

## Editorial Comment

## Epicardial Adipose Tissue and No-Reflow Phenomenon: Adipokines as Regulators of Coronary Microcirculation?

ALEXIOS S. ANTONOPOULOS<sup>1,2</sup>, CHARALAMBOS ANTONIADES<sup>2</sup>, DIMITRIS TOUSOULIS<sup>1</sup>

<sup>1</sup>First Cardiology Department, Hippokraton Hospital, Athens Medical School, Greece; <sup>2</sup>RDM Division of Cardiovascular Medicine, University of Oxford, Oxford, UK

Key words: **Adipose tissue, myocardium, ischaemic heart disease.**

Address:  
Alexios S.  
Antonopoulos

First Department of  
Cardiology  
Hippokraton Hospital,  
Athens Medical School,  
114 Vas. Sofias Ave.  
115 27 Athens, Greece  
[alexios.antonopoulos@  
cardiov.ox.ac.uk](mailto:alexios.antonopoulos@cardiov.ox.ac.uk)

**T**he no-reflow phenomenon is defined as a lack of coronary blood flow after removal of a coronary obstruction.<sup>1</sup> No-reflow is considered to be dependent on the structural damage to the microvasculature during the ischaemic period, but the exact mechanisms remain unclear.<sup>2</sup> No-reflow is associated with a higher risk of malignant arrhythmias, early congestive heart failure, and mechanical complications (such as cardiac rupture) post-acute myocardial infarction.<sup>2,3</sup> Importantly, no-reflow is also associated with a doubling in 5-year mortality risk after primary percutaneous coronary intervention (PCI), independently of classic risk factors or infarct size,<sup>3</sup> and therefore poses a major challenge for the management of AMI patients in the era of PCI.

In this issue of the *Hellenic Journal of Cardiology*, Zencirci et al<sup>1</sup> provide data on the association between no-reflow and epicardial adipose tissue (EAT) thickness in a cohort of 114 STEMI patients undergoing primary PCI. It is shown that patients with no-reflow had significantly greater EAT thickness (measured by echocardiography) compared to subjects with normal reflow ( $6.1 \pm 2.1$  vs.  $3.9 \pm 1.7$ mm, respectively,  $p < 0.001$ ). On prospective follow up, no-reflow (but not EAT thickness) was an independent pre-

dictor for heart failure admission. The association between no-reflow and heart failure is well-established; the inability to restore coronary blood flow and salvage myocardial tissue at risk increases infarct size and negatively affects cardiac remodelling.<sup>1-3</sup> Nevertheless, the presented relationship between EAT thickness and the no-reflow phenomenon is novel and merits further investigation.

The pathophysiology of no-reflow is considered to be primarily associated with ischaemic damage to the microvasculature, but multiple factors may contribute to it; cellular oedema in the capillaries, cell contracture in the ischaemic zone, endothelial dysfunction, oxygen free-radical production during reperfusion, intravascular plugging by fibrin, platelets or leukocytes, may all contribute to the occurrence of the no-reflow phenomenon.<sup>2</sup>

Adipose tissue is known to affect cardiovascular physiology via the release of active adipokines in a paracrine (via local release and diffusion) or endocrine (via the systemic circulation) manner.<sup>4-6</sup> EAT is of special interest to coronary and myocardial physiology, given its close spatial affinity with the heart. Secretory products from EAT can induce cardiomyocyte dysfunction and myocardial fibrosis,<sup>7</sup> while pericoronary EAT-released leptin pro-

motes coronary endothelial dysfunction.<sup>8</sup> In clinical studies, increased EAT volume has been associated with coronary atherosclerosis progression<sup>9</sup> and plaque vulnerability,<sup>10</sup> and is an independent predictor of future cardiovascular events in subjects undergoing computed tomography.<sup>10,11</sup> The use of epicardial adipose tissue measurements as a biomarker in ischaemic heart disease is summarised in Table 1.

To date, only limited data exist on the association between EAT and the no-reflow phenomenon. In a previous small cohort of 66 subjects undergoing coronary angiography, an association between EAT thickness (assessed by echocardiography) and slow coronary blood flow was demonstrated.<sup>12</sup>

Currently, it is unclear how EAT could be involved in the no-reflow phenomenon, but recent findings from translational studies may hold the key to its understanding. We have recently shown that there

is a crosstalk between perivascular adipose tissue (PVAT) and human vascular wall; PVAT receives signals from the vascular wall and under conditions of increased vascular oxidative stress, adiponectin released by human PVAT suppresses vascular O<sub>2</sub> generation by NADPH oxidase,<sup>5</sup> enhances endothelial nitric oxide (NO) activity and coupling,<sup>6</sup> and therefore vascular NO bioavailability. In a similar way, imbalances in adipokines released by EAT could alter NO bioavailability and the redox state of coronary microcirculation and human myocardium, which is involved in the pathophysiology of no-reflow.<sup>2</sup> Adipose tissue secretory products that regulate endothelial function and vasorelaxation (such as leptin or hydrogen sulphide) may also be important for the function of the coronary microcirculation.<sup>4-8</sup> Angiotensin-like protein 4 (ANGPTL4), which controls vascular wall integrity and protects against myocardial injury and

**Table 1.** Clinical studies of the use of epicardial adipose tissue measurements as a biomarker in ischaemic heart disease.

Study	Population	Major findings
EAT thickness by echocardiography:		
Wang T et al <sup>15</sup>	373 AMI patients	EAT thickness predicted major in-hospital events
Ozcan et al <sup>16</sup>	144 UA/NSTEMI patients	EAT thickness was associated with higher TIMI score
Altun et al <sup>17</sup>	65 ACS patients	EAT thickness was positively correlated with the severity of CAD but not with prognosis of ACS patients
EAT volume by computerised tomography:		
Mahabadi et al <sup>11</sup>	4093 disease free individuals	EAT was associated with increased risk for future CVD events
Hajsadeghi et al <sup>18</sup>	245 subjects undergoing CTA	EAT volume was associated with increased risk for CVD events
Yerramasu et al <sup>9</sup>	333 asymptomatic diabetics with no known CAD	EAT volume was positively associated with CAD and CAC progression
Ulucan et al <sup>19</sup>	564 consecutive patients undergoing CT	EAT volume was associated with increased odds ratio for CV events
Forouzandeh et al <sup>20</sup>	760 with acute chest pain	EAT volume was independently associated with future MACE
Nakanishi et al <sup>10</sup>	517 CAD patients	EAT volume predicted atherosclerosis progression
Kunita et al <sup>21</sup>	722 CAD patients	EAT volume was associated with increased risk for CVD events
Harada et al <sup>22</sup>	170 ACS patients	For EAT volume >100 mL, increased odds ratio for cardiovascular events
Ito et al <sup>23</sup>	117 ACS patients	EAT volume (highest tertile) was an independent predictor for ACS subjects
Cordeiro et al <sup>24</sup>	277 CKD patients	EAT volume was associated with increased risk for CV events

ACS – acute coronary syndrome; AMI – acute myocardial infarction; CAD – coronary artery disease; CKD – chronic kidney disease; CVD – cardiovascular disease; EAT – epicardial adipose tissue; MACE – major adverse coronary events; NSTEMI – non-ST elevation myocardial infarction; UA – unstable angina.

no-reflow in experimental animal models,<sup>13</sup> is also expressed by human adipose tissue and could have a role in no-reflow. The biology of EAT and the biosynthesis of its secretory products – e.g. adiponectin, leptin, hydrogen sulphide and/or ANGPTL4 – could change with hypertrophy of EAT and this may account for the relationship between EAT thickness and the no-reflow phenomenon in the cohort of STEMI patients reported by Zencirci et al.<sup>1</sup>

So far, little is known regarding the relationship between EAT and the pathophysiology of ischaemic heart disease, but clinical evidence has highlighted that cardiac adiposity and expansion of EAT is an independent risk factor for cardiovascular disease,<sup>9,11</sup> probably because of parallel changes in EAT biology that affect both the coronary circulation and the heart.<sup>7,8</sup> Even though in the cohort of Zencirci et al<sup>1</sup> EAT thickness did not predict future HF admission in STEMI patients, the study was limited by the small sample size and the assessment of EAT thickness by echocardiography, which is less reliable compared to volumetric measurements of EAT by computed tomography.<sup>9,11</sup> The predictive role of EAT quantitation in patients with ischemic heart disease may also be lost in the presence of heart failure and related alterations in EAT mass.<sup>14</sup> Despite these limitations, the findings of Zencirci et al<sup>1</sup> are important, since they link EAT with no-reflow and imply that EAT may have important effects on the coronary microcirculation and myocardial defence mechanisms. Future studies are required to clarify the role of EAT in the pathogenesis of ischaemic heart disease and the no-reflow phenomenon in humans.

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