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*Original Article*

# Association of hyper-sensitive C-reactive protein with arterial stiffness and endothelial function in patients with hyperlipidemia

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**Abstract:** Hyperlipidaemia is an important risk factor for atherosclerosis and cardiovascular diseases. As a marker of inflammation, high sensitivity C-reactive protein (hs-CRP) is significantly associated with atherosclerosis and can independently predict cardiovascular events. Both arterial stiffness and endothelial dysfunction have been reported as predictors for cardiovascular events in clinical and healthy populations. The aim of the present study was to investigate the association of hs-CRP with arterial stiffness and endothelial dysfunction in hyperlipidaemia participants. We measured several cardiovascular risk factors, including hs-CRP, ba-PWV, and RHI in 153 hyperlipidemic subjects (aged 26-68 years) selected by medical screening from the employee of Talimu Oil Field in Korla of China. Through correlation analysis, we demonstrated that hs-CRP was positively correlated with ba-PWV, a measurement of arterial stiffness, and RHI, a determinant of endothelial dysfunction. Subsequent stepwise multiple linear regression analysis indicated that hs-CRP was a significant and independent predictor for arterial stiffness and endothelial dysfunction after adjustment for other confounding factors. In conclusion, we have stated that serum hs-CRP levels were significantly associated with both ba-PWV and RHI in hyperlipidemia individuals. Therefore, a combination of hs-CRP, ba-PWV, and RHI detection will benefit the diagnosis, prevention, therapy of atherosclerosis and other cardiovascular diseases.

**Keywords:** Hyperlipidaemia, atherosclerosis, C-reactive protein, arterial stiffness, endothelial dysfunction

## Introduction

Hyperlipidaemia is characterized by alterations in the profile of plasma lipoprotein including elevated plasma levels of total cholesterol (TC) or triglyceride (TG), low concentrations of high-density lipoprotein cholesterol (HDL-C) and the appearance of small and dense low-density lipoproteins (LDL) particles. It is well-known that hyperlipidaemia plays a central role in the development of atherosclerosis and is an important risk factor for cardiovascular diseases [1, 2].

Arterial inflammation plays an important role in the pathogenesis of atherosclerosis and cardiovascular diseases. Serum high sensitivity C-reactive protein (hs-CRP) is one of the most extensively studied and established biomarkers of vascular inflammation. A body of evidence has demonstrated that serum levels of hs-CRP are significantly associated with atherosclerosis and can independently predict adverse cardiovascular events [3, 4].

Hyperlipidaemia and atherosclerosis are conditions related with vascular alterations including increased arterial stiffness and endothelial dysfunction [5-8]. Arterial stiffness, one of the major signs of vascular aging due to decreased arterial compliance, is usually assessed by pulse wave velocity (PWV), which has been demonstrated as a useful predictor for future cardiovascular events in clinical and healthy populations [9-12]. The PWV between brachium and ankle (baPWV), due to its simple measurement and high reproducibility, is routinely used as an arterial stiffness marker in previous studies [13, 14]. Endothelial dysfunction is one of the most important pathological chang-

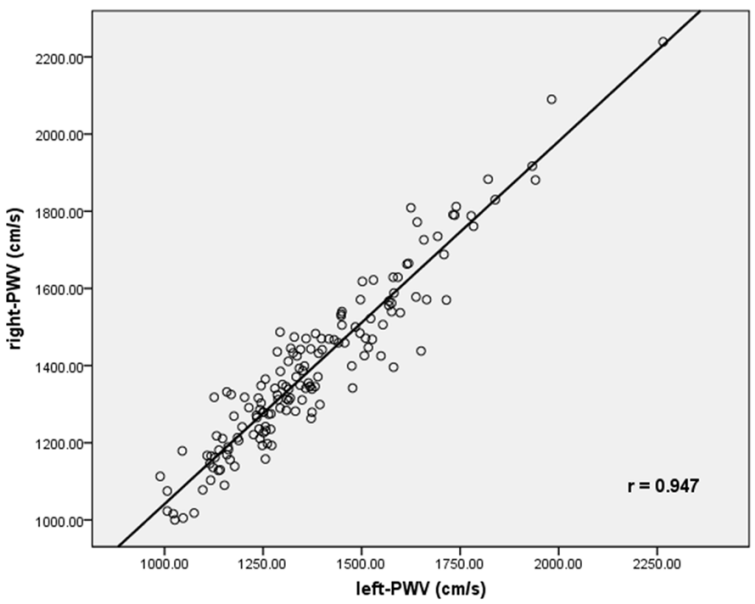


**Figure 1.** Correlation between left-baPWV and right baPWV.

es in the very early stage of atherosclerosis, for which the assessment of endothelial dysfunction in the early subclinical period of atherosclerotic diseases is of great significance. Peripheral arterial tonometry (PAT) is a widely accepted method determining endothelial dysfunction; it is also a reliable and noninvasive and method for analyzing peripheral arterial dynamics and function by measuring changes in digital pulse volume during reactive hyperemia (RH) [15]. The reactive hyperemia index (RHI), measured by PAT, is suggested to be a surrogate marker of endothelial function [15]. The Framingham Heart Study demonstrated that RHI is related to multiple traditional and metabolic risk factors [16]. Additionally, multiple prospective studies have investigated the possible role of PAT in stratification of cardiovascular risk and predicting cardiovascular events in high-risk populations [17-20].

However, no studies have yet examined whether ba-PWV and RHI are feasible for cardiovascular risk screening in hyperlipidemic populations. Therefore, the present study was designed to determine which established cardiovascular risk factors are correlated with baPWV and RHI, and to investigate the association of hs-CRP with arterial stiffness and endothelial dysfunction in cardiovascular risk assessment within hyperlipidaemia subjects.

## Material and methods

### *Study subjects*

Subjects of this study were selected by medical screening from the employee of Talimu Oil Field in Korla City of China. A total of 206 subjects with hyperlipidaemia, diagnosed based on serum TC greater than 5.18 mmol/L or serum LDL-C greater than 4.14 mmol/L, were initially enrolled in this study, but we excluded 53 patients during the evaluation of the data. Subjects with any of the following conditions were excluded from participation: a history of diabetes mellitus, endocrine diseases, renal disease, digestive diseases, respiratory disorders, immune systemic diseases, or cardiovascular disease. Therefore, the study consisted of 153 subjects aged 26-68 years (men, n = 84; women, n = 69) for the present analysis. Each subject was face-to-face interviewed using a structured questionnaire to document demographic data and medical history. All studies were approved by the Local Research Ethics Committee, and written informed consent was obtained from all participants.

### *General information collection and serum index detection*

Weight was measured by an electronic balance with participants wearing light hospital clothes and body height was measured by a stadiometer with participants in bare feet. Body mass index (BMI) was calculated as weight (kg) divided by the square of height ($m^2$). After resting in a sitting position for at least 5 min, systolic and diastolic blood pressures were measured twice in the right arm with an automated device (HEM-907, O mron, Tokyo, Japan), and the mean was taken as the subject's reading. Pulse pressure was calculated according to systolic and diastolic blood pressures. Overnight fasting serum and plasma samples were obtained by venipuncture for measurements of TC, TG, HDL-C, LDL-C, fasting plasma glucose (FPG), glycosylated hemoglobin A1c (GHbA1C), apoli-

**Table 1.** Baseline characteristics of subjects by sex

| Variables | Mean ± SD or NO. (%) | | *P* values |
|---|---|---|---|
| | Male (n = 84; 54.9%) | Female (n = 69; 45.1%) | |
| Age (years) | 42.4±1.04 | 42.5±1.3 | ns |
| Height (cm) | 170.6±5.2 | 161.0±4.7 | < 0.0001 |
| Weight (kg) | 73.0±10.1 | 61.7±9.8 | < 0.0001 |
| BMI (kg/m$^2$) | 25.0±2.9 | 23.8±3.8 | < 0.05 |
| HR (beats/min) | 74.6±6.5 | 75.5±5.8 | ns |
| SBP (mmHg) | 125.6±9.0 | 120.3±10.5 | < 0.05 |
| DBP (mmHg) | 75.2±6.8 | 70.6±6.2 | < 0.05 |
| PP (mmHg) | 50.4±7.4 | 49.7±7.5 | ns |
| FPG (mmol/L) | 5.8±0.4 | 5.7±0.5 | ns |
| GHbA1C (mmol/L) | 5.4±0.4 | 5.5±0.4 | ns |
| TC (mmol/L) | 4.06±0.22 | 3.35±0.24 | < 0.05 |
| HDL-C (mmol/L) | 1.75±0.06 | 1.78±0.06 | ns |
| LDL-C (mmol/L) | 3.6±0.9 | 3.4±0.7 | ns |
| TG (mmol/L) | 1.93±0.14 | 1.54±0.17 | < 0.05 |
| ApoA (mmol/L) | 1.15±0.16 | 1.21±0.17 | < 0.05 |
| ApoB (mmol/L) | 1.17±0.25 | 1.09±0.19 | < 0.05 |
| UA (μmol/L) | 371.5±78.6 | 288.9±67.3 | < 0.0001 |
| History smoking (%) | 58 (69%) | 9 (13%) | < 0.0001 |
| Lipid-lowering drugs (%) | 34 (40.1%) | 31 (45%) | ns |
| baPWV (cm/s) | 1429±23.3 | 1394±26.2 | ns |
| hs-CRP (mg/dl) | 3.67±0.23 | 2.99±0.25 | ns |
| RHI | 1.97±0.04 | 2.13±0.05 | < 0.05 |

Data for quantitative variables as mean ± standard deviation and qualitative variables are expressed as n (%). BMI, Body mass index; HR: Heart rate; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; PP: Pulse pressure; FPG: Fasting plasma glucose; GHbA1C : Glycosylated Hemoglobin A1c; TC: Total cholesterol ; TG: Triglyceride ; HDL-C: High-density lipoprotein cholesterol; LDL-C: Low-density lipoprotein cholesterol; apoA: Apolipoprotein A ; apoB: Apolipoprotein B; UA: Uric acid ; baPWV: Brachial-ankle Pulse Wave Velocity; hs-CRP: High-sensitive C-reactive protein; RHI: Reactive hyperemia index.

poprotein A (ApoA), apolipoprotein B (ApoB), and uric acid (UA). Serum hs-CRP levels were quantitatively detected using latex-enhanced immunoturbidimetric assay (*N Latex CRP, Dade Behring*, Deerfield, IL, USA) on a *Dade Behring* Nephelometer II analyzer (Dade-Behring, Germany).

*Brachial-ankle pulse wave velocity assessment*

After resting for at least 5 minutes in a supine position, ba-PWV were measured using an automated device (VP-1000; Colin Corp., Komaki, Japan), as described previously [21]. The ba-PWV was calculated according to the following equation: baPWV = (*D*1-*D*2)/*PTT*, where *D*1 is the distance between heart and ankle, *D*2 the distance between heart and brachium, and *PTT* the pulse transit time between the brachial and tibial arterial waveforms. Then the higher of the right and left ba-PWV was selected as the representative ba-PWV for statistical analysis. Participants were advised to abstain from smoking, vigorous exercise, and consuming alcoholic or caffeinated beverages for at least 12 h prior to assessment. There was a significantly positive correlation between right and left ba-PWV (r = 0.947, P < 0.0001), as shown in **Figure 1**, and we used a mean of bilateral ba-PWV value for analysis.

*Reactive hyperaemia peripheral arterial tonometry*

The RH-PAT index was measured using Endo-PAT2000 (Itamar Medical, Caesarea, Israel), as described previously [22]. Briefly, a blood pressure cuff was placed proximally (above elbow) on one dominant arm while the contralateral arm served as the control. PAT probes were placed on the index finger of each hand. After a 5 min equilibration period, the cuff was inflated to 60 mmHg above the systolic pressure (but no less than 200 mmHg) for 5 min and then deflated to induce reactive hyperemia. The RH-PAT data were digitally analyzed online (EndoPAT2000 software version 3.0.4). The reactive hyperaemic index (RHI) was calculated using the following equation: RHI = (A/B)/(C/D) × baseline correction, where *A* is the mean digital pulse volume during the reactive hyperaemia, *B* the baseline mean digital pulse volume, and *C* and *D* the respective values obtained in the control arm.

*Statistical analysis*

Statistical analyses were performed using SPSS18.0 software (SPSS Inc., Chicago, IL, USA), with t-test used for quantitative data presented as mean ± SEM and Chi-square test applied for enumeration data. The correlation analysis

**Table 2.** Correlation between baPWV and other variables

| Variables | r# values | *P* values |
|---|---|---|
| Sex | 0.082 | 0.313 |
| Age (years) | 0.567 | < 0.0001 |
| Height (cm) | -0.022 | 0.788 |
| Weight (kg) | 0.071 | 0.381 |
| BMI (kg/m$^2$) | 0.100 | 0.217 |
| HR (beats/min) | -0.059 | 0.466 |
| SBP (mmHg) | 0.293 | < 0.0001 |
| DBP (mmHg) | 0.239 | 0.003 |
| PP (mmHg) | 0.169 | 0.037 |
| FPG (mmol/L) | 0.065 | 0.428 |
| GHbA1C (mmol/L) | 0.133 | 0.102 |
| TC (mmol/L) | 0.518 | < 0.0001 |
| TG (mmol/L) | -0.007 | 0.936 |
| HDL-C (mmol/L) | -0.313 | < 0.0001 |
| LDL-C (mmol/L) | 0.138 | 0.088 |
| ApoA (mmol/L) | 0.07 | 0.393 |
| ApoB (mmol/L) | 0.121 | 0.135 |
| UA (μmol/L) | 0.166 | 0.04 |
| History smoking | 0.463 | 0.032 |
| Lipid-lowering drugs | -0.201 | 0.045 |
| hs-CRP (mg/dl) | 0.624 | < 0.0001 |
| RHI | -0.693 | < 0.0001 |

Abbreviations are same as in **Table 1**. #r values of Pearson's correlation coefficients between variables.

between baPWV or RHI and other variables (sex, age, height, weight, BMI, heart rate, systolic blood pressure, diastolic blood pressure, pulse pressure, fasting plasma glucose, glycosylated Hemoglobin A1c, total cholesterol, triglyceride, HDL-C, LDL-C, apoA, apoB, uric acid, use of lipid-lowering drugs, history of smoking, and hs-CRP) were evaluated by Pearson's correlation analysis. Stepwise multiple linear regression analysis was performed to determine which variables were independently correlated with ba-PWV or RHI. Variables for the stepwise linear regression model were chosen based on simple correlation analyses. *P* values < 0.05 were considered statistically significant.

## Results

### *Subject characteristics*

A total of 153 subjects aged 26-68 years and including 84 men (54.9%) and 69 women (40.1%) were eligible for the current analysis. Clinical characteristics of the study population, values of biomarkers, and mean ba-PWV values and mean RHI values considered by sexes are presented in **Table 1**. Men had higher height, weight, body mass index, systolic and diastolic blood pressures, total cholesterol, triglycerides, apoB, uric acid, and prevalence of smoking than women. However, women had higher apoA and RHI than men. The percentage of lipid-lowering drug use was not significantly different between men and women. Men and women had similar mean age, heart rate, pulse pressure, fasting plasma glucose, glycosylated hemoglobin A1c, HDL-C, LDL-C, hs-CRP levels, and ba-PWV.

### *The association between hs-CRP and ba-PWV in the participants*

We performed correlation analysis for the relationship between ba-PWV with other atherosclerotic and cardiovascular risk factors in all participants. **Table 2** shows the result of Pearson's correlation analyses, which indicated that age (r = 0.567, P < 0.0001), systolic blood pressure (r = 0.293, P < 0.001), diastolic blood pressure (r = 0.239, P = 0.003), pulse pressure (r = 0.169, P = 0.037), total cholesterol (r = 0.518, P < 0.0001), uric acid (r = 0.166, P = 0.04), and hs-CRP levels (r = 0.624, P < 0.0001) were positively correlated with ba-PWV, while HDL-C (r = -0.313, P < 0.0001) was negatively correlated with ba-PWV. Stepwise multiple linear regression analysis was then conducted to evaluate which of the correlated variables is the dominant predictor of baPWV in the study population. As shown in **Table 3**, greater age (standardized β = 0.259, P = 0.003) and higher hs-CRP levels (standardized β = 0.444, P < 0.0001) were potentially contributing variables to an increased baPWV, revealing that hs-CRP was a significantly independent factor in predicting arterial stiffness in hyperlipidemia subjects. The correlation between baPWV and hs-CRP is depicted in a scatter plot (**Figure 2**).

### *The association between hs-CRP and RHI in the participants*

**Table 4** presents the correlation coefficients obtained in the Pearson correlation analysis between RHI and other factors in the study population. Variables including male sex (r = -0.262, P = 0.001), age (r = -0.562, P < 0.0001), systolic blood pressure (r = -0.251, P = 0.002),

**Table 3.** Multiple stepwise regression analysis for variables independently associated with baPWV

| Variables | β | Standardized β | t values | *P* values |
|---|---|---|---|---|
| Age (years) | 5.614 | 0.259 | 3.018 | 0.003 |
| hs-CRP (mg/dl) | 45.089 | 0.444 | 5.172 | < 0.0001 |

hs-CRP: High-sensitive-C-reactive protein.

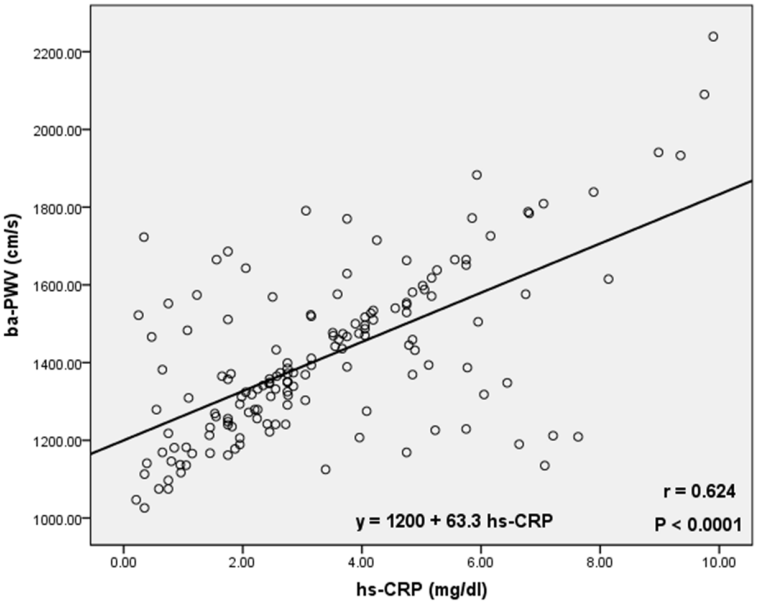


**Figure 2.** Scatter plots depicting the correlation between ba-PWV and hs-CRP.

diastolic blood pressure (r = -0.270, P = 0.001), total cholesterol (r = -0.508, P < 0.0001), triglycerides (r = -0.195, P = 0.016), apoB (r = -0.163, P = 0.043), uric acid (r = -0.221, P = 0.006), and hs-CRP (r = -0.680, P < 0.0001) were negatively associated with RHI, whereas HDL-C (r = 0.452, P < 0.0001) was positively related with RHI. Furthermore, stepwise multiple linear regression analysis was performed by including sex, age, systolic blood pressure, diastolic blood pressure, total cholesterol, triglycerides, uric acid, and hs-CRP as independent variables and RHI as dependent variable to determine the dominant factor in predicting endothelial dysfunction in hyperlipidemia subjects. The results of multiple linear analyses are presented in **Table 5**, which showed that male gender (standardized β = -0.187, P = 0.002), greater age (standardized β = -0.179, P = 0.028), and higher hs-CRP levels (standardized β = -0.452, P < 0.0001) were associated with lower RHI, while higher HDL-C (standardized β = 0.159, P = 0.015) was associated with higher RHI. The correlation between RHI and hs-CRP depicted as scatter plot was showed in **Figure 3**.

## Discussion

In this study, we investigated the association of the inflammatory marker hs-CRP with measurements of arterial stiffness and endothelial function in hyperlipidemia subjects selected from an oil field in Korla city of China. To the best of our knowledge, the results of the present study demonstrate for the first time that the serum hs-CRP levels were significantly and independently correlated with ba-PWV and RHI after adjusting for confounding factors in hyperlipidemia individuals.

Arterial inflammation plays a key role in the process of atherosclerosis [23, 24]. As an important indicator of vascular inflammation, hs-CRP is a well-known independent predictor of adverse cardiovascular events [3, 25]. Increased arterial stiffness and endothelial dysfunction are important determinants of cardiovascular events [26, 27]. The predictive role of baPWV and RH-PAT indicates that they have the potential to significantly impact the field of cardiovascular research and prevention of cardiovascular disease. Our data suggest that both arterial stiffness and endothelial dysfunction are significantly correlated with the level of systemic inflammation, and that inflammation may be an important determinant for arterial stiffening and endothelial dysfunction in hyperlipidemia patients.

The serum levels of hs-CRP have been reported to be positively related with indices of arterial stiffness in apparently healthy individuals, older adults, subjects with essential hypertension, and community-based samples in previous studies [28-31]. Multiple lines of evidence have revealed that elevated arterial stiffness is significantly associated with cardiovascular diseases and is an independent predictor of an increased risk of cardiovascular morbidity and

**Table 4.** Correlation between RHI and other variables

| Variables | r# values | *P* values |
|---|---|---|
| Sex | -0.262 | 0.001 |
| Age (years) | -0.562 | < 0.0001 |
| Height (cm) | -0.089 | 0.273 |
| Weight (kg) | -0.094 | 0.250 |
| BMI (kg/m$^2$) | -0.068 | 0.404 |
| HR (beats/min) | -0.076 | 0.352 |
| SBP (mmHg) | -0.251 | 0.002 |
| DBP (mmHg) | -0.270 | 0.001 |
| PP (mmHg) | -0.086 | 0.288 |
| FPG (mmol/L) | -0.078 | 0.339 |
| GHbA1C (mmol/L) | -0.092 | 0.256 |
| TC (mmol/L) | -0.508 | < 0.0001 |
| TG (mmol/L) | -0.195 | 0.016 |
| HDL-C (mmol/L) | 0.452 | < 0.0001 |
| LDL-C (mmol/L) | -0.087 | 0.285 |
| ApoA (mmol/L) | 0.037 | 0.651 |
| ApoB (mmol/L) | -0.163 | 0.043 |
| UA (μmol/L) | -0.221 | 0.006 |
| History smoking | -0.342 | 0.005 |
| Lipid-lowering drugs | 0.253 | 0.043 |
| hs-CRP (mg/dl) | -0.482 | < 0.0001 |
| BaPWV (cm/s) | -0.680 | < 0.0001 |

Abbreviations are same as in **Table 1**. #r values of Pearson's correlation coefficients between variables.

mortality in hypertensive and diabetic populations [32, 33]. Some studies have shown that arterial stiffness in patients with lipid disorders is markedly increased [5, 34]. In our current study, we demonstrated that hs-CRP levels were independently and positively associated with ba-PWV, indicating an important role of hs-CRP in predicting increased arterial stiffness in subjects with hyperlipidemia.

Endothelial dysfunction, characterized by impaired endothelium-dependent vasodilation resulting from a reduction in the bioavailability of vasodilators, especially NO, is believed to promote atherosclerosis and consequent cardiovascular diseases [35-37]. Inflammatory reaction is known to repress the endothelium-dependent vasodilatation [38]. Some studies have also shown that increased CRP levels are associated with impaired endothelial function [39, 40]. As a surrogate marker of endothelial function, RHI has been shown to correlate with cardiovascular risk factors in the Framingham Heart Study [41], and low RHI has been reported to be significant predictor of adverse cardiovascular events in patients with heart failure, coronary artery disease, and chronic kidney disease [17-20]. In this study, a negative relationship of serum hs-CRP levels with RHI was observed by correlation analysis, and hs-CRP was an independent predictor of endothelial dysfunction even after controlling for other risk factors in hyperlipidemia subjects.

Therefore, the relationship among hyperlipidemia, inflammation, arterial stiffness, and endothelial dysfunction could collectively facilitate the pathological process of atherosclerosis and even consequent cardiovascular diseases. We speculate that hyperlipidemia-induced inflammation may cause alterations in the functional properties of arteries by inducing metabolic and structural arterial changes. Inflammation may cause structural changes in the arterial bed via mediating an imbalance of elastin breakdown and synthesis [42], such to increase arterial stiffness. Endothelial-derived NO plays an important role in the functional regulation of arterial stiffness *in vivo* [43]. Through an adverse effect on endothelial function, vascular inflammation contributes to the increased arterial stiffness. The malproduction and dysfunction of NO may lead to the formation of a proinflammatory, proliferative, and procoagulatory milieu that promotes atherogenesis [44]. However, mechanisms remain speculative and require further studies.

In conclusion, we have demonstrated that the serum hs-CRP levels were significantly and independently associated with both ba-PWV and RHI after adjustment for other established cardiovascular risks factors. Our data suggest that hs-CRP could be a useful marker of increased arterial stiffness and endothelial dysfunction, and a combination of detection of hs-CRP, ba-PWV, and RHI could be conducive to an early diagnosis, prevention, and therapy of atherosclerosis and other cardiovascular diseases in hyperlipidemic individuals.

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**Table 5.** Multiple stepwise regression analysis for variables independently associated with RHI

| Variables | β | Standardized β | t values | *P* values |
|---|---|---|---|---|
| Sex | -0.168 | -0.187 | -3.224 | 0.002 |
| Age (years) | -0.008 | -0.179 | -2.224 | 0.028 |
| HDL (mmol/L) | 0.127 | 0.159 | 2.461 | 0.015 |
| hs-CRP (mg/dl) | -0.096 | -0.452 | -5.469 | < 0.0001 |

hs-CRP: High-sensitive-C-reactive protein; HDL-C: High-density lipoprotein cholesterol.

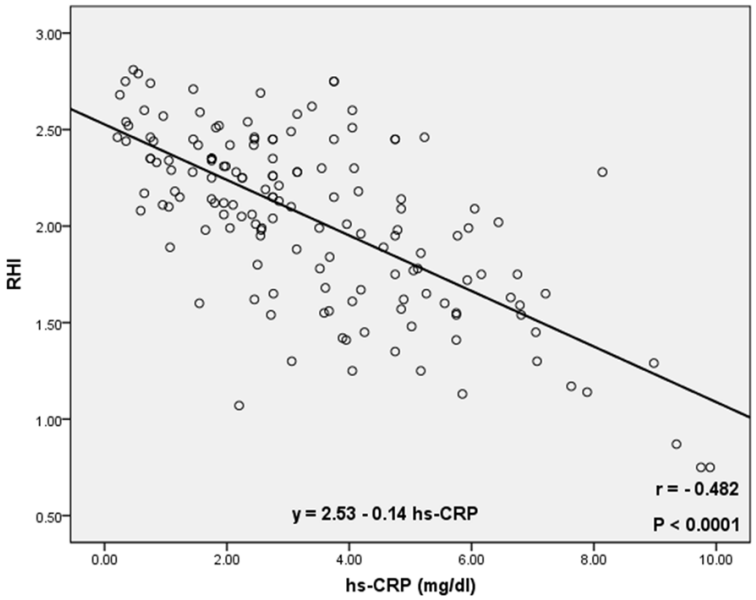


**Figure 3.** Scatter plots depicting the correlation between RHI and hs-CRP.

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## Disclosure of conflict of interest

None.

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