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ORIGINAL PAPER

Subclinical left ventricular dysfunction assessed by two-dimensional speckle tracking echocardiography in asymptomatic patients with carotid stenosis

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Abstract

The relationship between subclinical left ventricular (LV) dysfunction and atherosclerosis may have been underestimated in the past, which might be responsible for the high incidence of premature death in individuals with carotid stenosis. We sought to evaluate the underlying myocardial dysfunction in asymptomatic carotid stenosis patients using speckle tracking echocardiography (STE). Fifty patients with carotid stenosis ≥ 50% and a preserved LV ejection fraction (LVEF), and 45 controls without carotid stenosis who were matched in terms of vascular comorbidities were enrolled. All participants underwent carotid ultrasound and echocardiographic examination. The global LV longitudinal strain (GLS) was measured using STE. Compared with the control group, the e' of the mitral annular velocity and GLS were decreased in asymptomatic carotid stenosis patients ($p < 0.05$), however, the LVEF was well preserved. Based on a predefined cutoff for subclinical LV systolic dysfunction that was defined at a GLS < − 18%, this dysfunction was detected in 22 patients with carotid stenosis (44%) and in 10 patients in the control group (22%) ($p < 0.05$). The GLS was negatively correlated with the levels of low-density lipoprotein cholesterol ($r = -0.356$, $p < 0.05$) and triglyceride ($r = -0.396$, $p < 0.05$). In conclusion, LV diastolic and systolic functioning were significantly decreased in patients with asymptomatic carotid stenosis, and dyslipidemia likely contributed to the subclinical LV dysfunction in these patients. Our findings indicated the importance of detecting LV subclinical dysfunction and early intervention in this patient population.

Keywords Subclinical · Left ventricular · Dysfunction · Strain

Introduction

Cardiovascular disease remains the leading cause of death and disability worldwide [1]. Atherosclerosis has long been considered a major contributor to cardiovascular disease, and the early identification and intervention of atherosclerosis is crucial in terms of reducing cardiovascular burden [2]. Previous study suggested that even in patients with normal carotid structure, the subclinical atherosclerosis are significantly associated with cardiovascular risk factors [3, 4]. Moreover, patients with minor carotid stenosis are at higher risk of myocardial infarction, and the risk of future cardiovascular events increased according to the degree of subclinical atherosclerosis [5].

Although effective medical treatment, including smoking cessation and the reduction of blood pressure and lipid levels, could significantly reduce cardiovascular mortality in patients with atherosclerosis, a large proportion of people

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still have adverse outcomes, and the early identification of cardiac dysfunction has the potential to prevent further cardiovascular disease in these patients. Previous studies have indicated a possible association between the presence of carotid atherosclerosis, left ventricular (LV) morphology and high prevalence of coronary artery disease [6, 7], which might account for the increased risk of cardiovascular events in such patients. However, the relationship between cardiac function and atherosclerosis may have been underestimated in patients with carotid stenosis, and this might be responsible for the high incidence of premature death in these individuals [8].

Speckle tracking echocardiography (STE) is a robust tool for the assessment of underlying myocardial function. In the present study, we aimed to evaluate the underlying myocardial dysfunction using STE in asymptomatic carotid stenosis patients, which might be of great importance in terms of reducing cardiovascular risk.

Methods

Patient selection

This study was a prospective study, and patients were enrolled after approval by the Liaoning University of Traditional Chinese Medicine Institutional Review Board. Written informed consent was obtained from all participants. A total of 50 patients with carotid artery stenosis $\geq 50\%$ and preserved LV ejection fraction (LVEF) at the First and Second Affiliated Hospital of the Liaoning University of Traditional Chinese Medicine were enrolled in the study. Carotid stenosis was diagnosed according to the ultrasound criteria, and preserved LVEF was defined by an LVEF $\geq 50\%$ [9]. An asymptomatic status was confirmed by a review of the patient's history, a physical examination, and the numeric National Institutes of Health Stroke Scale [10]. Patients with previous stroke or transient ischemic attack, carotid revascularization, prior myocardial infarction, valvular heart disease, cardiomyopathy, severe pulmonary disease, arrhythmia and an LVEF $< 50\%$ were excluded from this study.

A control group with one or more vascular risk factors was also recruited. Each stenosis patient and stenosis-free control subject had their demographic features recorded and were assessed by a vascular risk factor profile, an echocardiographic examination, and a carotid ultrasound upon enrollment.

Vascular risk profiles

Systolic blood pressure (SBP), diastolic blood pressure (DBP), fasting blood glucose (FBG), glycosylated hemoglobin (HbA1c), total cholesterol (TC), triglyceride (TG), serum high-density lipoprotein cholesterol (HDL-C), and low-density lipoprotein cholesterol (LDL-C) were collected before echocardiography.

Vascular risk factors including hypertension, diabetics, hyperlipidemia, current smoking, prior coronary artery disease and peripheral arterial disease were defined according to consensus criteria [11], and therapies including antiplatelet, lipid-lowering, anti-hypertension was recorded.

Duplex ultrasound

The common carotid artery (CCA), carotid bulb and the internal carotid artery (ICA) were examined by duplex ultrasound in our vascular laboratory using a Philips ultrasound system (IU-22, Philips, Inc., Bothell, WA, USA) with a 3–9 MHz linear array probe and a 1–5 MHz curvilinear array probe. The subjects were examined in the prone position and both the left and right carotids were scanned. The head was positioned approximately 45° to the side that was contralateral to the site of examination, and B-mode and Doppler ultrasound images were acquired. A transverse scan starting at the clavicle and progressing cranially up to the mandible was conducted for orientation to locate the CCA, carotid bulb, ICA and plaque; longitudinal images were subsequently obtained. Doppler waveforms were acquired at a less than 60° angle between the long axis of the artery and the ultrasound beam. The highest peak systolic and end-diastolic velocity measurements from the CCA and the ICA were obtained to further confirm the degree of stenosis. The Doppler velocity thresholds used to determine the degree of stenosis were defined according to criteria that were previously described [10, 12]. The images were analyzed offline by independent observers blinded to clinical findings.

Echocardiography

Standard echocardiography with Doppler studies was performed using a Vivid 7 Dimension ultrasound system (GE Healthcare, Waukesha, WI, USA) equipped with a 2–4 MHz phased array probe. All images and measurements were acquired from standard views and digitally stored for offline analysis. The LV diameters and volumes, the mass of the hypertrophic LV, and the LVEF were measured in accordance with the ASE guidelines [13]. The left atrial diameter (LAD), the LV end-diastolic and systolic dimension (LVEDD and LVESD, respectively), the interventricular septal and posterior wall thicknesses (IVSD and PWD, respectively), and the LV mass index (LVMI) were measured and calculated. The LVEF was measured using the biplane modified Simpson's method. The peak early (E) and late (A) diastolic velocities across the mitral valve were measured, and the E/A ratios were calculated. The peak early diastolic mitral annular velocity (e′) was measured at the levels of the

mitral septal annulus (e'_{sep}) and lateral annulus (e'_{lat}) with an apical four-chamber view, and the E/e′ ratio was calculated.

STE data collection

For the LV strain analysis, dynamic two-dimensional ultrasound images of three cardiac cycles from the long-axis, apical four-chamber, and two-chamber views were acquired at a frame rate of 57–72 fps. The images were analyzed using customized software with the EchoPAC workstation (GE Healthcare). The endocardial LV boundary was delineated manually, and subsequently the software automatically drew the epicardial boundary. The widths of the regions of interest were manually adjusted to match the endocardial and epicardial boundaries. The global LV peak longitudinal systolic strain (GLS) was calculated. The final strain parameters were the averages of the values obtained from the three apical views. The predefined cutoff for subclinical LV systolic dysfunction in patients with preserved LVEF was defined by a GLS $< -18\%$ according to previous researches [14, 15].

Statistical analysis

Statistical analysis was performed using SPSS version 17.0 software (SPSS, Inc., Chicago, IL, USA). The descriptive data are presented as the percentage frequency for categorical variables and the mean standard deviation (SD) for continuous variables. The differences in continuous variables between two groups were analyzed using an unpaired Student's *t*-test or a Mann–Whitney U-test, and categorical data were analyzed using a Fisher exact test or a chi-square test, as appropriate. The Pearson coefficient was used for correlation analysis. A two-tailed probability (p) value < 0.05 was considered statistically significant. The intra- and interobserver variability were determined according to the coefficients of variation, which were calculated as the SDs of the differences between repeated measurements divided by the average value of those measurements and expressed as percentages.

Results

Clinical characteristics

The clinical characteristics of the analyzed patients are summarized in Table 1. The mean age was 67 ± 8 years and 66 ± 8 years in carotid stenosis patients and controls, respectively. There was a high proportion of patients with diabetes (62% vs. 60%, p = 0.842), hypertension (84% vs. 84%, p = 0.953), dyslipidemia (76% vs. 71%, p = 0.589), and smoking (80% vs. 73%, p = 0.442) in both carotid stenosis and control groups. The TC, TG, LDL-C were significantly

Table 1 Comparison of clinic characteristics of patients with study controls

	Control (n = 45)	Carotid stenosis (n = 50)	p value
Age (years)	66 ± 8	67 ± 8	0.76
Male sex (%)	41 (91%)	46 (92%)	0.878
Systolic blood pressure (mmHg)	152 ± 24	147 ± 22	0.351
Diastolic blood pressure (mmHg)	88 ± 10	86 ± 11	0.233
Fasting blood glucose (mmol/L)	5.45 ± 0.36	5.60 ± 0.84	0.875
Total cholesterol (mg/dL)	183.5 ± 38.4	202.0 ± 37.5*	0.020
Triglyceride (mg/dL)	101.6 ± 41.2	152.7 ± 88.7*	0.001
HDL-C (mg/dL)	60.4 ± 12.9	59.4 ± 13.6	0.733
LDL-C (mg/dL)	100.4 ± 25.9	114.2 ± 25.2*	0.01
Lipid-lowering treatment (%)	20 (44%)	21 (42%)	
Antiplatelet treatment (%)	15 (34%)	16 (32%)	
Anti-hypertension treatment (%)	22 (58%)	20 (48%)	
Stenosis features (%)			
Right		28 (56%)	
50–69% stenosis		36 (72%)	
70–79% stenosis		8 (16%)	
80–99% stenosis		6 (12%)	

Use of anti-hypertension and lipid-lowering treatments were recorded only in those who had hypertension and dyslipidemia

HDL-C high-density lipoprotein cholesterol, *LDL-C* low-density lipoprotein cholesterol

*$p < 0.05$ versus control group

high in asymptomatic carotid stenosis patients compared with the control group subjects ($p < 0.05$).

Left ventricular function and associated factors

The differences in the LVEDD, LVESD and LVEF were not statistically significant between control and asymptomatic carotid stenosis patients; however, the LVMI, LAD and IVS were increased in patients with carotid stenosis compared with controls ($p < 0.05$). Moreover, the mitral E/a ratio and the e′ of the mitral annular velocity were significantly decreased in asymptomatic carotid stenosis patients compared with the control group subjects ($p < 0.05$, Table 2).

The GLS was significantly reduced in patients with carotid stenosis compared with that in controls ($p < 0.05$, Fig. 1). With the predefined cutoff for subclinical LV systolic dysfunction defined by a GLS $< -18\%$, this dysfunction was detected in 22 patients (44%) with asymptomatic carotid stenosis; however, only 10 patients (22%) had subclinical LV dysfunction in the control group ($p < 0.05$). The comparison between patients with a GLS $< -18\%$ and $\geq -18\%$ are summarized in Table 3. Compared to patients with a GLS $\geq -18\%$, the e′ of the mitral annular velocity was significantly decreased in patients with a GLS $< -18\%$ ($p < 0.05$). The TG, LDL-C, LV diameter and LVMI in patients with a GLS $< -18\%$ tended to be higher in patients with asymptomatic carotid stenosis; however, the differences were not statistically significant.

Table 2 Comparison of echocardiography of carotid stenosis patients versus study controls

	Control (n = 45)	Carotid stenosis (n = 50)	p value
LVEDD (mm)	47.32 ± 3.25	46.46 ± 4.95	0.317
LVESD (mm)	31.95 ± 3.14	32.24 ± 5.12	0.744
IVS (mm)	7.66 ± 0.75	8.10 ± 0.95*	0.024
PW (mm)	7.60 ± 0.72	7.52 ± 0.68	0.624
LVMI (g/m^2)	68.53 ± 14.25	78.63 ± 18.07*	0.021
LAD (mm)	32.76 ± 4.38	33.31 ± 4.32*	0.009
LVEF (%)	62.90 ± 4.79	61.10 ± 3.38	0.144
Mitral E/A	0.95 ± 0.33	0.86 ± 0.27*	< 0.001
e'_{sep} (cm/s)	8.97 ± 2.12	7.95 ± 2.42*	0.046
e'_{lat} (cm/s)	12.72 ± 3.50	5.92 ± 2.05*	< 0.001
Mitral E/e′	7.36 ± 1.93	7.89 ± 2.95	0.364
GLS (%)	19.85 ± 2.02	18.46 ± 3.07*	0.013
GLS < 18% (n, %)	10 (22%)	22 (44%)*	0.025

LVEDD left ventricular end-diastolic diameter, *LVESD* left ventricular end-systolic diameter, *LVMI* left ventricular mass index, *LAD* left atrium diameter, *LVEF* left ventricular ejection fraction, *GLS* global longitudinal strain

*$p < 0.05$ versus control group

According to the correlation analysis, the GLS was negatively correlated with the levels of LDL-C ($r = -0.356$, $p < 0.05$), TG ($r = -0.396$, $p < 0.05$), calcium ($r = -0.309$, $p < 0.05$) and phosphorus ($r = -0.318$, $p < 0.05$) in all patients (Fig. 2).

Reproducibility

Twenty patients were randomly selected for repeated measurements. The intra- and inter-observer coefficients of variation were 5.9% and 7.8% for the GLS measurements, respectively.

Discussion

The major findings of the present study were that LV diastolic and systolic functioning were significantly decreased in asymptomatic patients with carotid stenosis, despite the preservation of LVEF; in addition, subclinical LV longitudinal dysfunction might be associated with dyslipidemia. Our findings may be clinically useful for the management of such patients.

The LV myocardium consists of right-handed helical fibers in the endocardial layer and left-handed helical fibers in the epicardial layer. The complex structure allows LV deformation along different planes, including the longitudinal, radial, and circumferential planes. Longitudinal strain is a well-known parameter of LV function that is sensitive to the impairment of the subendocardial myocardium [16]. Therefore, it can be very useful to detect subclinical myocardial dysfunction in the early stages of many cardiac disorders, including hypertension, diabetes and ischemic heart diseases, that mainly involve the subendocardium but in which the LVEF is well preserved [17].

Longitudinal strain can be assessed by multiple imaging modalities, including STE, tissue Doppler imaging (TDI) and cardiovascular magnetic resonance (CMR) [16]. Compared to the high cost and limited availability of CMR, STE provides a cost effective and reliable method for the assessment of LV strain that overcomes the shortcomings of TDI, which include high angle-dependent and inter- and intraobserver variability [17]. Although STE cannot be considered a recent technique, it has been applied in numerous ways in clinical settings over the past decade. Therefore, in the present study, we employed STE to detect the subclinical dysfunction of LV functioning. Previous studies have suggested that LV longitudinal systolic dysfunction should be defined at a GLS $< -18\%$, since patients with a GLS $< -18\%$ showed evidence of adverse LV remodeling at the 3-year follow-up, while those patients with a GLS $\geq -18\%$ showed no evidence of significant LV remodeling at follow-up [14,

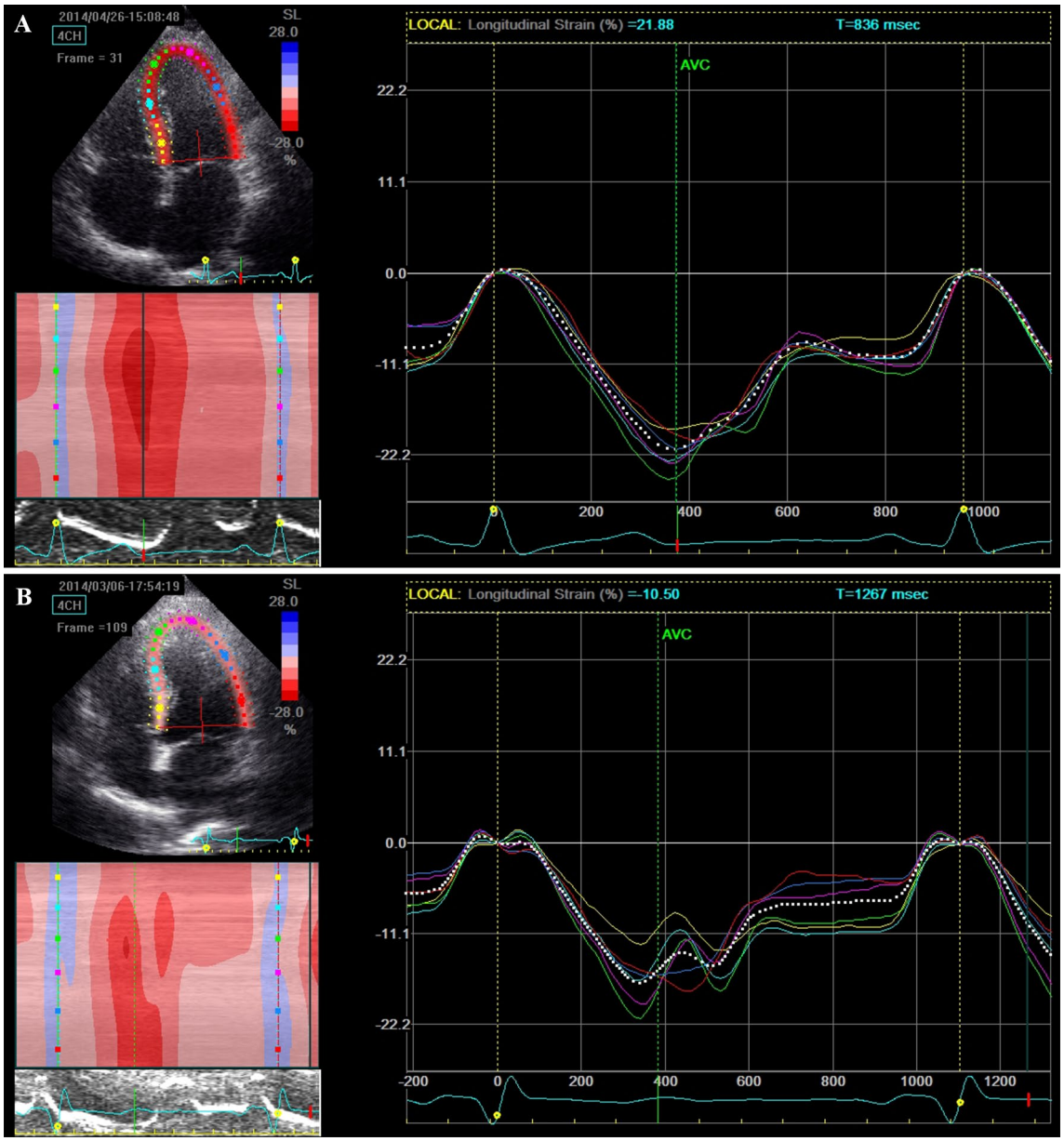

Fig. 1 Peak systolic longitudinal strain in control subjects (**a**) and carotid stenosis patients (**b**). The peak longitudinal strain was decreased in patients with carotid stenosis

18]. In addition, we used the same software as previous studies, to avoid the software algorithm issues [14, 18].

Our study revealed that although the LVEF was preserved, the GLS was decreased in patients with asymptomatic carotid stenosis. The mechanism underlying the association between GLS and carotid stenosis is uncertain. It is widely accepted that a relationship exists between carotid stenosis and coronary artery disease, since atherosclerosis is a systemic inflammatory vascular disorder [19, 20]. Previous study has indicated that asymptomatic coronary atherosclerosis was more prevalent in patients with carotid stenosis [20], and even transit experimental coronary occlusion could stimulate myocardial growth and account for myocardial impairment [21]. As atherosclerosis is a systemic condition, concomitant silent coronary artery disease might responsible for the development of subclinical LV dysfunction in the present study. Moreover, inflammation and immune mechanisms in patients with carotid stenosis might contribute to the decreased LV function [19]. In addition, previous study has described the relationship between concentric LV hypertrophy and coronary atherosclerosis extent, possibly due to the presence of coronary microcirculation dysfunction in those patients [22]. Consistently, in our population, LVMI was higher in patients with carotid stenosis than control

Table 3 Comparison between patients with and without subclinical myocardial dysfunction

	GLS ≥ −18% (n = 28)	GLS < −18% (n = 22)	p value
Age (years)	62 ± 8	72 ± 6	0.669
Male sex (%)	26 (93%)	20 (91%)	1.000
SBP (mmHg)	145 ± 23	151 ± 22	0.351
DBP (mmHg)	86 ± 11	86 ± 10	0.872
FBG (mmol/L)	5.58 ± 0.93	5.63 ± 0.72	0.816
Total cholesterol (mg/dL)	199.3 ± 38.9	205.5 ± 36.2	0.571
Triglyceride (mg/dL)	150.2 ± 98.3	155.7 ± 77.0	0.830
HDL-C (mg/dL)	60.1 ± 15.0	58.6 ± 11.9	0.689
LDL-C (mg/dL)	111.6 ± 25.0	117.5 ± 25.7	0.423
LVEDD (mm)	45.43 ± 4.49	47.77 ± 5.30	0.097
LVESD (mm)	31.29 ± 4.94	33.45 ± 5.20	0.138
LVMI (g/m^2)	73.65 ± 10.94	80.95 ± 21.27	0.127
e'_{sep} (cm/s)	8.69 ± 2.35	7.02 ± 2.22*	0.014
e'_{lat} (cm/s)	6.45 ± 2.02	5.23 ± 1.92*	0.035
Mitral E/e′	7.27 ± 2.77	8.68 ± 3.04	0.105

*$p < 0.05$ versus patients with GLS ≥ −18%

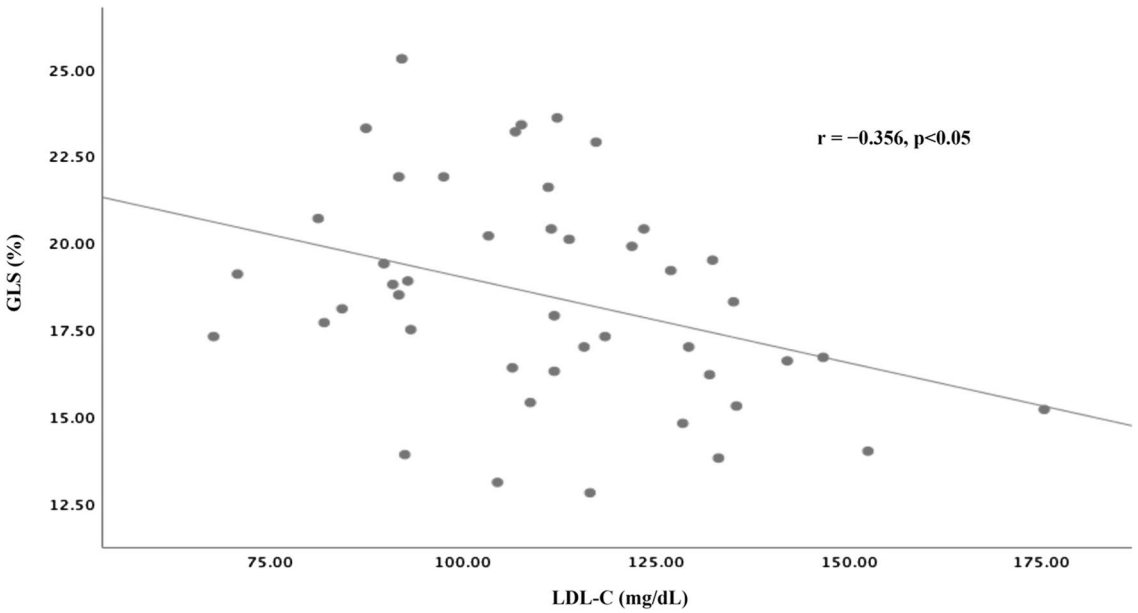

Fig. 2 Distribution of global longitudinal strain values and LDL-C levels in all participants

groups. However, further studies are also required to validate the hypothesis.

Moreover, previous reports have suggested that the rate of myocardial infarction after carotid stenting and carotid endarterectomy was relatively high [23, 24]; in addition to myocardial damage or fetal myocardial infarction resulting from hemodynamic instability, subclinical myocardial dysfunction might make the myocardium more vulnerable to the procedure, further increasing the cardiovascular risk. In addition, a previous study suggested that atherosclerosis leads to increased LV afterload and impaired myocardial blood flow by decreasing coronary perfusion pressure [25]. These changes might account for subclinical LV dysfunction, which is consistent with the findings of the present study.

We also observed significantly decreased LV diastolic function in patients with asymptomatic carotid stenosis. Diastolic functioning is determined by the interaction of the active process of relaxation with LV passive elastic properties [26]. Alterations in the extramyocardial collagen network and changes within cardiomyocytes resulting from advancing age are likely responsible for diastolic

abnormalities [27, 28]; however, the presence of comorbidities, including hypertension, diabetes and dyslipidemia, might accelerate the changes in patients with asymptomatic carotid stenosis. The relationship between diastolic dysfunction and the prognosis of heart failure with preserved ejection fraction has been well described [29], and this might contribute to poor prognosis in patients with asymptomatic carotid stenosis as well.

Dyslipidemia is a well-established risk factor for cardiovascular events. Even in healthy individuals without conventional cardiovascular risk factors, LDL-C levels are independently linked to atherosclerotic burden and potentially play a central role in early atherogenesis in humans [30]. Additionally, statin therapy may be related to the improvement of LV function and carotid stiffness in patients with dyslipidemia [31], which further highlights the relationship between dyslipidemia and LV dysfunction, especially in patients with carotid stenosis. In the present study, we found that the levels of LDL-C and TG were significantly high in patients with carotid stenosis, and levels of LDL-C and TG negatively correlated with GLS, and dyslipidemia is likely responsible for the development of carotid stenosis and myocardial dysfunction in these patients. Therefore, our results support the use of more effective lipid level reduction measures for preventing the impairment of myocardial function and the progression of atherosclerosis.

Study limitations

Our findings were based on a relatively small number of patients. Long-term follow-up is needed to verify the prognostic value of LV dysfunction in patients with asymptomatic carotid stenosis. However, whether treatment for subclinical LV dysfunction prior to carotid revascularization can prevent perioperative or long-term cardiovascular events should be investigated in a randomized controlled trial.

Conclusions

In this study, we found that LV diastolic and systolic functioning were decreased in patients with asymptomatic carotid stenosis and subclinical LV dysfunction associated with dyslipidemia, suggesting that routine screening and early intervention for subclinical LV dysfunction in patients with asymptomatic carotid stenosis should be considered in clinical practice. The subclinical systolic impairment in STE might help inform future treatment strategies in terms of reducing cardiovascular mortality in patients with asymptomatic carotid stenosis.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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