Plasma Homocysteine Is Associated with Aortic Arterial Stiffness but not Wave Reflection in Chinese Hypertensive Subjects

Wenkai Xiao¹, Yongyi Bai¹, Ping Ye¹, Leiming Luo¹, Dejun Liu¹, Hongmei Wu¹, Jie Bai²

¹Department of Geriatric Cardiology, Chinese PLA General Hospital, Beijing, China, ²Department of Clinical Biochemistry, Chinese PLA General Hospital, Beijing, China

Abstract

Objective: Elevated plasma total homocysteine (tHcy) acts synergistically with hypertension to exert a multiplicative effect on cardiovascular diseases risk. The aim of this study was to determine the relationship between tHcy concentration and blood pressure, and to evaluate the role of plasma tHcy in arterial stiffness and wave reflection in hypertension.

Methods: In this cross-sectional study, a community-based sample of 1680 subjects (mean age 61.6 years) was classified into four groups according to tHcy level (<21.6 vs. ≥21.6 μmol/l) and blood pressure (hypertensive vs. normotensive). Levels of plasma tHcy and other biochemical parameters (e.g., lipids, glucose) were determined. Central arterial blood pressure, reflected pressure wave, and carotid-femoral pulse wave velocity (cf-PWV) were assessed by tonometry within 2 days of obtaining the blood specimen.

Results: Neither peripheral nor central blood pressure differed according to tHcy levels in normotensive and hypertensive subjects. Differences in cf-PWV according to tHcy were observed only in hypertensive subjects; differences in cf-PWV in normotensive subjects were not significant after adjusting for confounding factors. Central augmentation index did not differ according to tHcy level in either normotensive or hypertensive subjects. Results of univariate analysis revealed significant correlations between blood pressure parameters and tHcy concentration only among normotensive subjects; however, these correlations were not significant in a partial correlation analysis. Results of multiple regression analysis showed that plasma tHcy levels were independently correlated with cf-PWV in hypertensive subjects (β = 0.713, P = 0.004). The independent relationship between tHcy and central augmentation index was not significant by further multiple analyses in normotensive or hypertensive individuals.

Conclusions: Plasma tHcy level is strongly and independently correlated with arterial stiffness measured as cf-PWV only in hypertensive subjects. Thus, hypertension is a major link between tHcy and aortic arterial stiffness.

Introduction

Recent studies have reported that elevated tHcy may be deleterious in individuals with hypertension or other risk factors (e.g., cigarette smoking, hypercholesterolemia), with which it acts synergistically to exert a multiplicative effect on cardiovascular disease (CVD) risk [1–2]. In patients with coronary heart disease, those with both hypertension and high tHcy levels had more severe coronary atherosclerosis and more diffuse atherosclerosis than those without this association [3]. This combination of elevated tHcy and hypertension has been described as “H-type hypertension” [4–5].

The pathological mechanisms underlying the interaction between hypertension and hyperhomocysteinemia in CVD and cerebrovascular diseases are not fully understood but may include their similar effects on the vascular system or oxidative stress [6].

Arterial stiffness can be detected before the appearance of clinically significant vascular disease, suggesting that it may be a marker for the development of atherosclerotic disease [7] or a causative factor in atherosclerosis [8–9]. Although previous studies have reported the association of plasma tHcy with arterial stiffness, those results are controversial because of differences in study populations and methods of assessing arterial stiffness [10–11]. Furthermore, few prospective studies have investigated the role of tHcy and hypertension on arterial stiffness in Asian populations [6], which have patterns of cerebrovascular disease and CVD that are distinct from those of Caucasians and African Americans. Therefore, further investigation is needed to clarify the relationship between plasma tHcy and arterial stiffness in hypertension.

The purpose of this study was to investigate the following in a large community-based sample from China: (1) relationship...
between hypertension complicated by hyperhomocysteinemia with increased arterial stiffness and wave reflection; (2) relationship between tHcy and peripheral, central arterial blood pressure (BP); (3) influence of plasma tHcy and other risk factors on arterial stiffness and wave reflection by measuring pulse wave velocity (PWV) and augmentation index (AIx) in hypertensive and normotensive individuals.

**Methods**

**Study Population**

This community-based cross-sectional study was carried out in the Pingguoyuan area of Shijingshan district, Beijing, China. A total of 1859 community residents reporting for a health examination in two communities were randomly recruited to the study. We excluded 31 individuals with severe systemic diseases including collagenesis, endocrine and metabolic diseases other than diabetes mellitus (DM), inflammation, neoplastic disease, or severe liver or renal disease. We attempted to assess arterial stiffness in the remaining 1828 subjects; however, adequate tonometry was either not attempted or not obtained in 86 participants. Another 37 participants were excluded because of missing data (plasma tHcy level or other biochemical measurements). An additional 25 participants were excluded because of missing covariate data needed for multivariable analysis. The remaining 1680 participants were eligible for analysis. This study was approved by the ethics committee of People’s Liberation Army General Hospital, and written informed consent was obtained from all participants.

**Clinical Data Collection**

All participants were interviewed and completed a standardized questionnaire that included questions about prevalent diseases, family history of CVD, medication use, and lifestyle factors. Physical examinations and interviews were carried out by trained medical doctors. Self-reported smoking status was categorized as current, former, or never. Height and weight were measured in a standing position without shoes. Body mass index was calculated as weight in kilograms divided by the square of height in meters. Peripheral BP was measured two times in the right brachial artery; measurements were taken at 5-min intervals, and the average systolic blood pressure (SBP) and diastolic blood pressure (DBP) measurements were used for analysis and further calculation. Mean arterial blood pressure (MAP) was calculated as DBP+[1/3 × (SBP – DBP)]. Hypertension was defined exclusively by the peripheral BP measurement.

**Biochemical Measurements**

All subjects underwent full laboratory evaluation (lipidemic profile, Hepatic and renal function indices). After a 12-h fasting (no alcohol), blood was collected from the antecubital vein between 8 a.m. and 10 a.m., with the subject in a sitting position. Biochemical variables of all blood specimens were measured with an automated analyzer (Roche Cobas e601, Switzerland) in the same laboratory, following the criteria of the World Health Organization Lipid Reference Laboratories. All participants without a history of DM underwent the standard 75-g oral glucose tolerance test (OGTT). The estimated glomerular filtration rate (eGFR) was calculated using the Chinese modification of the formula (C-MDRD) equation [12]: eGFR (ml/min/1.73 m²) = 175 × standard creatinine (mg/dl)¹⁻¹.⁷⁵ × age (year)⁻⁰.⁰⁷⁹ × 0.79 if female. Plasma tHcy level was determined by high-performance chromatography with fluorometric detection, with a lower limit of detection of 0.5 μmol/l, and inter-assay variation of 4.1%.

**Measurements of Arterial Properties**

Measurement of arterial properties was conducted in the morning, in a quiet environment, at a stable temperature. The subjects were asked to abstain from caffeine, smoking, alcohol, and taking vasoactive medication for at least 12 h before this assessment.

**Central pressure waveforms.** Central arterial BP and wave reflection were assessed using a SphygmoCor pulse wave analysis system (AtCor Medical, Sydney, Australia). The probe was placed at the site of the strongest radial artery pulse to record a stable pulse wave. After 20 sequential waveforms were acquired, a validated, generalized transfer function was used to generate the corresponding central aortic pressure waveform. The central blood pressures (e.g., cSBP, cDBP, central pulse pressure [cPP]) were automatically calculated. Augmentation indices of the central waveform were measured as indices of wave reflection; AIx (a composite measure of arterial stiffness and wave reflection) was defined as augmented pressure divided by pulse pressure and expressed as a percentage [13–14]. To take into account the potential effect of heart rate on AIx, an index normalized for the heart rate of 75 bpm was synchronously analyzed.

**Arterial stiffness.** After participants rested in the supine position for 5 to 10 min, PWV was determined using a Compilior SP device (Artech Medical, France), which allows online pulse wave recording and automatic calculation of PWV. Two transducers were used: one positioned at the base of the neck over the common carotid artery and the other over the femoral artery. Two different pulse waves were obtained simultaneously at two sites, the measurement was repeated over 10 different cardiac cycles, and the mean value was used for the final analysis. PWV was calculated from the pulse transit time and distance traveled by the pulse between the two recording sites (measured on the surface of the body in meters), according to the following formula: PWV (m/s) = distance (m)/transit time (s) [15]. Carotid-femoral PWV is a well-established index of aortic arterial stiffness [16].

**Definition of Variables**

Essential hypertension was defined as (i) systolic blood pressure (SBP) ≥140 mmHg, and/or (ii) diastolic blood pressure (DBP) ≥90 mmHg, and/or (iii) self-reported use of antihypertensive medication [17]. A subject with any of the following was considered to have DM: (i) fasting venous blood glucose ≥7.0 mmol/l, (ii) 2-h plasma glucose ≥11.1 mmol/l during an OGTT, (iii) symptoms of hyperglycemia and casual plasma glucose ≥11.1 mmol/l, or (iv) the subject was taking antihyperglycemic medication [18].

**Statistical Analysis**

Results are expressed as percentages for dichotomous variables, and mean±SD or median (interquartile range) for continuous variables; tHcy level and other biomarkers were normalized by natural logarithm transformation, as necessary. Plasma tHcy levels were categorized as quartile 1 (≤14.0 μmol/l, n = 420), quartile 2 (14.1–17.1 μmol/l, n = 420), quartile 3 (17.2–21.5 μmol/l, n = 420), and quartile 4 (≥21.6 μmol/l, n = 420). Quartiles 1 to 3 were defined as low tHcy (<21.6 μmol/l), and quartile 4 was defined as high tHcy (≥21.6 μmol/l). Arterial properties included in the analyses were brachial BP, central arterial BP, cf-PWV, and heart rate-corrected AIx. Subjects were classified into four groups according to BP (hypertensive vs. normotensive) and tHcy level (<21.6 vs. ≥21.6 μmol/l).
Table 1. Clinical characteristics of study participants according to blood pressure and tHcy level.

| Characteristics       | Normotension | Hypertension |
|-----------------------|--------------|--------------|
|                       | Low tHcy     | High tHcy    | Low tHcy     | High tHcy     | p       |
| No. of subjects       | 672          | 161          | 587          | 260           |         |
| Age (years)           | 57.77±10.76  | 62.27±10.81  | 63.40±9.53   | 66.92±9.63    | <0.001  |
| Males [n (%)]         | 216 (32.14)  | 106 (65.84)  | 227 (38.67)  | 160 (61.54)   | <0.001  |
| Height (cm)           | 161.71±7.64  | 164.52±8.46  | 161.19±8.36  | 163.89±9.25   | <0.001  |
| Weight (Kg)           | 64.13±10.42  | 68.34±11.58  | 67.96±11.11  | 71.70±11.59   | <0.001  |
| Body mass index (kg/m²)| 24.48±3.31   | 25.19±3.62   | 26.14±3.54   | 26.67±3.59    | <0.001  |
| Waist-hip ratio       | 0.86±0.06    | 0.87±0.06    | 0.88±0.06    | 0.90±0.06     | <0.001  |
| Current smokers [n (%)] | 136 (20.24)  | 51 (31.68)   | 144 (24.53)  | 89 (34.23)    | <0.001  |
| Total cholesterol (mmol/l) | 5.05±0.89    | 4.95±0.85    | 5.11±0.95    | 5.02±0.95     | 0.178   |
| HDL-cholesterol (mmol/l) | 1.45±0.38    | 1.35±0.36    | 1.35±0.34    | 1.29±0.31     | <0.001  |
| LDL-cholesterol (mmol/l) | 2.94±0.73    | 2.90±0.69    | 3.03±0.75    | 3.02±0.73     | 0.056   |
| Triglycerides (mmol/l) | 1.65±1.13    | 1.76±1.32    | 1.92±1.21    | 1.97±1.35     | <0.001  |
| FBG (mmol/l)          | 5.37±1.68    | 5.16±1.32    | 5.62±1.80    | 5.40±1.48     | 0.003   |
| 2-hPBG (mmol/l)       | 7.30±3.92    | 7.22±3.75    | 8.71±4.08    | 8.02±3.93     | <0.001  |
| eGFR (ml/min/1.73m²)  | 108.03±26.99 | 97.13±28.43  | 105.80±27.82 | 95.68±26.81   | <0.001  |
| Uric acid (μmol/l)    | 273.07±68.90 | 304.57±72.46 | 296.79±70.71 | 325.68±74.41  | <0.001  |
| Homocystine (μmol/l)  | 15.0 (12.2,17.5) | 26.7 (23.3,31.5) | 16.1 (13.9,18.5) | 26.2 (23.4,30.9) | <0.001  |
| History of CVD [n (%)] | 63 (9.37)    | 23 (14.29)   | 113 (19.25)  | 61 (24.66)    | <0.001  |
| Diabetes [n (%)]      | 104 (15.48)  | 30 (18.63)   | 162 (26.70)  | 66 (25.38)    | <0.001  |
| Antihypertensive drugs|             |              |             |               |         |
| CCB [n (%)]           | –            | –            | 169 (28.79)  | 104 (40.00)   | <0.05   |
| Diuretics [n (%)]     | –            | –            | 71 (12.09)   | 34 (13.08)    | 0.462   |
| Beta-blockers [n (%)] | –            | –            | 118 (20.10)  | 76 (29.23)    | <0.05   |
| ACEI [n (%)]          | –            | –            | 85 (14.48)   | 45 (17.31)    | 0.349   |
| ARB [n (%)]           | –            | –            | 54 (9.20)    | 29 (11.15)    | 0.857   |

Continuous variables are expressed as mean (±SD) or median (interquartile range), and categorical variables are expressed as counts and percentages. Low tHcy was defined as tHcy concentration <21.6 μmol/l; high tHcy was defined as tHcy concentration ≥21.6 μmol/l.

Results

Clinical Characteristics of Subjects Categorized by BP and tHcy Level

Of the 1680 subjects included in the analysis, 709 were male (42.2%), and the mean age was 61.55±10.90 years (range 24–96 years). Of these, 847 had hypertension (50.4%), 362 had DM (21.5%), and 420 were current smokers (25.0%). The median value of plasma tHcy concentration was 17.2 μmol/l.

Participants were divided into four groups based on blood pressure and plasma tHcy level: 672 were normotensive with low tHcy (<21.6 μmol/l), 161 were normotensive and high tHcy (≥21.6 μmol/l), 587 were hypertensive with low tHcy, and 260 were hypertensive with high tHcy (Table 1). All CVD risk factors other than total cholesterol and low-density lipoprotein (LDL) cholesterol levels differed significantly among the four groups.

Influence of tHcy on Central Arterial BPs and Arterial Stiffness

Peripheral blood pressures (SBP, DBP, PP, MAP) and central arterial blood pressures (cSBP, cDBP, cPP, cPP amplification) did
Table 2. Peripheral and central blood pressure values and arterial stiffness according to blood pressure and tHcy level.

| Variable                | Low tHcy | High tHcy | Crude P  | Corrected P |
|-------------------------|----------|-----------|----------|-------------|
| Brachial SBP (mmHg)     | 120.45±10.91 | 122.12±11.94 | 0.076    | 0.304       |
| Brachial DBP (mmHg)     | 72.77±7.84  | 72.82±7.79  | 0.934    | 1           |
| Brachial PP (mmHg)      | 47.68±9.33  | 49.29±10.44 | 0.067    | 0.268       |
| Brachial MAP (mmHg)     | 88.66±7.83  | 89.32±7.99  | 0.372    | 1           |
| Heart rate (bpm)        | 75.41±9.42  | 74.40±9.37  | 0.219    | 0.876       |
| Central SBP (mmHg)      | 110.65±12.11| 112.22±11.62| 0.187    | 0.748       |
| Central DBP (mmHg)      | 72.75±9.56  | 72.54±8.77  | 0.818    | 1           |
| Central PP (mmHg)       | 38.17±9.10  | 40.03±10.40 | 0.058    | 0.232       |
| PP amplification(%)     | 128.69±22.82| 127.08±23.32| 0.417    | 1           |
| cf-PWV (s/m)            | 10.47±2.55  | 11.16±2.47  | 0.007    | 0.028       |
| Central AIx P75 (%)     | 26.20±9.78  | 25.13±9.06  | 0.192    | 0.768       |
| cf-PWV*(s/m)            | 10.83±2.04  | 10.95±2.16  | 0.473    | 1           |
| Central AIx P75** (%)   | 25.86±7.22  | 26.54±6.98  | 0.289    | 1           |

SBP: systolic blood pressure; DBP: diastolic blood pressure; PP: pulse pressure; MAP: mean arterial blood pressure; cf-PWV: carotid-femoral pulse wave velocity; central AIx P75: central augmentation index corrected for a heart rate of 75 bpm. Low tHcy was defined as tHcy <21.6 μmol/l; high tHcy was defined as tHcy ≥21.6 μmol/l. PP amplification was calculated as the peripheral/central pulse pressure ratio.

*After adjustment for age, gender, heart rate, MAP, blood glucose, and current smoking; **after adjustment for age, gender, body mass index, MAP, blood glucose, and current smoking.

Table 3. Univariate and partial correlation analyses of tHcy levels and blood pressures.

| Correlation          | Brachial systolic BP | Brachial diastolic BP | Brachial pulse pressure | Brachial MAP | Central systolic BP | Central diastolic BP | Pulse pressure amplification |
|----------------------|----------------------|-----------------------|-------------------------|--------------|--------------------|----------------------|-----------------------------|
|                      | r                    | R                     | r                       | R            | r                  | R                    | r                           |
| Ln(tHcy) in normotension | 0.109**              | −0.031                | 0.020                   | 0.110**      | 0.065              | 0.076                | 0.125**                     |
| Ln(tHcy) in hypertension | 0.056                | 0.25                  | −0.016                  | 0.063        | 0.016              | 0.017                | 0.001                       |

r: Pearson correlation coefficient; R: partial correlation coefficient. *P<0.01; *P<0.05. BP: blood pressure; MAP: mean arterial blood pressure; Ln(tHcy): natural logarithm-transformed plasma total homocysteine.

Relationship between Plasma tHcy and BP Parameters

In bivariate analyses, correlations between plasma tHcy and BP parameters were significant only among normotensive subjects; no statistically significant correlations were observed among hypertensive individuals (Table 3). In normotensive subjects, tHcy concentration (natural logarithm-transformed) correlated with brachial SBP (r = 0.109, P<0.001), brachial PP (r = 0.110, P=0.001), central SBP (r = 0.076, P = 0.025) and central PP (r = 0.125, P<0.001). However, partial correlation analysis revealed that these correlations were not significant after adjusting for other risk factors known to influence tHcy level. No significant
association between tHcy concentration and BP parameters was observed in the study population.

**Multivariate Analysis of the Relationships between tHcy and cf-PWV and AIx**

To determine independent predictors of cf-PWV, multiple regression analysis was performed using the stepwise procedure (Table 4). The analysis showed that for hypertensive subjects tHcy was an independent determinant of cf-PWV; other parameters entered in the model were age, MAP, fasting blood glucose, HDL cholesterol, and height. However, for normotensive subjects the independent predictors of cf-PWV were age, MAP, fasting blood glucose, HDL cholesterol, height, and heart rate, plasma tHcy did not enter the model.

Plasma tHcy was not an independent predictor of central AIx among either normotensive or hypertensive individuals (Table 4). Gender, MAP, heart rate, height, and weight were among the independent predictors of central AIx.

**Discussion**

Several important findings emerged from our study evaluating central arterial BP and indices of arterial stiffness in a large community-based sample from China. First, we detected a significant positive association between plasma tHcy and arterial stiffness, measured as cf-PWV (aortic PWV), only among hypertensive subjects. Second, plasma tHcy was not an independent predictor of central AIx, and tHcy concentration was not associated with peripheral or central BP. To the best of our knowledge, this is the first study to include both normotensive and hypertensive individuals to evaluate the relationships between circulating tHcy level and BP and arterial stiffness.

The main finding of this study was that plasma tHcy is positively associated with cf-PWV only in hypertension. This finding suggests a potential role for tHcy in arterial wall remodeling in hypertension, leading to arterial stiffness. PWV is a known marker of arterial stiffness and indicator of vascular damage [19], and cf-PWV is associated with the severity of arteriosclerosis and is a predictor of future CVD events [20]. However, the relationship between tHcy and PWV is controversial [10–11]. Our results are in line with some previous studies reporting a positive correlation between tHcy concentration and PWV among individuals at increased risk for CVD, i.e., with DM [21], a high risk to develop hypertension [22–23], or end-stage renal disease [24]. This relationship between tHcy level and arterial stiffness indices usually has not observed in healthy individuals [25–26] or those at low risk for CVD [11].

The mechanisms underlying the relationship between tHcy and arterial stiffness are not entirely clear but may include endothelial dysfunction [27–28], smooth muscle cell proliferation [29], collagen synthesis [30], and deterioration of elastin [31], resulting in impaired arterial compliance. Our observations, together with results of published reports, suggest that tHcy may be not a direct cause of arterial stiffness but contributes to vascular damage after the initial vascular dysfunction has already developed. First, the presence of hypertension or more advanced stage of atherosclerotic disease may make the arterial wall (in particular, the endothelium) more susceptible to the deleterious effect of high plasma tHcy [32]. Second, hypertension is a major link between tHcy and aortic arterial stiffness, suggesting that hypertension may interact with tHcy to produce synergistic effects [33]. Hyperhomocysteinemia appears to increase BP, impair the vasorelaxation activity of endothelial-derived nitric oxide, and accelerate BP-induced oxidative stress on endothelial cells [34]. Tayama et al. [6] found that higher circulating tHcy is associated with increased systemic arterial stiffness, which may enhance BP reactivity to stress in hypertensive patients. The mechanical effects of high BP and the toxic effects of tHcy on the endothelium may trigger the “response to injury” phenomenon [3].

The second important finding of this study is that tHcy was not independently associated with central AIx in hypertension or normotension. These results are consistent with those reported by the B-PROOF study [33], which found that Hcy was associated with aortic PWV but not AIx in elderly individuals. This lack of

---

**Table 4. Independent determinants of cf-PWV and AIx in hypertensive and normotensive subjects.**

| variables          | cf-PWV              | Central AIx          |
|--------------------|---------------------|----------------------|
|                    | β       | SE     | P     | β       | SE     | P     |
| Hypertensive subjects (R² = 0.519) |               |                     |
| Age                | 0.130  | 0.010  | <0.001 | MAP                | 0.241  | 0.033  | <0.001 |
| MAP                | 0.025  | 0.009  | <0.001 | Female             | 4.015  | 0.834  | <0.001 |
| ln(tHcy)           | 0.713  | 0.247  | 0.004  | Heart rate         | −0.418 | 0.033  | <0.001 |
| FBG                | 0.083  | 0.020  | <0.001 | Height             | −0.315 | 0.047  | <0.001 |
| HDL-C              | −0.588 | 0.203  | 0.013  | Weight             | −0.181 | 0.037  | <0.001 |
| Height             | 0.026  | 0.013  | 0.036  |                     |        |        |       |
| Normotensive subjects (R² = 0.436) |               |                     |
| Age                | 0.107  | 0.006  | <0.001 | MAP                | 0.295  | 0.043  | <0.001 |
| MAP                | 0.031  | 0.009  | <0.001 | Female             | 5.175  | 1.012  | <0.001 |
| FBG                | 0.087  | 0.021  | <0.001 | Heart rate         | −0.507 | 0.036  | <0.001 |
| HDL-C              | −0.632 | 0.192  | 0.001  | Height             | −0.369 | 0.059  | <0.001 |
| Height             | 0.037  | 0.014  | 0.038  | Weight             | −0.182 | 0.037  | 0.021 |
| Heart rate         | 0.030  | 0.008  | <0.001 | Smoking            | 2.524  | 0.876  | 0.004 |

β: regression coefficient; MAP: mean arterial blood pressure; ln(tHcy): natural logarithm-transformed plasma total homocysteine; FBG: fasting blood glucose; HDL-C: high-density lipoprotein cholesterol; cf-PWV: carotid-femoral pulse wave velocity; AIx: augmentation index.

doi:10.1371/journal.pone.0085938.t004
relationship between tHcy and AIx may be explained by the fact that pressure wave reflections are generated primarily from arteries [36], suggesting that Hcy does not affect the walls of small arteries. Furthermore, numerous factors other than arterial stiffness influence the height of the reflected wave [37], including physiologic factors such as gender, height, and heart rate and pathological factors such as age, BP, smoking, and medication [38–39]. These factors should be taken into account when using AIx as a marker of arterial stiffness. Moreover, although the progression of atherosclerosis stiffen the aortic wall, it does not affect the central AIx [40], and the ability of AIx to assess wave reflection in normotensive healthy individuals is limited [41]. AIx may be a more sensitive marker of arterial stiffness and CVD risk in younger individuals [42].

Finally, this study did not detect an association between tHcy concentration and peripheral or central BP. The association of tHcy levels with high BP has been reported in some but not all prior studies. The Framingham Heart Study did not find a relationship between baseline tHcy with hypertension incidence or with longitudinal blood pressure progression [43]. Eikelboom et al. [44] reported similar conclusions in a case-control study; however, Nygard and colleagues [45] found a weak association between higher tHcy levels and higher DBP in a sample of >12000 men and women from western Norway. However, that study did not report the relationship between SBP and tHcy, and the association between tHcy and DBP was confined to individuals 40 to 42 years of age. The Third National Health and Nutrition Examination Survey (n = 5978) also found a modest association between tHcy and higher DBP and SBP (0.5–1.2 mmHg per 1-SD increment in tHcy) [46]. These discrepancies may be attributed to several factors. First, there were differences in study populations. Our study evaluated community-based population from Beijing consisting of older individuals with more CVD risk factors. Second, most previously published studies focused on the relationship between high tHcy levels and greater risk for hypertension [2,46,47], whereas few studies estimated the strength of the association between tHcy and BP throughout its continuous range [48]. Third, most studies used only brachial BP as the BP parameter, whereas our study evaluated both peripheral and central BP.

There are several potential limitations of our study. First, all participants were from Beijing; therefore, conclusions drawn from our study cannot be generalized to other ethnic groups. Second, because of the cross-sectional design of our study, we have no direct evidence for a cause–effect relationship. The role of elevated tHcy in increased aortic stiffness requires further investigation by interventional prospective studies. Third, the multiple comparisons may increase the likelihood of type I error. To address this limitation, Bonferroni procedure was used for correction of multiple testing.

Conclusion

In conclusion, we found that plasma tHcy level is independently associated with arterial stiffness (i.e., cf-PWV) in hypertensive subjects only. This study raises the possibility that reducing plasma tHcy may decrease arterial stiffness in hypertensive individuals.

Acknowledgments

We thank colleagues at the Department of Laboratory Medicine, the PLA General Hospital for help with biochemical measurements. We are also grateful to all study participants for their participation in the study.

Author Contributions

Conceived and designed the experiments: PY. Performed the experiments: WX DL. Analyzed the data: WX YB. Contributed reagents/materials/analysis tools: LL HW JY. Wrote the paper: WX.

References

1. Troughton JA, Woodside JV, Young IS, Arveiller D, Amouyal P, et al. (2007) Homocysteine and coronary heart disease risk in the PRIME study. Atherosclerosis 191: 90–97.
2. Mizrahi EH, Noy S, Sela BA, Fleissig Y, Arad M, et al. (2003) Further Evidence of Interrelation between Homocysteine and Hypertension in Stroke Patients: A Cross-Sectional Study. Isr Med Assoc J 5: 791–794.
3. Montalescot G, Anki A, Chadefaux-Vekemans B, Blacher J, Philippe F, et al. (1997) Plasma homocysteine and the extent of atherosclerosis in patients with coronary artery disease. Int J Cardiol 60: 295–300.
4. Hu DY, Xu XP (2008) Prevention of stroke relies on valid control “H” type hypertension. Zhonghua Nei Ke Za Zhi 47: 976–977.
5. Wang HL, Tan S, Song B, Mao W, Gao Y, et al. (2012) Correlation of H-type hypertension and prognosis of ischemic stroke. Zhonghua Yi Xue Za Zhi 92: 1183–1186.
6. Tayama J, Munakata M, Yoshinaga K, Toyota T (2006) Higher plasma Homocysteine concentration is associated with more advanced systemic arterial stiffness and greater blood pressure response to stress in hypertensive patients. Hypertens Res 29: 403–409.
7. Yinghongchen T, Limpjantik T, Jongjirasiri S, Laothamatas J, Yamwong S, et al. (2012) Arterial stiffness contributes to coronary artery disease risk prediction beyond the traditional risk score (RAMA-EGAT score). Heart Asia 4: 77–82.
8. Tsucherla S, Shoji T, Kimoto E, Shinohara K, Hatouda S, et al. (2010) Central versus peripheral arterial stiffness in association with coronary, cerebral and peripheral arterial disease. Atherosclerosis 211: 480–485.
9. Oberoi S, Schoepf UJ, Meyer M, Henderz T, Rowe GW, et al. (2013) Progression of arterial stiffness and coronary atherosclerosis: longitudinal evaluation by cardiac CTA. Ann Roentgenol 200: 780–784.
10. Vyssoudis G, Karpanos E, Kyvelou SM, Adamopoulou D, Galisnem T, et al. (2010) Associations between plasma homocysteine levels, aortic stiffness and wave reflection in patients with arterial hypertension, isolated office hypertension and normotensive controls. Journal of Human Hypertension 24: 183–189.
11. Nakhia-Pour HR, Grobbe DE, Bots ML, Muller M, van der Schouw YJ (2007) Circulating homocysteine and large arterial stiffness and thickness in a population based sample of middle-aged and elderly men. J Hum Hypertens 21: 942–948.
12. Ma YC, Zuo L, Chen JH, Liao Q, Yu XQ, et al. (2006) Modified glomerular filtration rate estimating equation for Chinese patients with chronic kidney disease. J Am Soc Nephrol 17: 2937–2944.
13. Yasmin, Brown MJ (1999) Similarities and differences between augmentation index and pulse wave velocity in the assessment of arterial stiffness. QJM Med 92: 595–600.
14. Pannier BM, Avello PA, Hooks A, Mancia G, Takazawa K (2002) Methods and devices for measuring arterial compliance in humans. Am J Hypertens 15: 743–753.
15. O’Rourke MF, Staessen JA, Vlachopoulos C, Duprez D, Plante GE (2002) Clinical applications of arterial stiffness; definitions and reference values. Am J Hypertens 15: 426–444.
16. William-Hansen T, Staessen JA, Torp-Pedersen G, Rasmussen S, Thijl L, et al. (2006) Prognostic value of aortic pulse wave velocity as index of arterial stiffness in the general population. Circulation 113: 664–670.
17. Mancia G, Fagard R, Narkiewicz K, Redon J, Zanchetti A, et al. (2013) 2013 ESH/ESC 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). Eur Heart J 34: 2159–2219.
18. Sacks DB, Arnold M, Bakris GL, Bruns DE, Hoyarth AR, et al. (2011) Guidelines and recommendations for laboratory analysis in the diagnosis and management of diabetes mellitus. Diabetes Care 34: e61–99.
19. Weber T, Wassunerheuer S, Rammer M, Haaden A, Hametner B, et al. (2012) Wave reflections, assessed with a novel method for pulse wave separation, are associated with end-organ damage and clinical outcomes. Hypertension 60: 849–854.
20. Verbeke F, Van Biesen W, Honkanen E, Wikstro¨m B, Jensen PB, et al. (2011) Prognostic value of aortic stiffness and calcification for cardiovascular events and mortality in dialysis patients: outcome of the calcification outcome in renal disease (CORD) study. Clin J Am Soc Nephrol 6: 153–159.
21. Anan F, Masaki T, Umeno Y, Yonemochi H, Eshima N, et al. (2007) The association between plasma homocysteine and atherosclerosis in Japanese type 2 diabetic patients. Metabolism 56: 1390–1395.
22. Yasmin E, Falsone R, Brown MJ (2004) Determinants of arterial stiffness in offspring of families with essential hypertension. Am J Hypertens 17: 292–296.
Plasma Homocysteine and Arterial Stiffness

23. Kim BJ, Seo M, Huh JK, Kwon CH, Kim JT, et al. (2011) Associations of plasma homocysteine levels with arterial stiffness in prehypertensive individuals. Clin Exp Hypertens 33: 411–417.

24. Blacher J, Demuth K, Guerin AP, Safar ME, Moatt N, et al. (1998) Influence of biochemical alterations on arterial stiffness in patients with end-stage renal disease. Arterioscler Thromb Vasc Biol 18: 535–541.

25. De Bree A, Menen LI, Zurek M, Durcos V, Guillaud JC, et al. (2006) Homocysteine is not associated with arterial thickness and stiffness in healthy middle-aged French volunteers. Int J Cardiol 113: 332–340.

26. Woodside JV, McMahon R, Gallagher AM, Cran GW, Boreham CA, et al. (2004) Total homocysteine is not a determinant of arterial pulse wave velocity in young healthy adults. Atherosclerosis 177: 337–344.

27. Tousoulis D, Antoniades C, Marinou K, Vaxiadou C, Bouras G, et al. (2008) Methionine-loading rapidly impairs endothelial function, by mechanisms independent of endothelin-1: evidence for an association of fasting total homocysteine with plasma endothelin-1 levels. J Am Coll Nutr 27: 379–386.

28. Moat SJ, McDowell IF. (2005) Homocysteine and endothelial function in human subjects. Semin Vasc Med 5: 172–182.

29. Chiang JK, Sung ML, Yu HR, Chang HI, Kuo HC, et al. (2011) Homocysteine induces smooth muscle cell proliferation through differential regulation of cyclins A and D1 expression. J Cell Physiol 226: 1017–1026.

30. Miller A, Mujumdar V, Shek E, Guillot J, Angelo M, et al. (2000) Homocysteine decreases blood flow to the brain due to vascular resistance in carotid artery. Neurochem Int 33: 214–219.

31. Kumar M, Tyagi N, Moshal KS, Sen U, Kundu S, et al. (2000) Homocysteine decreases blood flow to the brain due to vascular resistance in carotid artery. Neurochem Int 33: 214–219.

32. Antoniades C, Antonopoulos AS, Tousoulis D, Marinou K, Stefanadis C. (2009) Homocysteine and coronary atherosclerosis: from folate fortification to the recent clinical trials. Eur Heart J 30: 6–15.

33. Bortolotto LA, Safar ME, Billaud E, Lacroix C, Asmar R, et al. (1999) Plasma homocysteine, Aortic Stiffness, and Renal Function in Hypertensive Patients. Hypertension 34: 837–842.

34. Sen U, Mishra PK, Tyagi N, Tyagi SC. (2010) Homocysteine to hydrogen sulfide transduction of acute and long-term aerobic exercise on arterial stiffness in the elderly. Hypertens Res 30: 895–902.

35. van Dijk SC, Smulders YM, Enneman AW, Swart KM, van Wijngaarden JP, et al. (2007) Effect of acute and long-term aerobic exercise on arterial stiffness in the elderly. Am J Hypertens 20: 311–317.

36. Woodside JV, McMahon R, Gallagher AM, Cran GW, Boreham CA, et al. (2004) Total homocysteine is not a determinant of arterial pulse wave velocity in young healthy adults. Atherosclerosis 177: 337–344.

37. Sharman JE, Davies JE, Jenkins C, Marwick TH. (2009) Augmentation index, left ventricular contractility, and wave reflection. Hypertension 54: 1099–1105.

38. Tabara Y, Yuasa T, Oshiumi A, Kobayashi T, Miyawaki Y, et al. (2007) Effect of acute and long-term aerobic exercise on arterial stiffness in the elderly. Hypertens Res 30: 895–902.

39. Filipovska J, Ticha M, Cikova R, Lanska V, Stastna V, et al. (2005) Large artery stiffness and pulse wave reflection: results of a population-based study. Blood Press 14: 45–52.

40. Katnuda S, Miyake M, Kobayashi D, Hazama A, Kusanagi M, et al. (2013) Does the augmentation index of pulse waves truly increase with progression of atherosclerosis? An experimental study with hypercholesterolemic rabbits. Am J Hypertens 26: 311–317.

41. Hughes AD, Park C, Davies J, Francis D, McG Thom SA, et al. (2013) Limitations of augmentation index in the assessment of wave reflection in normotensive healthy individuals. PLoS One 8: e59371.

42. McIntyre CM, Yasmin, Hall IR, Qaseem A, Wilkinson IB, et al. (2005) Normal vascular aging: differential effects on wave reflection and aortic pulse wave velocity: the Anglo-Caerifl Collaborative Trial (ACCT). J Am Coll Cardiol 46: 1753–1760.

43. Sundstrom J, Sullivan L, D’Agostino RB, Jacques PF, Selhub J, et al. (2003) Plasma homocysteine, hypertension incidence, and blood pressure tracking: the Framingham Heart Study. Hypertension 42: 1100–1105.

44. Eikelboom JW, Hankey GJ, Anand SS, Lofthouse E, Staples N, et al. (2000) Association between high homocysteine and ischemic stroke due to large and small artery disease but not other etiologic subtypes of ischemic stroke. Stroke 31: 1069–1075.

45. Nygard O, Vollset SE, Refsum H, Stenstvedt I, Tverdal A, et al. (1995) Total plasma homocysteine and cardiovascular risk profile: the Hordaland Homocysteine Study. JAMA 274: 1526–1533.

46. McEniery CM, Yasmin, Hall IR, Qaseem A, Wilkinson IB, et al. (2005) Normal vascular aging: differential effects on wave reflection and aortic pulse wave velocity: the Anglo-Caerifl Collaborative Trial (ACCT). J Am Coll Cardiol 46: 1753–1760.

47. Sharman JE, Davies JE, Jenkins C, Marwick TH. (2009) Augmentation index, left ventricular contractility, and wave reflection. Hypertension 54: 1099–1105.

48. Tsai JC, Kuo HT, Chiu YW, Hwang SJ, Chuang HY, et al. (2005) Correlation of plasma homocysteine level with arterial stiffness and pulse pressure in hemodialysis patients. Atherosclerosis 182: 121–127.