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REVIEW

Inflammation as a cardiovascular risk factor and pulse wave velocity as a marker of early-stage atherosclerosis in the Japanese population

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Abstract Inflammation and pulse wave velocity (PWV) are a potential risk factor and marker, respectively, for atherosclerosis in the primary prevention setting. Atherosclerosis is now generally accepted to be an inflammatory disorder of the arterial wall, and the high-sensitivity C-reactive protein (hs-CRP) level has been reported to be a strong predictor of cardiovascular events. High-sensitivity-CRP is associated with two factors related to inflammation: (1) the local production of CRP by atheromatous tissue or coronary artery smooth muscle cells and (2) adipose tissue as a potent source of inflammatory cytokines. Based on studies in North America and Europe, hs-CRP has been established as a cardiovascular risk factor and a cut-off value has been recommended. However, Japanese have lower hs-CRP values than their Western counterparts, partly because Japanese have a lower body mass index (BMI), which correlates positively to hs-CRP, and partly because lifestyle and genetic factors can affect hs-CRP values. Therefore, a cut-off value needs to be established by cohort studies for the Japanese population. Carotid-femoral PWV is most commonly measured by applanation tonometry, particularly in Europe, but this method is critically dependent upon the accurate placing of transducers over the arteries and is both time-consuming and complex. A novel device has been recently developed in Japan that measures brachial-ankle PWV (baPWV) using a volume-rendering method. Brachian-ankle PWV is a suitable screening method because of its technical simplicity and shorter measurement time. It is associated not only with conventional cardiovascular risk factors but also with new risk factors, such as inflammation, γ-glutamyltransferase, chronic kidney disease, and psychosocial factors. However, a suitable cut-off value has yet to be established.

Keywords Arterial stiffness · Atherosclerosis · C-reactive protein · Inflammation · Pulse wave velocity

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Introduction

Cardiovascular diseases are a leading cause of death in developed countries. As such, their prevention is an important public health objective, and preventative measures need to be taken at the earliest possible stage of atherosclerosis.

Atherosclerosis is now generally accepted to be an inflammatory disorder of the arterial wall [1], and the high-sensitivity C-reactive protein (hs-CRP) level is a strong predictor of cardiovascular events [2–4]. The majority of research on hs-CRP as a cardiovascular risk factor has been performed in North America and Europe. It has been reported that the hs-CRP level among the Japanese general

population is an order of magnitude smaller than that found in Western populations [5, 6], although conventional cardiovascular risk factors, such as blood pressure, blood glucose, and low-density lipoprotein cholesterol, are similar in magnitude. There is, therefore, a need to investigate the significance and role of inflammation in general and hs-CRP in particular as a risk factor for the development of atherosclerosis in the Japanese population.

Pulse wave velocity (PWV) is an indicator of arterial stiffness [7], and a higher PWV value has been associated with the development of atherosclerotic disease [8, 9]. The most common method used to measure carotid-femoral PWV (cfPWV), particularly in Europe, is applanation tonometry. However, this method is critically dependent upon the accurate placing of the transducers over the arteries and is both time-consuming and complex [10]. A novel device has been recently developed in Japan which measures brachial-ankle PWV (baPWV) by a volume-rendering method. This instrument determines baPWV by simultaneous oscillometric measurement of pulse waves in all four extremities and is considered to be more appropriate for screening a large population than previous methods because of its technical simplicity and shorter measurement time [11]. Thus, the significance and role of baPWV as an early marker of atherosclerosis should also be investigated in the Japanese population.

Inflammation and hs-CRP

Although several inflammatory markers are known, such as P-selectin, interleukin (IL)-6, IL-1, tumor necrosis factor (TNF), soluble intercellular adhesion molecule-1, and fibrinogen, hs-CRP has emerged as the most powerful inflammatory predictor of future cardiovascular risk [12, 13]. Moreover, because the hs-CRP test is relatively cheap and easy to perform in serum, it can be used in primary prevention.

There are two possible mechanisms of hs-CRP elevation that may be relevant to the prevention of atherosclerotic diseases: (1) the local production of CRP by atheromatous tissue or coronary artery smooth muscle cells [14] and (2) adipose tissue as a potent source of inflammatory cytokines, including TNF and IL-6, which induce hepatic production of CRP [15]. Results from studies in Europe and the USA indicate that the hs-CRP level is associated with body mass index (BMI) and waist circumference [16, 17], and Japanese, as well as having lower hs-CRP levels, also have a lower BMI than Western populations. We have therefore explored the relationships between fatness and visceral obesity parameters (by anthropometry, bioelectrical impedance analysis, and abdominal computed tomography) and hs-CRP in the Japanese population [5]. We found that the association with hs-CRP was stronger for parameters of visceral obesity (waist circumference, waist-to-hip ratio, and visceral adipose tissue accumulation) than for other parameters of obesity after adjustment for age, gender, and smoking.

Several lifestyle factors are related to variations in hs-CRP level. Smoking increases the IL-6 level [18] and is associated with hs-CRP elevation [2, 19]. In contrast, moderate drinking [20] and physical activity, independent of weight loss [21], may lower the hs-CRP level.

Genetic factors may also affect hs-CRP level. The IL-6–174G/C polymorphism, which may have functional effects, may affect the hs-CRP level [22, 23], but the data are controversial [24]. The C allele of the IL-6–174G/C polymorphism is common among Caucasians but extremely rare among East Asians. However, the G allele of the IL-6–634C/G polymorphism, which may also have functional effects, is common among East Asians [25, 26]. Based on the results of our earlier study, we reported that the hs-CRP level differed significantly among IL-6–634C/G genotype groups in nonsmokers (P for trend = 0.007), whereas there was no significant difference in current smokers; a comparison between −634CC and C/G + G/G groups revealed a significant interaction between smoking and the IL-6 −634C/G genotype (P = 0.007) [19]. These findings suggest that the impact of the −634G allele on hs-CRP elevation is greater in nonsmokers than in current smokers. Moreover, other inflammation-related polymorphisms, such as TNF-alpha and CRP itself, have been reported as able to modify the hs-CRP level [27, 28].

In North America and Europe, concentrations of hs-CRP of <1, 1–3, and >3 mg/l are considered to confer low, intermediate, and high risk, respectively [29]. However, the distribution of hs-CRP levels among Japanese is probably an order of magnitude lower than that in Western populations (Table 1). Saito et al. reported the hs-CRP concentrations of the general Japanese population [30] subject to external quality control of the hs-CRP measurement using a latex particle-enhanced immunoassay (N Latex CRPII; Dade Behring, Tokyo, Japan) [31]. The hs-CRP concentrations in our previous studies were measured using the same method (latex particle-enhanced immunoassay; N Latex CRPII, Dade Behring) at a commercial laboratory (intra-assay coefficient of variation 2.0%) [5, 32]. However, a specific cut-off point for hs-CRP in Japanese is needed, even though other cut-off values for traditional risk factors, such as blood pressure, blood glucose, and lipids, are almost the same as in Westerners. On the basis of studies performed on the relationship between hs-CRP and metabolic syndrome, including our previous study [33], Oda et al. have suggested that the optimal cut-off point for hs-CRP may be

Table 1 Comparison of high-sensitivity C-reactive protein levels and obesity parameters

Study	Country	Sex	Age (years)[a]	*n*	BMI (kg/m^2)[b]	hs-CRP (mg/dl)[c]
Yudkin et al. [59]	UK	Both	59.0 ± 10.9	107	25.9 ± 4.5	0.135 (0.057–0.218)
Hak et al. [16]	Netherlands	Female	50.9 ± 2.3	186	24.9 ± 4.0	0.068 (0.033–0.144)
Lemieux et al. [17]	Canada	Male	43.3 ± 7.9	159	30.3 ± 3.9	0.221 ± 0.196
Yamada et al. [6]	Japan	Both	55.8 ± 11.5	5903	22.9 ± 3.6	0.012 (0.003–0.030)
Forouhi et al. [60]	UK	Male	40–55	28	26.1 ± 0.7	0.092 (0.034–0.161)
		Female	40–55	29	24.9 ± 0.7	0.070 (0.041–0.170)
Chambers et al. [61]	UK	Male	49.4 ± 6.5	507	26.7 ± 4.0	0.147 ± 0.162
Saijo et al. [5]	Japan	Male	40.4 ± 10.7	52	22.9 ± 4.3	0.052 (0.023–0.090)
		Female	32.3 ± 10.3	67	20.1 ± 2.3	0.010 (0.005–0.024)
Saijo et al. [32]	Japan	Male	48.4 ± 6.8	3412	23.8 ± 2.9	0.045 (0.023–0.089)
		Female	46.8 ± 7.2	854	21.8 ± 3.4	0.025 (0.023–0.052)
Saito et al. [30]	Japan	Male	64.9 ± 10.2	5213	23.5 ± 3.0	0.060 (0.030–0.131)
		Female	62.9 ± 10.6	7071	23.1 ± 3.3	0.045 (0.022–0.094)

hs-CRP high-sensitivity C-reactive protein, *BMI* body mass index

[a] Mean ± SD, or range

[b] Mean ± SD

[c] Mean ± SD, or median (interquartile range)

0.65 mg/dl in the Japanese population [34]. However, the cut-off point for hs-CRP should be determined by prospective studies of cardiovascular events and, consequently, further prospective studies are needed to clarify which cut-off point should be used in the Japanese population.

Atherosclerosis is now generally accepted to be an inflammatory disorder of the arterial wall, and many have suspected that an infectious agent, such as *Cytomegalovirus* or *Chlamydia pneumoniae*, is responsible for chronic inflammation in atheroma [35]. Although a recent meta-analysis found no significant association between *Helicobacter pylori* seropositivity and coronary heart disease [36], several Japanese studies have revealed a positive association [37–39]. Furthermore, we have found a significant association between *H. pylori* seropositivity and baPWV elevation, and a combination of hs-CRP elevation and *H. pylori* seropositivity shows a stronger association with baPWV elevation [40]. Because Japanese have a higher prevalence of *H. pylori* seropositivity compared with the populations of other developed countries [41], there is a particular need for the influence of chronic *H. pylori* infection on atherosclerosis to be elucidated in the Japanese population.

Brachial-ankle PWV as an early atherosclerosis marker

We previously reviewed and briefly reported the relationships between baPWV and conventional cardiovascular risk factors [42]. We have since surveyed large population-based studies to investigate the relationship of baPWV with various risk factors.

Table 2 Adjusted brachial-ankle pulse wave velocity values by gender according to quartiles of hs-CRP

Gender/quartile	hs-CRP range (mg/dl)	Mean PWV[a]	95% CI
Men			
Quartile			
1	<0.004–0.023	1358	1349–1367
2	0.024–0.045	1362	1353–1371
3	0.046–0.089	1374	1366–1383
4	0.090–9.400	1381	1372–1390
P value (for trend)		<0.01 (<0.001)	
Women			
Quartile			
1	<0.004–0.012	1241	1225–1256
2	0.013–0.025	1248	1233–1263
3	0.026–0.052	1247	1232–1262
4	0.053–3.34	1266	1250–1282
P value (for trend)		0.12 (0.055)	

CI confidence interval, *PWV* pulse wave velocity

[a] Adjusted for age, BMI, systolic blood pressure, heart rate, total cholesterol, high-density lipoprotein (HDL)-cholesterol, fasting blood glucose, log triglycerides, uric acid, estimated glomerular filtration rate (GFR), smoking status, alcohol consumption, frequency of exercise, hypertension, hyperlipidemia, and diabetes [32]

Inflammation also has a possible role in baPWV elevation. Table 2 shows the adjusted baPWV values of 3412 men and 854 women according to quartiles of hs-CRP. We observed a significant, progressive increase in baPWV

across the quartiles of hs-CRP in male subjects after controlling for age, BMI, systolic blood pressure, heart rate, total cholesterol, log triglycerides, high-density lipoprotein cholesterol, fasting glucose, uric acid, white blood cells, estimated glomerular filtration rate (GFR), smoking, alcohol, exercise, past history of hypertension, hyperlipidemia, and diabetes. In female subjects, the relationship of quartile hs-CRP with baPWV had marginal significance after adjustment for the variables mentioned above and postmenopausal status [32]. β_2-Microglobulin (β2m) is related to inflammatory diseases, but there have been few reports of a relationship between β2m and atherosclerosis. When adjusted mean baPWV values were compared with the quartiles of β2m, significant differences in baPWV were observed across the quartiles ($P = 0.037$). β2m is a marker of GFR, which is a strong confounder in analyses of the association between β2m and arterial stiffness, and our analyses were adjusted for estimated GFR. We speculate, therefore, that the inflammatory factor β2m is related to arterial stiffness [43].

Serum γ-glutamyltransferase (GGT) is a potential marker of cardiovascular disease [44]. In multiple regression analysis of male subjects, the serum GGT level was significantly associated with baPWV after adjustment for conventional cardiovascular risk factors, alcohol consumption, alanine aminotransferase, and hs-CRP. Serum γ-glutamyltransferase is involved in the antioxidant system, and this may cause its association with atherosclerosis independently of alcohol and liver function [45].

Psychosocial factors also affect cardiovascular diseases [46]. Using baPWV, we examined the relationships of two theoretical stress models, the demand–control model (DCM) and the effort–reward imbalance (ERI) model. In women, high job strain from the joint effects of low job control and high job demands (DCM) conferred a higher risk of baPWV elevation. However, high job strain in men and a high level of ERI in both genders were not related to a high value of baPWV [47]. Several studies have reported that high occupational stress evaluated using the ERI model is related to an imbalance between the coagulation and fibrinolysis systems [48–50]. This has lead to the suggestion that occupational stress, especially as evaluated using a high-stress ERI model, may have a greater effect on cardiovascular events. Women may be more sensitive to the high stress evaluated with the DCM than to that assessed with the ERI model [51], thereby explaining the significant result in women but not in men. We also examined the relationships of educational level and employment grade with baPWV. In men, educational level was found to be significantly associated with the baPWV value after adjusting for cardiovascular risk factors (P for trend <0.0001). With respect to employment grade, only low-level non-manual workers had a significantly lower baPWV value compared with manual workers in a fully adjusted model. In women, however, neither educational level nor employment grade was associated with the baPWV value [52]. It has been speculated that analyses of the effect of socioeconomic gradient on women's health in Japan may be better performed using household-based measures of socioeconomic status because wage differences between men and women are large and there is a strong dependence on family responsibility in welfare provision that is focused around the high-earning male breadwinner [53].

Chronic kidney disease is associated with an increased risk of cardiovascular disease. The Japanese Society of Nephrology [54] has recently proposed the use of estimated GFR (eGFR), using the Modification of Diet in Renal Disease equation for Japanese patients. Multiple regression analysis of data on 647 outpatients revealed that baPWV correlated negatively with eGFR, independently of traditional risk factors ($P < 0.0001$) [55]. Thus, chronic kidney disease involves not only cardiovascular events but also early atherosclerosis.

A broadly acceptable cut-off value for baPWV has not been established. In 2007, the Guidelines for the Management of Arterial Hypertension of the European Society of Hypertension and the European Society of Cardiology recommended the use of the PWV measurement to stratify total cardiovascular risk, and the cut-off value of cfPWV was given as <1.2 m/s [56]. There is an opinion that a cut-off value of 1800 cm/s for baPWV should be recommended because baPWV is roughly 1.5-fold the magnitude of cfPWV [57]. It has also been reported that receiver operating characteristic curve analysis suggests that 1800 cm/s is the best cut-off value of baPWV for the identification of increased intima-media thickness in hypertensive patients [58]. However, these cut-off values are for patients in the clinical setting, and a cut-off value for primary prevention is also required. Thus, the cut-off value needs to be established according to its association with cardiovascular events in earlier population-based cohort studies.

Conclusion

Inflammation and PWV are a potential risk factor and marker, respectively, for atherosclerosis in the secondary prevention setting. In particular, an hs-CRP-based global risk classification system has been established in North America and European countries, and a cut-off value has been recommended. However, Japanese have lower hs-CRP values than Westerners, partly because Japanese have a lower BMI, which correlates to hs-CRP, and partially because lifestyle and genetic factors can affect hs-CRP values. Consequently, there is a need to establish a cut-off value for hs-CRP in population cohort studies in Japan.

The baPWV was developed in Japan as a suitable measure for use in the secondary prevention setting because of its technical simplicity and shorter measurement time. It is associated not only with conventional cardiovascular risk factors but also with newer risk factors, such as inflammation, GGT, chronic kidney disease, and psychosocial factors. However, a suitable cut-off value for baPWV has yet to be established.

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