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Insulin resistance aggravates myocardial fibrosis in non-diabetic hypertensive patients by altering the function of epicardial adipose tissue: a cardiac magnetic resonance study

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Abstract

Background The effect of insulin resistance (IR) on epicardial adipose tissue (EAT) remains uncertain. This study aimed to investigate how early-stage IR influences EAT, contributing to myocardial fibrosis and left ventricular dysfunction in non-diabetic patients with hypertension.

Methods A total of 166 hypertensive patients who underwent cardiovascular magnetic resonance (CMR) treatment at two medical centers in China from June 2015 to August 2024 were included. Triglyceride-glucose index (TyG) was calculated, cardiac MRI parameters and EAT were measured. Patients were divided into two groups based on the median TyG. Binary logistic regression model, subgroup analysis and causal mediation analysis were used to evaluate the correlation between EAT, TyG and CMR parameters. Thirty healthy volunteers served as the control group.

Results The high TyG group exhibited greater EAT volume, higher Native T1, and increased ECV (All $P < 0.001$) compared to the low TyG group. Additionally, significant differences were observed in GRS ($P = 0.025$), GLS ($P = 0.015$), and GCS ($P = 0.048$). Binary logistic regression analysis indicated that TyG and indexed EAT volume were independently associated with high ECV value (TyG: OR 2.808, $p = 0.002$;indexed EAT volume: OR 1.038, $p = 0.002$), with results remaining stable after adjusting for confounding factors. Mediation analysis showed that even after adjusting for confounding factors, EAT continued to play a role in TyG-mediated ECV (indirect effect: 0.8844, [95% CI 0.4539–1.3666]).

Conclusions IR in non-diabetic individuals at an early stage may change the physiological function of EAT and lead to the onset of myocardial fibrosis. Addressing IR early on could potentially improve the physiological function of EAT.

Keywords Epicardial adipose tissue, Hypertensive, Triglyceride-glucose index, Insulin resistance, Myocardial fibrosis

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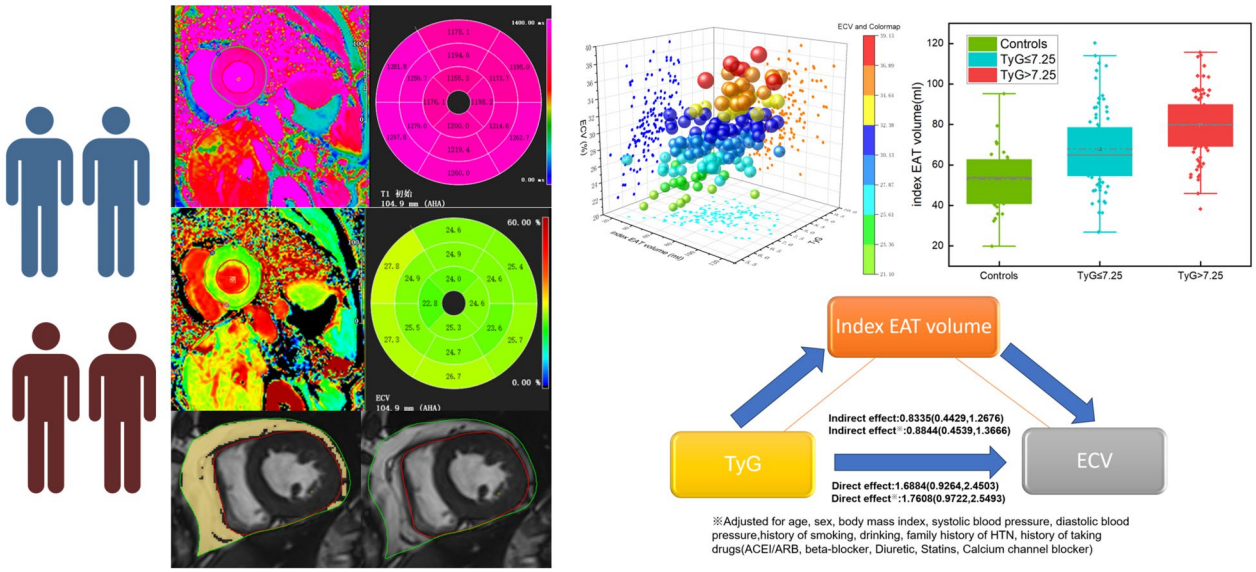
Graphical Abstract



Introduction

Hypertension(HTN) is a major chronic disease that endangers human health. Patients with long-term poorly managed hypertension face a heightened risk for left ventricular diffuse fibrosis and diastolic dysfunction [1]. HTN often coexists with diabetes or insulin resistance(IR). IR is physiologically characterized by a decreased response of insulin-targeted tissues to elevated physiological insulin levels and is considered a causative factor in many modern diseases, such as metabolic syndrome, metabolic dysfunction-associated steatotic liver disease (MASLD), atherosclerosis, and type 2 diabetes mellitus (T2DM) [2]. Metabolic syndrome and IR markedly elevate the risk of adverse cardiovascular outcomes. However, the relationship between insulin resistance (IR) and myocardial fibrosis in hypertensive patients remains inadequately elucidated. It is important to note that in patients with other diseases, such as coronary heart disease(CAD), myocardial fibrosis is primarily attributed to ischemic injury-induced cardiomyocyte death, and this type of fibrosis is typically irreversible. In contrast, patients with hypertension may exhibit myocardial fibrosis and hypertrophy at an early stage, and these changes are generally reversible [3]. Therefore, early intervention to control IR is crucial for delaying or reversing fibrosis progression and reducing the incidence of adverse cardiovascular events in hypertensive patients.

Epicardial adipose tissue(EAT) has received significant attention because of its unique physiological function. EAT can act as a substantial protector of the adjacent myocardium through its dynamic thermogenesis function resembling brown fat. However, it can also cause serious harm through paracrine or vascular secretion of proinflammatory and growth-promoting cytokines [4]. In patients with metabolic syndrome and IR, the active, dysregulated, and abnormal metabolism of epicardial fat may aggravate myocardial fibrosis and diastolic dysfunction, leading to a higher risk of poor prognosis [5].

TyG serves as a new metric that reflects IR. Studies have demonstrated a strong correlation between the TyG and myocardial fibrosis, as quantified by extracellular volume measured by cardiovascular magnetic resonance(CMR) [6]. Additionally, substantial evidence has shown that the TyG is closely related to poor cardiovascular outcomes [7]. This study aims to explore the relationship between the TyG, EAT, and myocardial fibrosis in hypertensive patients who do not have diabetes.

Methods

Subjects

One hundred sixty-six subjects with HTN were enrolled between June 2015 and August 2024 at two medical centers in China. Patients with HTN history with and without evidence of left ventricular hypertrophy (LVH) were enrolled. These patients had HTN systolic blood pressure (SBP) $\geq$ 130mmHg and/or diastolic blood pressure (DBP) $\geq$ 80mmHg [8] measured at least twice, or were taking one or more medications for

hypertension.Fifty-five patients with suspected cardiac hypertrophy on previous echocardiography were used to further assess the extent of cardiac hypertrophy or to assess the response to medical therapy. Sixty-three patients underwent a comprehensive cardiac function evaluation due to symptoms similar to heart failure. Suspected arrhythmia detected by electrocardiogram (ECG) was investigated for potential myocardial fibrosis or scarring in 21 patients. In addition, twenty-seven patients underwent CMR examination to further detect potential myocardial abnormalities without obvious clinical symptoms.The exclusion criteria were patients with diabetes mellitus, coronary heart disease, significant valvular disease, renal impairment (glomerular filtration rate < 45 ml/min/1.73 m^2) or reduced systolic function (LV ejection fraction [LVEF] < 45%) (Fig. 1) [9]. Thirty age-, sex- and BMI-matched healthy subjects served as controls, satisfying the following criteria: normal physical examination, optimal blood pressure levels (systolic blood pressure < 130 mmHg and diastolic blood pressure < 80 mmHg), unremarkable electrocardiogram (ECG) findings, absence of chest pain or dyspnea history, no diabetes or hyperlipidemia, and normal results from both 2D echocardiography and Doppler examinations. None of the participants were taking any medications. Any potential subjects displaying evidence of heart disease, HTN, or other systemic disorders were excluded from this study. The ethics committee of local Hospital approved all study procedures.

Clinical data

Clinical data were collected, including history of smoking (defined as smoking one cigarette a day for at least 6 months currently or in the past) and drinking (defined as consuming alcohol once every week for at least 6 months currently or in the past) [10], family history of hypertension, and history of antihypertensive medication use. Total cholesterol (TC),high density lipoprotein cholesterol (HDL-C), low density lipoprotein cholesterol (LDL-C), triglyceride (TG),fasting blood glucose (FBG) and other biochemical indicators were collected by collecting fasting elbow venous blood on the second morning of admission. The TyG index was calculated using the formula Ln[TG (mg/dL) × FBG (mg/dL) /2] [11].

CMR protocol

A 3.0-T (MAGNETOM Prisma, Siemens Healthcare) or 1.5-T (MAGNETOM Avanto, Siemens Healthcare) magnetic resonance scanner was used to perform CMR examinations utilising standard protocols [12], which included breath-hold cine imaging, pre- and post-enhancement T1mapping imaging, and steady-state free precession (SSFP). The following were typical parameters for the cine picture protocol: Flip Angle: 80°, repetition time (TR)/echo time (TE) = 1.43/3.26 ms, slice thickness: 7 mm. Ten minutes following an intravenous dose of 0.2 mmol/kg gadopentetate dimeglumine (North Road Pharmaceutical Co., LTD.), CMR scans were performed again. Three short-axis levels (basal, middle, and apical) of myocardial T1 values were recorded under breath holding and ECG gating using a modified Look Locker inversion recovery procedure. Before and after administration,

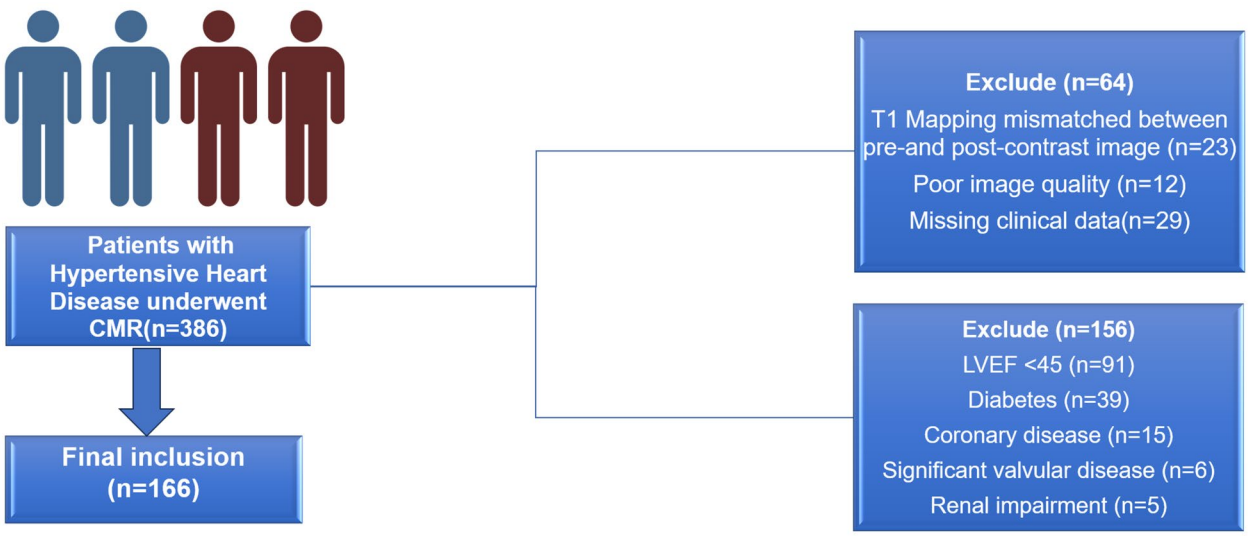


Fig. 1 Flowchart shows the selection process of patients with Hypertension based on inclusion and exclusion criteria. *CMR* cardiac magnetic resonance, *LVEF* Left Ventricular Ejection Fractions

T1 mapping was carried out using the 5(3 s)3 and 4(1 s)3(1 s)2 procedures, respectively. The scanning parameters for T1 mapping before contrast agent injection were as follows: a bSSFP single-shot readout with a 35° excitation flip angle, rate-2 parallel imaging, matrix size of 256×164, pixel size of 1.3 mm×1.3 mm, slice thickness of 8 mm, minimum inversion time (TI) of 189 ms and incremented by 80 ms, TE/TR echo spacing of 1.15 ms/2.77 ms. After the contrast agent injection, the T1 imaging parameters were modified to include a bSSFP single-shot readout with a reduced excitation flip angle of 20°, rate-2 parallel imaging, matrix size of 192×164, pixel size of 1.9 mm×1.9 mm, slice thickness of 8 mm, minimum TI of 100 ms with 80 ms increments, and TE/TR echo spacing of 1.01 ms/2.44 ms. The typical cine image protocol parameters were as follows: repetition time (TR)/echo time (TE) = 1.43/3.26 ms, flip angle = 80°, and 7-mm slice thicknes [13, 14].

CMR image analyis

Using commercial postprocessing software CVI42 (version 5.12), two senior CMR physicians independently contoured and assessed all CMR pictures without knowledge of the images.(A-D of Fig. 2). Manual delineation of endocardial and epicardial contours was performed for the basal, mid-, and apical segments of the LV. Raw and post-contrast T1 values were calculated from the excluded apex region based on the 17-segment American Heart Association (AHA) model [15, 16]. Every slice's papillary muscles, moderator bands, and epicardial boundary were carefully removed [17–19]. Before calculating extracellular volume (ECV), hematocrit levels were obtained, and the blood pool was manually drawn [20, 21]. ECV was calculated using the following equation [22]:

$$MyocardialECV = (1 - Hematocrit) \times \frac{\left(\frac{1}{\text{Post contrast myocardial T1}} - \frac{1}{\text{Native myocardial T1}}\right)}{\left(\frac{1}{\text{Post contrast blood T1}} - \frac{1}{\text{Native blood T1}}\right)}$$

Using feature tracking methods on SSFP cine sequences, the global longitudinal strain (GLS), global circumferential strain (GCS), and global radial strain (GRS) of the LV were determined.

Epicardial adipose tissue

The Tissue signal intensity module of commercial software (CVi42, version 5.12) was utilized to measure the EAT volume. Adipose tissue situated between the visceral layer of the pericardium and the lateral wall of the myocardium is referred to as EAT. EAT was manually delineated on end-diastolic short-axis slices, starting from the most basal slice around the atria and progressing towards the most apical slice surrounding the ventricles. To ensure the accuracy of EAT volume measurements, we performed meticulous manual corrections. During EAT segmentation, non-EAT regions such as pericardial

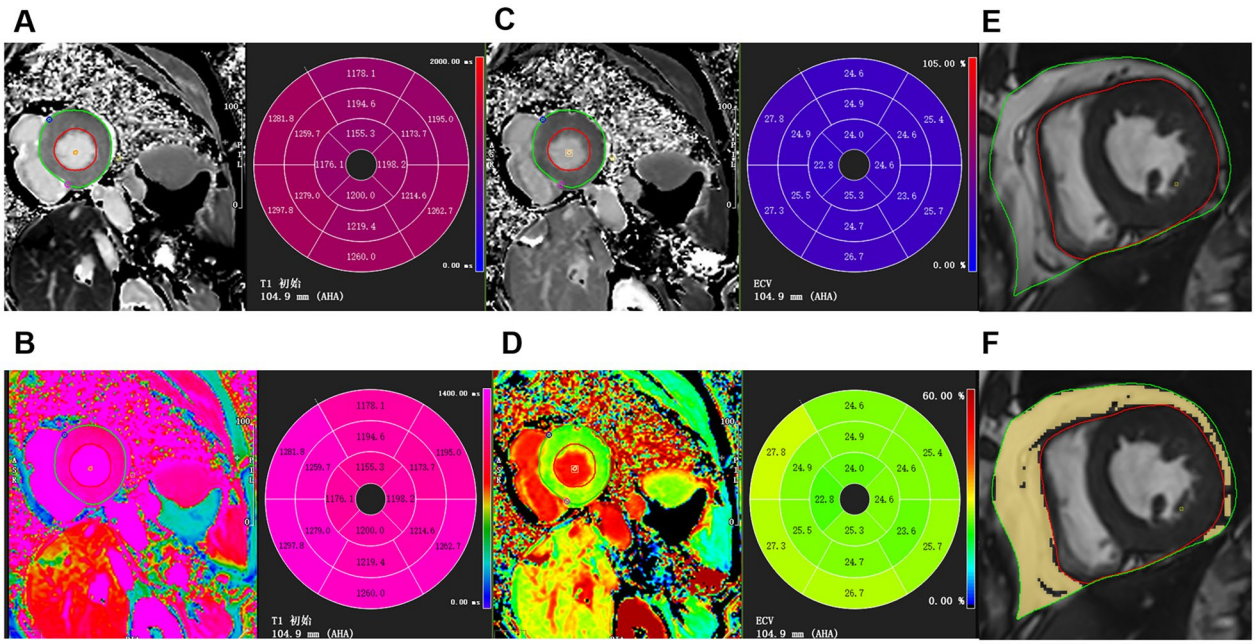


Fig. 2 The process of cardiac magnetic resonance image post-processing and delineation of epicardial fat

fat and intrapericardial adipose tissue were excluded from analysis. Slice-level validation was conducted to refine EAT boundaries, with manual adjustments correcting misclassified myocardial or vascular regions and the brush tool supplementing under-segmented EAT areas. Prior to segmentation, image quality optimization, including contrast and brightness adjustments, was performed to enhance the delineation of EAT boundaries. Furthermore, uniform slice thickness across all datasets was strictly maintained to minimize volumetric discrepancies in cross-sectional analyses. These procedures adhered to standardized cardiac imaging protocols to ensure reproducibility in EAT quantification (Fig. 2E, F).

Statistical analysis

According to the median value of the TyG, patients with HTN were divided into two groups: the TyG ≤ 7.24 group and the TyG > 7.24 group. Statistical analysis was performed using SPSS statistical software (version 26.0). All tests were two-tailed, with a significance level set at $P < 0.05$. The distribution of variables was assessed using the Shapiro–Wilk test. Continuous variables were expressed as mean ± SD or median with interquartile range (IQR) and compared using either a Welch's t-test or Mannwhitney-U test, depending on their distribution characteristics. Categorical variables were presented as frequencies and percentages and analyzed by chi-square test for comparison purpose. Pearson or Spearman's correlation coefficient was employed to explore the associations among indexed EAT volume(EAT volume/BSA), CMR parameters, and the TyG in patients with HTN,depending on their distribution characteristics.Binary logistic regression analysis was used to evaluate the independent impact of EAT volume and TyG on ECV value(divided into high/low fibrosis groups by the median). Morphological and functional parameters, EAT volume and TyG were included as continuous variables in the univariable analysis. Covariates for adjustment included sex, age, body mass index, SBP, DBP, history of smoking and drinking, family history of HTN, and history of taking antihypertensive and lipid-lowering drugs. In the multivariate regression, the covariates in the model 1 were selected based on P-value and Akaike Information Criterion (AIC) in a stepwise algorithm,with $P < 0.05$ and the difference in AIC between two models > 2 representing significant and moderate difference, respectively.Four models were used to adjust for potential confounders in the multivariate models: model 2 was adjusted for age, sex, BMI, SBP, and DBP; model 3 was further adjusted for history of smoking, drinking, and family history of HTN; model 4 was further adjusted for history of taking antihypertensive and lipid-lowering drugs; model 5 incorporated all variables into a backward selection model. Furthermore, we replaced the dependent variable with native T1 value to further validate the experimental conclusion.

Pre-specified subgroup analyses were conducted to examine potential interaction effects and quantify heterogeneity across key demographic and clinical subgroups. In the subgroup analysis, the relationship between the indexed EAT volume and TyG was examined according to age (≤ 50 years vs. > 50 years), sex (male vs. female), obesity (BMI < 27.5 vs. BMI > 27.5) [23], history of smoking,drinking,family history of HTN (no vs. yes), and history of taking relevant antihypertensive drugs (no vs. yes). Interactions between subgroups were assessed using the likelihood ratio test. Furthermore, a mediation analysis was conducted to examine whether TyG affected the association of EAT volume with any cardiac measure.

Results

Profile of patients

Table 1 shows the baseline characteristics of our study cohort. Our cohort included 166 hypertensive patients, of which 126 were men (76%), with a median [IQR] age of 51 [36, 62] years, along with 30 healthy controls matched for sex and age. No significant differences were observed among the three participant groups in terms of age, sex, and BMI. Additionally, the group with TyG > 7.24 had a higher incidence of beta-blocker drug usage and elevated mean levels of plasma triglycerides, total cholesterol, HDL, LDL, and fasting plasma glucose (all $P < 0.05$). Other clinical indicators showed no significant differences.

Table 2 summarizes the CMR characteristics for all patients with hypertension and healthy controls. Hypertensive patients exhibited greater LV volume and mass, along with a reduced LVEF, compared to the control group. However, no significant difference was observed in LV volume, mass, and LVEF between the TyG > 7.24 group and the TyG ≤ 7.24 group.

Compared to healthy controls, patients with hypertension exhibited increased native T1 values, ECV fraction, GRS, GCS, GLS, and indexed EAT volume (All $P < 0.001$). Similarly, the TyG > 7.24 group showed higher native T1 values, ECV fraction, and indexed EAT volume (All $P < 0.001$), GRS ($P = 0.025$), GCS ($P = 0.048$), and GLS ($P = 0.015$) in comparison to the TyG ≤ 7.24 group (Fig. 3A, B,Supplementary Figure S1-S4). A positive association was noted between indexed EAT volume and TyG in both groups (Pearson rho = 0.38, $P < 0.001$). Likewise, a positive association was also observed between TyG and ECV (Pearson rho = 0.45, $P < 0.001$) (Fig. 4). After controlling for age and sex, the results remained stable.A

Table 1 Demographic and clinical characteristics of participants based on high or low TyG index

Patients with hypertensive heart disease						
	TYG ≤ 7.24 (n = 83)	**TYG > 7.24 (n = 83)**	**P***	**All patients (n = 166)**	**Healthy controls (n = 30)**	**P¥**
Age (years)	50 [36,61]	52 [35,63]	0.775	51 [36,62]	50 [37,63]	0.989
Male sex, n (%)	61 (73)	65 (78)	0.468	126 (76)	21 (70)	0.492
BMI (kg/m^2)	26.42 [24.62,29.98]	27.01 [24.61,31.11]	0.525	26.67 [24.62,30.12]	26.30 [23.88,30.45]	0.971
Systolic BP (mm Hg)	160 [146,180]	160 [150,170]	0.964	160 [147,175]	115 [106,127]	< 0.001
Diastolic BP (mm Hg)	96 [87,110]	95 [87,101]	0.236	95 [87,105]	72 [64,78]	< 0.001
Heart rate (beats/min)	67 [62,74]	70 [64,77]	0.056	69 [63,76]	70 [58,78]	0.950
Smoking, n (%)	31 (37)	35 (42)	0.526	66 (40)	6 (20)	0.039
Drinking, n (%)	34 (41)	35 (42)	0.875	69 (42)	5 (17)	0.010
Family history, n (%)	14 (17)	14 (17)	1.000	28 (17)	4 (13)	0.630
ACEI/ARB (n, %)	41 (49)	39 (47)	0.756	80 (48)	–	–
beta-blocker, n (%)	38 (46)	25 (30)	0.038	63 (38)	–	–
Diuretic (n, %)	30 (36)	24 (29)	0.320	54 (33)	–	–
Statins (n, %)	36 (43)	32 (39)	0.528	68 (41)	–	–
Calcium channel blocker (n, %)	25 (30)	15 (18)	0.070	40 (24)		
Plasma triglycerides (mmol/L)	1.13 [0.87,1.43]	2.66 [2.07,3.24]	< 0.001	1.73 [1.13,2.66]	1.32 [1.10,1.68]	0.028
Total cholesterol (mmol/L)	3.44 [2.26,4.60]	3.83 [3.05,4.76]	0.042	3.64 [2.74,4.65]	2.97 [2.77,3.14]	0.014
HDL (mmol/L)	1.25 [1.04,1.39]	1.17 [0.92,1.33]	0.042	1.22 [0.99,1.36]	1.26 [1.08,1.66]	0.049
LDL (mmol/L)	2.61 [2.03,2.97]	3.04 [2.83,3.34]	< 0.001	2.88 [2.36,3.25]	2.34 [2.00,2.89]	0.003
Fasting plasma glucose (mmol/L)	4.82 [4.37,5.44]	5.64 [4.85,6.13]	< 0.001	5.12 [4.53,5.92]	4.71 [4.10,5.57]	0.013
TyG	6.74 ± 0.37	7.80 ± 0.41	< 0.001	7.27 ± 0.66	6.94 ± 0.41	< 0.001

P*-value comparing patients with TyG ≤ 7.24 and TyG > 7.24, P¥-value comparing all patients with hypertensive and healthy controls; *BMI* body mass index, *BP* blood pressure, *TyG* Triglycerise-glucose index. p < 0.05 indicates statistical significance

Table 2 CMR characteristics based on High or Low TyG index

Patients with hypertensive heart disease						
	TyG ≤ 7.24 (n = 83)	**TyG > 7.24 (n = 83)**	**P***	**All patients (n = 166)**	**Healthy controls (n = 30)**	**P¥**
Native T1 (ms)	1251.16 ± 51.05	1278.06 ± 44.26	< 0.001	1264.61 ± 49.63	1225.94 ± 38.89	< 0.001
Extracellular volume	28.42 ± 3.45	31.03 ± 3.41	< 0.001	29.72 ± 3.67	26.89 ± 1.68	< 0.001
GRS	23.41 ± 7.14	20.90 ± 7.11	0.025	21.64 [16.92,26.90]	36.04 [31.70,38.96]	< 0.001
GCS	−16.11 ± 3.99	−14.87 ± 3.94	0.048	−15.49 ± 4.01	−20.12 ± 2.67	< 0.001
GLS	−14.28 ± 3.78	−12.94 ± 3.16	0.015	−13.61 ± 3.55	−17.09 ± 2.09	< 0.001
index EAT volume (ml)	67.84 ± 18.83	79.72 ± 15.73	< 0.001	73.78 ± 18.34	52.92 ± 15.47	< 0.001
LVEF (%)	54[47,61]	52 [47,67]	0.677	53 [47,64]	64 [60,72]	< 0.001
LVEDVi (mL/m2)	81.65 [68.40,101.00]	76.76 [59.60,108.73]	0.811	77.61 [60.57,106.64]	65.34 [57.35,79.07]	0.004
LVESVi (mL/m2)	36.62 [23.24,54.03]	38.84 [18.69,64.43]	0.890	36.62 [22.44,59.70]	23.63 [17.94,31.16]	< 0.001
LVCI (L/min/m2)	2.68 [2.11,3.38]	2.70 [2.20,3.47]	0.957	2.70 [2.19,3.45]	2.73 [2.35,3.33]	0.545
LVMI (g/m2)	81.90 [61.60,112.10]	88.88 [71.51,108.04]	0.385	86.70 [65.20,111.74]	53.98 [47.49,65.21]	< 0.001

P*-value comparing patients with TyG ≤ 7.24 and TyG > 7.24, P¥-value comparing all patients with hypertensive and healthy controls. *ECV* Extracellular volume, *GRS* Global radial strain, *GCS* Global circumferential strain, *GLS* Global longitudinal strain, *EAT* epicardial adipose tissue, *LVEF* Left Ventricular Ejection Fractions, *LVEDVi* left ventricular end-diastolic volume index, *LVESVi* left ventricular end-systolic volume index, *LVCI* left ventricular cardiac index, *LVMI* left ventricular mass index

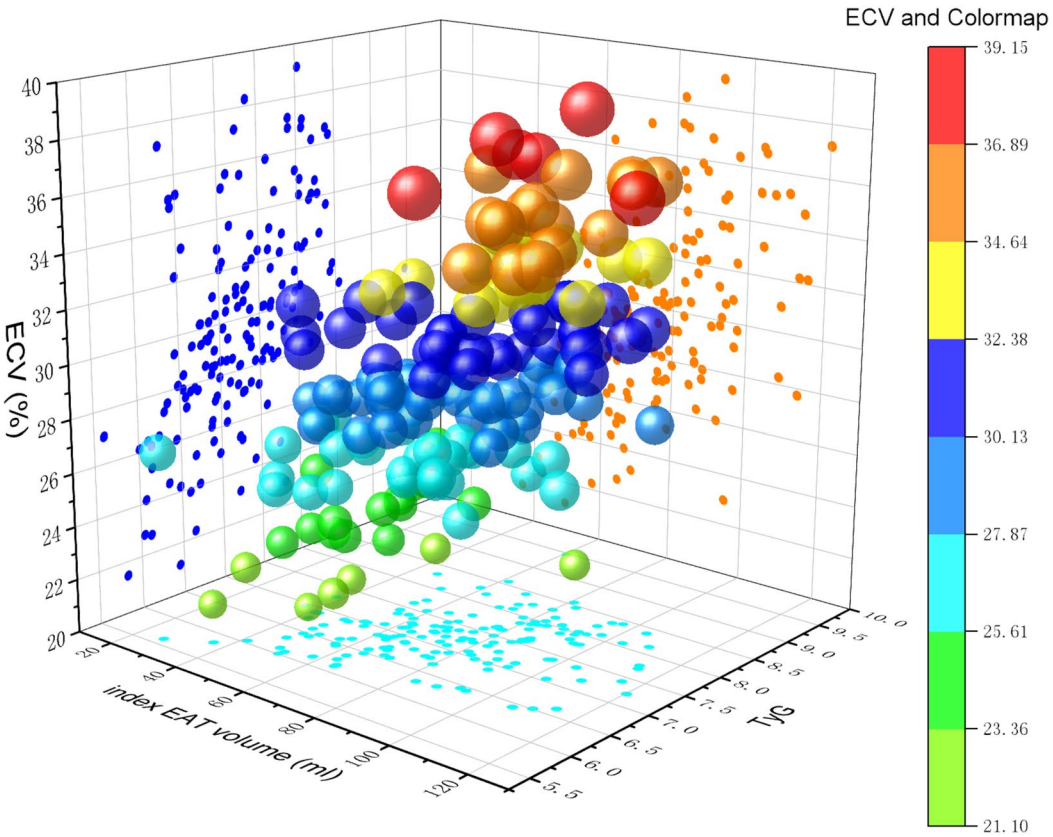


Fig. 3 3D scatter plot of the relationship among indexed EAT volume, ECV, and TyG index. ECV reflects the level of myocardial fibrosis. TyG reflects the level of insulin resistance. The red, orange, and yellow color-coded areas indicate that patients with higher insulin resistance levels exhibit increased EAT volume and more severe myocardial fibrosis. *ECV* Extracellular volume, *EAT* epicardial adipose tissue, *TyG* Triglycerise glucose index

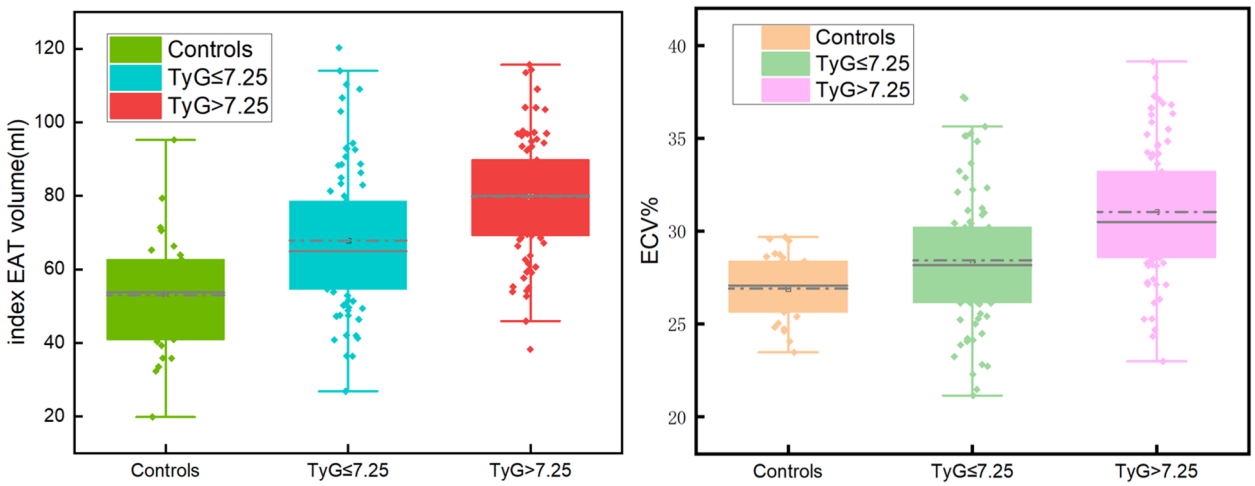


Fig. 4 **A** Boxplot showing the distribution of indexed EAT volume in the groups classified by TyG index and in the normal control group. **B** Boxplot showing the distribution of extracellular volume fraction in the groups classified by TyG index and in the normal control group. Patients with a TyG index greater than 7.25 exhibit a significantly higher EAT volume and are at an elevated risk of developing myocardial fibrosis. *ECV* Extracellular volume, *EAT* epicardial adipose tissue, *TyG* Triglycerise glucose index

similar relationship was found for native T1, GRS, GCS, and GLS (Supplementary Figure S5-S8).

Univariate and multivariate analysis of variables for TyG index,magnetic resonance parameters and high ECV value group

As shown in Table 3, after adjusting for common risk factors, indexed EAT volume, TyG, GRS,GCS(All P < 0.001), GLS,LVMI (P = 0.001), LVEDVi (P = 0.004) and LVESVi (P = 0.007) demonstrated a significant association with the high ECV value group.

Subsequently, variables that showed a significant association with the high ECV value group in the univariate analysis (p < 0.05) were included in the multivariate model. Through backward stepwise selection, GCS, GLS, LVEDVi, LVESVi, and LVMI were excluded until the AIC value reached its minimum.The results presented in Table 4 demonstrate that in the multivariate logistic regression model, indexed EAT volume (OR 1.038, p = 0.002) and TyG (OR 2.808, p = 0.002) continue to be significantly associated with the high ECV value group. (model 1) indexed EAT volume (OR 1.041, p = 0.002) and TyG (OR 2.968, p = 0.002) remained associated with the high ECV value group after adjusting for age, sex, BMI, SBP, and DBP (model 2). Furthermore, after adjusting for history of smoking, drinking, and family history of HTN (model 3), TyG (OR 2.756, p = 0.003) and indexed EAT volume (OR 1.044, p = 0.001) were also linked to the high ECV value group. With adjustments for baseline HTN medications (model 4), TyG (OR 2.876, p = 0.002) and indexed EAT volume (OR 1.040, p = 0.002) remained significantly associated with the high ECV value group. In the backward selection model (Model 5), age, SBP, and drinking history were retained, with TyG (OR 3.158, p = 0.001) and indexed EAT volume (OR 1.036, p = 0.004) maintaining significant associations with the high ECV group.Reconstruct the model by replacing the dependent variable with native T1, and the result remains stable.

Furthermore, we conducted additional validation by re-constructing the regression model using the native T1 values as the dependent variable. Importantly, the key associations presented here have demonstrated significant consistency (TyG OR 1.988, p = 0.021; indexed EAT volume: OR 1.041, p < 0.001). The reliability of our core findings was enhanced by methodological validation using different outcome indicators.(Supplement Table S1).

Subgroup analysis and mediation analysis for indexed EAT volume, TyG and ECV

Subgroup analysis demonstrated that demographic factors (age, sex, obesity) and clinical history did not significantly modify the associations among EAT volume, TyG index, and ECV (all interaction p > 0.05). However, subgroup analysis revealed a significant interaction between β-blocker use and indexed EAT volume (p = 0.036) (Table 5).

Mediation analyses were performed to explore the possible effects that EAT may mediate the relationship between TyG index and ECV in patients with HTN.We chose the TyG index, indexed EAT volume and ECV as the independent variable, the mediator, and the dependent variable, respectively.After adjusting for confounding factors, EAT also exhibited a mediating effect on the relationship between TyG index and ECV(Indirect effect = 0.8844, 95%

Table 3 Associations of cardiac measures with high or low ECV value

	OR	95%CI	P-value	OR_adjusted※	95%CI_adjusted※	P-value_adjusted※
GRS	0.876	[0.830,0.925]	< 0.001	0.866	[0.814,0.921]	**< 0.001**
GCS	1.213	[1.109,1.326]	< 0.001	1.200	[1.091,1.319]	**< 0.001**
GLS	1.202	[1.092,1.324]	< 0.001	1.192	[1.077,1.319]	**0.001**
index EAT volume	1.053	[1.031,1.076]	< 0.001	1.065	[1.038,1.092]	**< 0.001**
HR	1.011	[0.981,1.042]	0.491	1.008	[0.976,1.042]	0.615
LVEF	0.965	[0.936,0.995]	0.023	0.969	[0.936,1.004]	0.081
LVCI	1.180	[0.839,1.660]	0.341	1.441	[0.964,2.152]	0.075
LVEDVi	1.014	[1.004,1.024]	0.005	1.017	[1.005,1.029]	**0.004**
LVESVi	1.017	[1.005,1.029]	0.004	1.019	[1.005,1.032]	**0.007**
LVMI	1.015	[1.005,1.025]	0.002	1.020	[1.009,1.032]	**0.001**
TyG	4.243	[2.356,7.643]	< 0.001	5.205	[2.688,10.080]	**< 0.001**

Bold values indicate P < 0.05 after adjusting for confounding factors

ECV Extracellular volume, *GRS* Global radial strain, *GCS* Global circumferential strain, *GLS* Global longitudinal strain, *EAT* epicardial adipose tissue, *LVEF* Left Ventricular Ejection Fractions, *LVEDVi* left ventricular end-diastolic volume index, *LVESVi* left ventricular end-systolic volume index, *LVCI* left ventricular cardiac index, *LVMI* left ventricular mass index, *TyG* Triglycerise-glucose index

※Adjusted for age, sex, body mass index, systolic blood pressure, diastolic blood pressure,history of smoking, drinking, family history of HTN, history of taking drugs(ACEI/ARB, beta-blocker, Diuretic, Statins, Calcium channel blocker)

Table 4 Multivariate regression analysis between cardiac measures and high or low ECV value

	OR (95%CI) Model 1	P-value	OR (95%CI) Model 2	P-value	OR (95%CI) Model 3	P-value	OR (95%CI) Model 4	P-value	OR (95%CI) Model 5	P-value
GRS	0.892 (0.840–0.947)	**0.002**	0.869 (0.811–0.931)	**< 0.001**	0.894 (0.841–0.950)	**< 0.001**	0.902 (0.849–0.959)	**0.001**	0.876 (0.818–0.938)	**< 0.001**
Index EAT volume	1.038 (1.014–1.063)	**0.002**	1.041 (1.015–1.067)	**0.002**	1.044 (1.017–1.072)	**0.001**	1.040 (1.014–1.066)	**0.002**	1.036 (1.011–1.062)	**0.004**
TyG	2.808 (1.460–5.403)	**0.002**	2.968 (1.503–5.859)	**0.002**	2.756 (1.419–5.352)	**0.003**	2.876 (1.452–5.696)	**0.002**	3.158 (1.581–6.307)	**0.001**

Bold values indicate $P < 0.05$

Model 1 incorporated all variables significant in univariate analyses ($P < 0.05$). Through backward stepwise selection, GCS, GLS, LVEDVi, LVESVi, and LVMI were excluded until the Akaike Information Criterion (AIC) value reached its minimum. The resulting model showed a ΔAIC of 5.30 compared to the original model

Model 2 adjusted for age, sex, body mass index, systolic blood pressure, diastolic blood pressure

Model 3 adjusted for history of smoking, drinking, family history of HTN

Model 4 adjusted for history of taking drugs(ACEI/ARB, Bta-blocker, Diuretic, Statins, Calcium channel blocker)

Model 5 gradually added confounding factors and screened out insignificant variables through backward selection model. Eventually, Age, SBP, history of drinking were retained

ECV Extracellular volume, *EAT* epicardial adipose tissue, *GRS* Global radial strain, *GCS* Global circumferential strain, *GLS* Global longitudinal strain, *LVEDVi* left ventricular end-diastolic volume index, *LVESVi* left ventricular end-systolic volume index, *LVMI* left ventricular mass index, *TyG* Triglycerise-glucose index

Table 5 Subgroup analysis for indexed EAT volume,TyG index and ECV

Subgroup	The association between the index EAT volume and ECV				The association between the TyG index and ECV		
	n (%)	OR (95%CI)	*P*	P for interaction	OR (95%CI)	*P*	P for interaction
Age				0.719			0.691
≤ 50 years	81 (48.80)	3.86 (1.50 ~ 9.95)	0.005		3.21 (1.29 ~ 8.00)	0.012	
> 50 years	85 (51.20)	4.93 (1.93 ~ 12.63)	< 0.001		4.17 (1.67 ~ 10.38)	0.002	
Gender				0.982			0.668
Male	126 (75.90)	4.63 (2.19 ~ 9.81)	< 0.001		4.01 (1.91 ~ 8.41)	< 0.001	
Female	40 (24.10)	4.55 (1.18 ~ 17.52)	0.028		2.89 (0.79 ~ 10.57)	0.109	
Obesity				0.151			0.728
BMI < 27.5	93 (56.02)	3.02 (1.30 ~ 7.03)	0.010		3.33 (1.42 ~ 7.81)	0.006	
BMI > 27.5	73 (43.98)	8.10 (2.84 ~ 23.07)	< 0.001		4.20 (1.58 ~ 11.17)	0.004	
History of smoking				0.661			0.430
No	100 (60.24)	4.37 (1.85 ~ 10.32)	< 0.001		4.53 (1.95 ~ 10.51)	< 0.001	
Yes	66 (39.76)	6.00 (1.95 ~ 18.48)	0.002		2.68 (0.99 ~ 7.26)	0.052	
History of drinking				0.984			0.922
No	97 (58.43)	4.79 (1.98 ~ 11.59)	< 0.001		3.76 (1.62 ~ 8.72)	0.002	
Yes	69 (41.57)	4.86 (1.66 ~ 14.25)	0.004		3.52 (1.30 ~ 9.52)	0.013	
Family history of HTN				0.775			0.782
No	138 (83.13)	4.95 (2.40 ~ 10.20)	< 0.001		3.52 (1.75 ~ 7.10)	< 0.001	
Yes	28 (16.87)	3.81 (0.74 ~ 19.66)	0.110		4.50 (0.91 ~ 22.15)	0.064	
History of taking drugs							
ACEI/ARB				0.367			0.851
No	86 (51.81)	3.61 (1.47 ~ 8.88)	0.005		3.61 (1.47 ~ 8.88)	0.005	
Yes	80 (48.19)	6.72 (2.46 ~ 18.33)	< 0.001		4.09 (1.58 ~ 10.59)	0.004	
Beta-blocker				**0.036**			0.312
No	103 (62.05)	2.69 (1.21 ~ 5.97)	0.015		2.97 (1.32 ~ 6.66)	0.008	
Yes	63 (37.95)	12.50 (3.77 ~ 41.40)	< 0.001		6.09 (1.95 ~ 18.97)	0.002	
Diuretic				0.166			0.853
No	112 (67.47)	3.15 (1.45 ~ 6.85)	0.004		4.36 (1.95 ~ 9.74)	< 0.001	
Yes	54 (32.53)	9.00 (2.53 ~ 31.96)	< 0.001		3.80 (1.12 ~ 12.84)	0.032	
Statins				0.574			0.133
No	98 (59.04)	3.86 (1.67 ~ 8.93)	0.002		2.52 (1.12 ~ 5.70)	0.026	
Yes	68 (40.96)	5.67 (1.99 ~ 16.13)	0.001		7.14 (2.41 ~ 21.19)	< 0.001	
Calcium channel blocker				0.292			0.297
No	126 (75.90)	3.71 (1.78 ~ 7.76)	< 0.001		3.00 (1.45 ~ 6.21)	0.003	
Yes	40 (24.10)	8.84 (2.11 ~ 37.11)	0.003		7.07 (1.68 ~ 29.83)	0.008	

Bold values indicate P for interaction < 0.05

BMI body mass index, *TyG* Triglycerise-glucose index, *ECV* Extracellular volume, *EAT* epicardial adipose tissue, *HTN* hypertension

CI [0.4539,1.3666]) (Fig. 5A,Supplementary Table S2). The same relationship occurred for Native T1 and TyG index(Indirect effect = 11.3161, 95% CI [5.8029,17.4204]) (Fig. 5B,Supplementary Table S2).

Discussion

The primary findings of our research are as follows: 1) Compared to healthy controls, patients with HTN exhibited elevated native T1, ECV, and indexed EAT volume, alongside reduced GRS, GCS, and GLS. Likewise, patients in the TyG > 7.24 group had higher native T1, ECV, and indexed EAT volume, and lower GRS, GCS, and GLS than those in the TyG ≤ 7.24 group. 2) Binary logistic regression analysis revealed that TyG and indexed EAT volume independently correlated with the high ECV value, and the results remained stable after adjusting for confounding factors. The findings were consistent when patients were categorized according to baseline and clinical characteristics.

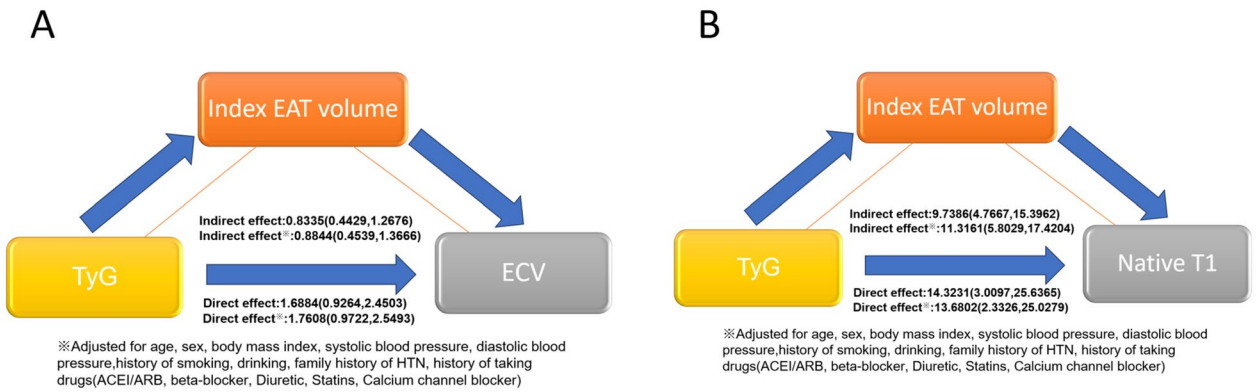


Fig. 5 TyG mediates the processes of indexed EAT volume and ECV. The figure shows that higher levels of insulin resistance may aggravate myocardial fibrosis through EAT. *ECV* Extracellular volume, *EAT* epicardial adipose tissue, *TyG* Triglycerise glucose index

3) Furthermore, we found that EAT exhibited a mediating effect on the relationship between TyG index and ECV after adjusting for confounding factors. The same relationship occurred for Native T1 and TyG index.This suggests that IR may aggravate myocardial fibrosis by changing the function of EAT.

Diabetes is a well-established risk factor for cardiovascular disease, with extensive studies demonstrating that individuals with diabetes or an elevated TyG index exhibit a significantly higher risk of adverse clinical events [24]. Diabetes mellitus frequently coexists with hypertension and is strongly associated with myocardial fibrosis and cardiac dysfunction in hypertensive patients.A large number of studies have shown that diabetes can exacerbate myocardial fibrosis and cardiac dysfunction in hypertensive patients. Pua et al. utilized myocardial fibrosis assessed by ECV and strain degree assessed by RS, CS, and LS based on CMR, discovering that hypertensive patients with diabetes had higher ECV and worse multidirectional strain [25]. Similarly, Zhang et al. suggested that DM was an independent determinant of impaired LV strains in all three directions [26]. In fact, many patients with undiagnosed diabetes have long been in an IR state, yet this has often been overlooked. In our study, the TyG was used to assess IR, the ECV,GRS,GCS,GLS was used to assess LV diffuse fibrosis and strain based on CMR imaging. We observed that in hypertensive subjects without diabetes, those with a high TyG already showed more severe diffuse fibrosis and worse strain. This finding underscores the importance of early clinical intervention to combat IR. However, the precise mechanism by which IR leads to myocardial fibrosis and cardiac dysfunction remains unclear.

EAT may contribute to the development of myocardial fibrosis and cardiac dysfunction. EAT can promote collagen deposition by secreting pro-inflammatory and pro-fibrotic factors, which in turn activate cardiac fibroblasts. Simultaneously, EAT releases free fatty acids and reactive oxygen species (ROS), contributing to oxidative stress and mitochondrial dysfunction [27]. This cascade of events exacerbates myocardial inflammation and fibrosis. CT Ng et al. demonstrated a significant correlation between EAT volume and both myocardial fibrosis burden as well as left ventricular systolic dysfunction, as quantified by CMR-derived ECV fraction and GLS parameters [28]. Ishikawa et al. further established a significant independent association between EAT accumulation and impaired left ventricular diastolic function [29]. Epicardial fat is affected by a variety of factors. There is growing evidence that epicardial fat metabolism in IR patients is active, dysregulated, and abnormal. Under conditions of low oxidative stress, normal epicardial adipocytes secrete adiponectin, which reduces inflammation and fibrosis in the coronary arteries and myocardium, thereby decreasing the risk of adverse clinical events [30–32]. However, IR patients may experience increased oxidative stress [33], leading to the release of more proinflammatory or profibrotic factors from EAT, which can result in myocardial fibrosis and cardiac dysfunction. In addition, IR may stimulate fibrosis by inducing lipotoxic cardiomyocyte injury, which leads to the accumulation of harmful lipids that interfere with organelle function, resulting in cardiomyocyte injury and subsequent activation of inflammatory and fibrotic processes [34]. Our study found that the high TyG group had a greater EAT volume and a higher ECV value. These associations remained independent after controlling for some confounding factors. Subgroup analysis revealed that age, sex, BMI, clinical history, and antihypertensive drugs did not affect the relationship among TyG,EAT and ECV. However, there were differences between EAT and ECV when categorizing patients by beta-blocker use, possibly

attributable to the anti-fibrotic properties of these medications (ACEIs/ARBs or beta-blockers) and their potential impact on IR [35, 36]. Although antihypertensives may theoretically reduce myocardial fibrosis, our cohort data suggest that patients receiving these medications had longer disease durations and more advanced fibrosis, potentially masking detectable protective effects. Further mediation analysis suggested that IR might change the physiological function of EAT and lead to more severe myocardial fibrosis.

Epicardial fat is a modifiable cardiovascular risk factor and a potential new therapeutic target. New treatments, such as glucagon-like peptide 1 receptor (GLP1R) agonists and sodium-dependent glucose transporter 2 (SGLT2) inhibitors, have shown promise in reducing epicardial fat volume or thickness [37–40]. Nonetheless, our study suggests that IR may aggravate the risk associated with EAT. Therefore, it is equally important to focus on regulating the growth factor environment or administering antioxidants as therapeutic targets for IR-related fibrosis [41]. When considering the categorization according to the risk of EAT, it is important to take into account not only the thickness and volume of EAT but also the presence of IR. Early intervention to improve IR may alleviate the pro-fibrotic effects of epicardial fat, thereby reducing the incidence of poor prognosis.

Study limitation

The current research has several limitations.First, the limited sample size introduced instability in the coefficient estimates, despite adjustment for existing confounders. This limitation hindered our ability to test the sensitivity of key coefficients to the addition or deletion of variables. Secondly, the TyG index is potentially influenced by pharmacological interventions, dietary patterns, physical activity levels, and other lifestyle-related variables. Although no significant differences in medication usage were detected between high- and low-TyG groups within our cohort, residual confounding effects from these factors cannot be definitively excluded in observational analyses. Moreover, due to the the limitations of retrospective studies, we did not conduct detailed investigations on patients' exercise patterns, nutritional patterns, socioeconomic status,family history of coronary artery disease, etc. Thirdly,the retrospective nature of this study may introduce bias into the findings. Our study was mainly based on CMR, which may have missed some patients with milder disease who would normally undergo cardiac ultrasound, thus limiting the generalization of our findings.It is recommended that future research efforts should include multicenter prospective studies with larger sample sizes and provide more detailed research to ensure the accuracy of the study.

Conclusion

The present study revealed that patients with elevated TyG exhibited significantly greater EAT volume, ECV, native T1, and worse LV multidirectional response compared to hypertensive patients with low TyG and controls. Moreover, we propose that EAT is involved in the effect of TyG on ECV. Early IR improvement could potentially mitigate the profibrotic effect of EAT, thereby reducing the incidence of poor prognosis.

Abbreviations

HTN	Hypertension
IR	Insulin resistance
EAT	Epicardial adipose tissue
ECV	Extracellular volume
TyG	Triglycerise-glucose index
BMI	Body mass index
SBP	Systolic blood pressure
DBP	Diastolic blood pressure
LVEF	Left Ventricular Ejection Fractions
LVEDVi	Left ventricular end-diastolic volume index
LVESVi	Left ventricular end-systolic volume index
LVCI	Left ventricular cardiac index
LVMI	Left ventricular mass index

Supplementary Information

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Supplementary material 1.

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Author contributions

RZZ, WXW and ZYC designed the study. RZZ interpreted the data and wrote the manuscript. RZZ,WXW analyzed the data and gave advice on data presentation. RZZ,YG and JW were responsible for collecting and sorting statistical data.BWL,HG,SFY participated in editing and review of the manuscript. Technical support was provided by CSJ and XSY.XMW supervised the overall study and reviewed the manuscript. All authors read and approved the final manuscript.

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Availability of data and materials

The datasets analyzed during the current study are available from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate

This retrospective study was approved by the institutional review board of Shandong Provincial Hospital Affiliated to Shandong First Medical University. The requirement for informed patient consent was waived.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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