



The design and rationale of the Beijing Vascular Disease Patients Evaluation Study (BEST study)

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ABSTRACT

Aims: Arteriosclerosis and arterial stiffness increasing are the basic pathophysiological changes of vascular-related diseases, and also the predictor factors of future cardiovascular events. Plasma biomarkers such as glucose, lipids, Homocysteine (Hcy), N-terminal pro-brain natriuretic peptide (NT-proBNP) have been shown to be involved in the development of arteriosclerosis. The present study is a prospective observational and follow-up study of the characteristics of subclinical vascular disease detected by non-invasive methods that can predict progression of clinical overt vascular events in a Chinese population.

Methods: The study including both genders with age of 45 years to 75 years was designed as observational research by questionnaires and 3-year follow-up with vascular functional and structural parameters evaluation without any interventions. Questionnaire was designed to survey the lifestyle, personal history, family history of the study population. Arterial function indexes such as pulse wave velocity, cardio-ankle vascular index, flow mediated vascular dilation, ankle brachial index, carotid intima-media thickness, and plasma biomarkers such as glucose, lipids, Hcy, NT-pro BNP, Glycosylated hemoglobin, insulin resistance index, uric acid are collected. The outcome is the composite of acute myocardial infarction or coronary reperfusion therapy or stroke or peripheral vascular diseases.

Conclusions: 2858 subjects were enrolled into our present study at baseline, and this present study will provide important information on the metabolic related traditional and new risk factors, establish a new vascular disease early detection system and scoring systems based on comprehensive vascular disease risk factors and vascular function and structure evaluation indexes.

1. Introduction

Vascular-related diseases such as coronary heart disease (CHD), stroke are the most common cause of increasing mortality and morbidity [1]. Arteriosclerosis and arterial stiffness increasing are the basic pathophysiological changes of vascular-related diseases, and also the predictor factors of future cardiovascular events. Arterial stiffness could be measured by pulse wave velocity (PWV) [2] and cardio-ankle vascular index (CAVI) suggested by Chinese guideline for early vascular disease detection (2011 s report) [3]. Our previous studies showed that PWV was positively correlated with pulse pressure and it was increased in hypertension patients with left ventricular hypertrophy [4,5]. And our recent study showed that PWV is significantly higher in healthy subjects with a positive family history of hypertension [6]. CAVI was significantly higher in hypertension subjects with DM or CHD [7,8]. In addition, there are some other parameters to evaluate arterial function

such as flow mediated vascular dilation (FMD) [9], ankle brachial index (ABI) [10], carotid intima-media thickness (CIMT) [11].

Plasma biomarkers such as fasting plasma glucose (FPG), total cholesterol (TC), triglyceride (TG), high-density lipoprotein cholesterol (HDL-C), Homocysteine (Hcy), N-terminal pro-brain natriuretic peptide (NT-proBNP) have been shown to be involved in the development of arteriosclerosis. Our previous studies showed that there was positive correlation between CAVI, PWV and plasma lipids and Hcy in vascular-related diseases [12]. HOPE study showed combining traditional risk factors with NT-pro BNP can provide the best clinical prediction of recurrent cardiovascular events in the secondary-prevention population [13]. And high-normal hemoglobin A1c (HbA1c) level was independently associated with arterial stiffness in the general population without diabetes [14]. These studies suggest biomarkers could provide some information about the prediction role of future cardiovascular events.

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As above shown, arterial function lesion is the pathophysiological changes of cardiovascular disease, so if we could find the vascular function abnormality early, we could treat it early before cardiovascular diseases attack. This is very important to reduce the incidence of myocardial infarction or other serious cardiovascular diseases. So the early detection and treatment of high-risk patients has been enforced as a key strategy in the prevention of cardiovascular diseases to reduce the incidences of death and disability of cardiovascular diseases apart from the treatment of serious vascular events. Our team studies showed that arterial function evaluation was more important than arterial structure evaluation [15]. So we proposed the early vascular detection technology including many vascular function evaluation indexes such as pulse pressure, PWV, CAVI, FMD, ABI, CIMT [3]. And this technology was approved by Ministry of Health of the People's Republic of China to be promoted to the whole China in 2004. Recently, we proposed new established vascular health classification (namely Beijing Vascular Health Classification) which assessed both the vascular functional and structural lesion changed [16].

Recently, we started a prospective study named Beijing Vascular Disease Patients Evaluation Study (BEST). This study was to investigate and select appropriate indicators and effective joint, and then establish vascular disease early detection system and scoring systems including arterial function indexes to predict the incidence of terminal events.

2. Study organization

The BEST (ClinicalTrials.gov Identifier: NCT02569268) organizational structures and responsibilities were similar to many previous clinical studies. BEST study was sponsored by Beijing Health Bureau and included three clinical center networks such as Peking University Shougang Hospital, Beijing Hospital and Beijing Mentougou district traditional Chinese medicine Hospital, the coordinating centers, and Peking University Health Science Center representatives formed the steering committee to design and conduct the study. Each clinical center network consisted of multiple collaborating clinical centers, which were primarily responsible for the recruitment, blood pressure management, safety, and follow-up of participants. The clinical center networks were responsible for recruiting and providing oversight of these clinical centers. The coordinating center was responsible for overall trial coordination, data collection and analysis, and for oversight of the central units.

This study was approved by the ethics committee of Peking University Shougang Hospital in China. And all participants will complete informed consent.

3. Cohort design

The study was designed as observational research by questionnaires and follow-up with vascular functional and structural parameters evaluation without any interventions. The cohort components of the study involved sampling, recruitment, clinic examinations, annual telephone follow-up, and identification, investigation, and diagnosis of clinical events. Questionnaire was designed to survey the lifestyle, personal history, family history, and medication used of the study population. And these subjects would be followed for three years to record the occurrence of end vascular events including cardiovascular events (acute myocardial infarction, coronary reperfusion therapy), stroke, peripheral vascular diseases.

4. Study population, sampling and recruitment

BEST study surveillance covered all communities and provided an opportunity for testing the consistency of study results across three geographic locations including Dongcheng District, Shijingshan District and Mentougou District in Beijing. The present study included both genders with age of 45 years to 75 years and also healthy volunteers,

and subjects were selected by non-probability sampling. The inclusion criteria were as follows: 1. with informed consent; 2. healthy subjects with or without history of vascular-related diseases; 3. or hypertension subjects; 4. or diabetes mellitus subjects; 5. or coronary artery disease; 6. or cerebrovascular disease; 7. or peripheral arterial occlusive disease; 8. or hyperlipidemia subjects. And the exclusion criteria were as follows: 1. without informed consent; 2. infectious diseases and inflammatory diseases; 3. liver and kidney failure; 4. cancer; 5. immunological diseases; 6. hematological system disease.

5. Study design decisions

According to the new 7-grade classification of vascular health (Beijing Vascular Health Classification, BVHC) put forward by our research group [16], that is:

Grade I: Normal stage: No structural and functional damage

Grade II: Arterial endothelial dysfunction stage: FMD < 10%

Grade III: Arterial stiffness stage: C-FPWV > 9 m/s and/or CAVI > 9

Grade IV: Vascular structural lesions early stage (Vascular lumen stenosis < 50%)

a: the formation of atherosclerotic plaque, Vascular elasticity Normal (C-FPWV ≤ 9 m/s and/or CAVI ≤ 9)

b: the formation of atherosclerotic plaque, Vascular elasticity Reduced (C-FPWV > 9 m/s and/or CAVI > 9)

Grade V: Vascular structural lesions middle stage (Vascular lumen stenosis 50%–75%)

a: The formation of atherosclerosis, Vascular elasticity Normal (C-FPWV ≤ 9 m/s and/or CAVI ≤ 9)

b: The formation of atherosclerosis, Vascular elasticity Reduced (C-FPWV > 9 m/s and/or CAVI > 9)

Grade VI: Vascular structural lesions end stage, Vascular lumen stenosis > 75% (heart, brain, kidney, Lower extremity vasculum)

Grade VII: Vascular events stage (need hospitalization)

FMD: Flow Mediated Dilation; C-FPWV: Carotid-Femoral Artery Pulse Wave Velocity; CAVI: Cardio Ankle Vascular Index.

Thus, in the present study, we will detect the vascular structure and function comprehensively as well as blood sample markers and also will apply this new classification to the research population.

6. Outcome definitions

The outcome is the composite of acute myocardial infarction or coronary reperfusion therapy or cardiac arrest or stroke or peripheral vascular diseases. Outcome events will be as reported by the investigator and will not be independently adjudicated.

Acute myocardial infarction is diagnosed according to the guideline published in Chinese Journal of Cardiology (2015, 43(05): 380–393.) including ischemic signs, development of pathological Q waves or changes indicative of new ischemia (i.e. new ST-T changes or new left bundle branch block) on electrocardiogram, imaging evidence of new loss of viable myocardium, or new regional wall motion abnormality. Coronary reperfusion therapy is defined as percutaneous coronary intervention or coronary artery bypass graft.

Stroke is defined as an abrupt onset of a focal neurological deficit that is not initiated by an identifiable non-vascular cause and that either is associated with symptoms lasting > 24 h or results in death within 24 h of symptom onset. And computed tomography and/or magnetic resonance imaging will be used.

Peripheral vascular diseases was defined as ABI < 0.9 with 1) tiredness, intermittent claudication, or 2) pain, numbness, silent (rest) pain, or 3) decrease or loss of arterial pulse, or 4) ischemic arterial ulcer, dry & wet gangrene, or 5) stent implantation.

7. Expected objectives

The primary objective of BEST is to select appropriate indicators including arterial function indexes and biomarkers to establish vascular disease early detection system and scoring systems.

8. Main detections will be shown as following

8.1. Evaluation of vascular endothelial function

Participates were measured at supine position after relaxing 10 min. It is measured by detecting the change rate of right brachial artery diameters at baseline and after blood flow occlusion using color Doppler ultrasound apparatus (EUB-7500, Hitachi, Japan) by a linear array probe. We measure the right arm 3–5 cm above the cubital fossa and measure the baseline diameter of brachial artery in a longitudinal view. Then we will mark the same position with a marking pen and tie the cuff at 5 cm above the cubital fossa. The cuff is inflated to above the systolic blood pressure 50 mmHg, and after 5 min release the cuff. Then we will measure the diameter again and calculate the FMD ($\text{FMD} = \frac{\text{Diameter after cuff releasing} - \text{baseline diameter}}{\text{baseline diameter}} \times 100\%$).

8.2. Detection of pulse wave velocity (PWV)

PWV is one of the noninvasive evaluation methods of arterial stiffness using the Complior SP (Artech Medical, Pantin, France) apparatus automatically. Knowing the distance and pulse transit time, the velocity can be calculated. Patients were placed in supine position and, after a 10-minute rest, underwent PWV measurement and carotid-femoral PWV (CF-PWV) was obtained automatically.

8.3. Examination of cardio ankle vascular index (CAVI)

CAVI was recorded using a VaseraVS-1000 vascular screening system (Fukuda Denshi, Tokyo, Japan) with the participant resting in a supine position. ECG electrodes were placed on both wrists, a microphone for detecting heart sounds was placed on the sternum, and cuffs were wrapped around both the arms and ankles. After automatic measurements, obtained data were analyzed by software, and the value of CAVI was obtained automatically.

8.4. Evaluation of ankle brachial index (ABI)

ABI was measured automatically by VS-1000 vascular screening system (Fukuda Denshi Co. LTD, Japan), which is the same apparatus with CAVI. ABI can be calculated by the measurement of four limbs blood pressure and was defined as the ratio of ankle blood pressure and brachial blood pressure.

8.5. Assessment of subclinical atherosclerosis

Carotid color Doppler ultrasound apparatus (EUB-7500, Hitachi, Japan) with 7.0–12.0 MHz linear array probe was used to assess subclinical atherosclerosis by detecting the presence of carotid plaque and carotid intima-media thickness (CIMT). CIMT was measured from the media-adventitia interface to the intima-lumen interface on the far wall of the common carotid artery at least 5 mm below its end in a longitudinal view. And $\text{CIMT} > 0.9 \text{ mm}$ is defined as subclinical atherosclerosis and plaque is defined as thickness $> 1.5 \text{ mm}$.

8.6. Measurements of other vascular bed by ultrasonography

Doppler ultrasound apparatus with abdominal and linear vascular probes can be used for the evaluation of other vascular bed, such as abdominal artery, renal artery and lower extremity artery. In the new

Beijing Vascular Health Classification [19], imaging technologies are as one of assessment methods. Thus, in the study, we will conduct a non-invasively detection of ultrasonography to assess the vascular structure damages.

8.7. Laboratory measurements

Blood samples were drawn from an ante cubital vein in the morning after overnight fasting and collected into vacuum tubes containing EDTA for the measurement of plasma lipid and lipoprotein levels. FPG, TC, TG and HDL-C levels were analyzed using colorimetric enzymatic assays with the use of an auto analyzer (HITACHI-7170, Hitachi, Tokyo, Japan) at the Central Chemistry Laboratory of the Peking University Shougang Hospital. Low-density lipoprotein cholesterol (LDL-C) levels were calculated. Homocysteine (Hcy) and high sensitive C reactive protein (hs-CRP) were also determined by colorimetric methods of related metabolic products using the same auto analyzer. The level of N-Terminal pro-brain natriuretic peptide (NT-pro BNP) was measured using the method of bidirectional lateral flow immunoassay (ReLIA) according to the procedure. Glycosylated hemoglobin (HbA1c), insulin resistance index (HOMA-IR), uric acid (UA) and D-Dimer were measured in Peking University Shougang Hospital.

8.8. Statistical analysis

SPSS V.22.0 was used as statistical software in the present study. The differences between 7-grade classification different groups were analyzed by Student *t*-test and one-way analysis of variance and least-significant difference (LSD) at baseline and end of the follow-up. Proportions were analyzed by χ^2 test at baseline and end of the follow-up. Correlation coefficient was done to find linear relation between different variables using Spearman correlation coefficient. Multiple linear regressions were used to estimate the coefficients of the linear equation, involving independent variables that affected the value of the dependent variables. Logistic regression analysis was used to find variables which were risk factors or protecting factors at the end of the follow-up. We also use Cox's proportional hazards regression model and other related statistical methods to analyze the outcome data. Values were shown as mean \pm SD unless stand otherwise and $p < 0.05$ (two-tailed) was considered statistically significant.

9. Quality control and safety monitoring

The present study is an observational and following-up study without any interventions. All measurements referred above are non-invasive, except for drawing blood, which may be slight redness and swelling, and soon that will be better.

10. Baseline results

As shown in Table 1, 2858 subjects were enrolled into our present study June 2012 to June 2015, and 903 subjects with histories of hypertension, or diabetes mellitus, or coronary artery disease, or cerebrovascular disease, or peripheral arterial occlusive disease, and 1955 subjects without these diseases. There were significant difference about age, gender, body mass index, pressure, lipids and arterial stiffness between these two groups.

11. Discussion

BEST study was to establish a new vascular disease early detection system and scoring systems based on comprehensive vascular disease risk factors and vascular function and structure evaluation indexes.

Report on cardiovascular diseases in China (2012) showed that there are 230 million patients suffered from cardiovascular diseases and the number is growing rapidly in future. The mortality of cardiovas-

Table 1
Clinical characteristics in different groups.

	Without vascular-related disease (n = 1955)	With vascular-related disease (n = 903)	p
Age	56.58 ± 12.90	67.29 ± 11.91	< 0.001
Gender (M/F)	969/986	490/413	0.039
BMI	24.19 ± 5.66	25.33 ± 3.80	< 0.001
SBP	137.13 ± 17.88	139.50 ± 20.82	0.003
DBP	83.66 ± 11.00	83.72 ± 11.57	0.892
FPG	4.33 ± 2.82	5.84 ± 2.44	< 0.001
TC	3.78 ± 2.39	4.31 ± 1.30	< 0.001
TG	1.42 ± 1.54	1.59 ± 1.37	0.002
HDL-C	0.92 ± 0.60	1.32 ± 6.03	0.004
LDL-C	2.32 ± 1.53	2.67 ± 0.93	< 0.001
UA	242.18 ± 160.9	307.83 ± 111.8	< 0.001
HCY	6.81 ± 8.18	14.28 ± 8.46	< 0.001
CF-PWV	10.69 ± 2.16	12.05 ± 2.75	< 0.001
CAVI	8.10 ± 1.15	8.83 ± 1.53	< 0.001
RABI	1.11 ± 0.13	1.05 ± 0.18	< 0.001
LABI	1.11 ± 0.13	1.06 ± 0.17	< 0.001

Note: BMI: body mass index; CAVI: Cardio-ankle vascular index; SBP: systolic blood pressure; DBP: diastolic blood pressure; FPG: fasting plasma glucose; UA: uric acid; TC: cholesterol; LDL-C: low-density lipoprotein cholesterol. HDL-C: high-density lipoprotein cholesterol. TG: triglycerides. HCY: homocysteine. CFPWV: carotid-femoral pulse wave velocity; RABI: right ankle brachial index; LABI: left ankle brachial index.

cular disease was significantly higher in China than in other developed countries. And CHD, stroke, and peripheral vascular disease have been remaining as the hot points in the world governments and academic circles. With the enhancing cognitive level of these diseases, we have known that the overall clinical progression of human arterial tree is the core link to bring about various important organ dysfunctions. The progression of arteriosclerosis is caused by various risk factors such as hypertension, obesity, diabetes mellitus, and metabolic syndrome and so on. These factors could cause macro- and micro-vascular complications, such as aortic atherosclerosis and retinal artery arteriosclerosis, leading to an increase of arterial wall thickness, endothelial dysfunction and calcification, finally leading to an increase of arterial stiffness. Arterial stiffness is a strong predictor of future cardiovascular events and all-cause mortality. And it is one of the earliest detectable manifestations of adverse structural and functional changes within the vessel wall [17]. Both Danish population study [18] and Baltimore Longitudinal Study of Aging (BLSA) study [19] have showed the predictor role of arterial stiffness for cardiovascular outcomes beyond traditional cardiovascular risk factors.

A recent consensus concluded that hemoglobin A1c, microalbuminuria, C-reactive protein certain, lipoprotein-associated phospholipase, coronary calcium, carotid intima-media thickness, and ankle/brachial index can be used as clinical risk prediction measurement [20]. Furthermore, changes including total cholesterol, HDL-C, systolic blood pressure, daily smoking, body mass index, diabetes mellitus, resting heart rate and physical activity accounted for 66% of the decline in coronary heart disease events [21]. Also MORGAM study confirmed adding NT-proBNP, C-reactive protein, and sensitive troponin I to a conventional risk model can improve 10-year risk estimation for cardiovascular events [22]. However, these models predicted the traditional risk factors instead of vascular itself and lack of recent vascular health assessment.

As previous stated, arterial function lesion is the pathophysiological changes of cardiovascular disease, so if we could find the vascular function abnormality early, we could treat it early before cardiovascular diseases attack. This is very important to reduce the incidence of myocardial infarction or other serious cardiovascular diseases. Thus, vascular disease can be prevented by early detection and there are also many risk prediction models which are of great importance in the primary practice [23]. However, these models predicted the traditional

risk factors instead of vascular function itself and lack of recent vascular health assessment. Thus, the new classification combined the above non-invasive evaluation measurements together and assess the vascular health status comprehensively [16]. However, combined indexes could simultaneously detect abnormalities from multiple levels of structure and function, and make up shortcomings of single indicator in clinical applications. In addition, all indicators testing not only cause time consuming, but also increase the burden on patients, resulting unnecessary waste of medical resources. The BEST study was to select appropriate indicators and effective joint, and then establish vascular disease early detection system and scoring systems to predict the incidence of terminal events.

The present study design has the following strengths. First, it included all kinds of early noninvasive vascular function and structure indexes and biomarkers together to evaluate the systematic vessels comprehensively. Second, our research team put forward a new vascular health classification including all above detections, and the present study was designed to apply the new classification and confirm its great clinical significance. Third, the present study designation will provide a new concept of the prevention of vascular diseases, we should regard the cardiac, brain, kidney and peripheral vessels as a whole and assess comprehensively. Fourth, this study was supported by The Capital Health Research and Development of Special Project, and 2858 subjects were enrolled into our present study from June 2012 to June 2015, and all of laboratory and physiological tests were done in these subjects. So we got very integral baseline data. However, we also have some limitations about the designation. First, the detection of the whole vessels by ultrasound is highly dependent on the examiners although all detection will be done by the same person. Also the evaluation of vascular endothelial is by ultrasound, so it is dependent on the technique of the examiner. Second, because the study is conducted partly in the hospital, so the duration of related detection may vary according to different conditions. Third, the sample size may not meet the need for the establishment of a new prediction system, but will provide information on the application of the new classification. In addition, BEST study has been registered in Clinical Trial (<https://clinicaltrials.gov>), and [ClinicalTrials.gov](https://clinicaltrials.gov) Identifier is NCT02569268, however, the trial has completed, and we did not publish our methodology of BEST study before. However, our present study could provide more information about arterial function in the development of vascular diseases.

In conclusion, arterial function evaluation is becoming more important in recent research than structure evaluation. BEST study will provide vascular disease early detection system and scoring systems according to comprehensive vascular disease risk factors and vascular function.

Declaration of conflicting interests

No conflicts of interest, financial or otherwise, are declared by the authors.

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