Original Article

Effect of quantitative parameters of contrast-enhanced ultrasound on the long-term prognosis of patients with chronic coronary syndrome

Jia Li[1#], Chunyan Ma[2#], Haixia Sun[1], Fang Li[1], Yao She[3], Tianhong Yi[3]

[1]Cardiovascular Ultrasound Room, Qinghai Provincial People's Hospital, Xining, China; [2]Department of Ultrasound, Central South University Xiangya School of Medicine Affiliated Haikou Hospital, Haikou, China; [3]Department of Ultrasound, Yueyang People's Hospital, Yueyang, China

Contributions: (I) Conception and design: J Li, C Ma; (II) Administrative support: T Yi; (III) Provision of study materials or patients: All authors; (IV) Collection and assembly of data: All authors; (V) Data analysis and interpretation: All authors; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

[#]These authors contributed equally to this work.

Correspondence to: Tianhong Yi, MD. Department of Ultrasound, Yueyang People's Hospital, 263, Baling East Road, Yueyanglou District, Yueyang 414000, China. Email: yitianhong2023@sina.com.

Background: Ultrasound is one of the most commonly used examination methods in patients with coronary artery disease (CAD) and is valuable in evaluating patient prognosis. Although contrast-enhanced ultrasound (CEUS) can assess more in depth the vascular lesions of patients, there is still a lack of relevant research on the value of quantitative parameters of CEUS in predicting the long-term prognosis of patients with chronic coronary syndrome (CCS), thus, we designed this study.

Methods: From January 2016 to December 2017, a total of 473 patients with CCS admitted to Yueyang People's Hospital were retrospectively enrolled. The patients were followed up for five years. According to whether the patients had major adverse cardiovascular events (MACE), patients were divided into the MACE group (n=113) and the control group (n=360). The CEUS was performed to detect the myocardial perfusion status. The value of quantitative parameters of CEUS in predicting the MACE in patients with CCS was analyzed using the receiver operating characteristic (ROC) curve.

Results: Peak intensity of contrast agent at platform stage, rising rate of microbubble reperfusion, and left ventricular ejection fraction (LVEF) were found to be valuable in predicting the risk of MACE in patients with CCS. Among them, the peak intensity of contrast agent at platform stage had the highest predictive value, and the area under the curve (AUC) was 0.860 [95% confidence interval (CI): 0.827–0.894, P<0.001]. Multivariate logistics regression analysis showed that the peak intensity of contrast agent at platform stage <4.54 dB and rising rate of microbubble reperfusion <0.275 s were independent risk factors of MACE in patients with CCS. The relative risks were 12.238 (95% CI: 6.632–22.585) and 5.724 (95% CI: 3.149–10.405), respectively.

Conclusions: Quantitative parameters of CEUS can be used as predictors of MACE in patients with CCS, and strengthening the management of such high-risk patients may be beneficial to reduce the incidence of MACE.

Keywords: Contrast-enhanced ultrasound (CEUS); chronic coronary syndrome (CCS); major adverse cardiovascular events (MACE)

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Introduction

In recent years, with the change of diet and living habits, the incidences of arterial hypertension, diabetes, and hyperlipidemia have increased year by year, the incidence of coronary artery disease (CAD) has subsequently increased year by year, which is one of the main risk factors for death in middle-aged and elderly people (1-4). Chronic coronary syndrome (CCS) refers to the absence of major adverse cardiovascular events (MACE) such as myocardial infarction on the basis of severe stenosis of the coronary arteries. When the myocardial loading is increased due to exercise, transient myocardial ischemia and hypoxia symptoms can occur, manifested as transient angina. In addition, patients with CCS can experience MACE such as myocardial infarction, malignant arrhythmia, heart failure, and cardiac arrest. MACE is a major contributor to death in patients with CCS (5). Therefore, it is important to identify patients at a high risk of MACE. Coronary angiography has high value in predicting prognosis of patients with CCS, but it is invasive and difficult to measure dynamically (6-8). Ultrasound examination is non-invasive. However, in the early stage of CCS, due to the compensatory effect of the myocardium, left ventricular ejection fraction (LVEF) may not be significantly reduced. Contrast-enhanced ultrasound (CEUS), which has emerged in recent years, can assess the severity of myocardial ischemia (9,10). Therefore, we speculated that the quantitative parameters of CEUS can better assess the long-term prognosis of patients with CCS. Due to the lack of relevant studies, we designed this study. We present this article in accordance with the STARD reporting checklist (available at https://jtd.amegroups.com/article/view/10.21037/jtd-23-1267/rc).

Highlight box

Key findings

- The quantitative parameters of contrast-enhanced ultrasound (CEUS) can be used as predictors of major adverse cardiovascular events (MACE) in patients with chronic coronary syndrome.

What is known and what is new?

- At present, there is a lack of research on the value of quantitative parameters of CEUS in predicting the long-term prognosis of patients with chronic coronary syndrome.
- Peak intensity of contrast agent at platform stage <4.54 dB and rising rate of microbubble reperfusion <0.275 s were found to be independent risk factors of MACE in patients with chronic coronary syndrome.

What is the implication, and what should change now?

- Quantitative parameters of CEUS can be used as predictors of MACE in patients with chronic coronary syndrome, and strengthening the management of such high-risk patients may be beneficial to reduce the incidence of MACE.

Methods

General information

From January 2016 to December 2017, a total of 473 patients with CCS admitted to Yueyang People's Hospital were continuously and retrospectively enrolled and followed up for five years. According to whether the patients developed MACE or not, the patients were divided into the MACE group (n=113) and the control group (n=360). The inclusion criteria were as follows: (I) CCS (coronary diameter stenosis degree >50%, no MACE such as myocardial infarction in the past three months, but with the increase of myocardial loading due to exercise, occurrence of transient myocardial ischemia and hypoxia symptoms manifested as transient angina); (II) age ≥18 years; (III) complete clinical data. The exclusion criteria were as follows: (I) malignant tumor; (II) combined with other heart diseases such as congenital heart disease; (III) functional insufficiency of important organs such as the liver and kidneys; (IV) loss to follow-up. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This retrospective clinical study was approved by the Yueyang People's Hospital Ethics Committee (No. 20220072), and individual consent for this retrospective analysis was waived. The flowchart of the inclusion process is shown in *Figure 1*.

Inspection method

The ultrasounds were performed using a Philips IE33 Elite ultrasound diagnostic instrument (Philips Healthcare, Andover, MA, USA), with a X5-1 matrix probe (1.0–5.0 MHz); the contrast agent used was sulfur hexafluoride microbubbles (Brocoo Company, Italy, 59 mg). The real-time myocardial ultrasound imaging model was equipped. The second harmonic and pulse coding phase reversal harmonic imaging technology were used. The mechanical index was 0.08. We measured peak intensity of contrast agent at platform stage (reflecting myocardial blood volume) and rising rate of microbubble reperfusion (reflecting the average myocardial blood flow velocity). At the same time,

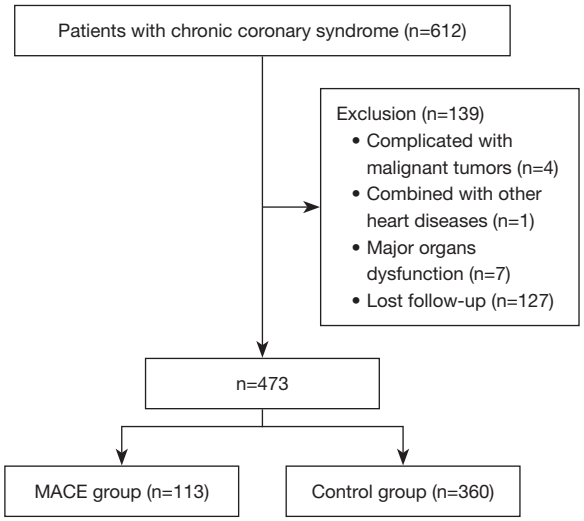

Figure 1 Patients' inclusion flowchart. MACE, major adverse cardiovascular events.

routine ultrasound was performed to measure the LVEF. No intolerance nor allergic reactions occurred during the study period.

Data collection

(I) General information: age, gender, body mass index, arterial hypertension, diabetes, hyperlipidemia and medications taken; (II) ultrasound-related parameters: peak intensity of contrast agent at platform stage, rising rate of microbubble reperfusion, LVEF; (III) biochemical indexes: N-terminal pro-B-type natriuretic peptide (NT-proBNP) and high sensitivity c reactive protein; (IV) coronary artery stenosis: the number of coronary artery stenosis and the average degree of coronary stenosis.

Statistical analysis

The software SPSS 26.0 (IBM Corp., Armonk, NY, USA) was used to complete the data analysis, and a two-tailed P<0.05 indicated that the difference was statistically significant. The measurement data of the two groups were expressed by mean ± standard deviation, and the independent sample *t*-test was used to analyze the differences in the measurement data between the two groups. The counting data of the two groups were expressed by n (%), and the Chi-squared test was used to analyze the difference in the counting data between the two groups. The receiver operating characteristic (ROC) curve was used to analyze the value of ultrasound related parameters in predicting the occurrence of MACE in patients with CCS. Multivariate logistics regression analysis was used to explore the risk factors of MACE in patients with CCS.

Results

Comparison of clinical features of the two groups

There were statistical differences in the peak intensity of contrast agent at platform stage, rising rate of microbubble reperfusion, the LVEF, the number of coronary artery stenosis, and the average degree of coronary stenosis between the two groups (P<0.05) (*Table 1*).

The value of average degree of coronary stenosis in predicting MACE in patients with CCS

The average degree of coronary stenosis was shown to be valuable in predicting MACE in patients with CCS, and the area under the curve (AUC) was 0.693 [95% confidence interval (CI): 0.636–0.750, P<0.001], the optimal diagnostic cut-off was 77.50%, and the sensitivity and specificity were 0.681 and 0.603, respectively (*Figure 2*).

The value of peak intensity of contrast agent at platform stage, rising rate of microbubble reperfusion, and LVEF in predicting MACE in patients with CCS

The peak intensity of contrast agent at platform stage, rising rate of microbubble reperfusion, and LVEF were found to be valuable in predicting the absence of MACE in patients with CCS. Among them, the peak intensity of contrast agent at platform stage had the highest predictive value, and the AUC was 0.860 (95% CI: 0.827–0.894, P<0.001) (*Figure 3* and *Table 2*).

Risk factor of MACE in patients with CCS

Multivariate logistics regression analysis showed that the peak intensity of contrast agent at platform stage <4.54 dB and rising rate of microbubble reperfusion <0.275 s were independent risk factors of MACE in patients with CCS. The relative risks were 12.238 (95% CI: 6.632–22.585) and 5.724 (95% CI: 3.149–10.405), respectively (*Table 3*).

Table 1 Comparison of clinical features of the two groups

Variable	MACE group (n=113)	Control group (n=360)	t/χ^2 value	P value
Age (years), mean ± SD	61.50±11.77	61.49±12.04	0.005	0.996
Gender, n (%)			0.247	0.619
Male	72 (63.72)	220 (61.11)		
Female	41 (36.28)	140 (38.89)		
Body mass index (kg/m^2), mean ± SD	26.36±3.25	26.27±3.03	0.281	0.779
Arterial hypertension, n (%)	82 (72.57)	250 (69.44)	0.401	0.527
Diabetes, n (%)	45 (39.82)	122 (33.89)	1.326	0.250
Hyperlipidemia, n (%)	100 (88.50)	300 (83.33)	1.756	0.185
Antihypertensive drugs, n (%)	82 (72.57)	250 (69.44)	0.401	0.527
Hypoglycemic drugs, n (%)	45 (39.82)	122 (33.89)	1.326	0.250
Lipid lowering drugs, n (%)	100 (88.50)	300 (83.33)	1.756	0.185
Aspirin, n (%)	108 (95.58)	330 (91.67)	1.917	0.166
Peak intensity of contrast agent at platform stage (dB), mean ± SD	4.04±0.50	5.04±0.71	13.959	<0.001
Rising rate of microbubble reperfusion (s), mean ± SD	0.24±0.03	0.29±0.04	12.275	<0.001
Left ventricular ejection fraction (%), mean ± SD	49.69±6.17	52.59±6.41	4.236	<0.001
NT-proBNP (pg/mL), mean ± SD	413.65±166.51	387.93±190.66	1.288	0.198
High sensitivity C reactive protein (mg/L), mean ± SD	3.04±0.67	2.98±0.62	0.880	0.379
Number of coronary artery stenosis, n (%)			21.982	<0.001
Single	39 (34.51)	215 (59.72)		
Multiple	74 (65.49)	145 (40.28)		
Average degree of coronary stenosis, mean ± SD	81.19±10.18	72.18±10.60	7.956	<0.001

MACE, major adverse cardiovascular events; SD, standard error; NT-proBNP, N-terminal pro-B-type natriuretic peptide.

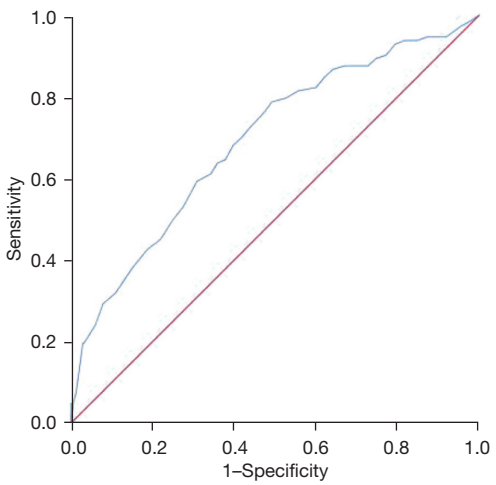

Figure 2 Predictive value of mean coronary stenosis for MACE in patients with chronic coronary syndrome. MACE, major adverse cardiovascular events.

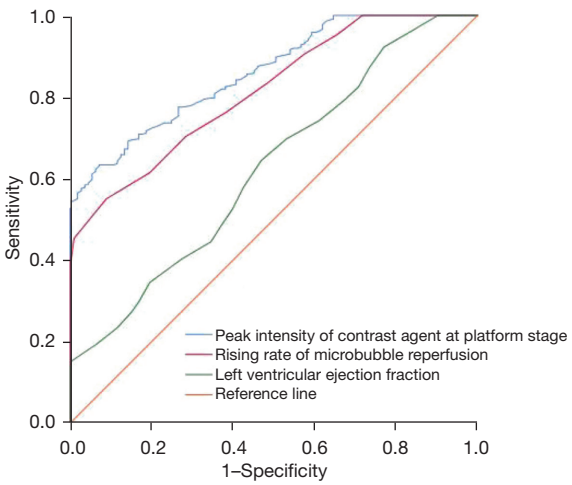

Figure 3 The predictive value of different indicators in the absence of MACE in patients with chronic coronary syndrome. MACE, major adverse cardiovascular events.

Table 2 The value of different indicators in predicting the absence of MACE in patients with chronic coronary syndrome

Variables	Area (95% CI)	Standard error	P value	Optimal diagnostic threshold	Sensitiveness	Specificity
Peak intensity of contrast agent at platform stage (dB)	0.860 (0.827–0.894)	0.017	<0.001	4.54 dB	0.708	0.832
Rising rate of microbubble reperfusion (s)	0.815 (0.774–0.855)	0.021	<0.001	0.275 s	0.614	0.805
Left ventricular ejection fraction (%)	0.626 (0.567–0.684)	0.030	<0.001	49.50%	0.644	0.531

MACE, major adverse cardiovascular events; CI, confidence interval.

Table 3 Risk factors of MACE in patients with chronic coronary syndrome

Variables	B value	Standard error	Wald value	P value	Relative risk (95% CI)
Peak intensity of contrast agent at platform stage <4.54 dB	2.505	0.313	64.193	<0.001	12.238 (6.632–22.585)
Rising rate of microbubble reperfusion <0.275 s	1.745	0.305	32.743	<0.001	5.724 (3.149–10.405)
Left ventricular ejection fraction <49.5%	0.736	0.284	6.733	0.009	2.087 (1.197–3.639)
Multiple coronary artery stenosis	1.054	0.288	13.439	<0.001	2.870 (1.633–5.044)
Average degree of coronary stenosis >81.50%	1.155	0.286	16.314	<0.001	3.174 (1.812–5.559)
Constant	–9.222	1.041	78.513	<0.001	0.000

MACE, major adverse cardiovascular events; CI, confidence interval.

Discussion

The basis of lesions in patients with CAD is coronary atherosclerosis, which leads to coronary stenosis, which in turn leads to insufficient blood supply to the myocardium. Long-term chronic myocardial ischemia can also lead to myocardial remodeling that progresses to MACE (11). In patients with CCS, there may be no significant change or only with a mild decrease in LVEF at early stage due to myocardial compensation (12-14). The present study also showed that LVEF was poor in predicting the MACE. However, in the early stages of CCS, patients exhibit changes in myocardial microvascular perfusion (15-17). Researchers have evaluated microvascular perfusion using CEUS (18,19), and this study explored the relationship between quantitative parameters of myocardial CEUS and the occurrence of MACE in patients with CCS. In the present study, the peak intensity of contrast agent at platform stage and rising rate of microbubble reperfusion were measured by myocardial CEUS. The peak intensity of contrast agent at platform stage represents myocardial blood volume; a rising rate of microbubble reperfusion reflects the average blood flow velocity of the myocardium. The decrease in the peak intensity of contrast agent at platform stage and rising rate of microbubble reperfusion indicate that myocardial hypoxia and ischemia are severe, and MACE is more likely to occur (18). CEUS has become a very important and promising development direction for ultrasound diagnosis (20,21). CEUS is the observation of coronary arteries, heart valves, and other conditions under ultrasound based on the distribution of contrast agents. CEUS is valuable in checking the tumors arterial stenosis and thrombosis.

In the present study, special ultrasound imaging techniques were used to observe the microvascular perfusion of myocardium, which could sensitively reflect the microperfusion of myocardium and provide a better way to identify CCS patients with high-risk of MACE.

The limitation of this study includes it retrospective nature and its failure to dynamically monitor the quantitative parameters of CEUS. Additionally, we failed to study more prognostic factors in this retrospective study.

Conclusions

Predicting the prognosis of different diseases is currently a hot topic and focus of research (22-25). Quantitative parameters of CEUS can be used as predictors of MACE

in patients with CCS, and strengthening the management of such high-risk patients may be beneficial to reduce the incidence of MACE.

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Footnote

Reporting Checklist: The authors have completed the STARD reporting checklist. Available at https://jtd.amegroups.com/article/view/10.21037/jtd-23-1267/rc

Data Sharing Statement: Available at https://jtd.amegroups.com/article/view/10.21037/jtd-23-1267/dss

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://jtd.amegroups.com/article/view/10.21037/jtd-23-1267/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This retrospective clinical study was approved by the Yueyang People's Hospital Ethics Committee (No. 20220072), and individual consent for this retrospective analysis was waived.

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