Multi-center study on new cardiovascular remodeling and function parameters in hypertension （Observational study）

Project undertaker: Qilu Hospital of Shandong University

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Research Protocol

Participant centers

Qilu Hospital of Shandong University

Qilu Hospital of Shandong University (Qingdao)

Shenzhen People’s Hospital

The Affiliated Sichuan Provincial People's Hospital

West China Hospital, Sichuan University

First Affiliated Hospital, School of Medicine, Shihezi University

The First Affiliated Hospital of Xinjiang Medical University

The First Affiliated Hospital of China Medical University

Sun Yat-sen Memorial Hospital, Sun Yat-sen University

China-Japan Union hospital of Jilin University

The Second Affiliated Hospital of Harbin Medical University

The First Affiliated Hospital of Guangxi Medical University

Wuhan Asia Heart Hospital

Zhongshan Hospital, Fudan University

Henan Provincial People's Hospital

Tangdu Hospital of Air Force Medical University of PLA

Shengjing Hospital of China Medical University

Beijing Anzhen Hospital, Capital Medical University

The First Affiliated Hospital of Harbin Medical University

The People’s Hospital of Liaoning Province

BACKGROUND

Hypertension is the most important risk factor for the morbidity and mortality of cardiovascular and cerebrovascular diseases in China. Useful treatment of hypertension can reduce the incidence of cardiovascular and cerebrovascular diseases. Hemodynamic overload caused by hypertension can lead to left ventricular remodeling and functional changes, usually manifested as significant changes in the geometric configuration of the left ventricle, such as concentric hypertrophy (CH) and eccentric hypertrophy (EH). Left ventricular hypertrophy is an adaptive process after the increase of hemodynamic load, and also cause damages of target organs. Studies have shown that left ventricular hypertrophy (LVH) and left atrial enlargement caused by hypertension are independent risk factors for cardiovascular events. Epidemiological studies have confirmed that changes in the geometry of left ventricular remodeling may be harmful and increase the risk of incidence rate and mortality of cardiovascular disease. The different types of left ventricular remodeling are related to cardiovascular events and all-cause mortality. Different left ventricular geometric configurations had different prognosis. Studies show that CH has the larger left ventricular mass and worse prognosis, than EH, concentric remodeling (CR) and normal left ventricular geometry (NG). In patients with essential hypertension, ventricular remodeling and hypertrophy always occur, and myocardial diastolic and systolic function decline gradually, eventually leading to heart failure. Another study showed that the mortality of patients transferred from CR to NG significantly decreased, and the mortality of patients transferred from CR to LVH was significantly higher. Antihypertensive treatment could significantly reduce LVH and prevent or reverse the abnormal geometry of left ventricle. Therefore the type, distribution characteristics and configuration outcome of left ventricular hypertrophy remodeling, evaluate left ventricular systolic and diastolic function and left atrial size can improve the early prevention and attention of heart failure, and early intervention and treatment are of great significance for reducing the occurrence of cardiovascular events and evaluating the progress and prognosis of the

disease.

Most researches on hypertension configuration adopt the Ganau classification, and evaluation of left ventricular hypertrophy ultrasonic technology in hypertension guidelines is also based on this classification standard. However, the reference values in this classification standard, including left ventricular mass index (LVMI) and relative wall thickness (RWT), are from European and American populations. It is not clear whether the criteria for defining the type of left ventricular remodeling is suitable for the Chinese population, and whether this classification method has an impact on the constituent ratio of left ventricular remodeling types. As we all know, the normal value of left ventricular mass (LVM) varies with gender, race, age, height and weight. Now body surface area (BSA) is usually used for index, but always over corrected. The international reference standard for left ventricular configuration recommended in the 2015 ASE/EACVI guidelines for quantitative measurement of adult heart echocardiography, in which the left ventricular mass is indexed by BSA, and its abnormal threshold is LVMI>115g/m2 (male) or LVMI>95g/m ² (female). The newly issued hypertension management guidelines in 2018 mentioned that $height^{2.7}$ should be used to calibrate LVM to define left ventricular hypertrophy, and its abnormal threshold is>50 $g/m^{2.7}$ (male) or>47 $g/m^{2.7}$ (female). The two different index methods affecting the configuration distribution characteristics remains to be determined. Recent studies have found that the normal reference values of the echocardiographic parameters from Chinese and Western people are different. With the normal reference values of echocardiographic parameters in the Study of Echocardiographic Measurements for Normal Chinese Han Adults (EMINCA Study), LVM was indexed by the two above indexed methods, to speculate that the range of normal reference values of LVMI and RWT, the indicators for Ganau classification, were different from those recommended in previous European and American guidelines, and the distribution of hypertension configurations was also different, as well as in WASE study.

Persistent hemodynamic overload in patients with hypertension will not only lead to myocardial remodeling and ventricular and atrial remodeling, but also seriously damage the function of ventricle and atrium. The early cardiac damage in patients with

hypertension is mainly manifested as left ventricular hypertrophy, left atrial enlargement and other remodeling phenomena. With long-term high blood pressure, myocardial fibers will increase thickness, which will lead to reduction of myocardial compliance, increase of left ventricular filling pressure, and damage the diastolic function of the heart. When the left ventricular hypertrophy caused by long-term high blood pressure exceeds the compensatory threshold of the heart, it will inhibit the pumping function of the heart and reduce the contractility of the myocardium. When the disease continues to progress, it will even cause the continuous expansion of the heart cavity, increase of the tension of the ventricular wall and cause heart failure with reduced systolic function. Except for LVEF, the global longitudinal strain (GLS) of the left ventricle is more sensitive to the early damage of the left ventricular myocardium and has predictive value, which is widely concerned by people. LVGLS is affected by the wall shear stress, myocardial ischemia and myocardial fibrosis. Recently some studies have found that the increase of left ventricular afterload is significantly related to the decrease of GLS. Myocardial work (MW), a new indicator of the combination of GLS and cardiac afterload, can reflect the changes of the heart at the early stage of many diseases including assessing the systolic capacity of the heart and reflecting the remodeling of the left ventricle. With the construction and analysis of left ventricular pressure volume loop (PSL), we can get the global work index (GWI), global constructive work (GCW), global wasted work (GWW) and global work efficiency (GWE) of myocardium. Therefore, the index of myocardial work can provide us with more information about ventricular remodeling and afterload changes, which is helpful for us to evaluate the left ventricular remodeling caused by afterload changes.

Echocardiography is a commonly used clinical examination method， with ease of operation, safety, non-invasive, real-time imaging, strong repeatability, low cost and so on, which is widely used to evaluate the structure and function of the heart and cardiac hemodynamics. Framingham et al. found that there is a strong correlation between LVM detected by echocardiography and the incidence rate and mortality of cardiovascular diseases, and LVM is also the most commonly used tool for clinical diagnosis of left

ventricular diastolic dysfunction (LVDD).

The LVM and LAV derived from the normal value data of Chinese healthy adults have been reported to be different from the recommended reference values in guidelines, and the distribution characteristics of hypertension remodeling are also different. However, this difference still lacks of large multi-center research to further confirm it. Meanwhile, the characteristics and outcomes of cardiac remodeling in Chinese hypertensive population and whether this difference in configuration has an impact on the treatment, prognosis and cardiovascular events of hypertensive population are still needed to be explored.

OBJECTIVES:

This study was to observe the relationship between blood pressure and cardiovascular remodeling evaluated by different standards in hypertensive population; to compare the relationship between different cardiac configurations and cardiovascular events in Chinese hypertensive population.

RESEARCH DESIGN

Studies have shown that different configurations of left ventricle and left atrial enlargement in hypertensive patients can predict the occurrence of cardiovascular events. The standards of left ventricular remodeling and left atrial enlargement based on European and American populations may not be applicable to Chinese populations. This study was a multicenter study to verify different left ventricular remodeling in Chinese hypertensive population, and explore the influence of different left ventricular remodeling standards on the treatment options and prognosis.

Participant:

Participants with essential hypertension and healthy volunteers in the outpatient and hospital in research centers.

Groups:

Healthy volunteers: volunteers without chronic disease history such as hypertension, diabetes, coronary heart disease, cerebrovascular disease, and transthoracic echocardiography showed normal cardiac structure and function.

Hypertensions: grouped with ultrasonic cardiogram parameters (including LVMI, RWT and LAVI)

(1) Left ventricle remodeling groups:

2015 ASE/EACVI guideline standard:

Normal left ventricular geometry, NG: LVMI≤115g/m^2（male）or LVMI≤95g/m^2（female）and RWT≤0.42

Concentric remodeling, CR: LVMI≤115g/m^2（male）or LVMI≤95g/ m^2（female）and RWT>0.42

Eccentric hypertrophy, EH: LVMI>115g/ m^2（male）or LVMI>95g/ m^2（female）and RWT≤0.42

Concentric hypertrophy, CH: LVMI>115g/ m^2（male）or LVMI>95g/ m2（female）and RWT>0.42

Reference Values for Chinese (EMINCA) and Configuration Analysis Based on Ganau Typing:

Normal left ventricular geometry, NG: LVMI≤108g/ m^2（male）and RWT≤0.51 or LVMI≤99g/ m^2（female）and RWT>0.49

Concentric remodeling, CR: LVMI≤108g/ m^2（male）and RWT>0.51 or LVMI≤99g/ m^2（female）and RWT>0.49

Eccentric hypertrophy, EH: LVMI>108g/ m^2（male）and RWT≤0.51or LVMI>99g/ m^2（female）and RWT≤0.49

Concentric hypertrophy, CH: LVMI>108g/ m^2（male）and RWT>0.51 or LVMI>99g/ m^2（female）and RWT>0.49

(2) Left atrium remodeling groups:

2015 ASE/EACVI guideline standard:

Left atrium enlargement groups: LAVI>34ml/m^2（male, female）

Reference Values for Chinese (EMINCA) with BSA indexed:

Left atrium enlargement groups: LAVI>34.3ml/m^2 (male) or LAVI>35.5ml/m^2

(female)

Inclusion criteria for hypertension:

(1) Age 30-75 years old;
(2) No antihypertensive drugs were used and three blood pressure measurements were conducted on different days, with systolic blood pressure ≥ 140 mmHg (1 mmHg=0.133 kPa) and/or diastolic blood pressure ≥ 90 mmHg; or have a history of hypertension and are using antihypertensive drugs, even if the blood pressure is lower than 140/90 mmHg;
(3) Left ventricular ejection fraction was normal (LVEF ≥ 0.5).
(4) All patients agreed to participate in the experiment and signed the informed consent form.

Exclusion criteria for hypertension:

(1) Secondary hypertension caused by renal parenchymal diseases, renal vascular diseases, coarctation of aorta and endocrine system diseases;
(2) Severe cardiovascular and cerebrovascular diseases; heart valve disease; persistent atrial fibrillation and severe arrhythmia; previously undergone cardiovascular disease surgery;
(3) Abnormal liver function; abnormal renal function and diabetes;
(4) Pregnant or breastfeeding women;
(5) Expected survival time due to non-cardiovascular disease<4 years;
(6) Patients with poor echocardiographic image quality.

EFFICACY ASSESSMENT

Primary study endpoints: emerging atrial fibrillation, transient ischemic attack (TIA) or stroke, unstable angina, myocardial infarction, heart failure, coronary revascularization, cardiovascular death;

Secondary study endpoints: decreased cardiac function with preserved ejection fraction; new cardiac remodeling; aortic aneurysm or aortic dissection; ECG showed that QTc (QT interval corrected by heart rate) was more than 500ms or QTc was longer than the baseline level for more than 60ms, emerging torsade de pointes ventricular tachycardia and other serious arrhythmias; the relationship between the deviations of blood pressure within the same day and the difference of cardiac function indexes.

RESEARCH PLAN

Estimation of Sample Size

Use PASS 11.0.7 software, bilateral inspections, $\alpha = 0.05$, with the incidence rate of cardiovascular adverse events in the left ventricular hypertrophy group was 4.9%, and the incidence rate of cardiovascular adverse events in the left ventricular non-hypertrophy group was 2.2%, at least 986 hypertensive patients were included in the left ventricular hypertrophy group and the left ventricular non hypertrophy group, respectively. Considering the 10% loss rate, at least 1085 patients were included. With 20 research centers, we planned to collect at least 110 patients with hypertension (including 55 patients in left ventricular hypertrophy group and 55 patients in left ventricular non hypertrophy group), 5-10 healthy volunteers (aged 30-60 years) in each center. Then 2200 patients with hypertension in total, and 100 healthy volunteers will be selected in this study.

The main test indicators in the selection and follow-up period

(1) Clinical data

1) Demographic characteristics: name, hospitalization number/outpatient number, gender, age, nationality, occupation, address, postal code, telephone number;

2) Baseline clinical data: blood pressure, body mass index, smoking history, drinking history, medication history, family history (smoking is defined as continuous or

cumulative smoking for 6 months or more in a lifetime);

3) Routine physical examination;

4) Medication history: antihypertensive drugs, statins, aspirin, etc.

(2) Accessory examination

1) ECG examination: use resting ECG to evaluate arrhythmia and ST-T changes, etc.

2）Laboratory tests:

Fasting for more than 6 hours, blood routine, urine routine, fasting blood glucose, alanine aminotransferase, aspartate aminotransferase, blood urea nitrogen, creatinine, plasma total cholesterol, triglyceride, low-density lipoprotein cholesterol, high-density lipid Protein cholesterol, high-sensitivity C-reactive protein, prothrombin time, serum troponin, NT-proBNP.

3）Transthoracic echocardiography:

Two-dimensional dynamic images of left ventricular parasternal long axis, apical four-chamber heart, apical two-chamber heart, apical long axis, left ventricular apex level, papillary muscle level, and mitral valve level short-axis view; measure left ventricular ejection fraction (LVEF); Pulse wave Doppler was used to obtain the diastolic mitral valve orifice blood flow spectrum, and tissue Doppler was used to obtain the mitral valve annulus motion spectrum, and E/e' was calculated; Using speckle tracking imaging (STI) ultrasound technology to measure global longitudinal strain (GLS)/strain rate, global circumferential strain, global radial strain, global area strain (3D-GAS), left ventricular torsion, left ventricular rotation/untwisting speed, systolic dissynchrony index (SDI) and right ventricular free wall systolic peak strain (RVFWS) and so on.

4）Carotid ultrasound examination: the patient was the occipital supine position, with slightly raised jaw, the face was turned to one side, and the sternocleidomastoid muscle was fully exposed. The probe scans from the posterior edge of the sternocleidomastoid muscle to display the long axis and short axis images of the common carotid artery, internal and external carotid arteries, and bifurcation. The intima-media thickness, internal diameter and blood flow velocity were measured at 1-2 cm before the

bifurcation of the common carotid artery.

(3) The main observation and detection indicators of the first follow-up

Hypertensions will be followed up in the 12th, 24th, 36th and 48th months after being enrolled in this study. They can be followed up through outpatient service or telephone. Each follow-up shall not exceed two weeks before and after the specified follow-up time. Perform physical examination, ECG examination, laboratory examination, echocardiography, etc. Record the treatment and whether there are adverse cardiovascular clinical events (myocardial infarction, heart failure, cardiovascular death, unstable angina requiring hospitalization, aortic aneurysm or aortic dissection, stroke). Record the time when the adverse event occurred.

Standard operation procedure of echocardiography and carotid ultrasound

(1) Personnel requirements:

The ultrasonic inspection personnel must be trained and have the qualification certificate to undertake the ultrasonic inspection of the research project. One or two ultrasonic examiners in the same research center will be fixed to participate in this study. All data shall be stored by DVD or hard disk in DICOM format. Each patient is a folder, including each image acquisition time and operator. The image information is sent by the person in charge of each center to the central laboratory via email for summary and storage, and then measured by two experienced ultrasound physicians through offline analysis software. Each data is measured three times and averaged data are stored. The data with poor image quality will be reviewed by professionals, analyzed repeatedly, and finally decided whether to use.

(2) Application of cardiac and carotid ultrasound probe

Probe models: S5-1, M5Sc, X5-1, 4D, PLI-2004BX; instrument models: Philips EPIQ7C, GE vivid E95 and Canon-Toshiba Ultrasound. The image display, storage and measurement modes will be uniformly preset by Philips, GE and Canon-Toshiba 's professional clinical doctors.

(3) Echocardiographic and carotid examination process

1) Use the standardized section specified in the ASE/EACVI guidelines to perform routine echocardiography and save the image (in DICOM format);

2) Connect ECG and record dynamic images (frame rate>40fps) of at least 5 cardiac cycles to ensure clear images (endocardium) and complete images (including epicardium); adjust the frame rate to 40% of the subject's heart rate;

3) M-mode images: M-mode images were recorded at the level of the chordae tendineae of the parasternal left ventricle in the long axis section, and the systolic displacement of the tricuspid annulus plane at the lateral wall of the tricuspid annulus was recorded at the apical four chamber section (TAPSE);

4) Two dimensional images: dynamic images were recorded and stored on the parasternal left ventricular long axis section, the parasternal left ventricular short axis section (mitral annulus level, papillary muscle level, apex level), the apical two chamber section, the apical three chamber section, the apical four chamber section, and the focused right ventricular four chamber section respectively;

5) Pulse Doppler image: mitral diastolic blood flow spectrum, tricuspid diastolic blood flow spectrum, aortic systolic blood flow spectrum and pulmonary systolic blood flow spectrum were recorded respectively;

6) Tissue Doppler images: TDI dynamic images were recorded in apical four chamber view; Pulsed tissue doppler images of mitral annular septum/lateral wall and tricuspid lateral wall were recorded on apical four chamber view;

7) 3D image: full volume imaging mode of Philips system: use the transthoracic real-time 3D probe X5-1 to collect images to ensure good connection of ECG signals. The four-chamber view of the left ventricular chamber fully displayed/the four-chamber view of the left atrium gathered/the four-chamber view of the right ventricle focused can be obtained on the apical view. Adjust the frame rate to more than 30 frames/second. Touch the Full Volume and rotate the 3D Opt key to the 4Beat position, Instruct the patient to hold his breath at the end of breath, press the Acquire button on the operation panel, and obtain the full volume information of the left ventricle (if EpiQ7c used, the Heart Model image will be retained after obtaining the ideal section). Four dimensional imaging mode of GE system: after entering the 4D mode, ensure that the ECG signal is

well connected, obtain four-chamber view images that fully display the left ventricular cavity/four-chamber view images that focus on the left atrium/four-chamber view images that focus on the right ventricle on the apical view, adjust the number of cardiac cycles (4-6 cardiac cycles), make the image frame rate meet the requirements (the image frame rate is required to be more than 40% of the subject's heart rate), instruct the patient to hold his breath after deep breath, Stabilize the probe and view the "splicing" artifacts in the volume reconstruction and front plane in the lower left window of the screen, or use Multi-Slice to evaluate the suture quality. If no artifacts are seen in several cardiac cycles, press Freeze. You can collect multiple cardiac cycles and then use the Cycle select control to select the best cycle. Press Img. on the operation panel Store saves the collected images.

8) Carotid image: adjust the position of probe to adjust with the targeted vessel straightly, and start the VFM program to collect the original data. After the images are collected, the data are further analyzed and processed using the online software of the machine. Trace the blood flow and the vascular wall at the junction of the vascular wall on the frame image of the cardiac cycle which the blood flow was fullest, and then run the software to automatically track the trace points and calculate the shear force at the corresponding position. To check the range shown at the edge of the screen and the automatic calculation results, and calibrate the calculation deviation caused by aliasing frame. Then the shear stress values of each cardiac cycle of this segment of blood vessel can be obtained.

Echocardiographic and carotid measurement parameters

(1) M-mode and two-dimensional ultrasonic parameters:

1) Left ventricular end-diastolic diameter (LVEDD), left ventricular end-systolic diameter, left ventricular long diameter at end-diastolic, left ventricular basal transverse diameter and left ventricular middle transverse diameter;

2) End-diastolic ventricular septal thickness (IVSTd), end-diastolic left ventricular posterior wall thickness (LVPWTd);

3) Left atrial antero-posterior diameter, left atrial long diameter, left atrial transverse diameter, left atrial area and left atrial volume at end-systolic (Simpson method);

4) The antero-posterior diameter of right ventricle, the transverse diameter of right ventricular basal segment, the transverse diameter of right ventricular middle segment and the long diameter of right ventricle at end-diastolic;

5) The parasternal, proximal and distal diameters of the right ventricular outflow tract;

6) Right atrial long diameter, right atrial transverse diameter, right atrial area and right atrial volume at end-systolic (Simpson method);

7) The middle systolic aortic annulus diameter, the end-diastolic aortic sinus diameter, the end-diastolic aortic sinus tube junction diameter and the end-diastolic ascending aorta diameter;

8) Left ventricular end diastolic volume, end-systolic volume and ejection fraction were measured by Simpson method in apical four-chamber view;

9) TAPSE;

10) RVFAC;

(2) Doppler ultrasound parameters:

1) Deceleration time EDT of mitral valve E peak, A peak, E/A peak and E peak;

2) s', e 'and a' at the interventricular septum of mitral annulus;

3) s', e 'and a' at the lateral wall of mitral annulus;

4) E peak and A peak of tricuspid valve;

5) s', e ', a' at the lateral wall of tricuspid annulus;

6) Left ventricular Tei index: the ratio of the sum of left ventricular isovolumic systolic time (ICT) and isovolumic diastolic time (IRT) to ejection time (ET);

7) Right ventricular Tei index: the ratio of the sum of right ventricular isovolumic systolic time (ICT) and isovolumic diastolic time (IRT) to ejection time (ET).

(3) Relevant parameters of two-dimensional speckle tracking:

1) Segmental longitudinal strain and strain rate of 17 segments of left ventricular myocardium, and global longitudinal strain and strain rate;

2) Segmental circumferential strain and strain rate, global circumferential strain and strain rate of 17 segments of left ventricular myocardium;

3) Segmental radial strain and strain rate, global radial strain and strain rate of 17 segments of left ventricular myocardium;

4) Left ventricular bottom angular displacement, apex angular displacement, myocardial torsion torque;

5) The longitudinal strain of the intima and adventitia of 17 segments of left ventricular myocardium, and global longitudinal strain of the intima and adventitia;

6) The circumferential strain of the intima and adventitia of 17 segments of left ventricular myocardium, and the circumferential strain of global intima and adventitia;

7) The radial strains of the intima and adventitia of 17 segments of left ventricular myocardium, and global radial strains of the intima and adventitia;

(4) Myocardial work parameters:

According to the patient's blood pressure, left ventricular outflow tract spectral Doppler image, apical four chamber heart, apical two chamber heart, and apical three chamber heart section dynamic images, the pressure strain loop (PSL) is obtained by offline analyzing and calculating with Echopac software. Then the global work index (GWI), global constructive work (GCW), global wasted work (GWW), global work efficiency (GWE) and other indicators are obtained.

(5) The left ventricular remodeling parameters required in this study are calculated from the above obtained ultrasound parameters as follows:

$LVM=0.8\times1.04\times[(IVSTd+LVEDD+LVPWTd)^3 -LVEDD^3] +0.6$

$RWT =(LVPWTd\times2)/LVEDD$

(6) Cardiac morphological changes:

Record whether there is pericardial effusion (small, medium and large) and pericarditis during follow-up, and whether there is mitral valve, tricuspid valve, aortic valve, pulmonary valve and other valve diseases, such as valve sclerosis, stenosis, etc. When each valve has regurgitation or stenosis, note the peak flow rate, peak pressure difference and average pressure difference, especially tricuspid regurgitation;

(7) Three-dimensional ultrasound parameters:

Echopac software and QLAB software were used to analyze the retained three-dimensional images to obtain three-dimensional left ventricular volume parameters,

three-dimensional left ventricular ejection fraction, three-dimensional left ventricular strain, three-dimensional left atrial volume parameters, three-dimensional left atrial strain parameters, three-dimensional right ventricular volume parameters.

(8) Carotid ultrasound parameters:

Diameters, blood flow velocities and plaques and shear force strains of the common carotid artery, internal and external carotid arteries, and bifurcation.

(9) Development of artificial intelligence analysis software:

Using the images of hypertensive population collected by the project, we would measure, analyze and calculate to collect the two-dimensional, three-dimensional, Doppler, strain, work and remodeling parameters of hypertension. Combining with the artificial intelligence technology, we will establish an ultrasonic data bank of Chinese hypertensive population. Meanwhile, we will compare the data with the EMINCA database of Chinese healthy adults, and use machine learning methods to build an artificial intelligence measurement module. The combination of ultrasonic dynamic image and neural network algorithm can achieve the rapid, dynamic and real-time evaluation of the cardiac structure and function of hypertension, automatically measure and identify normal and abnormal thresholds, and help hypertensions get more accurate diagnosis, evaluation and treatment.

DIAGRAM OF RESEARCH SCHEME

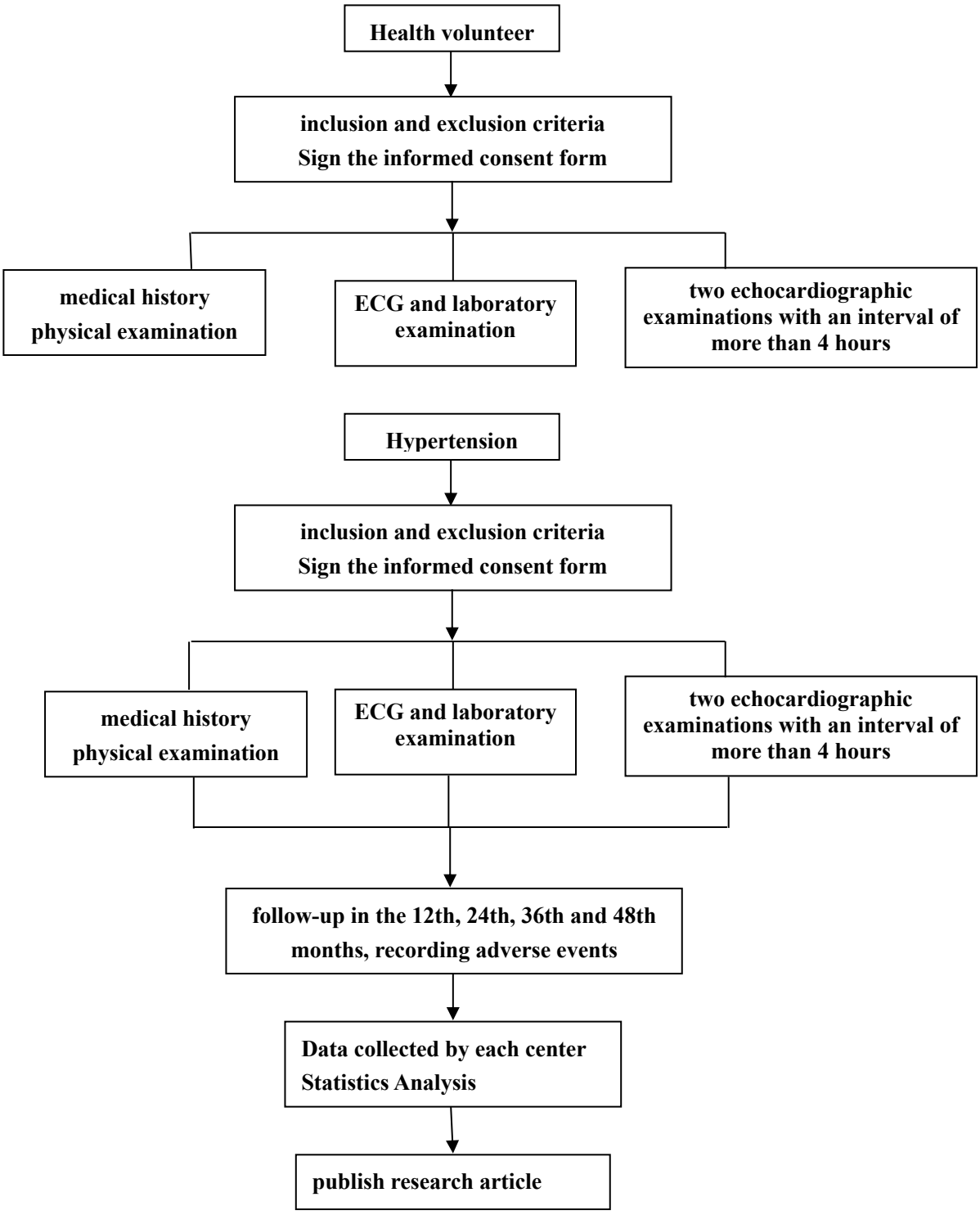
Health volunteer
inclusion and exclusion criteria
Sign the informed consent form
medical history
physical examination
ECG and laboratory examination
two echocardiographic examinations with an interval of more than 4 hours
Hypertension
inclusion and exclusion criteria
Sign the informed consent form
medical history
physical examination
ECG and laboratory examination
two echocardiographic examinations with an interval of more than 4 hours
follow-up in the 12th, 24th, 36th and 48th months, recording adverse events
Data collected by each center
Statistics Analysis
publish research article

CHART OF RESEARCH SCHEME

Follow-up time	**0 month**	**12th month**	**24th month**	**36th month**	**48th month**
Information	●				
Medical history	●				
Inclusion Criteria	●				
Informed consent	●				
Electrocardiogram	●	●	●	●	●
Physical examination	●	●	●	●	●
Laboratory examination	●				
Echocardiography	●		●		●
Arterial ultrasound	●		●		●
Drugs treatments	●	●	●	●	●
Adverse events		●	●	●	●

ETHICS

(1) In the process of clinical research, the personal rights and interests of the subjects must be fully guaranteed, and the reliability of the research must be ensured. The rights, safety and health of subjects must be higher than the consideration of scientific and social interests.

(2) The research scheme can only be implemented after being reviewed, agreed and signed by the Ethics Committee. During the study, any modification of the study protocol shall be approved by the Ethics Committee.

(3) The investigator or its designated representative must explain the details of the clinical study to the subject, and obtain the informed consent after fully explained the study.

(4) Informed consent of the subject (see the Informed Consent Form for details).

Before each patient is enrolled in this study, the physician has the responsibility to completely and comprehensively introduce the purpose, procedure, possible benefits and risks of this study to him or his designated representative in written form. Patients should be made aware of their right to withdraw from the study at any time. Before enrollment, each patient must be given a written informed consent form (included in the protocol in the form of appendix) so that the subject can understand and agree. Only after signing the informed consent form voluntarily, they could be included in the clinical trial. The informed consent form will be kept as one of the original data of the clinical trial for future reference.

ELECTRONIC DATA MANAGEMENT (eCDM)

This test adopts the electronic data management system (DAS for eCDM).

(1) Construction of electronic case report form (eCRF): the data administrator constructs eCRF according to the research scheme and research medical record.

(2) Permission allocation: The data administrator creates accounts and grants different permissions to access eCDM according to different identities of main research center, supervisor, inspector, etc. If the researchers in each center can only see the contents of the center and have the right to modify the data, the main research centers are limited to browsing all cases; The monitors and auditors can read the case information of each center, but they have no authority to modify the data, but they can insert comments or questions.

(3) Data entry: clinical investigators or data entry personnel designated by researchers

timely and accurately enter the data in the study medical records into eCRF. eCRF is not used as the original record, and its content is derived from the "study medical record".

(4) Data questions and answers: The supervisor conducts the audit through eCDM, and raises questions online at any time when problems are found. The researcher will answer the questions online, correct the wrong data, and if necessary, the supervisor can repeat the questions.

(5) Data locking and export: after each subject completes the test and is checked by the supervisor, the data administrator will lock the data until the last subject's data is locked. After all the data are locked, the data administrator will import them into the designated database and submit them to the statisticians for statistical analysis.

6. After the study ends, eCRF was printed and archived as required. The data management center will keep the electronic data until 5 years. During this period, if SFDA needs to audit, the data management center can open the system at any time after making an appointment.

STATISTICAL TREATMENT

(1) Analysis data set

Full analysis set (FAS): the patient enrolled according to the principle of Intention To Treat (ITT), and the data composed of all enrolled hypertensive patients. The patients who failed to observe adverse cardiovascular and cerebrovascular events were treated as deletion and carried outsides in the last follow-up date.

PPS: refers to the cases that meet the inclusion criteria but do not meet the exclusion criteria, and the cases that meet the test protocol and complete the CRF requirements are analyzed (PP analysis).

(2) Statistical methods

Demographic Analysis

1) Measurement data: mean, standard deviation, median, maximum, minimum and quartile are used for description;

2) Counting data: described by frequency and composition ratio.

(3) Group analysis:

1) For the healthy volunteers and hypertensive patients enrolled in the group: between 9:00

a.m. and 17:00 p.m. on the day of enrollment, at an interval of more than 4 hours, the patients performed two echocardiographic examinations in a calm state, measured and recorded their blood pressure at the same time (three measurements at an interval of 1-2 minutes), and measured the indicators at the two baseline levels on the day of enrollment. The changes of left ventricular global longitudial strain (GLS) and myocardial work (MW) in hypertension and healthy volunteer were compared, and the correlation between them and the changes of blood pressure was analyzed;

2) Analysis for hypertensive patients with different left ventricular configurations: configuration analysis was conducted based on the left ventricular remodeling standards recommended by ASE/EACVI 2015 guidelines and the EMINCA study combined with Ganau classification. Hypertensive patients were divided into normal left ventricular configuration group, left ventricular remodeling group, left ventricular eccentric hypertrophy group and left ventricular concentric hypertrophy group. Baseline, 12months, 24months, 36months and 48months echocardiography images were recorded and analyzed, compared the cardiac structure and functional indicators, and recorded clinical adverse events;

(2) Analysis for hypertensive patients with different left atrial configurations: according to the abnormal threshold of left atrial enlargement recommended by ASE/EACVI 2015 guidelines and the standard of Chinese left atrial enlargement recommended by EMNICA study, hypertensive patients were divided into normal left atrial group and left atrial enlargement group. Baseline, 12months, 24months, 36months and 48months echocardiography images were recorded and analyzed, compared the cardiac structure and functional indicators, and recorded clinical adverse events.

(4) Analysis of main endpoint events:

1) Cox regression was used to analyze the predictive value of different types of left ventricular remodeling and left atrial enlargement on adverse cardiovascular events. ROC analysis was used to compare the incremental effect of left ventricular remodeling, left ventricular hypertrophy and left atrial enlargement on the predictive ability of hypertensive cardiovascular events; NRI [net corrected classification, i.e. (new sensitivity + new specificity) - (old sensitivity + old specificity)] was used to evaluate and compare the ability

of left ventricular remodeling, left ventricular hypertrophy and left atrial enlargement to re stratify and optimize the risk of cardiovascular events in hypertension. Multivariate regression analysis was used to analyze the factors affecting left ventricular remodeling and left atrial enlargement in hypertension.

2) The incidence time of adverse cardiovascular events was stratified by left ventricular remodeling, left ventricular hypertrophy and left atrial enlargement. Cox regression analysis was used to calculate the hazard ratio and its bilateral 95% confidence interval of different influencing factors.

(5) Statistical software: SAS 9.4 or SPSS software was used for analysis. Bilateral tests were used for statistical tests. $P \leq 0.05$ were considered statistically significant.

(6) Interim analysis: No interim analysis will be conducted in this study. If special cases occur, the main research center, researchers and statistical experts will discuss and decide.

QUALITY CONTROL

(1) The main research centers and researchers perform their duties, strictly follow the clinical research scheme, adopt standard operating procedures, and verify all relevant observations and findings to ensure the implementation of the quality control and quality assurance system of the clinical research;

(2) The investigator must provide necessary training for all personnel participating in the clinical study, explain relevant data, operation specifications and responsibilities, and ensure the data truthfully, accurately, completely, timely and legally recorded in the medical records and CRF. CRF must be kept by special person. Participants have project training certificates.

(3) The supervisors dispatched by the main research centers follow the standard operating procedures, supervise the implementation of the research scheme, confirm that all data records and reports are correct and complete, and all CRF are correctly informed and consistent with the original data.

(4) The results were uniformly verified by Qilu Hospital of Shandong University, and analyzed by two professionals. Each analyst repeated the measurements twice a week apart.

(5) Major research centers can entrust auditors to systematically check the activities and documents related to clinical research to evaluate whether the research is conducted in

accordance with the protocol, standard operating procedures and relevant regulations.

(6) All examination data in clinical research must be accurate, and the original or the copy of the report should be pasted on the case report form.

(7) Medical statisticians should include the research data into the report quickly, completely and without error, and all the steps involved in data management should be recorded in order to check the data quality and research implementation.

(8) The statistical analysis process of clinical research data and the expression of its results must adopt standardized statistical methods. Medical statisticians are required to participate in all stages of clinical research. The statistical report of the clinical study must be consistent with the clinical study summary report.

(9) All parties conduct clinical research in accordance with the approved protocol, and any deviation from the protocol should be recorded. The modification of the research scheme should be described and reported to the Ethics Committee for approval before implementation.

RESEARCH PLAN

(1) Case entry stage: from May 2022 to May 2023—complete the entry of each group of cases.

(2) Follow-up time: 48 months. For follow-up time points, please refer to the attached trial procedure.

(3) Data analysis: May 2023 to December 2027—Data collection and analysis, writing papers.

(4) Periodic analysis: summarize the periodic research results and submit them to relevant committees for evaluation.

PAPER PUBLISHING PLAN

After the collection and analysis of case follow-up data, articles will be published on clinical journals in the cardiovascular field in the form of research papers.

The author of the paper is determined according to the researchers' contributions to scheme design, trial implementation and data analysis. The authors of this study are as follows:

Zhang Yun is the first person in charge of the author, other authors are listed in order according to their contributions (number of effective cases collected), and Zhang Yun is the corresponding author. Each participating center can provide 1-2 researchers to be included in the list of researchers. All authors are responsible for improving the scheme, writing the draft and verifying the paper before submitting. The names of the advisory committee, academic committee, data security and supervision committee, clinical event determination committee and other researchers who do not meet the author's qualification will be shown in the "Shandong Hypertension Prevention and Control Researchers" section of the paper attachment. The Data Security and Supervision Committee will review the papers before publication. After the study, each center will use the database for further analysis according to contribution.

The source of funds has no influence on the data processing and analysis and the publication of papers.