Normal Reference Values in Han Adults of Extremity Arterial Structure and hemodynamics by High-frequency Ultrasound: a Multi-center Study in China

(NOVAEA-HFUS Study)

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[Research Background]

The extremity artery is the peripheral blood vessel of the whole body, and it is often involved early in the diseases that are easy to damage the small vessels, such as atherosclerosis and connective tissue diseases. Early lower limb atherosclerosis mainly occurs in the dorsal foot artery, which is commonly seen in people with diabetes and long-term smoking. Connective tissue diseases such as systemic sclerosis and systemic lupus erythematosus also mainly involve small blood vessels, and vascular lesions may appear earlier than those of other specific organs such as heart and lung. Because of its shallow location, the extremity artery can be better used as a screening site for vascular diseases, and it is the window for early reaction of vascular diseases.However, the early stage of extremity artery disease is easy to be ignored, and patients often have pain and numbness of the affected limb. When the disease is severe, it can lead to ulcer not healing, and even limb gangrene and amputation, which greatly affects the quality of life and brings huge troubles and economic pressure to the patients. Therefore, early diagnosis of extremity arterial lesions is of great significance for early diagnosis of microvascular injury diseases such as atherosclerosis and connective tissue diseases, reducing the incidence of complications, and reducing the rate of amputation and mortality.

Ultrasound is a non-invasive imaging technique widely used in clinic. In recent years, with the development of ultrasound technology, the frequency of ultrasonic probes has been increasing. Because of its higher resolution, high-frequency ultrasound can clearly display the superficial vascular structure and blood flow, detect vascular lesions early, and accurately quantify the degree of stenosis, providing a new and beneficial tool for clinical observation of the structure and blood flow of the extremity artery. The purpose of this multi-center clinical study was to establish the normal value of high frequency ultrasound for the structure and blood flow of the extremities of Chinese Han adults, and to explore its influencing factors, so as to provide a quantitative reference for the early diagnosis, degree evaluation and curative effect observation of the structure and blood flow of the extremities.

[Research Objective]

1. To establish the normal values of the structure and hemodynamic parameters of the extremity artery in Chinese Han adults by high-frequency ultrasound;
2. Identify the factors affecting the structure and hemodynamic parameters of the extremity artery.

[Study Protocol]

1. Overall process

This is a prospective multicenter clinical study conducted in the People's Republic of China. The multi-center clinical study method was adopted.

The plan is to start preparatory work, training and other preliminary work in May 2023, and to start implementation in August 2023, for a period of 18 months. The first 12 months are the data collection stage, and the last 6 months are the data analysis and summary stage. Through the sample size calculation, high frequency ultrasound data of the structure and hemodynamic parameters of the extremity arteries of 540 healthy Chinese Han adults were collected for analysis and statistics.

Each participating unit shall provide a registered doctor with experience in ultrasound examination as the person in charge and specific implementer, and conduct centralized training in advance.

Subjects were screened strictly according to clinical manifestations, blood pressure and blood biochemistry. According to the guidelines of Chinese Medical Association for superficial and vascular ultrasound, the images were collected using unified standards, and standardized arterial structure and hemodynamic parameters were measured.

The participating units shall ensure that the relevant data of the candidates shall be recorded in the case report form (CRF) in a true, accurate, complete and timely manner. The CRF is kept by a special person, and the ultrasonic examination results collected by each unit are uniformly verified and analyzed by professionals.

Duration of the study process: It is planned to start in August 2023 and last for 18 months.

2023.08-2024.7 Data collection phase

2024.08-2024.10 Data analysis phase

2024.11-2025.01 Data summary phase

2. Experimental equipment

Canon Aplio i900 ultrasonic diagnostic instrument, image acquisition unified use of PLI-3003BX probe.

3. Research objects

A total of 540 healthy Han Chinese adults were included, 270 male and 270 female.

3.1 Inclusion criteria:

Each volunteer must meet the following criteria to be included in the study:

(1) Han nationality;

(2) Ages 18-79;

(3) Normal blood pressure (139-90/89-60mmHg);

(4) Body mass index < 30 kg/m2;

(5) Blood routine, fasting blood glucose, blood lipid, liver and kidney function, electrocardiogram were normal;

(6) No history of cyanosis of hands and feet, cold stimulation without discomfort, no Raynaud phenomenon has occurred in all parts of the body;

(7) No cardiovascular disease, diabetes, rheumatic connective tissue disease, serious liver and kidney dysfunction;

(8) No history of drug use affecting cardiovascular system.

3.2 Exclusion criteria：

(1) Patients with hypertension, diabetes, hyperthyroidism, arrhythmia and other diseases;

(2) Patients with systemic lupus erythematosus, polymyositis, rheumatoid arthritis and other connective tissue diseases;

(3) A history of related blood diseases;

(4) Have taken vasoconstrictor drugs in the past 1 month;

(5) Gangrene of fingers and toes or history of trauma or surgery;

(6) Have a history of handicraft, hammering, digging and other related work;

(7) Have a long history of smoking and drinking;

(8) Peripheral vascular disease, arterial occlusion can not detect blood flow signal;

(9) Unable to cooperate with the examiner.

4. Eligibility of subjects

Subjects are required to meet all inclusion criteria without any exclusion criteria and sign an informed consent form. In addition, the subjects are required to provide copies of blood routine, liver function, kidney function, blood glucose, blood lipids, electrocardiogram and other reports within the past 3 months.

5. Confidentiality of subject information

The personal information of all cases will be hidden to ensure the privacy of the subjects.

[Quality control]

1. Initial qualification of researchers

(1) All participants should have at least 1 year of relevant ultrasound experience and have performed at least 100 vascular ultrasound examinations.

(2) All participating centers are required to have a Canon Aplio i900 ultrasonic diagnostic instrument equipped with a PLI-3003BX probe.

(3) All participating researchers are required to follow the same skin ultrasound reporting principles, i.e. standard sampling sites and measurement methods.

2. Training

(1) Intensive training: mainly includes basic operation, collection position, quality control methods, influencing factors, and understanding of case report form (CRF) and reporting tools.

(2) After centralized training, each sub-center should complete:

Standard mode presets: according to the requirements of inspection mode in centralized training, standardized presets are made for parameters such as two-dimensional gray scale image, color Doppler image and spectral Doppler image.

Image acquisition quality control: Complete the collection of 2 cases according to the standardized collection process, and upload all materials.

Case collection form quality control: Upload the data information of the above 2 cases according to the standard CRF form filling and submission process. The information will be reviewed by PI. If there is any non-compliance with the regulations, PI will give modification suggestions. Normal image collection can be carried out only after all materials of the 2 cases meet the qualification standards.

3. Quality control standards of member institutions

If the following circumstances occur and are confirmed by PI assessment, you will automatically withdraw from this study:

The research institution fails to pass the qualification examination; Researchers who fail to pass the qualification examination; Each research center must submit more than the specified number of cases per month, if it cannot provide them on time; The proportion of sample shedding (including unqualified case images, untrue case data collection, failure to complete and submit forms in time, etc.) should be controlled within 20%. If the sample drop rate exceeds 20%, the PI assessment will give a reminder, warning, and withdrawal from the study.

The head of the main research unit and the investigator should perform their respective duties, strictly follow the clinical study protocol, use standard operating procedures, and verify all measurement results to ensure the quality control of clinical studies and the implementation of quality assurance systems.

[Risk pre-assessment and disposal plan]

Pre-risk assessment: Medical ultrasound imaging systems have been proven to be one of the safest imaging devices and have been used in daily care. Ultrasonic non-invasive, no ionizing radiation. Therefore, the likelihood that the

subject will be at risk from the ultrasound is almost zero.

Subject safety: According to the purpose of the study, the ultrasonic safety management in this study followed the ALARA principle (As Low As Reasonably Achievable, the reasonable use of low dose), that is, the lowest ultrasonic energy was used on the basis of available effective data. This study did not use any of the new drugs in the study for intervention.

Helsinki Declaration: The conduct of this research will be guided by the ethical principles of medical research involving human subjects, which was formulated by the Joint General Assembly of the World Medical Associations in 1964 and revised in 1975 (Tokyo), 1983 (Venice), 1989 (Hong Kong), 1996 (West Somerset) and 2000 (Edinburgh).

[Distribution of research results]

1. The research resources, research results and database generated during the research process shall be owned by PI unit. For papers and other theoretical results produced by this research, PI is the corresponding author in principle, the first author is produced by PI unit, and the person in charge of other sub-centers is the author of the paper. The journal may limit the number of authors, according to the order of contribution; If the new addition is selected as a quality control unit, the ranking will move forward, and the remaining signature order will be determined according to the contribution of the sub-center to the case data meeting the requirements.

2. Papers and theoretical results based on the research results of each research center shall be shared by each of them. However, if any relevant papers are published, they should be conducted after the publication of the papers of this multicenter study. Each research center is encouraged to use the single center data of its own sub-center to publish papers or submit relevant results.

3. If each research center needs to use multi-center case data for research, it needs to apply to PI, and can use it after PI's approval.

4. The patent formed shall be enjoyed by the applicant, and the income from the transfer shall be enjoyed by the applicant. The results of applied

research, such as the clinical protocols developed, are shared by all participating research centers.

5. When applying for the national incentive results of this research, one PI unit: the First Affiliated Hospital of China Medical University will be the first applicant, and the research leader will be the first applicant.

6. Research centers are encouraged to apply for other levels of awards, and are obliged to apply and explain to PI in advance if they need to use the case data content of multi-center studies.

[Project management scheme]

1. Researchers and research management structures

Each clinical investigator is responsible for conducting the study in accordance with protocol, all applicable laws, regulations, and ICH Guidelines (GCP).

2. Ethics Committee approval

The PI Unit investigator is responsible for ensuring that all aspects of the ethics review are conducted in accordance with the current guidelines of the Commission and/or in accordance with local and regional laws (to the extent that maximum protection is provided to study subjects). The protocol and any information provided to subjects to obtain informed consent (including written ICFs, subject recruitment procedures [such as advertisements] and written information [such as information leaflets]) must be reviewed and approved by a qualified EC prior to subject enrollment. Prior to inclusion, the responsible person must receive the EC's approval of the study/proposal.

Amendments to the protocol and amendments to informed consent must also be submitted to the EC for approval before they are implemented by the Research Centre.

The investigator must provide the EC with a progress report at the time interval required by the EC and re-evaluate and approve the study as required. Copies of progress reports and study re-approval documents must be sent to the responsible person.

After the completion or termination of the study, the investigator must submit a final report to the EC and send a copy of this report to the responsible person.

3. Ethics

This study will be conducted using guidelines designed to protect the rights and well-being of human subjects participating in biomedical research, in compliance with all applicable national or local EC audit and informed consent requirements.

4. Patient information and informed consent

Informed consent must be obtained before each patient is enrolled in the study, and the requirements specified in the NHFPC guidelines, health regulations, and/or local regulations must be complied with (whichever provides the greatest degree of protection). Written and oral information describing the nature and duration of the study must be provided to each patient in an understandable manner. In addition, patients must be given sufficient time to consider the potential risks and benefits associated with participating in the study. The informed consent must also contain language that allows the responsible person (or designated representative), the regulatory authority and the EC to have direct access to the patient's medical records for review.

Informed consent forms must be signed and dated by the patient. The ICF must also be signed and dated by the person who obtained the informed consent. As part of the study documentation, the investigator must retain a signed and dated ICF and must provide a copy to each subject or their authorized representative.

Subjects have the right to withdraw from the study at any time during the study.

5. Confidentiality of subject information

Affirms and supports the principle that subjects have the right to privacy protection. During the study period and during all data analysis, all subjects' data will be identified by subject identification number and initials only.