Association of hemoglobin with arterial stiffness evaluated by carotid-femoral pulse wave velocity among Chinese adults

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Abstract

Objective: Increased hemoglobin (Hb) levels are known to be associated with increased cardiovascular events and mortalities. Therefore, we assumed that high Hb levels were associated with arterial stiffness. Pulse wave velocity (PWV) is a simple and noninvasive method for measuring arterial stiffness to assess cardiovascular disease in general populations. Accordingly, we conducted a cross-sectional study to explore the association of Hb with PWV.

Methods: A total of 6642 adults aged 54.5 ± 11.2 years undergoing physical examinations were enrolled, 71.7% of whom were males. Arterial stiffness was evaluated by carotid-femoral PWV (cfPWV). Multivariable regression analyses were performed to determine the relationship between Hb and increased cfPWV.

Results: In this study, the mean Hb (per 10 g/L increase) was 144.7 ± 13.9 g/L, and the mean cfPWV was 15.1 ± 3.1 m/s. cfPWV was significantly higher in high hemoglobin groups (≥15.4 g/L; Quartile 4) than in the lowest hemoglobin group (Quartile 1; <13.6 g/L; P < 0.001). Multiple linear regression analysis revealed that Hb positively correlated with cfPWV (β = 0.16, P < 0.01). Univariate Logistic regression analysis revealed that Hb was associated with increased cfPWV, with an odd ratio (OR) of 1.46 (95% confidence interval [CI], 1.39–1.54). After adjusting for potential confounders, Hb and the highest Hb quartile group were also independently associated with increased cfPWV, with a fully adjusted OR of 1.11 (95% CI, 1.02–1.20) and 1.45 (95% CI, 1.01–2.08), respectively.

Conclusion: This study demonstrated that Hb levels significantly correlate with increased cfPWV.

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Keywords: Hemoglobin; Pulse wave velocity; Arterial stiffness; Cardiovascular diseases

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Introduction

In the general population, cardiovascular and cerebrovascular diseases have become the main cause of mortality and morbidity worldwide.\textsuperscript{1,2} Pulse wave velocity (PWV) refers to the velocity of the pulse wave of the arterial system between two fixed points. According to the Moens–Korteweg equation,\textsuperscript{3} the PWV is proportional to the square root of the elastic coefficient. Pulse waves propagate faster in the arterial system as a result of reduced arterial elasticity. Several studies have shown that arterial stiffness is associated with the risk of cardiovascular disease (CVD)\textsuperscript{4} and is predictive of future vascular events in the general population.\textsuperscript{5–8} The consensus document of the European Journal of Cardiology indicated that carotid-femoral PWV (cfPWV) is the gold standard for atherosclerosis measurement.\textsuperscript{9} Recently, high hemoglobin (Hb) concentrations were shown to be associated with elevated cardiovascular and all-cause mortalities,\textsuperscript{10} but the underlying mechanism remains unclear. To clarify this phenomenon, we conducted this study to measure the association of Hb with arterial stiffness, evaluated by cfPWV.

Methods

Study population

In this cross-sectional study, a total of 6642 adults who visited the Health Checkup Clinic at the Qianfoshan Hospital, which is affiliated to the Shandong University, from April 2010 to December 2010 were enrolled. The participants came from all over Jinan to receive regular paid health examinations. The exclusion criteria were: 1) age \textless 18 years, 2) infection, 3) pregnant women, 4) presence of cardiovascular and cerebrovascular diseases, such as myocardial infarction, cardiac failure, angina pectoris, dilated cardiomyopathy, sick sinus syndrome, arrhythmia, ischemic cerebrovascular disease, hemorrhagic cerebrovascular disease, et al, 5) presence of a major illness such as cancer, liver disease and chronic consumptive disease, 6) presence of immunological disease, 7) taking drugs such as erythropoietin, iron, and folic acid supplements.

The study protocol was approved by the ethics committee of Qianfoshan Hospital (2016s001) and informed consent was provided before data collection.

Blood biochemistry measurements and biometric parameters

Blood samples were drawn after overnight fasting for at least 10 hours. Hb, fasting blood glucose, serum uric acid (UA), serum creatinine, serum total cholesterol (TC), low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, and triglycerides (TG) were measured by an automatic biochemistry analyzer in the central laboratory of Qianfoshan Hospital.

Sociodemographic characteristics, health histories (eg., hypertension, diabetes), and lifestyle behaviors (eg., smoking) were recorded using questionnaires. Body mass indices (BMIs) were calculated by dividing weight (in kilograms) by the square of height (in meters). Diabetes was defined as fasting blood glucose levels \textgreater 7.0 mmol/L, the use of hypoglycemic agents, or a self-reported history of diabetes. Hypertension was defined as systolic blood pressure greater than 140 mmHg, diastolic blood pressure greater than 90 mmHg, or both, or the use of antihypertensive medication. The estimated glomerular filtration rate (eGFR) was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation.\textsuperscript{11,12} Decreased eGFR (DeGFR) was defined as an eGFR < 60 ml·min\textsuperscript{-1}·1.73 m\textsuperscript{2}. Proteinuria was measured from a morning urine sample using a urinary dipstick test. A dipstick result of trace or more urine protein was defined as proteinuria. CKD was defined as “kidney damage for 3 months, as defined by structural or functional abnormalities with or without decreased glomerular filtration rate (GFR), or a GFR of 60 ml·min\textsuperscript{-1}·1.73 m\textsuperscript{2} or less, with or without kidney damage.”

Measurement of PWV

The pulse of the right carotid and femoral artery waveforms was assessed using the SphygmoCor device (version 7.1, AtCor Medical Ltd., Sydney, Australia).\textsuperscript{13} All individuals were examined after resting in the supine position for at least five minutes. A measuring tape was used to assess the distance between the carotid and femoral artery recording sites. cfPWV was calculated automatically, by dividing this distance by the time interval between the rapid upstroke in the pulse wave at the carotid and femoral arteries, using the peak of the R-wave on electrocardiography as a reference point.\textsuperscript{9} The 25, 50, and 75 percentiles of cfPWV were 12.97, 14.31 and 16.64 m/s, respectively.
According to the 2007 European Society of Hypertension/European Society of Cardiology (ESH/ESC) guidelines for the management of arterial hypertension, cfPWV ≥12.0 m/s was termed increased cfPWV. Furthermore, some studies have defined increased cfPWV according to the highest cfPWV quartile.

Results

Among the 6642 participants in this study, the mean age was 54.5 ± 11.2 years (range 23–88 years), and 71.7% of them were males. The mean cfPWV was 15.1 ± 3.1 m/s, and the mean Hb was 144.7 ± 13.9 g/L. Age, BMI, blood urea nitrogen (BUN), TG, TC, LDL cholesterol, and cfPWV were higher in the highest quartile Hb group (Hb ≥ 15.4 g/L) compared with the lowest quartile Hb group (Hb ≤ 13.6 g/L). Table 1 shows the characteristics of each subject's background factors, categorized according to Hb quartile.

The multivariable stepwise linear regression analysis showed that Hb levels were significantly associated with cfPWV (β = 0.16, P < 0.01), after adjusting for potential confounders (Table 2).

We analyzed the OR of variables associated with increased cfPWV. In the univariate logistic regression analysis, hemoglobin was associated with increased cfPWV (OR: 1.46, 95% CI: 1.39–1.54). After
Table 2

| Variables                          | Unstandardized coefficients (95% CI) | Standardized coefficients | P value |
|-----------------------------------|--------------------------------------|---------------------------|---------|
| (Constant)                        | 3.66 (2.64–4.69)                     | /                         | <0.01   |
| Age, years                        | 0.14 (0.14–0.15)                     | 0.52                      | <0.01   |
| Sex (1 = male, 2 = female)        | −0.14 (−0.32–0.05)                   | −0.02                     | 0.15    |
| BMI, kg/m²                        | 0.01 (−0.01–0.02)                    | 0.01                      | 0.50    |
| Habitual drinking                 | −0.03 (−0.16–0.11)                   | −0.004                    | 0.70    |
| Current smoking                   | −0.18 (−0.30 to −0.05)               | −0.03                     | <0.01   |
| UA, μmol/L                        | 0.001 (0–0.002)                      | 0.03                      | 0.01    |
| Total cholesterol, mmol/L         | −0.38 (−0.55 to −0.21)               | −0.11                     | <0.01   |
| Triglycerides, mmol/L             | 0.14 (0.09–0.19)                     | 0.05                      | <0.01   |
| HDL cholesterol, mmol/L           | 0.05 (−0.21–0.31)                    | 0.004                     | 0.72    |
| LDL cholesterol, mmol/L           | 0.63 (0.37–0.90)                     | 0.11                      | <0.01   |
| CKD                               | 1.14 (0.80–1.47)                     | 0.06                      | <0.01   |
| HBP                               | 1.83 (1.71–1.95)                     | 0.28                      | <0.01   |
| DM                                | 0.79 (0.62–0.97)                     | 0.08                      | <0.01   |
| Hemoglobin, per 10 g/L increase   | 0.16 (0.11–0.21)                     | 0.07                      | <0.01   |
| HCT,%                             | 0.06 (0.04–0.08)                     | 0.07                      | 0.14    |
| MCH, pg                           | 0.03 (0.002–0.06)                    | 0.02                      | 0.04    |
| MCHC, g/L                         | 0.004 (−0.001–0.001)                 | 0.01                      | 0.14    |

PWV: pulse wave velocity; SE: standard errors; CI: confidence interval; BMI: body mass index; UA: uric acid; HDL: high-density lipoprotein; LDL: low-density lipoprotein; CKD: chronic kidney disease; HBP: high blood pressure; DM: diabetes mellitus; HCT: hematocrit; MCH: mean corpuscular hemoglobin; MCHC: mean corpuscular hemoglobin concentration.

adjusting for potential confounders, including age and sex, Hb was independently associated with increased cfPWV (OR: 1.24, 95% CI: 1.15–1.34). After adjusting for potential confounders, including age, sex, hypertension, diabetes, BMI, uric acid, current smoking, habitual drinking, TC, TG, LDL cholesterol, and HDL cholesterol, Hb and the highest Hb quartile group were also independently associated with increased cfPWV, with a fully adjusted OR of 1.11 (95% CI: 1.02–1.20) and 1.45 (95% CI: 1.01–2.08), respectively (Table 3).

Patients were divided into five subgroups, CKD, non-CKD, non-diabetes (non-DM) and non-hypertension (non-HBP), male and female groups, respectively. In the univariate logistic regression analysis, after adjusting for potential confounders, including age, sex, BMI, uric acid, current smoking, habitual drinking, TC, TG, LDL, and HDL, Hb (per 10 g/L increase) was independently associated with increased cfPWV in non-CKD, non-DM and non-HBP, and male groups, after being adjusted for potential confounders, including age, sex, BMI, uric acid, current smoking, habitual drinking, TC, TG, LDL cholesterol, and HDL cholesterol.

Discussion

To determine the contribution of increased Hb to arterial stiffness in the general population, we analyzed the relationship between Hb and PWV, which is a surrogate marker for and an independent predictor of mortality and morbidity in cardiovascular diseases. In our study, high Hb was independently associated with increased cfPWV. As a categorical outcome, hemoglobin was also independently associated with increased cfPWV in non-DM and non-HBP groups, after adjusting for potential confounders.

According to the Framingham equation, Blacher et al. observed a significant correlation between PWV and atherosclerosis alterations (AA). The presence of a PWV >13 m/s, taken alone, appeared to be a strong predictor of cardiovascular mortality with high performance values. Furthermore, it showed that aortic PWV was strongly associated with the presence and extent of atherosclerosis and constitutes a forceful marker and predictor of cardiovascular risk in patients with hypertension. The relations between PWV and other risks (myocardial infarction, coronary heart...
Table 3
Multivariate logistic regression analysis for different variables associated with increased cfPWV.

| Variables                        | Crude OR (95% CI) | Age- and sex-adjusted OR (95% CI) | Multivariable adjusted OR (95% CI) |
|----------------------------------|-------------------|-----------------------------------|------------------------------------|
| Age, years                       | 1.13 (1.12–1.14)  | 1.13 (1.12–1.14)                  | 1.11 (1.09–1.12)                   |
| Sex                              | 0.29 (0.25–0.34)  | 0.29 (0.24–0.34)                  | 0.75 (0.53–1.06)                   |
| Hemoglobin, per 10g/L increase   | 1.46 (1.39–1.54)  | 1.24 (1.15–1.34)                  | 1.11 (1.02–1.20)                   |
| Hemoglobin, quartiles            |                   |                                   |                                    |
| Quartile 1                       | Ref               | Ref                               | Ref                                |
| Quartile 2                       | 2.47 (2.02–3.02)  | 1.54 (1.18–2.00)                  | 1.18 (0.89–1.55)                   |
| Quartile 3                       | 3.10 (2.50–3.84)  | 1.85 (1.34–2.54)                  | 1.28 (0.92–1.78)                   |
| Quartile 4                       | 3.95 (3.12–5.00)  | 2.35 (1.66–3.32)                  | 1.45 (1.01–2.08)                   |
| BMI, kg/m²                       | 1.17 (1.14–1.20)  | 1.10 (1.07–1.13)                  | 1.02 (0.99–1.06)                   |
| Habitual drinking                | 1.85 (1.58–2.18)  | 1.49 (1.17–1.90)                  | 1.18 (0.91–1.52)                   |
| Current smoking                  | 2.64 (2.18–3.21)  | 1.45 (1.14–1.83)                  | 1.33 (1.04–1.70)                   |
| UA, µmol/L                       | 1.01 (1.00–1.01)  | 1.00 (1.00–1.01)                  | 1.002 (1.001–1.003)                |
| Total cholesterol, mmol/L        | 1.66 (1.51–1.83)  | 1.39 (1.25–1.54)                  | 1.36 (1.02–1.83)                   |
| Triglycerides, mmol/L            | 2.23 (1.94–2.58)  | 1.66 (1.46–1.90)                  | 1.29 (1.12–1.48)                   |
| HDL cholesterol, mmol/L          | 1.66 (1.21–2.28)  | 1.19 (0.82–1.72)                  | 0.99 (0.62–1.58)                   |
| LDL cholesterol, mmol/L          | 2.30 (1.99–2.67)  | 1.61 (1.36–1.90)                  | 0.77 (0.49–1.19)                   |
| CKD                              | 5.24 (3.82–7.19)  | 1.05 (0.46–2.43)                  | 0.70 (0.29–1.69)                   |
| HBP                              | 15.17 (10.61–21.71) | 7.06 (4.89–10.19) | 5.96 (4.08–8.71) |
| DM                               | 7.06 (4.14–12.05) | 3.07 (1.77–5.30)                  | 2.34 (1.33–4.09)                   |

cfPWV: carotid-femoral pulse wave velocity; OR: odds ratio; CI: confidence interval; BMI: body mass index; UA: uric acid; HDL: high-density lipoprotein; LDL: low-density lipoprotein; CKD: chronic kidney disease; HBP: high blood pressure; DM: diabetes mellitus.

Hemoglobin was 13.6, 14.6 and 15.4 g/L at the 25, 50 and 75 percentile, respectively.

* OR was adjusted for age, sex, hypertension, diabetes, BMI, uric acid, smoking, drinking, total cholesterol, triglycerides, LDL cholesterol and HDL cholesterol.

Table 4
Multivariate logistic regression analysis for hemoglobin (per 10 g/L increase) associated with increased cfPWV according to subgroups and different models.

| Participants | Model 1 | Model 2 |
|--------------|---------|---------|
|              | Crude OR (95% CI) | Age- and sex-adjusted OR (95% CI) | Multivariable adjusted OR (95% CI) | Crude OR (95% CI) | Age- and sex-adjusted OR (95% CI) | Multivariable adjusted OR (95% CI) |
| CKD (n = 170) | 1.01 (0.63–1.61) | 0.77 (0.37–1.60) | 0.52 (0.18–1.49) | 0.92 (0.76–1.12) | 1.01 (0.77–1.33) | 0.96 (0.69–1.33) |
| Non-CKD (n = 6472) | 1.48 (1.40–1.56) | 1.25 (1.16–1.35) | 1.11 (1.02–1.21) | 1.18 (1.12–1.23) | 1.38 (1.29–1.48) | 1.20 (1.11–1.29) |
| Non-DM and non-HBP (n = 3854) | 1.38 (1.31–1.46) | 1.18 (1.09–1.28) | 1.10 (1.01–1.20) | 1.07 (0.98–1.15) | 1.30 (1.15–1.47) | 1.25 (1.10–1.43) |
| Male (n = 4760) | 1.09 (0.98–1.21) | 1.26 (1.12–1.43) | 1.14 (1.00–1.30) | 0.97 (0.91–1.03) | 1.30 (1.20–1.40) | 1.14 (1.05–1.24) |
| Female (n = 1882) | 1.47 (1.31–1.65) | 1.21 (1.10–1.34) | 1.09 (0.98–1.21) | 1.47 (1.31–1.65) | 1.47 (1.26–1.72) | 1.30 (1.09–1.54) |

cfPWV: carotid-femoral pulse wave velocity; OR: odds ratio; CI: confidence interval; CKD: chronic kidney disease; DM: diabetes mellitus; HBP: high blood pressure.

Hemoglobin was 13.6, 14.6 and 15.4 g/L at the 25, 50 and 75 percentile, respectively.

The 25, 50 and 75 percentile of cfPWV was 12.97, 14.31 and 16.64 m/s, respectively.

Model 1: cfPWV ≥ 12.0 m/s was termed increased cfPWV.

Model 2: cfPWV ≥ 16.64 m/s was termed increased cfPWV (the highest cfPWV quartile).

* Adjusted for age, sex, hypertension, diabetes, BMI, uric acid, smoking, drinking, total cholesterol, triglycerides, LDL cholesterol, HDL cholesterol and CKD.

disease, death from coronary heart disease, stroke, and death from cardiovascular disease) had the same levels of statistical significance, with correlation coefficients ranging from 0.44 to 0.50. Furthermore, at a given age, PWV appeared to be the strongest predictor of cardiovascular mortality. The OR of being in the high-risk cardiovascular mortality group for patients with PWV > 13.5 m/s was 7.1 (95% CI: 4.5–11.3).

The close association between increased Hb levels and increased PWV, which is a marker of increased arterial stiffness, might be explained by the following mechanisms. First, there was evidence that increased...
Hb levels in the general population are associated with increased blood pressure.\textsuperscript{18–20} According to the Poiseuille–Hagen Equation, Hb affects peripheral vascular resistance in two ways: primarily by influencing the viscosity of blood,\textsuperscript{21} and secondarily by affecting the caliber of peripheral arterioles. Persistently elevated blood pressure accelerates atherosclerosis, arterial smooth muscle hyperplasia and hypertrophy, and collagen synthesis, thereby increasing arterial stiffness. Second, several studies have demonstrated that Hb is independently related to insulin resistance and compensatory hyperinsulinemia in the general, nonobese population.\textsuperscript{22,23} Insulin resistance independently influences arterial stiffness.\textsuperscript{24} Moreover, in 455 normoglycemic normotensive postmenopausal women, insulin resistance was independently associated with PWV.\textsuperscript{25} Additionally, in 1541 nondiabetic Japanese subjects who were undergoing health examinations, insulin resistance was independently associated with brachial-ankle PWV.\textsuperscript{26} Third, based on the literature and previous studies, hemeoxygenase-1 (HO-1) deficiency might be involved in hypertension and increased arterial stiffness.\textsuperscript{27–29} HO-1 was found to play an important role in attenuating oxidative stress and inflammation by regulating vascular endothelial growth factor in hypertension.\textsuperscript{27–29} HO-1 is the inducible rate-limiting enzyme in the degradation of hemoglobin, which generates free iron, biliverdin, and carbon monoxide (CO),\textsuperscript{27} which has vasodilating properties. But in the CKD group, hemoglobin did not significantly increase with increased cPWV levels. There may be two reasons for this: one is the small sample size in the CKD group, and the other is probably due to renal anemia.

This study has several limitations. First, the use of a cross-sectional design limits the formation of causal relationships between Hb and PWV. Second, although a number of potential confounding factors, such as age, sex, hypertension, diabetes, BMI, uric acid, current smoking, habitual drinking, total cholesterol, triglycerides, LDL cholesterol, and HDL cholesterol were controlled in the multivariable regression analysis, the existence of other unrecognized confounding variables is always possible. For example, we could not collect detailed data on the medications that the participants received. Third, hemoglobin levels were determined through a single assessment, which may introduce a misclassification bias. Finally, this study used a convenient sample that was not determined from a community-based screening program, which limits the application of our results to the general population.

In conclusion, this study demonstrated that increased hemoglobin is associated with increased PWV risk in the general population, which suggests that we should pay attention to the screening of atherosclerosis in high hemoglobin populations. The direct relationship between Hb and PWV suggests that increased arterial stiffness might represent the link between high Hb levels and increased cardiovascular events and mortality.

**Conflicts of interest**

The authors declare that they have no competing interests.

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