Journal of Geriatric Cardiology (2016) 13: 768–775

Research Article · **Open Access** ·

Influence of increased epicardial adipose tissue volume on 1-year in-stent restenosis in patients who received coronary stent implantation

Ying ZHOU[1,2*], Hua-Wei ZHANG[1*], Feng TIAN[1], Jin-Song CHEN[1,3], Tian-Wen HAN[1], Ya-Hang TAN[1,4], Jia ZHOU[1,5], Tao ZHANG[1], Jing JING[1], Yun-Dai CHEN[1]

[1]*Department of Cardiology, Chinese PLA General Hospital, Beijing, China*
[2]*VIP Medical Service Department, Beijing SHIJITAN Hospital, Beijing, China*
[3]*Department of Cardiology, Chinese PLA 175 Hospital, Fujian, China*
[4]*School of Medicine, Nankai University, Tianjin, China*
[5]*Department of Cardiology, Tianjin Chest Hospital, Tianjin, China*

Abstract

Background Epicardial adipose tissue (EAT) is significantly associated with the formation and composition of coronary atherosclerotic plaque, cardiac events and the clinical prognosis of coronary heart disease. But, whether increased EAT deposition may affect the incidence of in-stent restenosis (ISR) is currently unclear. This study used coronary computed tomography angiography (CCTA) as a mean to investigate whether increased EAT volume was associated with ISR. **Methods** A total of 364 patients who underwent 64-slice CCTA examination for the evaluation of suspected coronary artery disease, and subsequently underwent percutaneous coronary intervention (PCI) for the first time, and then accepted coronary angiography (CA) follow-up for ISR examination in one year, were retrospectively included in this study. EAT volume was measured by CCTA examination. CA follow-up was obtained between 9 and 15 months. ISR was defined as ≥ 50% luminal diameter narrowing of the stent segment or peri-stent segment. EAT volume was compared between patients with and without ISR and additional well-known predictors of ISR were compared. **Results** EAT volume was significantly increased in patients with ISR compared with those without ISR (154.5 ± 74.6 mL *vs.* 131.0 ± 52.2 mL, $P < 0.001$). The relation between ISR and EAT volume remained significant after adjustment for conventional cardiovascular risk factors and angiographic parameters. **Conclusions** EAT volume was related with ISR and may provide additional information for future ISR.

J Geriatr Cardiol 2016; 13: 768–775. doi:10.11909/j.issn.1671-5411.2016.09.012

Keywords: Computed tomography; Drug-eluting stents; Epicardial adipose tissue; In-stent restenosis

1 Introduction

Despite major improvements in stents material, interventional techniques and drug therapies, in-stent restenosis (ISR) after stents implantation is still 5%–15%, even in drug-eluting stents (DESs) era.[1–3] The predictive performance of conventional risk factors (such as age, hypertension, diabetes mellitus, smoking, C reaction protein, severe calcification and diffuse lesions, long and multiple stents, etc) seems to be not satisfying. To date, we still lack effective and accurate methods to identify who are at high risk of ISR, thereby can't offer them with relevant drug therapy before repeated revascularization. Epicardial adipose tissue (EAT) is directly deposited around the pericardium and coronary artery. By autocrine and paracrine means, it can generate various kinds of proinflammatory mediators and free fatty acids.[4,5] Those biological indicators can affect the state of endothelial function, promote inflammation and oxidative stress, and aggravate proliferation and migration of smooth muscle cells.[4–8] As we know, endothelial dysfunction, inflammation, oxidative stress, smooth muscle cells proliferation and migration are all key points that associated with coronary atherosclerosis and ISR.[9–12] Multiple clinical researches have shown that increased EAT deposition plays an important role in the development and progression of atherosclerosis, metabolic syndrome and cardiac events.[13–16] Whether increased EAT deposition may affect the incidence of ISR is currently unclear. In this study, we sought to iden-

*The first two authors contributed equally to this manuscript.
Correspondence to: Yun-Dai CHEN, Department of Cardiology, Chinese PLA General Hospital, 28 Fuxing Road, Beijing 100853, China.
E-mail: cyundai@vip.163.com.
Telephone: +86-10-5549-9246 **Fax:** +86-10-5549-9246
Received: January 7, 2016 **Revised:** June 29, 2016
Accepted: July 18, 2016 **Published online:** September 28, 2016

tify whether there is a relationship between ISR and EAT volume detected by coronary computed tomography angiography (CCTA).

2 Methods

2.1 Study population

From May 2013 to April 2014, a total of 364 patients who underwent 64-slice CCTA examination for the evaluation of suspected coronary artery disease, and subsequently underwent percutaneous coronary intervention (PCI) in the Chinese PLA General Hospital for the first time within one month, then accepted coronary angiography (CA) follow-up for ISR examination in 9–15 months, were retrospectively included in this study. The inclusion criteria were as follows: age ≥ 18 years; accepted selective PCI in our hospital for the first time after CCTA examination within one month; all stents implanted were DESs; stents diameter was 2.5–4.0 mm; the time interval of CA was 9–15 months. The exclusion criteria were as follows: severe heart dysfunction or severe left ventricle dysfunction (left ventricle ejection < 30%); severe renal insufficiency (serum creatinine > 1.5 mg/dL); previous coronary artery bypass graft (CABG) or previous PCI; CCTA images with motion artifact or impaired image quality. The study was approved by our institutional review board. All patients were fully explained the procedure of the examination, and the written informed consents were obtained.

2.2 CCTA imaging and analysis

All patients underwent a dual-source CT scanner (Somatom Definition Flash, Siemens Healthcare, Forchheim, Germany) for the evaluation of suspected coronary artery disease. Patients were instructed in breath-holding technique before the scan to minimize the breathing artifact. All patients without contraindications were given a 0.5 mg nitroglycerin sublingually 3 min before the scan. Patients with heart rate (HR) > 70 beats/min were intravenously given a 50–100 mg esmolol hydrochloride injection before the scan unless contraindicated. The scan range was from the carina or the pulmonary artery segment down to 1 cm below the diaphragm. Electrocardiograph was continuously monitored throughout the entire scan. Dual-head power injector (SCT 210, Medrad, USA) and the nonionic contrast medium (Ultravist®, 370 mgI/mL, Schering AG, Guangzhou, China) were used during the scan.

Prospectively ECG-triggered high-pitch spiral acquisition or prospectively ECG-triggered sequential acquisitions were used to acquire the CCTA images. The scan parameters were as follows: detector collimation 2 × 128 × 0.6 mm; gantry rotation time 0.28 ms; slice thickness 0.6 mm; tube voltage 80 to 120 kV (modified by Care kV technique to minimize the radiation dose) and tube current 290 to 560 mAs/rotation (modified by CareDose 4D technique to minimize the radiation dose); pitch was 3.4 for flash acquisition and 0.17–0.24 depending on HR for prospectively acquisition.

All CCTA data were sent to a dedicated software (QAngio CT Research Edition version 2.1.9.1, Medical Imaging Systems, Leiden, the Netherlands) for plaque analysis. Two skilled radiologists unaware of the patients' clinical information independently evaluated the CCTA data. Disagreements analysis in all CCTA images between the two readers were resolved by consensus reading. Coronary artery classification was evaluated referring the 15 segments model of the American Heart Association.[17] Patients with coronary stenosis greater or equal to 75% were defined as ones that should accepted CA examination and further stent implantation.

2.3 EAT volume measurement

Total EAT volume was measured by two experienced radiologists using the same sets of images acquired from CCTA. The radiologists were blinded to the purpose of the study and the patients' anthropometric data. A cursor pointer was used to manually trace the pericardial contour with 0.75-mm-thick reconstructed axial slices (Figure 1). Pericardium contour was traced for every 10 mm starting from the lower visible level of pulmonary artery bifurcation until the last slice where pericardium is still visible (Figure 2).[18] The pericardium contour is extrapolated by the software (Syngo Volume, Siemens Medical Solutions) for the non-traced slices and rechecked by the operator. EAT was identified using the adipose tissue attenuation references between –190 and –30 Hounsfield unit.[19] Pericardial adipose fat (fat depot outside the visceral pericardium and on the external surface of the parietal pericardium) were excluded from analysis.

The total EAT volume were evaluated by two independent radiologists who were blinded to the other's measurements for the assessment of inter-observer agreements in 50 randomly selected patients. The intra and inter-observer correlation coefficients for EAT volume measurements were 0.96 and 0.92, respectively.

2.4 Coronary angiography and stent implantation

Patients with coronary stenosis greater or equal to 75% accepted CA after CCTA examination within one month. Patients who accepted elective PCI with coronary stent implantation in our hospital after CCTA for the first time were

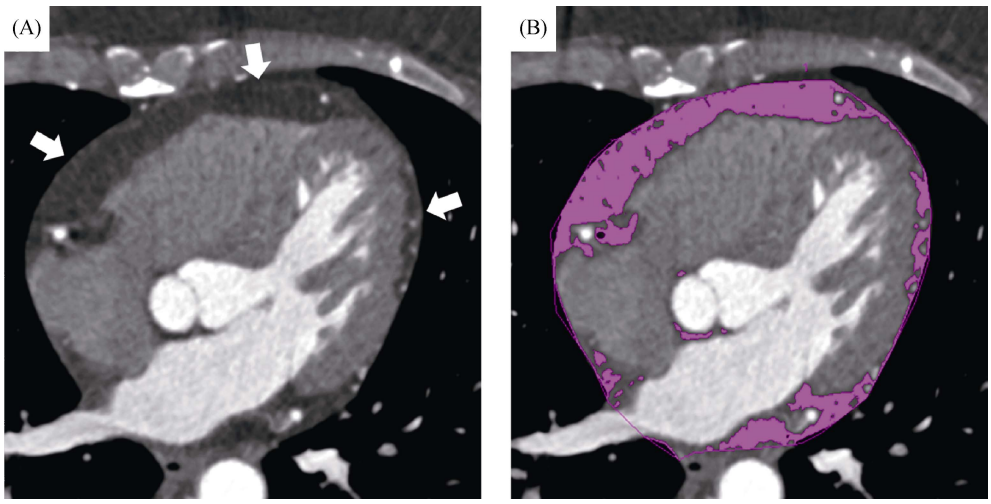

Figure 1. Example of EAT volume quantification by CCTA. (A): EAT was defined as the adipose tissue within the visceral layer of the pericardium (arrows on A); (B): Total EAT volume was quantified by manually tracing the pericardium on the contrast-enhanced CT imaging, then calculated and highlighted with a threshold of –30 to –190 HU by the software (Syngo Volume, Siemens Medical Solutions). Purple area represent EAT. CCTA: coronary computed tomography angiography; EAT: epicardial adipose tissue.

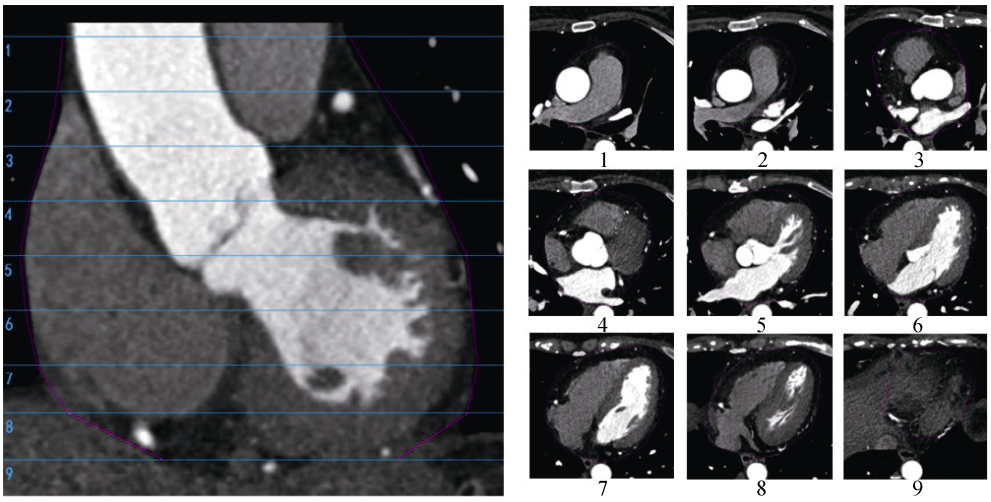

Figure 2. Measurement of EAT volume. The axial slices used for pericardial tracking is shown in a coronal projection. EAT was identified within the limits of pericardium sac using the adipose tissue attenuation references (–30 to –190 HU). Pericardium contour was traced for every 10 mm, starting from the lower visible level of pulmonary artery bifurcation until the last slice where pericardium is still visible. Final EAT volume quantification was calculated as the sum of all slices fat values. EAT: epicardial adipose tissue.

enrolled in this study. Experienced cardiologists performed PCIs and DESs implantation using standard techniques via the right radial (or femoral) artery in all enrolled patients. During the PCI procedure, direct stenting, balloon pre-dilatation or post-dilatation techniques were used according to the cardiologist's decision. The ratio of stent diameter to distal reference vessel diameter was 1: 1 to 1.1: 1, and stent delivery pressure was at least 13 atm. The available stent lengths were 10–36 mm, and the stent diameters were 2.5, 3.0, 3.5, and 4.0 mm. All results of coronary angiography were analyzed at an independent core laboratory. The quantitative coronary angiography (QCA) software package from Medis CMS (Leiden, the Netherlands) was used for imaging analysis.

2.5 Drug treatment and CA follow- up at one year

All patients accepted conventional anti-atherosclerosis treatments, including one year dual antiplatelet therapy (aspirin 100 mg/day and clopidogrel 75 mg/day) and statin treatment. All patients accepted CA examination at an in-

terval of 9–15 months to follow up ISR and coronary atherosclerosis state. The primary end point of this study was angiographic ISR, defined as ≥ 50% luminal diameter narrowing of the stented or peri-stent segment (defined as a length of 5 mm proximal and distal to the stent edge); patent stent was defined as < 50% or no stenosis.[20]

2.6 Statistical analysis

Continuous variables were presented as mean ± SD and categorical variables were presented as *n* (%). Continuous variables with normal distribution were compared using unpaired Student's *t*-test and with abnormal distribution were compared using Mann-Whitney *U* test or Wilcoxon's signed-rank test. Categorical variables were compared using Chi-squared test or Fisher's exact test if necessary. Simple correlations between clinical parameters and EAT volume were evaluated using Spearman's correlation coefficient. Intra and inter-observer correlations were assessed using intraclass correlation coefficients in 50 randomly selected patients. Variables (including clinical, angiographic variables and EAT volume) known or suspected to be associated with the presence of ISR were assessed using univariable and multivariable logistic regression analysis. A *P*-value < 0.05 was considered statistically significant. All statistical analyses were performed using SPSS (version 17.0 for Windows, SPSS, Inc., Chicago, IL, USA).

3 Results

3.1 Clinical characteristics

In the final analysis, 364 patients received a mean of 12.7 ± 2.6 months CA follow-up. During the one year CA follow-up, ISR was seen in 46 (12.6%) patients, and intima hyperplasia was seen in 30 (8.2%) patients.

As shown in Table 1, there were no significant differences in variables such as age, gender, body weight, body mass index (BMI), systolic blood pressure, hypertension, hyperlipidemia, family history of coronary artery disease, medications, and laboratory and echocardiography data (all $P > 0.05$). Significantly differences were observed between ISR and Non-ISR group in terms of diastolic blood pressure (72.9 ± 10.4 mmHg *vs*. 76.9 ± 11.4 mmHg, $P = 0.025$), patients with diabetes mellitus (43.5% *vs*. 25.8%, $P = 0.013$), and current smoking (54.3% *vs*. 32.1%, $P = 0.005$). Patients with ISR had a significantly higher EAT volume compared to patients without ISR (154.5 ± 74.6 mL *vs*. 131.0 ± 52.2 mL, $P = 0.008$).

The basic angiographic parameters were listed in Table 2. ISR group showed more stents planted compared to non-ISR group (2.0 ± 1.0 stents *vs*. 1.7 ± 0.8 stents, $P = 0.022$).

Table 1. Clinical characteristics of the study population.

Variable	ISR group (*n* = 46)	Non-ISR group (*n* = 318)	*P* value
Age, yrs	61.9 ± 12.7	60.3 ± 11.5	0.374
Gender, male	32 (69.6%)	226 (71.1%)	0.834
Body weight, kg	72.2 ± 15.7	72.7 ± 10.7	0.831
BMI, kg/m^2	25.5 ± 4.1	25.9 ± 2.9	0.545
Systolic blood pressure, mmHg	134.4 ± 21.1	137.3 ± 17.1	0.294
Diastolic blood pressure, mmHg	72.9 ± 10.4	76.9 ± 11.4	0.025
Cardiovascular risk factors			
Diabetes mellitus	20 (43.5%)	82 (25.8%)	0.013
Hypertension	31 (67.4%)	207 (65.1%)	0.760
Hyperlipidemia	22 (47.8%)	123 (38.7%)	0.236
Current smoking	25 (54.3%)	102 (32.1%)	0.005
Family history of CAD	21(45.7%)	152(47.8%)	0.785
Medication			
Statins	35 (76.1%)	230 (72.3%)	0.592
β-blockers	33 (71.7%)	209 (65.7%)	0.419
ACEIs/ARBs	19 (41.3%)	147 (46.2%)	0.531
CCB	18 (39.1%)	124 (39.0%)	0.986
Laboratory data			
On admission			
Total cholesterol, mmol/	4.1 ± 1.1	4.3 ± 1.0	0.358
Triglycerides, mmol/L	1.5 ± 0.7	1.7 ± 1.1	0.102
LDL-C, mmol/L	2.4 ± 1.0	2.5 ± 0.9	0.275
HDL-C, mmol/L	1.0 ± 0.2	1.1 ± 0.3	0.270
Creatinine, mg/dL	80.7 ± 56.6	75.4 ± 19.4	0.213
FBG, mmol/L	6.8 ± 2.6	6.6 ± 2.0	0.543
At follow-up			
Total cholesterol, mmol/L	3.1 ± 0.7	3.3 ± 1.0	0.191
Triglycerides, mmol/L	1.4 ± 0.8	1.5 ± 0.9	0.476
LDL-C, mmol/L	1.9 ± 0.6	2.0 ± 0.8	0.416
HDL-C, mmol/L	1.0 ± 0.3	1.1 ± 0.4	0.104
Echocardiography			
LVDd, mm	45.6 ± 6.1	45.6 ± 4.6	0.957
LVDs, mm	31.9 ± 5.6	31.3 ± 4.4	0. 389
EF, %	57.1 ± 7.3	58.7 ± 7.2	0.159
CT finding			
Epicardial fat volume, mL	154.5 ± 74.6	131.0 ± 52.2	0.008

Data are presented as mean ± SD or *n* (%). ACEIs/ARBs: angiotensin-converting enzyme inhibitors/angiotensin receptor blockers; BMI: body mass index; CAD: coronary artery disease; CCB: calcium channel blocker; CT: computed tomography; EF: ejection fraction; FBG: fasting blood-glucose; HDL-C: high density lipoprotein cholesterol; ISR: in-stent restenosis; LDL-C: low density lipoprotein cholesterol; LVDd: left ventricular diastolic diameter; LVDs: left ventricular systolic diameter.

Significantly differences were observed between ISR and Non-ISR group in terms of stent length (26.1 ± 6.1 *vs*. 22.4 ± 5.6 mm, $P = 0.003$).

Table 2. Basic angiographic data of the study population.

Variable	ISR group (n = 46)	Non-ISR group (n = 318)	P value
Target vessels			
LM	4 (8.7%)	8 (2.5%)	0.122
LAD	37 (80.4%)	244 (77.0%)	0.846
LCX	16 (34.8%)	96 (30.2%)	0.891
RCA	35 (76.1%)	223 (70.1%)	0.854
Multi-vessels	10 (21.7%)	47 (14.8%)	0.225
Lesions			
Bifurcation	8 (17.4%)	52 (16.4%)	0.859
CTO	7 (15.2%)	48 (15.1%)	0.983
Stents parameter			
Number of stents, n	2.0 ± 1.0	1.7 ± 0.8	0.022
Mean stent diameter, mm	2.9 ± 0.4	3.1 ± 0.7	0.059
Mean stent length, mm	26.1 ± 6.1	22.4 ± 5.6	0.003
Sirolimus	70 (76.1%)	308 (74.9%)	0.818
Paclitaxel	22 (23.9%)	103 (25.1%)	0.818
Stenting technique			
Pre-dilation	43 (93.5%)	308 (96.9%)	0.466
Direct stenting	3 (6.5%)	10 (3.1%)	0.466
Post-dilation	36 (78.3%)	254 (79.9%)	0.799
CA follow-up interval, m	12.7 ± 2.1	13.1 ± 3.4	0.438

Data are presented as mean ± SD or n (%). CA: coronary angiography; CTO: chronic total occlusion; LAD: left anterior descending; LCX: left circumflex coronary artery; LM: left main artery; RCA: right coronary artery.

3.2 Relationship between clinical parameters and EAT volume

EAT volume showed significant correlations with BMI (r = 0.348, P < 0.001) and diabetes mellitus (r = –0.127, P = 0.016) in all 364 patients. EAT volume also showed significant correlations with BMI both in ISR and Non-ISR group (r = 0.379, P = 0.009 and r = 0.351, P < 0.001 respectively). In ISR group, left ventricular diastolic diameter (r = 0.358, P = 0.015), left ventricular systolic diameter (r = 0.354, P = 0.016) and ejection fraction (r = –0.308, P = 0.037) were also correlated with EAT volume. While, significant correlations were showed among age (r = 0.210, P < 0.001), gender (r = 0.282, P < 0.001), total cholesterol (r = –0.170, P = 0.003), triglycerides (r = 0.261, P < 0.001), high density lipoprotein cholesterol (HDL-C) (r = –0.251, P < 0.001) and low density lipoprotein cholesterol (LDL-C) (r = –0.130, P = 0.024) in Non-ISR group.

3.3 The relationship between EAT volume and in-stent restenosis

In the univariate logistic regression analysis, the conventional predictors for ISR such as diabetes mellitus, current smoking, diastolic blood pressure, LDL-C at follow-up, mean stent length, and mean stent diameter were all statistically significant risk factors for ISR (Table 3). The unadjusted odds ratio was 1.007 (95% CI: 1.002–1.012, P = 0.010) for EAT volume to predict ISR (Table 3).

In the multivariable logistic regression analysis to determine the predictors of ISR, after adjusted for conventional cardiac risk factors and the angiographic data (mean stent length and mean stent diameter), the odds ratio was 1.009 (95% CI 1.002–1.016, P = 0.009) for EAT volume to predict ISR (Table 4) .

Table 3. Univariate logistic regression analysis of predictors for ISR.

Variable	OR	95% CI	P Value
Age	1.012	0.985–1.012	0.373
Diabetes mellitus	2.214	1.173–4.177	0.014
Current smoking	2.521	1.348–4.715	0.004
Diastolic blood pressure	0.968	0.940–0.996	0.026
LDL-C on admission	0.820	0.574–1.171	0.274
LDL-C at follow-up	0.552	0.331–0.922	0.023
Mean stent length	1.122	1.057–1.191	0.001
Mean stent diameter	0.288	0.115–0.720	0.008
Epicardial fat volume	1.007	1.002–1.012	0.010

ISR: in-stent restenosis; LDL-C: low density lipoprotein cholesterol.

Table 4. Multivariate logistic regression analysis of predictors for ISR at approximately one year after PCI.

Variable	OR	95% CI	P Value
Age	0.988	0.956–1.020	0.461
Diabetes mellitus	2.256	1.012–5.030	0.047
Current smoking	1.706	0.758–3.838	0.197
Diastolic blood pressure	0.972	0.940–1.005	0.091
LDL-C on admission	0.906	0.585–1.405	0.906
LDL-C at follow-up	0.383	0.191–0.769	0.007
Mean stent length	1.122	1.048–1.201	0.001
Mean stent diameter	0.217	0.066–0.710	0.012
Epicardial fat volume	1.009	1.002–1.016	0.009

ISR: in-stent restenosis; LDL-C: low density lipoprotein cholesterol; PCI: percutaneous coronary intervention.

4 Discussion

The present study of 364 patients with DESs implantation showed that patients with ISR had increased EAT deposition compared with patients without ISR. The major finding was that the association of EAT volume with ISR in patients with DESs, was independent of conventional cardiovascular risk factors, treatment factor and angiographic parameter (mean stent length and mean stent diameter). This

study, to the best of our knowledge, was the first analysis aimed at finding out the relationship between EAT volume and the presence of ISR using CCTA as a non-invasive imaging method. A different group has already described that EAT is associated with ISR, but it used echocardiography, a much less sensitive tool to quantify EAT.[21] As we known, CCTA is now a recognized tool to quantify EAT volume because it can quantify the coronary atherosclerosis at the same time.

EAT is the adipose tissue deposited directly surrounding the major coronary arteries and their braches. Adipose tissue recently is found to be an endocrine organ which can secretes plenty of adipocytokines, free fatty acid and pro-inflammation markers.[4–6] Increased EAT deposition can cause superfluous pro-inflammation mediators secreted into the blood or paracrine to the adjacent tissue. Multiple exocrine and paracrine factors secreted by EAT can directly influence coronary artery wall homeostasis by altering the function of endothelial cells, arterial smooth muscle cells and macrophages. It can cause inflammation, oxidative stress, endothelial injury, vascular smooth muscle cells (VSMCs) proliferation and migration, lipid metabolic disorders and microphage infiltration in the adjacent coronary artery wall and other pathological changes.[4–6,22]

The proliferation and migration of VSMCs is the main pathophysiological processes of coronary ISR. Increase EAT can secret plenty of factors that may promote (visfatin, resistin and angiopoietin-like protein, etc) or inhibit (adiponectin) VSMCs proliferation and migration. Visfatin can stimulate VSMCs proliferation via nicotinamide mononucleotide (NMN)-mediated ERK 1/2 and p38 signaling.[23] Angiopoietin-like protein secreted by peri-vascular adipose tissue can accelerate neointimal hyperplasia after endovascular injury.[24] Resistin could promote VSMC proliferation through activation of ERK1/2 and phosphatidylinositol 3-kinase (PI3K) pathways.[25] The role of adiponection on VSMC proliferation and migration is opposed to resistin.[26] Zhang, *et al*.[27] found that adiponectin could up-regulate the expression of mitofusin-2 (MFN2), inhibiting the Ras-Raf-ERK1/2 signaling pathway, which could lead to the inhibition of VSMC proliferation and the induction of VSMC apoptosis. Resistin also significantly increase p42/44 mitogen-activated protein kinase (MAPK) phosphorylation within rat VSMCs, whereas adiponectin inhibited resistin-induced MAPK phosphorylation.[26] Therefore, increased EAT deposition can cause imbalance between promoting and inhibiting pro-inflammation markers, which may finally affect the ISR by act on the proliferation and migration of VSMCs.

Inflammation also plays a pivotal role in the development of ISR by acting on the neointimal tissue at the sites of coronary stenting. In recent years, several studies have shown that ISR may be the result of neoatherosclerosis caused by the delayed re-enothelialization.[28] As researches showed that EAT from patients with CAD was with higher levels of interleukin (IL)-1β, IL-6, tumor necrosis factor α (TNF-α) and MCP-1 than patients without CAD.[29–31] Expression of these factors associated with inflammatory cells infiltrates may affect the development or progression of atherosclerosis. So, EAT may also accelerate the pathological process of ISR by promoting neoatherosclerosis via inflammation pathway.

Researches using drug treatments aimed at reducing EAT volume or improve inflammatory states of EAT have shown considerable results. A serial CCTA study recently have shown that intensive statin therapy can reduce the EAT volume of Europeans.[32] Simvastatin and pioglitazone combined treatment can reduce the inflammatory markers of epicardial adipose tissue of coronary patients with metabolic syndrome.[33] Low dose aspirin is reported to be associated with plasma chemerin levels and may reduce adipose tissue inflammation.[34] So treatments aimed at reducing the volume or improve the inflammation state of EAT may also reduce the incidence of ISR. Previous researches reported have shown that EAT was significant associated with BMI.[30] In our study, a strong relationship between epicardial tissue and BMI was also seen either in ISR patients or non-ISR patients. Hence, losing weight may also lower EAT volume, change the pathological state and reduce the pro-inflammation mediators secreted by EAT, which may finally result in lower incidence of ISR and cardiovascular risk.

In conclusions, this study demonstrated that EAT is an independent predictor for ISR in approximately 1-year follow-up using CCTA as a non-invasive imaging method. Increased EAT deposition may be an early warning of ISR. Thus we should pay more attentions to increased EAT deposition for patients with DESs after PCI. Treatments aimed at reducing EAT volume or improve inflammatory states of EAT may reduce the incidence of ISR.

There were some limitations of this study. First, the sample size was not large enough and this study was a single-center investigation. The predictive role of conventional risk factors in ISR, such as ages, diabetic mellitus, hypertension, smoking, stent diameter, stent length and treatment therapy, were unseen that might be attributed to the small sample size. So, larger sample size studies should be further investigated to verify the correlation between epicardial adipose tissue and ISR. Second, we were unable to identify the precise mechanism by which EAT accumulation could

contribute to ISR. However, our results showed that serum lipid and glucose were not elevated in both groups, this might suggested that serum lipid and glucose were good controlled and the progression of ISR might be attributed to systemic inflammation, oxidative stress, endothelial injury, smooth muscle cell proliferation and migration and microphage infiltration may also play a role in the process of ISR. Third, CCTA has the potential risk of radiation exposure, which represents an important consideration. It is unclear whether the benefits of epicardial adipose tissue can overcome the risk of radiation exposure. But, in our study, several techniques such as tube voltage and tube current regulation, prospectively ECG-triggered high-pitch spiral acquisition and heart rate lowing method, were used to better lowering the radiation dose.

Acknowledgments

This study was supported by grant B13061 from the Scientific Innovation Research Fund of Chinese PLA General Hospital. The authors declared no conflict of interest.

References

1 Holmes DR, Jr. Leon MB, Moses JW, *et al*. Analysis of 1-year clinical outcomes in the SIRIUS trial: a randomized trial of a sirolimus-eluting stent versus a standard stent in patients at high risk for coronary restenosis. *Circulation* 2004; 109: 634–640.

2 Dangas GD, Claessen BE, Caixeta A, *et al*. In-stent restenosis in the drug-eluting stent era. *J Am Coll Cardiol* 2010; 56: 1897–1907.

3 Lemos PA, Serruys PW, van Domburg RT, *et al*. Unrestricted utilization of sirolimus-eluting stents compared with conventional bare stent implantation in the "real world": the Rapamycin-Eluting Stent Evaluated At Rotterdam Cardiology Hospital (RESEARCH) registry. *Circulation* 2004; 109: 190–195.

4 Sacks HS, Fain JN. Human epicardial adipose tissue: a review. *Am Heart J* 2007; 153: 907–917.

5 Iacobellis G, Bianco AC. Epicardial adipose tissue: emerging physiological, pathophysiological and clinical features. *Trends Endocrinol Metab* 2011; 22: 450–457.

6 Iacobellis G, Corradi D, Sharma AM. Epicardial adipose tissue: anatomic, biomolecular and clinical relationships with the heart. *Nat Clin Pract Cardiovasc Med* 2005; 2: 536–543.

7 Barandier C, Montani JP, Yang Z. Mature adipocytes and perivascular adipose tissue stimulate vascular smooth muscle cell proliferation: effects of aging and obesity. *Am J Physiol Heart Circ Physiol* 2005; 289: H1807–H1813.

8 Iozzo P. Myocardial, perivascular, and epicardial fat. *Diabetes care* 2011; 34 Suppl 2: S371–S379.

9 Lafont A, Durand E, Samuel JL, *et al*. Endothelial dysfunction and collagen accumulation: two independent factors for restenosis and constrictive remodeling after experimental angioplasty. *Circulation* 1999; 100: 1109–1115.

10 Kubo M, Miyoshi T, Oe H, *et al*. Prognostic significance of endothelial dysfunction in patients undergoing percutaneous coronary intervention in the era of drug-eluting stents. *BMC Cardiovasc Disord* 2015; 15: 102.

11 Munk PS, Staal EM, Butt N, *et al*. High-intensity interval training may reduce in-stent restenosis following percutaneous coronary intervention with stent implantation: A randomized controlled trial evaluating the relationship to endothelial function and inflammation. *Am Heart J* 2009; 158: 734–741.

12 Casscells W. Migration of smooth muscle and endothelial cells. Critical events in restenosis. *Circulation* 1992; 86: 723–729.

13 Mahabadi AA, Berg MH, Lehmann N, *et al*. Association of epicardial fat with cardiovascular risk factors and incident myocardial infarction in the general population: the Heinz Nixdorf Recall Study. *J Am Coll Cardiol* 2013; 61: 1388–1395.

14 Wu FZ, Huang YL, Wang YC, *et al*. Impact of location of epicardial adipose tissue, measured by coronary artery calcium-scoring computed tomography on obstructive coronary artery disease. *Am J Cardiol* 2013; 112: 943–949.

15 Groves EM, Erande AS, Le C, *et al*. Comparison of epicardial adipose tissue volume and coronary artery disease severity in asymptomatic adults with versus without diabetes mellitus. *Am J Cardiol* 2014; 114: 686–691.

16 Chung JH, Kwon BJ, Song SW, *et al*. Epicardial adipose tissue: relationship between measurement location and metabolic syndrome. *Int J Cardiovasc Imaging* 2014; 30: 195–204.

17 Austen WG, Edwards JE, Frye RL, *et al*. A reporting system on patients evaluated for coronary artery disease. Report of the *Ad Hoc* Committee for Grading of Coronary Artery Disease, Council on Cardiovascular Surgery, American Heart Association. *Circulation* 1975; 51: 5–40.

18 Bettencourt N, Toschke AM, Leite D, *et al*. Epicardial adipose tissue is an independent predictor of coronary atherosclerotic burden. *Int J Cardiol* 2012; 158: 26–32.

19 Yoshizumi T, Nakamura T, Yamane M, *et al*. Abdominal fat: standardized technique for measurement at CT. *Radiology* 1999; 211: 283–286.

20 Mehran R, Dangas G, Abizaid AS, *et al*. Angiographic patterns of in-stent restenosis: classification and implications for long-term outcome. *Circulation* 1999; 100: 1872–1878.

21 Park JS, Choi BJ, Choi SY, *et al*. Echocardiographically measured epicardial fat predicts restenosis after coronary stenting. *Scand Cardivasc J* 2013; 47: 297–302.

22 Talman AH, Psaltis PJ, Cameron JD, *et al*. Epicardial adipose tissue: far more than a fat depot. *Cardiovasc Diagn Ther* 2014; 4: 416–429.

23 Wang P, Xu TY, Guan YF, *et al*. Perivascular adipose tissue-

derived visfatin is a vascular smooth muscle cell growth factor: role of nicotinamide mononucleotide. *Cardiovasc Res* 2009; 81: 370–380.

24 Tian Z, Miyata K, Tazume H, *et al*. Perivascular adipose tissue-secreted angiopoietin-like protein 2 (Angptl 2) accelerates neointimal hyperplasia after endovascular injury. *J Mol Cell Cardiol* 2013; 57: 1–12.

25 Calabro P, Samudio I, Willerson JT, *et al*. Resistin promotes smooth muscle cell proliferation through activation of extracellular signal-regulated kinase 1/2 and phosphatidylinositol 3-kinase pathways. *Circulation* 2004; 110: 3335–3340.

26 Hirai H, Satoh H, Kudoh A, *et al*. Interaction between resistin and adiponectin in the proliferation of rat vascular smooth muscle cells. *Mol Cell Endocrinol* 2013; 366: 108–116.

27 Zhang W, Shu C, Li Q, *et al*. Adiponectin affects vascular smooth muscle cell proliferation and apoptosis through modulation of the mitofusin-2-mediated Ras-Raf-Erk1/2 signaling pathway. *Mol Med Rep*2015; 12: 4703–4707.

28 Takano M, Yamamoto M, Inami S, *et al*. Appearance of lipid-laden intima and neovascularization after implantation of bare-metal stents extended late-phase observation by intracoronary optical coherence tomography. *J Am Coll Cardiol* 2009; 55: 26–32.

29 Mazurek T, Zhang L, Zalewski A, *et al*. Human epicardial adipose tissue is a source of inflammatory mediators. *Circulation* 2003; 108: 2460–2466.

30 Harada K, Amano T, Kataoka T, *et al*. Impact of abdominal and epicardial fat on the association between plasma adipocytokine levels and coronary atherosclerosis in non-obese patients. *Atherosclerosis* 2014; 237: 671–676.

31 Cherian S, Lopaschuk GD, Carvalho E. Cellular cross-talk between epicardial adipose tissue and myocardium in relation to the pathogenesis of cardiovascular disease. *Am J Physiol Endocrinol Metab* 2012; 303: E937–E949.

32 Alexopoulos N, Melek BH, Arepalli CD, *et al*. Effect of intensive versus moderate lipid-lowering therapy on epicardial adipose tissue in hyperlipidemic post-menopausal women: a substudy of the BELLES trial (Beyond Endorsed Lipid Lowering with EBT Scanning). *J Am Coll Cardiol* 2013; 61: 1956–1961.

33 Grosso AF, de Oliveira SF, Higuchi Mde L, *et al*. Synergistic anti-inflammatory effect: simvastatin and pioglitazone reduce inflammatory markers of plasma and epicardial adipose tissue of coronary patients with metabolic syndrome. *Diabetol Metab Syndr* 2014; 6: 47.

34 Herova M, Schmid M, Gemperle C, *et al*. Low dose aspirin is associated with plasma chemerin levels and may reduce adipose tissue inflammation. *Atherosclerosis* 2014; 235: 256–262.