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(619 649 400)
Level 10
50 Clarence Street
SYDNEY NSW 2000
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Cardiovascular Reviews

Focus and Scope

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BIO-BYWORD SCIENTIFIC PUBLISHING PTY LTD
Level 10
50 Clarence Street
Sydney NSW 2000
Website: www.bbwpublisher.com
Email: info@bbwpublisher.com

2026, Volume 4, Issue 3

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Cardiovascular Reviews, 2026, Volume 4, Issue 3
https://bbwpublisher.com/journal/CR
Online ISSN: 2981-8109
Print ISSN: 3083-4880

Metformin Improves Myocardial Fibrosis in Spontaneously Hypertensive Rats via the TGF-β/Smads Signaling Pathway

Hong Zhao*, Wenfei Zhao, Qian Jin, Cong Wang

North China University of Science and Technology Affiliated Hospital, Tangshan 063000, Hebei, China

Author to whom correspondence should be addressed.

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Abstract: *Objective:* Effects of metformin on myocardial fibrosis in spontaneously hypertensive rats. *Method:* Twenty spontaneously hypertensive rats (SHR) were randomly divided into a model group and a metformin treatment group, with 10 rats in each group. The control group consisted of 8 Wistar-Kyoto (WKY) rats. In the treatment group, metformin was administered intragastrically for six months at a dose of 100 mg/kg /d, and the rats were fed a high-fat, high-sugar diet. The model group and the control group were administered gastric irrigation with the same amount of physiological saline. During the period, body weight was monitored every week, and blood pressure was recorded every seven weeks. Echocardiography was performed before sampling. The heart tissue of rats was taken, and a part of the heart tissue was fixed in formalin. The paraffin wax embedding method was used. Sirius red staining of pathological sections was performed to observe myocardial cells and calculate myocardial collagen volume fraction (CVF). In the other part of the heart tissue, TGF-β1, Smad2, Smad3, and Smad7 proteins were analyzed by Western blotting. *Results:* In the statistical comparative analysis of SBP, DBP, MBP, HR, SV, aortic blood flow velocity, pulmonary artery flow velocity, and mitral blood flow velocity in the metformin group, there was no significant difference between the treatment group and the SHR group. However, metformin intervention in SHR significantly improved EF, FS, heart weight, myocardial fibrosis, and myocardial cell hypertrophy. In the comparison map of FS, EF, and heart weight, there were significant differences between the metformin group and the SHR group. EF and FS of hypertensive rats were significantly lower than those of healthy rats, and SHR rats in the metformin treatment group were significantly higher than those in the model group. It can be seen from the comparison results of cardiac weight and pathological sections that metformin inhibits hypertension-induced myocardial hypertrophy, cardiac mass gain, and myocardial fibrosis. Western Blot results show that metformin can inhibit TGF-β / Smads signaling pathway. *Conclusion:* Metformin ameliorates hypertension-induced myocardial fibrosis in SHR rats by inhibiting TGF-β/Smads signaling pathway.

Keywords: Metformin; SHR; Myocardial fibrosis

Online publication: September 30, 2026

1. Introduction

Chronic hypertension constantly stresses the myocardium, causing cardiomyocytes to grow larger and leading to an uneven mix of proteins called collagen, resulting in damaged myocardial tissue that is unable to function properly during beats, and it is the main source of all the trouble when there is hypertensive heart failure [1]. Transforming growth factor–beta (TGF - β) / Smads signaling pathway plays an important role in the regulation of myocardial collagen synthesis and the fibroproliferative process, with its excessive activation causing myocardial interstitial remodeling [2]. Research has demonstrated that metformin has a protective effect against cardiovascular disease, which has also been confirmed in non-T2DM patients [3]. Metformin can regulate AMPK phosphorylation, which inhibits TGF-β1 expression [4]. Moreover, metformin induces excessive repair damage in cardiomyocyte fibrosis [5]. Smad proteins are the main downstream activating proteins of TGF - β, which affect the proliferation of the extracellular matrix (ECM), such as tissue fibroblasts and collagen [6]. Also, many other studies have found that it actually has some sort of cardioprotective effect, such as lowering, you know, blood sugar levels, but no. But this still does not mean that, if metformin can reduce high blood pressure-caused myocardial cell fibrosis without lowering your hypertension, there isn't any direct evidence from an in vivo experiment done yet to see if metformin could work that way or not. We use Spontaneously Hypertensive Rats (SHR) as our animal model, control group, Hypertension Model group, and metformin intervention group. By using echocardiography, Sirius Red histopathological staining, and Western blotting, we will try to find out how good an impact metformin has on hypertensive myocardial fibrosis, as well as see if it has something to do with the modification of TGF-β / Smad. It aims to provide a non-antihypertensive experimental pharmacological prevention and cure for hypertensive myocardial injury.

2. Materials and methods

2.1. Animal strains

In total, twenty SHR rats and eight WKY rats were utilized. The experimental animals were sourced from Beijing Vital River Laboratory Animal Technology Co., Ltd., Laboratory Animal Production License Number: SCXK (Beijing) 2021-0006. They were male, SPF-grade, and aged 49- 55 days.

2.2. Drugs and reagents

Bristol Myers Squibb makes metformin (Glucophage) in Shanghai, China. Running buffer (Cat. No. P0014B), PVDF membranes, PVDF membrane activation solution (Cat. No. P0021S), and ECL hypersensitive chemiluminescence kit (Cat. No. W0001) were from Beyotime Biotechnology Co., Ltd. Anti-TGF-β1 rabbit polyclonal antibody, Anti-Smad3 recombinant rabbit monoclonal antibody, Anti-β-actin antibody, Anti-Smad2 recombinant rabbit monoclonal antibody, and Anti-Smad7 recombinant rabbit monoclonal antibody all were from HuaAn Biotechnology Co., Ltd.

2.3. Instruments

Color Doppler ultrasound device(Mindray Medical International Limited), Softron's smart BP monitor, Thermo Fisher cold spinning equipment(4 degrees C), LABGIC TH - Mini portable grinding mixer, ChemiScope fluorescence & chemiluminescence imaging setup(Clinx Science).

2.4. Experimental methods

2.4.1. Experimental protocol

The disease in this trial is myocardial fibrosis after hypertension in SHRs—Wistar-Kyoto (WKY) rats: Normal control group. After two weeks of acclimation, feedings would then occur, with all of the rats being ranked based on their current weights in order for them to fit within one specific diet according to strict criteria set via a random assignment process through a number sequence generator system (Random Number Generator) known as complete randomization. The WKY rats do not have any more subgroups; however, the SHR rats were separated into the model group that got no treatment, as well as the group given only metformin through gavage. Blood pressure, echocardiogram, and HE were taken to determine if hypertension was created in the hearts, as we would also observe metformin for heart health. After a 2-week adaptation period, the rats were randomly assigned and treated with their respective dose via gavage for 6 months. Monitor changes in body weight and blood pressure weekly; perform an echocardiogram before collecting the sample. At the end of administration, measure blood pressure again and perform an Echocardiogram again after tissue has been sampled. Heart tissues were obtained for Sirius Red staining and pathological examination; Western blot was carried out for TGF-β1, Smad2, Smad3, and Smad7 protein quantification. Anesthesia with sodium pentobarbital by intraperitoneally injected Echocardiography and tissue collection were done under anesthesia induced by intraperitoneal injection of sodium pentobarbital.

(1) Grouping, drugs, and dosage

Rat grouping is shown below.

Table 1. Experimental grouping and dosage

Group	Rat Strain	Sex	Body Weight	Number (n)	Drug	Dosage
SHR group	SHR	Male	182–215 g	10	Distilled water	Equal volume
Treatment group	SHR	Male	182–215 g	10	Metformin	100 mg/kg/day
Control group	WKY	Male	182–215 g	8	Distilled water	Equal volume

(2) Drugs and administration

- Myocardial fibrosis model group: 10 SHR rats received an equivalent volume of saline as metformin, administered by daily gavage for 6 months.

- Metformin treatment group: 10 SHR rats received metformin at 100 mg/kg/day, administered by daily gavage for 6 months.

- Blank control group: 8 WKY rats received an equivalent volume of saline as metformin, administered by daily gavage for 6 months.

2.4.2. Blood pressure measurement method

Rats that were acquired between 49-55 days of age had 4 weeks of getting used to eating there. The first BP was measured @ 11W of age. The second was measured 7 weeks later, at 18 weeks of age. The third measurement was taken 7 weeks later, at 25 weeks of age.

In this research, blood pressure was taken indirectly from the rats' tail artery by using a non-invasive sensor cuff and a smart sphygmomanometer. The cuff would be used on the tail to block off the flow, then slowly released. Measure them each week, taking three measurements at once on the conscious but minimally stressed animal, and take the mean. This way there won't be any experimental injuries for our rats, and also

it's very simple to carry out; therefore we can do multiple readings over seven-week periods if necessary. However, it does not provide for continual real-time monitoring. Also, the different measurements at various times will have a bit of a difference. And the measuring process might bring about some stress responses too, which might influence our blood pressures. To reduce errors in the experiment, the mean of three consecutive readings is adopted as the blood pressure reading of each session. Each one was measured at one o'clock on their own body when doing those directions which came along with these RBP-1's rat-tail-artery blood-pressure/heart-rates.

Table 2. Blood pressure measurement parameters

Abbreviation	Full Name	Chinese Full Name	Measurement Dates
HR (beats/min)	Heart Rate	心率	21/9/30, 21/11/25, 22/1/18
SBP (mmHg)	Systolic Blood Pressure	收缩压	
DBP (mmHg)	Diastolic Blood Pressure	舒张压	
MBP (mmHg)	Mean Blood Pressure	平均动脉压	

2.4.3. Echocardiography method

After anesthesia, rats were shaved, placed, and fixed in place. Coupling gel was applied around the cardiac area. Echocardiography and other parameters were carried out by medical personnel in the Department of Ultrasound and the related parameter department at North China University of Science and Technology Affiliated Hospital to record the results.

2.4.4. Rat heart collection

Rats were weighed and given a lethal dose of anesthesia via intraperitoneal injection of sodium pentobarbital (0.04 g/kg). The chest was shaved, and animals were held on a foam board by their nails. A thoracotomy was performed to access the heart. Post-extraction, the heart was washed under chilled physiologic saline to wash away the blood inside all the chambers. Blotted dry using filter paper and weighted right then. Then the heart was sectioned across using a scalpel along the coronal plane. Take a part with a full-cut surface & place it within a prearranged fixative liquid (quantity ranging between ten-fold to thirty-fold as compared to the quantity of tissue) designed mainly for preserving its properties before further staining procedure. The second half, after snapping, was quickly frozen in liquid nitrogen and put into -80 degrees freezer for storage before Western blot.

2.4.5. Paraffin sectioning and sirius red staining of rat heart tissue

The heart tissue was immersed in a 4% paraformaldehyde fixative solution overnight, at least 24 h (fixative ratio: 10-30:1 w/v). Tissues were then graded in alcohols as follows: 80% ethanol, 24 h; 95% ethanol, 1 h; 100% ethanol I, 1 h; 100% ethanol II, 10min; xylene I, 30min; xylene II, 30min; soft paraffin, 1 h; hard paraffin, 30min. We embedded the myocardium in paraffin such that the coronal plane was centered on the embedding cassette. We sectioned it using a microtome. We baked the sections for 1 hour at 56°C. We performed Sirius Red staining as follows: paraffin section was deparaffinized with xylene I (30 min), xylene II (30 min), absolute alcohol I (30 min), absolute alcohol II (30 min), 95% ethanol (5 min), 90% ethanol (5 min), 80% ethanol (5 min), 70% ethanol (5 min), distilled water. Mayer's hematoxylin & Sirius Red stain was prepared according to the manufacturer's instructions, and sections were stained as per instructions.

2.4.6. Western blot detection method

(1) Western Blot: A protein immunoblotting technique where certain antibodies find those special bits of stuff (the targets) inside your body or tissue cells. It's an extremely accurate as well as easy way of performing a qualitative and quantitative measure. Detection steps include extracting protein, denaturing it, SDS-PAGE Electropherisis, membrane transfer, immunoreaction, and developing.

(2) Total protein isolation: About 40mg of tissue is placed inside a 1.5 mL centrifuge tube with lysis buffers. To avoid quantification being impacted by proteolytic decay, a blend of protease inhibitors was introduced. The tissue was mashed up, homogenized, and lysed for 20 minutes; then the material was spun. Take supernatants (200μL) from each and transfer them into the next tubes 1.5 ml. Use the BCA method to determine the total protein concentration. Add 50 μL of 5×protein loading buffer to each supernatant. Samples were boiled at 100 degrees Celsius for 5 min to denature completely, storedata-20°C.

(3) SDS - PAGE electrophoresis: The electrophoresis was carried out on ice. The stacking gel was run at 80V for 30 minutes and the separating gel at 120 V for 60 mins.

(4) Membrane transfer: The PVDF membranes were activated by immersion in the activation solution and then soaked in the transfer buffer for 5 min. After gel cutting, protein was transferred onto the PVDF membrane using 110v for 1.5 hours.

(5) Immunoreaction:

Block: On the shaker, the membrane was blocked for 2 hours at RT.

Washing: Membranes were washed 3 times using 1x TBST in a shaking incubator for 10 mins x 3 at RT.

Primary antibody incubation: The membrane was incubated with Anti–TGF–β1 Rabbit Polyclonal Antibody, Anti - Smad3 Recombinant Rabbit Monoclonal Antibody, Anti–Beta Actin antibody, Anti-Smad2 Recombinant Rabbit Monoclonal Antibody, and Anti - Smad7 Recombinant Rabbit Monoclonal Antibody.

Washing: Same as step (2).

Secondary antibody incubation was done at RT for an hour, and half of the secondary antibodies were diluted 1:5000 with TBST; after the incubation, membranes were washed with TBST, shaking at RT, for another 3 times of 10 minutes each.

A chemiluminescent reaction was performed.

(6) Development: The blots were developed by adding HRP substrate, and the gel was imaged. Gray values obtained with ImageJ were used to quantify TGF-ß1, Smad2, Smad3, and Smad7 protein expression.

2.5. Statistical analysis

All Statistical Analyses were done using SPSS IBM STAT 25. For the three groups, WKY, SHR, and MET: 1 way anova for significant differences and variance analysis.

3. Results

3.1. Analysis of blood pressure outcomes

Figure 1A shows the three repeated measurements of systolic blood pressure (SBP), diastolic blood pressure (DBP), and mean blood pressure (MBP) of rats. The first measurement was made before intragastric administration, and the other two measurements were made at week 7 post-intragastric treatment and week 14 post-intragastric treatment, respectively. As can be seen from **Figure 1A**, there is a positive relationship

between the SBP, DBP, and MBP values of rats and the rat's age in months. With respect to the control group composed of the WKY rats, it became very clear that there were significant differences between the metformin-treated group and the SHR model group ($P < 0.01$, N = 5). Both BP of the metformin group and SHRs were also higher than the normal level. However, no statistically significant difference was found between the metformin-treated group and the SHR Hypertensive Model Group, suggesting that metformin does not affect blood pressure in Hypertensive Rats.

SHR rats have higher HR than normal rats (**Figure 1B**, $P < 0.05$, N = 5-6). After 7 weeks of intragastric metformin, there were no big changes in heart rate for both the treated group and model group (**Figure 1A**). **Figure 1B**'s line from week seven through week fourteen indicated an inclination for heart rate in the metformin-treated group to go back toward typical values. But significance testing proved there wasn't any statistical difference. All with continuous 14 week of metformin dose is 100mg/kg/d had NO impact on heart rate in SHR rats. According to the curve shape of **Figure 1**, if we increase the amount of metformin or extend the treatment time, heart rate abnormalities in hypertensive rats can possibly be improved. But more metformin and longer treatment still fail to change blood pressure in SHR rats.

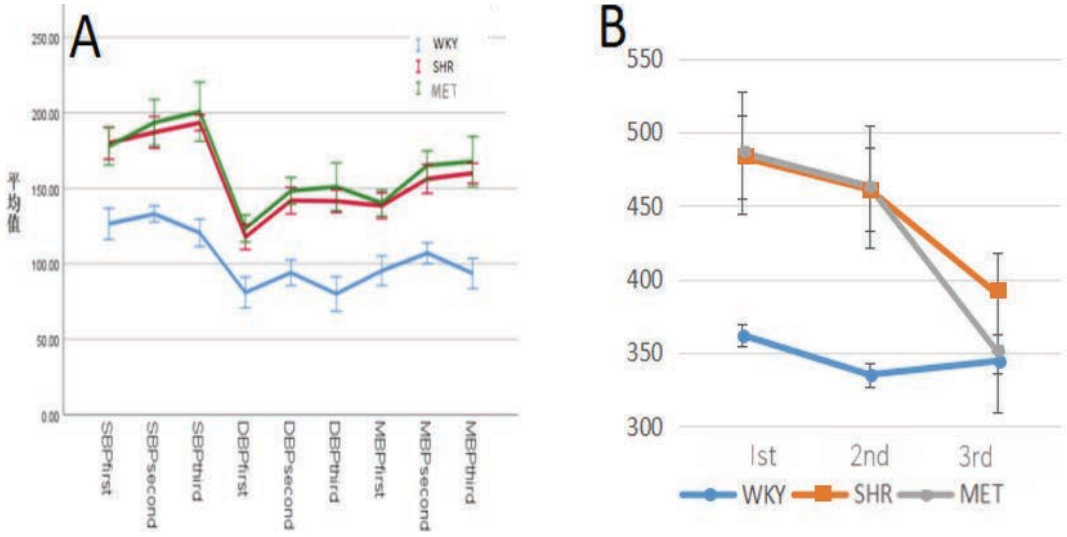


Figure 1. The comparison of blood pressure and heart rate measurements among three groups of rats over three time points.(A) is the comparison between the 3 measurement times (SBP, DBP & MBP) for all 3 rats, and (B) shows the difference between the 3 heart rate measurements for all three groups. One-way analysis of variance (ANOVA) was performed using SPSS. Results: No notable influence of metformin on SBP, DBP, MBP, and HR of SHRs was found.

3.2. Effects of metformin on echocardiographic parameters in rats

The detected index items are LVIDd, LVIDs, EDV, ESV, FS, EF, SV, pulmonary artery blood flow speed, maximum mitral blood flow speed, and maximum aortic blood flow speed. Formula for calculating FS and EF: FS= (LVIDd- LVIDs) / LVIDd) *100%, EF = (EDV - ESV) / EDV)* 100%. To obtain the plot, one-way ANOVA was performed on the obtained FS and EF values in **Figure 2C**.

Statistical results between different groups of SHR and WKY were significant ($P < 0.01$, N = 3), which means myocardial ejection function declined in hypertensive rats compared with normal rats. Compared to the SHR disease model group, the metformin-treated group showed greatly improved cardiac function ($P < 0.01$, N = 3). Also, when comparing the treatment group with the control group (WKY), there was a very

obvious difference ($P < 0.05$, N = 3). Altogether, it shows that metformin gives heart protection and improves the squeezing ability of the heart muscles in SHRs.

From the information in other people's work: In hypertension, the rat myocardial pump decreases because of sustained myocardial fiber hypertrophy. Metformin helps with the hypertension-caused heart trouble in these SHR things, so it's like it could be doing some kind of guard thing for your heart. More importantly, we saw in our previous portion that we did find no signs that metformin was causing any reduction in blood pressure in these hypertensive animal specimens; therefore, this may also indicate that perhaps those cardiac-protecting actions were unrelated to lowering one's blood pressure. In the next parts, it is shown more on the effect and mechanism behind metformin in causing the changes in myocardial fibrosis with help from stained slides and western blots.

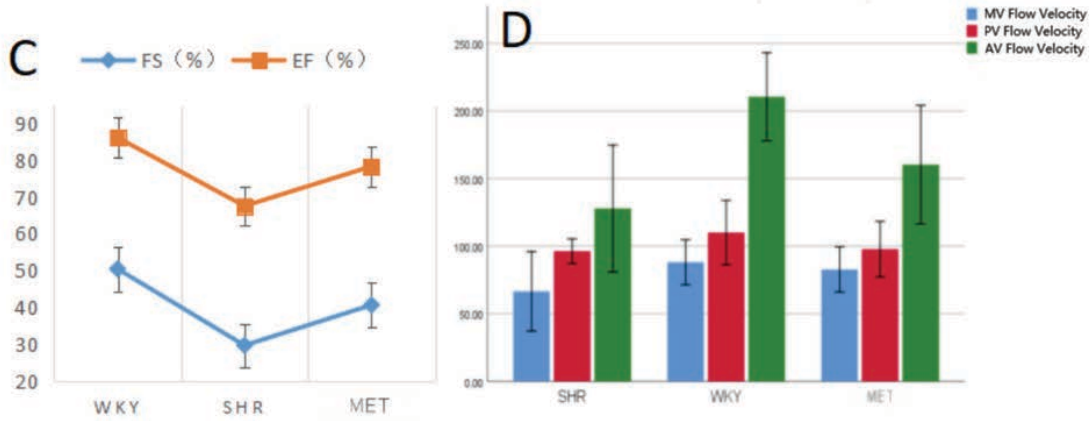


Figure 2. Comparison of Echocardiographic EF, FS, and flow velocities at the mitral valve orifice, aortic valve orifice, and pulmonary valve orifice among three groups of rats after treatment.

3.3. Effects of metformin on heart weight of SHR rats

When hypertension happens, we have these kinds of things happening to your heart muscle cells, where they start getting bigger in size because there are more cardiac myocytes around, as well as an increase in proliferation of those fibrous cells known as fibroblasts, overall leading towards increased heart mass. There is a large change in heart weight among hypertensive rats compared with normal control rats (**Figure 3F**, $P < 0.01$, N = 5). Compared to untreated hypertensive rats, metformin-treated hypertensive rats manifest a marked decrease in heart weight with statistically significant differences(**Figure 3F**, $P < 0.05$, N = 5); however, no distinct difference could be found between the treatment group and the normal control group. Metformin makes hypertension-induced cardiac weight gain less severe. Metformin did not decrease blood pressure, according to what we said earlier (**Figure 1A**). This indicates that Metformin's decrease in cardiomyocytes and extracellular matrix in SHR rats is not by way of decreasing blood pressure. Instead, metformin blocks the compensatory growth in cardiomyocytes and ECM expansion.

The SHRE Group differs from the WKY Group and metformin groups (Panel C, $P < 0.01$, N = 3). Metformin has no impact on PA flow velocities. For MV and AOA flow velocities (Panel D), there are no apparent variations between the metformin group and the SR or WKY groups; however, there is an obvious distinction between the SR group and the WKY group ($P < 0.05$, N = 5).

Comparative statistical analyses of stroke volumes (SV), it can be seen that it does not change cardiac

stroke volume (Panel E) under effect of metformin. But the metformin group's SV values are still a little bit higher when compared with SHRs'. As the Met-treated group can largely increase myocardial EF and FS, it may be due to the short duration or lower drug level, which is why we do not find much SV difference among these groups.

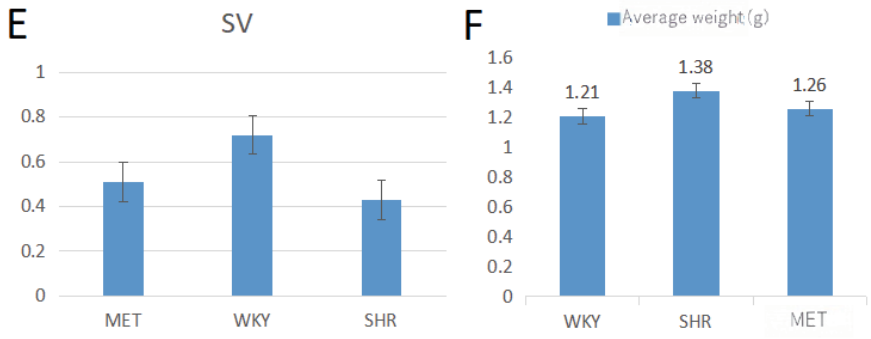


Figure 3. Comparison of SV and mean heart weight among three groups of rats after treatment

Metformin showed no changes in cardiac stroke volume (SV) of SHR rats (E). Metformin lessened heart weight growth in SHR rats. Comparison of treatment group with model group (F, $P < 0.05$, N = 5); comparison between treatment group and control group $P < 0.05$, N = 5). Comparison of model group vs control group (F, $P < 0.01$, N = 5).

3.4. Histopathological slice observation

Sirius Red staining helps determine how big your heart muscle cells are, as well as how things are arranged within them. If there's fibrous scar tissue (heart disease), we should be able to see it with a special kind of microscope called polarized microscopy after some time has passed since the problem began. A 400× magnification microscopic view of the myocardium from all three groups showed obvious cardiomyocyte hypertrophy and severe myocardial fibrosis in untreated SHR and treated SHR with metformin, in contrast to healthy control rat cardiomyocytes with hypertrophy and fibrosis. Although the metformin-treated group had slightly less cardiomyocyte hypertrophy and decreased fibrotic lesions than the untreated SHR group, this also verified that metformin has great protective effects against myocardial fibrosis in hypertension-induced rats.

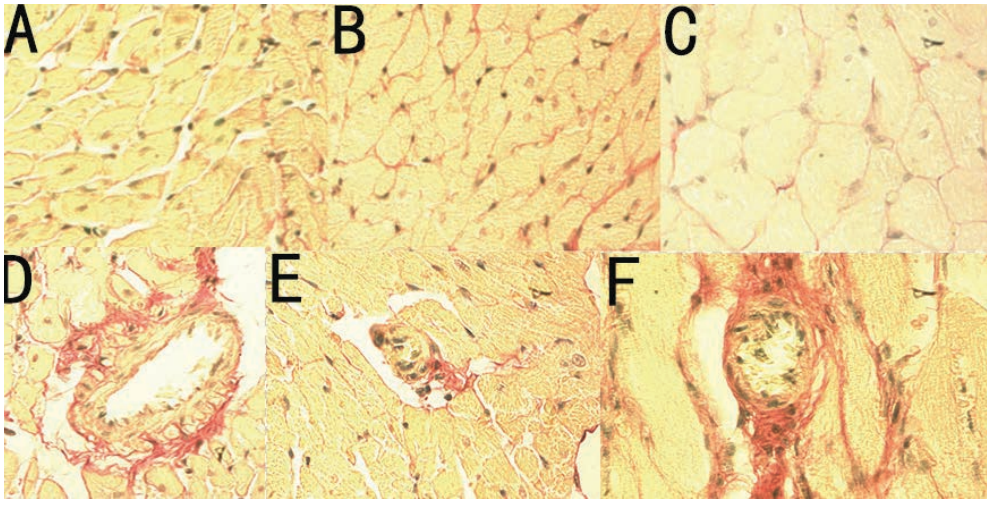


Figure 4. Polarized light micrographs of Sirius Red staining (magnification × 400).

In **Figure A** and **D**, we have WKY blank controls; in **Figure B** and **E**, we have our metformin-treated groups; and in **Figure C** and **F**, we have our SHR disease controls. Under a microscope, the WKY rat has normal heart tissue, but when looking at it, we see enlarged and disorganized muscle in the SHR rat, along with a lot of scar tissue. Compared to the SHR group, the metformin group showed that cardiomyocyte hypertrophy was relieved, with more orderly cell arrangements and a significant decrease in myocardial fibrosis.

3.5. Western Blot analysis of the effects of metformin on TGF-β1, Smad2, Smad3 and Smad7 protein expression

As seen in **Figure 5**, it shows that Metformin reduces the Protein levels of TGF-Beta 1, Smad 2 &3 but increases the expression of Smad7, $P < 0.01$, N = 3. TGF-beta1/Smad signaling mainly involves the phosphorylation of Smad2 and Smad3, and they bind together with Smad4 to regulate the inflammatory response and fibrosis. Smad7 functions as a negative regulator of this pathway. Metformin inhibits TGF-β1 / Smads.

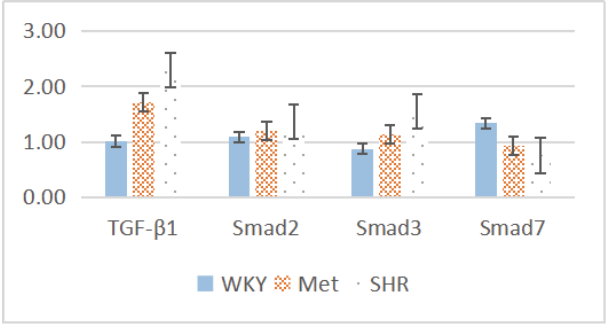


Figure 5. Western Blot detection of the effects of metformin on TGF-β1, Smad2, Smad3, and Smad7 protein levels.

Western blot was performed to detect the protein levels of TGF-β1, Smad2, Smad3, and Smad7, with β-actin as the internal reference, with units of ng/ml. One-way ANOVA analysis revealed that metformin downregulated the expression of TGF-β1, Smad2, and Smad3 proteins while upregulating Smad7 protein expression ($P < 0.01$, N = 3).

4. Discussion

Myocardial fibrosis means too much healing that results from damage to the heart; it's like normal heart cells in parts that aren't hurt start changing into myofibroblast cells (special helper cells), and there's lots of lumpy stuff filling up the space between the heart muscles. This pathological process affects the heart's ability to pump, causes extra thickening and beating of the heart muscle, and further damage through an ongoing cycle of inflammation and more hardening of tissue, eventually leading to heart problems. The cause of myocardial fibrosis is many things; we know some risk factors like having high blood sugar, having high blood pressure, or changes in glands that make hormones called adrenaline and thyroxine. A heart attack leads to an inflammatory reaction, oxidative stress, and abnormal signals like the TGF-β cascade. But there is a lot about what contributes, so all of those specific answers at the very tiny level remain mostly unknown to people; therefore, more investigation has to occur as time moves forward. The current work wanted to figure out how

much effect was caused by metformin on hypertension-related myocardial fibrosis, mainly paying attention to what kind of regulatory effect would be exerted if metformin worked within the context of a TFG-β/smad system and also looking at whether this medication would provide improvement against myocardin fibrosis observed among SHRs.

In total, there are 20 SHRs; they were split evenly into 2 groups randomly using a random number table, with each group having 10 rats: the first group is referred to as 'the model group', while the second group stands for 'the metformin i.g.'. 8 Wistar Kyoto (WKY) rats are our controls. Rats ate a high-fat, high-sugar diet. After the adaptation period of two weeks, oral feeding was done intragastrically and administered at 100 mg/kg/day. The model group and control group were given normal saline (i.g.) at equal doses by volume. Take body weight before taking drugs and check it weekly after that; take blood pressure every 7 weeks. Echocardiography was done before collecting the tissue. Cardiac tissues were then cut up and split in half. One part was put in formaldehyde, wrapped up in wax, and cut into bits with a dye called Sirius red so we could see how bad the hardening and growth of the heart muscle was. The other half went through Western Blot analysis to figure out how much of the TGF-β1, Smad2, Smad3, and Smad7 proteins were present. Parameters of 3 groups were compared statistically.

Compared with the SHR model group, a significant difference in fraction shortening(FS), ejection fraction(EF), and heart weight was found in the metformin group. The EF and FS of hypertensive SHRs are obviously below those of healthy WKY rats. After the metformin intervention, we saw an increase in SHRs EF and FS; however, they did not reach the same levels as the WKY rats, though they did reach much higher levels than SHRs before treatment. Heart weights also showed a lowering effect of metformin on hypertension-induced myocardial hypertrophy, as well as weight gain. Collectively, metformin improved myocardial hypertrophy and cardiac ejection function in SHRs.

There isn't a statistical difference in SBP, DBP, MBP, HR, SV, aortic blood flow, pulmonary artery flow, and mitral valve flow between the metformin group and the SHR model group. Many different studies mention that they have some kind of effect that can lower blood pressure in this hypertensive animal, but there is no decrease in blood pressure in this experiment we are doing right now. Using the line chart/column chart based on the raw data showed slight rising trends in post-metformin treatment SV/aortic/pulmonary artery/mitral blood flow velocities; however, all comparison results gave $P > 0.05$. Metformin didn't show any considerable impact on HR during the initial seven weeks of usage, but it began trending down toward regular values around week 14 without being statistically meaningful ($P > 0.05$). Previously, it had been found that administering continuous intragastric metformin (200 mg/kg/d) for 6 weeks could improve ischemia-reperfusion-induced HR, SV, and AFBV [7]. So even though it's not quite statistical but just looking at what I can see on the plot, seems like maybe more metformin dose or maybe if it goes on for some more time there would be like some big improvement in SBP and then DBP and also in MBP, also heart beat per second, also strokes per minute, and also those kind of arterial bloods flowing through all kinds of valves.

Under the microscope, using Sirius Red staining, we can see that metformin reduces myocardial fibrosis. Compared with the SHR model group, metformin-treated rats had neatly arranged and smaller cardiomyocytes. SHHs were organized and smaller compared to WHYs when examined, unlike SHRs, whose cardiomyocytes were disorganized with interstitial collagen accumulation and cardiomyocyte hypertrophy compared with Wkys. This confirmed the anti-fibrotic effects of metformin. In order for us to know more exactly how metformin reduced the hypertension-related myocardial fibrosis, we excluded a reduction in

blood pressure from being the cause because there was no decrease in blood pressure in the mice used. Liang et al. [8] thought that metformin protected the heart by stopping the TGF-β signaling pathway and, later, SMAD. So, Western blot is used here to measure the level of TGF-β1, Smad2, Smad3, and Smad7.

TGF-β/SMAD signaling canonical pathway goes like this: TGF-β1 binds transmembrane TβR II, after this event happens. TβRI is activated [9]. TβRI activates the phosphorylation of Smad2 & Smad3; these get transformed into different forms, then pair up together in something known as a master transcription factor. Smad7 becomes an inhibitor within this pathway. Inhibiting TGF-β1, Smad2 and Smad3. Inhibiting interaction among all three of the above. We can find that we also have some evidence through our protein quantification for downregulating TGF-β1 by Met and then Smad2, Smad3 up, as well as Smad7 up. So that's probably telling us that it must be doing its work with this modulation of the TGF - Beta slash Smads.

5. Conclusion

In short, hypertension induces myocardial fibrosis, cardiomyocyte enlargement, impairment of the heart's ejection function, as well as tachycardia. Metformin can reduce these kinds of hypertensive cardiac injuries through the way it controls TGF-β/ Smads signals. Metformin reduces hypertension-induced myocardial fibrosis in SHRs via TGF-β/Smads signaling cascade.

Funding

Hebei Traditional Chinese Medicine Joint Fund Cultivation Project (Project No.: H202309042)

Disclosure statement

The authors declare no conflict of interest.

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Publisher's note

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Cardiovascular Reviews, 2026, Volume 4, Issue 3
https://bbwpublisher.com/journal/CR
Online ISSN: 2981-8109
Print ISSN: 3083-4880

Association between White Blood Cell Count and Remnant Cholesterol Inflammatory Index in Middle-Aged and Older Adults: A Cross-National Database Study Using NHANES and CHARLS

Zhan Ye*

Hebei Medical University, Shijiazhuang 050017, Hebei, China

***Corresponding author*: Zhan Ye, 3303065125@qq.com

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Abstract: *Objectives:* The remnant cholesterol inflammatory index (RCII) is a novel composite biomarker that integrates lipid residual risk and inflammatory status. White blood cell (WBC) count, one of the most routine clinical inflammatory indicators, has an undefined association with RCII and unknown joint prognostic significance. This study aimed to investigate the cross-sectional association and longitudinal prognostic implications of WBC and RCII in middle-aged and older populations, so as to deepen the understanding of the "lipid-inflammation" cycle. *Methods*: Cross-sectional analyses were performed in two cohorts of adults aged 45 years and older: NHANES (2015–2016, n = 2,839) and CHARLS (2011, n = 5,955). Multivariable logistic regression and restricted cubic spline (RCS) analyses were used to assess the association and its nonlinearity. Longitudinal analyses utilized CHARLS follow-up data (2011–2015), applying Kaplan-Meier curves and Cox proportional hazards models to examine differences in long-term survival across categories of RCII and WBC. *Results*: In fully adjusted models, WBC was significantly and positively associated with RCII in both cohorts (NHANES: OR = 1.097, 95% CI: 1.038–1.158; CHARLS: OR = 1.309, 95% CI: 1.266–1.354). RCS analyses further revealed a nonlinear relationship. Longitudinal analyses demonstrated a noteworthy interactive phenomenon: in the low RCII group, individuals with high WBC exhibited significantly lower 5-year survival than those with low WBC, whereas in the high RCII group, the survival curves for different WBC levels tended to overlap. *Conclusion*: WBC count is nonlinearly and positively associated with RCII in both U.S. and Chinese middle-aged and older adults, with elevated WBC independently predicting higher mortality specifically in low-RCII individuals. This supports WBC as a low-cost adjunctive marker for risk stratification and highlights its prognostic value beyond RCII alone.

Keywords: China health and retirement longitudinal study; White blood cell count; National health and nutrition examination survey; Remnant cholesterol inflammatory index; Middle-aged and older adults

Online publication: September 30, 2026

1. Introduction

Cardiovascular disease (CVD) is the leading cause of global mortality, imposing substantial burdens on middle-aged and older populations [1]. Chronic inflammation is pivotal in CVD pathogenesis. The remnant cholesterol inflammatory index (RCII), a novel cardiovascular risk biomarker, integrates lipid residual risk and systemic inflammation. White blood cell (WBC) count, a routine clinical indicator, reflects inflammatory status. However, the quantitative relationship between WBC and RCII remains unexplored [2].

Remnant cholesterol (RC), calculated as total cholesterol minus HDL-C and LDL-C, is a key CVD risk factor. High-sensitivity C-reactive protein (hs-CRP) is used for both inflammation monitoring and CVD risk assessment [3]. Middle-aged and older adults have higher atherosclerotic burden and chronic inflammation [4]. Although RC and hs-CRP independently predict cardiovascular residual risk, they represent intertwined dimensions of the "lipid-inflammation" axis [5]. Evaluating either alone may underestimate high-risk individuals with acceptable lipid levels but chronic inflammation. RCII was thus proposed to capture the synergistic effects of dyslipidemia and inflammation [6]. Its computational simplicity makes it a potential tool for epidemiological research and primary care [7].

WBC count is a readily available peripheral blood indicator. Even within the normal range, subtle WBC fluctuations may reflect low-grade systemic inflammation [8], closely linked to atherosclerosis. WBC thus serves as both an "alarm" for infection and a "barometer" of cardiometabolic risk [9]. However, whether a quantitative association exists between WBC and RCII, and whether this association carries differentiated clinical significance, remains largely unexplored.

This association is rooted in a "lipid-inflammation" vicious cycle [10]. Oxidized remnant cholesterol particles activate endothelial cells and monocytes, releasing IL-6, TNF-α, and MCP-1 [11]. These cytokines stimulate hepatic CRP synthesis (elevating RCII) and activate bone marrow hematopoiesis (raising WBC). Conversely, inflammatory cells infiltrate the vessel wall, exacerbating plaque progression [12]. Thus, the WBC-RCII association is a population-level manifestation of this cycle.

2. Methods

2.1. Study design and participants

This study utilized data from two nationally representative cohorts: NHANES (2015–2016) and CHARLS (2011), including participants aged ≥45 years. After applying inclusion and exclusion criteria, 2,839 NHANES and 5,955 CHARLS participants were included.

2.2. Definition of white blood cell count

WBC count ($\times 10^9$/L) was obtained from laboratory data in both cohorts. RC was calculated as: RC (mg/dL) = TC − (HDL-C + LDL-C). RCII was computed as: in NHANES, RCII = RC (mg/dL) × hs-CRP (mg/L); in CHARLS, RCII = RC (mg/dL) × CRP (mg/dL) / 10 (unit conversion for consistency).

Covariates included sociodemographic characteristics (age, sex, race/ethnicity [NHANES only], education, marital status, income), health status (hypertension, diabetes, coronary heart disease, stroke, cancer, based on self-reported physician diagnosis or measured parameters), and physical/laboratory measurements (BMI, etc.).

2.3. Calculation of RC and RCII

Remnant cholesterol (RC) was calculated as: RC (mg/dL) = total cholesterol (TC) − [high-density lipoprotein cholesterol (HDL-C) + low-density lipoprotein cholesterol (LDL-C)]. The remnant cholesterol inflammatory index (RCII) was computed as follows: in NHANES, RCII = RC (mg/dL) × hs-CRP (mg/L); in CHARLS, because the measurement unit for C-reactive protein is mg/dL, these units were converted to maintain consistency of magnitude with NHANES, and the formula used was: RCII = RC (mg/dL) × CRP (mg/dL) / 10.

2.4. Covariate assessment

Covariates were collected through standardized questionnaires and physical examinations, covering three main categories of information:

(1) sociodemographic characteristics, including age, sex, race/ethnicity (NHANES only), education level, marital status, and household income level;

(2) health status and disease history, with hypertension defined as self-reported physician diagnosis, current use of antihypertensive medication, or measured systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg; other self-reported chronic disease histories including diabetes, coronary heart disease (encompassing heart failure, angina pectoris, and myocardial infarction), stroke, and cancer, all based on physician diagnosis reported by participants;

(3) physical measurements and laboratory indicators, including body mass index (BMI), among others.

2.5. Statistical analysis

Analyses were performed using RevMan 5.4. Cross-sectionally, WBC and RCII were continuous variables. Logistic regression and RCS assessed the association. Longitudinally, Cox regression and Kaplan-Meier curves examined survival. Statistical significance was set at two-sided $P < 0.05$.

3. Results

3.1. Baseline characteristics

Table 1. Baseline characteristics of the CHARLS database stratified by RCII

Variable	Low RCII group	High RCII group	*p* value
Sex	0.5 ± 0.5	0.5 ± 0.5	0.0202
Age	60.20 ± 9.64	61.56 ± 9.63	0.0000
Hypertension	22%	35%	0.0000
Dyslipidemia	7%	13%	0.0000
Diabetes	4%	8%	0.0000
Region	0.0%	0.0%	0.3840
Education category	1.1 ± 0.3	0.7 ± 0.4	0.2700
BMI	22.80 ± 13.58	24.35 ± 10.33	0.0000
Body mass category	8.0%	7.5%	0.0002
MetS	59.0%	65.6%	0.0000
Platelet count	208.24 ± 75.39	214.51 ± 82.38	0.0022
Blood urea nitrogen	16.10 ± 4.79	15.74 ± 4.48	0.0028
Blood glucose	104.27 ± 25.42	117.93 ± 47.09	0.0000

Variable	Low RCII group	High RCII group	*p* value
Creatinine	0.77 ± 0.21	0.80 ± 0.23	0.0000
Total cholesterol	189.18 ± 35.45	197.99 ± 40.86	0.0000
Triglycerides	94.21 ± 41.59	168.39 ± 115.69	0.0000
HDL-C	56.84 ± 14.84	45.90 ± 13.94	0.0000
LDL-C	113.49 ± 34.94	119.27 ± 35.38	0.0000
C-reactive protein	0.78 ± 0.69	5.20 ± 11.55	0.0000
HbA1c	5.18 ± 0.68	5.40 ± 0.97	0.0000
Uric acid	4.21 ± 1.16	4.70 ± 1.30	0.0000
Serum creatinine	41.23 ± 6.25	41.91 ± 6.38	0.0000
Hemoglobin	14.18 ± 2.22	14.56 ± 2.32	0.0000
Cystatin C	1.02 ± 0.24	1.06 ± 0.32	0.0000
White blood cell count	5.87 ± 1.68	6.70 ± 2.76	0.0000

Table 2. Baseline characteristics of the NHANES database stratified by RCII

Variable	High RCII group	Low RCII group	*p* value
Sex (Male %)	51.9	65.4	0.0364
Sex (Female %)	48.1	34.6	0.0258
Age	62.4 ± 10.9	0.0066	<0.0001
Race/ethnicity	64 ± 10.3	47 ± 6.6	<0.0001
Education (College % or above)	86 ± 13.8	90 ± 12.7	<0.0001
Marital status (Married %)	58.5	53.2	<0.0001
White blood cell count (LBXWBCSI)	7.0 ± 2.7	6.2 ± 2.2	<0.0001
Red blood cell count (LBXRBCSI)	4.6 ± 0.5	6.5 ± 0.4	<0.0001
Dyslipidemia	14.1	13.7	<0.0001
Hematocrit (LBXHCT)	41.4 ± 4.0	40.4 ± 4.2	<0.0001
Mean corpuscular volume (LBXMCVSI)	90.5 ± 5.5	90.8 ± 6.3	0.3886
Platelet count (LBXPLTSI)	235.5 ± 60.1	223.7 ± 63.0	0.0005
Hypertension (%)	56.4	49.5	0.0229
Urine microalbumin (URXUMA)	374.1 ± 71.6	312.0 ± 53.3	0.0335
Urine creatinine (URXCRS)	10476.5 ± 5888.0	10352.7 ± 6089.8	0.0079
Diabetes	26.4	21.7	<0.0001
Aspartate aminotransferase (LBXSASSI)	26.7 ± 17.9	25.1 ± 12.8	0.0743
Alkaline phosphatase (LBXSAPSI)	74.0 ± 34.9	69.5 ± 24.0	0.0064
Calcium (LBXSCA)	9.4 ± 0.4	9.3 ± 0.3	0.0208
Creatine kinase (LBXSCK)	144.5 ± 121.6	127.2 ± 13.3	0.0079
Total cholesterol (LBXSCH)	200.8 ± 43.1	186.6 ± 40.0	<0.0001
Creatinine (LBXSCR)	1.0 ± 0.4	0.9 ± 0.6	0.8190
γ-glutamyl transferase (LBXSGTSI)	34.6 ± 2.8	26.1 ± 3.3	0.0001
Blood glucose (LBXSGL)	114.1 ± 40.8	103.9 ± 29.5	<0.0001
Total cholesterol (LBXTC)	203.3 ± 42.4	188.7 ± 40.0	<0.0001
LDL-C (LBDLDL)	120.2 ± 38.9	112.5 ± 33.6	0.0001
HDL-C (LBDHDD)	48.2 ± 11.7	60.2 ± 16.9	<0.0001
RC	34.9 ± 11.7	16.0 ± 3.8	<0.0001

Table 1 and **Table 2** summarize the baseline characteristics of the CHARLS (n = 5,955) and NHANES (n = 2,588) cohorts stratified by RCII. In both populations, the high RCII group exhibited significantly higher WBC counts (CHARLS: 6.70 vs. 5.87 ×10⁹/L; NHANES: 7.0 vs. 6.2 ×10⁹/L, both $p < 0.001$) and a greater burden of cardiometabolic risk factors, including hypertension, diabetes, dyslipidemia, and elevated BMI, triglycerides, and blood glucose ($p < 0.05$).

3.2. Weighted univariate analysis

Table 3. Weighted univariate logistic regression analysis in the CHARLS database

Variable	OR	95% CI lower	95% CI upper	*P* value	Sample size
WBC	1.272	1.235	1.311	0.0000	5955
Age	1.015	1.009	1.020	0.0000	5955
Sex	0.945	0.854	1.047	0.2807	5955
Hypertension	1.887	1.683	2.117	0.0000	5955
Dyslipidemia	1.795	1.508	2.136	0.0000	5955
Diabetes	2.012	1.612	2.511	0.0000	5955
Income	1.000	1.000	1.000	0.1124	5955
Education	1.010	0.958	1.065	0.7074	5955
BMI	1.072	1.058	1.087	0.0000	5955
MetS	3.380	3.017	3.786	0.0000	5797
Total cholesterol	1.006	1.005	1.007	0.0000	5955
Marital status	0.973	0.848	1.116	0.6961	5955
Education level	0.935	0.785	1.114	0.4517	5955
Platelet count	1.001	1.000	1.002	0.0024	5954

Table 4. Weighted univariate logistic regression analysis in the NHANES database

Variable	OR	95% CI lower	95% CI upper	*P* value	Sample size
Sex (RIAGENDR)	0.830	0.565	1.219	0.3568	1332
Age (RIDAGEYR)	1.002	0.983	1.022	0.8075	1332
Race/ethnicity (RIDRETH3)	0.942	0.800	1.110	0.4877	1332
Education (DMDEDUC2)	0.836	0.738	0.947	0.0125	1332
Marital status (DMDMARTL)	0.994	0.901	1.096	0.9002	1332
Hypertension (BPQ020)	0.655	0.425	1.009	0.0728	1332
WBC (LBXWBCSI)	1.279	1.183	1.383	0.0000	1332
Platelet count (LBXPLTSI)	1.004	1.002	1.007	0.0076	1332
Total cholesterol (LBXTC)	1.008	1.005	1.011	0.0002	1332

Table 5. Weighted logistic regression analysis of the association between white blood cell count and remnant cholesterol inflammatory index in the CHARLS database (stepwise adjustment)

Model	Sample size	OR	95% CI lower	95% CI upper	*P* value
Model 2: +Age	5955	1.272	1.235	1.311	<0.001
Model 3: +Income	5955	1.273	1.235	1.312	<0.001
Model 4: +Education	5955	1.274	1.236	1.313	<0.001

Model	Sample size	OR	95% CI lower	95% CI upper	*P* value
Model 5: +Hypertension5955	1.271	1.233	1.310	<0.001	<0.001
Model 6: +Sex	5955	1.275	1.237	1.315	<0.001
Model 7: +Urban residence5955	1.309	1.266	1.354	<0.001	<0.001

Note: Model 1 (unadjusted) OR=1.272 (95% CI: 1.235–1.311, $P < 0.001$)

Table 6. Logistic regression analysis of the association between white blood cell count and remnant cholesterol inflammatory index in the NHANES database (stepwise adjustment)

Model	OR	95% CI lower	95% CI upper	*P* value
Model 1 (univariate)	1.075	1.028	1.124	0.0059
Model 2 (+demographics)	1.126	1.060	1.196	0.0032
Model 3 (+socioeconomic)	1.110	1.050	1.174	0.0217
Model 4 (+hypertension)	1.097	1.038	1.158	0.0458

Table 7. Association between white blood cell count quartiles and remnant cholesterol inflammatory index in the NHANES database

Group	OR	95% CI	*P* value
Q1	1.000	Reference	Reference
Q2 vs Q1	0.755	0.354 – 1.613	0.601
Q3 vs Q1	0.982	0.540 – 1.785	0.962
Q4 vs Q1	1.273	0.574 – 2.825	0.659
Test for trend	1.109	0.845 – 1.456	0.508

Weighted univariate logistic regression (**Tables 3–4**) identified WBC as a significant correlate of high RCII in both cohorts (CHARLS: OR=1.272, 95% CI: 1.235–1.311; NHANES: OR=1.279, 95% CI: 1.183–1.383). Metabolic syndrome and its components (hypertension, diabetes, dyslipidemia) were strongly associated with RCII in CHARLS; in NHANES, higher education emerged as a protective factor (OR=0.836, p=0.0125), while hypertension did not reach significance.

3.3. Multivariable logistic regression analysis of WBC and RCII

After stepwise adjustment (**Tables 5–6**), the WBC-RCII association remained significant in both cohorts. In CHARLS, the fully adjusted OR was 1.309 (95% CI: 1.266–1.354); in NHANES, it was 1.097 (95% CI: 1.038–1.158) (**Table 7**). Categorical analyses revealed a graded relationship: in NHANES (tertiles, **Table 8**), the ORs for T2 and T3 were 1.532 and 1.982, respectively; in CHARLS (quartiles, **Tables 9–10**), the adjusted OR for Q4 versus Q1 was 3.537 (95% CI: 2.997–4.174, $p < 0.001$).

Table 8. Association between white blood cell count tertiles and remnant cholesterol inflammatory index in the NHANES database

Group	OR	95% CI	*P* value
T1	1.000	Reference	Reference
T2 vs T1	1.532	1.086 – 2.160	0.015
T3 vs T1	1.982	1.389 – 2.828	<0.001

Group	OR	95% CI	*P* value
T1	1.000	Reference	Reference
Test for trend	1.402	1.176 – 1.672	<0.001

Table 9. Association between white blood cell count quartiles and remnant cholesterol inflammatory index in the CHARLS database (unadjusted)

Group	OR	95% CI	*P* value
Q1	1.000	Reference	Reference
Q2	1.383	1.198 – 1.598	<0.001
Q3	2.072	1.791 – 2.397	<0.001
Q4	3.072	2.649 – 3.561	<0.001

Table 10. Association between white blood cell count quartiles and remnant cholesterol inflammatory index in the CHARLS database (adjusted for all covariates)

Group	OR	95% CI	*P* value
Q1	1.000	Reference	Reference
Q2	1.464	1.255 – 1.708	<0.001
Q3	2.257	1.926 – 2.643	<0.001
Q4	3.537	2.997 – 4.174	<0.001

3.4. Nonlinear analysis

Table 11. Restricted cubic spline analysis: OR at specific percentiles of white blood cell count

Percentile	WBC	OR	95% CI
5%	3.80	0.571	0.409 – 0.797
25%	5.00	0.797	0.576 – 1.102
75%	7.30	1.457	1.062 – 1.999
95%	9.70	2.556	1.836 – 3.559

Restricted cubic spline analysis confirmed a nonlinear association between WBC and RCII in both cohorts (**Table 11**, **Figures 1–2**). The inflection points differed markedly: ~3.79 $\times 10^9$/L in CHARLS versus ~10.01 $\times 10^9$/L in NHANES, suggesting population-specific thresholds in the lipid-inflammation cycle.

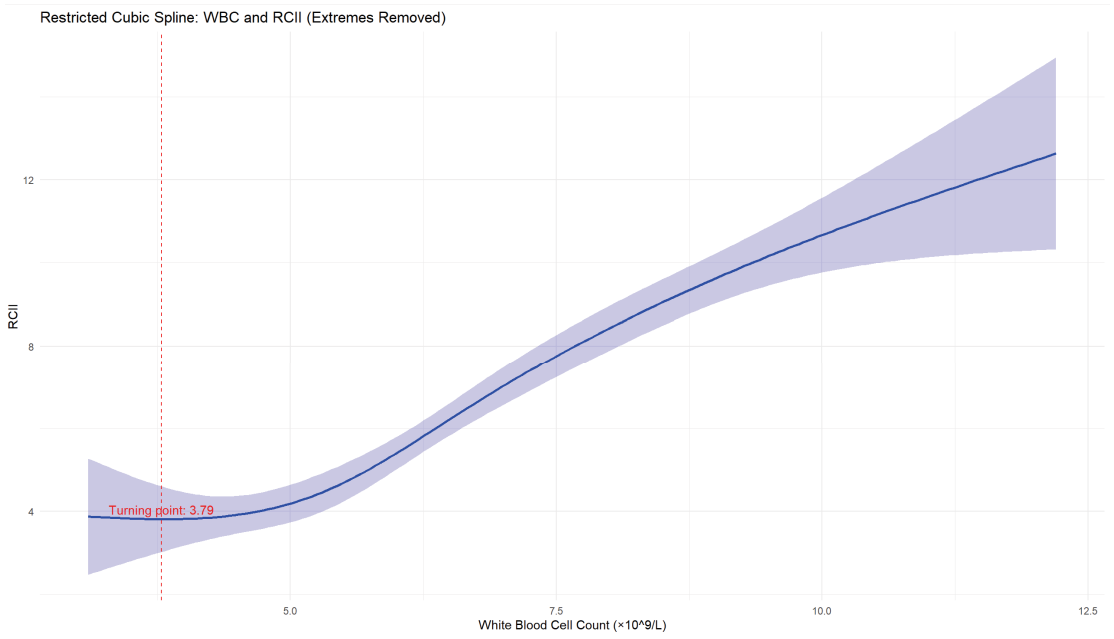


Figure 1. Restricted cubic spline analysis (RCS analysis) with extreme values excluded — CHARLS results.

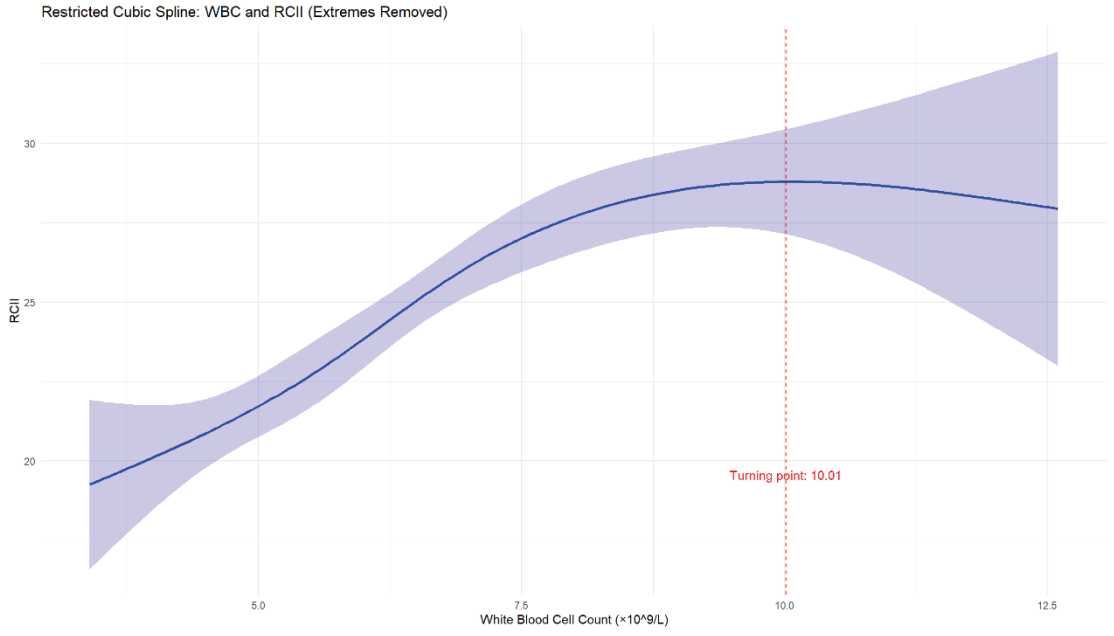


Figure 2. Restricted cubic spline analysis (RCS analysis) with extreme values excluded — NHANES results.

3.5. Subgroup analysis and interaction tests

Table 12. Description of white blood cell count in different subgroups of the CHARLS database

Subgroup	N	Mean ± SD	95% CI	*P* value
Overall	5955	6.29 ± 2.32	6.23 – 6.34	0.0000
Male	2780	6.43 ± 2.74	6.33 – 6.53	0.0000
Female	3175	6.17 ± 1.93	5.98 – 6.25	0.0000

Subgroup	N	Mean ± SD	95% CI	*P* value
Hypertension	1696	6.43 ± 3.16	6.28 – 6.58	0.0000
No hypertension	4259	6.23 ± 1.89	6.17 – 6.28	0.0000
Hyperlipidemia	598	6.32 ± 1.89	6.16 – 6.47	0.0000
No hyperlipidemia	5357	6.28 ± 2.37	6.22 – 6.35	0.0000
Diabetes	369	6.68 ± 1.93	6.48 – 6.87	0.0001
No diabetes	5586	6.26 ± 2.35	6.20 – 6.32	0.0000
Older age group	2928	6.29 ± 1.91	6.22 – 6.36	0.0000
Younger age group	3027	6.28 ± 2.66	6.19 – 6.38	0.0000
High BMI group	2977	6.38 ± 2.66	6.29 – 6.48	0.0000
Low BMI group	2978	6.19 ± 1.92	6.12 – 6.25	0.0000
Metabolic syndrome	3706	6.37 ± 1.89	6.31 – 6.43	0.0000
No metabolic syndrome	2091	6.11 ± 2.93	5.99 – 6.24	0.0000
High total cholesterol group	2968	6.45 ± 1.90	6.38 – 6.52	0.0000
Low total cholesterol group	2987	6.12 ± 2.67	6.02 – 6.21	0.0000
High-income group	2976	6.19 ± 1.83	6.13 – 6.26	0.0000
Low income group	2979	6.38 ± 2.73	6.28 – 6.47	0.0000
Married	4978	6.27 ± 2.39	6.20 – 6.34	0.0045
Unmarried	977	6.36 ± 1.96	6.24 – 6.48	0.0000
High education group	401	6.01 ± 1.67	5.84 – 6.17	0.0023
Low education group	5554	6.31 ± 2.36	6.24 – 6.37	0.0000
High platelet group	2974	6.71 ± 2.72	6.61 – 6.81	0.0000
Low platelet group	2980	5.86 ± 1.75	5.80 – 5.92	0.0000

Table 13. Description of white blood cell count in different subgroups of the NHANES database

Subgroup	N	Mean ± SD	95% CI	*P* value
Overall	2839	6.85 ± 2.32	6.76 – 6.93	0.0000
Male	1392	6.91 ± 2.66	6.77 – 7.05	0.0002
Female	1447	6.79 ± 1.95	6.69 – 6.89	0.0000
Older age group	1388	6.81 ± 2.62	6.67 – 6.95	0.0054
Younger age group	1451	6.89 ± 2.00	6.78 – 6.99	0.0000
Hypertension	1475	7.00 ± 2.49	6.87 – 7.13	0.0011
No hypertension	1361	6.68 ± 2.11	6.57 – 6.79	0.0000
High total cholesterol group	1350	6.80 ± 2.32	6.68 – 6.93	0.0000
Low total cholesterol group	1396	6.85 ± 2.30	6.73 – 6.97	0.0000
High platelet group	1401	7.27 ± 1.99	7.16 – 7.37	0.0001
Low platelet group	1438	6.44 ± 2.55	6.31 – 6.57	0.0005
High WBC group	1414	8.41 ± 2.30	8.29 – 8.53	0.3243
Low WBC group	1425	5.30 ± 0.85	5.26 – 5.35	0.0000
Married	1636	6.82 ± 2.39	6.70 – 6.93	0.0000
Unmarried	1201	6.89 ± 2.23	6.76 – 7.02	0.0253
Less than high school	787	7.07 ± 2.52	6.89 – 7.25	0.1233
High school or above	2050	6.76 ± 2.24	6.67 – 6.86	0.0000
White	1119	7.17 ± 2.67	7.01 – 7.33	0.0037

Subgroup	N	Mean ± SD	95% CI	*P* value
Black	774	6.37 ± 2.18	6.22 – 6.53	0.1361
Mexican American	226	7.22 ± 1.90	6.98 – 7.47	0.1066
Other race	720	6.74 ± 1.88	6.61 – 6.88	0.0000

Subgroup descriptions of WBC are provided in **Table 9** (CHARLS) and **Table 10** (NHANES). In interaction analyses, nationality, sex, age, BMI, diabetes, smoking, stroke, and CKD significantly modified the WBC-RCII association (all interaction $p < 0.05$), whereas race/ethnicity and hypertension status were significant effect modifiers in NHANES.

3.6. Survival analysis

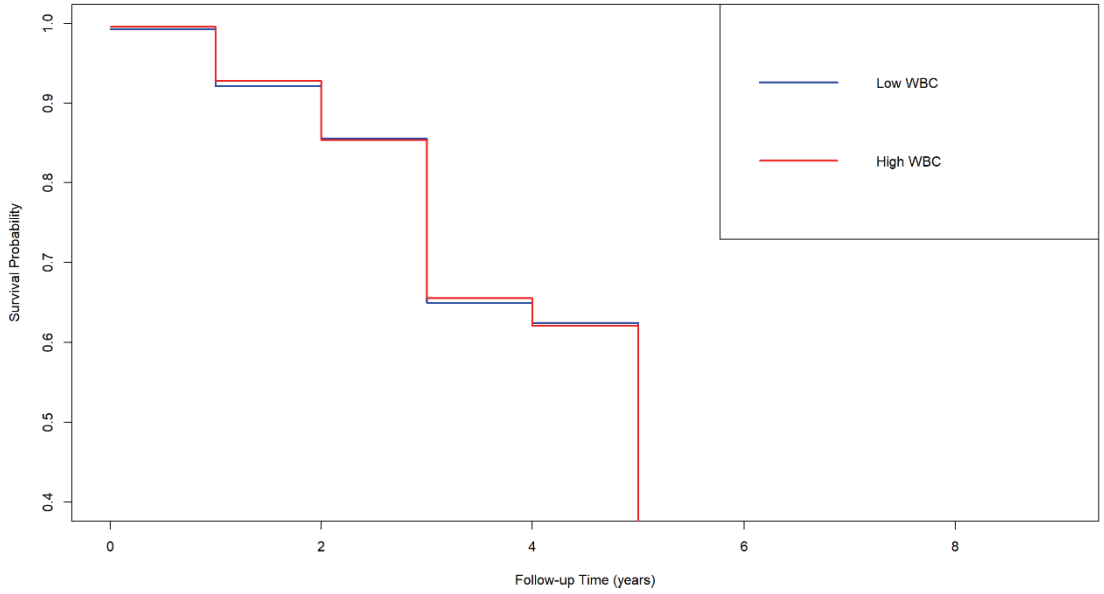


Figure 3. Kaplan-Meier survival curves for high WBC and low WBC.

Kaplan-Meier analysis of CHARLS longitudinal data (Figure 3) revealed a distinct interactive pattern. In the high RCII group, high and low WBC strata showed overlapping survival curves. In contrast, within the low RCII stratum, individuals with high WBC had markedly worse long-term survival, with a roughly 10–12 percentage point absolute risk difference emerging by year 8. This indicates that WBC offers incremental prognostic value specifically among those with a low residual cholesterol inflammatory burden.

4. Discussion

This study systematically evaluated the association between WBC and RCII by mining data from the CHARLS and NHANES databases. The principal findings can be summarized at three levels: first, in cross-sectional analyses, WBC exhibited a robust positive association with RCII in both populations, independent of traditional risk factors; second, restricted cubic spline analysis revealed that this association is nonlinear, displaying differentiated risk gradients across WBC intervals; third, longitudinal survival analysis further demonstrated that the prognostic value of WBC is highly dependent on the RCII background—among individuals with low RCII, elevated WBC can identify a group with significantly increased long-term

mortality risk, whereas among those with high RCII, WBC virtually loses additional risk discrimination capacity. This "context-dependent" interactive pattern is the most central finding of this study.

The positive association aligns with prior research on systemic inflammatory markers and cardiovascular residual risk. Evidence indicates that WBC, as a basic inflammatory marker, is closely linked to insulin resistance, endothelial dysfunction, and increased risk of future cardiovascular events [13]. On the other hand, remnant cholesterol (RC), as an important atherogenic lipid component, has been shown to independently promote inflammatory responses and increase metabolic syndrome risk [14]. By linking WBC with the composite indicator RCII, our study further reveals that the systemic inflammatory state characterized by WBC and the "lipid residual risk-chronic inflammation" axis characterized by RCII exhibit significant synchrony [15].

The underlying mechanism may be rooted in the "lipid-inflammation" cycle, a core pathobiological process [16]. Under conditions of chronic low-grade inflammation, an elevated WBC (especially neutrophils and monocytes) marks sustained immune activation, and the released pro-inflammatory cytokines such as IL-6 and TNF-α directly disrupt lipid metabolic homeostasis [17]. These inflammatory signals can stimulate the liver to increase VLDL synthesis while inhibiting lipoprotein lipase activity, impairing the clearance of triglyceride-rich lipoproteins and their remnants (i.e., RC), thereby driving RC accumulation in the blood [18]. This accumulated RC, especially after oxidative modification, is not an inert metabolic product [19]; it can act as a potent inflammatory stimulus, recognized and phagocytosed by macrophages within the vascular wall, which in turn activates intracellular signaling pathways such as the NLRP3 inflammasome and triggers the release of additional cytokines like IL-1β, further exacerbating systemic inflammation [20]. Thus, inflammation and disordered lipid metabolism constitute a self-reinforcing cycle [21]: inflammation promotes RC generation and retention, while RC acts as "fuel" to continuously aggravate the inflammatory response [22]. The synchronous elevation of WBC and RCII in this study is a population-level manifestation of this cycle—WBC reflects the level of activated immune cells in circulation [23], while RCII quantifies the composite lipid-inflammatory burden jointly characterized by RC and CRP [24].

The Chinese-American differences revealed in this study point to deeper mechanisms that multiple factors may modulate, and this basic mechanistic framework helps explain such cross-national heterogeneity [25]. First, differences in obesity types and fat distribution characteristics likely play a role. The obesity prevalence is higher in the U.S. population, with a predominance of subcutaneous fat accumulation; the obesity profile in the Chinese population differs markedly, primarily manifesting as a relatively lower obesity rate but a tendency for fat to accumulate in visceral adipose tissue, particularly in the abdominal area. Visceral adipose tissue is a potent source of inflammatory cytokines, and its inflammatory spillover effects may act more strongly on the liver, simultaneously exacerbating systemic inflammation (WBC elevation) and the generation of lipoprotein remnants, leading to a tighter "coupling" between WBC and RCII in the Chinese cohort. Second, differences in diet and gut microbiota may contribute: the U.S. diet is rich in saturated fats and refined carbohydrates, while the Chinese diet is primarily grain-based with higher dietary fiber. Third, genetic factors—owing to racial differences- the frequencies of relevant loci that significantly influence lipid metabolism and inflammatory response pathways may differ, modulating an individual's metabolic response to inflammatory stimuli.

Comparison with previous studies also highlights the innovations of this research. Most prior studies either analyzed the relationship between lipid profile and inflammation separately or focused on lipid

modulation in specific immune responses such as allergy [26]. In contrast, our study employs the composite indicator RCII and, for the first time, brings overall immune system activity (represented by WBC) and systemic residual inflammatory risk into the same analytical framework. Furthermore, through a design combining cross-sectional and longitudinal cohorts, we significantly enhance the credibility of the conclusions.

From a clinical application perspective, this study emphasizes that while focusing on the cardiovascular risk reflected by multidimensional composite indicators such as RCII, the independent value of classic hematological indicators like WBC should not be overlooked. Although WBC, as a coarse-grained inflammatory marker, has limited specificity, it features low testing cost, wide accessibility, and good applicability across populations. Therefore, WBC fluctuations can serve as a low-cost, high-efficiency screening tool to help clinicians identify potential high inflammatory response states at an early stage, especially in settings where resources are limited or refined biomarker testing is unavailable.

Nevertheless, several limitations should be acknowledged. First, although WBC count is a convenient hematological parameter, it lacks specificity; the impact of different leukocyte subtypes (e.g., neutrophils, lymphocytes) on RCII and cardiovascular risk may differ considerably. Future studies incorporating derived indicators such as the neutrophil-to-lymphocyte ratio may provide more refined information. Second, because publicly available databases were used, some variables relied on self-report and may be subject to recall bias or measurement error. Third, some of the cross-national differences observed in this study are difficult to fully explain through existing mechanisms and may involve unmeasured confounders.

Based on these findings and limitations, future research directions may include the following: first, prospective cohorts are needed to validate the predictive value of baseline WBC for long-term RCII changes or cardiovascular events, clarifying their temporal sequence and clinical utility; second, studies incorporating more precise inflammatory markers (e.g., IL-6, TNF-α) and detailed lipoprotein particle subfraction analyses should be conducted to reveal the specific molecular pathways underlying the WBC-RCII association; third, in cohorts with genomics, metabolomics, and microbiomics data, machine learning methods should be employed to explore the decisive biological and environmental factors contributing to cross-national heterogeneity and their interactions.

5. Conclusion

Through analysis of large-scale population data, this study reveals a significant nonlinear positive association between peripheral WBC and RCII levels, highly consistent across Chinese and U.S. populations. Notably, subgroup and survival analyses indicate that among individuals with lower RCII, even a slight rise in WBC is significantly associated with increased mortality risk, suggesting a special state of “low RCII but high inflammatory burden” that may relate to microvascular dysfunction or metabolic stress not fully captured by RCII. Clinically, WBC serves as a low-cost, accessible screening tool to identify high-risk inflammatory states, particularly in resource-limited settings. Pathophysiologically, the nonlinear association provides new insights into the “lipid-inflammation” cycle, positioning WBC not as a mere bystander but as a participant and driver of this vicious cycle. In summary, WBC is a valuable supplementary indicator when combined with RCII for multidimensional risk assessment in middle-aged and older adults. Future studies exploring WBC subtypes and anti-inflammatory interventions in low-RCII individuals may offer new entry points for

primary CVD prevention strategies.

Disclosure statement

The author declares no conflict of interest.

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Publisher's note

Bio-Byword Scientific Publishing remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Cardiovascular Reviews, 2026, Volume 4, Issue 3
https://bbwpublisher.com/journal/CR
Online ISSN: 2981-8109
Print ISSN: 3083-4880

Multimodal CT for Precision Diagnosis of Coronary Artery Disease: Integrating Anatomical and Functional Imaging

Xiaolei Diao[1,2], Wenjie Cai[1], Xianting Luo[3], Xiaoyong Zhu[2], Jianlong OuYang[3], Nuonan Li[2,4], Puhua Zhang[2]*

[1]School of Health Science and Engineering, University of Shanghai for Science and Technology, Shanghai 200093, China
[2]Department of Cardiology, Jiujiang University Affiliated Hospital, Jiujiang 332000, Jiangxi, China
[3]Department of Imaging, Jiujiang University Affiliated Hospital, Jiujiang 332000, Jiangxi, China
[4]Graduate Department, Gannan Medical University, Ganzhou 341000, Jiangxi, China.

***Corresponding author*: Puhua Zhang, zhangph6@126.com

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Abstract: Precision diagnosis of coronary artery disease (CAD) requires the integration of multidimensional data, including coronary anatomy and physiological function, for a comprehensive evaluation. This article reviews recent advances in multimodal computed tomography (CT) technologies for diagnosing CAD, analyzing their complementary strengths and limitations. In anatomical imaging, coronary computed tomography angiography (CCTA) assesses the degree of coronary stenosis and plaque characteristics but has limited specificity in evaluating functional ischemia. Functional imaging methods, such as fractional flow reserve derived from CT (CT-FFR), which simulates coronary pressure changes using fluid dynamics, and computed tomography perfusion (CTP) for myocardial ischemia detection, significantly enhance the accuracy and reliability of functional evaluations in CAD. The synergistic use of multimodal CT technologies addresses the limitations inherent to single imaging modalities, reduces unnecessary invasive procedures, and optimizes revascularization decisions, facilitating hierarchical precision assessment from anatomical stenosis to functional ischemia.

Keywords: CAD; CCTA; CT-FFR; CTP

Online publication: September 30, 2026

1. Introduction

CAD is one of the leading causes of death and disability worldwide, and its early and accurate diagnosis plays a crucial role in improving clinical outcomes for patients [1]. The pathological hallmark of CAD is atherosclerotic plaque formation, leading to coronary artery stenosis or occlusion, subsequently resulting

in myocardial ischemia, hypoxia, or necrosis. Although invasive coronary angiography (ICA) is considered the gold standard for anatomical assessment of coronary stenosis, the invasive nature of the procedure and associated risks have highlighted the urgent need for noninvasive imaging alternatives [2].

In recent years, CCTA has emerged as the preferred noninvasive modality for diagnosing CAD due to its high spatial resolution. However, the degree of coronary artery stenosis does not always correlate with hemodynamic abnormalities, and traditional morphological assessment often fails to accurately identify functional ischemia [3]. This limitation has spurred rapid advancements in functional CT techniques. Specifically, CT-FFR calculates pressure gradients across coronary stenoses using hemodynamic modeling; and CTP detects myocardial perfusion defects during stress testing. These methods have expanded CAD diagnostics beyond anatomical stenosis assessment, enabling quantitative analysis of functional ischemia and enhancing detection of hemodynamically significant lesions. Multimodal CT integrates anatomical stenosis assessment and functional ischemia analysis to establish a multidimensional diagnostic framework ("anatomical-functional"), systematically enhancing diagnostic accuracy for CAD.

2. Functional imaging: The role of CT-FFR and CTP in coronary hemodynamic assessment

2.1. CT-FFR

2.1.1. Principles and measurement techniques of CT-FFR

Invasive fractional flow reserve (FFR) is currently considered the gold standard for assessing coronary functional stenosis, defined as the ratio of maximum perfused blood flow through a stenotic lesion relative to maximal perfusion in the vessel under normal conditions [4]. However, its clinical application is significantly restricted by invasiveness, procedural complexity, and high costs [5]. Recent breakthroughs in non-invasive FFR measurement techniques based on CCTA have emerged. These methods utilize three-dimensional reconstructions derived from CCTA data to establish patient-specific coronary hemodynamic models, enabling quantitative simulation of pressure gradients across stenotic segments. Consequently, this technology allows for assessment of coronary functional ischemia without the need for stress-inducing medications or additional radiation exposure [6,7]. This advancement represents a major innovation in noninvasive cardiovascular functional assessment.

In clinical practice, CT-FFR is typically measured 1 to 2 cm distal to the target lesion [8]. A CT-FFR $\leq$ 0.75 indicates a significantly increased risk of myocardial ischemia, warranting revascularization, whereas a CT-FFR > 0.80 suggests lower risk and favors medical therapy. Values between 0.76 and 0.80 represent a "gray zone," necessitating comprehensive assessment of clinical symptoms and ancillary test results to guide decisions on revascularization [9]. This quantitative stratification strategy based on CT-FFR provides objective evidence for establishing revascularization indications and supports personalized, evidence-based treatment decisions.

2.1.2. Diagnostic value of CT-FFR for CAD

As a noninvasive imaging modality, CT-FFR can accurately evaluate hemodynamic changes resulting from CAD. Results from several large-scale clinical studies have confirmed its diagnostic value for identifying myocardial ischemia in CAD patients [5,10–12]. A prospective multicenter study employing a novel lumen-contour reconstruction algorithm demonstrated that CT-FFR achieved high sensitivity (95.3%), specificity

(89.8%), and overall accuracy (92.0%) at the vessel level, significantly outperforming CCTA alone (AUC 0.95 vs. 0.74, $P < 0.001$), with particular advantages observed in moderate stenoses and heavily calcified lesions [13]. A retrospective multicenter study further validated the superiority of CT-FFR over CCTA in detecting lesion-specific ischemia, showing moderate correlation with invasive FFR measurements ($r = 0.52$, $P < 0.001$) [11]. A comparative analysis by Driessen et al. [14] revealed that at the vessel level, CT-FFR exhibited significantly higher sensitivity (90%) compared to CCTA (68%), single-photon emission computed tomography (SPECT, 42%), and positron emission tomography (PET, 81%). Its specificity (86%) was comparable to CCTA (83%) and PET (76%), though slightly lower than SPECT (97%). Overall diagnostic accuracy (AUC 0.94) of CT-FFR significantly surpassed that of CCTA (0.83), SPECT (0.70), and PET (0.87) (all $P < 0.001$). However, previous studies, primarily composed of male subjects, failed to assess the influence of gender on diagnostic performance systematically. Fairbairn et al. [15] identified gender-related differences in CT-FFR values. Female patients demonstrated significantly higher CT-FFR values than male patients at equivalent stenosis levels (0.76 ± 0.10 vs. 0.73 ± 0.10, $P < 0.0001$), resulting in a 12.2% lower positive detection rate using the ≤ 0.80 threshold in women. This discrepancy may be attributed to women's higher coronary artery volume-to-myocardial mass ratios compared to men (26.17 ± 7.58 mm^3/g vs. 24.76 ± 7.22 mm^3/g, $P < 0.0001$). Despite smaller coronary artery volumes, women have lower myocardial mass, resulting in improved matching between myocardial oxygen demand and blood supply capacity. These findings underscore the need for gender-specific CT-FFR thresholds to avoid clinical decision biases resulting from uniform diagnostic criteria.

Machine learning (ML)-based CT-FFR technology employs algorithms, such as multilayer neural networks, to analyze and train models using coronary anatomical datasets and hemodynamic databases, establishing intrinsic relationships between anatomical features and hemodynamic parameters [16]. This approach enables CT-FFR values to be intelligently inferred directly from CCTA anatomical data, reducing the average analysis time to 8 minutes and achieving near-real-time CT-FFR assessment, thereby facilitating broader clinical application in CAD diagnosis [17]. Multicenter studies have confirmed that ML-based CT-FFR significantly enhances overall diagnostic performance compared to CCTA alone, increasing the AUC by approximately 10% to 25%. This technology demonstrates particular advantages in evaluating mid-to-proximal LAD and LCX stenoses (AUC improved from 0.65–0.84 to 0.72–0.90); however, diagnostic improvements for mid-RCA stenoses remain limited due to factors such as motion artifact interference and lower lesion prevalence (AUC 0.73 vs. 0.74) [18]. Clinical studies further validate ML-based CT-FFR, showing overall sensitivity and specificity of 85% and 94%, respectively, in diagnosing coronary artery-specific ischemia. For moderate stenoses (30–70%), ML-based CT-FFR maintains excellent sensitivity and specificity (84% and 92%), respectively [19]. However, current research predominantly uses invasive FFR as the reference standard, lacking validation through multimodal imaging technologies. Consequently, CT-FFR may erroneously attribute myocardial ischemia caused by microvascular lesions to large vessel stenosis or fail to detect ischemia resulting from microcirculatory abnormalities. In comparison, cardiac magnetic resonance (MR), which directly quantifies myocardial perfusion reserve and MBF, achieves higher specificity (95% vs. 82%) and accuracy (95% vs. 81%) [20]. Future research should therefore develop collaborative validation frameworks integrating CT-FFR with multimodal imaging modalities such as MR and PET, while incorporating parameters of microcirculatory function to minimize diagnostic errors.

2.1.3. Factors affecting the diagnostic accuracy of CT-FFR

The diagnostic performance of CT-FFR is closely associated with factors such as CAC load, CCTA image quality, and patient heart rate. Several studies have confirmed a significant negative correlation between coronary artery calcification burden and CT-FFR accuracy [21,22]. Tesche et al. [22] found that although CT-FFR outperformed CCTA in diagnosing myocardial ischemia across all CAC score levels, its accuracy decreased with increasing CAC score. In patients with mild-to-moderate calcification (CAC score 0–400), CT-FFR exhibited significantly higher diagnostic performance (AUC 0.86) than CCTA (AUC 0.63, $P < 0.001$). However, in cases of severe calcification (CAC score ≥ 400), this advantage diminished (CT-FFR AUC 0.71 vs. CCTA AUC 0.55, $P = 0.04$). A single-center study further demonstrated reduced concordance between CT-FFR and invasive FFR in patients with high calcification levels, characterized by decreased positive predictive value (PPV). This decline in predictive accuracy may lead to increased false-positive results, potentially prompting unnecessary revascularization procedures [23]. Notably, different CT-FFR algorithm models exhibit varying sensitivities to calcification artifacts. Traditional algorithms heavily rely on accurate geometric lumen segmentation. However, halo and beam-hardening artifacts induced by severe calcification can compromise coronary centerline identification and lumen segmentation accuracy, resulting in systematic biases during hemodynamic assessment. In contrast, newer algorithms integrating TAG and additional hemodynamic parameters maintain consistent diagnostic accuracy across coronary arteries with different calcification levels, remodeling indices, and CAC stratifications by optimizing boundary conditions [24]. Nevertheless, the performance of current CT-FFR models in patients with severe calcification requires further validation through large-scale studies. Consequently, there is an urgent need to develop CT-FFR models incorporating quantitative corrections based on calcification characteristics to mitigate assessment biases and enhance diagnostic reliability.

Image quality is another critical factor influencing the diagnostic accuracy of CT-FFR. A multicenter retrospective study demonstrated significantly higher diagnostic performance in the high-quality image group compared to the low-quality group (AUC: 0.93 vs. 0.80; specificity: 0.98 vs. 0.86; PPV: 0.95 vs. 0.82), confirming that reduced image quality diminishes the accuracy of vascular morphology reconstruction and lesion feature extraction [25]. The same study also revealed that heart rate significantly affects diagnostic accuracy. Patients with low heart rates (≤ 70 bpm) exhibited superior specificity (0.98 vs. 0.89) and PPV (0.96 vs. 0.77) compared to those with higher heart rates (> 80 bpm). This difference primarily arises because stable heart rates reduce motion artifacts, thus optimizing the accuracy of vascular morphology reconstruction [25]. Therefore, rigorous adherence to cardiovascular CT imaging protocols, optimization of scan parameters, and effective heart-rate control strategies are essential for improving CT-FFR diagnostic accuracy.

2.2. CTP

2.2.1. Principles and techniques of CTP

CCTA provides anatomical information regarding the coronary arteries, while CT-FFR allows noninvasive FFR assessment. However, neither modality can directly evaluate myocardial perfusion. To address this limitation, myocardial CTP technology has been introduced, enabling direct evaluation of myocardial perfusion status and microcirculatory function. The fundamental principle of CTP involves detecting reduced or delayed myocardial contrast uptake through subjective assessment and quantitative analysis [26]. Specifically, following intravenous contrast injection via the antecubital vein, CTP identifies perfusion abnormalities by assessing

contrast distribution characteristics during its initial passage through the myocardium. A marked reduction in contrast concentration indicates potential myocardial perfusion defects [27,28].

CTP scanning protocols include resting and stress modes. At rest, MBF can remain normal even with coronary artery stenosis up to 85%, facilitated by collateral circulation or compensatory vasodilation. However, under stress conditions, microcirculation within stenotic vascular territories cannot adequately dilate, resulting in reduced regional MBF [29]. Due to differences in blood flow regulatory mechanisms, the primary limitation of resting CTP is its difficulty detecting cases with impaired coronary flow reserve but preserved resting perfusion. Conversely, stress CTP effectively exposes coronary flow reserve abnormalities through cardiac stress stimulation, significantly enhancing myocardial ischemia detection. In stress testing, adenosine is widely used due to its short half-life but is contraindicated in patients with airway hyperresponsiveness, such as chronic obstructive pulmonary disease (COPD), owing to its bronchoconstrictive effects. Lexiscan, a selective coronary vasodilator with rapid onset, prolonged action, and milder side effects, represents a preferable alternative for COPD patients [27].

2.2.2. Diagnostic value of CTP for CAD

The diagnostic efficacy of CTP has been validated in multiple studies. A comparative study by Nous et al.[30] demonstrated that combining dynamic CTP with CCTA significantly improved diagnostic specificity (89% vs. 72%) and overall accuracy (88% vs. 78%) compared to CCTA alone. This advantage was especially notable when distinguishing moderate stenoses (50–69%), elevating diagnostic accuracy from 44% to 71%. Although the combined method exhibited slightly lower sensitivity compared to CCTA alone (84% vs. 96%), it provided significant additional value through hemodynamic assessment. The median MBF in ischemic regions was 97 mL/100 mL/min, significantly lower than in non-ischemic regions (158 mL/100 mL/min), thereby offering important quantitative evidence for clinical decision-making. However, definitions of MBF thresholds vary across studies, and the lack of standardized parameters directly limits broader clinical adoption of CTP. Comparative studies indicate that dynamic CTP combined with CCTA achieves sensitivity and specificity comparable to MR and PET in detecting myocardial ischemia, surpassing SPECT. This combined modality is particularly suitable for patients contraindicated for MR or PET[31]. Notably, most current CTP studies utilize dual-source CT platforms and commonly exclude obese patients (BMI >30 kg/m2). Future prospective, multicenter studies involving conventional CT equipment and obese patient subgroups are needed to validate the clinical generalizability of this technology.

Evidence from multicenter studies shows clear advantages of integrating CTP with CCTA for optimizing ICA indications [32–35]. Notably, the PERFECTION study demonstrated that combining static CTP with CCTA significantly improved specificity (95% vs. 76%) and PPV (87% vs. 61%) compared to anatomical assessment alone, while maintaining high sensitivity (92%) [33]. This combined approach accurately identifies functionally ischemic lesions warranting revascularization, effectively excluding cases of anatomical stenosis without associated hemodynamic abnormalities, thus reducing false positives and unnecessary ICA procedures. However, the AMPLIFiED study found that dynamic CTP combined with CCTA improved specificity (from 36% to 75%) compared to CCTA alone but reduced sensitivity (from 93% to 72%). This sensitivity reduction may be related to the selected MBF threshold and the complexity of multivessel disease [32]. Therefore, considering its operational simplicity and high specificity, static CTP may be preferable for screening high-risk populations. Dynamic CTP, due to its longer imaging time and greater susceptibility to

artifacts, may lack sufficient resolution or demonstrate significant measurement inaccuracies when assessing multivessel disease or extensive perfusion defects.

2.2.3. Limitations and future directions of CTP

Although the clinical value of CTP in CAD diagnosis has been clearly demonstrated, radiation exposure remains a primary limitation hindering its broader clinical adoption. Static CTP has a significantly lower radiation dose than dynamic CTP (2.8 ± 1.2 mSv vs. 5.3 ± 0.7 mSv) [36]. Due to radiation safety concerns, clinical practice currently favors static CTP because of its lower radiation dose. Radiation exposure from CTP can be further minimized through techniques such as low-tube-voltage scanning and wide-coverage CT scanners [36,37].

In the future, PCCT is expected to enable precise quantitative analysis of myocardial contrast distribution, leveraging enhanced detector sensitivity and spatial resolution to substantially improve the accuracy of perfusion assessments [38]. Concurrently, deep learning (DL)-based image processing algorithms offer notable advantages for artifact suppression and image contrast enhancement, providing innovative solutions for optimizing CTP image quality.

3. Conclusion

Multimodal CT technology has reshaped the diagnostic paradigm for CAD by integrating anatomical imaging and functional assessment. As the cornerstone of anatomical imaging, CCTA has become the gold standard for noninvasive diagnosis of coronary artery stenosis due to its high spatial resolution. However, it inherently possesses limitations, including calcification artifacts and a lack of functional information. In functional imaging, CT-FFR employs computational fluid dynamics to simulate FFR, and CTP visualizes myocardial ischemia. Their combined use advances CAD diagnosis from anatomical stenosis evaluation to functional ischemia assessment, significantly reducing unnecessary invasive interventions. Multimodal CT integrates three-dimensional anatomical and functional information through single-visit examinations, elevating CAD assessment from purely anatomical description to comprehensive quantification. This integrated approach offers clinicians a more holistic perspective to support decision-making.

Funding

National Natural Science Foundation of China (Project No.: 82260147, 82460170, 82360626 and 82560886), Natural Science Foundation of Jiangxi Province (Project No.: 20224BAB206030, 20242BAB20370 and 20252BAC240556), Science and Technology Research Project of Jiangxi Provincial Department of Education (Project No.: GJJ2201920, GJJ2201941, GJJ2401806 and GJJ2401825)

Disclosure statement

The authors declare no conflict of interest.

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Publisher's note

Bio-Byword Scientific Publishing remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Cardiovascular Reviews, 2026, Volume 4, Issue 3
https://bbwpublisher.com/journal/CR
Online ISSN: 2981-8109
Print ISSN: 3083-4880

Summary of Professor Guo Shuwen's Academic Thoughts and Experience in Diagnosing and Treating Heart Failure

Dongmei Zang, Jing Wang, Shuwen Guo

Beijing University of Chinese Medicine Fangshan Hospital, Beijing 102400, China

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Abstract: Professor Guo Shuwen is a mentor for the seventh batch of national academic experience inheritance work for veteran traditional Chinese medicine experts, the head of the expert team for the Beijing Famous Traditional Chinese Medicine Practitioners' Support Project, the mentor for the third batch of ChaoYang District Famous Traditional Chinese Medicine Experts' grassroots and academic experience inheritance project, the mentor for the ninth batch of national excellent doctoral dissertation in traditional Chinese medicine, the recipient of the Outstanding Contribution Award for Innovation and Entrepreneurship at Beijing University of Chinese Medicine, and an evaluation expert for special projects of the Ministry of Science and Technology, the Ministry of Education, and national natural science foundation projects. With 39 years of medical experience, he is primarily dedicated to the clinical practice, teaching, and scientific research of cardiovascular diseases. He inherits the classics, adheres to principles while innovating, possesses a unique understanding of heart failure, and has developed a distinctive diagnostic and treatment approach. He believes that deficiency of heart-Yang Qi is the fundamental pathogenesis of heart failure, blood stasis and fluid retention are its core pathological products, and fluid invading the lungs is the key to acute exacerbations of heart failure. He advocates supplementing Qi and invigorating Yang to address the root cause, and draining the lungs and promoting diuresis to treat the symptoms. He also emphasizes that heart failure should be treated in stages. During acute exacerbations, the main methods are nourishing Qi and boosting Yang, and purging the lungs and promoting diuresis. During remission periods, the focus shifts to nourishing Qi and boosting Yang, promoting blood circulation to remove blood stasis, and strengthening the body's vital energy and foundation.

Keywords: Guo Shuwen; Experience of renowned veteran Chinese medicine practitioners; Heart failure; Method of nourishing Qi and invigorating Yang purging the lung and promoting diuresis

Online publication: September 30, 2026

1. Introduction

Heart failure (HF) is a complex clinical syndrome resulting from structural or functional abnormalities of the heart that impair ventricular filling or ejection capacity. It represents the terminal stage of various

cardiovascular diseases and remains associated with persistently high morbidity and mortality worldwide, imposing a heavy burden on public health systems [1]. Modern medicine has made remarkable progress in the treatment of HF, particularly with the application of pharmacological agents such as angiotensin receptor–neprilysin inhibitors (ARNIs) and sodium–glucose cotransporter 2 inhibitors (SGLT2i), as well as the widespread use of devicebased therapies including cardiac resynchronization therapy and implantable cardioverterdefibrillators, which have greatly improved the prognosis of some patients [2]. Nevertheless, clinical practice still faces numerous challenges, such as suboptimal symptom control, limited improvement in quality of life, adverse drug reactions, recurrent episodes, and high hospitalization rates [3]. Moreover, for heart failure with preserved ejection fraction (HFpEF), there remains a lack of effective therapies that definitively reduce mortality [4]. These unmet clinical needs continue to drive the exploration of novel therapeutic strategies within the medical community.

In traditional medical systems, Chinese medicine classifies HF as “palpitations”, “severe palpitations”, “dyspnea syndrome”, “edema”, and “cardiac edema”, with a long history of documented understanding [5]. Traditional Chinese medicine (TCM) theory holds that the heart governs the blood vessels, and that the propelling and warming actions of heart Qi and heart Yang are essential for maintaining normal blood circulation. The core pathogenesis of HF is generally summarized as “root deficiency with branch excess”, with the deficiency of heart Yang and Qi as the root, and blood stasis and fluid retention as the branch [6]. This central pathogenetic view of “heart Qi deficiency, blood stasis, and fluid retention” not only focuses on the heart itself but also emphasizes the interconnections with other zangfu organs, including the lung, spleen, kidney, and liver, forming a diagnostic and therapeutic feature of holistic syndrome differentiation and fiveorgan correlation [7]. This epistemology, which starts from the overall functional state and dynamically captures the evolution of disease, provides a unique theoretical framework for TCM intervention in HF.

HF is the terminal stage of various cardiovascular diseases, such as coronary heart disease, arrhythmias, cardiomyopathies, and hypertension, all of which can lead to HF [1]. However, with the changing disease spectrum, the proportion of HF attributable to coronary heart disease has been increasing. An epidemiological survey of cardiovascular diseases conducted at a hospital in Shanghai from 2019 to 2021 showed that coronary heart disease accounted for as high as 47.92% of HF cases [8]. Based on this, Professor Guo Shuwen, building upon the principle of “supplementing Qi and activating blood circulation” for treating coronary heart disease, proposed the important academic doctrine of “supplementing Qi, invigorating Yang, draining the lung, and promoting diuresis” for HF treatment. This approach aims to reverse the declining trend of Yang Qi and rapidly alleviate the critical condition of fluid retention attacking the lung, representing a model of simultaneous reinforcement and elimination. Its core lies in addressing the complex pathogenesis of “heart Yang and Qi deficiency, blood stasis and fluid retention, and fluid attacking the lung” by adopting a comprehensive strategy of “supporting the upright and dispelling the pathogenic, and treating both heart and lung simultaneously”. This doctrine profoundly embodies the holistic concept and the essence of syndromebased differentiation in TCM treatment of acute and critical illnesses.

2. Understanding the pathogenesis of heart failure

Although the term “heart failure” does not appear in ancient TCM texts, based on its clinical manifestations—such as dyspnea, edema, palpitations, and fatigue—it has been classified under categories such as “cardiac edema”, “dyspnea syndrome”, “palpitations”, “heart impediment”, “severe palpitations”, and “edema” [5].

The Suwen·Wei Lun states: “The heart governs the blood vessels of the whole body”, clearly indicating the heart’s function of propelling blood circulation. Adequate heart Qi is a prerequisite for normal blood movement. The Suwen·Zhi Zhen Yao Da Lun states: “All dampness, edema, and fullness belong to the spleen”; and the Suwen·Shui Re Xue Lun states: “Its root is in the kidney, its end in the lung, and both are associated with water accumulation”. These statements indicate that edema is closely related to dysfunction of the lung, spleen, and kidney, forming the theoretical origin of “its control lies in the spleen and its root lies in the kidney” for HF. The term “cardiac edema” first appeared in the Jin Gui Yao Lue·Shui Qi Bing Mai Zheng Bing Zhi: “Cardiac edema manifests as heaviness of the body, shortness of breath, inability to lie down, restlessness and agitation, and genital edema”. This description closely matches the typical symptoms of HF patients, including dyspnea, orthopnea, irritability, and lower extremity and genital edema. The text also established the therapeutic principle of “warming Yang and promoting diuresis” and provided classic formulas, such as Zhenwu Decoction for warming kidney Yang to promote diuresis, and Linggui Zhugan Decoction for warming heart and spleen Yang to resolve fluid retention, which remain classic prescriptions for HF treatment today. The Shanghan Lun discusses various critical conditions caused by Yang deficiency and fluid retention and provides emergency formulas, reflecting the concept of “supporting Yang and securing the root”, which is of significant guiding value for the treatment of acute exacerbations of HF.

Based on the inheritance of classics and combined with modern pathology, Professor Guo Shuwen believes that heart failure is a complex and dynamic process in which lesions in the heart itself affect other zang-fu organs. The disease is located in the heart but often involves the lung, spleen, kidney, and liver. In terms of nature, it is generally characterized as root deficiency with branch excess, with intermingled deficiency and excess. The pattern of evolution: in the early stage, it mainly presents as heart Qi deficiency, which then progresses to heart Yang deficiency with the appearance of blood stasis; as Yang deficiency further worsens, fluid retention and phlegmturbidity accumulate, causing generalized edema and invading the heart and lung; in the advanced stage, Yang deficiency may impair yin, leading to the critical condition of dual deficiency of both yin and yang. This profound understanding provides a solid theoretical basis for the TCM therapeutic principles of “supplementing Qi, invigorating Yang, activating blood circulation to remove stasis, and draining the lung to promote diuresis”, and has enabled TCM to play a unique role in improving symptoms, enhancing quality of life, and reducing rehospitalization rates in HF patients.

Professor Guo Shuwen, through indepth study of the classics, summarized the pathogenesis of HF as follows:

(1) Deficiency of heart Qi and Yang is the fundamental pathogenesis of HF. The heart governs Yang Qi, and the decline of heart Yang is the primary driving force behind HF. Deficiency of heart Qi leads to weakened blood propulsion, resulting in blood stasis; deficiency of heart Yang fails to warm and transform body fluids, leading to internal retention of fluid. This is the principle of “edema due to Yang deficiency”.

(2) Blood stasis and fluid retention are the core pathological products of HF. Blood stasis and fluid retention mutually interact and spread throughout the triple burner. Stagnant blood obstructs the collaterals, further hindering the circulation of Qi and body fluids, thereby exacerbating fluid retention; conversely, widespread fluid retention obstructs the free flow of Yang Qi and damages heart yang.

(3) Fluid attacking the lung is the key to acute exacerbations of HF. When fluid retention ascends and obstructs the lung, lung Qi becomes congested, and the lung’s dispersing and descending functions are

impaired. This is the direct cause of acute worsening of HF, manifesting as wheezing, inability to lie flat, and coughing up frothy sputum (pulmonary edema), indicating that the disease has shifted from the heart to the lung and signifies a critical condition.

3. Basic therapeutic principles

Adhering to the principle of "treating the root cause while addressing the branch manifestations", and targeting the core pathogenesis of "root deficiency and branch excess" in HF, the following treatment strategies are established.

3.1. Strengthening the root and consolidating the foundation – The major approach for treating the root

This addresses the deficiencies of heart Qi, Yang, Yin, and blood.

3.1.1. Supplementing Qi and invigorating Yang method

This is the most core and commonly used therapeutic method.

(1) Indications: Suitable for HF patients presenting with manifestations of heart Qi and Yang deficiency, such as palpitations, shortness of breath, fatigue, spontaneous sweating, chilliness, and cold extremities. This method is key to improving cardiac function and providing cardiac energy.

(2) Supplementing Qi: Vigorously replenish heart Qi using herbs such as Astragalus (Huangqi), Ginseng (Renshen), and Codonopsis (Dangshen), aiming to restore the heart's basic function of propelling blood circulation and providing the driving force for "activating blood".

(3) Invigorating yang: Warm and invigorate the declining heart Yang using herbs such as Aconite (Fuzi), Cinnamon (Guizhi), and Dried Ginger (Ganjiang). When heart Yang is restored, it can warm the body and transform fluids, fundamentally preventing the generation of fluid retention. This is the principle of "enhancing the source of fire to dispel the overcast".

(4) Commonly used formulas include: Bao Yuan Tang to supplement heart Qi, Shen Fu Tang to rescue heart Yang, and Zhen Wu Tang to warm kidney Yang and thereby support heart Yang. Clinical practice frequently adopts Zhen Wu Tang from the Treatise on Febrile Diseases (Shang Han Lun) combined with Tingli Dazao Xiefei Tang from the Essentials from the Golden Cabinet (Jin Gui Yao Lue) as the foundational prescription, with modifications based on individual conditions. Zhen Wu Tang embodies the principle of "supplementing Qi, activating Yang, and promoting diuresis", while the addition of Tinglizi (Semen Lepidii) and Sangbaipi (Cortex Mori) reflects the strategy of "draining the lung". This is often combined with blood-activating and stasis-resolving herbs, such as Danshen (Salviae Miltiorrhizae Radix), Yimucao (Leonuri Herba), and Zelan (Lycopi Herba), to address the concomitant pathogenesis of "blood stasis", thereby embodying the holistic approach of "regulating water and blood simultaneously".

(5) The combination of Fuzi (Aconiti Lateralis Radix Praeparata) with HuangQi (Astragali Radix) serves to supplement Qi, warm Yang, strengthen the heart, and consolidate the root. The pairing of Tinglizi with Dazao (Jujubae Fructus) drains the lung and relieves dyspnea without compromising healthy Qi. The compatibility of Guizhi (Cinnamomi Ramulus) with Fuling (Poria) warms and unblocks heart Yang, transforms Qi, and promotes diuresis.

This therapeutic approach serves as the cornerstone of treatment, adhering to the principle that "where there is a trace of Yang Qi, there is a ray of vitality".

Difference between "supplementing Qi and invigorating Yang" and "supplementing Qi and warming Yang": "Invigorating Yang" emphasizes "functional stimulation"—the term "invigorate" implies arousing, stimulating, and elevating. It does not directly replenish the material basis of Yang qi; rather, by greatly supplementing the primordial Qi, it enables sufficient Qi to propel, stimulate, and elevate the clear Yang of the spleen and stomach. The core issue it addresses is "sufficient Qi but stagnant yang". "Warming yang" emphasizes "state of warmth"—the term "warm" implies heating and dispelling cold. "Warming Yang" directly supplements and warms the deficient Yang Qi of the body. Since Yang deficiency often develops from Qi deficiency, it is usually combined with Qi-supplementing methods, i.e., "supplementing Qi and warming yang". The core issue it addresses is "Yang deficiency leading to internal cold".

Based on this differentiation between "invigorating yang" and "warming yang", Professor Guo Shuwen places particular emphasis on supplementing Qi in clinical practice, while also paying attention to stimulating the body's own Qi in terms of generation, ascent, and descent, fully leveraging the propelling, stimulating, and warming effects of Qi. He commonly uses herbs such as Astragalus, Ginseng, Codonopsis, and Pseudost ellaria (Taizishen), and rarely uses highly hot and toxic herbs like Aconite and Aconitum (Wutou); even when used, they are started at small doses to ensure medication safety.

The academic thought of "supplementing Qi, invigorating Yang, draining the lung, and promoting diuresis" is highly consistent with modern HF treatment principles: "supplementing Qi and invigorating Yang" is analogous to cardiotonic effects and improving myocardial energy metabolism, such as positive inotropic agents. "Promoting diuresis" directly corresponds to the use of diuretics to reduce cardiac preload. "Draining the lung" effectively alleviates symptoms of acute pulmonary edema. The overall therapeutic approach reflects a holistic regulation of the neuroendocrine system rather than singletarget intervention.

3.1.2. Supplementing Qi and nourishing Yin method

(1) Indications: Suitable for HF patients with prolonged disease or coexisting diabetes mellitus, presenting with manifestations of dual deficiency of both Qi and Yin, such as shortness of breath, fatigue, dry mouth and throat, feverish sensation in palms and soles, and red tongue with little coating. Commonly seen in diastolic HF or after longterm diuretic use.

(2) Representative formula: Shengmai San is the basic formula for supplementing Qi and nourishing yin; Zhigancao Decoction (or Baked Licorice Decoction) for supplementing Qi and nourishing yin, unblocking Yang and restoring the pulse.

(3) Commonly used medicinal herbs: Panax ginseng / Panax quinquefolius (American ginseng), Ophiopogon japonicus (dwarf lilyturf), Schisandra chinensis (five-flavor berry), Polygonatum odoratum (fragrant Solomon's seal), and Rehmannia glutinosa (Chinese foxglove).

3.2. Dispelling pathogenic factors and treating the symptoms – The major approach for addressing the manifestations

This targets pathological products such as blood stasis, fluid retention, and phlegmturbidity.

3.2.1. Activating blood circulation and removing stasis – Applied throughout the entire course

(1) Indications: Suitable for all HF patients presenting with manifestations of blood stasis, such as chest

tightness and pain, cyanotic lips and nails, dark purple tongue with petechiae and ecchymoses, and distended neck veins. Blood stasis syndrome runs through the entire course of HF; therefore, the method of activating blood circulation is applied throughout, which is consistent with the understanding of the pathogenesis of coronary heart disease [9], making it particularly suitable for HF patients due to coronary heart disease.

(2) Representative formulas: Xuefu Zhuyu Decoction and Taohong Siwu Decoction.

(3) Commonly used herbs: Salvia miltiorrhiza (Danshen), Ligusticum chuanxiong (Chuanxiong), Carthamus tinctorius (Honghua), Prunus persica (Taoren), and Angelica sinensis (Danggui). For severe blood stasis, insect-based remedies such as Hirudo (Shuizhi, leech), Pheretima (Dilong, earthworm), and Eupolyphaga (Tubiechong, ground beetle) are skillfully employed to search out and dredge the collaterals.

3.2.2. Promoting diuresis and reducing edema – Addressing the main symptom

(1) Indications: Suitable for HF patients with fluid retention manifestations such as edema, oliguria, ascites, and dyspnea preventing recumbency. This is an urgent measure for treating the symptoms and is key to symptom relief.

(2) Representative formulas: Wuling San for unblocking Yang, transforming Qi, and promoting diuresis; and Wupi Yin for promoting diuresis and reducing edema.

(3) Commonly used herbs: Poria, Polyporus (Zhuling), Alisma (Zexie), Plantago (Cheqianzi), and Descur ainiae (Tinglizi). Tinglizi drains the lung, relieves dyspnea, and promotes diuresis, and is an important herb in modern treatment of HFrelated edema.

3.2.3. Draining the lung and relieving dyspnea – Primarily for acute conditions

(1) Indications: Suitable for acute leftsided HF attacks, where fluid retention attacks the lung, manifesting as critical conditions such as wheezing, breathlessness, coughing up pink frothy sputum, and orthopnea. This therapeutic approach aligns with the views of Professor Xu Xinru, a nationally renowned senior TCM practitioner [10-12].

(2) Representative formula: Tingli Dazao Xiefei Decoction specifically drains fluid from the lung.

(3) Commonly used herbs: Tinglizi, Morus (Sangbaipi), and Armeniacae (Xingren).

In clinical practice, the above therapeutic methods are often combined organically according to the needs of the condition, forming composite strategies with enhanced efficacy.

4. Dynamic syndrome differentiation and staged treatment

Acute exacerbation stage: The predominant pattern is “branch excess”, and treatment focuses on “draining the lung, promoting diuresis, activating blood, and removing stasis” to rapidly alleviate symptoms.

Stable remission stage: The predominant pattern is “root deficiency” or a mixture of deficiency and excess, and treatment focuses on “supplementing Qi and invigorating Yang / supplementing Qi and nourishing Yin, activating blood and removing stasis” to improve cardiac function and delay disease progression.

5. Holistic concept and regulating other Zangfu organs

Although the disease is located in the heart, HF is closely related to the kidney, spleen, lung, and liver [13]. In treatment,

it is often necessary to warm kidney Yang to assist heart Yang, strengthen the spleen to eliminate the source of phlegm generation, drain the lung to relieve acute conditions, and soothe the liver to regulate Qi and blood.

6. Integration of Traditional Chinese and Western Medicine for complementary advantages

Emphasis is placed on combining TCM with standardized modern medical treatments, including diuretics, betablockers, sacubitril/valsartan, aldosterone receptor antagonists, SGLT2 inhibitors, and vericiguat [1]. TCM has unique advantages in improving symptoms, enhancing quality of life, reducing rehospitalization rates, and regulating neuroendocrine functions.

The treatment of HF is a complete system with clear hierarchical levels, simultaneous attention to both root and branch, and dynamic adjustments. Its essence lies in accurate syndrome differentiation and flexible application of the two major strategies of "supporting the upright" and "dispelling the pathogenic", through the combination of multiple therapeutic methods to achieve the goal of regulating overall body function and reversing pathological states.

In conclusion, the method of "supplementing Qi, invigorating Yang, draining the lung, and promoting diuresis" represents an academic thought in TCM that treats both the root and branch simultaneously, combining reinforcement and elimination. It precisely grasps the dynamic pathogenetic evolution of "deficient Yang – fluid retention – blood stasis" in HF. Particularly in managing acute critical conditions with fluid retention attacking the lung, through the combination of warming Yang to transform Qi and draining the lung to promote diuresis, it can effectively break the vicious cycle, relieve symptoms, and improve prognosis, fully demonstrating the multitarget integrative advantages of TCM in treating complex diseases.

7. Summary

Heart failure is an acute and critical illness in cardiology, characterized by complex pathogenesis and diverse complications. During the acute stage, integrated traditional Chinese and Western medicine is emphasized to stabilize the condition as soon as possible. At this stage, the predominant pattern is "branch excess", and treatment focuses on "draining the lung, promoting diuresis, activating blood, and removing stasis" to rapidly alleviate symptoms. In the stable remission stage, the predominant pattern is "root deficiency" or a mixture of deficiency and excess, and treatment focuses on "supplementing Qi and invigorating Yang / supplementing Qi and nourishing Yin, activating blood and removing stasis" to improve cardiac function and delay disease progression.

8. Conclusion

The theory and practice of traditional Chinese medicine (TCM) in the prevention and treatment of heart failure (HF), after longterm development, have formed a complete understanding system with "root deficiency and branch excess" as the general outline and "Qi deficiency, blood stasis, and fluid retention" as the core pathogenesis. This system not only deeply grasps the dynamic process of disease development but has also achieved theoretical deepening and clinical innovation through continuous dialogue and integration with modern medicine. Currently, research in this field has made significant progress, and its value and potential are increasingly prominent.

From the perspective of clinical evidence, a large number of studies have consistently shown that, on the basis of standard Western medical treatment for HF, the addition of TCM (including classic formulas, proprietary Chinese medicines, and individualized decoctions) can further improve the patient's cardiac function classification, alleviate core symptoms such as palpitations, shortness of breath, and edema, and significantly enhance exercise tolerance and overall quality of life. Importantly, existing clinical observations suggest that this combined intervention regimen is welltolerated without increasing additional risks. This provides a solid practical basis for TCM as an important component of comprehensive HF management.

HF prevention is of paramount importance. The management of the cardiovascular continuum advocated in modern medicine is highly instructive. Early prevention and treatment of highrisk factors and related diseases can effectively reduce the occurrence and progression of HF. Throughout Professor Guo Shuwen's thoughts on the prevention and treatment of atherosclerosis, coronary heart disease, and HF, there is a striking similarity to the management of the cardiovascular continuum, reflecting many core TCM concepts such as "preventive treatment", "holistic concept", and "treating different diseases with the same method".

Future research still needs to seek breakthroughs in several key directions. First, clinical studies should move toward higher levels of evidence, with active design and implementation of largescale, multicenter, randomized doubleblind trials to generate more convincing highlevel evidence. Second, efforts should be made to explore a precision treatment model of "formulasyndrome correspondence". The dynamic evolution of TCM syndrome types in HF, and how to combine modern medical disease classification and staging with precise TCM syndrome differentiation to achieve individualized and optimized treatment, is a core issue for improving clinical efficacy. Finally, mechanism studies need to embrace complexity. TCM compound formulas are complex chemical systems acting on the human body as a complex, giant system. Future research should utilize cuttingedge technologies such as systems biology, network pharmacology, and metabolomics to elucidate the key pharmacodynamic material bases in compound formulas and the integrative effects of their interactions, constructing a complete network map of action from multiple levels of "organism–system–cell–molecule".

In summary, TCM demonstrates unique theoretical advantages and clinical value in the prevention and treatment of HF. The path forward lies in adhering to equal emphasis on TCM and Western medicine, taking clinical efficacy as the foundation, employing modern technology as a means, conducting indepth mechanistic studies on the treatment of HF by renowned senior TCM practitioners, and optimizing clinical protocols. By completing the modern transformation from "empirical inheritance" to "evidence support" and "mechanism elucidation", TCM will surely contribute more distinctive Chinese wisdom and solutions to the global prevention and treatment pattern of HF.

Funding

Guo Shuwen Studio, the Seventh Batch of National Project for Inheriting the Academic Experience of Veteran Traditional Chinese Medicine Experts (Project No.: National Traditional Chinese Medicine Personnel Education Letter [2022] No. 76); Beijing Xinhuo Chuan Cheng "3+3" Guo Shuwen Grassroots Traditional Chinese Medicine Inheritance Studio (Project No.:Beijing Traditional Chinese Medicine Science Character [2023] No. 114); Fangshan District "Spring Seedling Top-notch Plan" Guo Shuwen Famous Traditional Chinese Medicine Inheritance Studio (Project No.:Jing Fang Wei [2021] No. 46)

Disclosure statement

The authors declare no conflict of interest.

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Publisher's note

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Cardiovascular Reviews, 2026, Volume 4, Issue 3
https://bbwpublisher.com/journal/CR
Online ISSN: 2981-8109
Print ISSN: 3083-4880

Calculation Method of Coronary Artery OCT Quantitative Flow Fraction (OFR) to Evaluate the Morphological and Functional Effects of Enhanced Lipid-Lowering Therapy on Primary Coronary Vulnerable Plaques

Tianbao Xu, Dong Xu, Jinghe Zhao, Maihemitijiang Keyoumu, Muneer Zairi*

Kizilsu Prefecture People's Hospital, Kizilsu 845350, Xinjiang Uygur Autonomous Region, China

Author to whom correspondence should be addressed.

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Abstract: *Objective*: Based on the quantitative calculation method of coronary optical coherence tomography (OCT) for blood flow fraction (OFR), this study aimed to evaluate the intervention effects of intensive lipid-lowering therapy on plaque morphological characteristics and vascular functional parameters in patients with primary coronary vulnerable plaques, providing clinical evidence for precise lipid-lowering treatment and improvement of vascular function in coronary artery disease (CAD). *Methods*: A total of 40 patients with primary coronary vulnerable plaques admitted to our hospital from June 2025 to June 2026 were enrolled as study subjects and randomly divided into a control group and an experimental group, with 20 cases in each group. The control group received conventional-dose statin therapy, while the experimental group underwent intensive lipid-lowering therapy with atorvastatin calcium 40mg combined with tafolecimab 150mg administered subcutaneously once every two weeks, with an intervention period of 12 months. OCT was used to assess morphological indicators of vulnerable plaques before and after intervention in both groups, and standardized OFR calculation methods were employed to evaluate changes in vascular functionality. The improvements in plaque morphology and vascular function recovery were compared between the two groups. *Results*: After intervention, the plaque fibrous cap thickness in the experimental group was significantly greater than that in the control group; plaque lipid area, plaque burden, and minimum lumen area were all significantly superior to those in the control group ($P < 0.05$); the OFR value in the experimental group was significantly higher than that in the control group, and the incidence of vascular dysfunction was significantly lower ($P < 0.05$); the improvement in lipid profiles in the experimental group was significantly more pronounced than in the control group, with statistically significant differences between the groups. *Conclusion*: The OFR calculation method enables precise assessment of vascular functional status in coronary artery lesions. Intensive lipid-lowering therapy effectively improves the morphological characteristics of primary coronary vulnerable plaques, stabilizes plaques, reduces vascular stenosis, significantly enhances blood flow reserve function in affected vessels, and lowers the risk of cardiovascular adverse events, demonstrating high clinical value.

Keywords: OCT quantitative flow fraction; OFR calculation method; Enhanced lipid-lowering therapy; Coronary artery

Online publication: September 30, 2026

1. Introduction

Coronary artery disease (CAD) has become one of the leading causes of death from cardiovascular diseases globally, with acute cardiovascular events such as acute myocardial infarction and sudden cardiac death mainly caused by the rupture of vulnerable coronary plaques followed by thrombogenesis. In recent years, increasing clinical evidence has shown that the instability of vulnerable plaques is closely associated with abnormal lipid metabolism, and lipid-lowering therapy is a core intervention measure to stabilize plaques and reduce the risk of adverse cardiovascular events. However, there is still controversy in clinical practice over whether enhanced lipid-lowering therapy can bring additional benefits in improving plaque characteristics and vascular function compared with conventional-dose statin therapy, and how to evaluate the intervention effect accurately.

Coronary optical coherence tomography (OCT) has high spatial resolution and can clearly display the microstructural characteristics of coronary plaques, which is recognized as an important means for identifying vulnerable plaques. The OFR technology derived from OCT imaging realizes the simultaneous evaluation of plaque morphology and vascular function by integrating morphological information with hemodynamic calculation, which avoids the additional damage and examination cost brought by invasive functional measurement. At present, relevant research on applying OFR to evaluate the effect of enhanced lipid-lowering therapy on primary vulnerable coronary plaques is still relatively limited in China. Based on this, this study took patients with primary coronary vulnerable plaques treated in our hospital as the research subjects and used the OCT-based OFR quantitative calculation method to evaluate the effect of intensive lipid-lowering intervention on plaque morphology and vascular function, aiming to provide a reliable reference for the optimization of clinical lipid-lowering treatment strategies for CAD.

2. Materials and methods

2.1. General information

A total of 40 patients who were diagnosed with primary coronary vulnerable plaques and who were admitted to the Cardiology Department of our hospital during the period from June 2025 to June 2026 participated in this study. All of the participants underwent a process of definitive confirmation of the primary vulnerable plaques by means of coronary optical coherence tomography (OCT) imaging, and this imaging consistently showed the hallmark morphological characteristics of such plaques, that is to say, thin fibrous caps that enclose large cores that are rich in lipid. Then, the patients were randomly assigned, using a computer - generated random number table, to either a control group or an experimental group, and there were 20 cases allocated to each group to ensure a balanced distribution. The attributes at the demographic and clinical baseline of the two cohorts were as follows: The group that was taken as the control included 12 males and 8 females. There was an age distribution ranging from 48 years old to 75 years old. The age which was an average was 61.36 plus or minus 5.82 years. As for the involvement of coronary artery disease, 14 cases were

found to have single-vessel disease. However, the remaining 6 cases were found to have dual-vessel disease. On the contrary, the group that was set as the experimental group had 11 males and 9 females. The ages ranged from 47 years old to 76 years old. The age which was a mean was 60.92 plus or minus 5.65 years. Inside this group, 13 cases were identified to have single-vessel lesions, and 7 cases were shown to have dual-vessel lesions. Prior to the initiation of the study interventions, comprehensive statistical analyses were conducted to compare these baseline parameters between the two cohorts. The results showed that there were no statistically significant differences that could be seen between the control group and the experimental group when it comes to important baseline characteristics. These characteristics include things like age, the proportion of genders, the number of diseased coronary arteries, the profiles of baseline serum lipids, and relevant medical histories (and all of the *P* values were greater than 0.05). This lack of remarkable differences in the baseline data successfully proved the equality of the two groups for the comparative research. The whole research project was reviewed formally and was authorized by the Medical Ethics Committee of our institution. Also, in strict accordance with ethical standards, all of the patients who were enrolled were fully informed about the nature of the study, the procedures involved, the possible risks, and the advantages. As a consequence, each and every patient provided their informed consent and officially signed the formal consent forms prior to joining the study.

2.2. Case selection criteria

To do this research, there was a series of standards that were strictly set out, and these standards were applied to ensure that a cohort of uniform and suitable patients was recruited. The requirements for entry were multi-dimensional, and it was required that every participant should meet four different conditions. First, it was necessary to have a clear diagnosis of primary coronary vulnerable plaques, and this diagnosis was confirmed through a full optical coherence tomography (OCT) assessment of the coronary arteries. Second, candidates did not have any previous experience of having coronary interventional therapies, like percutaneous coronary intervention (PCI), and they had not gone through any intensive or long-lasting lipid-lowering drug plans before being enrolled. Third, participants had to be in the age range of 45 to 76 years old. Finally, they needed to show dyslipidemia that met the clinical criteria which were pre-specified for starting statin - based pharmaceutical lipid-lowering therapy. Fifth, it is required that the participants who take part in the trial have to do the thing of maintaining the condition of clinical stability, which is characterized by the state of having stable vital signs. They should be both able and willing to carry out all of the follow-up imaging assessments that have been scheduled, and they must have clinical medical documentation that can be fully retrieved. The criteria for exclusion encompass the following: some individuals have severe impairment of the liver or the kidney; some are hypersensitive to statins or have had unfavorable reactions to them; some patients have a previous history of having coronary stent placed or coronary artery bypass grafting (CABG) done; some subjects have been found to have acute myocardial infarction, severe cardiac arrhythmias, or severe heart failure (NYHA Classes III to IV) during the screening phase; some patients have active autoimmune disorders or a history of cancer; some are expected to stop the study treatment ahead of time, to become lost during the follow-up process, or to withdraw from the study on their own initiative; and some individuals have coronary artery lesions that are mainly made up of multiple severe calcified plaques.

2.3. Method

2.3.1. Control group

The control group received conventional-dose statin therapy for the purpose of lipid regulation. Specifically, it involved orally taking 20 mg atorvastatin calcium tablets each night before sleep for a period of 12 months . At the same time, these patients carried out the action of following standard coronary heart disease basic management protocols. These protocols included standardized antiplatelet treatment, strict control of blood pressure and blood glucose, adherence to a low-salt, low-fat diet, and moderate physical activity. The action of using aggressive lipid-lowering regimens was not carried out. During the entire treatment phase, the action of regularly assessing lipid panels and liver/renal function was done, and patients had the action of educating them be carried out so that they would strictly abide by the standardized medication schedule in order to ensure the action of treatment adherence be achieved.

2.3.2. Experimental group

The cohort that was used for the experiment was given a strategy of lowering lipids in an intensified way along with standard and fundamental care. Oral atorvastatin calcium tablets 40mg once every bedtime, combined with tafolecimab 150mg subcutaneous injection once every two weeks (ih Q2w), for a total intervention duration of 12 months. The management protocols at the starting point were made to be the same as those of the group that was used for control. This included the act of avoiding, in a rigorous manner, the risk factors that can be changed. These risk factors included patterns of diet that lead to high lipid levels, the act of using tobacco, and the intake of alcohol. There was also a systematic surveillance of lipid profiles and indicators of liver and kidney function. And there was the act of creating treatment regimens that were made for each person. These regimens were adjusted according to the tolerability of each individual patient so as to guarantee both the safety and the effectiveness. Before the intervention took place and after the intervention was finished, both groups underwent evaluations using coronary optical coherence tomography (OCT). The status of blood vessel function was measured in a quantified way through the standardized calculation of the oxidative flow reserve (OFR).

OFR calculation method: A specialized system for OCT hemodynamic analysis is used to carry out three-dimensional reconstruction of the vessel of the target lesion, automatically delineate the contour of the lumen, and identify the branch vessels. By using a velocity of congested blood flow that is population-standardized and has a value of 0.35 m/s as a reference, the state of congestion of the coronary artery is simulated to calculate the ratio of pressure between the segment of the proximal part and the segment of the distal part of the lesion vessel, and this ratio is used to determine the value of the OFR. When an OFR is greater than or equal to 0.80, it shows that the function of the blood flow of the vessel is normal, while when an OFR is less than 0.80, it shows that there is functional ischemia. All the analysis of the image and the computation of the data were carried out independently by two radiologists who are senior, and cross-validation was applied in order to make sure that the accuracy of the result and to cut down the bias that is subjective.

2.4. Observation indicators

(1) Plaque morphological parameters

(2) Vascular functional indicators.

(3) Lipid parameters.

2.5. Statistical analysis

Data were analyzed using SPSS 26.0 statistical software.

3. Results

3.1. Comparison of plaque morphology and lipid profile parameters between the two patient groups after intervention

See **Table 1** for details.

Table 1. Comparison of plaque morphology and lipid profile parameters

Group	Number of Cases	Hair cap thickness (μm)	Lipid area (mm^2)	Plaque burden (%):	Minimum lumen area (mm^2)	LDL-C(mmol/L)
Control group	20	132.36 ± 15.24	3.85 ± 0.62	72.35 ± 6.85	2.15 ± 0.42	2.86 ± 0.52
Experimental group	20	186.52 ± 12.38	2.12 ± 0.45	58.62 ± 5.36	2.89 ± 0.36	1.62 ± 0.38
t	-	12.458	10.265	7.965	6.125	8.752
P	-	<0.05	<0.05	<0.05	<0.05	<0.05

3.2. Comparison of vascular functional indicators between the two groups

See **Table 2** for details.

Table 2. Comparison of vascular functional indicators

Group	Number of Cases	OFR	Incidence of vascular ischemia [n (%)]
Control group	20	0.76 ± 0.05	9（45.00）
Experimental group	20	0.85 ± 0.04	2（10.00）
t/χ^2	-	6.258	5.625
P	-	<0.05	<0.05

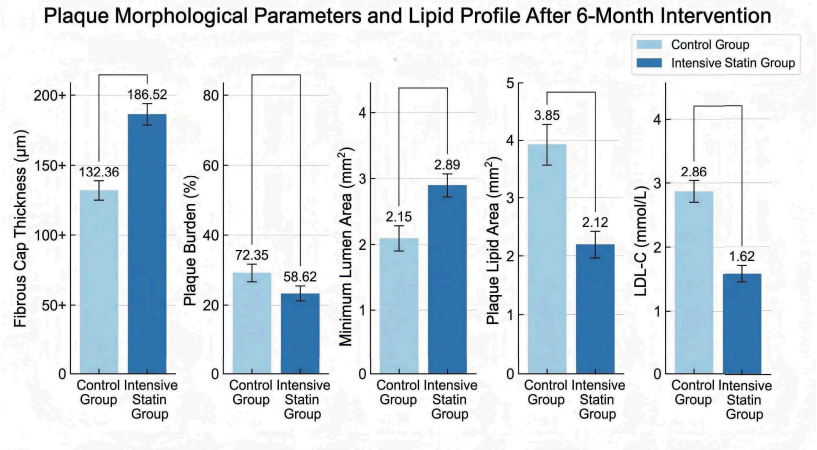


Figure 1. Plaque morphological parametersand lipid profile comparison

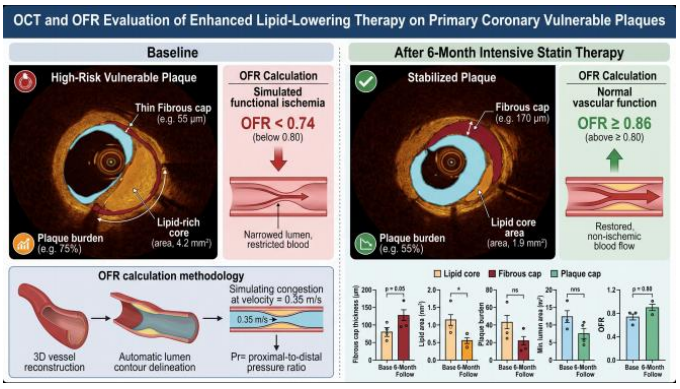


Figure 2. Schematic mechanism of plaque stabilizationand hemodynamic restoration assessed by OCT/OFR

4. Discussion

Acute coronary syndrome and sudden cardiac death are mainly caused by vulnerable coronary plaques [1]. These vulnerable plaques are defined in such a way that they have a fibrous cap that is thin, a lipid core that is large, a susceptibility to rupture that is heightened, and a tendency for secondary thrombosis [2]. These features make it so that their risk of having adverse cardiovascular events is elevated when compared to stable plaques.

Statins are the cornerstone drug for stabilizing coronary vulnerable plaques. Conventional lipid-lowering therapy can slightly improve blood lipid levels, but has limited efficacy in stabilizing high-risk vulnerable plaques [3]. Intensive therapy of lowering lipid can very obviously make the cholesterol of low - density lipoprotein go down, carry out the suppression of inflammation of vascular endothelial, do the reduction of lipid accumulation, make the thickening of fibrous caps speed up, and bring about the reduction of lipid cores [4]. All of these things work in order to make vulnerable plaques become stable and reverse the early progression of plaque lesions.

The improvement of vascular function is a key indicator to evaluate the long-term prognosis of coronary heart disease, because the improvement of plaque morphology alone cannot fully reflect the real blood perfusion capacity of blood vessels [5]. In the course of the present and ongoing investigation, a method that has been standardized was employed for the purpose of calculating what is known as the oxygen flow reserve (OFR) so as to carry out an assessment of vascular function [6]. The outcomes of the investigation demonstrated that after the intervention had taken place, the measurement of the OFR in the experimental group showed an increase that was quite notable.

To summarize, the quantitative assessment method of the OFR makes it possible to carry out an accurate and straightforward evaluation of the vascular function of the coronary artery lesion [7]. When it is integrated with the morphological analysis based on OCT, it helps to carry out a comprehensive assessment of the efficacy of lipid-lowering therapy [8]. Intensive lipid-lowering therapy can effectively improve the morphological features of the primary coronary vulnerable plaques, stabilize the high - risk plaques [9], remarkably improve the blood flow function in the diseased vessels [10], reduce the risk of myocardial ischemia, and show therapeutic outcomes that are superior compared with the conventional lipid - lowering regimens. Therefore, it is very suitable for being applied widely among the patients who have high - risk coronary artery disease and vulnerable plaques [11].

Funding

Tianshan Talent Program for High-Level Medical and Health Professionals (Project No.: TSYC202401B215)

Disclosure statement

The authors declare no conflict of interest.

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Cardiovascular Reviews, 2026, Volume 4, Issue 3
https://bbwpublisher.com/journal/CR
Online ISSN: 2981-8109
Print ISSN: 3083-4880

Application Effect of Enhanced External Counterpulsation in Patients with Chronic Heart Failure Comorbid with Type 2 Diabetes Mellitus

Aihua Liu, Zhihua Cui*, Zhiru Ren, Lina Sun, Xiaoying Gao, Yaoxiang Ren

Department of Cardiovascular Medicine, The First People's Hospital of Lvliang, Lvliang 033000, Shanxi, China

***Corresponding author*:** Zhihua Cui, 2294757951@qq.com

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Abstract: *Objective:* To analyze the effects of enhanced external counterpulsation on cardiac function, blood glucose, and exercise tolerance in patients with chronic heart failure comorbid with type 2 diabetes mellitus, and to evaluate the application efficacy of this therapy in this population. *Methods:* From August 2025 to October 2026, patients with chronic heart failure and diabetes admitted to our hospital were enrolled and randomly divided into a control group (n = 75) and an observation group (n = 75) using a random number table method. The control group received standard medication and routine health education, while the observation group received additional external counterpulsation therapy, 30 minutes per session, twice daily, 6 hours per week, for a total of 6 weeks, accumulating one course of counterpulsation with a total duration of 36 hours. *Results:* In terms of cardiac function indicators, after one course of treatment and at 3 months, the observation group showed higher left ventricular ejection fraction (LVEF) and lower left ventricular enddiastolic diameter (LVEDD) and Nterminal proBtype natriuretic peptide (NTproBNP) compared with the control group ($P < 0.05$). For exercise tolerance, the 6minute walk test (6MWT) distance, anaerobic threshold (AT), and maximal metabolic equivalent (METS) were all higher in the observation group than in the control group ($P < 0.05$). Regarding glycemic control, fasting plasma glucose (FPG), 2hour postprandial glucose (2hPG), and glycated hemoglobin (HbA1c) were all lower in the observation group ($P < 0.05$). *Conclusion:* External counterpulsation therapy in patients with chronic heart failure and type 2 diabetes mellitus can improve cardiac function, enhance exercise tolerance, and ameliorate glycemic levels, representing a nonpharmacological treatment modality worthy of broader clinical promotion.

Keywords: Chronic heart failure; Type 2 diabetes mellitus; Enhanced external counterpulsation

Online publication: September 30, 2026

1. Introduction

Chronic heart failure (CHF) is a complex clinical syndrome resulting from abnormal changes in cardiac

structure and/or function due to various causes, leading to impaired ventricular systolic and/or diastolic function, and represents the terminal stage of all cardiac diseases [1-2]. Diabetes mellitus (DM) is a chronic metabolic disorder characterized by impaired glucose homeostasis, among which type 2 diabetes mellitus (T2DM) is the most common type in the Chinese population, accounting for more than 90% of diabetic patients in China [3]. Numerous studies have shown that the prevalence of diabetes is higher in CHF patients than in the general population, and CHF significantly affects the prognosis of diabetic patients. Compared with T2DM patients without CHF, those with comorbid CHF present with more pronounced clinical symptoms and signs, worse New York Heart Association (NYHA) functional class, poorer quality of life, and worse prognosis [4-6]. This highly intertwined coexistence significantly increases hospitalization rates, mortality, and healthcare burden, necessitating multidisciplinary collaboration, early screening, and comprehensive management to improve clinical outcomes [7-8]. How to reduce mortality and improve long-term quality of life in patients with CHF and comorbid diabetes through effective therapeutic strategies has become a clinical focus and hotspot. This study aimed to observe the changes in cardiac function, blood glucose, and exercise tolerance in patients with CHF and T2DM after treatment with enhanced external counterpulsation (EECP), to analyze the efficacy of EECP in this population, and to provide a new non-pharmacological intervention option for the treatment of patients with CHF and T2DM, thereby expanding traditional therapy toward a more diversified approach.

2. Materials and methods

2.1. General information

2.1.1. Study participants

This study was approved by the Ethics Committee of our hospital, and all patients provided signed informed consent. A total of 150 patients with chronic heart failure and comorbid diabetes mellitus admitted to the Department of Cardiology of Lvliang People's Hospital from August 2025 to October 2026 were enrolled. Patients were randomly divided into a control group (n = 75) and an observation group (n = 75) using a random number table method. General clinical data of both groups, including sex, age, body mass index, and smoking history, were recorded and analyzed. There were no significant differences in baseline characteristics between the two groups ($P > 0.05$), as shown in **Table 1**.

Inclusion criteria: met the diagnostic criteria for CHF and T2DM according to the 2024 Chinese Guidelines for the Diagnosis and Treatment of Heart Failure and the Chinese Guidelines for the Prevention and Treatment of Type 2 Diabetes; NYHA functional class II–III; age between 40 and 65 years, regardless of sex; hemodynamically stable; normal audiovisual function; and able to complete outofhospital followup via telephone or WeChat. Exclusion criteria: significant hemodynamic fluctuations; severe heart failure in the acute phase or acute exacerbation; complicated by severe arrhythmias or uncontrolled hypertension; aortic aneurysm; mean pulmonary artery pressure (mPAP) > 50 mmHg; recent use of anticoagulants; congenital heart disease; deep vein thrombosis (DVT) or presence of infectious foci in the lower extremities; lower limb deformities; pregnancy; refusal to participate or inability to cooperate. Termination/withdrawal criteria: occurrence of serious cardiovascular adverse events during counterpulsation therapy; judged by the investigator as needing termination; voluntary withdrawal by the participant; loss to followup or inability to complete the required counterpulsation treatment.

Table 1. Baseline characteristics analysis

Group	n	Gender (%)		Age (years)		BMI (kg/m²)		Smoking history (%)	
		Male	Female	Range	Mean	Range	Mean	Yes	No
Control group	75	44 (58.67)	31 (41.33)	4165	60.61 ± 7.51	18.837.7	26.48 ± 2.11	38 (50.67)	37 (49.33)
Observation group	75	46 (61.33)	29 (38.67)	4065	60.72 ± 7.62	18.637.9	26.51 ± 2.19	36 (48.00)	39 (52.00)
χ^2/t value	–	0.1111		0.0890		0.0854		0.1067	
P value	–	0.7389		0.9292		0.9320		0.7439	

2.2. Methods

Both groups received conventional pharmacotherapy recommended by clinical guidelines, including SGLT2 inhibitors (dapagliflozin), ACEI, betablockers, mineralocorticoid receptor antagonists (spironolactone), cardiotonic agents, metformin, and other medications.

Educational booklets on heart failure and glycemic management were developed and distributed free of charge to enrolled patients. The main content included guidance on calculating fluid intake and output, recognizing and managing symptoms, monitoring blood glucose, regulating BMI, daily exercise and dietary recommendations, and rational medication use. Diseaserelated knowledge was disseminated through patient education lectures, popular science videos, WeChat group communications, and online conferences. Regular telephone followups were conducted to minimize patient attrition.

The observation group additionally received enhanced external counterpulsation (EECP) using a PECP/TI device (Chongqing Pusikang Technology Development Co., Ltd.). The treatment protocol consisted of 30 minutes per session, twice daily, 6 hours per week, for a total of 6 weeks, completing one full course of counterpulsation with a cumulative duration of 36 hours. The procedure was as follows:

(1) ECG leads were attached and secured.
(2) The device was calibrated, the ECG input function was activated, and changes in ECG and exhaust waveforms were monitored on the display screen.
(3) Pneumatic cuffs were wrapped around the calves, thighs, and buttocks.
(4) The counterpulsation pump was activated, and the counterpulsation pressure was set at 0.025–0.035 Pa, gradually increased from low to high. During the procedure, patients' treatment responses were closely monitored, with continuous surveillance of blood pressure, ECG, and other parameters, while pressure and timing settings were adjusted as needed. Adverse reactions such as dizziness and lowerlimb soreness were observed throughout the EECP sessions.

2.3. Observation indicators

Cardiac function, exercise tolerance, and glycemic parameters were compared between the two groups before treatment, after one course of treatment, and at 3 months posttreatment.

(1) Cardiac function indicators: left ventricular ejection fraction (LVEF), left ventricular enddiastolic diameter (LVEDD), and Nterminal proBtype natriuretic peptide (NTproBNP).
(2) Exercise tolerance indicators: 6minute walk test (6MWT) distance, anaerobic threshold (AT), and maximal metabolic equivalent (METS).
(3) Glycemic indicators: fasting plasma glucose (FPG), 2hour postprandial plasma glucose (2hPG), and

glycated hemoglobin (HbA1c).

2.4. Statistical analysis

Data were processed using SPSS version 25.0. Continuous variables are expressed as mean ± standard deviation (SD) and were compared using the *t*test. Categorical variables are presented as frequencies (percentages) and were analyzed using the chisquare test. A *P* value of < 0.05 was considered statistically significant.

3. Results

3.1. Cardiac function

At the time points of one treatment course and 3 months posttreatment, the observation group demonstrated superior cardiac function indicators compared to the control group ($P < 0.05$). See **Table 2**.

Table 2. Cardiac function indicators (mean ± SD)

Group	LVEF (%)			LVEDD (mm)			NTProBNP (pg/ml)		
	Before treatment	After 1 course	After 3 months	Before treatment	After 1 course	After 3 months	Before treatment	After 1 course	After 3 months
Control group (n=75)	46.19 ± 5.38	47.35 ± 5.71	48.92 ± 5.75	57.95 ± 5.15	57.41 ± 5.24	56.01 ± 5.33	1989.52 ± 22.42	1846.22 ± 19.36	1815.44 ± 16.51
Observation group (n=75)	46.22 ± 5.42	51.31 ± 5.84	53.46 ± 5.96	57.96 ± 5.17	55.03 ± 5.06	53.79 ± 4.98	1989.61 ± 22.38	1460.88 ± 15.47	1204.51 ± 13.28
t	0.0340	4.1989	4.7476	0.0119	2.8296	2.6357	0.0246	134.6618	249.7058
P	0.9729	<0.01	<0.01	0.9905	<0.01	<0.01	0.9804	<0.01	<0.01

3.2. Exercise endurance

At the time points of one treatment course and three months, the observation group showed higher exercise endurance indicators than the control group ($P < 0.05$). As shown in **Table 3**.

Table 3. Exercise endurance indicators (mean ± SD)

Group	6MWT (m)			AT (mL/kg·min)			METS		
	Before treatment	1 course	3 months	Before treatment	1 course	3 months	Before treatment	1 course	3 months
Control group (n=75)	331.88 ± 8.25	342.51 ± 10.15	348.21 ± 14.25	9.49 ± 0.89	9.91 ± 1.02	9.86 ± 1.41	4.75 ± 0.68	4.83 ± 0.81	4.91 ± 0.96
Observation group (n=75)	331.92 ± 8.33	377.68 ± 11.85	402.69 ± 15.16	9.47 ± 0.91	10.88 ± 1.25	11.38 ± 1.62	4.79 ± 0.71	5.42 ± 0.96	5.97 ± 0.99
t	0.0295	19.5210	22.6767	0.1361	5.2068	6.1292	0.3524	4.0679	6.6568
P	0.9765	<0.01	<0.01	0.8919	<0.01	<0.01	0.7251	<0.01	<0.01

3.3. Blood glucose

At time points including after one course of treatment and at 3 months, blood glucose levels in the observation group were lower than those in the control group ($P < 0.05$), as shown in **Table 4**.

Table 4. Blood glucose indicators (mean ± SD).

Group	FPG (mmol/L)			2hPG (mmol/L)			HbA1c (%)		
	Before treatment	1 course	3 months	Before treatment	1 course	3 months	Before treatment	1 course	3 months
Control group (n=75)	8.48 ± 0.68	7.96 ± 0.58	7.81 ± 0.53	11.39 ± 1.02	10.48 ± 0.89	10.05 ± 0.81	7.85 ± 0.76	7.49 ± 0.53	7.29 ± 0.49
Observation group (n=75)	8.51± 0.71	7.06 ± 0.55	6.22 ± 0.47	11.37 ± 1.08	9.26 ± 0.73	8.39 ± 0.66	7.82 ± 0.78	7.08 ± 0.48	6.78 ± 0.35
t	0.2643	9.7512	19.4385	0.1166	9.1787	13.7590	0.2386	4.9657	7.3348
P	0.7919	<0.01	<0.01	0.9073	<0.01	<0.01	0.8118	<0.01	<0.01

4. Discussion

Chronic heart failure (CHF) represents the terminal stage of cardiovascular disease and ranks as the second most common cardiovascular complication in diabetes mellitus. In patients with CHF, excessive activation of the reninangiotensinaldosterone system and reduced activity of the natriuretic peptide system can both impair insulin secretion. As cardiac function deteriorates, physical activity limitation and cachexia in CHF patients lead to reduced muscle mass, which further exacerbates insulin resistance. Diabetes mellitus is an independent risk factor for heart failure; approximately 25% of patients with chronic heart failure have coexisting type 2 diabetes mellitus (T2DM), and over 40% of T2DM patients are repeatedly hospitalized due to worsening heart failure. Moreover, T2DM also increases the risk of heart failurerelated complications, including death [911]. In addition, T2DM can accelerate the progression of heart failure through multiple mechanisms (e.g., myocardial metabolic disorders, microangiopathy, chronic inflammation, etc.). The two conditions mutually reinforce each other, forming a vicious cycle. Compared with patients with CHF alone or T2DM alone, the comorbid state significantly increases the risk of major adverse cardiovascular events and elevates hospital readmission rates. Furthermore, in patients with both conditions, longterm and large fluctuations in blood glucose levels, along with persistently impaired mitochondrial function in cardiomyocytes and suppressed myocardial energy metabolism, lead to progressive deterioration of systolic and diastolic function. The circulatory disturbances resulting from worsening CHF further interfere with systemic glucolipid metabolism, widening glycemic fluctuations and consequently compromising the therapeutic effects of both antiheartfailure and hypoglycemic treatments, thereby increasing the clinical complexity of management.

Enhanced external counterpulsation (EECP) is a noninvasive external assisted circulatory device that has demonstrated therapeutic efficacy in conditions such as angina pectoris and ischemic heart failure. By sequentially compressing the calves, thighs, and buttocks, EECP increases diastolic blood perfusion to the heart and other vital organs, augments coronary blood flow, and improves myocardial oxygen supply; it also reduces cardiac afterload, increases cardiac output, and improves cardiac function [12]. In effect, EECP mimics the hemodynamic changes induced by intraaortic balloon counterpulsation. Beyond the immediate hemodynamic effects mentioned above, EECP promotes the opening of collateral circulation and ameliorates myocardial ischemia and hypoxia; it also modulates systemic shear stress, promotes the release of nitric oxide (NO), increases NO bioavailability, and maintains normal vascular endothelial function [13]. Compared with invasive circulatory assist techniques, EECP offers advantages of high safety and minimal invasiveness, making it suitable for repeated application in the treatment of CHF patients. This aligns well

with the longterm rehabilitation needs of CHF patients with coexisting T2DM, while avoiding the risks of infection, vascular injury, and other complications associated with invasive procedures. At the same time, EECP provides sustained hemodynamic modulation, which is conducive to improving peripheral tissue microcirculatory perfusion and enhancing insulin sensitivity, thereby breaking the vicious cycle in which heart failure and diabetes mutually exacerbate each other. This offers a novel therapeutic avenue for the comprehensive management of patients with comorbid conditions.

5. Conclusion

In summary, external counterpulsation therapy represents a safe, stable, and efficacious treatment option for patients with CHF and coexisting T2DM. It can improve cardiac function, enhance exercise tolerance, and ameliorate glycemic control, and thus merits wider adoption as a nonpharmacological therapeutic modality.

Funding

Lvliang Key R&D Project (Project No.: 2025SHFZ10)

Disclosure statement

The authors declare no conflict of interest.

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Publisher's note

Bio-Byword Scientific Publishing remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Cardiovascular Reviews, 2026, Volume 4, Issue 3
https://bbwpublisher.com/journal/CR
Online ISSN: 2981-8109
Print ISSN: 3083-4880

The Application of Traditional Chinese Health-Preserving Exercises in Postoperative Rehabilitation After Cardiovascular Surgery: Theoretical Logic, Mechanisms of Action, and Research Agenda

Jieyu Cao, Jia Liu, Xiangyang Hu, Zhengwen Lei*

Department of Cardiothoracic and Vascular Surgery, The First Affiliated Hospital of Hengyang Medical School, University of South China, Hengyang 421001, Hunan, China

***Corresponding author:** Zhengwen Lei, leizhengwen0803@163.com

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Abstract: Postoperative rehabilitation after cardiovascular surgery faces multiple barriers, including decline in physiological function, kinesiophobia, and low exercise adherence. Among the traditional Chinese health-preserving exercises—such as Tai Chi, Baduanjin, Wuqinxi, and Liuzijue—there is an established triad of features labeled "body regulation–breath regulation–mind regulation," which seems to offer special benefits for cardiovascular rehabilitation. The present article gives a coherent account of both the theory and the practical mechanisms of such exercises as they pertain to postoperative care of the cardiovascular system. From a physiological standpoint, Tai Chi can greatly lower systolic blood pressure (SBP) and diastolic blood pressure (DBP), and Baduanjin is of value for left ventricular ejection fraction (LVEF) and 6-minute walk distance (6MWD). In terms of neural function, traditional Chinese health-preserving exercises seem to help remodel the brain—by means of increased functional coupling of the prefrontal cortex–amygdala complex or of the default mode network (DMN). With regard to psychological aspects, their mindful attention component may help to achieve fear extinction and relieve kinesiophobia. The prevalence of postoperative kinesiophobia following cardiovascular surgery is as high as 39.20%–82.57%, making it a basic bottleneck for rehabilitation. With this in mind, this article proposes a theoretical pathway of "brain functional remodeling as a factor in kinesiophobia → better long-term prognosis (in general)" and recommends advancing progress along four lines—specifically, theoretical model construction, multimodal neuroimaging mechanism validation, well-organized randomized controlled trials (RCTs), and guideline translation- this being a theoretical justification for the kind of standardized treatment—using traditional Chinese health-preserving exercises—for postoperative rehabilitation following cardiovascular surgery.

Keywords: Traditional Chinese forms of health-promoting exercise; Cardiovascular surgery; Rehabilitation after operation; Kinesiophobia; Functional remodeling of the brain; Theoretical mechanisms

Online publication: September 30, 2026

1. Introduction

Cardiovascular disease is by far the main source of death and of disability throughout the world—hence a major burden for health services. In recent years—given developments in surgery—the success rate of cardiovascular surgery is now much better than it used to be; still, surgical success is not an end but rather a beginning of treatment, and the quality of postoperative rehabilitation is directly related to the long-term prognosis and quality of life [1]. However, after cardiovascular surgery, rehabilitation presents many problems—among them, a frequent drop in cardiopulmonary performance [2], a decrease in capacity for exercise endurance [3], certain psychological conditions—specifically anxiety or depression [4]- as well as behavioral conditions—among them kinesiophobia [5]. Studies have shown that the prevalence of kinesiophobia following cardiac surgery is as high as 39.20%–82.57% [6]. Kinesiophobia is not merely a direct limitation lowering one's confidence in exercise and bringing on anxiety or depression; in the long run, it is associated with progressive loss of cardiopulmonary capacity and with higher chances of serious cardiovascular events (MACE). If one is confronted with such difficulties, it is true that standard cardiac rehabilitation regimens lower both mortality and the risk of hospital admission [7], yet their use in China is not widespread. Certain obstacles—regional disparities in care, fragmented referral pathways, and patients' psychological concerns about exercise—restrict the promotion of cardiac rehabilitation [8]. A number of scholars have noted that cultural expectations of Chinese patients favor pharmacological treatment over exercise management, further exacerbating the difficulty of cardiac rehabilitation participation [7]. With that in mind, it is worth identifying—among possible solutions—a safe, efficient, widely available, and culturally congruent rehabilitation approach, which is of great clinical and social importance.

Traditional Chinese health-preserving exercises—Tai Chi, Baduanjin, Wuqinxi, Liuzijue, etc.—are characterized by the integrated triad of "body regulation–breath regulation–mind regulation" and possess the dual functions of physical activity and mind-body regulation. In recent years, the application of these traditional exercises in cardiovascular rehabilitation has attracted increasing attention. A systematic review and meta-analysis including 60 studies (39 randomized controlled trials [RCTs]) showed that Tai Chi can significantly reduce systolic blood pressure (SBP) (mean difference [MD] −6.14 mmHg, 95% confidence interval [CI] −8.44 to −3.84) and diastolic blood pressure (DBP) (MD −3.45 mmHg, 95% CI −4.50 to −2.40) [9]. A network meta-analysis including 48 RCTs (4,184 patients) indicated that Baduanjin was most effective in reducing heart rate (standardized mean difference [SMD] = −1.60) and improving vascular endothelial function [10]. However, research on the application of traditional Chinese health-preserving exercises in postoperative rehabilitation after cardiovascular surgery is almost absent, and their theoretical logic and mechanisms of action urgently need to be systematically elucidated.

This article aims to elaborate systematically, at the theoretical level, the application logic and mechanisms of action of traditional Chinese health-preserving exercises in postoperative rehabilitation after cardiovascular surgery, explore their unique value distinguishing them from ordinary aerobic exercise, and propose a future research agenda, with the aim of providing a theoretical framework for clinical research and practice in this field (**Figure 1**).



Figure 1. Traditional qigong in postoperative rehabilitation after cardiac surgery. SBP, systolic blood pressure; DBP, diastolic blood pressure; LVEF, left ventricular ejection fraction; 6MWD, 6-minute walk distance; DMN, default mode network; MACE, major adverse cardiovascular events; RCT, randomized controlled trial.

2. Traditional Chinese health-preserving exercises: Concepts and classification

2.1. Main exercises and their characteristics

Traditional Chinese health-preserving exercises have a long history and have developed into multiple exercise systems represented by Tai Chi, Baduanjin, Wuqinxi, Liuzijue, etc. Tai Chi centers on slow, continuous, and circular limb movements, with an emphasis on "directing qi with the mind and mobilizing the body with qi"; Tai Chi is based upon slow, unbroken, circular limb motion; it has a moderate level of exercise and little joint loading, making it suitable for people of all ages. Baduanjin has eight sections—each one designed to help a particular viscera or part of the body—yet they are not difficult to perform and have clear effects of strengthening the body. Wuqinxi is an imitation—more or less—of the movements of five animals—tiger, deer, bear, monkey, and bird—along with their limb stretching and breath coordination. In Liuzijue one finds six exhalation techniques— "xu, he, hu, si, chui, xi"—with an eye to the relation of breath regulation and bodily functions.

2.2. The core characteristic of the integrated triad of "body regulation–breath regulation–mind regulation"

The main trait which sets off traditional Chinese health-preserving exercises from ordinary aerobic exercise is their mind-body model of the combined triad of "body regulation–breath regulation–mind regulation." "Body regulation" refers to slow, continuous, rhythmic motions of the body—above all, accuracy and coordination of movements. "Breath regulation" stands for deep, long, okay—abdominal breathing is fine, and it affects the autonomic nervous system's function via control of the respiratory rhythm; "mind regulation" describes a form of attention—physical and mental—that is centered and undistracted relaxation—something with a built-in element of meditation. Here are the three; each one of them helps the others—thus forming the

singular mind-body model of traditional Chinese health-preserving exercises as an intervention. Some published studies now claim that traditional Chinese health-preserving exercises—by virtue of their integrative effects on body and mind—can lead to a variety of beneficial results (physiological, mental, or neural) at many levels [11].

2.3. Similarities and differences from common forms of aerobic activity and of mindfulness meditation

The central difference between traditional Chinese health-preserving exercises and ordinary aerobic exercise lies in their mind-body synergy. Common aerobic activities, such as brisk walking and swimming, are mainly aimed at improving cardiopulmonary endurance through exercise intensity, duration, and frequency. Traditional Chinese exercises, by contrast, help maintain health. In moderate-intensity aerobic exercise, they are characterized by breath regulation and focused attention; these two together form a special "exercise + meditation" composite model. One controlled study looked at brain functional connectivity—among Tai Chi users and among people who do aquatic aerobic exercises—and concluded that the Tai Chi group had unique functional connectivity in both resting state and cognitive tasks—particularly enhanced connectivity of the anterior cingulate cortex and insula—areas that are strongly linked with interoceptive awareness, with regard to cognitive control, or to motor organization [12]. This finding suggests that the mechanisms by which traditional Chinese health-preserving exercises affect brain function may differ from those of ordinary aerobic exercise.

Compared with mindfulness meditation, traditional Chinese health-preserving exercises, while maintaining mindful attention, add the dimension of physical movement, giving rise to a unique model of "cultivating stillness within movement." Mindfulness meditation primarily promotes fear extinction and emotion regulation through enhanced functional connectivity of the prefrontal cortex–amygdala pathway [13]; traditional Chinese health-preserving exercises, however, may produce more comprehensive neuromodulatory effects through the synergy of movement, breath, and mindfulness.

3. Needs and problems of postoperative rehabilitation: An analysis of cardiovascular surgery

3.1. Physiological level: Diminished cardiopulmonary function and reduced exercise endurance

Although cardiovascular surgery can correct certain structural defects of the heart and its major vessels, most patients face difficulties in cardiopulmonary performance and exercise endurance after surgery. With regard to acute Stanford type A aortic dissection (AD), for instance, even with a fully successful operation, patients' exercise capacity remains greatly reduced. Patients after AD surgery face a unique rehabilitation dilemma: on the one hand, exercise training can lower heart rate, blood pressure, and body weight and improve cardiovascular health; on the other hand, exercise-related abrupt increases in blood pressure may increase the risk of recurrent aortic events. This contradiction of "exercise is beneficial but risks coexist" often makes clinicians hesitant when prescribing exercise. Studies have shown that 71% of patients after AD surgery hope to receive clear guidance on exercise safety, but current guidelines lack specific threshold parameters for blood pressure or heart rate [14].

3.2. Psychological level: Kinesiophobia, anxiety and depression, and post-traumatic stress

Kinesiophobia is one of the core psychological barriers in postoperative rehabilitation after cardiovascular surgery. Kinesiophobia refers to an excessive, irrational fear of physical activity arising from the concern that activity may lead to re-injury or adverse consequences. In patients after cardiovascular surgery, this fear is particularly prominent—patients have experienced life-threatening acute events and traumatic surgery, and after surgery they are often told to "avoid strenuous exercise" and "control blood pressure," yet lack clear guidance on "what exercise is safe and what intensity is appropriate," leading many patients to remain afraid to move even after obtaining medical clearance.

A scoping review showed that influencing factors of kinesiophobia after cardiac surgery include demographic characteristics, pain severity, frailty, exercise self-efficacy, disease-related factors, and psychosocial factors [15]. Kinesiophobia leads to adverse health outcomes such as delayed recovery, prolonged hospital stay and reduced quality of life, but intervention studies targeting postoperative kinesiophobia are extremely limited. Intervention studies based on the fear-avoidance model have initially shown that graded activity, functional feedback, goal setting, and structured education can significantly improve patients' perceived physical ability and thereby indirectly reduce kinesiophobia levels [16]. It seems likely that traditional Chinese health-preserving exercises—being of low intensity, safe, and easily controlled—may alleviate kinesiophobia through similar mechanisms.

3.3. Behavioral level: Low degree of exercise adherence and low cardiac rehabilitation involvement

Exercise adherence is a key factor affecting the effectiveness of cardiac rehabilitation.

Studies have shown that exercise self-efficacy, as a core psychological mechanism of cardiac rehabilitation, not only predicts exercise behavior but also maintains exercise motivation; however, most patients have low levels of exercise self-efficacy [17]. A direct negative relationship exists between kinesiophobia and exercise self-efficacy—more intense kinesiophobia means a lower likelihood of regular exercise by the patient. For China as a whole, low cardiac rehabilitation participation is a serious issue. A number of systematic reviews now indicate that Chinese cardiac rehabilitation runs into many difficulties, namely, a regional imbalance in available medical resources, fragmented referral pathways, and a serious shortage of rehabilitation facilities. Cultural factors also play a role—many patients tend to prefer pharmacological treatment over exercise management [18]. Therefore, choosing an exercise rehabilitation approach that aligns with patients' cultural identity and is highly accessible is of great significance for improving cardiac rehabilitation participation.

3.4. Social level: Lack of standardized protocols and uneven distribution of medical resources

Postoperative rehabilitation after cardiovascular surgery lacks targeted standardized protocols. Systematic reviews indicate that high-quality evidence in the field of cardiac rehabilitation after AD surgery is severely lacking, and existing studies are mostly observational [14,19]. Although the 2022 American Heart Association/American College of Cardiology (AHA/ACC) guidelines recommend cardiac rehabilitation after AD surgery, the supporting evidence is extremely limited [20]. A recent multicenter RCT preliminarily confirmed the safety and feasibility of moderate-intensity home-based exercise in AD survivors, but the sample size was small and long-term follow-up was lacking [21].

4. Mechanisms of action of Traditional Chinese health-preserving exercises

4.1. Physiological mechanisms: Hemodynamics, cardiac function, autonomic nervous system, and inflammation

The protective effects of traditional Chinese health-preserving exercises on the cardiovascular system have now been verified in many populations having cardiovascular disease. A systematic review and meta-analysis provide strong evidence that Tai Chi reduces SBP (MD −6.14 mmHg) and DBP (MD −3.45 mmHg), as well as resting heart rate (SMD = −0.57), which is an indication of better autonomic nervous function [9]. With regard to vascular endothelial function, Baduanjin can significantly increase nitric oxide (NO) levels (SMD = 0.96) and reduce endothelin-1 (ET-1) concentrations (SMD = −0.91). As far as cardiac function is concerned, a systematic review of 13 RCTs (involving 1,293 patients) gives the result that Baduanjin is of major value in improving LVEF (MD = 6.20%, 95% CI 3.14–9.25) as well as 6MWD (MD = 60.21 m, 95% CI 17.96–102.46) for patients who have undergone percutaneous coronary intervention (PCI) [22]. The practice of Baduanjin also resulted in a very substantial reduction in anxiety and depressive symptoms—Hamilton Anxiety Scale (HAMA) scores showed a mean decrease of 1.40 points, and Hamilton Depression Scale (HAMD) scores showed a mean decrease of 2.80 points [23]. These findings indicate that traditional Chinese health-preserving exercises, while improving cardiovascular function, also exert significant psychological regulatory effects. As far as inflammatory regulation is concerned, traditional Chinese health-preserving exercises may act through autonomic nervous regulation and inflammation/stress-related pathways.

4.2. Psychological aspects: Self-efficacy, fear extinction—along with emotion regulation

Conventional Chinese practices for preserving one's health deal at once with the mental, the emotional, and the behavioral sides of kinesiophobia with regard to the three-dimensional interaction called "body regulation–breath regulation–mind regulation." At the cognitive level, the "body regulation" component helps patients rebuild the cognitive association of "exercise = safety" through slow, manageable, and safe movement experiences. A persistent reinforcement of these safe exercise experiences seems helpful in reversing the conditioned fear linked to "exercise = danger." From an emotional standpoint, the "breath regulation" and "mind regulation" components encourage the body's own desensitization to fear responses by activating the parasympathetic nervous system and lowering sympathetic nervous tension. As far as behavior is concerned, the three-dimensional synergistic effect promotes not only confidence but also persistence in exercising—by means of better self-efficacy.

A nursing intervention study based on the fear-avoidance model provides indirect support for the above mechanisms. The research now shows that an intervention based on graded activity, functional feedback, goal setting, and structured education significantly reduces levels of kinesiophobia by improving patients' perceived physical ability (indirect effect ab = −1.879, 95% CI −3.702 to −0.288) [24]. The "body regulation" component of traditional Chinese health-preserving exercises is highly consistent with the concept of graded activity—helping patients gradually build confidence in exercise through low-intensity, progressive movement experiences.

4.3. Neural mechanisms: Prefrontal cortex–amygdala pathway, DMN, and central autonomic network (CAN)

The regulatory effects of traditional Chinese health-preserving exercises involving the brain—i.e., mental exercises—now draw growing attention in neuroscience research. A systematic review and a meta-analysis

provide strong evidence that mind-body exercise has major impacts—on brain activation, on functional neural connections, and on structure [25]. As far as functional brain connectivity is concerned, Tai Chi practitioners show improved functional connectivity between the anterior cingulate cortex and the insula—areas connected to interoception, to cognitive control, and to motor patterns. One study reports that Tai Chi is capable of improving the functional coupling of the amygdala with the medial prefrontal cortex, supporting therapeutic strategies that promote emotion regulation—specifically, reinforcement of the prefrontal cortex–amygdala connection [26].

The core neural circuits for the expression of fear memories involve the prefrontal cortex–amygdala pathway—here, the ventromedial prefrontal cortex regulates the expression of fear memories by actively inhibiting the amygdala, and its activation or thickness is important for successful fear memory extinction. It is now known that mindfulness meditation helps to improve ventromedial prefrontal cortex–amygdala structural or functional connectivity—this seems to encourage fear extinction learning. The "mind regulation" part of the traditional Chinese health-preserving exercises—centered attention and physical and mental relaxation—has, by its very nature, certain similarities with mindfulness meditation and is possibly helpful in bringing about the extinction of kinesiophobia via similar mechanisms. On a larger network scale, the CAN functions as a regulatory hub—linking the prefrontal cortex, insula, anterior cingulate cortex, and amygdala—and brings about integration of autonomic nervous activity by means of top-down regulation and bottom-up physiological feedback. With regard to dynamic causal modeling, it has been shown that effective connectivity from the amygdala to the anterior cingulate cortex and ventrolateral prefrontal cortex is linked negatively to heart rate variability and positively connected to heart rate—this indicates that the prefrontal cortex–amygdala pathway is directly involved in the control of cardiovascular function [27]. With regard to the "breath regulation" and "mind regulation" components, traditional Chinese health-preserving exercises seem capable of helping the prefrontal cortex to exert top-down inhibition of the amygdala—thus achieving a better autonomic nervous state while reducing kinesiophobia. Among the considerations connected with the DMN, traditional Chinese health-preserving exercises seem to help with self-reference and stress regulation, which may be achieved by means of optimized functional connectivity in, or between, DMN networks. Tai Chi users have distinctive resting-state functional connectivity patterns that seem to show how long-term practice may lead to functional specialization of the brain.

4.4. Behavioral mechanisms: Formation of an exercise habit, improved adherence, or greater social support

The group practice tradition—along with the sociocultural features—of traditional Chinese health-preserving exercises is helpful in producing certain behavioral effects. Of these, Tai Chi and Baduanjin are examples of exercises that have a very solid grassroots basis in China, and one may find that practice groups—whether held in a community or in a park—can provide social backing and peer encouragement. That kind of social support is helpful both in starting and in maintaining an exercise habit over time. Exercise self-efficacy—taken as a central psychological factor for exercise adherence—can be gradually improved through successful experiences of the "body regulation" item among the traditional Chinese exercises for health.

5. Theoretical logic: Why traditional Chinese health-preserving exercises are suitable for postoperative rehabilitation after cardiovascular surgery

5.1. Mind-body synergy: Treatment at once of certain physical and mental conditions

The main difficulty of postoperative rehabilitation following cardiovascular surgery is to be considered in connection with physiological dysfunction and psychological or behavioral disorders. Conventional rehabilitation programs often implement physiological training and psychological intervention separately, whereas the integrated triad model of "body regulation–breath regulation–mind regulation" in traditional Chinese health-preserving exercises deals at once with physiological function and psychological condition—both part of one training process. With regard to meta-analytic findings, traditional Chinese exercises that help to preserve one's health may also improve cardiac function (LVEF rose by 6.20%) and are of considerable value in reducing anxiety or depression symptoms—this gives an opportunity to highlight the special value of mind-body synergy intervention [28].

5.2. Low-intensity safety: An option for high-risk cardiovascular populations

Patients who have undergone cardiovascular surgery are a high-risk population for exercise, with safety of the prescription as the main concern. For patients who have had AD surgery, it is necessary to avoid heavy isometric exertion or the Valsalva maneuver; in general, exercise intensity is best kept limited—ideally between 3 and 5 metabolic equivalents (METs). Among traditional Chinese forms of health-preserving exercise, the level of intensity is exactly to be found in the low-to-moderate category—i.e., the energy expenditure of Tai Chi is roughly 2.5–4.0 METs, and that of Baduanjin is about 2.0–3.5 METs—thereby satisfying the criterion of safe exercise (≤4.0 METs) and the intensity needs of groups with a high cardiovascular risk. On the other hand, traditional Chinese forms of health promotion make use of slow motions, little joint strain, and techniques adaptable to individual conditions, and offer high safety. A new multicenter RCT has preliminarily established the fact that moderate-intensity home-based exercise is safe in AD survivors in this regard; there is no higher risk of recurrent dissection or aortic surgery [14].

5.3. Cultural identity: High acceptance and accessibility among Chinese patients

Traditional Chinese practices for preserving one's health rest upon Chinese culture and enjoy a long-established cultural foundation. With regard to the standard training and monitored exercise now known to be among Western models of cardiac rehabilitation, traditional Chinese health-preserving exercises seem to meet Chinese patients' needs more readily and may be done independently—without medical supervision—in local communities and homes, with less need for medical help. Systematic reviews have pointed out that the important reasons for the low participation rate in cardiac rehabilitation in China are insufficient rehabilitation infrastructure and low patient recognition of exercise management [18], while the cultural affinity and low resource requirements of traditional Chinese health-preserving exercises can precisely compensate for these deficiencies [29,30].

5.4. Gradual adjustability: Adjustable intensity and duration according to individual conditions

Traditional Chinese health-preserving exercises possess good adjustability. Exercise intensity can be adjusted through movement amplitude, practice duration, and breathing depth, and the exercise format can be flexibly selected according to the patient's physical fitness level and rehabilitation stage. This gradual adjustability

enables them to meet the needs of different rehabilitation stages after cardiovascular surgery, progressively transitioning from low-intensity breathing exercises and simple movements in the early postoperative period, to complete routine practice in the middle period, and then to maintenance training in the later period.

6. Special application logic concerning postoperative rehabilitation after AD

6.1. Particular features of postoperative rehabilitation after AD

Rehabilitation following an operation for acute Stanford type A aortic dissection (AD) presents special challenges. First, those who have AD must be kept under strict blood pressure control following surgery—so as to avoid recurrent dissection or progression of dissection. Second, patients have experienced life-threatening acute events and major traumatic surgery, and the postoperative kinesiophobia levels they show are very high—there is widespread confusion about "what exercise is safe and what intensity is appropriate." Third, present-day guidelines do not specify any parameters for the prescription of exercise following AD surgery, which is a topic about which clinicians are somewhat uncertain. Fourth, patients after AD surgery have impaired long-term quality of life; compared with the general population, they score significantly lower on multiple dimensions of the 36-Item Short Form Health Survey (SF-36) and have higher bodily pain scores (**Figure 2**).



Figure 2. Traditional health-preserving practices for rehabilitation after cardiovascular surgery. AD, aortic dissection; CAN, central autonomic network; DMN, default mode network; PFC, prefrontal cortex.

6.2. Potential advantages of traditional Chinese health-preserving exercises after AD surgery

Traditional Chinese health-preserving exercises have multiple potential advantages in postoperative rehabilitation after AD surgery. First, with regard to the deep, prolonged abdominal breathing of the "breath regulation" component, it is possible to stimulate the parasympathetic nervous system—thus helping with

blood pressure and with autonomic balance. Second, the slow, rhythmic motions of the "body regulation" component avoid strenuous isometric exercise and the Valsalva maneuver—thereby meeting the safety requirements following AD surgery. Third, the kind of mindful attention given to the "mind regulation" part may be helpful in overcoming kinesiophobia and in bringing about a gradual return to exercise. Fourth, traditional Chinese health-preserving exercises are suited to non-medical environments—thereby lowering the threshold and cost of rehabilitation participation.

6.3. Theoretical pathway of "brain functional remodeling → extinction of kinesiophobia → improved long-term prognosis"

Based upon such an analysis, the present paper proposes a theoretical pathway for traditional Chinese health-preserving exercises in postoperative rehabilitation following AD surgery: through the three-dimensional synergy of "body regulation–breath regulation–mind regulation," traditional Chinese health-preserving exercises help enhance functional connectivity of the prefrontal cortex–amygdala link and optimize DMN functional connectivity, thereby promoting brain functional remodeling; brain functional remodeling further enhances top-down inhibition of the amygdala by the prefrontal cortex and promotes the extinction of kinesiophobia; the extinction of kinesiophobia reduces avoidance of exercise, improves adherence to it and cardiopulmonary function, and so improves long-term prognosis (reduced MACE and enhanced quality of life). This theoretical pathway relates neural mechanisms to clinical outcomes and formulates—on that basis—a scientifically testable hypothesis for later study.

7. Research agenda

7.1. Theoretical model construction—conceptual framework and formulation of a hypothesis

Traditional Chinese health-preserving exercises—when considered as interventions—should be dealt with theoretically in future work on kinesiophobia following cardiovascular surgery. Let us now consider this model:

(1) the relation between the components of intervention (body regulation, breath regulation, mind regulation) and the targets (cognitive, emotional, behavioral, or neural);
(2) the mediating pathways and interaction effects between the various targets;
(3) the influence of moderating variables—age, sex, kind of surgery, initial kinesiophobia level, etc.—with regard to intervention effects. To build a theoretical model, one has to combine several disciplines—psychology (the fear-avoidance idea, self-efficacy theory), neuroscience (circuits for fear extinction, CAN), and sports medicine (exercise prescription theory).

7.2. Validation of mechanisms: A study combining neuroimaging and cardiovascular tests

Validation of a mechanism is best carried out with multimodal neuroimaging techniques—such as resting-state functional magnetic resonance imaging (fMRI), diffusion tensor imaging (DTI), or task-related fMRI—to consider the regulatory effects of traditional Chinese health-promoting exercises with regard to the functional connectivity of the prefrontal cortex–amygdala pathway, the DMN, and the CAN. At the same time, cardiopulmonary exercise testing, ambulatory measurement of blood pressure, and analysis of heart rate variability are all worth combining to assess the link between variations in neural mechanisms and progress

in cardiovascular function. With regard to mediation analysis, a causal model of "changes in brain functional connectivity → changes in kinesiophobia scores → improvement in cardiopulmonary function" should be established.

7.3. Intervention research: Some important design elements for good RCTs

With regard to high-quality RCTs, the following items are worth considering:

(1) clearly specifying inclusion and exclusion criteria to ensure homogeneous groups of participants;
(2) adopting assessor-blinded and analyst-blinded arrangements;
(3) choosing the Tampa Scale of Kinesiophobia Heart (TSK-SV Heart) as the primary outcome measure;
(4) setting a sufficiently long follow-up period (of at least 12 months) to evaluate long-term prognosis;
(5) strictly attending to safety and to adverse effects of the exercise treatment;
(6) adopting a standardized teaching protocol for traditional Chinese health-preserving exercises—so as to ensure homogeneity and reproducibility of the treatment.

7.4. Guideline translation: With an eye to evidence and clinical recommendations

One must now consider how to encourage, on the part of medical authorities, the use of traditional Chinese methods of health preservation in guidelines for post-cardiac surgery care. The following is needed:

(1) the establishment of standardized protocols for traditional Chinese methods of health maintenance in postoperative cardiovascular rehabilitation—specifically, the choice of exercise and intensity grading, with details about suitable frequency and duration;
(2) specifying contraindications and the standards of safety monitoring;
(3) making health economic assessments—i.e., analyses of the cost-effectiveness of traditional Chinese health-preserving forms of exercise rehabilitation;
(4) strengthening the training of clinicians—so as to raise their awareness and readiness to recommend traditional Chinese forms of exercise for health purposes.

8. Conclusion

Traditional Chinese health-preserving exercises, characterized by the integrated triad of "body regulation–breath regulation–mind regulation," have a well-organized theoretical basis as well as wide room for application in postoperative rehabilitation after a cardiovascular operation. Their various mechanisms of action can be considered at four levels—physiological, psychological, neural, and behavioral. At the physiological level, they may improve hemodynamics, cardiac performance, and autonomic nervous balance. At the psychological level, they may help to raise self-efficacy with regard to exercise, promote fear extinction, and regulate emotions. From a neural standpoint, they can promote functional connectivity of the prefrontal cortex–amygdala pathway and work toward optimizing DMN functional connectivity. From a behavioral point of view, they may help to form exercise habits or to maintain them. Traditional Chinese methods of health preservation are particularly well adapted—among other things—to post-cardiac-surgery rehabilitation; their advantages—mind-body interaction, low-intensity safety, cultural identity, and gradual adjustability—render them especially suitable for rehabilitation following high-risk cardiovascular operations such as AD. It is now time to plan systematically four future directions: theoretical models, multimodal neuroimaging validation of mechanisms, good-quality RCT designs, and guidelines—so as to establish

an unambiguous evidence base that supports standardization of traditional Chinese methods of health preservation in postoperative rehabilitation following cardiovascular surgery.

Funding

Hunan Provincial Degree and Postgraduate Teaching Reform Research and Postgraduate Scientific Research Innovation Project (Project No.: 2025JGYB286)

Disclosure statement

The authors declare no conflict of interest.

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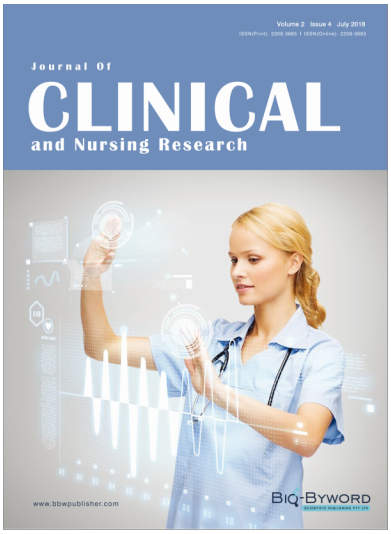
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