Comparison of Application Value of Global Longitudinal Strain and Myocardial Work in Predicting Severe Coronary Artery Stenosis by Echocardiography

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Abstract

ABSTRACT Background: Conventional echocardiography identifies STEMI by regional wall motion abnormality (RWMA), but it still has a great challenge to identify other types of coronary artery disease (CHD). The Two-dimensional Speckle Tracking Echocardiography (2D-STE) makes up for some of the deficiency, especially by using the myocardial work which combined with the left ventricular pressure condition. By this way, the dysfunctional region of myocardium can be identified more accurately, which is expected to be a new non-invasive prediction method for CHD. **Methods:** According to the exclusion criteria, 140 patients who had received coronary angiography (CAG) were included in this study. According to the stenosis rate of coronary artery, the patients were divided into CHD group and control group. The predictive efficacy of GLS and GWI for severe coronary artery stenosis were compared by ROC curve. Then, the 140 patients were respectively re-grouped according to the stenosis rate of LAD, LCX and RCA three times. The regional GLS and GWI are recorded as GLS $_{R}$ and GWI $_{R}$ according to the PRI method described in this article. The efficacy of GLS $_{R}$ and GWI $_{R}$ in predicting severe coronary artery stenosis were compared. Certainly the prediction efficiency between PRI method and traditional method (using the value of GLS and GWI directly) were also compared. **Results:** In predicting severe coronary artery stenosis, compared with GLS $_{R}$, GWI $_{R}$ showed significantly higher sensitivity (95.2% vs 70.2%) and similar specificity (87.5% vs 91.1%). In the aspect of identification of certain coronary artery with severe stenosis, the sensitivity of GWI $_{R}$ was significantly higher than GLS $_{R}$ in predicting severe stenosis of LAD, LCX, and RCA (LAD: 96.5% vs 64.9%; LCX: 65.6% vs 50.0%; RCA: 50% vs 20%). Compared with traditional method, the *"positive region identification" method* has higher AUC in the ROC curve. **Conclusion:** GWI is more sensitive than GLS in identifying patients with CHD that couldn't be detected by conventional echocardiography and performs better in accurately disclosing the culprit coronary arteries with severe stenosis. Compared with the traditional method, the PRI method can be used to judge whether there is severe stenosis in any coronary artery more accurately and confidently. **Keywords: echocardiography, speckle-tracking echocardiography, pressure-strain loop, myocardial work, global longitudinal strain, coronary artery disease, coronary artery stenosis**

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ABSTRACT

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Methods: According to the exclusion criteria, 140 patients who had received coronary angiography (CAG) were included in this study. According to the stenosis rate of coronary artery, the patients were divided into CHD group and control group. The predictive efficacy of GLS and GWI for severe coronary artery stenosis were compared by ROC curve. Then, the 140 patients were respectively re-grouped according to the stenosis rate of LAD, LCX and RCA three times. The regional GLS and GWI are recorded as GLS_R and GWI_R according to the PRI method described in this article. The efficacy of $GLS_R$and GWI_R in predicting severe coronary artery stenosis were compared. Certainly the prediction efficiency between PRI method and traditional method (using the value of GLS and GWI directly) were also compared.

Results: In predicting severe coronary artery stenosis, compared with GLS_R, GWI_R showed significantly higher sensitivity (95.2% vs 70.2%) and similar specificity (87.5% vs 91.1%). In the aspect of identification of certain coronary artery with severe stenosis, the sensitivity of GWI_R was significantly higher than GLS_Rin predicting severe stenosis of LAD, LCX, and RCA (LAD: 96.5% vs 64.9%; LCX: 65.6% vs 50.0%; RCA: 50% vs 20%). Compared with traditional method, the *"positive region identification" method*has higher AUC in the ROC curve.

Conclusion: GWI is more sensitive than GLS in identifying patients with CHD that couldn't be detected by conventional echocardiography and performs better in accurately disclosing the culprit coronary arteries with severe stenosis. Compared with the traditional method, the PRI method can be used to judge whether there is severe stenosis in any coronary artery more accurately and confidently.

Keywords: echocardiography, speckle-tracking echocardiography, pressure-strain loop, myocardial work, global longitudinal strain, coronary artery disease, coronary artery stenosis

INTRODUCTION

Coronary heart disease (CHD) is a kind of heart disease caused by stenosis or occlusion of the coronary artery caused by atherosclerosis, resulting in myocardial ischemia, hypoxia or necrosis. With the improvement of people's material living standard and the change of life style, the number of patients with CHD is increasing year by year. In line with the Global Burden of Disease (GBD) estimates from 2001, 43% of all Cardio Vascular Disease (CVD) deaths are related to CHD.[1] In 2015, CHD accounted for 8.9 million deaths and 164.0 million Disability Adjusted Life Years (DALYs).[2] And the growth rate is continuing to climb, especially in developing countries[3].

CHD is generally divided into chronic coronary artery disease (CAD) and acute coronary syndrome (ACS) according to different pathogenesis and treatment principles, and the latter can be further subdivided into unstable angina pectoris (UA), non-ST-segment elevation myocardial infarction (NSTEMI) and ST-segment elevation myocardial infarction (STEMI).

STEMI can be diagnosed and treated promptly and accurately due to its obvious symptoms, typical ECG and echocardiogram findings. However, the definitive diagnosis of CHD, UA, and NSTEMI is challenging and often requires the help of coronary computed tomography angiography (CTA) or coronary angiography (CAG). CTA is not suitable for routine screening of coronary artery disease due to its semi-invasive and relatively high cost. Because CAG is invasive and risky, it often needs to be implemented under the condition of hospitalization[4]. Echocardiography, as a rapid, convenient, inexpensive, real-time visual and non-invasive means of heart detection, can not only provide patients with a series of valuable information, such as LVEF, myocardial motion status, chamber size, cardiac valves' function and abnormal cardiac anatomical structure, but also carry out a series of functional analysis to improve the sensitivity and specificity of diagnosis and differential diagnosis. It is a relatively comprehensive non-invasive means of cardiac examination, which has been widely used in clinical and scientific research.[5]

Therefore, early identification and treatment of CHD patients is critical, and it is particularly important to be able to find an accurate, non-invasive, and convenient assessment method. In the past decade, thanks to the application of Two-dimensional Speckle Tracking Echocardiography (2D-STE), the Global Longitudinal Strain (GLS) can be used to assess myocardial function. It can quantitatively assess the motion status of each segment of myocardium during the whole cardiac cycle, and identify the scope of myocardium with poor performance more sensitively than visual observation. This enables echocardiography to identify the range of myocardium with slight decrease in myocardial function due to early myocardial ischemia, making it possible for echocardiography to predict coronary artery stenosis at the early stage of the disease.[6-11]

However, recent studies have shown that the GLS only reflect the length variation of myocardium during cardiac cycle but ignores the load condition of the left ventricle during systolic and diastolic periods.[12] The latest pressure-strain loop (PSL) technology and Global Myocradial Work parameters overcomes the load dependence of LVEF and longitudinal strain and can quantitatively analyze the work of the whole and segmental myocardium.[13-14]

The purpose of this study is to compare the ability of GLS and Global work index (GWI) to predict the presence of severe coronary artery stenosis, and to provide a new prediction model which can indirectly diagnose coronary artery with severe stenosis more accurately, so as to provide a reliable non-invasive means of detection for clinical practice, select patients suitable for CAG more accurately and avoid the abuse of invasive examination. Eventually achieve the goal of providing more sensitive and accurate information for clinical work.

MATERIALS AND METHODS

Study Population

A total of 167 patients diagnosed with clinically suspected coronary artery disease who planned to undergo coronary angiography (CAG) in *The First Affiliated Hospital of Soochow University* from January 2020 to October 2022 were prospectively selected and evaluated by echocardiography. The following conditions will be excluded: (1) the regional wall motion abnormality (RWMA) diagnosed by echocardiography; (2) at least one coronary artery had been completely occluded with the history of myocardial infraction; (3) imaging or clinical evidence of any kind of cardiomyopathy; arrhythmia or bundle branch block; (4) echocardiography confirmed that LVEF[?]50%, indicating systolic heart failure; (5) moderate and severe stenosis or regurgitation of any valve; (6) abnormal origin or abnormal course of coronary artery; (7) poor image quality. Finally, 140 patients were included and 27 patients were excluded, the latter including 2 patients of Hypertrophic Cardiomyopathy, 1 patient of complete left bundle branch block, 1 patient of abnormal coronary origin, 4 patients did not undergo coronary angiography, and 19 patients of poor image quality. All study procedures were in accordance with the ethical standards of the responsible committee on human experimentation of our hospital. Written informed consent was obtained from all patients.

Transthoracic Echocardiography

All patients were instructed to take brachial arterial blood pressure measurement in sitting position. The GE Vivid E95 ultrasound system, equipped with M5s transducer with frequency of 1.5~4.0MHz, was used for image acquisition. Then echocardiography, according to the guideline of ASE[15], will be took in left decubitus position and the electrocardiograph was connected synchronously. Clear and complete three-chamber, four-chamber and two-chamber apical dynamic images were obtained, which clearly showed the interface between myocardium and intracardiac blood. Each image lasts for 3 consecutive cardiac cycles under the situation of FPS[?]60.

Left ventricular wall thickness, left ventricular end-diastolic diameter, left ventricular end-systolic diameter were measured by M-mode ultrasound. We obtained the maximum left anterior and posterior atrial diameter by two-dimensional ultrasonic measurement. Simpson biplane method was used to calculate LVEF. Spectral Doppler was used to obtain the peak rates of mitral E velocity and A velocity during diastolic period. Tissue Doppler was used to measure the value of the e' of the septal and the lateral mitral annulus. The maximum velocity of tricuspid regurgitation was measured by continuous Doppler.

Global Longitudinal Strain (GLS) and Myocardial Work Index (GWI)

The echocardiographic images of each patient were post-processed by EchoPAC (Version 203) software. Echocardiographic images were interpreted by two experienced doctors blind to each other's findings and clinical information. Successively choose three-chamber, four-chamber and two-chamber apical dynamic images and enter the "2D-Strain" mode. When the two-dimensional speckle tracking technique was processing, the endocardial border, epicardial border and width of myocardial region of interest (ROI) were manually adjusted. After confirming the myocardial ROI was tracked in real time, we would get LV 17-segment bull's eye diagram of GLS, then the value of each segment and the mean value of the GLS were recorded.

"Myocardial work" was performed after the blood pressure was inputted and aortic valve opening time was confirmed. The bull's eye diagram of "Myocardial Work" in the left ventricle were obtained. The following parameters were calculated: (1) global work index (GWI): total work within the area of the LV pressure-strain loop from mitral valve closing to mitral valve opening including isovolumic relaxation (IVR); (2) global constructive work (GCW): work performed by the LV contributing to LV ejection during systole, which is the sum of work by the myocytes shortening during systole and the myocytes lengthening during IVR phase; (3) global waste work (GWW): work performed by the LV that does not contribute to LV ejection, which is the sum of work by lengthening of myocytes during systole and shortening during the IVR phase; (4) global work efficiency (GWE): GCW/(GCW+GWW). The myocardial work index in each section was recorded, as well as the mean value of GWI, GCW, GWW and GWE.

Positive Region Identification (PRI) Method

First of all, please allow us to define the concepts of "myocardial circle floor" (MCF) and "positive segment" (PS). MCF refers to the three circles of the base segment, the middle segment and the apex segment in the 17-segment mode(Figure 1). If the parameter value of the myocardium in a certain segment is lower than the average value of all segments in the MCF in which it is located, this myocardium segment is judged as "PS-to-be", the segments who can't be judged as "PS-to-be" will be named "normal segment". If the parameter value of the "PS-to-be" is less than 90% of the mean value of all the "normal segment" of the MCF in which it is located, the "PS-to-be" is judged as "PS". According to the assignment of segments to coronary arterial territories[16], 1, 2, 3, 7, 8 and 9 segment were assigned to the "anterior wall region" of the LAD territory; 5, 6, 11 and 12 segments were assigned to the "lateral wall region" of the LCX territory; 3, 4, 5, 9, 10 and 11 segments were assigned to the "inferior wall region" of the RCA territory. If half or more of the "PS" are present in a certain coronary artery territory and at least two of the "PS" are anatomically adjacent, the region is called "positive region" and the coronary artery is judged to have severe stenosis. Some typical cases are demonstrated in Figure 2 and the flow chart is shown in Figure 3.

Coronary Angiography

All patients underwent coronary angiography after the completion of transthoracic echocardiography. Coronary angiography was performed using the standard technique from the percutaneous femoral approach by two experienced interventionists. All patients were grouped based on the results of angiography. Narrowing of [?]50% in the left main coronary artery and [?]70% in at least one major coronary arteries was enrolled into CHD group. Other patients without significant coronary stenosis were enrolled into control group.

Statistical Analysis

The data were analyzed using IBM SPSS Statistics version 23.0. Continuous variables are expressed by their mean and standard deviation ($x\pm$s) if normally distributed. Those do not conform to the normal distribution are represented by the median and interquartile spacing (M (Q1, Q3)). Continuous data were compared using the Student t test or Kruskal-Wallis rank sum test between two groups. Categorical data are expressed in terms of frequencies and percentage and were compared with the Chi-square test. Correlation between GLS and MW parameters of the left ventricle was analyzed by Pearson correlation analysis. In ROC curve analysis, the area under the curve (AUC) was calculated to obtain the best cut-off values of GLS_R and GWI_R for predicting the presence of severe coronary artery stenosis. For multivariable logistic regression analyses, variables with significant P-values on univariable analyses (P <0.1) were included in the models to detect independent risk factors for predicting severe coronary artery stenosis. Intra-observer and inter-observer reproducibility for GLS and GWI parameters was assessed using Bland-Altman analysis. All tests were two-sided, and P values < 0.05 were considered to indicate statistical significance.

RESULTS

Baseline Characteristics

Table 1 presents baseline data for all patients (N=140) enrolled in this study. Compared with the control group, more male patients were in CHD group (69 vs 28 males, 82.1% vs 50%, P¡0.001), and also more diabetes (25 vs 7 cases, 29.8% vs 12.5%, P=0.017) and smokers (42 vs 10 cases, 50% vs 17.9%, P¡0.001), while others baseline and clinical variables have no statistical significance (P > 0.05) between groups.

Echocardiography Data

Conventional echocardiogram data are presented in Table 2. There were statistical significance between two groups in left ventricular wall thickness (9 (9, 10) vs 9 (8, 10), P=0.013), left ventricular end-systolic diameter (31.5 (29.8, 34.0) vs 31.0 (29.0, 32.0), P=0.019), LVEF (61(59,64)% vs 64(60,65)%, P=0.007) and mean mitral annular e' velocity (7.3+-1.6 vs 8.1+-1.7, P=0.004), while no statistical significance in other conventional parameters.

In terms of Longitudinal Strain and Myocardial Work parameters, between the two groups, GLS, GWI, GCW, GWW and GWE were statistically different (P < 0.05). GLS, GWI, GCW and GWE in the CHD group were significantly lower than those in control groups (P < 0.05) while GWW was higher. (Table 2)

Comparison of Efficacy Between GLS and GWI in Predicting Severe Coronary Artery Stenosis

According to PRI method described in "MATERIALS AND METHODS", the results of CAG and the results of GLS and GWI were respectively tested by Four-cell Table Chi-square test. The results showed that the predictive effectiveness of GWI was obviously better than that of GLS, which was reflected in higher sensitivity (95.2% vs 70.2%) and lower missed diagnosis rate (4.8% vs 29.8%), despite a slight reduction in specificity (87.5% vs 91.1%) and a slight decrease in misdiagnosis (8.0% vs 8.9%). GWI had higher Youden's Index (0.827 vs 0.613) and OR value (140.0 vs 24.1) than GLS. ROC curve analysis results showed that the GWI's AUC was 0.914 (P < 0.001, 95%CI: 0.856-0.971) while the GLS's was 0.807 (P < 0.001, 95%CI: 0.732-0.881). (Table 3)

Comparison of The Ability of GLS and GWI to Accurately Identify Coronary Artery With Severe Stenosis.

The prediction results of LAD, LCX and RCA with GLS and GWI model were compared with CAG, which was tested by Four-table Chi-square. The results showed (Table 4-1˜3) that the sensitivity of GWI was significantly higher than that of GLS in predicting severe stenosis (LAD: 96.5% vs 64.9%; LCX: 65.6% vs 50.0%; RCA: 50% vs 20%), and the specificity was not significantly worse than GLS (LAD: 81.9% vs 86.7%; LCX: 89.8% vs 91.7%; RCA: 94% vs 96%).

Cut-off Value of GLS_R and GWI_R

The results of this study showed that the cut-off values of predicting severe stenosis in LAD by GLS_A and GWI_Awere -18.6% and 1814mmHg%; in LCX, GLS_L and GWI_L were -16.9% and 1771mmHg%; in RCA, GLS_I and GWI_I were -17.9% and 1991mmHg%. (Table 5)

Univariate and Multivariate Analyses of Risk Factors Related to CHD

The univariate logistic analysis demonstrated no significant correlation between age, BMI, SBP, DBP, Hypertension, and Hyperlipidemia. The further multivariate logistic analysis (Model 1) demonstrated that smoking and PRI method by GLS were independently related to CHD (smoking: OR 3.701, 95%CI 1.414-9.690 $P < 0.001$; PRI method by GLS: OR 21.155, 95%CI 7.195-62.201, $P < 0.001$). When PRI method by GWI was added in the model instead of PRI method by GLS (Model 2), PRI method by GWI were independently related to CHD (OR 173.816, 95% CI 38.407-786.630, $P < 0.001$). (Table 6)

Inter-observer and Intra-Observer Variability Analyses

Measurements of GLS and GWI were repeated in 20 randomly selected data sets to test their reliability. The observer, blind to previous analysis results, measured these parameters twice 2 weeks apart to assess intra-observer variability. Inter-observer variability was evaluated between two independent observers blind to each other's results. Both observers were blind to coronary angiography results and any other patient's medical chart. (Table 7)

DISCUSSION

The non-invasive method of "positive region identification" proposed in this paper was used to determine whether patients had severe coronary artery disease. The results showed that both GLS and GWI parameters were well matched with CAG results (GLS: sensitivity 70.2%, specificity 91.1%; GWI: sensitivity 95.2%, specificity 87.5%). The univariate logistic analysis showed that age, BMI, blood pressure, hypertension and hyperlipidemia had no significant correlation with CHD, while further multivariate logistic analysis showed that in the GLS model, smoking and GLS method were independently correlated with CHD. When GLS was replaced by GWI to construct the model, we found that only GWI was independently associated with CHD.

The morbidity and mortality of coronary artery disease are increasing year by year. Although more and more patients have chest tightness, chest pain and other symptoms suspected of CHD, routine examination means cannot identify whether they are suffering from severe CHD accurately and timely. Only when they undergo coronary CTA or even CAG examination can accurate results be known. As a result, it is also inevitable to abuse coronary CTA and CAG examination. As one of the important means of routine cardiac examination, if echocardiography can identify and diagnose patients with coronary artery disease earlier, even if it is highly suspected, it can greatly improve the early detection rate of CHD and will provide patients with more appropriate indications for coronary CTA and CAG examination, and greatly reduce the abuse of these invasive examinations, which is not only the good news for the majority of patients, but also reduce the burden of physician, save costs, and avoid unnecessary examinations.

Based on the above clinical needs, we attempted to use noninvasive Two-dimensional Speckle Tracking Echocardiography (2D-STE) and Myocardial Work analysis to identify patients suffered CHD who had not yet developed severe myocardial insufficiency and myocardial infarction. Conventional echocardiography is often used to determine whether a patient has a myocardial infarction and severe myocardial insufficiency based on regional wall motion abnormality (RWMA).[17] Unfortunately, in most cases, patients have already suffered myocardial infarction and have missed the optimal time for treatment before diagnosed. In recent years, due to the universal application of 2D-STE technology, the diagnosis of CHD by echocardiography has gradually changed from experimental judgment to more sensitive and accurate quantitative analysis.[18-19]

However, some recent studies[20-23] have found that although 2D-STE can greatly improve the diagnostic sensitivity of echocardiography for most kinds of heart disease, such as CHD, hypertensive heart disease, cardiomyopathy and heart-related metabolic diseases, it still has some shortcomings mainly manifested in lacking the consideration of load condition. Therefore, compared with GLS, GWI is more sensitive. Above all, the region of functional abnormalities of the myocardium can be displayed more individually by the bull's eye diagram which takes into account the effect of the after-load on LV systolic function. The "positive region identification method" proposed in this study attempts to identify patients with CHD at an early stage, before myocardial infarction occurred, and to provide them with more reliable information and to guide the direction of treatment. In our study, CAG results were used as the "gold standard" to compare the predictive efficacy of the two models (GLS and GWI). Myocardial work parameters often provides more information compared with GLS, which can be said to be a further complement to GLS.[24] In the final statistical process, we found that there were indeed a number of cases in which the dysfunctional myocardium could not be identified by GLS alone, which most likely due to the limitations of 2D-STE. It only considered the length change of the myocardium during the entire cardiac cycle, without taking into account the load changing, which makes myocardial work analysis more sensitive than GLS to identify the region of dysfunctional myocardium.

This approach is based on the experience in clinical work rather than simple statistics. The reason why our study proposed "positive region identification method" to build a model instead of using continuous parameters is various. Firstly, When we retrospectively analyzed these cases, we found that many patients in the CHD group would be simply judged as "normal" just according to the cut-off value, but their bull's eye diagram can actually reflect the region of functional abnormalities of the myocardium. Secondly, the patients were excluded with their complete coronary artery occlusion identified by CAG, as well as patients with regional wall motion abnormality (RWMA) identified by conventional echocardiography, which may narrow the difference between the groups. Thirdly, there are differences between patients' individualization, especially when their blood pressure were take into account. For example, the GWI parameters of a hypertensive patient's myocardium with functional abnormalities may be higher than the one without CHD and hypertension. If we only pay attention to the mean parameter of the all segments of myocardium, the difference between groups is likely to be diluted.

Of course, we contrasted traditional methods with our "positive region identification" method. The regional average GLS and GWI values in the "anterior wall region" of the LAD territory were recorded as GLS_A (anterior wall region of GLS) and GWI_A (anterior wall region of GWI); similarly, LCX's and RCA's were recorded as GLS_L (lateral wall region of GLS), GWI_L (lateral wall region of GWI), GLS_I (inferior wall region of GLS) and GWI_I (inferior wall region of GWI). All 140 subjects were re-divided into CHD group and Control group three times (respectively for LAD, LCX and RCA) by the stenosis rate ([?]70%) of corresponding coronary artery. When we focused on LAD, GLS_R and GWI_R stand for GLS_A and GWI_A; when for LCX, GLS_R and GWI_R stand for GLS_L and GWI_L; when for RCA, GLS_R and GWI_R stand for GLS_I and GWI_I. The results showed that the GLS_R and GWI_R decreased in the corresponding coronary artery's territory. When severe stenosis happened in RCA, GLS_I decreased but GWI_Idid not, which may be explained by two reasons: Firstly, it may varies greatly between individuals about the territory of RCA. Secondly, it may due to the significant difference in blood pressure between the "RCA" and "RCA control" groups in this study, which covered up the slight variation in GWI_I but had little influence on GLS_I. (Table 8)

Although the statistical results of this method were basically satisfactory, the ROC curve analysis (Figure 4) showed that the AUC of predicting LAD with severe stenosis directly by using the values of GLS_A and GWI_A were unsatisfactory, and the prediction efficiency of GWI_A was even not better than GLS_A. However, the " *The Method of Predicting Severe Coronary Artery Stenosis* " proposed in this study support the idea that if half or more of the PS (positive segment) are present in a certain coronary artery territory and at least two of the PS are anatomically adjacent, the coronary artery is judged to have severe stenosis. In fact, by this way, an individual analysis was carried out on each case, and the PS was determined according to the GLS and GWI values of each segment of the myocardium of each case. Then the number and distribution of the PS were used to determine whether there was functional abnormality of the regional myocardium, so as to predict whether the corresponding coronary artery has severe stenosis. The AUC of the ROC curve was obviously higher than conventional method which directly predicted by values of GLS_A and GWI_A. It has same conclusion when it happened to LCX or RCA. It was not difficult to find that GWI was actually better at predicting coronary artery with severe stenosis than GLS. As for RCA, we even find that using the value of GWI_I could not predict severe stenosis of RCA ($P > 0.05$), but by using " *The Method of Predicting Severe Coronary Artery Stenosis* " proposed in our study could achieve a breakthrough.

In this study, a new scheme is proposed to not only predict whether severe stenosis exists in coronary artery, but also accurately identify it from normal. In fact, this method has strong clinical practicability. We do not have to compare the parameter value of each clinical case with the research results of each center, but only need to carry out individualized analysis according to this method to draw a conclusion. According to this approach, GWI is more valuable than GLS. Finally, it is worth mentioning that there was no inter-group difference in GWI_I between the RCA (+) and RCA (-) groups in the results grouped according to the rate of stenosis in RCA. This may indicate that GWI_I value alone cannot be used to predict severe stenosis in RCA, but further analysis using the method proposed in this study may improve the accuracy of diagnosis, and the application value of GWI is higher than GLS. It also reminds clinicians to be more cautious when using STE and non-invasive PSL to predict severe stenosis in RCA. As is well known that even the most ideal prediction method or model is different from the actual situation. The purpose of our study is to propose a method with a better clinical practical value.

CONCLUSION

For patients with coronary artery disease can't be recognized by conventional echocardiography because of lack of performance of regional wall motion abnormality (RWMA), both GLS and GWI can not only better predict whether there is severe stenosis in their coronary arteries, but also further accurately identify which one it is. However, compared with GLS, GWI has better sensitivity and almost the same specificity in both the ability of identification of coronary artery with severe stenosis and picking it out from normal coronary arteries without severe stenosis.

Compared with the traditional method, the "positive region identification" method performed better in predicting whether there is severe stenosis in any coronary artery before the invasive examination CAG accomplished.

LIMITATION

The application of GLS and GWI are somewhat limited because of their image quality dependence of two-dimensional echocardiography. Although most cases of coronary artery domination are similar described in this study, individual differences still exist. In addition, the formation of collateral circulation of coronary artery is not taken into account, so the results may still be biased to some extent.

The influence of diabetes on coronary peripheral vessels and the possible existence of undiagnosed cardiomyopathy may also lead to the regional reduction of GLS and GWI parameters, leading to the deviation of the predicted results.

Finally, it is worth mentioning that the new method described in this study may have poor performance when used for patients with severe stenosis in all three coronary arteries, despite the proportion is very low, and may even be misjudged as the non-severe coronary artery stenosis, which is related to the method described in this study to predict the existence of severe coronary artery stenosis. Therefore, in practical clinical application, the specific values of relevant parameters still need to be combined.

DECLARATIONS

Ethical Approval

No animal studies are presented in this manuscript. The studies involving human participants were reviewed and approved by **The First Affiliated Hospital of Soochow University Ethics Committee** . The patients/participants provided their written informed consent to participate in this study. No potentially identifiable human images or data is presented in this study.

Competing interests

We declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Authors' contributions

Jiawei Zhou and Ying Xu completed the manuscript writing, Changsheng Ma was responsible for data collection and analysis, Bingyuan Zhou and Caiming Zhao completed data interpretation and verification, Chao Wei completed the CAG result statistics, Shengda Hu prepared all figures and tables, and Cao Zou was responsible for the review and delivery of the manuscript. All authors reviewed the manuscript.

(Jiawei Zhou is the first author and Ying Xu is the co-first author. Cao Zou is the corresponding author and the Shengda Hu is the joint corresponding author)

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The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author/s.

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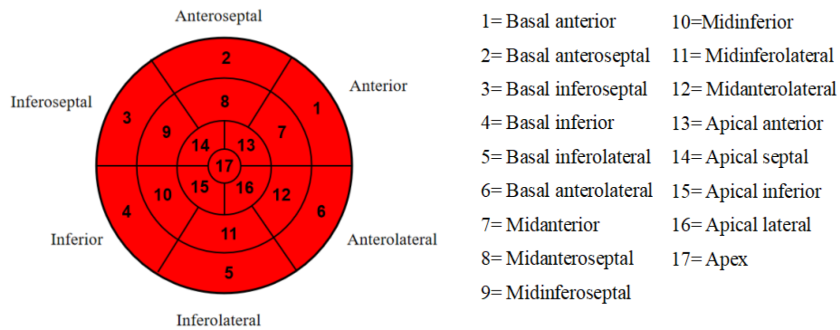
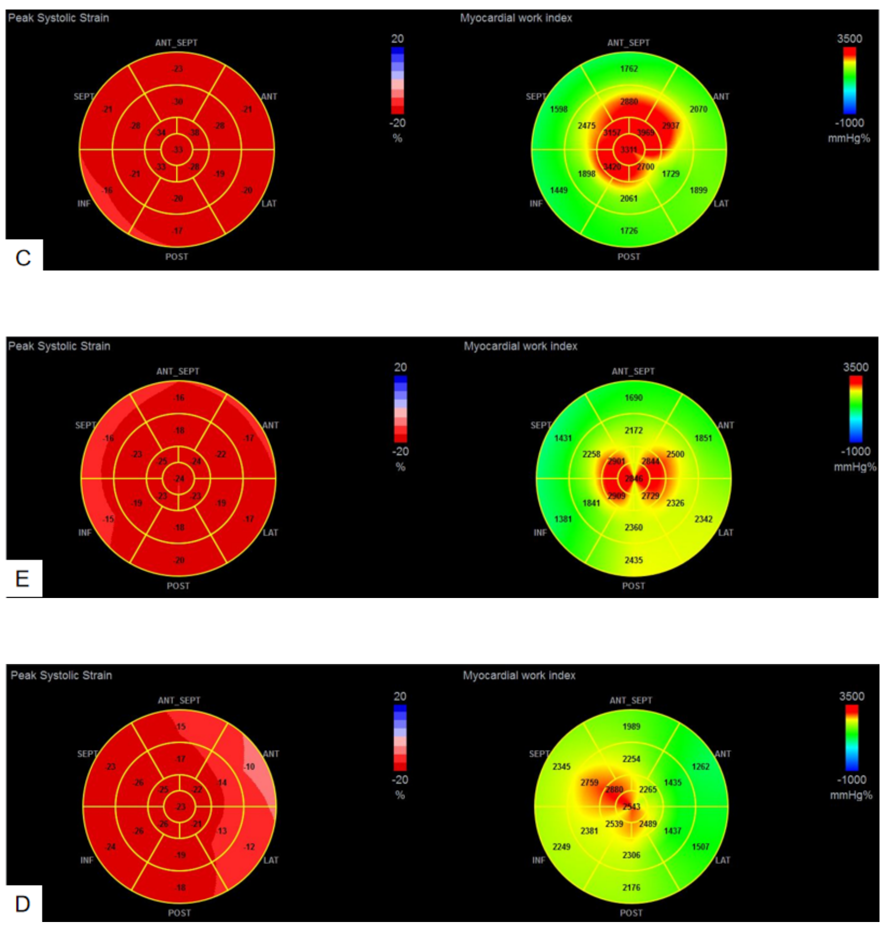


Figure 1. Left ventricular segmentation. According to the most common anatomical

distribution of the coronary arteries (RCA dominance), segments 1,2,3,7,8 and 9 were classified as “anterior wall region” of the LAD domination. Segments 5,6,11 and 12 were classified as “lateral wall region” of the LCX. Segments 3,4,5,9,10 and 11 were classified as “inferior wall region” of the RCA. LAD, left anterior descending artery; LCX, left circumflex artery; RCA, right coronary artery.



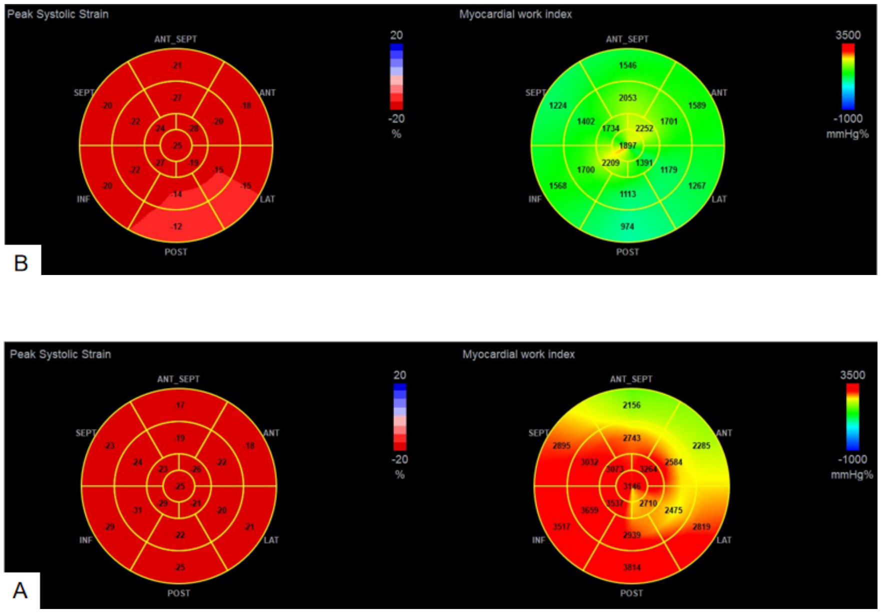


Figure 2. A, GWI revealed that the "positive region" matched LAD territory but GLS reveal normal. B, GLS and GWI revealed that the "positive region" matched LCX territory. C, GWI reveal that the "positive region" matched RCA territory but GLS reveal normal. D, GLS and GWI revealed that the "positive region" matched LAD and LCX territory. E, GWI revealed that the "positive region" matched LAD and RCA territory but GLS was short of the evidence.

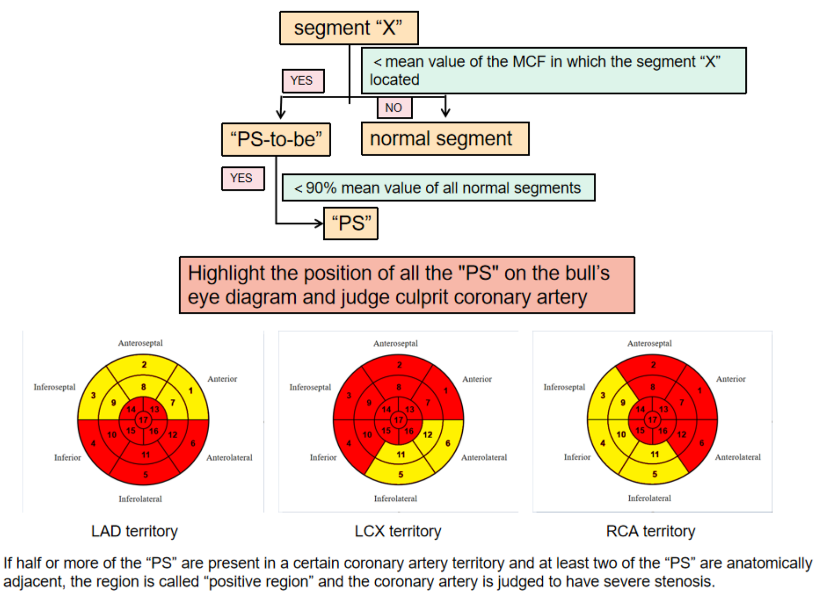


Figure 3. The flow chart of the *Method of Predicting Severe Coronary Artery Stenosis—— "positive region identification" Method.*

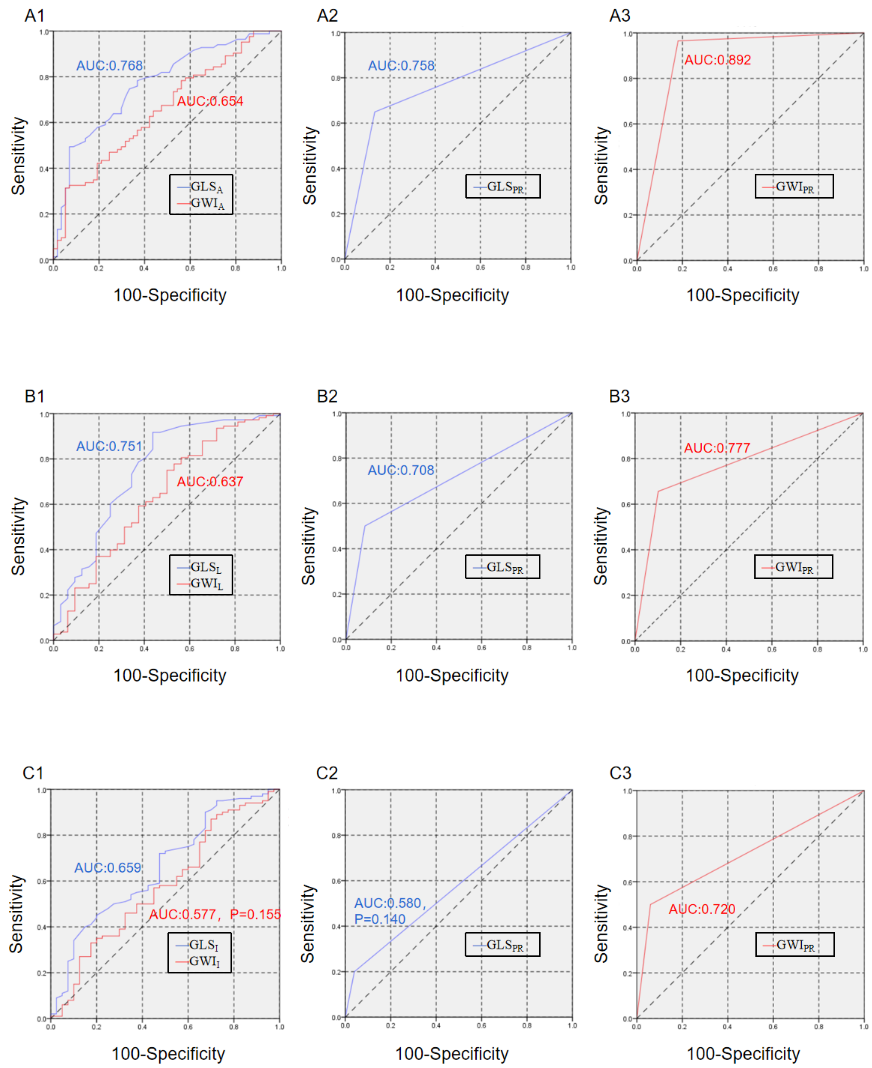


Figure 4. A1, directly using GLS_A and GWI_A to predict severe stenosis in LAD. A2˜3, using “positive region identification” method to predict severe stenosis in LAD. B1, directly using $GLS_L$and GWI_L to predict severe stenosis in LCX. B2˜3, using “positive region identification” method to predict severe stenosis in LCX. C1, directly using $GLS_I$and GWI_I to predict severe stenosis in RCA. C2˜3, using “positive region identification” method to predict severe stenosis in RCA. GLS_{PR}, identify “positive region” based on territorial GLS. GWI_{PR}, identify “positive region” based on territorial GWI.

Table 1. Baseline and clinical variables.

Variable	CHD group(N=84)	Control group(N=56)	*t*、*Z*、 *2*	*P* value
Age, years	61.5±9.8	62(56,69.8)	-0.353	0.724
Male, n(%)	69(82.1%)	28(50%)	16.313	¡0.001
BMI, kg/m^2	24.3±2.8	23.9±2.8	-0.832	0.407
SBP, mmHg	129.8±16.4	125.6±13.7	-1.616	0.108
DBP, mmHg	77.8±10.6	77.5±7.7	-0.141	0.888
Hypertension, n(%)	58(69%)	33(58.9%)	1.512	0.219
Diabetes, n(%)	25(29.8%)	7(12.5%)	5.678	0.017

Smoking, n(%)	42(50%)	10(17.9%)	14.869	¡0.001
Hyperlipidemia, n(%)	6(7.1%)	2(3.6%)	0.271	0.603

SBP: systolic blood pressure, DBP: diastolic blood pressure, t: Student t test value, Z, Kruskal-Wallis rank sum test valve,χ^2 :Chi-square test value.

Table 2. Conventional echocardiography parameters, GLS and myocardial work parameters.

Variable	CHD group(N=84)	Control group(N=56)	t、Z	P value
LAd (mm)	38.0(36.0,40.8)	37.1±4.5	-1.419	0.156
LVWT (mm)	9(9,10)	9(8,10)	-2.481	0.013
LVDd (mm)	47.4±3.9	46.4±4.2	1.382	0.169
LVDs (mm)	31.5(29.8,34.0)	31.0(29.0,32.0)	-2.352	0.019
LVEF(Simpson) (%)	61(59,64)	64(60,65)	-2.697	0.007
TRMP (mmHg)	20(18,24)	20(18,25)	-0.827	0.408
Mitral E (cm/s)	62(54,73)	63(52,85)	-0.853	0.394
Mitral A (cm/s)	80.3±18.5	75.3±19.1	1.537	0.127
Mitral E/A ratio	0.8(0.7,1.0)	0.9(0.7,1.2)	-1.661	0.097
Mean e' (cm/s)	7.3±1.6	8.1±1.7	-2.917	0.004
E/e' ratio	9.0±2.7	7.9(6.6,9.8)	-1.463	0.143
GLS (-%)	21.3±3.0	24.3±2.5	-6.123	¡0.001
GWI (mmHg%)	2149±418	2362±395	-3.011	0.003
GCW (mmHg%)	2456±473	2681±452	-2.811	0.006
GWW (mmHg%)	54.5(38.0,79.5)	45.5(26.5,60.0)	-2.444	0.015
GWE (%)	97(96,98)	98(97,98)	-3.432	0.001

LAd: left atrial diameter, LVWT: mean left ventricular wall thickness, LVDd: left ventricular end-diastolic diameter, LVDs: left ventricular end-systolic diameter, LVEF: left ventricular ejection fraction, TRMP: maximum pressure of tricuspid regurgitation, mean e': the average of septal and lateral e' velocity of mitral annular, GLS, global longitudinal strain, GWI, global work index, GCW, global constructive work, GWW, global wasted work, GWE, global work efficiency.

Table 3. The comparison of using *"positive region identification" Method* to judge CHD by GLS and GWI.

Model	CHD group(N=84)	Control group(N=56)	χ^2	P value	sensibility	specificity	Rate of misdiagnosis	[illegible]
GLS	59	51	50.893	¡0.001	70.2%	91.1%	8.9%	2
GWI	80	49	97.771	¡0.001	95.2%	87.5%	8.0%	4

Table 4-1. The Chi-square test for comparison of GLS and GWI in predicting LAD with severe stenosis.

Model	LAD group (N=57)	LAD Control group (N=83)	χ^2	P value	Sensibility	specificity	Rate of misdiagn
GLS	37	72	40.027	¡0.001	64.9%	86.7%	13.3%
GWI	55	68	72.792	¡0.001	96.5%	81.9%	18.1%

Table 4-2. The Chi-square test for comparison of GLS and GWI in predicting LCX with severe stenosis.

Model	LCX group (N=32)	LCX Control group (N=108)	χ^2	*P* value	sensibility	specificity	Rate of misdiagnosis	Rate of missed diagnos
GLS	16	99	29.217	¡0.001	50.0%	91.7%	8.3%	50.0%
GWI	21	97	43.030	¡0.001	65.6%	89.8%	10.2%	34.4%

Table 4-3. The Chi-square test for comparison of GLS and GWI in predicting RCA with severe stenosis.

Model	RCA group (N=40)	RCA Control group (N=100)	χ^2	*P* value	sensibility	specificity	Rate of misdiag
GLS	8	96	7.403*	0.007	20%	96%	4%
GWI	20	94	36.578	¡0.001	50%	94%	6%

*: Correct Chi-square test

Table 5. Cut-off Value of GLS_R and GWI_R

Coronary artery	Variable	AUC	95%CI	*P*	Cut-off value	Youden's Index
LAD	GLS_A(-%)	0.937	0.899˜0.974	¡0.001	18.6	0.745
	GWI_A(mmHg%)	0.768	0.686˜0.850	¡0.001	1814	0.426
LCX	GLS_L(-%)	0.978	0.956˜1.000	¡0.001	16.9	0.882
	GWI_L(mmHg%)	0.886	0.821˜0.952	¡0.001	1771	0.649
RCA	GLS_I(-%)	0.954	0.897˜1.000	¡0.001	17.9	0.839
	GWI_I(mmHg%)	0.786	0.670˜0.903	0.001	1991	0.472

Table 6. Univariate and Multivariate Analyses of Risk Factors Related to CHD.

Variable	Univariate analysis OR	Univariate analysis 95%CI	Univariate analysis P-Value	Multivariate analysis (Model 1) OR
Age	1.009	0.975-1.044	0.603	
Male	4.600	2.139-9.891	¡0.001	1.016
BMI	1.054	0.932-1.192	0.404	
SBP	1.019	0.996-1.042	0.110	
DBP	1.003	0.967-1.039	0.887	
Hypertension	0.643	0.318-1.302	0.220	
Diabetes	0.337	0.134-0.846	0.021	1.366
Smoking	0.217	0.097-0.487	¡0.001	3.701
Hyperlipidemia	0.481	0.094-2.476	0.382	
PRI method by GLS	0.681	0.585-0.792	¡0.001	21.155
PRI method by GWI	0.999	0.998-1.000	0.004	

Table 7. Intra- and interobserver variabilities for GLS and GWI.

Variable	Intraobserver ICC	Intraobserver 95%CI	interobserver ICC	interobserver 95%CI
GLS(-%)	0.972	0.930˜0.989	0.960	0.902˜0.984
GWI(mmHg%)	0.983	0.957˜0.993	0.976	0.941˜0.990

ICC, Intraclass correlation coefficient; CI, confidence interval.

Table 8. The comparison of territorial GLS and GWI between severe and non-severe stenosis group.

Variable	CHD group	Control group	t、Z	P value
GLS_A(-%)	18.2(16.4, 19.9)	21.0±2.9	-5.388*	¡0.001
GWI_A(mmHg%)	1766±373	1997±385	-3.544	0.001
GLS_L(-%)	16.8±3.1	19.7±2.8	-4.899	¡0.001
GWI_L(mmHg%)	1826±467	2028±400	-2.410	0.017
GLS_I(-%)	19.5±3.3	21.4±3.1	-3.293	0.001
GWI_I(mmHg%)	1952(1603, 2187)	2064±399	-1.421*	0.155

*: Z value of Kruskal-Wallis rank sum test, (+): severe stenosis group,(-): non-severe stenosis group, GLS_A: anterior wall region of GLS, GWI_A: anterior wall region of GWI, GLS_L: lateral wall region of GLS, GWI_L: lateral wall region of GWI, GLS_I: inferior wall region of GLS, GWI_I: inferior wall region of GWI.