Changes in pulse pressure × heart rate, hs-CRP, and arterial stiffness progression in the Chinese general population: a cohort study involving 3978 employees of the Kailuan Company

Hao XUE1,*, Jun-Juan LI2,*, Jian-Li WANG2,*, Shuo-Hua CHEN2, Jing-Sheng GAO2, Yun-Dai CHEN1,#, Shou-Ling WU2,#

1Department of Cardiology, Chinese People’s Liberation Army General Hospital, Beijing, China
2Department of Cardiology, Kailuan Hospital, Hebei United University, Tangshan, China

Abstract

Background Pulse wave velocity (PWV) is a marker of arterial stiffness, which represents sub-clinical atherosclerosis. Pulsatile stress and high-sensitivity C-reactive protein (hs-CRP) are associated with arteriosclerosis. However, there is no prospective data confirming whether changes in pulsatile stress and inflammatory markers affect the progression of arterial stiffness. The aim of this study was to investigate the relationships over time between the effects of changes in pulsatile stress and hs-CRP, and arterial stiffness progression during a 2-year follow-up. Methods We performed a longitudinal study involving 3978 participants. All participants underwent a physical examination in 2010–2011 and 2012–2013, during which we measured participants’ hs-CRP levels, brachial–ankle pulse wave velocity (baPWV), and pulsatile stress. Results Baseline hs-CRP was correlated with baPWV (r = 0.18, P = 0.000); however the correlation was weaker than that with systolic blood pressure (r = 0.65), pulsatile stress (r = 0.57), and rate-pressure product (r = 0.58). Multiple linear regression analysis demonstrated that changes in pulsatile stress, mean arterial pressure, and low-density lipoprotein-C (LDL-C) were positively correlated with changes in baPWV, with correlation coefficients of 0.27, 0.25, and 0.07, respectively, but not with changes in hs-CRP. Moreover, each 100-aU increase in pulsatile stress, 1 mmHg increase in mean blood pressure, and 1 mmol/L increase in LDL-C was associated with a 3 cm/s, 4.78 cm/s, and 17.37 cm/s increase in baPWV, respectively. Conclusions Pulsatile stress increases are associated with arterial stiffness progression, but that changes in hs-CRP had no effect on arterial stiffness progression. Hs-CRP may simply be a marker of inflammation in arterial stiffness and has no association with arterial stiffness progression.

Keywords: Atherosclerosis; Blood vessels; Brachial–ankle index; C-reactive protein; Pulse wave velocity

1 Introduction

Atherosclerosis is a risk factor for cardiovascular disease,[1,2] and pulse wave velocity (PWV) is an indirect marker of arterial stiffness, which is a predictor of atherosclerosis and cardiovascular morbidity and mortality.[3–5] Brachial–ankle pulse wave velocity (baPWV) can be measured conveniently and noninvasively. Recent studies showed that PWV can be reversible under certain condition such as antihypertensive treatment, exercise, healthy diet or weight loss.[6] However, the relationship between baPWV and atherosclerosis is not yet clear. Previous studies have shown that pulse pressure × heart rate (pulsatile stress), as a parameter of hemodynamic stress on vessel walls, may contribute to increased arterial stiffness.

The inflammatory marker, high-sensitivity C-reactive protein (hs-CRP) is also associated with arteriosclerosis.[7,8] Cross-sectional studies demonstrated that CRP is associated with PWV.[9,10] Moreover, animal models showed that vascular calcification is an inflammation-driven process that can lead to increased arterial stiffness.[11,12] Therefore, inflammation may lead to endothelial dysfunction and decreased vascular elasticity.[13] However, the contribution of pulsatile stress and hs-CRP to changes in baPWV has not been evaluated in the Chinese population.
An understanding of the factors affecting changes in arterial stiffness is important to prevent cardiovascular disease. Therefore, the aim of this study was to investigate the relationship over time between changes in pulsatile stress, hs-CRP levels, and changes in PWV in a Chinese general-population cohort (ChiCTR-TNC-11001489).

2 Methods

2.1 Participants

A total of 101,510 employees of the Kailuan Company underwent initial physical examinations at the Kailuan General Hospital and its 10 affiliated hospitals between 2006 and 2007. Among the participants, we randomly selected 5440 adults ≥ 40 years of age for inclusion in this longitudinal study. Patients then underwent two physical examinations, one in 2010–2011 and another in 2012–2013. Of the 5440 patients, 265 had missing data for baPWV and hs-CRP values from 2010–2011, and 1114 had missing data for these measurements from 2012–2013. We also excluded patients with a baPWV value higher than the 99% quantile from 2010–2011 (n = 43) and from 2012–2013 (n = 40). Finally, 3978 participants were enrolled in this study (2282 men, 1696 women; mean age, 53.8 ± 11.11 years) (Figure 1).

We measured baPWV during both examinations. The inclusion criteria were: (1) patients aged ≥ 40 years; (2) completed questionnaires; (3) informed consent. Patients with the following criteria were excluded: (1) incomplete study data; (2) serum hs-CRP > 10 mg/L; (3) infectious diseases, cancer, blood-based diseases, or severe liver, heart or kidney dysfunction, or autoimmune diseases; (4) immunomodulator use in the past three months; (5) history of ischemic stroke, transient ischemic attack, coronary heart disease, and myocardial infarction; and (6) recent surgical or trauma history.

All participants were of the Han nationality. The study was approved by the Ethics Committee of the Kailuan General Hospital and was performed according to the guidelines of the Helsinki Declaration and our State Food and Drug Administration guidelines. All participants provided written informed consent.

2.2 Data collection

Questionnaires were administered in-person by investigators as previously described. A detailed medical history was recorded, including age, sex and family history of hypertension, diabetes mellitus, coronary heart disease, stroke, general medical history, alcohol intake, smoking status, and body mass index (BMI). BMI was calculated using the formula weight (kg)/height (m²).

2.3 Biochemical variables

A venous blood sample was collected after overnight fasting, and we then measured fasting blood glucose (FBG), total cholesterol, triglycerides, low-density lipoprotein-C (LDL-C), and high-density lipoprotein-C (HDL-C) using an automatic biochemical analyzer (Hitachi 747; Hitachi, Tokyo, Japan). Serum high-sensitivity C-reactive protein (hs-CRP) was determined using a commercial, high-sensitivity particle-enhanced immunonephelometry assay (Cias Latex CRP-H, Kanto Chemical Co., Inc., Tokyo, Japan). In-house intra-, inter-, day-, and total-assay coefficients of variation for hs-CRP were 6.53%, 4.78%, 6.61%, and 9.37%, respectively.

Figure 1. Study flow chart. baPWV: brachial-ankle pulse wave velocity.

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2.4 baPWV measurements

baPWV was measured in all participants with a wave-form analyzer device (BP-203RPE III; Omron Healthcare, Kyoto, Japan) in the supine position. Measurements were repeated twice at 5-min intervals, with the second data considered the final value. The larger value from the left and right side was analyzed. Systolic (SBP) and diastolic blood pressure (DBP) and heart rate were also simultaneously measured by the automated device during the baPWV measurement. Pulse pressure was calculated as SBP minus DBP. Mean blood pressure (MAP) was calculated as DBP plus pulse pressure/3. Pulsatile stress was calculated as resting heart rate × pulse pressure. Rate pressure product (RPP) was assessed as heart rate × SBP and represented peak systolic stress. Changes in baPWV (ΔbaPWV) were calculated as the baPWV value in 2012–2013 minus the value in 2010–2011.

2.5 Statistical analysis

We created a database using EpiData software (EpiData Association, Odense, Denmark, http://www.epidata.dk/). All statistical analyses were performed using SPSS version 13.0 (SPSS, IBM, Inc., Armonk, NY, USA). Continuous variables were presented as mean ± SD and analyzed using Student’s t test. Categorical variables were described as numbers and percentages, and between-group comparisons were analyzed using the chi-squared test. Hs-CRP had a positively-skewed distribution, which was used for analyses of numbers and percentages, and between-group comparisons were analyzed using the Mann–Whitney test. P values < 0.05 were considered statistically significant.

3 Results

3.1 Participants’ Clinical Characteristics

Participants’ clinical characteristics are shown in Table 1. SBP, DBP, heart rate, BMI, FBG, total cholesterol, triglycerides, LDL-C, and HDL-C for both physical examinations were in the normal ranges. No differences were found in BMI, hs-CRP, FBG, triglycerides, and MAP for either physical examination. DBP, heart rate, baPWV, and heart rate × SBP were higher in 2012–2013 than in 2010–2011.

| Table 1. Comparison of the baseline characteristics of the study population. |
| --- | --- | --- | --- |
| 2010–2011 | 2012–2013 | P value |
| N | 3978 | 3978 |
| Age, yrs | 53.8 ± 11.11 | 56.3 ± 10.92 | < 0.001 |
| Brachial SBP, mmHg | 136.8 ± 20.61 | 133.09 ± 23.34 | < 0.001 |
| Brachial DBP, mmHg | 81.79 ± 11.91 | 85.83 ± 20.96 | < 0.001 |
| Brachial PP, mmHg | 55.01 ± 13.06 | 47.25 ± 30.25 | < 0.001 |
| Brachial MAP, mmHg | 103.98 ± 15.73 | 103.01 ± 17.89 | > 0.05 |
| HR, beats/min | 70.26 ± 10.58 | 73.01 ± 8.78 | < 0.001 |
| BMI, kg/m² | 24.94 ± 3.24 | 24.88 ± 3.27 | > 0.05 |
| hs-CRP, mg/L | 1.52 ± 4.11 | 1.73 ± 1.66 | < 0.05 |
| TC, mmol/L | 5.06 ± 0.99 | 5.18 ± 1.49 | < 0.001 |
| HDL-C, mmol/L | 1.64 ± 0.43 | 1.42 ± 0.47 | < 0.001 |
| LDL-C, mmol/L | 2.6 ± 0.74 | 2.52 ± 1.14 | < 0.001 |
| baPWV, cm/s | 1547.4 ± 362.71 | 1604.56 ± 436.79 | < 0.001 |
| Pulsatile stress, aU | 3863.04 ± 1107.18 | 3453.22 ± 2273.48 | < 0.001 |
| RPP, Au | 9640.22 ± 2223.58 | 9735.94 ± 2175.61 | < 0.001 |
| Smoking | 1443 (36.3%) | 899 (22.6%) | < 0.001 |
| Alcohol intake | 1341 (33.7%) | 865 (21.7%) | < 0.001 |
| Hypertension | 292 (7.3%) | 219 (5.6%) | < 0.001 |
| Hypolycemic agents consumption | 746 (18.8%) | 511 (12.8%) | < 0.001 |
| Hypolycemic agents consumption | 217 (5.5%) | 219 (4.0%) | < 0.001 |

Data are presented as mean ± SD or n (%). Pulsatile stress = heart rate × pulse pressure; PP = SBP–DBP; RPP = heart rate × SBP. baPWV: brachial-ankle pulse wave velocity; BMI: body mass index; DBP: diastolic blood pressure; FBG: fasting blood glucose; HDL-C: high-density lipoprotein cholesterol; HR: heart rate; hs-CRP: high-sensitivity C-reactive protein; LDL-C: low-density lipoprotein cholesterol; MAP: mean arterial pressure; PP: pulse pressure; RPP: rate-pressure product; SBP: systolic blood pressure; TC: total cholesterol; TG: triglycerides.

rate × SBP were higher in 2012–2013 than in 2010–2011. SBP, HDL-C, and heart rate × SBP were lower in 2012–2013 than in 2010–2011.

3.2 Association between baseline baPWV, ΔbaPWV, and changes in hs-CRP and traditional cardiovascular risk factors

Baseline baPWV was significantly positively associated with age, SBP, DBP, pulse pressure, MAP, heart rate, hs-CRP, pulsatile stress, and RPP with correlation coefficients of 0.64, 0.65, 0.51, 0.56, 0.65, 0.21, 0.18, 0.57, and 0.58, respectively, in bivariate correlation analysis (Table 2). ΔbaPWV was also positively-correlated with changes in SBP, DBP, pulse pressure, MAP, heart rate, LDL-C, pulsatile...
Table 2. Correlation coefficients for comparisons between baPWV and other variables.

| Variables          | Baseline baPWV Pearson correlation | P  |
|--------------------|-----------------------------------|----|
| Age, yrs           | 0.64                              | 0.000 |
| Brachial SBP, mmHg | 0.65                              | 0.000 |
| Brachial DBP, mmHg | 0.51                              | 0.000 |
| Brachial PP, mmHg  | 0.56                              | 0.000 |
| Brachial MAP, mmHg | 0.65                              | 0.000 |
| HR, beats/min      | 0.21                              | 0.000 |
| BMI, kg/m²         | 0.02                              | 0.132 |
| Log hs-CRP         |                                  |     |
| FBG, mmol/L        | 0.08                              | 0.000 |
| TC, mmol/L         | 0.14                              | 0.000 |
| HDL-C, mmol/L      | −0.04                             | 0.01 |
| LDL-C, mmol/L      | 0.07                              | 0.000 |
| RPP, aU            | 0.58                              | 0.000 |
| Pulsatile stress, aU | 0.57                             | 0.000 |

RPP = heart rate × SBP; pulsatile stress = heart rate × pulse pressure; pulse pressure = SBP−DBP. The values for hs-CRP are presented as a normal distribution after log transformation. ΔbaPWV = baPWV(2012–2013)−baPWV(2010–2011). Other variables were calculated using the same method.

baPWV: brachial–ankle pulse wave velocity; BMI: body mass index; DBP: diastolic blood pressure; FBG: fasting blood glucose; HDL-C: high-density lipoprotein-C; HR: heart rate; LDL-C: low-density lipoprotein-C; MAP: mean arterial pressure; PP: pulse pressure; RPP: rate-pressure product; SBP: systolic blood pressure; TC: total cholesterol; TG: triglycerides.

Table 3. Correlation coefficients for comparisons between changes in baPWV (ΔbaPWV) and other variables.

| Variables          | ΔbaPWV Pearson correlation | P  |
|--------------------|----------------------------|----|
| ΔAge, yrs          | 0.02                       | 0.240 |
| ΔBrachial SBP, mmHg| 0.33                       | 0.000 |
| ΔBrachial DBP, mmHg| 0.20                       | 0.000 |
| ΔBrachial PP, mmHg | 0.10                       | 0.000 |
| ΔBrachial MAP, mmHg| 0.31                       | 0.000 |
| ΔHR, beats/min     | 0.08                       | 0.000 |
| ΔBMI, kg/m²        | 0.02                       | 0.170 |
| ΔLog hs-CRP        | −0.01                      | 0.483 |
| ΔFBG, mmol/L       | 0.01                       | 0.823 |
| ΔTG, mmol/L        | 0.011                      | 0.790 |
| ΔTC, mmol/L        | 0.011                      | 0.968 |
| ΔHDL-C, mmol/L     | −0.02                      | 0.290 |
| ΔLDL-C, mmol/L     | 0.06                       | 0.005 |
| ΔRPP, aU           | 0.12                       | 0.000 |
| ΔPulsatile stress, aU | 0.29                  | 0.000 |

ΔbaPWV = baPWV(2012–2013)−baPWV(2010–2011). Other variables were calculated with the same method. BMI: body mass index; ΔbaPWV: change in brachial–ankle pulse wave velocity; DBP: diastolic blood pressure; FBG: fasting blood glucose; HDL-C: high-density lipoprotein-C; HR: heart rate; LDL-C: low-density lipoprotein-C; MAP: mean arterial pressure; PP: pulse pressure; RPP: rate-pressure product; SBP: systolic blood pressure; TC: total cholesterol; TG: triglycerides.

Table 4. Multivariate linear regression analyses for the association between ΔbaPWV and Δpulsatile stress, Δhs-CRP, ΔMAP, and ΔLDL-C.

| Variables          | B     | Beta  | P     | 95%CI |
|--------------------|-------|-------|-------|-------|
| Δpulsatile stress  | 0.03  | 0.27  | 0.000 | 0.02–0.03 |
| Δhs-CRP            | −3.72 | −0.02 | 0.334 | −11.27–3.83 |
| ΔMAP               | 4.78  | 0.25  | 0.000 | 4.11–5.46 |
| ΔLDL-C             | 17.37 | 0.07  | 0.000 | 9.01–25.74 |

Pulsatile stress = heart rate × pulse pressure. The values for hs-CRP are presented as a normal distribution after log transformation. ΔbaPWV = baPWV(2012–2013)−baPWV(2010–2011). hs-CRP: high-sensitivity C-reactive protein; LDL-C: low-density lipoprotein-C; MAP: mean arterial pressure.
Table 5. Multivariate linear regression analyses for associations between ΔbaPWV and ARPP, Δhs-CRP, ΔMAP, and ΔLDL-C.

| Variables | B     | Beta  | P       | 95% CI          |
|-----------|-------|-------|---------|-----------------|
| ΔRPP      | 0.003 | 0.02  | 0.144   | −0.001 to 0.01  |
| Δhs-CRP   | −2.16 | −0.01 | 0.582   | −9.84 to 5.53   |
| ΔMAP      | 6.35  | 0.32  | 0.000   | 5.69 to 7.01    |
| ΔLDL-C    | 16.21 | 0.06  | 0.000   | 7.7 to 24.73    |

RPP = heart rate × SBP, pulse pressure = SBP−DBP. The values for hs-CRP are presented as a normal distribution after logit transformation. ΔbaPWV = baPWV(2012−2013)−baPWV(2010−2011). baPWV: brachial-ankle pulse wave velocity; hs-CRP: high-sensitivity C-reactive protein; LDL-C: low-density lipoprotein-C; MAP: mean arterial pressure; RPP: rate-pressure product.

3.3 Effects of changes in pulsatile stress, hs-CRP, LDL-C, and MAP on baPWV during the 2-year follow-up

Results of the Mann–Whitney U test showed that ΔbaPWV increased with increasing Δpulsatile stress, ΔMAP, and ΔLDL-C during the 2-year follow-up. However, changes in hs-CRP had no effect on ΔbaPWV (Figure 2).

4 Discussion

In the present study, we found that baseline hs-CRP was correlated with baseline baPWV levels; baPWV increased with increasing pulsatile stress, MAP, and LDL-C during the 2-year follow-up. However, no association was found between changes in hs-CRP and baPWV in our prospective study. This finding is consistent with results reported by Jae, et al.,[16] who found that changes in pulsatile stress and RPP were associated with changes in baPWV after a 1-year follow-up. Consistent findings have suggested that pulsatile stress was responsible for accelerated PWV progression in over a 6-year period in treated patients with hypertension and in normotensive patients; changes in inflammatory markers were not correlated with changes in PWV.[17] However, previous studies have shown that PWV was correlated with changes in hs-CRP after a 20-year follow-up. But the baseline baPWV was not evaluated in this study, which does not reflect a causal relationship between PWV and hs-CRP.[18] Pulsatile stress and MAP represent hemodynamic stress, which contributes to progression of arterial stiffness. However, hs-CRP may simply be a marker, reflecting inflammatory burden; therefore, we hypothesized that the degree of inflammation might parallel the degree of atherosclerosis, although both pulsatile stress and MAP
could be better predictors of arterial stiffness progression. LDL-C is also a factor involved in accelerated progression of arterial stiffness; therefore, control of hemodynamic load including reducing pulse pressure, heart rate, MAP, and LDL-C levels may reverse arterial stiffness in the long-term.

To further clarify the relationships between pulsatile stress, hs-CRP, and baPWV, we investigated the effect of increased and decreased hsCRP, pulsatile stress, MAP, and LDL-C on baPWV. We found that baPWV increased with increasing MAP and pulsatile stress during the 2-year follow-up, whereas, changes in inflammatory markers were not associated with changes in baPWV. These results imply that pulsatile stress and changes in MAP may contribute to arterial stiffness.

The mechanism of pulsatile stress and MAP in the pathogenesis of arterial stiffness remains unclear. Previous studies have evaluated pulsatile stress as heart rate × pulse pressure, which is responsible for the effects of cumulative/repeated mechanical pressure on the vessel wall. This cyclic pressure on vessel walls leads to strained elastic fibers, followed by smooth muscle cell hypertrophy, proliferation, and, eventually, arterial stiffness.[18–20] Increased MAP could also increase the pressure on the vessel wall and subsequently lead to increased aortic stiffness.[12,21] Therefore, pulsatile stress and MAP could be hemodynamic mechanisms involved in atherosclerotic vascular damage, but not inflammation, and hs-CRP may be a marker of arterial stiffness.

Certain limitations in our study must be considered. First, we measured hs-CRP during physical examinations separated by two years, and factors affecting hs-CRP levels could have affected ΔbaPWV between the two physical examinations. Second, the duration of follow-up was insufficient to evaluate the progression of arterial stiffness; however, changes in baPWV were seen during the relatively short follow-up. Third, we did not consider the effects of certain drugs on participants’ heart rate and blood pressure. Nevertheless, our sample size in this study was large, so the results can be extended to clinical practice.

In conclusion, the present study showed that the pulsatile stress increase was associated with arterial stiffness progression, but that changes in hs-CRP had no effect on arterial stiffness progression. hs-CRP may simply be a marker of inflammation that parallels the degree of arterial stiffness, and not a driver of arterial stiffness progression. Considering the longitudinal design of our study, the contribution of pulsatile stress and hs-CRP to arterial stiffness needs to be further investigated by using interventional studies.

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