortic pressure waveform as [(second systolic peak-first systolic peak)/ pulse pressure x 100].[3] All the measurements were taken by a single operator. For PWV, aortic and brachial BP, one measurement was taken from each subject.

Measurement of blood parameters. Blood samples were drawn from the antecubital vein. The samples were then sent to a private laboratory (Gribbles Pathology Lab, Petaling Jaya, Malaysia) for measurement of total cholesterol (TC), high-density lipoprotein (HDL), low-density lipoprotein (LDL), triglycerides (TG) and high-sensitivity CRP (hs-CRP). This laboratory had obtained International Organization of Standardization (ISO: MS ISO 15189) for the quality control. The serum TC, HDL cholesterol and TG were measured using enzymatic methods (Siemens Advia 2400 Chemistry Analyzer, Japan). The hs-CRP was measured via immunological methods (Advia 2400 Chemistry Analyzer, Japan). The blood glucose (whole blood) was measured via ACCU-CHECK portable glucose meter (Roche Diagnostics Corporation, Indiana, USA) based on glucose oxidase method. The inter-assay coefficient of variant (CV) for blood lipids ranged between 1.4-3.5%. For hs-CRP, the inter-assay CV ranged from 2.0-2.4%.

Definition of other CV risk factors. A smoker was defined as a person who had been smoking daily and was continuing at the time of the examination.[18] Diabetes was defined as those with fasting blood sugar of >6.1 mmol/L or on medication.[22] Abdominal obesity was defined as those having waist circumference more than 90 cm.[23]

Statistical analysis. The data were presented as mean (confidence interval) if the distributions were normal and as median ± inter quartile range (IQR) if the distribution was skewed. All the parameters were normally distributed except for hs-CRP, which was skewed. Hs-CRP values were logarithm transformed to improve the skewness, and logarithm hs-CRP was used

for data analysis. The relationships between PWV_{CF} logarithm hs-CRP, and AI with other characteristics were analyzed by Pearson's correlation. The strength of the associations were determined by the Pearson's correlation coefficient (r). Multiple linear regression was used to determine the independent determinants of PWV and AI. The given adjusted R^2 value represents the percentage of variation in PWV and AI that was explained by the determinants. The determinants were also used as confounders in comparing PWV and AI between Malays and Chinese. This comparison was analyzed by using general linear model (GLM) univariate. Next, the difference between those with and without MetS were compared with independent t test and by chi-square test for smoker. For AI, further comparison analysis was carried out with GLM univariate to adjust for the ethnic effect. To determine the association between high hs-CRP and increased PWV and AI in subjects with and without MetS, each group was divided into those having high hs-CRP (≥3 mg/L) and low hs-CRP (<3 mg/L) and the PWV_{CF}, AI and other parameters in each group were compared by independent t test and by chi-square test for smoker. For AI, further comparison analysis was carried out with GLM univariate to adjust for the race effect. Three mg/L was chosen as the cut off point as this value was used in previous papers and corresponded to high-risk group addressed by American Heart Association.[8,24]

Data was analyzed via Statistical Package of Social Science (SPSS) Version 15 (SPSS Inc., Chicago, USA) and the level of significance was set at $p<0.05$. The confidence interval for proportion was calculated (computer generated) via a web.[25]

Results. The general characteristics of the subjects were shown in **Table 1**. The subjects were males, who were aged between 40-80 years. Of all the subjects, 84% had abdominal obesity, 54% had elevated BP and 33% were diabetic. Seventeen percent of them had hs-CRP ≥3 mg/L. By using harmonized and IDF criteria, approximately 60% of the Malays had MetS while the prevalence among Chinese was approximately 52%.

Table 2 shows the correlation between PWV, AI, and logarithm hs-CRP with other parameters for the whole subjects. PWV, AI and logarithm hs-CRP had significant correlation with most of the major cardiovascular risk factors. Multiple linear regression analysis reveal that the independent determinants of PWV are age, brachial SBP and HR (adjusted R^2=0.37) and age, height, aortic SBP, HR, smoking status and race are the determinants for AI (adjusted R^2=0.24). The PWV for Malays was 8.7 m/s (8.4-8.9 m/s) and for Chinese was 8.2 m/s (8.1-8.4 m/s). After adjustment for confounders (age, brachial SBP and HR), no difference was noted for PWV between these 2 races (p=0.07). The AI for Malays was 17.1% (16.1-18.2) and for Chinese was 15.6% (15.0-16.4). After adjustment for confounders (age, height, aortic SBP, HR and smoker), there was significant difference obtained for AI (p=0.009) with the Malays had significantly higher AI compared to the Chinese.

The profiles of those who were having MetS in comparison to those did not have MetS based on IDF and harmonized criteria were tabulated (**Tables 3 & 4**). Those with MetS had higher levels of hs-CRP and PWV compared to non-MetS group, regardless of the criteria used. No significant difference was obtained for AI between these 2 groups by using IDF criteria and this remained insignificant after adjustment for race. By using harmonized criteria, those with MetS had significantly higher AI compared to non-MetS, however, this became insignificant after adjustment for race.

The differences between those who were categorized as having high hs-CRP (>3 mg/L) in comparison to those who were having low hs-CRP (<3 mg/L) in the group with MetS or not having MetS, by using IDF and harmonized criteria were tabulated (**Tables 5 & 6**). In MetS group, those with high hs-CRP had significantly higher PWV_{CF}, with no difference in AI, compared to those with low hs-CRP in both criteria. The result for

Table 1 - Patient's characteristics in 380 patients.

Patient's characteristics	Mean
Age (years)	53.2 (52.3-54.1)
Heart rate (bpm)	60.0 (59.0-60.9)
Body mass index (kg/m^2)	25.2 (24.7-25.6)
Waist circumference (cm)	97.3 (96.3-98.3)
Systolic blood pressure (mm Hg)	140.3 (138.5-142.1)
Diastolic blood pressure (mm Hg)	84.9 (83.8-85.9)
Aortic SBP (mm Hg)	133.6 (131.9-135.3)
Aortic DBP (mm Hg)	84.6 (83.4-85.8)
PWV_{CF} (m/s)	8.4 (8.2-8.5)
Augmentation index (%)	16.1 (15.5-16.7)
Fasting blood sugar (mmol/L)	6.2 (6.0-6.3)
Total cholesterol (mmol/L)	5.7 (5.6-5.8)
Low-density lipoprotein (mmol/L)	3.7 (3.6-3.8)
Triglyceride (mmol/L)	1.7 (1.5-1.8)
High-density lipoprotein (mmol/L)	1.3 (1.26-1.32)
High-sensitivity C reactive protein* (mg/L)	0.6 ± 1.7
Smoker (%)	21.0 (16.9-25.1)

*Data is presented as median ± inter quartile range (IQR) while others are presented as mean (confidence interval) and for smoker, percentage (confidence interval). SBP - systolic blood pressure, DBP - diastolic blood pressure, PWV_{CF} - carotid femoral pulse wave velocity

AI remained insignificant after adjustment for the race. In non-MetS group, no significant different obtained for PWV_{CF} and AI between the 2 groups by using both criteria. For AI, the results remained insignificant after adjustment for the race.

Discussion. The novel risk predictors of CVD such as high sensitivity C reactive protein (hs-CRP), pulse wave velocity (PWV) and augmentation index (AI) are widely recognized.[13,14,26] The current study provided additional data on these values among the urban men with and without MetS in Klang Valley. In addition, despite the use of harmonized or IDF criteria, both classifications generally provide almost similar number of patients. This may occur due to high proportion of abdominal obesity (~84%) in the present study. A

Table 2 - Correlations between PWV_{CF}, hs-CRP and AI with other major cardiovascular risk factors.

Variables	PWV_{CF}		Logarithm hs-CRP		Augmentation index	
	r	*P*-value	r	*P*-value	r	*P*-value
Age (years)	0.50	0.0001	-0.02	0.70	0.22	0.0001
Heart rate (bpm)	0.25	0.0001	0.26	0.0003	-0.28	0.0001
Body mass index (kg/m^2)	-0.12	0.73	0.32	0.0001	0.10	0.06
Waist circumference (cm)	-0.05	0.37	0.30	0.0001	0.07	0.91
Height (cm)	0.01	0.80	0.04	0.51	-0.19	0.0002
Brachial SBP (mmHg)	0.39	0.0001	0.17	0.004	0.15	0.004
Brachial DBP (mmHg)	0.19	0.0002	0.21	0.0002	0.09	0.10
Aortic SBP (mmHg)	0.37	0.0001	0.16	0.005	0.27	0.0001
Aortic DBP (mmHg)	0.16	0.002	0.20	0.0002	0.09	0.11
PWV_{CF} (m/s)	-	-	0.15	0.009	0.03	0.52
Augmentation index (%)†	0.03	0.52	0.06	0.32	-	-
Fasting blood sugar (mmol/L)	0.22	0.0001	0.13	0.02	-0.11	0.03
Total cholesterol (mmol/L)	0.02	0.74	0.09	0.13	0.03	0.63
Low-density lipoprotein (mmol/L)	0.01	0.84	0.04	0.46	0.07	0.22
Triglycerides (mmol/L)	0.02	0.68	0.14	0.01	-0.01	0.80
High-density lipoprotein (mmol/L)	-0.14	0.007	-0.19	0.008	-0.13	0.01
Logarithm hs-CRP	0.15	0.009	-	-	0.06	0.32

SBP - systolic blood pressure, DBP - diastolic blood pressure, PWV_{CF} - carotid femoral pulse wave velocity, AI - augmentation index, FBS - fasting blood sugar, hs-CRP - high sensitivity C reactive protein

Table 3 - Characteristic differences between metabolic syndrome (MetS) subjects and non-MetS based on International Diabetes Federation (IDF) criteria.

Variables	Non-MetS (N=171)	MetS (N=209)	*P*-value
Age (years)	52.7 (51.2-54.2)	53.6 (52.6-54.7)	0.30
Heart rate (bpm)	58.2 (56.9-59.6)	61.4 (60.0-62.8)	0.002
Body mass index (kg/m^2)	23.3 (22.8-23.8)	26.7 (26.2-27.2)	0.0001
Waist circumference (cm)	92.8 (91.2-94.5)	100.8 (99.9-101.7)	0.0001
Brachial SBP (mm Hg)	132.7 (130.3-135.1)	146.4 (144.1-148.7)	0.0001
Brachial DBP (mm Hg)	80.3 (78.8-81.7)	88.5 (87.2-89.9)	0.0001
Aortic SBP (mm Hg)	126.1 (123.8-128.5)	139.6 (137.4-141.8)	0.0001
Aortic DBP (mm Hg)	79.9 (78.2-81.7)	88.3 (86.9-89.7)	0.0001
PWV_{CF} (m/s)	8.2 (8.0-8.4)	8.5 (8.3-8.7)	0.03
Augmentation index (%)†	15.5 (14.7-16.3)	16.6 (15.8-17.4)	0.11
Fasting blood sugar (mmol/L)	5.6 (5.5-5.7)	6.6 (6.3-6.9)	0.0001
Total cholesterol (mmol/L)	5.7 (5.6-5.9)	5.7 (5.5-5.8)	0.42
Low-density lipoprotein (mmol/L)	3.8 (3.6-3.9)	3.6 (3.4-3.7)	0.04
Triglycerides (mmol/L)	1.3 (1.1-1.4)	2.0 (1.8-2.1)	0.0001
High-density lipoprotein (mmol/L)	1.4 (1.34-1.44)	1.2 (1.17-1.24)	0.0001
Hs-CRP* (mg/L)	0.4 ± 1.1	0.9 ± 2.0	0.0007
Smoker (%)	18.8 (12.9-24.7)	22.7 (17.0-28.4)	0.38

*Data is presented as median ± interquartile range (IQR) while others are presented as mean (confidence interval) and for smoker, percentage (confidence interval). †After adjustment for race. SBP - systolic blood pressure, DBP - diastolic blood pressure, PWV_{CF} - carotid femoral pulse wave velocity, hs-CRP - high sensitivity C reactive protein

Table 4 - Characteristic differences between metabolic syndrome (MetS) subjects and non-MetS based on harmonized criteria.

Variables	Non-MetS (n=174)	MetS (n=206)	*P*-value
Age (years)	52.3 (50.9-53.8)	53.9 (52.8-55.0)	0.07
Heart rate (bpm)	57.8 (56.5-59.2)	61.7 (60.4-63.1)	0.0001
Body mass index (kg/m^2)	23.4 (22.9-24.0)	26.6 (26.1-27.1)	0.0001
Waist circumference (cm)	93.8 (92.2-95.3)	100.2 (99.1-101.3)	0.0001
Brachial SBP (mm Hg)	133.4 (131.0-135.9)	146.0 (143.7-148.3)	0.0001
Brachial DBP (mm Hg)	80.6 (79.2-82.1)	88.3 (87.0-89.7)	0.0001
Aortic SBP (mm Hg)	126.9 (124.5-129.2)	139.2 (137.0-141.4)	0.0001
Aortic DBP (mm Hg)	80.2 (78.4-81.9)	88.3 (86.8-89.7)	0.0001
PWV_{CF} (m/s)	8.2 (8.0-8.4)	8.5 (8.4-8.7)	0.007
Augmentation index (%)†	15.4 (14.6-16.3)	16.7 (15.9-17.5)	0.07
Fasting blood sugar (mmol/L)	5.6 (5.5-5.7)	6.7 (6.4-6.9)	0.0001
Total cholesterol (mmol/L)	5.7 (5.5-5.8)	5.7 (5.6-5.9)	0.59
Low-density lipoprotein (mmol/L)	3.7 (3.6-3.8)	3.6 (3.5-3.8)	0.28
Triglycerides (mmol/L)	1.2 (1.1-1.3)	2.1 (1.9-2.3)	0.0001
High-density lipoprotein (mmol/L)	1.4 (1.36-1.45)	1.2 (1.16-1.23)	0.0001
Hs-CRP* (mg/L)	0.4 ± 1.1	0.8 ± 1.9	0.002
Smoker (%)	19.7 (13.8-25.6)	22.1 (16.4-27.8)	0.61

*Data is presented as median ± interquartile range (IQR) while others are presented as mean (confidence interval) and for smoker, percentage (confidence interval). †After adjustment for race, SBP - systolic blood pressure, DBP - diastolic blood pressure, PWV_{CF}= carotid femoral pulse wave velocity, hs-CRP - high sensitivity C reactive protein

Table 5 - Characteristic differences between those having high hs-CRP and low hs-CRP in MetS and non-MetS subjects based on International Diabetes Federation (IDF) criteria.

Variables	Non-MetS			MetS		
	Hs-CRP <3 mg/L (n=146)	Hs-CRP ≥3 mg/L (n=25)	*P*-value	Hs-CRP <3 mg/L (N=163)	Hs-CRP ≥3 mg/L (N=46)	*P*-value
Age (years)	53.1 (51.4-54.8)	51.1 (47.1-55.01)	0.41	53.2 (52.0-54.5)	55.0 (52.8-57.3)	0.18
HR (bpm)	57.8 (56.3-59.3)	60.1 (56.2-63.9)	0.32	60.1 (58.7-61.6)	65.4 (62.1-68.8)	0.002
BMI (kg/m^2)	23.1 (22.5-23.6)	24.5 (23.1-25.8)	0.09	26.2 (25.6-26.7)	28.3 (27.1-29.4)	0.001
WC (cm)	92.3 (90.6-94.0)	95.4 (88.5-102.3)	0.25	100.0 (99.0-101.0)	103.7 (101.6-105.8)	0.001
Brachial SBP (mm Hg)	131.7 (129.1-134.3)	138.3 (130.3-146.4)	0.09	145.3 (142.8-147.8)	151.6 (146.0-157.2)	0.03
Brachial DBP (mm Hg)	79.5 (77.8-81.0)	84.5 (80.8-88.2)	0.03	87.6 (86.0-89.2)	91.0 (88.4-93.6)	0.05
Aortic SBP (mm Hg)	125.1 (122.6-127.6)	131.8 (124.3-139.3)	0.08	138.5 (136.1-141.0)	144.7 (139.3-150.0)	0.03
Aortic DBP (mm Hg)	79.0 (77.0-81.0)	84.5 (80.8-88.2)	0.06	87.4 (85.7-89.1)	91.1 (88.4-93.7)	0.04
PWV_{CF} (m/s)	8.2 (8.0-8.4)	8.3 (7.6-8.9)	0.80	8.4 (8.2-8.6)	8.9 (8.5-9.2)	0.03
AI (%)†	15.1 (14.3-16.0)	17.5 (14.5-20.5)	0.09	16.5 (15.6-17.5)	16.9 (15.1-18.8)	0.86
FBS (mmol/L)	5.6 (5.5-5.7)	5.4 (5.2-5.6)	0.16	6.6 (6.3-6.9)	6.7 (6.0-7.3)	0.91
TC (mmol/L)	5.7 (5.6-5.9)	5.8 (5.3-6.2)	0.77	5.7 (5.5-5.8)	5.7 (5.3-6.0)	0.91
LDL (mmol/L)	3.7 (3.6-3.9)	4.0 (3.6-4.4)	0.16	3.6 (3.4-3.7)	3.6 (3.2-4.0)	0.84
TG (mmol/L)	1.3 (1.1-1.4)	1.3 (1.1-1.4)	0.92	2.0 (1.8-2.2)	2.0 (1.5-2.4)	0.87
HDL (mmol/L)	1.4 (1.36-1.50)	1.2 (1.10-1.34)	0.01	1.2 (1.17-1.26)	1.2 (1.10-1.24)	0.32
Hs-CRP* (mg/L)	0.3 ± 0.7	5.0 ± 3.9	0.0001	0.6 ± 1.0	4.7 ± 2.1	0.0001
Smoker (%)	19.6 (13.2-26.0)	10.5 (0.0-22.5)	0.53	21.6 (15.3-27.9)	26.2 (13.5-38.9)	0.54

*Data is presented as median ± interquartile range (IQR) while others are presented as mean (confidence interval) and for smoker, percentage (confidence interval). †After adjustment for race. MetS - metabolic syndrome; BMI - body mass index, HR - heart rate, WC - waist circumference, SBP - systolic blood pressure, DBP - diastolic blood pressure, PWV_{CF} - carotid femoral pulse wave velocity, AI - augmentation index, FBS - fasting blood sugar, TC - total cholesterol, LDL - low-density lipoprotein, HDL - high-density lipoprotein, TG - triglycerides; hs-CRP - high sensitivity C reactive protein

Table 6 - Characteristic differences between those with high hs-CRP and low hs-CRP in MetS and non-MetS subjects based on harmonized criteria.

Variables	Non-MetS			MetS		
	Hs-CRP < 3mg/L (N=151)	Hs-CRP≥3 mg/L (N=23)	*P*-value	Hs-CRP < 3 mg/L (N=164)	Hs-CRP ≥ 3 mg/L (N=42)	*P*-value
Age (years)	52.8 (51.1-54.4)	50.5 (47.2-53.8)	0.31	53.5 (52.2-54.8)	55.8 (53.4-58.2)	0.12
Heart rate (bpm)	57.0 (55.5-58.5)	61.1 (57.5-64.8)	0.04	60.8 (59.4-62.3)	65.3 (61.7-69.0)	0.01
Body mass index (kg/m^2)	23.1 (22.5-23.7)	25.0 (23.6-26.4)	0.01	26.1 (25.6-26.7)	28.3 (27.2-29.5)	0.001
Waist circumference (cm)	93.0 (91.4-94.6)	97.1 (91.2-103.1)	0.08	99.3 (98.0-100.5)	103.5 (101.4-105.7)	0.002
Brachial SBP (mmHg)	132.0 (129.3-134.6)	140.6 (133.2-147.9)	0.02	144.9 (142.4-147.4)	151.6 (145.6-157.6)	0.03
Brachial DBP (mmHg)	79.5 (77.8-81.1)	85.1 (82.0-88.2)	0.01	87.5 (85.9-89.1)	91.3 (88.5-94.2)	0.03
Aortic SBP (mmHg)	125.4 (122.9-128.0)	133.9 (126.9-140.8)	0.02	138.1 (135.7-140.5)	144.8 (139.0-150.5)	0.02
Aortic DBP (mmHg)	78.9 (76.9-80.9)	85.1 (82.0-88.2)	0.02	87.4 (85.7-89.1)	91.4 (88.6-94.3)	0.04
PWV_{CF} (m/s)	8.1 (7.9-8.4)	8.3 (7.7-8.8)	0.62	8.4 (8.2-8.6)	8.9 (8.5-9.3)	0.04
Augmentation index (%)†	15.1 (14.3-16.0)	17.2 (14.4-20.1)	0.13	16.5 (15.6-17.5)	17.1 (15.2-18.9)	0.75
Fasting blood sugar (mmol/L)	5.6 (5.5-5.7)	5.3 (5.2-5.5)	0.11	6.6 (6.3-7.0)	6.8 (6.2-7.5)	0.64
Total cholesterol (mmol/L)	5.6 (5.5-5.8)	5.7 (5.3-6.1)	0.72	5.7 (5.6-5.9)	5.7 (5.3-6.1)	0.93
LDL (mmol/L)	3.7 (3.6-3.8)	3.9 (3.5-4.3)	0.25	3.6 (3.5-3.8)	3.6 (3.2-4.0)	0.93
TG (mmol/L)	1.2 (1.0-1.3)	1.3 (1.1-1.4)	0.53	2.1 (1.9-2.3)	2.0 (1.6-2.5)	0.81
HDL (mmol/L)	1.4 (1.38-1.48)	1.2 (1.11-1.38)	0.01	1.2 (1.16-1.24)	1.1 (1.08-1.20)	0.16
Hs-CRP* (mg/L)	0.3 ± 0.7	4.8 ± 3.2	0.0001	0.6 ± 0.9	4.70 ± 2.1	0.0001
Smoker (%)	19.9 (13.5-26.3)	13.0 (0.0-26.7)	0.57	21.3 (15.0-27.6)	26.3 (13.0-39.6)	0.52

*Data is presented as median ± interquartile range (IQR) while others are presented as mean (confidence interval) and for smoker, percentage (confidence interval).†After adjustment for race. MetS - metabolic syndrome, BMI - body mass index, SBP - systolic blood pressure, DBP - diastolic blood pressure, PWV_{CF} - carotid femoral pulse wave velocity, TC - total cholesterol, LDL - low-density lipoprotein, HDL - high-density lipoprotein, TG - triglycerides, hs-CRP - high sensitivity C reactive protein.

high percentage of MetS (~55%) was observed in the current study compared to previous studies in Malaysia (IDF criteria ~37%, harmonized criteria = 42.5%), since we adopted a purposive sampling, which is a type of a non-randomized sampling.[10,27] Sampling around Klang Valley, which is an urban area would also be a factor. It was reported that the prevalence of MetS in Greek hypertensive was around 38%.[28] In the current study, which involved 54% hypertensive subjects, it is expected that the prevalence of MetS should be less than 38%.

Pulse wave velocity, augmentation index and races. Previous studies found that ethnicity differences influence arterial function. From 3497 healthy subjects, Chirinos et al[15] found that Africans and Andean Hispanics showed much higher values of AI than British whites of the same age. In another study, which involved 152 young adults, blacks were found to have larger annual PWV increases when compared to the whites.[29] In a study, which involved 2488 old subjects, Li et al[16] found that blacks had higher PWV compared to the whites. High value of PWV and AI were also observed among the African-American adolescents compared to Caucasian.[30]

This study found that Malays had much higher values of AI compared to Chinese. This difference should be investigated in future studies. It may be related to the difference in the diet intake or physical activity level between these 2 races. Nevertheless, this is an important finding for future research. In comparing the AI in 2 groups of subjects, which involves Malays, and Chinese in Malaysia, it is recommended that the comparison should take into account ethnicity as the confounder.

Pulse wave velocity, AI, and metabolic syndrome. The associations between MetS and PWV have been studied extensively. Many studies found that MetS is associated with increased PWV.[19,31,32] Another study found no association.[33] The current study slightly differs from previous studies, in which harmonized criteria was used. It was found that PWV was higher in the MetS compared to the non-MetS subjects using either IDF or harmonized criteria. This also means that IDF and harmonized criteria had similar potential to identify subjects with increased arterial stiffness. Several studies in Asian subjects had also observed similar results.[34,35] However, these studies used brachial ankle PWV as the measure of arterial stiffness. The present

study focused on carotid femoral pulse wave velocity, which is the gold standard for measurement of arterial stiffness. Several mechanisms have been implicated for the increased in PWV in MetS, such as the presence of insulin resistance, high degree of inflammation, high leptin level and endothelial dysfunction.[8,36-38] AS occurs when there is increased in the collagen and reduced in elastin in the arterial wall. Stiffness also occurs when there is increased arterial tone, which is due to the high sympathetic activity.[39] All the conditions in MetS as stated above may have been caused by either one or both effects. For AI, as it is influenced by AS, it is expected to be increased in MetS which has increased in PWV. However, no significant difference was obtained between MetS group and non-MetS using either criteria in this study. The results of the present study were in agreement with past studies in MetS.[40,41] Study by Cozma et al,[40] which involved 214 old patients found that PWV was increased, but not AI, in the male subjects with MetS. Vyssoulis et al[41] also found that PWV was increased and not AI in the MetS subjects. In contrast, Ghiadoni et al.[32] found that both PWV and AI were increased in the MetS compared to the healthy. The lack of increased of AI in the current study can be attributed to the presence of other factors that influence AI such as heart rate, height of the subjects and total peripheral resistance (TPR).[3] AI has inverse relationship with height and heart rate, and would be low in the presence of peripheral vasodilatation.[42,43] In this study, the height between the groups was insignificantly different, but the MetS group had significantly higher heart rate, which may reduce the AI. Due to the influence of the heart rate, previous study proposed to normalize the value of AI to a standard heart rate, for example 75 bpm.[44] Admittedly, this could not be done in our study due to technical limitation. Another possible explanation for the discrepancies between PWV and AI is the role of inflammation. In the current study, the MetS group had higher degree of inflammation. Previous study found that acute inflammation in humans increased large artery stiffness and reduced the AI.[43] In that particular study, the inflammation was induced by giving Salmonella typhi vaccination to the subjects and the levels of inflammatory mediators such as CRP and interleukin-6 were significantly increased after the vaccination. The authors proposed that the reduction in AI might due to the low reflected pressure wave as a consequence of peripheral vasodilatation induced by inflammation.[43] It was shown that pure human CRP increases the bioavailability of nitric oxide (NO) in in-vitro artery, which may lead to peripheral vasodilatation.[45] Increased AS with normal AI was also observed in patients with chronic inflammatory disease.[46] This signifies that inflammation may modulate the association between AS and AI. Besides inflammation, peripheral vasodilatation might also occur in hyper-insulinemia state, a condition that is related to MetS. Research reports in hypertensive subjects depict that insulin potentiate vasodilatation via endothelium dependent pathways.[47] Admittedly, in the present study, we did not venture to measure the TPR to confirm the presence of peripheral vasodilatation, which could influence the wave reflection.

Pulse wave velocity, AI, and hs-CRP in metabolic syndrome. The result of higher degree of PWV_{CF} in those with high hs-CRP was also obtained by Tomiyama et al.[8] In contrast, Saijo et al[48] found that combining MetS and CRP data did not enhance the prediction of higher AS compared to the use of MetS criteria alone. High level of hs-CRP reflects the burden of inflammation in the body. High degree of inflammation may increase AS via several mechanisms. First, inflammation may promote endothelial dysfunction, which was found to be correlated to arterial stiffness.[49,50] Secondly, increasing level of matrix metalloproteases (MMPs) secreted by inflammatory cells might cause collagen and elastin breakdown.[39,51] Thirdly, inflammation is related to insulin resistance, where there is increased production of advanced glycation end products collagen (AGEs-link collagen) in the arterial wall.[52,53] AGE-link collagen is stiffer than normal collagen.[39] The European Society of Hypertension (ESH) and European Society of Cardiology (ESC) identified AS as one of the target organ damage or specifically, subclinical vascular damage.[54] Since high CRP reflects increased AS, the measurement of CRP among MetS subjects may add more prognostic value for CVD risk assessment, especially in centers where measurement of AS is not available. The information might be helpful in terms of the aggressiveness in the management of patient's cardiovascular risk factor. However, this finding is limited to IDF and harmonized criteria. It should be evaluated for other definition of MetS. The new finding of this study was that there was significant difference in terms of AI between 2 major races in Malaysia (Malays and Chinese). This study also provides reference value of PWV_{CF}, AI and hs-CRP among MetS and non-MetS subjects in Malaysia, which may be important for other local researches.

Study limitations. First, only the men subjects were involved. Second, the use of AI, which was not adjusted to the HR, and lastly, the non-randomized sampling of the subjects, which did not allow for robust estimation of the prevalence of MetS in Malaysia and involved more Chinese compared to Malays.

In conclusion, Malays had higher AI compared to the Malaysian Chinese. Metabolic syndrome is associated with higher level of PWV_{CF} and hs-CRP. Furthermore, among those with MetS, high hs-CRP level (≥3mg/L) is associated with higher level of AS. The measurement of hs-CRP among MetS subjects might add more information on the level of subclinical vascular damage in individuals. This may be helpful in terms of the aggressiveness in the management of the patient's cardiovascular risk factor.

Acknowledgment. *The authors wish to express their thanks to the technical assistants: Gabriel, Suraya, Mohd Hanapi, Norizam, Musmarlina, and Nur Ahlina.*

References

1. Grundy SM. Metabolic syndrome pandemic. ***Arterioscler Thromb Vasc Biol*** 2008; 28:629-36.
2. Gami AS, Witt BJ, Howard DE, Erwin PJ, Gami LA, Somers VK, et al. Metabolic syndrome and risk of incident cardiovascular events and death: A systematic review and meta-analysis of longitudinal studies. ***J Am Coll Cardiol*** 2007; 49: 403-414.
3. Laurent S, Cockcroft J, Bortel LV, Boutouyrie P, Giannattasio C, Hayoz D, et al. Abridged version of the expert consensus document on arterial stiffness. ***Artery Res*** 2007; 1: 2-12.
4. Rein P, Saely CH, Beer S, Vonbank A, Drexel H. Roles of the metabolic syndrome, HDL cholesterol, and coronary atherosclerosis in subclinical inflammation. ***Diabetes Care*** 2010; 33: 1853-1855.
5. Sattar N, Gaw A, Scherbakova O, Ford I, O'Reilly DSJ, Haffner SM, et al. Metabolic syndrome with and without C-reactive protein as a predictor of coronary heart disease and diabetes in the West of Scotland Coronary Prevention Study. ***Circulation*** 2003; 108: 414-419.
6. Ridker PM, Buring JE, Cook NR, Rifai N. C-reactive protein, the metabolic syndrome, and risk of incident cardiovascular events: an 8-year follow-up of 14 719 initially healthy American women. ***Circulation*** 2003; 107: 391-397.
7. Saijo Y, Yoshioka E, Fukui T, Kawaharada M, Kishi R. Metabolic syndrome, C-reactive protein and increased arterial stiffness in Japanese subjects. ***Hypertens Res*** 2006; 29: 589-596.
8. Tomiyama H, Koji Y, Yambe M, Motobe K, Shiina K, Gulnisa Z, et al. Elevated C-reactive protein augments increased arterial stiffness in subjects with the metabolic syndrome. ***Hypertension*** 2005; 45: 997-1003.
9. Alberti KGMM, Eckel RH, Grundy SM, Zimmet PZ, Cleeman JI, Donato KA, et al. Harmonizing the metabolic syndrome: A joint interim statement of the International Diabetes Federation Task Force on epidemiology and prevention; National Heart, Lung and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; and International Association for the study of Obesity. ***Circulation*** 2009; 120: 1640-1645.
10. Mohamud WN, Ismail AS, Sharifuddin A, Ismail IS, Musa KI, Kadir KA, et al. Prevalence of metabolic syndrome and its risk factors in adult Malaysians: Results of a nationwide survey. ***Diabetes Res Clin Pract*** 2011; 91: 239-245.
11. Alberti KG, Zimmet P, Shaw J. Metabolic syndrome--a new world-wide definition. A Consensus Statement from the International Diabetes Federation. ***Diabet Med*** 2006; 23: 469-480.
12. Fantin F, Francesco VD, Rossi A, Giuliano K, Marino F, Cazzadori M, et al. Abdominal obesity and subclinical vascular damage in the elderly. ***J Hypertens*** 2010; 28: 333-339.
13. Vlachopoulos C, Aznaouridis K, Stefanadis C. Prediction of cardiovascular events and all-cause mortality with arterial stiffness: A systematic review and meta-analysis. ***J Am Coll Cardiol*** 2010; 55: 1318-1327.
14. Manisty C, Mayet J, Tapp RJ, Parker KH, Sever P, Poulter NH, et al. Wave reflection predicts cardiovascular events in hypertensive individuals independent of blood pressure and other cardiovascular risk factors: An ASCOT (Anglo-Scandinavian Cardiac Outcome Trial) substudy. ***J Am Coll Cardiol*** 2010; 56: 24-30.
15. Chirinos JA, Kips JG, Roman MJ, Medina-Lezama J, Li Y, Woodiwiss AJ, et al. Ethnic Differences in Arterial Wave Reflections and Normative Equations for Augmentation Index. ***Hypertens*** 2011; 57: 1108-1116.
16. Li S, Chen W, Srinivasan SR, Berenson GS. Influence of metabolic syndrome on arterial stiffness and its age-related change in young adults: the Bogalusa Heart Study. ***Atherosclerosis*** 2005; 180: 349-354.
17. Department of Statistics, Malaysia. Population distribution and basic demographic characteristics. (Updated: 2011 July. Accessed 2012 June 20). Available from URL: http://www.statistics.gov.my
18. Chin KY, Soelaiman IN, Mohamed N, Johari H, Ngah WZW. Ethnicity, smoking and body composition influence testosterone and estradiol levels in healthy young adult men in Malaysia: A pilot study. ***J Clin Endocrinol Metab*** 2012; 10: 404-410.
19. Ahluwalia N, Drouet L, Ruidavets JB, Perret B, Amar J, Boccalon H, et al. Metabolic syndrome is associated with markers of subclinical atherosclerosis in a French population-based sample. ***Atherosclerosis*** 2006; 186: 345-353.
20. Eng J. Sample Size Estimation: How Many Individuals Should Be Studied? ***Radiology*** 2003; 227: 309-313.
21. Pucci G, Whittaker L, Hickson SS, Cheriyan J, Schillaci G, Mceniery CM, et al. Vicorder apparatus for non-invasive assessment of central blood pressure: repeatability and comparison with the Sphygmocor devices. ***J Hypertens*** 2010; 28: 167.
22. Alberti KG, Zimmet PZ. Definition, diagnosis and classification of diabetes mellitus and its complications. Part 1: diagnosis and classification of diabetes mellitus provisional report of a WHO consultation. ***Diabetic Med*** 1998; 15: 539-553.
23. Tan CE, Ma S, Wai D, Chew S, Tai E. Can we apply the National Cholesterol Education Program Adult Treatment Panel Definition of the metabolic syndrome to Asians? ***Diabetes Care*** 2004; 27: 1182-1186.
24. Pearson TA, Mensah GA, Alexander RW, Anderson JL, Cannon RO III, Criqui M, et al. Markers of inflammation and cardiovascular disease. Application to clinical and public health practice: A statement for healthcare professionals from the Centers for Disease Control and Prevention and the American Heart Association. ***Circulation*** 2003; 107: 499-511.
25. McCallum Layton. Confidence Interval Calculator for Proportions. (Updated 2008, Accessed 2012 June 24). Available from URL: http://www.mccallum-layton.co.uk/stats/ConfidenceIntervalCalcProportions.aspx.

26. Cushman M, Arnold AM, Psaty BM, Manolio TA, Kuller LH, Burke GL, et al. C-Reactive Protein and the 10-Year Incidence of Coronary Heart Disease in Older Men and Women: The Cardiovascular Health Study. ***Circulation*** 2005; 112: 25-31.
27. Moy FM, Bulgiba A. The modified NCEP ATP III criteria maybe better than the IDF criteria in diagnosing metabolic syndrome among Malays in Kuala Lumpur. ***BMC Public Health*** 2010; 10: 678.
28. Vyssoulis GP, Karpanou EA, Liakos CI, Kyvelou SM, Tzamou VE, Michaelides AP, et al. Cardiovascular risk factor(s) prevalence in Greek hypertensives. Effect of gender and age. ***J Hum Hypertens*** 2012; 26: 443-451.
29. Wildman RP, Farhat GN, Patel AS, Mackey RH, Brockwell S, Thompson T, Tyrrell KS. Weight Change Is Associated With Change in Arterial Stiffness Among Healthy Young Adults. ***Hypertension*** 2005; 45: 187-192.
30. Shah AS, Dolan LM, Gao Z, Kimball TR, Urbina EM. Racial differences in arterial stiffness among adolescents and young adults with type 2 diabetes. ***Pediatr Diabetes*** 2012; 13: 170-175.
31. Sipilä K, Koivistoinen T, Moilanen L, Nieminen T, Reunanen A, Jula A, et al. Metabolic syndrome and arterial stiffness: The Health 2000 Survey. ***Metabolism*** 2007; 56: 320-326.
32. Ghiadoni L, Penno G, Giannarelli C, Plantinga Y, Bernardini M, Pucci L, et al. Metabolic Syndrome and Vascular Alterations in Normotensive Subjects at Risk of Diabetes Mellitus. ***Hypertens*** 2008; 51: 440-445.
33. Protogerou AD, Blacher J, Aslangul E, Jeunne CL, Lekakis J, Mavrikakis M, et al. Gender influence on metabolic syndrome's effects on arterial stiffness and pressure wave reflections in treated hypertensive subjects. ***Atherosclerosis*** 2007; 193: 151-158.
34. Satoh H, Kishi R, Tsutsui H. Metabolic syndrome is a significant and independent risk factor for increased arterial stiffness in Japanese subjects. ***Hypertens Res*** 2009; 32: 1067-1071.
35. Jae SY, Heffernan KS, Fernhall B, Oh YS, Park WH, Lee MK, et al. Association between cardiorespiratory fitness and arterial stiffness in men with the metabolic syndrome. ***Diabetes Res Clin Pract*** 2010; 90: 326-332.
36. Yki-Järvinen H, Westerbacka J. Insulin resistance, arterial stiffness and wave reflection. ***Adv Cardiol*** 2007; 44: 252-260.
37. Windham BG, Griswold ME, Farasat SM, Ling SM, Carlson O, Egan JM, et al. Influence of leptin, adiponectin and resistin on the association between abdominal adiposity and arterial stiffness. ***Am J Hypertens*** 2010; 23: 501-507.
38. Mertens I, Verrijken A, Michiels J, Planken MVD, Ruige J, Gaal LV. Among inflammation and coagulation markers, PAI-1 is a true component of the metabolic syndrome. ***Int J Obes*** 2006; 30: 1308-1314.
39. Zieman SJ, Melenovsky V, Kass D. Mechanisms, pathophysiology, and therapy of arterial stiffness. ***Arterioscler Thromb Vasc Biol*** 2005; 25: 932-943.
40. Cozma A, Sitar-Taut AV, Sitar-Taut DA, Orasan O, Leucuta DC, Pop D, Zdrenghea DT. Impact of the defining criteria and components of metabolic syndrome on arterial stiffness parameters. ***Applied Medical Informatics*** 2010; 27: 39-46.
41. Vyssoulis GP, Pietri PG, Karpanou EA, Vlachopoulos CV, Kyvelou SM, Spanos P, et al. Differential impact of metabolic syndrome on arterial stiffness and wave reflections: Focus on distinct definitions. ***Int J Cardiol*** 2010; 138: 119-125.
42. Nürnberger J, Keflioglu-Scheiber A, Opazo Saez AM, Wenzel RR, Philipp T, Schäfers RF. Augmentation index is associated with cardiovascular risk. ***J Hypertens*** 2002; 20: 2407-2414.
43. Vlachopoulos C, Dima I, Aznaouridis K, Vasiliadou C, Ioakeimidis N, Aggeli C, et al. Acute systemic inflammation increases arterial stiffness and decreases wave reflections in healthy individuals. ***Circulation*** 2005; 112: 2193-2200.
44. Weber T, Auer J, O'Rourke MF, Kvas E, Lassnig E, Lamm G, et al. Increased arterial wave reflections predict severe cardiovascular events in patients undergoing percutaneous coronary interventions. ***Eur Heart J*** 2005; 26: 2657-2663.
45. Clapp BR, Hirschfield GM, Storry C, Gallimore JR, Stidwill RP, Singer M, et al. Inflammation and endothelial function: direct vascular effects of human C-reactive protein on nitric oxide bioavailability. ***Circulation*** 2005; 111: 1530-1536.
46. Maki-Petaja KM, Hall FC, Booth AD, Wallace SML, Yasmin, Bearcroft PWP, et al. Rheumatoid arthritis is associated with increased aortic pulse-wave velocity, which is reduced by anti-tumor necrosis factor-{alpha} therapy. ***Circulation*** 2006; 114: 1185-1192.
47. Taddei S, Virdis A, Mattei P, Natali A, Ferrannini E, Salvetti A. Effect of insulin on acetylcholine-induced vasodilation in normotensive subjects and patients with essential hypertension. ***Circulation*** 1995; 92: 2911-2918.
48. Saijo Y, Yoshioka E, Fukui T, Kawaharada M, Kishi R. Metabolic Syndrome, C-Reactive Protein and Increased Arterial Stiffness in Japanese Subjects. ***Hypertens Res*** 2006; 29: 589-596.
49. Kharbanda RK, Walton B, Allen M, Klein N, Hingorani AD, MacAllister RJ, et al. Prevention of inflammation-induced endothelial dysfunction: a novel vasculo-protective action of aspirin. ***Circulation*** 2002; 105: 2600-2604.
50. Jadhav UM, Kadam N. Non-invasive assessment of arterial stiffness by pulse-wave velocity correlates with endothelial dysfunction. ***Indian Heart J*** 2005; 57: 226-232.
51. Wallace S, McEniery CM, Dakham Z, Pusalkar P, Maki-Petaja K, Ashby MJ, et al. Matrix metalloproteinase-9 (MMP-9), MMP-2, and serum elastase activity are associated with systolic hypertension and arterial stiffness. ***Arterioscler Thromb Vasc Biol*** 2005; 25: 372-378.
52. Festa A, D'Agostino R, Howard G, Mykkänen L, Tracy RP, Haffner SM. Chronic subclinical inflammation as part of the insulin resistance syndrome: the Insulin Resistance Atherosclerosis Study (IRAS). ***Circulation*** 2000; 102: 42-47.
53. Ramasamy R, Bucciarelli LG, Yan SF, Schmidt AM. Advanced Glycation End Products, RAGE, and Aging. In: Bondy S, Maiese K, editors. Aging and Age-Related Disorders, Oxidative Stress in Applied Basic Research and Clinical Practice. New York (NY): Springer Science+Business Media. 2010. p. 79-90.
54. Mancia G, De Backer G, Dominiczak A, Cifkova R, Fagard R, Germano G, et al. Guidelines for the management of arterial hypertension: The Task Force for the Management of Arterial Hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). ***J Hypertens*** 2007; 25: 1751-1762.