



Review

# The Role of Epicardial Adipose Tissue in Acute Coronary Syndromes, Post-Infarct Remodeling and Cardiac Regeneration

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**Abstract:** Epicardial adipose tissue (EAT) is a fat deposit surrounding the heart and located under the visceral layer of the pericardium. Due to its unique features, the contribution of EAT to the pathogenesis of cardiovascular and metabolic disorders is extensively studied. Especially, EAT can be associated with the onset and development of coronary artery disease, myocardial infarction and post-infarct heart failure which all are significant problems for public health. In this article, we focus on the mechanisms of how EAT impacts acute coronary syndromes. Particular emphasis was placed on the role of inflammation and adipokines secreted by EAT. Moreover, we present how EAT affects the remodeling of the heart following myocardial infarction. We further review the role of EAT as a source of stem cells for cardiac regeneration. In addition, we describe the imaging assessment of EAT, its prognostic value, and its correlation with the clinical characteristics of patients.

**Keywords:** epicardial adipose tissue; acute coronary syndromes; coronary artery disease; myocardial infarction; left ventricular remodeling; post-infarction heart failure; stem cells



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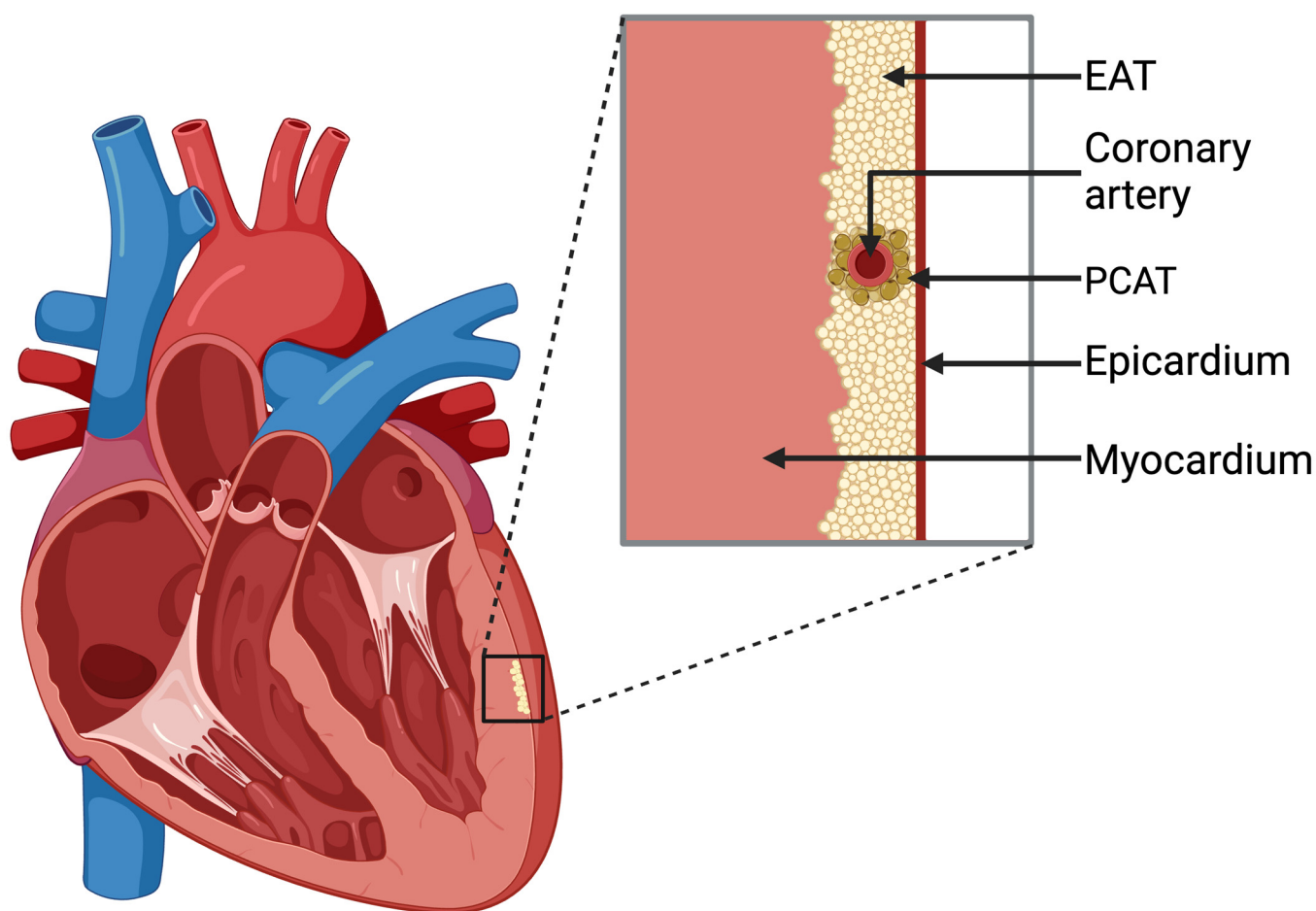
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## 1. Introduction

Epicardial adipose tissue (EAT) is the fat deposit situated between the myocardium and the visceral layer of the pericardium. Histologically, it is considered white but may exhibit beige or brown features. EAT is composed of adipocytes, ganglia, interconnecting neurons, stromovascular, and immune cells [1–4]. It also contains progenitor cells that could be transformed into myofibroblasts [5]. EAT is anatomically and functionally contiguous with the myocardium and coronary vessels [4,6], covers 80% of the heart's surface, and contributes to 20% of the heart's weight [7].

As a part of EAT, pericoronary adipose tissue (PCAT) is a fat deposit that surrounds coronary vessels and is adjacent to the adventitia of coronary arteries (Figure 1) [8,9]. That differentiation is important because EAT and PCAT could contribute to cardiovascular risk in distinct ways, giving different pathogenic effects [8,10]. It is also vital to distinguish EAT from pericardial adipose tissue (PAT) as they have different anatomical locations and functional properties [11].

Physiologically EAT displays metabolic and thermogenic properties. It also provides mechanical protection of the heart and coronary arteries [4]. Additionally, EAT appeared to be an endocrine organ, and as a rich source of adiponectin, adrenomedullin, resistin, and many other cytokines [6,12] may have pro- or anti-inflammatory effects on the heart [12,13]. Communication between EAT and myocardium can be achieved via paracrine and vasocrine signaling [4,14].



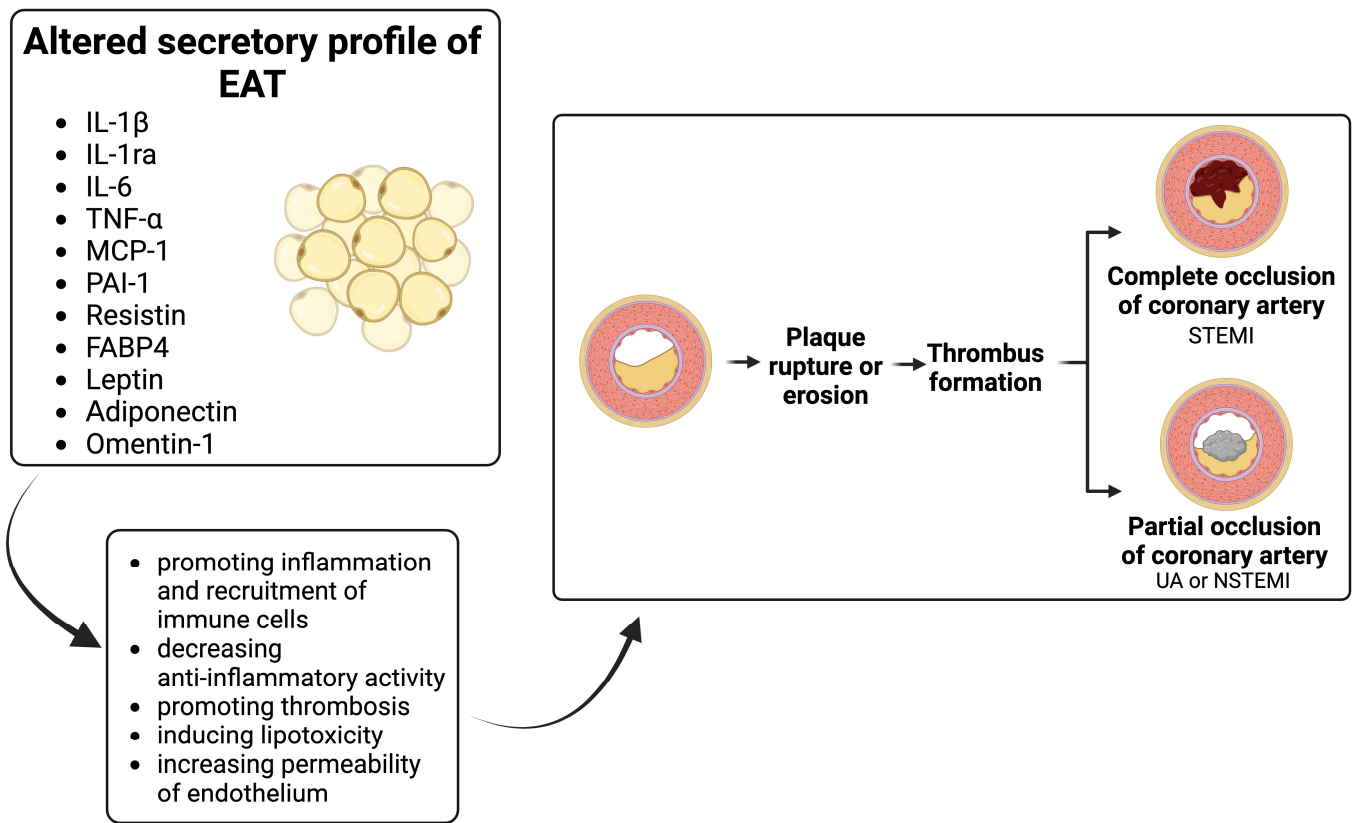
**Figure 1.** Schematic of the epicardial adipose tissue (EAT) and pericoronary adipose tissue (PCAT) locations within the heart wall. Created with BioRender.com (accessed on 13 February 2024).

Due to its unique structure and features, the role of EAT has drawn researchers' attention in terms of metabolic and cardiovascular (CV) disorders [15], including coronary artery disease (CAD) [16,17], heart failure (HF) [18], or atrial fibrillation (AF) [19]. Most research concerns the relationship between adipose tissue and atherosclerosis. Studies show that the paracrine activity of EAT may vary and, in certain circumstances, may contribute to the development of atherosclerotic plaque formation and its rupture [4,14,20]. Since it would be difficult to assess the metabolic activity of EAT, a good solution seems to be the assessment of its amount. It is not fully explored, however, whether the volume of EAT assessed by imaging studies may be positively associated with CV disorders [4,21–23].

As most studies focus on chronic coronary syndromes, this article aims to review associations between EAT and acute coronary syndromes (ACS) and to discuss possible mechanisms through which EAT contributes to cardiac remodeling following myocardial infarction (MI). The potential role of EAT as a source of stem cells, as well as imaging assessment, was also described.

## 2. The Contribution of Epicardial Adipose Tissue to Pathogenesis of Acute Coronary Syndromes

Various biological processes occurring in EAT may impact the myocardium, as they share a common microvasculature and are located in close proximity. EAT plays a role in the development of CAD which is the main underlying cause of ACS [14]. Several studies analyzed whether and how EAT contributes to the pathogenesis of ACS, therefore this topic requires to be summarized (Figure 2) (Table 1). Special attention was given to the role of inflammation and adipokines secreted by EAT.



**Figure 2.** Altered secretory profile of epicardial adipose tissue and its impact on the pathogenesis of acute coronary syndrome with proposed mechanisms. Abbreviations: FABP4, fatty acid binding protein 4; IL-1ra, interleukin-1 receptor antagonist; IL-1 $\beta$ , interleukin-1 $\beta$ ; IL-6, interleukin-6, MCP-1, monocyte chemoattractant protein-1; NSTEMI, non-ST-elevation myocardial infarction; PAI-1, plasminogen activator inhibitor-1; STEMI, ST-elevation myocardial infarction; TNF- $\alpha$ , tumor necrosis factor alpha; UA, unstable angina. Created with BioRender.com (accessed on 13 February 2024).

The most common mechanism leading to MI is the rupture of a vulnerable plaque and thrombotic occlusion of the coronary artery [24]. Cellular crosstalk between EAT and fibroatheromas may contribute to the development of their high-risk characteristics [25]. Thinning of the fibrous cap and necrotic core development may result from the apoptosis of smooth muscle cells and macrophages in the fibroatheromas. Interestingly, proteins related to apoptosis—tumor necrosis factor alpha (TNF- $\alpha$ ), interleukin-1 (IL-1) and monocyte chemoattractant protein-1 (MCP-1)—were found to be highly expressed in the EAT [26]. Increased volume of EAT is associated with high-risk plaques [27–31], which is discussed more extensively in the next chapters.

**Table 1.** Summary of the most important studies concerning the role of EAT in the pathogenesis of ACS and cardiac remodeling after MI.

First Author	Year	Study Population/Experimental Model	Main Findings	Reference
Moreno-Santos, I.	2019	Patients with ACS ( $n = 29$ ), stable CAD ( $n = 16$ ) or without CAD ( $n = 29$ )	<ul style="list-style-type: none"> <li>• Reduced expression of NPR-C, UCP1 and PGC1<math>\alpha</math> in EAT of ACS patients.</li> <li>• Decreased activation of p38 MAPK pathway in EAT samples from ACS patients.</li> </ul>	[32]

Table 1. Cont.

First Author	Year	Study Population/Experimental Model	Main Findings	Reference
Hao, S.	2023	Male Sprague Dawley rats: MI induction ( $n = 6$ ) or sham surgery ( $n = 6$ ); H9C2 cardiomyocytes	<ul style="list-style-type: none"> <li>After MI, EAT mediates cardiomyocytes' apoptosis by secretion of CFD, which causes PARP-1 activation.</li> </ul>	[33]
Pedicino, D.	2017	Patients with ACS ( $n = 18$ ), SA ( $n = 16$ ) or without CAD ( $n = 13$ )	<ul style="list-style-type: none"> <li>Enhanced NLRP3 and pro-IL1<math>\beta</math> expression in EAT from ACS patients.</li> <li>Many bacterial species were found in EAT samples from ACS and SA patients.</li> </ul>	[34]
Parisi, V.	2020	Patients with CCS ( $n = 54$ ) or recent ACS ( $n = 33$ )	<ul style="list-style-type: none"> <li>Reduced IL-1ra levels in EAT from ACS patients.</li> </ul>	[35]
Pedicino, D.	2022	Patients with ACS ( $n = 32$ ), CCS ( $n = 34$ ) or MVD ( $n = 12$ )	<ul style="list-style-type: none"> <li>Higher content of CD31, CHI3L1, CRP, ENG, IL-17, IL-33, MMP-9, MPO, NGAL, RBP-4, RETN, in EAT of ACS patients found in proteome profiling.</li> <li>Perturbation of the TRBV21 in EAT were associated with the first NSTEMI.</li> </ul>	[36]
Langheim, S.	2010	Patients with ACS ( $n = 32$ ), stable CAD ( $n = 34$ ) or without CAD ( $n = 23$ ); HUVEC	<ul style="list-style-type: none"> <li>Increased resistin expression in EAT of ACS patients.</li> <li>Supernatant of cultured EAT obtained from ACS patients increased permeability of endothelial cells in vitro.</li> <li>Greater number of CD68+ cells in was found EAT of ACS patients than stable CAD patients and controls.</li> </ul>	[37]
Rachwalik, M.	2014	Patients undergoing CABG with history of MI ( $n = 17$ ) or without previous MI ( $n = 16$ )	<ul style="list-style-type: none"> <li>Previous MI was associated with higher resistin content in EAT.</li> <li>EAT-CM through miR-134-5p/KAT7/MnSOD/catalase axis and increase in ROS intracellular levels promoted activation of cardiac fibroblasts into myofibroblasts.</li> </ul>	[38]
Hao, S.	2021	Male Sprague Dawley rats: MI induction ( $n = 20$ ) or sham surgery ( $n = 10$ ); H9C2 cardiomyocytes	<ul style="list-style-type: none"> <li>Knockdown of miR-134-5p limited myocardial fibrosis in vivo.</li> </ul>	[39]
Chang, H-X	2017	Sprague Dawley rats ( $n = 82$ ) which underwent MI (with or without EAT removal) or sham surgery	<ul style="list-style-type: none"> <li>Increased lipolysis of EAT after MI.</li> <li>EAT removal reduced infarct area, enhanced cardiac function, and decreased inflammation after MI.</li> </ul>	[40]

Abbreviations: ACS, acute coronary syndrome; CAD, coronary artery disease; CFD, complement factor D; CHI3L1, chitinase 3-like 1; CRP, C-reactive protein; EAT, epicardial adipose tissue; EAT-CM, conditioned media from epicardial adipose tissue; ENG, endoglin; IL-17, interleukin-17; IL-1ra, interleukin-1 receptor antagonist; IL-33, interleukin-33; KAT7, lysine acetyltransferase 7; MAPK, mitogen-activated protein kinase; MI, myocardial infarction; MMP-9, matrix metalloproteinase 9; MNSOD, manganese superoxide dismutase; MPO, myeloperoxidase; NGAL, neutrophil gelatinase-associated lipocalin (lipocalin 2); NLRP3, NLR family pyrin domain containing 3; NPR-C, natriuretic peptide receptor-C; NSTEMI, non-ST-elevation myocardial infarction; PARP-1, poly(ADP-ribose) polymerase 1; PGC1 $\alpha$ , peroxisome proliferator-activated receptor gamma coactivator alpha; pro-IL1 $\beta$ , pro-interleukin-1beta; RBP-4, retinol binding protein 4; RETN, resistin; ROS, reactive oxygen species; SA, stable angina; TRBV21, T cell receptor beta variable 21-1; UCP1, uncoupling protein 1.

EAT represents features of brown adipose tissue (BAT), whose activation is linked with cardioprotective effects [41,42]. Natriuretic peptides (NPs), apart from their role in maintaining cardiovascular homeostasis, may also affect adipose tissue. NP receptors (NPR) are expressed in this tissue, especially NPR-A and NPR-C [43]. NPs may induce lipolysis and promote lipid mobilization. These effects are associated with the activation of NPR-A and, consequently, increased intracellular levels of cyclic guanosine monophosphate [44,45]. Interestingly, NPs can also promote browning of white adipose tissue and enhance the expression of brown fat markers including proteins associated with thermogenesis [46]. The thermogenic role of EAT may diminish with age, obesity, or the presence of CAD [33]. Through the loss of this role, the risk of acute coronary syndromes (ACS) may increase. Patients with ACS had lower expression of NPR-C in EAT in comparison to individuals with stable CAD or without CAD. This was associated with decreased phosphorylation of p38 mitogen-activated protein kinase (MAPK), reduced expression of uncoupling protein 1 (UCP1) and peroxisome proliferator-activated receptor gamma coactivator alpha (PGC1 $\alpha$ ). This might suggest that the p38 MAPK signaling pathway is diminished, which results in lower expression of brown-like fat genes [32]. On the other hand, the p38 MAPK signaling pathway is strongly activated by cytokines and environmental stress, therefore its activation may contribute to inflammation or apoptosis [47]. However, the brown-like fat phenotype of EAT might be related to atherosclerotic plaque stability. Moreover, medications targeting NPR-C might potentially enhance ACS therapy [32]. PGC1 $\alpha$  overexpression in adipocytes alleviated metabolic dysfunction in mice fed a high-fat diet, which depended on heme oxygenase 1 (HO-1). This was associated with browning of adipose tissue and reduced inflammation [48]. In obese mice, PGC1 $\alpha$  and HO-1 levels were decreased in epicardial fat in comparison to visceral fat. Moreover, pharmacologically enhancing the activity of HO-1-PGC1 $\alpha$  was related to improved LV function in mice [49].

The role of EAT appears to be ambiguous, as it can exhibit both protective and destructive properties towards the heart. The analysis of gene expression in EAT of AF patients showed a high abundance of complement factor D (CFD) transcript [50]. In a study on rats with induced MI, CFD expression was found to be higher in EAT than in subcutaneous adipose tissue (SAT). Additionally, the EAT mass in the MI group was increased compared to that in the sham-operated group. Cardiomyocytes treated *in vitro* with EAT-conditioned medium (EAT-CM) presented higher rates of apoptosis. Further analysis revealed that EAT secretes CFD, which causes poly(ADP-ribose) polymerase 1 overactivation. This induces apoptosis independently of caspase activity. Moreover, *in vivo* inhibition of CFD activity was associated with a reduced rate of cardiomyocyte apoptosis and decreased myocardial injury, which confirms its aggravating role in MI-related damage [33].

### 2.1. The Role of Inflammation

Inflammation is directly related to the pathogenesis of atherosclerosis and, consequently, obstructive CAD. Numerous cell types, signaling pathways, and molecules play a role in this process. They could constitute potential treatment targets [51]. Interestingly, the inflammatory process contributing to the progression of this disease extends beyond the atherosclerotic plaques and vessels [52]. Adipose tissue, as a potent participant in local and systemic signaling, can also be engaged in inflammation [53]. Additionally, MI being a severe consequence of CAD is inevitably associated with inflammation [54]. Several studies have described the role of adipose tissue inflammation in ACS, with particular emphasis on EAT.

Inflammation of visceral adipose tissue can be assessed using a microscope. Scavenger macrophages surround dying adipocytes and form crown-like structures (CLS), which are histologic hallmarks of inflammatory processes in adipose tissue [55]. Malavazos et al. analyzed the CLS density in EAT samples obtained from patients undergoing CABG or valvular replacement. Unfortunately, due to the small number of included patients it is hard to consider the result as significant. However, it is worth mentioning that one patient with a rapid weight increase and a recent episode of MI had about 100 times higher CLS density



than the remaining CABG patients [56]. Unfortunately, the data concerning CLS formation in EAT are currently limited. Inflammatory cell infiltration in EAT from individuals with CAD is higher than in SAT [57]. The accumulation of mast cells, which secrete multiple vasoactive molecules, may contribute to the rupture of vulnerable plaque. [58]. Moreover, mast cells can activate T lymphocytes. CAD is associated with increased infiltration rates of EAT by T lymphocytes (CD3+) and B lymphocytes (CD20+) [57,59]. However, little is known about the impact of lymphocytes located in EAT on ACS development.

Pedicino et al. proved that EAT expression of NOD-like receptor protein 3 (NLRP3) and pro-interleukin-1 $\beta$  (pro-IL-1 $\beta$ ) is significantly enhanced in patients with non-ST-segment elevation acute coronary syndrome (NSTEMI-ACS) in comparison to individuals with stable angina (SA) or control group [34]. NLRP3 detects microbial patterns, danger signals, or cellular stress, which causes NLRP3 inflammasome assembly and activation. This leads to the release of pro-inflammatory cytokines IL-1 $\beta$  and IL-18 in a caspase-1-dependent manner [60]. These data indicate that ACS might be correlated with upregulation of the some inflammasome components in EAT. In another study, NLRP3 protein level in peripheral blood obtained from patients with ACS was higher than in the control group. It positively correlated with the number of atherosclerotic lesions and diseased coronary arteries [61]. Moreover, the expression of NLRP3 in SAT also positively correlated with the severity of coronary atherosclerosis suggesting that NLRP3 inflammasomes in SAT could be engaged in atherogenesis [62].

On the other hand, another study analyzing patients with ACS undergoing urgent CABG due to NSTEMI and patients with CAD referred to an elective CABG showed that both EAT and circulating IL-1 $\beta$  levels did not differ. However, ACS patients had significantly lower levels of both circulating and EAT IL-1 receptor antagonist (IL-1ra). These results could indicate reduced counterregulatory activity of IL-1ra against IL-1 $\beta$  and its pro-inflammatory role. Furthermore, EAT is actively engaged in the local inflammatory process. Interestingly, no correlation was found between IL-1 $\beta$  levels and markers of M1 macrophages in EAT [35]. In contrast, another study showed that the ratio of M1/M2 macrophages in EAT positively correlates with the levels of pro-inflammatory cytokines and the severity of CAD [63]. However, adipocytes could contribute to IL-1 $\beta$  levels as they can be a source of inflammatory cytokines [64]. Moreover, the inflammatory state of EAT is suggested to be connected to the pathogenesis of INOCA (ischemia with non-obstructive coronary artery) due to several possible mechanisms, such as endothelial function damage [65].

Therapies for atherosclerosis, CAD, and ACS could have an impact on EAT. Moreover, processes in EAT may potentially become therapeutic targets in the future. HMG-CoA reductase (HMGCR) inhibitors, known as statins, are traditionally used as cholesterol-lowering agents. However, their intake is associated with pleiotropic effects [66]. An in vivo study demonstrated that statin therapy was related to decreased EAT thickness and inflammatory profile in patients undergoing aortic valve replacement. Moreover, in vitro analysis showed that the reduction in pro-inflammatory cytokines concentrations was greater in EAT than in SAT, which indicates a possible selective impact of statin therapy on EAT [67]. Furthermore, anti-diabetic medications may affect EAT metabolism. Application of SGLT2 inhibitors in rats with induced AF led to reduced EAT inflammation. This was achieved by upregulation in ketone body levels, downregulated expression of acetyl-CoA carboxylase 1, and decreased GAPDH lysine residue malonylation in macrophages [68]. The use of glucagon-like peptide 1 receptor (GLP1R) agonist can decrease inflammation and adipogenesis, enhance free fatty acid oxygenation, and promote browning of adipocytes [14,69]. The use of SGLT2 inhibitors, GLP1R agonists, metformin and pioglitazone was related to decreased EAT quantity [14,70,71]. These mechanisms may partially explain the beneficial impact of anti-diabetic treatment on the cardiovascular system [14].

During analysis of microbiota composition in EAT, Pedicino and colleagues found DNA of 76 bacterial species. The main species in EAT obtained from ACS patients were Cyanobacteria Streptophyta and Proteobacteria Rickettsiales, whereas Moraxellaceae, Pseu-

domonas, and Bacteroides dominated in the SA group. It shows the potential role of bacteria in ACS pathogenesis. Unfortunately, it is not yet established if and how they participate in this process [34]. In another study, EAT proteome analysis revealed an elevated amount of pro-inflammatory proteins among NSTEMI patients in comparison to individuals with CAD. The former group had a specific T-cell clonal expansion. In the vast majority of these patients, it was the first CV event. In silico analysis led to a hypothesis that antigens derived from the microbiome are possible inducers of instability through antigen-driven immune response. Even though these results require further confirmation they could be an introduction to developing engineered epitope-based therapies [36].

## 2.2. Adipokines

Adipokines are described as bioactive peptides secreted by adipose tissue. These molecules impact adipose tissue by regulating adipogenesis and adipocyte metabolism and affecting migration of immune cells. However, adipokines may also affect targets at the systemic level. They play a part in inflammation and immune response, glucose metabolism, regulation of blood pressure, myocardial contractility, and other various processes [72]. Thus, adipokines are engaged in the pathogenesis of numerous diseases, and EAT, as both a source and potential recipient of these molecules, is also involved in these processes.

Resistin is an adipokine originally linked with insulin resistance, obesity, and diabetes. However, increasing evidence has revealed that its functions are well beyond that [73]. It has been shown that among patients with acute MI, elevated levels of resistin in the plasma serve as a predictor for all-cause mortality [74]. Another study demonstrated that the concentrations of resistin in EAT obtained from patients undergoing CABG are higher in individuals with prior MI [38]. Langheim et al. observed a higher EAT expression of resistin in ACS patients compared to stable CAD patients and controls. This was accompanied by an increased concentration of resistin in the ACS group. Moreover, in EAT obtained from ACS patients, there was the highest percentage of CD68+ cells (macrophages), which had a similar location as the distribution of resistin [37]. In humans, resistin is mainly secreted by mononuclear leukocytes including macrophages [73,75]. Both in ACS and stable CAD, there was enhanced expression of IL-6, plasminogen activator inhibitor-1 (PAI-1), and MCP-1, which indicates a proinflammatory cytokine profile. Examination with the use of an in vitro model of endothelial permeability showed that among adipokines secreted from EAT, the major player causing endothelial damage is resistin. This may lead to a hypothesis that EAT-derived resistin enters coronary arteries and contributes to the ACS initiation by maintaining aberrant permeability of the endothelium [37]. The exact mechanism is not fully understood. However, resistin may enhance the expression of endothelin-1 and adhesion molecules thus promoting endothelial dysfunction [76]. Moreover, factors secreted by adipocytes seem to enhance the secretion of pro-inflammatory cytokines by endothelial cells [77]. Therefore, activation of macrophages or suppression of resistin action might be potential therapeutic targets for ACS patients.

Fatty-acid-binding protein 4 (FABP4) is a lipid chaperone protein. Apart from its intracellular role, FABP4 is secreted from adipocytes in a controlled manner in response to fasting-related signals. It is also associated with atherosclerosis, diabetes, and other metabolic disorders [78,79]. Peeters et al. discovered that elevated FABP4 expression in carotid atherosclerotic plaques is related to instability of the plaque and correlates with adverse cardiovascular events [80]. Patients presented with acute MI had increased serum levels of fatty acid binding protein 4 (FABP4). Among them, the highest values of FABP4 levels had individuals with cardiac arrest due to ventricular fibrillation. The FABP4 expression was observed in adipose tissue, including EAT. Interestingly, the secretion of FABP4 from adipocytes is mediated through the activation of  $\beta$ 3-adrenergic receptors. This finding suggests that during MI, sympathetic signaling could induce lipolysis in EAT surrounding the heart, ultimately leading to the release of FABP4, which may be a potential marker of adrenergic overactivation in cardiovascular diseases [81]. FABP4 increases

endoplasmic reticulum (ER) stress, which contributes to the apoptosis of cardiomyocytes. Moreover, the application of FABP4 inhibitor alleviates these deleterious effects. Hence, it can be useful in MI treatment [82].

Omentin-1 is an adipokine that exerts many protective properties. It inhibits inflammation and contributes to vasodilatation by modulation of endothelial nitric oxide synthase phosphorylation and nitric oxide production [83,84]. Administration of omentin-1 in mice was associated with decreased infarct size following ischemia/reperfusion injury [85]. EAT levels of omentin-1 are significantly lower in patients with CAD. There was a negative association between the expression of omentin-1 in EAT and local coronary atherosclerosis [86]. Similarly, the expression of omentin-1 was reduced in EAT samples from patients with prior MI [87]. The plasma levels of omentin-1 increase following myocardial ischemia, whereas its expression in left ventricular tissue decreases.

No study analyzed directly the EAT expression of leptin and adiponectin in patients with ACS. However, based on the available data, it is likely that the secretion of these adipokines from the EAT may play a part in the ACS pathogenesis. Leptin is involved in the pathogenesis of cardiovascular metabolic diseases, including obesity, type 2 diabetes, atherosclerosis, and hypertension [88]. It can also affect plasma cholesterol metabolism [89]. EAT leptin expression was found to be increased in patients with CAD. This was accompanied by elevated serum leptin levels. Moreover, an increase in leptin mRNA expression in the EAT was a risk factor for local coronary artery stenosis [90]. Patients with ACS had higher serum leptin levels than individuals with stable angina [91]. Leptin derived from EAT induced myocardial injury in rats with metabolic syndrome independently from the circulating leptin effects. Furthermore, EAT-derived leptin causes induction of the mitochondrial pathway of apoptosis and promotes inflammation in H9C2 cardiomyocytes. These effects are mediated by protein kinase C/reduced nicotinamide adenine dinucleotide phosphate oxidase/reactive oxygen species pathway [92]. Levels of leptin seem to be inversely related to adiponectin, as they are regulated contrarily. The latter has beneficial effects on the cardiovascular system and exerts anti-inflammatory and anti-fibrotic properties [93]. Patients with coronary atherosclerosis had decreased adiponectin expression in epicardial adipose tissue which was associated with elevated expression of inflammatory cytokines [88,94]. Interestingly, elevated serum adiponectin levels in patients with ACS were related to higher rates of cardiovascular events and mortality in the future. An increase in circulating levels of adiponectin due to adiponectin resistance development is one of the suggested explanations. However, the exact mechanism is not established yet [95].

As presented above, there is evidence that adipokines secreted from EAT are involved in atherogenesis and CAD. However, the mechanisms through which they contribute to the pathogenesis of MI require further studies. Due to the presented findings, the secretory role of EAT should be given particular attention, as it may become a potential therapeutic target in the future.

### 3. Impact of Epicardial Adipose Tissue on Post-Infarct Cardiac Remodeling

Following MI, the cardiac muscle in survivors undergoes pathological changes due to adverse alterations in mechanical and neurohormonal conditions. This process is known as cardiac remodeling [96]. It leads to the development of HF which is related to a poor quality of life and significantly increased mortality [97]. Numerous factors can influence myocardial remodeling and EAT seems to play a role in this process. Various studies have analyzed the mechanisms through which EAT impacts cardiac remodeling.

A study using a rat model demonstrated a positive correlation between EAT mass and both the area of myocardial fibrosis and cardiomyocyte size after MI. Additionally, when rat cardiac fibroblasts were cultured in EAT-CM, it was observed that this environment promoted their activation into myofibroblasts, which produce collagen and therefore contribute to cardiac fibrosis. This effect was achieved by miR-134-5p/KAT7/MnSOD/catalase axis leading to an increase in ROS level. Knockdown of miR-134 in vivo relieved myocardial fibrosis and reduced cardiomyocyte size, thus reducing pathological myocardial



remodeling. Interestingly, the use of anti-activin-A antibodies prevented an increase in miR-134-5p levels, which may indicate that the presence of this cytokine in EAT-CM induced aberrant changes [39]. Other studies reported that plasma levels of miR-134-5p were significantly increased in patients with acute MI [98]. miR-134-5p can impact oxidative stress and apoptosis in cardiomyocytes via interaction with cAMP-responsive element binding protein 1 (Creb1) or X-linked inhibitor of apoptosis protein (XIAP) [99,100].

Venteclef et al. proved that EAT plays a role in mediating atrial myocardium fibrosis by secreting adipo-fibrokinases, with the main agent being activin A, a member of the TGF- $\beta$  superfamily. In contrast, the secretome obtained from SAT did not have profibrotic effects and the expression of activin A in SAT was significantly lower, which proves metabolic differences between EAT and SAT. Furthermore, EAT-CM and activin A itself enhanced expression of TGF- $\beta$ 1 and TGF- $\beta$ 2 in rat atria, potentially augmenting profibrotic effects. The levels of activin A in EAT secretome were higher in a subset of patients with left ventricular ejection fraction (LVEF) less than 45% [101]. Another study showed that HF patients had increased serum levels of activin A. These levels significantly correlated with NT-pro-BNP levels, decreased cardiac index, and increased LV end-diastolic pressure. This may indicate that activin A may play a role in the development of HF with reduced LVEF and myocardial remodeling after MI [102].

Type 2 diabetes mellitus (DM2) induces disturbances in the secretory profile of EAT. When cardiomyocytes were treated in vitro with EAT-CM obtained from patients with DM2, impaired contractile function was observed. The primary factors identified as responsible for this dysfunction were activin A and angiotensin-2 [103]. This is a valuable finding because DM2 is related to a 2-4-fold increase in the risk of HF [104]. Furthermore, DM was present in almost 33% of patients hospitalized due to heart failure [105].

Due to anatomical proximity, pathologies involving the myocardium can also affect EAT. Parisi et al. observed a remodeling of EAT at three months following STEMI. In some patients, the thickness of EAT increased, while in others it decreased. An increase in EAT amount was related to intensified myocardial remodeling and lower LVEF. Simultaneously, circulating levels of IL-13, an anti-inflammatory cytokine involved in cardiac regeneration, decreased three months after STEMI. This decrease was negatively associated with an increase in EAT thickness [106]. The downstream pathways of IL-13 involve ERK1/2 and Akt signaling, which possess pro-proliferative and anti-apoptotic capacities in cardiomyocytes [107,108]. Furthermore, increased circulating levels of IL-13 have been associated with the preservation of LVEF after STEMI [106]. The exact mechanisms of how myocardial ischemia contributes to EAT remodeling have not been established yet. We hypothesize that cardiokines, inflammatory cytokines, and extracellular vesicles (EVs) may play a role in this process. Interestingly, EVs secreted under myocardial ischemia/reperfusion may induce endoplasmic reticulum stress in adipocytes [109].

A quantitative proteomic analysis showed significant changes in the expression of 165 proteins in the EAT of patients with ischemic cardiomyopathy (ICM). The altered proteins were mainly related to cardiac structure or metabolism and immune response. Expression of extracellular matrix (ECM) proteins was significantly enhanced, which was accompanied by increased collagen volume. Activation of ERK1/2 seemed to have been involved in the regulation of ECM remodeling in the EAT of ICM patients, which is in contrast to the beneficial roles of this pathway mentioned above [110].

During the embryonic development of the heart, epicardial progenitors that express WT1 factor undergo epithelial-to-mesenchymal transition (EMT) and become epicardium-derived cells. They are relocated to the heart and form different types of cells [111]. Interestingly, MI leads to activation of the fetal program of the epicardium [112]. After MI, WT1+ mesothelial lineage cells can differentiate into EAT. However, this is possible only within a short period following MI. For this process, activation of the insulin-like growth factor 1 (IGF-1) receptor signaling pathway is required [113]. This may indicate a potential negative impact of IGF-1 pathway activity, even though it is rather depicted as cardioprotective [114,115].

An animal study presented that removal of EAT during the MI induction resulted in better cardiac function and lower infarct area following MI. This procedure was also associated with a decrease in leukocyte numbers in the infarcted hearts one month after MI. Notably, there was an increase in the percentage of CD68+ macrophages and a reduction in both, absolute and proportional number of neutrophils, suggesting an alleviation of inflammation. Moreover, the removal of EAT was accompanied by a decrease in the levels of inflammatory cytokines—TNF- $\alpha$  and IL-1 $\beta$  one month after MI. These results may indicate a possible role of surgical EAT removal in post-MI therapy [40].

#### 4. Epicardial Adipose Tissue as a Source of Stem Cells for Cardiac Regeneration

The proliferative potential of human cardiomyocytes (CMs) is limited, especially in adults [116]. The application of stem cells seems to be a possible solution to improve cardiac regeneration following MI. Stem cell therapies were examined in a wide range of cardiovascular pathologies, including HF [117,118]. Animal studies showed promising results of embryonic stem cell (ESC) transplantation [119,120]. However, the use of ESCs raises relevant questions concerning the ethical nature of such procedures [121]. Multiple clinical trials regarding stem cells obtained from various sources in MI therapies have yielded inconsistent results. Mesenchymal stem cells (MSCs) are interesting due to their properties, as they can differentiate into cardiomyocytes, smooth muscle cells or endothelial cells. Moreover, cytokines secreted by MSCs have anti-fibrotic and anti-angiogenic properties. They also promote the differentiation of stem cells resident in the heart [122]. A specific subset of MSCs, known as adipose-derived stem cells (ADSCs), has been isolated from EAT.

ADSCs have the potential to differentiate in many types of cells, including cardiomyocytes, endothelial cells and vascular smooth muscle cells [123–125]. ADSCs obtained from cardiac adipose tissue presented an immunophenotype similar to mesenchymal stem cells as they were robustly positive for CD105, CD44, CD166, CD29, and CD90 and negative for CD106, CD45, and CD14. Transplantation of cardiac ADSCs in an animal model of MI led to improved cardiac function and reduced scar size. Moreover, these cells can secrete proangiogenic factors and thus promote angiogenesis resulting in higher capillary density *in vivo* [126]. Similarly, Özkaynak et al. studied the use of EAT-derived MSCs in a MI rabbit model. The intramyocardial injection of these cells led to an increase in EF, which was accompanied by enriched vascular density and decreased scar size in the infarcted area [127].

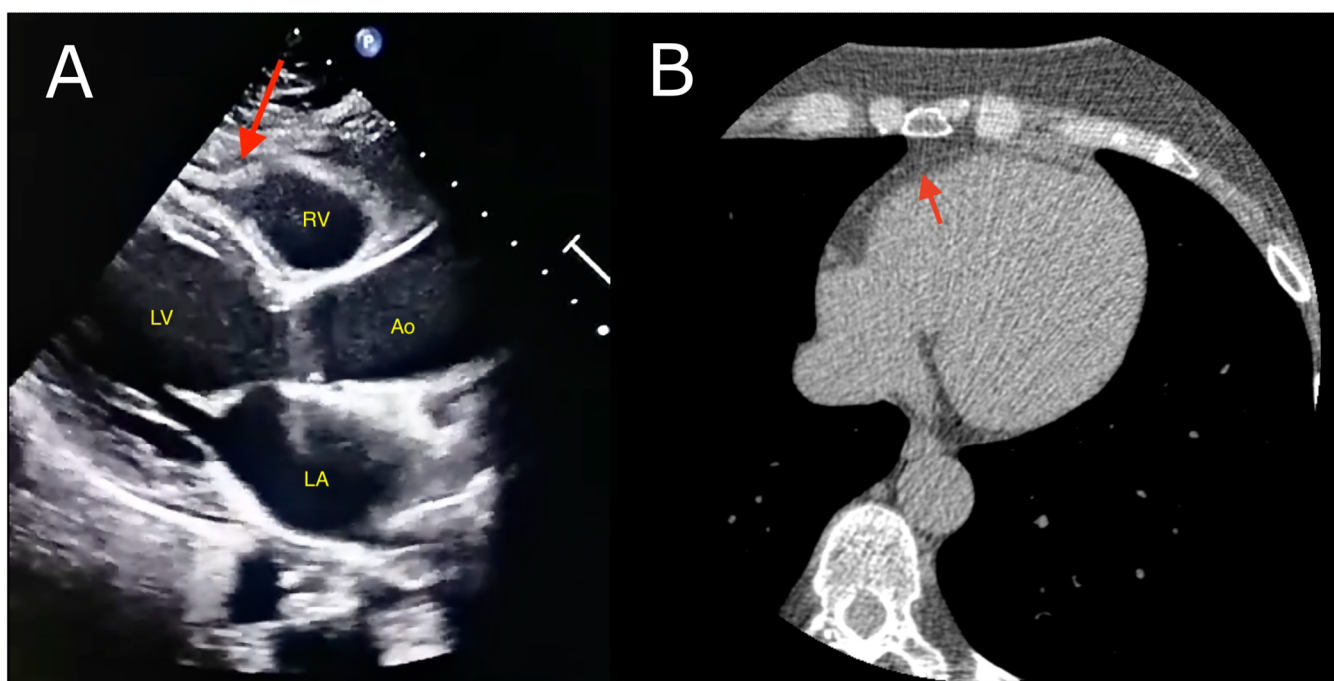
It has been established that ADSCs isolated from adipose tissue in distinct locations represent variations in functions, differentiation capacity and therapeutic potential in myocardial infarction. Cardiac ADSCs had significantly higher cell density and proliferation activity than ADSCs obtained from subcutaneous, visceral, and subscapular adipose tissue. They presented increased differentiation potential for cardiovascular cells. Moreover, cardiac ADSCs after systemic transfusion were more frequently recruited to the ischemic myocardium, which was related to improved cardiac recovery and enhanced cardiac functions after MI in mice [128]. Epicardial ADSCs had elevated proliferation potential in comparison to pericardial and omental ADSCs. They also presented the highest cardiomyogenic potential [129]. Epicardial ADSCs had significantly higher expression of GATA4 than pericardial and omental ADSCs [129]. GATA4 is a transcription factor which plays an essential role in myocardial morphogenesis [130,131].

Thankam and Agrawal obtained EAT from hyperlipidemic Yucatan microswine. The researchers isolated EAT-derived stem cells and subjected them to ischemia and/or reperfusion *in vitro*. With the use of single-cell RNA sequencing, they identified 18 different cell clusters, which may indicate that diverse phenotypes are present. Further analysis showed protective phenotypes presenting several mechanisms, which involve: “epigenetic regulation, myocardial homeostasis, cell integrity, and cell cycle, prevention of fibroblast differentiation, differentiation to myocardial lineage, anti-inflammatory responses, prevention of ER-stress, and increasing the energy metabolism” [132]. Another study with a similar design analyzed ribosomal proteins in exosomes from EAT-derived stem cells. Even

though many proteins were identified, the data concerning their extracellular functions are limited [133]. Treating cardiac fibroblasts in vitro with extracellular vesicles obtained from EAT-derived stem cells subjected to ischemia resulted in enhanced expression of cardiomyocyte lineage genes, transcription factors specific for cardiomyocytes (GATA-4, Nkx2.5, IRX4, and TBX5) and myofibroblast biomarker ( $\alpha$ SMA) with subsequent reduction in fibroblast (vimentin, FSP1, and podoplanin) and cardiac (connexin-43 and troponin-c) biomarker expression. Analysis with mass spectrometry showed that EVs carried proteins related to cardiac regeneration and inflammation. LGALS1, PRDX2, and CCL2 proteins were identified as important mediators engaged in tissue regeneration [134].

### 5. Imaging Assessment of Epicardial Adipose Tissue and Its Predictive Role

EAT parameters can be assessed using various imaging methods: echocardiography, computed tomography (CT) or magnetic resonance imaging (MRI) (Figure 3). Positron emission tomography (PET) plays a role in the evaluation of EAT metabolic activity. Each of them has advantages and disadvantages which indicate their utility in clinical practice. As EAT is considered as a biomarker of cardiovascular diseases [135–137] or a factor indicating future outcomes of patients [138,139], its assessment may become an important element in future diagnostic and therapeutic approaches. The clinical role of EAT is discussed in this chapter.



**Figure 3.** Epicardial adipose tissue (red arrows) visualized in: (A) transthoracic echocardiography—parasternal long axis view, (B) computed tomography. Abbreviations: Ao, aorta; LA, left atrium; LV, left ventricle; RV, right ventricle.

#### 5.1. Methods for Imaging Assessment of EAT

##### 5.1.1. Echocardiography

Echocardiography is a widely performed examination, primarily due to its cost-effectiveness and non-invasive nature, advantages that it holds over magnetic MRI and CT [140]. The measurement is done in transthoracic echocardiography on the free wall of the right ventricle from the parasternal long axis and short axis at end-systole or end-diastole. That region was shown to contain the highest EAT thickness and it allows optimal cursor beam orientation in each view. EAT appears as an echo-lucent space between the external wall of the myocardium and the visceral pericardium [6,141,142]. However, despite

its vast availability, it is unable to measure whole epicardial fat and there are conflicting results on the reproducibility of the method [136,142,143].

#### 5.1.2. Computed Tomography

CT enables the measurement of EAT thickness and volume. Additionally, attenuation (density) can be measured, and its less negative values serve as a marker of inflammation within the tissue [144]. Moreover, it grants an assessment of these parameters in the pericoronary adipose tissue (PCAT), which is the fat layer surrounding coronary vessels [145]. Altogether, these make CT more multi-functional in EAT evaluation than echocardiography. Nevertheless, it is numbered among the more expensive methods.

#### 5.1.3. Magnetic Resonance Imaging

MRI is stated as the best method to assess visceral fat depots and the EAT amongst them. Contrary to CT imaging it is a radiation-free method with high resolution allowing distinct exact borders of EAT as well as visualize it in many small cardiac spaces for example superior interventricular groove [146]. However, this approach is more expensive and time-consuming than CT and echocardiography.

#### 5.1.4. Positron Emission Tomography

It has been shown that fluorodeoxyglucose (FDG) uptake visualized by PET corresponds to macrophage infiltration within the tissue, therefore it can be used to assess the inflammatory properties of PCAT [147]. PET imaging is usually combined with CT (PET/CT), which allows both metabolic and anatomical evaluation.

### 5.2. EAT Parameters Assessed in Imaging Studies

#### 5.2.1. EAT Thickness

EAT thickness measured in echocardiography was associated with some CAD risk factors such as abdominal visceral adipose tissue, C-reactive protein level, waist circumference, age, and body mass index (BMI) [148]. A meta-analysis of nearly 5000 patients showed that EAT thickness is related to CAD and its severity [149]. Other studies also revealed EAT thickness measured in echocardiography to be a predictor of CAD [150,151] as well as an independent factor affecting its severity [152–154] and it was moreover reported to foresee the presence of multivessel disease [155]. Multiple studies identified EAT thickness measured in echocardiography to parallel with the Gensini score [151,155,156] and SYNTAX score [151,157], also in patients with ACS [137,156]. In addition, EAT thickness correlates with TIMI flow grade which is used for evaluation of coronary perfusion [158]. Moreover, a robust relationship with the number of thin-cap fibroatheromas was reported. Patients with thick EAT in echocardiography had approximately more and larger plaques, they were of higher mean burden index, with bigger necrotic core [159] and contained more lipids [160]. In a study on asymptomatic patients with type 2 diabetes, EAT thickness measured by MRI in the left atrioventricular groove revealed thicker EAT in patients with more severe coronary stenosis, yet no significant relation was showed between EAT thickness and silent myocardial ischemia [161].

The EAT thickness measured in CT showed a correlation with coronary artery calcium score (CAC), predicted CAD in asymptomatic patients [16] and negatively correlated with impairment in myocardial flow reserve [162]. Nonetheless, when combined with the calcium scoring, it gained little improvement in coronary stenosis diagnosis [163]. Picard et al. reported the EAT thickness on the free wall of the left ventricle correlated with the presence and severity of CAD. No such relation was detected for the right ventricle. The authors claim that the method has low diagnostic value compared to calcium scoring and CT coronary angiography [163].

Echocardiographic EAT thickness correlated weakly with the Framingham risk score, which is an algorithm used to estimate 10-year cardiovascular risk [164]. Tanindi et al. proved that EAT thickness might be used as a powerful predictor of acute MI. Echocardi-



graphic measurement of EAT may be a useful tool when deciding about aggressive therapy or as a follow-up parameter [165,166]. It also appeared to be an independent risk factor of NSTEMI, unstable angina pectoris [167], and restenosis after PCI [168]. Additionally, the EAT thickness in echocardiography occurred to be significantly predictive of adverse cardiovascular events in patients presenting with AF [169] and ACS during short-term and long-term follow-up [170,171]. Moreover, individuals with high echocardiographic EAT thickness were more likely to require target vessel revascularization. However, there was no significant dependence when it came to recurrent MI [172]. On the other hand, EAT thickness measured in CT in right, left, and anterior interventricular fossae predicted MI in patients with COVID-19 [173]. In a meta-analysis of over 6600 cases EAT thickness measured in either CT or echocardiography was proven to be increased in patients with myocardial infarction (MI) [136].

Nevertheless, the ability of echocardiographic EAT thickness to predict major adverse cardiovascular events (MACE) is denied by some results [174,175], especially in patients undergoing hemodialysis [176]. Some works deny the existence of any interaction with GRACE score and TIMI score, which are used to estimate the likelihood of adverse cardiac events [156,177]. Nonetheless, the latter was indicated by other researchers [167,178].

The EAT thickness measured in transthoracic echocardiography in subjects with MI corresponded positively with ST—segment resolution, reduction in LVEF, reduction in LV end-diastolic and end-systolic volume, and larger infarct size [171,179]. Furthermore, thick EAT was correlated with the presence of coronary collateral vessels (CCVs) in patients presenting with ACS. It suggests that EAT plays a role in the development of CCVs, which may contribute to alleviating ACS outcomes [180]. Excess echocardiographic EAT thickness was an independent predictor of no-reflow phenomenon in STEMI patients who underwent PCI [179,181], and coronary slow flow phenomenon, which appears as a slowed stream of contrast without visible stenosis in coronary angiography. It is an indicator of endothelial dysfunction and the early phase of atherosclerosis [182]. In addition, in STEMI subjects after PCI thick EAT assessed by echocardiography predicted the new onset of atrial fibrillation (AF) during hospital follow-up which means that the inflammatory properties of EAT may take a role in atrial myocardial remodeling [137].

### 5.2.2. EAT Volume

High EAT volume evaluated in CT showed a correlation with the presence of ACS [183], thin-capped fibroatheroma and high lipid content in the plaque [184]. Both ROMICAT trials also revealed the discriminative role of EAT volume assessed in CT for discovering high-risk lesions [185,186]. Excess EAT volume in CT correlated with vulnerable plaque characteristics, such as low density, presence of remodeling, and non-calcified component. However, there were weak associations with the amount of plaque [27–31].

The EAT volume and EAT volume indexed to the body surface (EATvi) measured in CT showed a correlation with CAC score and was associated with CAD [187–192]—this was also the case in patients with diabetes [193] and HIV [194]. High EAT volume evaluated in CT positively corresponded with CAC score in three main coronary arteries [195] and negatively correlated with impairment in myocardial flow reserve but was weaker than EAT thickness [162]. EAT volume measured in CT significantly correlated with the severity of CAD [196], but not with the severity of stenoses [189], and when combined with the calcium scoring it gained little improvement in coronary stenosis diagnosis [197]. Nonetheless, Milanese et al. denied the predictive role of EAT volume measured in CT regarding CAD [198]. Additionally, Goeller et al. showed in a population of patients without diagnosed CAD, that EAT volume evaluated in CT was higher in individuals with early atherosclerosis compared to those with more advanced disease. There was no correlation between EAT volume and CAC score value. Moreover, EAT volume was a strong predictor of cardiac death and MI [139].

The Framingham Heart Study and The Heinz Nixdorf Recall Study presented a significant relation between EAT volume measured in CT and the prevalence of fatal and



non-fatal coronary events [138,199]. This is supported by many trials which confirmed that increased EAT volume evaluated in CT, EATvi, and EAT indexed to the BMI are independent predictors of MI, cardiac death, and other coronary events [195,200–203], amongst patients with type 2 diabetes [204] and those with HIV [205]. EAT volume assessed in CT was positively associated with the prevalence of myocardial ischemia in diabetic patients. However, it did not correlate with its severity and there are conflicting results regarding the comparison of EAT and the CAC score performances [206–208]. Furthermore, EAT volume measured in CT was an independent factor related to the presence of coronary slow-flow phenomenon [209]. Nonetheless, no relation was observed between EAT volume and either fractional flow reserve (FFR) [210], or CT perfusion imaging [211].

Recently, AI has attracted much interest in the field of medical studies, including cardiology [212,213]. Deep learning (DL) models can be used to automatically quantify EAT from coronary CT angiography images [195]. Commandeur et al. used the machine learning (ML) model to predict the long-term risk of MI and cardiac death in asymptomatic subjects. Apart from many clinical parameters, the algorithm used CAC and EAT volume. The latter was calculated automatically with the use of a DL-based method. The ML model significantly better predicted the risks than the atherosclerotic cardiovascular disease risk score or CAC score alone [214]. In another study with a similar design, apart from clinical and imaging features, serum concentrations of biomarkers were also implemented in the ML model. This resulted in superior prediction of CV events than contemporary tools used for risk assessment [215].

In a retrospective analysis, Fisser et al. showed that EAT volume measured in MRI positively correlated with prevalence of MI, number of vessels obstructed, and amplitude of ST-elevation. However, there was no association with myocardial salvage index which is a tool presenting the treatment efficacy [216]. On the other hand, multiple studies exposed that more excess EAT volume evaluated in MRI goes along with smaller infarct size and lower number of vessels obstructed [217]. Nevertheless, there was still a positive correlation between EAT volume and myocardial salvage index [218]. A cross-sectional UK Biobank cardiovascular magnetic resonance imaging substudy acknowledged that CAD or history of MI did not correspond with the EATvi [219]. Homsy et al. demonstrated that more excess volume of EAT assessed in MRI predicted myocardial infarction in hypertensive men, yet there was no correlation with CAD or number of affected vessels [220].

### 5.2.3. EAT Attenuation and Mass

EAT attenuation measured in CT negatively correlated with CAC score [221] and CAC score in each of the three main coronary arteries, but not regarding the left circumflex coronary artery (LCx) [195]. In another study, there was no significant relation between the severity of CAD [196] and the presence of high-risk lesions in coronary arteries [186].

Patients presenting with MI had significantly higher EAT attenuation assessed in CT [202]. However, another study showed no significant difference between ischemic or non-ischemic lesions and EAT attenuation [222]. Goeller et al. presented that EAT attenuation measured in CT was relevantly lower in patients with early atherosclerosis when compared to ones with more advanced disease. In his study, no correlation was shown with the CAC score, yet EAT attenuation was a better predictor than EAT volume of cardiac death and MI [139]. Nonetheless, another study exhibited EAT attenuation to be a weaker predictor of myocardial ischemia and CAC score than EAT volume [208]. EAT attenuation evaluated in CT independently predicted long-term MACE in asymptomatic patients [195].

In patients with heart failure, the whole EAT mass evaluated in MRI was significantly lower than in healthy controls [223]. Moreover, it was lower in individuals with reduced LVEF separately from CAD. It indicates that the correlation between EAT mass and CAD severity is highly dependent on LVEF [224]. Furthermore, it was revealed that EAT mass (assessed in MRI) indexed to the body surface lower than 22 g/m<sup>2</sup> was a predictor of cardiac death [225].

#### 5.2.4. Pericoronary Adipose Tissue (PCAT)

Pericoronary adipose tissue is part of EAT which stays in direct contact with coronary vessels thus it has a paracrine effect on them. It can be measured using CT and cardiac MRI. Therefore, this subchapter describes associations of PCAT volume or attenuation with coronary arteries and cardiovascular outcomes [226].

In the CRISP-CT study, the authors revealed a relevant association between high fat attenuation index around LAD and RCA, and prospective cardiac mortality risk. However, it was diminished amongst patients who had been put on statins or aspirin therapy and there was no such correlation regarding LCx [227]. Combining PCAT volume measured in CT around RCA, LAD, and LCx showed statistically significant potential in distinguishing NSTEMI from unstable angina pectoris in contrast to EAT volume [228]. RCA-PCAT attenuation assessed in CT positively correlated with total atherosclerotic plaque burden and amount of calcified plaque, however, there was no relationship regarding the prevalence of MI, cardiac death or revascularization [229]. PCAT volume was found to be significantly associated with the presence of a culprit lesion in the artery. However, such a relation was absent for PCAT attenuation [230]. In another study, PCAT attenuation, but not PCAT volume, was markedly higher in patients with acute MI compared to individuals with stable CAD [196].

Shan et al. showed that only LAD-PCAT volume evaluated in CT correlated with myocardial ischemia measured by fractional flow reserve (FFR) and when combined with CAD-RADS categories it gave a huge improvement in the prediction of myocardial ischemia [210]. In contrast, Duncker et al. showed that only RCA-PCAT attenuation and average PCAT attenuation, both measured in CT were significantly related to myocardial ischemia assessed by FFR, which was false for every other PCAT volume and its attenuation as well as EAT and paracardial adipose tissue volume and attenuation [231]. Zhou et al. demonstrated that combining radiomics features of PCAT evaluated using CT with or without plaque characteristics was significantly related to FFR. However, plaque characteristics themselves gave poor performance. The authors conclude that PCAT characteristics may be of better predictive value regarding myocardial ischemia than the whole EAT [232].

Toya et al. presented the predictive ability of PCAT measured in MRI regarding MACE, especially those around the superior interventricular groove [233]. Amongst PCAT thickness indexed to the body surface, only the one measured in the superior interventricular groove using MRI showed statistical significance in prediction of MACE after STEMI [234].

Mazurek et al. presented nine patients with non-ST segment elevation ACS with PCAT showing higher FDG uptake evaluated in PET/CT than other fat depots, which indicates its pro-inflammatory properties. FDG uptake was also related to negative plaque characteristics and revealed a positive correlation with plaque burden and necrotic core rate as well as a negative correlation with fibrous plaque rate [147]. Furthermore, the authors exhibited that PCAT FDG uptake significantly paralleled with CAD presence. In overweight patients, it positively correlated with the percent of coronary stenosis indicating that weight gain influences PCAT inflammatory activity. Moreover, PCAT FDG uptake was an independent predictor of stenoses in RCA and LAD [235]. In another study, PCAT FDG uptake was higher in patients with vasospastic angina (VSA) in LAD and positively corresponded with the density of vasa vasorum in the artery. It suggests that VSA has an inflammatory background related to the activity of PCAT [236].

## 6. Conclusions

Numerous studies have confirmed that EAT contributes to the pathogenesis of CAD and can be useful in the prediction of ACS. EAT evaluation during routine imaging studies like echocardiography and CT could be potentially implemented in risk assessment scores. Additionally, EAT plays a role in cardiac remodeling following MI, primarily by promoting fibrosis, and medications that reduce the secretion of fibrokinases from EAT may mitigate this adverse cardiac remodeling. Conversely, EAT can exhibit cardioprotective properties and

can be a source of SCs capable of enhancing myocardial regeneration after MI. Therefore, we need significantly more research on the dual role of EAT before we can proceed with its application in clinical practice.

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## References

- Mukherjee, A.G.; Renu, K.; Gopalakrishnan, A.V.; Jayaraj, R.; Dey, A.; Vellingiri, B.; Ganesan, R. Epicardial adipose tissue and cardiac lipotoxicity: A review. *Life Sci.* **2023**, *328*, 121913. [[CrossRef](#)]
- Sacks, H.S.; Fain, J.N.; Bahouth, S.W.; Ojha, S.; Frontini, A.; Budge, H.; Cinti, S.; Symonds, M.E. Adult epicardial fat exhibits beige features. *J. Clin. Endocrinol. Metab.* **2013**, *98*, E1448–E1455. [[CrossRef](#)]
- Iacobellis, G.; Bianco, A.C. Epicardial adipose tissue: Emerging physiological, pathophysiological and clinical features. *Trends Endocrinol. Metab.* **2011**, *22*, 450–457. [[CrossRef](#)]
- Iacobellis, G. Local and systemic effects of the multifaceted epicardial adipose tissue depot. *Nat. Rev. Endocrinol.* **2015**, *11*, 363–371. [[CrossRef](#)]
- Hatem, S.N.; Sanders, P. Epicardial adipose tissue and atrial fibrillation. *Cardiovasc. Res.* **2014**, *102*, 205–213. [[CrossRef](#)] [[PubMed](#)]
- Iacobellis, G.; Corradi, D.; Sharma, A.M. Epicardial adipose tissue: Anatomic, biomolecular and clinical relationships with the heart. *Nat. Clin. Pract. Cardiovasc. Med.* **2005**, *2*, 536–543. [[CrossRef](#)] [[PubMed](#)]
- Rabkin, S.W. Epicardial fat: Properties, function and relationship to obesity. *Obes. Rev.* **2007**, *8*, 253–261. [[CrossRef](#)] [[PubMed](#)]
- Ma, R.; Fari, R.; van der Harst, P.; De Cecco, C.N.; Stillman, A.E.; Vliegenthart, R.; van Assen, M. Evaluation of pericoronary adipose tissue attenuation on CT. *Br. J. Radiol.* **2023**, *96*, 20220885. [[CrossRef](#)] [[PubMed](#)]
- Akoumianakis, I.; Antoniadou, C. The interplay between adipose tissue and the cardiovascular system: Is fat always bad? *Cardiovasc. Res.* **2017**, *113*, 999–1008. [[CrossRef](#)] [[PubMed](#)]
- Napoli, G.; Pergola, V.; Basile, P.; De Feo, D.; Bertrandino, F.; Baggiano, A.; Mushtaq, S.; Fusini, L.; Fazzari, F.; Carrabba, N.; et al. Epicardial and Pericoronary Adipose Tissue, Coronary Inflammation, and Acute Coronary Syndromes. *J. Clin. Med.* **2023**, *12*, 7212. [[CrossRef](#)]
- Iacobellis, G. Epicardial and pericardial fat: Close, but very different. *Obesity* **2009**, *17*, 625. [[CrossRef](#)]
- Iacobellis, G.; Barbaro, G. The double role of epicardial adipose tissue as pro- and anti-inflammatory organ. *Horm. Metab. Res.* **2008**, *40*, 442–445. [[CrossRef](#)]
- Iacobellis, G.; Malavazos, A.E.; Corsi, M.M. Epicardial fat: From the biomolecular aspects to the clinical practice. *Int. J. Biochem. Cell Biol.* **2011**, *43*, 1651–1654. [[CrossRef](#)]
- Iacobellis, G. Epicardial adipose tissue in contemporary cardiology. *Nat. Rev. Cardiol.* **2022**, *19*, 593–606. [[CrossRef](#)]
- Song, Y.; Tan, Y.; Deng, M.; Shan, W.; Zheng, W.; Zhang, B.; Cui, J.; Feng, L.; Shi, L.; Zhang, M.; et al. Epicardial adipose tissue, metabolic disorders, and cardiovascular diseases: Recent advances classified by research methodologies. *MedComm* **2023**, *4*, e413. [[CrossRef](#)]
- Bachar, G.N.; Dicker, D.; Kornowski, R.; Atar, E. Epicardial adipose tissue as a predictor of coronary artery disease in asymptomatic subjects. *Am. J. Cardiol.* **2012**, *110*, 534–538. [[CrossRef](#)]
- Si, Y.; Feng, Z.; Liu, Y.; Fan, W.; Shan, W.; Zhang, Y.; Shi, F.; Xing, E.; Sun, L. Inflammatory biomarkers, angiogenesis and lymphangiogenesis in epicardial adipose tissue correlate with coronary artery disease. *Sci. Rep.* **2023**, *13*, 2831. [[CrossRef](#)]
- van Woerden, G.; van Veldhuisen, D.J.; Westenbrink, B.D.; de Boer, R.A.; Rienstra, M.; Gorter, T.M. Connecting epicardial adipose tissue and heart failure with preserved ejection fraction: Mechanisms, management and modern perspectives. *Eur. J. Heart Fail.* **2022**, *24*, 2238–2250. [[CrossRef](#)]
- Nalliah, C.J.; Bell, J.R.; Raaijmakers, A.J.A.; Waddell, H.M.; Wells, S.P.; Bernasocchi, G.B.; Montgomery, M.K.; Binny, S.; Watts, T.; Joshi, S.B.; et al. Epicardial Adipose Tissue Accumulation Confers Atrial Conduction Abnormality. *J. Am. Coll. Cardiol.* **2020**, *76*, 1197–1211. [[CrossRef](#)]

20. Furuhashi, M.; Fuseya, T.; Murata, M.; Hoshina, K.; Ishimura, S.; Mita, T.; Watanabe, Y.; Omori, A.; Matsumoto, M.; Sugaya, T.; et al. Local Production of Fatty Acid-Binding Protein 4 in Epicardial/Perivascular Fat and Macrophages Is Linked to Coronary Atherosclerosis. *Arter. Thromb. Vasc. Biol.* **2016**, *36*, 825–834. [[CrossRef](#)]
21. Iacobellis, G.; Barbarini, G.; Letizia, C.; Barbaro, G. Epicardial fat thickness and nonalcoholic fatty liver disease in obese subjects. *Obesity* **2014**, *22*, 332–336. [[CrossRef](#)]
22. Tanami, Y.; Jinzaki, M.; Kishi, S.; Matheson, M.; Vavere, A.L.; Rochitte, C.E.; Dewey, M.; Chen, M.Y.; Clouse, M.E.; Cox, C.; et al. Lack of association between epicardial fat volume and extent of coronary artery calcification, severity of coronary artery disease, or presence of myocardial perfusion abnormalities in a diverse, symptomatic patient population: Results from the CORE320 multicenter study. *Circ. Cardiovasc. Imaging* **2015**, *8*, e002676. [[CrossRef](#)]
23. Mancio, J.; Azevedo, D.; Fraga-Marques, M.; Falcao-Pires, I.; Leite-Moreira, A.; Lunet, N.; Fontes-Carvalho, R.; Bettencourt, N. Meta-Analysis of Relation of Epicardial Adipose Tissue Volume to Left Atrial Dilation and to Left Ventricular Hypertrophy and Functions. *Am. J. Cardiol.* **2019**, *123*, 523–531. [[CrossRef](#)]
24. Frangiogiannis, N.G. Pathophysiology of Myocardial Infarction. *Compr. Physiol.* **2015**, *5*, 1841–1875. [[CrossRef](#)]
25. Nerlekar, N.; Brown, A.J.; Muthalaly, R.G.; Talman, A.; Hettige, T.; Cameron, J.D.; Wong, D.T.L. Association of Epicardial Adipose Tissue and High-Risk Plaque Characteristics: A Systematic Review and Meta-Analysis. *J. Am. Heart Assoc.* **2017**, *6*, e006379. [[CrossRef](#)]
26. Echavarría-Pinto, M.; Hernando, L.; Alfonso, F. From the epicardial adipose tissue to vulnerable coronary plaques. *World J. Cardiol.* **2013**, *5*, 68–74. [[CrossRef](#)]
27. Rajani, R.; Shmilovich, H.; Nakazato, R.; Nakanishi, R.; Otaki, Y.; Cheng, V.Y.; Hayes, S.W.; Thomson, L.E.; Friedman, J.D.; Slomka, P.J.; et al. Relationship of epicardial fat volume to coronary plaque, severe coronary stenosis, and high-risk coronary plaque features assessed by coronary CT angiography. *J. Cardiovasc. Comput. Tomogr.* **2013**, *7*, 125–132. [[CrossRef](#)]
28. Oka, T.; Yamamoto, H.; Ohashi, N.; Kitagawa, T.; Kunita, E.; Utsunomiya, H.; Yamazato, R.; Urabe, Y.; Horiguchi, J.; Awai, K.; et al. Association between epicardial adipose tissue volume and characteristics of non-calcified plaques assessed by coronary computed tomographic angiography. *Int. J. Cardiol.* **2012**, *161*, 45–49. [[CrossRef](#)]
29. Alexopoulos, N.; McLean, D.S.; Janik, M.; Arepalli, C.D.; Stillman, A.E.; Raggi, P. Epicardial adipose tissue and coronary artery plaque characteristics. *Atherosclerosis* **2010**, *210*, 150–154. [[CrossRef](#)]
30. Yamaura, H.; Otsuka, K.; Ishikawa, H.; Shirasawa, K.; Fukuda, D.; Kasayuki, N. Determinants of Non-calcified Low-Attenuation Coronary Plaque Burden in Patients Without Known Coronary Artery Disease: A Coronary CT Angiography Study. *Front. Cardiovasc. Med.* **2022**, *9*, 824470. [[CrossRef](#)]
31. Srinivasa, S.; Lu, M.T.; Fitch, K.V.; Hallett, T.R.; O'Malley, T.K.; Stone, L.A.; Martin, A.; Coromilas, A.J.; Burdo, T.H.; Triant, V.A.; et al. Epicardial adipose tissue volume and cardiovascular risk indices among asymptomatic women with and without HIV. *Antivir. Ther.* **2018**, *23*, 1–9. [[CrossRef](#)]
32. Moreno-Santos, I.; Macias-Gonzalez, M.; Porrás-Martin, C.; Castellano-Castillo, D.; Sanchez-Espin, G.; Gomez-Doblas, J.J.; de Teresa-Galvan, E.; Jimenez-Navarro, M. Role of epicardial adipose tissue NPR-C in acute coronary syndrome. *Atherosclerosis* **2019**, *286*, 79–87. [[CrossRef](#)]
33. Hao, S.; Zhang, J.; Pei, Y.; Guo, L.; Liang, Z. Complement factor D derived from epicardial adipose tissue participates in cardiomyocyte apoptosis after myocardial infarction by mediating PARP-1 activity. *Cell. Signal.* **2023**, *101*, 110518. [[CrossRef](#)]
34. Pedicino, D.; Severino, A.; Ucci, S.; Bugli, F.; Flego, D.; Giglio, A.F.; Trotta, F.; Ruggio, A.; Lucci, C.; Iaconelli, A.; et al. Epicardial adipose tissue microbial colonization and inflammasome activation in acute coronary syndrome. *Int. J. Cardiol.* **2017**, *236*, 95–99. [[CrossRef](#)]
35. Parisi, V.; Petraglia, L.; Cabaro, S.; D'Esposito, V.; Bruzzese, D.; Ferraro, G.; Urbani, A.; Grieco, F.V.; Conte, M.; Caruso, A.; et al. Imbalance between Interleukin-1beta and Interleukin-1 Receptor Antagonist in Epicardial Adipose Tissue Is Associated with Non ST-Segment Elevation Acute Coronary Syndrome. *Front. Physiol.* **2020**, *11*, 42. [[CrossRef](#)]
36. Pedicino, D.; Severino, A.; Di Sante, G.; De Rosa, M.C.; Pirolli, D.; Vinci, R.; Pazzano, V.; Giglio, A.F.; Trotta, F.; Russo, G.; et al. Restricted T-Cell Repertoire in the Epicardial Adipose Tissue of Non-ST Segment Elevation Myocardial Infarction Patients. *Front. Immunol.* **2022**, *13*, 845526. [[CrossRef](#)]
37. Langheim, S.; Dreas, L.; Veschini, L.; Maisano, F.; Foglieni, C.; Ferrarello, S.; Sinagra, G.; Zingone, B.; Alfieri, O.; Ferrero, E.; et al. Increased expression and secretion of resistin in epicardial adipose tissue of patients with acute coronary syndrome. *Am. J. Physiol. Heart Circ. Physiol.* **2010**, *298*, H746–H753. [[CrossRef](#)]
38. Rachwalik, M.; Zysko, D.; Diakowska, D.; Kustrzycki, W. Increased content of resistin in epicardial adipose tissue of patients with advanced coronary atherosclerosis and history of myocardial infarction. *Thorac. Cardiovasc. Surg.* **2014**, *62*, 554–560. [[CrossRef](#)]
39. Hao, S.; Sui, X.; Wang, J.; Zhang, J.; Pei, Y.; Guo, L.; Liang, Z. Secretory products from epicardial adipose tissue induce adverse myocardial remodeling after myocardial infarction by promoting reactive oxygen species accumulation. *Cell Death Dis.* **2021**, *12*, 848. [[CrossRef](#)]
40. Chang, H.X.; Zhao, X.J.; Zhu, Q.L.; Hou, Q.; Li, Y. Removal of epicardial adipose tissue after myocardial infarction improves cardiac function. *Herz* **2018**, *43*, 258–264. [[CrossRef](#)]
41. Berbee, J.F.; Boon, M.R.; Khedoe, P.P.; Bartelt, A.; Schlein, C.; Worthmann, A.; Kooijman, S.; Hoeke, G.; Mol, I.M.; John, C.; et al. Brown fat activation reduces hypercholesterolaemia and protects from atherosclerosis development. *Nat. Commun.* **2015**, *6*, 6356. [[CrossRef](#)]



42. Thoonen, R.; Ernande, L.; Cheng, J.; Nagasaka, Y.; Yao, V.; Miranda-Bezerra, A.; Chen, C.; Chao, W.; Panagia, M.; Sosnovik, D.E.; et al. Functional brown adipose tissue limits cardiomyocyte injury and adverse remodeling in catecholamine-induced cardiomyopathy. *J. Mol. Cell. Cardiol.* **2015**, *84*, 202–211. [[CrossRef](#)]
43. Sarzani, R.; Dessi-Fulgheri, P.; Paci, V.M.; Espinosa, E.; Rappelli, A. Expression of natriuretic peptide receptors in human adipose and other tissues. *J. Endocrinol. Investig.* **1996**, *19*, 581–585. [[CrossRef](#)]
44. Sengenès, C.; Berlan, M.; De Glisezinski, I.; Lafontan, M.; Galitzky, J. Natriuretic peptides: A new lipolytic pathway in human adipocytes. *FASEB J.* **2000**, *14*, 1345–1351. [[CrossRef](#)]
45. Lafontan, M.; Moro, C.; Sengenès, C.; Galitzky, J.; Crampes, F.; Berlan, M. An unsuspected metabolic role for atrial natriuretic peptides: The control of lipolysis, lipid mobilization, and systemic nonesterified fatty acids levels in humans. *Arter. Thromb. Vasc. Biol.* **2005**, *25*, 2032–2042. [[CrossRef](#)]
46. Bordicchia, M.; Liu, D.; Amri, E.Z.; Ailhaud, G.; Dessi-Fulgheri, P.; Zhang, C.; Takahashi, N.; Sarzani, R.; Collins, S. Cardiac natriuretic peptides act via p38 MAPK to induce the brown fat thermogenic program in mouse and human adipocytes. *J. Clin. Investig.* **2012**, *122*, 1022–1036. [[CrossRef](#)]
47. Morrison, D.K. MAP kinase pathways. *Cold Spring Harb. Perspect. Biol.* **2012**, *4*, a011254. [[CrossRef](#)]
48. Shen, S.H.; Singh, S.P.; Raffaele, M.; Waldman, M.; Hochhauser, E.; Ospino, J.; Arad, M.; Peterson, S.J. Adipocyte-Specific Expression of PGC1 $\alpha$  Promotes Adipocyte Browning and Alleviates Obesity-Induced Metabolic Dysfunction in an HO-1-Dependent Fashion. *Antioxidants* **2022**, *11*, 1147. [[CrossRef](#)]
49. Singh, S.P.; McClung, J.A.; Thompson, E.; Glick, Y.; Greenberg, M.; Acosta-Baez, G.; Edris, B.; Shapiro, J.I.; Abraham, N.G. Cardioprotective Heme Oxygenase-1-PGC1 $\alpha$  Signaling in Epicardial Fat Attenuates Cardiovascular Risk in Humans as in Obese Mice. *Obesity* **2019**, *27*, 1634–1643. [[CrossRef](#)]
50. Zhao, L.; Ma, Z.; Guo, Z.; Zheng, M.; Li, K.; Yang, X. Analysis of long non-coding RNA and mRNA profiles in epicardial adipose tissue of patients with atrial fibrillation. *Biomed. Pharmacother.* **2020**, *121*, 109634. [[CrossRef](#)]
51. Kong, P.; Cui, Z.Y.; Huang, X.F.; Zhang, D.D.; Guo, R.J.; Han, M. Inflammation and atherosclerosis: Signaling pathways and therapeutic intervention. *Signal Transduct. Target. Ther.* **2022**, *7*, 131. [[CrossRef](#)]
52. Kaplan, R.C.; Frishman, W.H. Systemic inflammation as a cardiovascular disease risk factor and as a potential target for drug therapy. *Heart Dis.* **2001**, *3*, 326–332. [[CrossRef](#)]
53. Toivonen, S.; Lehtinen, M.; Raivio, P.; Sinisalo, J.; Loimaala, A.; Uusitalo, V. The Presence of Residual Vascular and Adipose Tissue Inflammation on (18)F-FDG PET in Patients with Chronic Coronary Artery Disease. *Nucl. Med. Mol. Imaging* **2023**, *57*, 117–125. [[CrossRef](#)] [[PubMed](#)]
54. Zhang, Q.; Wang, L.; Wang, S.; Cheng, H.; Xu, L.; Pei, G.; Wang, Y.; Fu, C.; Jiang, Y.; He, C.; et al. Signaling pathways and targeted therapy for myocardial infarction. *Signal Transduct. Target. Ther.* **2022**, *7*, 78. [[CrossRef](#)] [[PubMed](#)]
55. Cinti, S.; Mitchell, G.; Barbatelli, G.; Murano, I.; Ceresi, E.; Faloia, E.; Wang, S.; Fortier, M.; Greenberg, A.S.; Obin, M.S. Adipocyte death defines macrophage localization and function in adipose tissue of obese mice and humans. *J. Lipid Res.* **2005**, *46*, 2347–2355. [[CrossRef](#)] [[PubMed](#)]
56. Malavazos, A.E.; Di Vincenzo, A.; Iacobellis, G.; Basilico, S.; Dubini, C.; Morricone, L.; Menicanti, L.; Luca, T.; Giordano, A.; Castorina, S.; et al. The density of crown-like structures in epicardial adipose tissue could play a role in cardiovascular diseases. *Eat. Weight Disord.* **2022**, *27*, 2905–2910. [[CrossRef](#)] [[PubMed](#)]
57. Fan, W.; Si, Y.; Xing, E.; Feng, Z.; Ding, Z.; Liu, Y.; Wei, C.; Tian, Y.; Zhang, Y.; Liu, J.; et al. Human epicardial adipose tissue inflammation correlates with coronary artery disease. *Cytokine* **2023**, *162*, 156119. [[CrossRef](#)] [[PubMed](#)]
58. Niccoli, G.; Montone, R.A.; Sabato, V.; Crea, F. Role of Allergic Inflammatory Cells in Coronary Artery Disease. *Circulation* **2018**, *138*, 1736–1748. [[CrossRef](#)] [[PubMed](#)]
59. Mazurek, T.; Zhang, L.; Zalewski, A.; Mannion, J.D.; Diehl, J.T.; Arafat, H.; Sarov-Blat, L.; O'Brien, S.; Keiper, E.A.; Johnson, A.G.; et al. Human epicardial adipose tissue is a source of inflammatory mediators. *Circulation* **2003**, *108*, 2460–2466. [[CrossRef](#)]
60. Swanson, K.V.; Deng, M.; Ting, J.P. The NLRP3 inflammasome: Molecular activation and regulation to therapeutics. *Nat. Rev. Immunol.* **2019**, *19*, 477–489. [[CrossRef](#)]
61. Afrasyab, A.; Qu, P.; Zhao, Y.; Peng, K.; Wang, H.; Lou, D.; Niu, N.; Yuan, D. Correlation of NLRP3 with severity and prognosis of coronary atherosclerosis in acute coronary syndrome patients. *Heart Vessel.* **2016**, *31*, 1218–1229. [[CrossRef](#)] [[PubMed](#)]
62. Bando, S.; Fukuda, D.; Soeki, T.; Nishimoto, S.; Uematsu, E.; Matsuura, T.; Ise, T.; Tobiume, T.; Yamaguchi, K.; Yagi, S.; et al. Expression of NLRP3 in subcutaneous adipose tissue is associated with coronary atherosclerosis. *Atherosclerosis* **2015**, *242*, 407–414. [[CrossRef](#)] [[PubMed](#)]
63. Hirata, Y.; Tabata, M.; Kurobe, H.; Motoki, T.; Akaike, M.; Nishio, C.; Higashida, M.; Mikasa, H.; Nakaya, Y.; Takanashi, S.; et al. Coronary atherosclerosis is associated with macrophage polarization in epicardial adipose tissue. *J. Am. Coll. Cardiol.* **2011**, *58*, 248–255. [[CrossRef](#)] [[PubMed](#)]
64. Yin, Z.; Deng, T.; Peterson, L.E.; Yu, R.; Lin, J.; Hamilton, D.J.; Reardon, P.R.; Sherman, V.; Winnier, G.E.; Zhan, M.; et al. Transcriptome analysis of human adipocytes implicates the NOD-like receptor pathway in obesity-induced adipose inflammation. *Mol. Cell. Endocrinol.* **2014**, *394*, 80–87. [[CrossRef](#)] [[PubMed](#)]
65. Shan, T.; Shuwen, Z.; Hengbin, W.; Min, Z. Can EAT be an INOCA goalkeeper. *Front. Endocrinol.* **2022**, *13*, 1028429. [[CrossRef](#)] [[PubMed](#)]



66. Zhang, Q.; Dong, J.; Yu, Z. Pleiotropic use of Statins as non-lipid-lowering drugs. *Int. J. Biol. Sci.* **2020**, *16*, 2704–2711. [[CrossRef](#)] [[PubMed](#)]
67. Parisi, V.; Petraglia, L.; D'Esposito, V.; Cabaro, S.; Rengo, G.; Caruso, A.; Grimaldi, M.G.; Baldascino, F.; De Bellis, A.; Vitale, D.; et al. Statin therapy modulates thickness and inflammatory profile of human epicardial adipose tissue. *Int. J. Cardiol.* **2019**, *274*, 326–330. [[CrossRef](#)]
68. Li, L.; Hua, C.; Liu, X.; Wang, Y.; Zhao, L.; Zhang, Y.; Wang, L.; Su, P.; Yang, M.F.; Xie, B. SGLT2i alleviates epicardial adipose tissue inflammation by modulating ketone body-glyceraldehyde-3-phosphate dehydrogenase malonylation pathway. *J. Cardiovasc. Med.* **2023**, *24*, 232–243. [[CrossRef](#)]
69. Dozio, E.; Vianello, E.; Malavazos, A.E.; Tacchini, L.; Schmitz, G.; Iacobellis, G.; Corsi Romanelli, M.M. Epicardial adipose tissue GLP-1 receptor is associated with genes involved in fatty acid oxidation and white-to-brown fat differentiation: A target to modulate cardiovascular risk? *Int. J. Cardiol.* **2019**, *292*, 218–224. [[CrossRef](#)]
70. Ziyrek, M.; Kahraman, S.; Ozdemir, E.; Dogan, A. Metformin monotherapy significantly decreases epicardial adipose tissue thickness in newly diagnosed type 2 diabetes patients. *Rev. Port. Cardiol. (Engl. Ed.)* **2019**, *38*, 419–423. [[CrossRef](#)]
71. Moody, A.J.; Molina-Wilkins, M.; Clarke, G.D.; Merovci, A.; Solis-Herrera, C.; Cersosimo, E.; Chilton, R.J.; Iozzo, P.; Gastaldelli, A.; Abdul-Ghani, M.; et al. Pioglitazone reduces epicardial fat and improves diastolic function in patients with type 2 diabetes. *Diabetes Obes. Metab.* **2023**, *25*, 426–434. [[CrossRef](#)]
72. Farkhondeh, T.; Llorens, S.; Pourbagher-Shahri, A.M.; Ashrafzadeh, M.; Talebi, M.; Shakibaei, M.; Samarghandian, S. An Overview of the Role of Adipokines in Cardiometabolic Diseases. *Molecules* **2020**, *25*, 5218. [[CrossRef](#)]
73. Jamaluddin, M.S.; Weakley, S.M.; Yao, Q.; Chen, C. Resistin: Functional roles and therapeutic considerations for cardiovascular disease. *Br. J. Pharmacol.* **2012**, *165*, 622–632. [[CrossRef](#)]
74. Lee, S.H.; Ha, J.W.; Kim, J.S.; Choi, E.Y.; Park, S.; Kang, S.M.; Choi, D.; Jang, Y.; Chung, N. Plasma adiponectin and resistin levels as predictors of mortality in patients with acute myocardial infarction: Data from infarction prognosis study registry. *Coron. Artery Dis.* **2009**, *20*, 33–39. [[CrossRef](#)] [[PubMed](#)]
75. Qatanani, M.; Szwegold, N.R.; Greaves, D.R.; Ahima, R.S.; Lazar, M.A. Macrophage-derived human resistin exacerbates adipose tissue inflammation and insulin resistance in mice. *J. Clin. Investig.* **2009**, *119*, 531–539. [[CrossRef](#)] [[PubMed](#)]
76. Verma, S.; Li, S.H.; Wang, C.H.; Fedak, P.W.; Li, R.K.; Weisel, R.D.; Mickle, D.A. Resistin promotes endothelial cell activation: Further evidence of adipokine-endothelial interaction. *Circulation* **2003**, *108*, 736–740. [[CrossRef](#)] [[PubMed](#)]
77. Sommer, G.; Kralisch, S.; Stangl, V.; Vietzke, A.; Kohler, U.; Stepan, H.; Faber, R.; Schubert, A.; Lossner, U.; Bluher, M.; et al. Secretory products from human adipocytes stimulate proinflammatory cytokine secretion from human endothelial cells. *J. Cell. Biochem.* **2009**, *106*, 729–737. [[CrossRef](#)] [[PubMed](#)]
78. Cao, H.; Sekiya, M.; Ertunc, M.E.; Burak, M.F.; Mayers, J.R.; White, A.; Inouye, K.; Rickey, L.M.; Ercal, B.C.; Furuhashi, M.; et al. Adipocyte lipid chaperone AP2 is a secreted adipokine regulating hepatic glucose production. *Cell Metab.* **2013**, *17*, 768–778. [[CrossRef](#)] [[PubMed](#)]
79. Hotamisligil, G.S.; Bernlohr, D.A. Metabolic functions of FABPs—mechanisms and therapeutic implications. *Nat. Rev. Endocrinol.* **2015**, *11*, 592–605. [[CrossRef](#)]
80. Peeters, W.; de Kleijn, D.P.; Vink, A.; van de Weg, S.; Schoneveld, A.H.; Sze, S.K.; van der Spek, P.J.; de Vries, J.P.; Moll, F.L.; Pasterkamp, G. Adipocyte fatty acid binding protein in atherosclerotic plaques is associated with local vulnerability and is predictive for the occurrence of adverse cardiovascular events. *Eur. Heart J.* **2011**, *32*, 1758–1768. [[CrossRef](#)]
81. Obokata, M.; Iso, T.; Ohyama, Y.; Sunaga, H.; Kawaguchi, T.; Matsui, H.; Iizuka, T.; Fukuda, N.; Takamatsu, H.; Koitabashi, N.; et al. Early increase in serum fatty acid binding protein 4 levels in patients with acute myocardial infarction. *Eur. Heart J. Acute Cardiovasc. Care* **2018**, *7*, 561–569. [[CrossRef](#)]
82. Sun, F.; Du, J.; Li, H.; Hao, S.; Zhao, G.; Lu, F. FABP4 inhibitor BMS309403 protects against hypoxia-induced H9c2 cardiomyocyte apoptosis through attenuating endoplasmic reticulum stress. *J. Cell. Mol. Med.* **2020**, *24*, 11188–11197. [[CrossRef](#)]
83. Yamawaki, H.; Kuramoto, J.; Kameshima, S.; Usui, T.; Okada, M.; Hara, Y. Omentin, a novel adipocytokine inhibits TNF-induced vascular inflammation in human endothelial cells. *Biochem. Biophys. Res. Commun.* **2011**, *408*, 339–343. [[CrossRef](#)]
84. Yamawaki, H.; Tsubaki, N.; Mukohda, M.; Okada, M.; Hara, Y. Omentin, a novel adipokine, induces vasodilation in rat isolated blood vessels. *Biochem. Biophys. Res. Commun.* **2010**, *393*, 668–672. [[CrossRef](#)] [[PubMed](#)]
85. Kataoka, Y.; Shibata, R.; Ohashi, K.; Kambara, T.; Enomoto, T.; Uemura, Y.; Ogura, Y.; Yuasa, D.; Matsuo, K.; Nagata, T.; et al. Omentin prevents myocardial ischemic injury through AMP-activated protein kinase- and Akt-dependent mechanisms. *J. Am. Coll. Cardiol.* **2014**, *63*, 2722–2733. [[CrossRef](#)] [[PubMed](#)]
86. Du, Y.; Ji, Q.; Cai, L.; Huang, F.; Lai, Y.; Liu, Y.; Yu, J.; Han, B.; Zhu, E.; Zhang, J.; et al. Association between omentin-1 expression in human epicardial adipose tissue and coronary atherosclerosis. *Cardiovasc. Diabetol.* **2016**, *15*, 90. [[CrossRef](#)]
87. Watanabe, K.; Watanabe, R.; Konii, H.; Shirai, R.; Sato, K.; Matsuyama, T.A.; Ishibashi-Ueda, H.; Koba, S.; Kobayashi, Y.; Hirano, T.; et al. Counteractive effects of omentin-1 against atherogenesis dagger. *Cardiovasc. Res.* **2016**, *110*, 118–128. [[CrossRef](#)]
88. Gruzdeva, O.V.; Dyleva, Y.A.; Belik, E.V.; Sinitsky, M.Y.; Stasev, A.N.; Kokov, A.N.; Brel, N.K.; Krivkina, E.O.; Bychkova, E.E.; Tarasov, R.S.; et al. Relationship between Epicardial and Coronary Adipose Tissue and the Expression of Adiponectin, Leptin, and Interleukin 6 in Patients with Coronary Artery Disease. *J. Pers. Med.* **2022**, *12*, 129. [[CrossRef](#)]

89. Hasty, A.H.; Shimano, H.; Osuga, J.; Namatame, I.; Takahashi, A.; Yahagi, N.; Perrey, S.; Iizuka, Y.; Tamura, Y.; Amemiya-Kudo, M.; et al. Severe hypercholesterolemia, hypertriglyceridemia, and atherosclerosis in mice lacking both leptin and the low density lipoprotein receptor. *J. Biol. Chem.* **2001**, *276*, 37402–37408. [\[CrossRef\]](#)
90. Zhang, T.; Yang, P.; Li, T.; Gao, J.; Zhang, Y. Leptin Expression in Human Epicardial Adipose Tissue Is Associated with Local Coronary Atherosclerosis. *Med. Sci. Monit.* **2019**, *25*, 9913–9922. [\[CrossRef\]](#)
91. Dubey, L.; Zeng, H.S.; Wang, H.J.; Liu, R.Y. Potential role of adipocytokine leptin in acute coronary syndrome. *Asian Cardiovasc. Thorac. Ann.* **2008**, *16*, 124–128. [\[CrossRef\]](#)
92. Chen, H.; Liu, L.; Li, M.; Zhu, D.; Tian, G. Epicardial Adipose Tissue-Derived Leptin Promotes Myocardial Injury in Metabolic Syndrome Rats Through PKC/NADPH Oxidase/ROS Pathway. *J. Am. Heart Assoc.* **2023**, *12*, e029415. [\[CrossRef\]](#)
93. Zhao, S.; Kusminski, C.M.; Scherer, P.E. Adiponectin, Leptin and Cardiovascular Disorders. *Circ. Res.* **2021**, *128*, 136–149. [\[CrossRef\]](#)
94. Zhou, Y.; Wei, Y.; Wang, L.; Wang, X.; Du, X.; Sun, Z.; Dong, N.; Chen, X. Decreased adiponectin and increased inflammation expression in epicardial adipose tissue in coronary artery disease. *Cardiovasc. Diabetol.* **2011**, *10*, 2. [\[CrossRef\]](#)
95. Nomura, H.; Arashi, H.; Yamaguchi, J.; Ogawa, H.; Hagiwara, N. Relation of Adiponectin to Cardiovascular Events and Mortality in Patients with Acute Coronary Syndrome. *Am. J. Cardiol.* **2021**, *140*, 7–12. [\[CrossRef\]](#)
96. Frantz, S.; Hundertmark, M.J.; Schulz-Menger, J.; Bengel, F.M.; Bauersachs, J. Left ventricular remodelling post-myocardial infarction: Pathophysiology, imaging, and novel therapies. *Eur. Heart J.* **2022**, *43*, 2549–2561. [\[CrossRef\]](#) [\[PubMed\]](#)
97. Savarese, G.; Becher, P.M.; Lund, L.H.; Seferovic, P.; Rosano, G.M.C.; Coats, A.J.S. Global burden of heart failure: A comprehensive and updated review of epidemiology. *Cardiovasc. Res.* **2023**, *118*, 3272–3287. [\[CrossRef\]](#)
98. Wang, K.J.; Zhao, X.; Liu, Y.Z.; Zeng, Q.T.; Mao, X.B.; Li, S.N.; Zhang, M.; Jiang, C.; Zhou, Y.; Qian, C.; et al. Circulating MiR-19b-3p, MiR-134-5p and MiR-186-5p are Promising Novel Biomarkers for Early Diagnosis of Acute Myocardial Infarction. *Cell. Physiol. Biochem.* **2016**, *38*, 1015–1029. [\[CrossRef\]](#) [\[PubMed\]](#)
99. Yang, J.; Liu, S.; Wang, H.; Liu, Y.; Liu, Y. miR-134-5p inhibition reduces infarct-induced cardiomyocyte apoptosis via Creb1 upregulation. *J. Stroke Cerebrovasc. Dis.* **2020**, *29*, 104850. [\[CrossRef\]](#) [\[PubMed\]](#)
100. Lu, M.; Qin, X.; Yao, J.; Yang, Y.; Zhao, M.; Sun, L. MiR-134-5p targeting XIAP modulates oxidative stress and apoptosis in cardiomyocytes under hypoxia/reperfusion-induced injury. *IUBMB Life* **2020**, *72*, 2154–2166. [\[CrossRef\]](#)
101. Venteclef, N.; Guglielmi, V.; Balse, E.; Gaborit, B.; Cotillard, A.; Atassi, F.; Amour, J.; Leprince, P.; Dutour, A.; Clement, K.; et al. Human epicardial adipose tissue induces fibrosis of the atrial myocardium through the secretion of adipo-fibrokinases. *Eur. Heart J.* **2015**, *36*, 795–805. [\[CrossRef\]](#) [\[PubMed\]](#)
102. Yndestad, A.; Ueland, T.; Oie, E.; Florholmen, G.; Halvorsen, B.; Attramadal, H.; Simonsen, S.; Froland, S.S.; Gullestad, L.; Christensen, G.; et al. Elevated levels of activin A in heart failure: Potential role in myocardial remodeling. *Circulation* **2004**, *109*, 1379–1385. [\[CrossRef\]](#) [\[PubMed\]](#)
103. Greulich, S.; Maxhera, B.; Vandenplas, G.; de Wiza, D.H.; Smiris, K.; Mueller, H.; Heinrichs, J.; Blumensatt, M.; Cuvelier, C.; Akhyari, P.; et al. Secretory products from epicardial adipose tissue of patients with type 2 diabetes mellitus induce cardiomyocyte dysfunction. *Circulation* **2012**, *126*, 2324–2334. [\[CrossRef\]](#)
104. Park, J.J. Epidemiology, Pathophysiology, Diagnosis and Treatment of Heart Failure in Diabetes. *Diabetes Metab. J.* **2021**, *45*, 146–157. [\[CrossRef\]](#)
105. Nieminen, M.S.; Brutsaert, D.; Dickstein, K.; Drexler, H.; Follath, F.; Harjola, V.P.; Hochadel, M.; Komajda, M.; Lassus, J.; Lopez-Sendon, J.L.; et al. EuroHeart Failure Survey II (EHFS II): A survey on hospitalized acute heart failure patients: Description of population. *Eur. Heart J.* **2006**, *27*, 2725–2736. [\[CrossRef\]](#) [\[PubMed\]](#)
106. Parisi, V.; Cabaro, S.; D'Esposito, V.; Petraglia, L.; Conte, M.; Campana, P.; Gerundo, G.; Abitabile, M.; Tuccillo, A.; Accadia, M.; et al. Epicardial Adipose Tissue and IL-13 Response to Myocardial Injury Drives Left Ventricular Remodeling after ST Elevation Myocardial Infarction. *Front. Physiol.* **2020**, *11*, 575181. [\[CrossRef\]](#)
107. Wodsedalek, D.J.; Paddock, S.J.; Wan, T.C.; Auchampach, J.A.; Kenarsary, A.; Tsaih, S.W.; Flister, M.J.; O'Meara, C.C. IL-13 promotes in vivo neonatal cardiomyocyte cell cycle activity and heart regeneration. *Am. J. Physiol. Heart Circ. Physiol.* **2019**, *316*, H24–H34. [\[CrossRef\]](#) [\[PubMed\]](#)
108. D'Uva, G.; Aharonov, A.; Lauriola, M.; Kain, D.; Yahalom-Ronen, Y.; Carvalho, S.; Weisinger, K.; Bassat, E.; Rajchman, D.; Yifa, O.; et al. ERBB2 triggers mammalian heart regeneration by promoting cardiomyocyte dedifferentiation and proliferation. *Nat. Cell Biol.* **2015**, *17*, 627–638. [\[CrossRef\]](#)
109. Gan, L.; Liu, D.; Xie, D.; Bond Lau, W.; Liu, J.; Christopher, T.A.; Lopez, B.; Liu, L.; Hu, H.; Yao, P.; et al. Ischemic Heart-Derived Small Extracellular Vesicles Impair Adipocyte Function. *Circ. Res.* **2022**, *130*, 48–66. [\[CrossRef\]](#)
110. Jiang, D.S.; Zeng, H.L.; Li, R.; Huo, B.; Su, Y.S.; Fang, J.; Yang, Q.; Liu, L.G.; Hu, M.; Cheng, C.; et al. Aberrant Epicardial Adipose Tissue Extracellular Matrix Remodeling in Patients with Severe Ischemic Cardiomyopathy: Insight from Comparative Quantitative Proteomics. *Sci. Rep.* **2017**, *7*, 43787. [\[CrossRef\]](#)
111. von Gise, A.; Pu, W.T. Endocardial and epicardial epithelial to mesenchymal transitions in heart development and disease. *Circ. Res.* **2012**, *110*, 1628–1645. [\[CrossRef\]](#) [\[PubMed\]](#)
112. Zhou, B.; Honor, L.B.; He, H.; Ma, Q.; Oh, J.H.; Butterfield, C.; Lin, R.Z.; Melero-Martin, J.M.; Dolmatova, E.; Duffy, H.S.; et al. Adult mouse epicardium modulates myocardial injury by secreting paracrine factors. *J. Clin. Investig.* **2011**, *121*, 1894–1904. [\[CrossRef\]](#) [\[PubMed\]](#)

113. Zangi, L.; Oliveira, M.S.; Ye, L.Y.; Ma, Q.; Sultana, N.; Hadas, Y.; Chepurko, E.; Spater, D.; Zhou, B.; Chew, W.L.; et al. Insulin-Like Growth Factor 1 Receptor-Dependent Pathway Drives Epicardial Adipose Tissue Formation after Myocardial Injury. *Circulation* **2017**, *135*, 59–72. [[CrossRef](#)]
114. Liao, Y.; Li, H.; Pi, Y.; Li, Z.; Jin, S. Cardioprotective effect of IGF-1 against myocardial ischemia/reperfusion injury through activation of PI3K/Akt pathway in rats in vivo. *J. Int. Med. Res.* **2019**, *47*, 3886–3897. [[CrossRef](#)]
115. Dai, W.; Kloner, R.A. Cardioprotection of insulin-like growth factor-1 during reperfusion therapy: What is the underlying mechanism or mechanisms? *Circ. Cardiovasc. Interv.* **2011**, *4*, 311–313. [[CrossRef](#)] [[PubMed](#)]
116. Mollova, M.; Bersell, K.; Walsh, S.; Savla, J.; Das, L.T.; Park, S.Y.; Silberstein, L.E.; Dos Remedios, C.G.; Graham, D.; Colan, S.; et al. Cardiomyocyte proliferation contributes to heart growth in young humans. *Proc. Natl. Acad. Sci. USA* **2013**, *110*, 1446–1451. [[CrossRef](#)] [[PubMed](#)]
117. Fadini, G.P.; Mehta, A.; Dhindsa, D.S.; Bonora, B.M.; Sreejit, G.; Nagareddy, P.; Quyyumi, A.A. Circulating stem cells and cardiovascular outcomes: From basic science to the clinic. *Eur. Heart J.* **2020**, *41*, 4271–4282. [[CrossRef](#)]
118. Domaszko, O.; Skwarek, A.; Wojciechowska, M. In Search of the Holy Grail: Stem Cell Therapy as a Novel Treatment of Heart Failure with Preserved Ejection Fraction. *Int. J. Mol. Sci.* **2023**, *24*, 4903. [[CrossRef](#)]
119. Caspi, O.; Huber, I.; Kehat, I.; Habib, M.; Arbel, G.; Gepstein, A.; Yankelson, L.; Aronson, D.; Beyar, R.; Gepstein, L. Transplantation of human embryonic stem cell-derived cardiomyocytes improves myocardial performance in infarcted rat hearts. *J. Am. Coll. Cardiol.* **2007**, *50*, 1884–1893. [[CrossRef](#)]
120. Shi, Y.; Zhao, Y.; Li, Y.; Yi, J.; Ma, Y.; Chen, Y. High concentrations of H7 human embryonic stem cells at the point of care for acute myocardial infarction. *Ann. Transl. Med.* **2020**, *8*, 1510. [[CrossRef](#)]
121. King, N.M.; Perrin, J. Ethical issues in stem cell research and therapy. *Stem Cell Res. Ther.* **2014**, *5*, 85. [[CrossRef](#)] [[PubMed](#)]
122. Carbone, R.G.; Monselise, A.; Bottino, G.; Negrini, S.; Puppo, F. Stem cells therapy in acute myocardial infarction: A new era? *Clin. Exp. Med.* **2021**, *21*, 231–237. [[CrossRef](#)] [[PubMed](#)]
123. Planat-Benard, V.; Menard, C.; Andre, M.; Puceat, M.; Perez, A.; Garcia-Verdugo, J.M.; Penicaud, L.; Casteilla, L. Spontaneous cardiomyocyte differentiation from adipose tissue stroma cells. *Circ. Res.* **2004**, *94*, 223–229. [[CrossRef](#)] [[PubMed](#)]
124. Shoji, T.; Li, M.; Mifune, Y.; Matsumoto, T.; Kawamoto, A.; Kwon, S.M.; Kuroda, T.; Kuroda, R.; Kurosaka, M.; Asahara, T. Local transplantation of human multipotent adipose-derived stem cells accelerates fracture healing via enhanced osteogenesis and angiogenesis. *Lab. Invest.* **2010**, *90*, 637–649. [[CrossRef](#)]
125. Harris, L.J.; Abdollahi, H.; Zhang, P.; McIlhenny, S.; Tulenko, T.N.; DiMuzio, P.J. Differentiation of adult stem cells into smooth muscle for vascular tissue engineering. *J. Surg. Res.* **2011**, *168*, 306–314. [[CrossRef](#)]
126. Bayes-Genis, A.; Soler-Botija, C.; Farre, J.; Sepulveda, P.; Raya, A.; Roura, S.; Prat-Vidal, C.; Galvez-Monton, C.; Montero, J.A.; Buscher, D.; et al. Human progenitor cells derived from cardiac adipose tissue ameliorate myocardial infarction in rodents. *J. Mol. Cell. Cardiol.* **2010**, *49*, 771–780. [[CrossRef](#)]
127. Ozkaynak, B.; Sahin, I.; Ozenc, E.; Subasi, C.; Oran, D.S.; Totoz, T.; Tetikkurt, U.S.; Mert, B.; Polat, A.; Okuyan, E.; et al. Mesenchymal stem cells derived from epicardial adipose tissue reverse cardiac remodeling in a rabbit model of myocardial infarction. *Eur. Rev. Med. Pharmacol. Sci.* **2021**, *25*, 4372–4384. [[CrossRef](#)]
128. Nagata, H.; Li, M.; Kohbayashi, E.; Hoshiga, M.; Hanafusa, T.; Asahi, M. Cardiac Adipose-Derived Stem Cells Exhibit High Differentiation Potential to Cardiovascular Cells in C57BL/6 Mice. *Stem Cells Transl. Med.* **2016**, *5*, 141–151. [[CrossRef](#)]
129. Wystrychowski, W.; Patlolla, B.; Zhuge, Y.; Neofytou, E.; Robbins, R.C.; Beygui, R.E. Multipotency and cardiomyogenic potential of human adipose-derived stem cells from epicardium, pericardium, and omentum. *Stem Cell Res. Ther.* **2016**, *7*, 84. [[CrossRef](#)]
130. Kuo, C.T.; Morrissey, E.E.; Anandappa, R.; Sigrist, K.; Lu, M.M.; Parmacek, M.S.; Soudais, C.; Leiden, J.M. GATA4 transcription factor is required for ventral morphogenesis and heart tube formation. *Genes Dev.* **1997**, *11*, 1048–1060. [[CrossRef](#)] [[PubMed](#)]
131. Zeisberg, E.M.; Ma, Q.; Juraszek, A.L.; Moses, K.; Schwartz, R.J.; Izumo, S.; Pu, W.T. Morphogenesis of the right ventricle requires myocardial expression of Gata4. *J. Clin. Invest.* **2005**, *115*, 1522–1531. [[CrossRef](#)]
132. Thankam, F.G.; Agrawal, D.K. Single Cell Genomics Identifies Unique Cardioprotective Phenotype of Stem Cells derived from Epicardial Adipose Tissue under Ischemia. *Stem Cell Rev. Rep.* **2022**, *18*, 294–335. [[CrossRef](#)]
133. Thankam, F.G.; Huynh, J.; Fang, W.; Chen, Y.; Agrawal, D.K. Exosomal-ribosomal proteins-driven heterogeneity of epicardial adipose tissue derived stem cells under ischemia for cardiac regeneration. *J. Tissue Eng. Regen. Med.* **2022**, *16*, 396–408. [[CrossRef](#)] [[PubMed](#)]
134. Thankam, F.G.; Sedighim, S.; Kuan, R.; Agrawal, D.K. Ischemia challenged epicardial adipose tissue stem cells-derived extracellular vesicles alter the gene expression of cardiac fibroblasts to cardiomyocyte like phenotype. *Transl. Res.* **2023**, *254*, 54–67. [[CrossRef](#)]
135. Xu, Y.; Cheng, X.; Hong, K.; Huang, C.; Wan, L. How to interpret epicardial adipose tissue as a cause of coronary artery disease: A meta-analysis. *Coron. Artery Dis.* **2012**, *23*, 227–233. [[CrossRef](#)]
136. Hendricks, S.; Dykun, I.; Balcer, B.; Totzeck, M.; Rassaf, T.; Mahabadi, A.A. Epicardial adipose tissue is a robust measure of increased risk of myocardial infarction—A meta-analysis on over 6600 patients and rationale for the EPIC-ACS study. *Medicine* **2021**, *100*, e28060. [[CrossRef](#)]
137. Eren, H.; Omar, M.B.; Kaya, U.; Ocal, L.; Yilmaz, M.F.; Akkan, S. Epicardial adipose tissue may predict new-onset atrial fibrillation in patients with ST-segment elevation myocardial infarction. *J. Cardiovasc. Med.* **2021**, *22*, 917–923. [[CrossRef](#)] [[PubMed](#)]



138. Mahabadi, A.A.; Massaro, J.M.; Rosito, G.A.; Levy, D.; Murabito, J.M.; Wolf, P.A.; O'Donnell, C.J.; Fox, C.S.; Hoffmann, U. Association of pericardial fat, intrathoracic fat, and visceral abdominal fat with cardiovascular disease burden: The Framingham Heart Study. *Eur. Heart J.* **2009**, *30*, 850–856. [[CrossRef](#)]
139. Goeller, M.; Achenbach, S.; Marwan, M.; Doris, M.K.; Cadet, S.; Commandeur, F.; Chen, X.; Slomka, P.J.; Gransar, H.; Cao, J.J.; et al. Epicardial adipose tissue density and volume are related to subclinical atherosclerosis, inflammation and major adverse cardiac events in asymptomatic subjects. *J. Cardiovasc. Comput. Tomogr.* **2018**, *12*, 67–73. [[CrossRef](#)]
140. Pierdomenico, S.D.; Pierdomenico, A.M.; Cucurullo, F.; Iacobellis, G. Meta-analysis of the relation of echocardiographic epicardial adipose tissue thickness and the metabolic syndrome. *Am. J. Cardiol.* **2013**, *111*, 73–78. [[CrossRef](#)] [[PubMed](#)]
141. Iacobellis, G.; Willens, H.J. Echocardiographic epicardial fat: A review of research and clinical applications. *J. Am. Soc. Echocardiogr.* **2009**, *22*, 1311–1319. [[CrossRef](#)]
142. Iacobellis, G.; Assael, F.; Ribaldo, M.C.; Zappaterreno, A.; Alessi, G.; Di Mario, U.; Leonetti, F. Epicardial fat from echocardiography: A new method for visceral adipose tissue prediction. *Obes. Res.* **2003**, *11*, 304–310. [[CrossRef](#)]
143. Saura, D.; Oliva, M.J.; Rodriguez, D.; Pascual-Figal, D.A.; Hurtado, J.A.; Pinar, E.; de la Morena, G.; Valdes, M. Reproducibility of echocardiographic measurements of epicardial fat thickness. *Int. J. Cardiol.* **2010**, *141*, 311–313. [[CrossRef](#)]
144. Pugliese, L.; Ricci, F.; Sica, G.; Scaglione, M.; Masala, S. Non-Contrast and Contrast-Enhanced Cardiac Computed Tomography Imaging in the Diagnostic and Prognostic Evaluation of Coronary Artery Disease. *Diagnostics* **2023**, *13*, 2074. [[CrossRef](#)]
145. Yuvaraj, J.; Cheng, K.; Lin, A.; Psaltis, P.J.; Nicholls, S.J.; Wong, D.T.L. The Emerging Role of CT-Based Imaging in Adipose Tissue and Coronary Inflammation. *Cells* **2021**, *10*, 1196. [[CrossRef](#)] [[PubMed](#)]
146. Leo, L.A.; Paiocchi, V.L.; Schlossbauer, S.A.; Ho, S.Y.; Faletra, F.F. The Intrusive Nature of Epicardial Adipose Tissue as Revealed by Cardiac Magnetic Resonance. *J. Cardiovasc. Echogr.* **2019**, *29*, 45–51. [[CrossRef](#)] [[PubMed](#)]
147. Mazurek, T.; Kochman, J.; Kobylecka, M.; Wilimski, R.; Filipiak, K.J.; Krolicki, L.; Opolski, G. Inflammatory activity of pericoronary adipose tissue may affect plaque composition in patients with acute coronary syndrome without persistent ST-segment elevation: Preliminary results. *Kardiol. Pol.* **2014**, *72*, 410–416. [[CrossRef](#)] [[PubMed](#)]
148. Ahn, S.G.; Lim, H.S.; Joe, D.Y.; Kang, S.J.; Choi, B.J.; Choi, S.Y.; Yoon, M.H.; Hwang, G.S.; Tahk, S.J.; Shin, J.H. Relationship of epicardial adipose tissue by echocardiography to coronary artery disease. *Heart* **2008**, *94*, e7. [[CrossRef](#)]
149. Wang, Q.; Chi, J.; Wang, C.; Yang, Y.; Tian, R.; Chen, X. Epicardial Adipose Tissue in Patients with Coronary Artery Disease: A Meta-Analysis. *J. Cardiovasc. Dev. Dis.* **2022**, *9*, 253. [[CrossRef](#)]
150. Eroglu, S.; Sade, L.E.; Yildirim, A.; Bal, U.; Ozbicer, S.; Ozgul, A.S.; Bozbas, H.; Aydinalp, A.; Muderrisoglu, H. Epicardial adipose tissue thickness by echocardiography is a marker for the presence and severity of coronary artery disease. *Nutr. Metab. Cardiovasc. Dis.* **2009**, *19*, 211–217. [[CrossRef](#)]
151. Verma, B.; Katyal, D.; Patel, A.; Singh, V.R.; Kumar, S. Relation of systolic and diastolic epicardial adipose tissue thickness with presence and severity of coronary artery disease (The EAT CAD study). *J. Fam. Med. Prim. Care* **2019**, *8*, 1470–1475. [[CrossRef](#)]
152. Jeong, J.W.; Jeong, M.H.; Yun, K.H.; Oh, S.K.; Park, E.M.; Kim, Y.K.; Rhee, S.J.; Lee, E.M.; Lee, J.; Yoo, N.J.; et al. Echocardiographic epicardial fat thickness and coronary artery disease. *Circ. J.* **2007**, *71*, 536–539. [[CrossRef](#)] [[PubMed](#)]
153. Sinha, S.K.; Thakur, R.; Jha, M.J.; Goel, A.; Kumar, V.; Kumar, A.; Mishra, V.; Varma, C.M.; Krishna, V.; Singh, A.K.; et al. Epicardial Adipose Tissue Thickness and Its Association with the Presence and Severity of Coronary Artery Disease in Clinical Setting: A Cross-Sectional Observational Study. *J. Clin. Med. Res.* **2016**, *8*, 410–419. [[CrossRef](#)] [[PubMed](#)]
154. Jehn, S.; Roggel, A.; Dykun, I.; Balcer, B.; Al-Rashid, F.; Totzeck, M.; Risse, J.; Kill, C.; Rassaf, T.; Mahabadi, A.A. Epicardial adipose tissue and obstructive coronary artery disease in acute chest pain: The EPIC-ACS study. *Eur. Heart J. Open* **2023**, *3*, oead041. [[CrossRef](#)] [[PubMed](#)]
155. Kamal, D.; Abd ElMoteleb, A.M.; Samir, R.; Saeed, M. Epicardial fat thickness can predict severity and multivessel distribution in Egyptian patients with atherosclerotic coronary artery stenosis. *Egypt. Heart J.* **2018**, *70*, 323–327. [[CrossRef](#)] [[PubMed](#)]
156. Akcay, M.; Sahin, M. Association of Epicardial Adipose Tissue Thickness with Extent and Complexity of Coronary Artery Disease in Patients with Acute Coronary Syndrome. *Acta Cardiol. Sin.* **2019**, *35*, 459–467. [[CrossRef](#)] [[PubMed](#)]
157. Wang, T.; Liu, Q.; Liu, C.; Sun, L.; Li, D.; Liu, A.; Jia, R. Correlation of echocardiographic epicardial fat thickness with severity of coronary artery disease in patients with acute myocardial infarction. *Echocardiography* **2014**, *31*, 1177–1181. [[CrossRef](#)]
158. Sen, F.; Yilmaz, S.; Balci, K.G.; Gul, M.; Balci, M.M.; Akboga, M.K.; Topaloglu, S.; Temizhan, A.; Aras, D.; Aydogdu, S. The Relationship between Epicardial Adipose Tissue Thickness and Infarct-Related Artery Patency in Patients with ST-Segment Elevation Myocardial Infarction. *Angiology* **2016**, *67*, 281–286. [[CrossRef](#)]
159. Park, J.S.; Choi, S.Y.; Zheng, M.; Yang, H.M.; Lim, H.S.; Choi, B.J.; Yoon, M.H.; Hwang, G.S.; Tahk, S.J.; Shin, J.H. Epicardial adipose tissue thickness is a predictor for plaque vulnerability in patients with significant coronary artery disease. *Atherosclerosis* **2013**, *226*, 134–139. [[CrossRef](#)]
160. Park, S.S.; Jung, J.; Mintz, G.S.; Jin, U.; Park, J.S.; Park, B.; Shin, H.B.; Seo, K.W.; Yang, H.M.; Lim, H.S.; et al. Epicardial Adipose Tissue Thickness Is Related to Plaque Composition in Coronary Artery Disease. *Diagnostics* **2022**, *12*, 2836. [[CrossRef](#)]
161. Kim, H.M.; Kim, K.J.; Lee, H.J.; Yu, H.T.; Moon, J.H.; Kang, E.S.; Cha, B.S.; Lee, H.C.; Lee, B.W.; Kim, Y.J. Epicardial adipose tissue thickness is an indicator for coronary artery stenosis in asymptomatic type 2 diabetic patients: Its assessment by cardiac magnetic resonance. *Cardiovasc. Diabetol.* **2012**, *11*, 83. [[CrossRef](#)]
162. Alam, M.S.; Green, R.; de Kemp, R.; Beanlands, R.S.; Chow, B.J. Epicardial adipose tissue thickness as a predictor of impaired microvascular function in patients with non-obstructive coronary artery disease. *J. Nucl. Cardiol.* **2013**, *20*, 804–812. [[CrossRef](#)]

163. Picard, F.A.; Gueret, P.; Laissy, J.P.; Champagne, S.; Leclercq, F.; Carrie, D.; Juliard, J.M.; Henry, P.; Niarra, R.; Chatellier, G.; et al. Epicardial adipose tissue thickness correlates with the presence and severity of angiographic coronary artery disease in stable patients with chest pain. *PLoS ONE* **2014**, *9*, e110005. [[CrossRef](#)]
164. Nelson, M.R.; Mookadam, F.; Thota, V.; Emani, U.; Al Harthi, M.; Lester, S.J.; Cha, S.; Stepanek, J.; Hurst, R.T. Epicardial fat: An additional measurement for subclinical atherosclerosis and cardiovascular risk stratification? *J. Am. Soc. Echocardiogr.* **2011**, *24*, 339–345. [[CrossRef](#)]
165. Tanindi, A.; Kocaman, S.A.; Erkan, A.F.; Ugurlu, M.; Alhan, A.; Tore, H.F. Epicardial adipose tissue thickness is associated with myocardial infarction and impaired coronary perfusion. *Anatol J Cardiol* **2015**, *15*, 224–231. [[CrossRef](#)]
166. Tanindi, A.; Erkan, A.F.; Ekici, B. Epicardial adipose tissue thickness can be used to predict major adverse cardiac events. *Coron. Artery Dis.* **2015**, *26*, 686–691. [[CrossRef](#)]
167. Ozcan, F.; Turak, O.; Canpolat, U.; Kanat, S.; Kadife, I.; Avci, S.; Isleyen, A.; Cebeci, M.; Tok, D.; Basar, F.N.; et al. Association of epicardial fat thickness with TIMI risk score in NSTEMI/USAP patients. *Herz* **2014**, *39*, 755–760. [[CrossRef](#)] [[PubMed](#)]
168. Park, J.S.; Choi, B.J.; Choi, S.Y.; Yoon, M.H.; Hwang, G.S.; Tahk, S.J.; Shin, J.H. Echocardiographically measured epicardial fat predicts restenosis after coronary stenting. *Scand Cardiovasc. J.* **2013**, *47*, 297–302. [[CrossRef](#)] [[PubMed](#)]
169. Chu, C.Y.; Lee, W.H.; Hsu, P.C.; Lee, M.K.; Lee, H.H.; Chiu, C.A.; Lin, T.H.; Lee, C.S.; Yen, H.W.; Voon, W.C.; et al. Association of Increased Epicardial Adipose Tissue Thickness with Adverse Cardiovascular Outcomes in Patients with Atrial Fibrillation. *Medicine* **2016**, *95*, e2874. [[CrossRef](#)] [[PubMed](#)]
170. Tscharre, M.; Hauser, C.; Rohla, M.; Freynhofer, M.K.; Wojta, J.; Huber, K.; Weiss, T.W. Epicardial adipose tissue and cardiovascular outcome in patients with acute coronary syndrome undergoing percutaneous coronary intervention. *Eur. Heart J. Acute Cardiovasc. Care* **2017**, *6*, 750–752. [[CrossRef](#)] [[PubMed](#)]
171. Islas, F.; Gutierrez, E.; Cachofeiro, V.; Martinez-Martinez, E.; Marin, G.; Olmos, C.; Carrion, I.; Gil, S.; Mahia, P.; Cobos, M.A.; et al. Importance of cardiac imaging assessment of epicardial adipose tissue after a first episode of myocardial infarction. *Front. Cardiovasc. Med.* **2022**, *9*, 995367. [[CrossRef](#)]
172. Park, J.S.; Lee, Y.H.; Seo, K.W.; Choi, B.J.; Choi, S.Y.; Yoon, M.H.; Hwang, G.S.; Tahk, S.J.; Shin, J.H. Echocardiographic epicardial fat thickness is a predictor for target vessel revascularization in patients with ST-elevation myocardial infarction. *Lipids Health Dis.* **2016**, *15*, 194. [[CrossRef](#)]
173. Mehta, R.; Bello-Chavolla, O.Y.; Mancillas-Adame, L.; Rodriguez-Flores, M.; Pedraza, N.R.; Encinas, B.R.; Carrion, C.I.P.; Avila, M.I.J.; Valladares-Garcia, J.C.; Vanegas-Cedillo, P.E.; et al. Epicardial adipose tissue thickness is associated with increased COVID-19 severity and mortality. *Int. J. Obes.* **2022**, *46*, 866–873. [[CrossRef](#)]
174. Albuquerque, F.N.; Somers, V.K.; Blume, G.; Miranda, W.; Korenfeld, Y.; Calvin, A.D.; Qin, R.; Lopez-Jimenez, F. Usefulness of epicardial adipose tissue as predictor of cardiovascular events in patients with coronary artery disease. *Am. J. Cardiol.* **2012**, *110*, 1100–1105. [[CrossRef](#)] [[PubMed](#)]
175. Zencirci, A.E.; Zencirci, E.; Degirmencioglu, A.; Erdem, A.; Karakus, G.; Ozden, K.; Karadeniz, F.; Buturak, A.; Belen, E.; Tipi, F.; et al. Predictive Value of the No-Reflow Phenomenon and Epicardial Adipose Tissue for Clinical Outcomes after Primary Percutaneous Coronary Intervention. *Hellenic. J. Cardiol.* **2015**, *56*, 311–319.
176. Chen, Y.C.; Lee, W.H.; Lee, M.K.; Hsu, P.C.; Tsai, W.C.; Chu, C.Y.; Lee, C.S.; Yen, H.W.; Lin, T.H.; Voon, W.C.; et al. Epicardial adipose tissue thickness is not associated with adverse cardiovascular events in patients undergoing haemodialysis. *Sci. Rep.* **2020**, *10*, 6281. [[CrossRef](#)]
177. Altun, B.; Colkesen, Y.; Gazi, E.; Tasolar, H.; Temiz, A.; Simsek, H.Y.; Barutcu, A.; Gungor, O.; Kirilmaz, B.; Ceyhan, K. Could epicardial adipose tissue thickness by echocardiography be correlated with acute coronary syndrome risk scores. *Echocardiography* **2013**, *30*, 1130–1134. [[CrossRef](#)]
178. Eren, H.; Omar, M.B.; Ocal, L. Epicardial fat tissue may predict new-onset atrial fibrillation in patients with non-ST-segment elevation myocardial infarction. *Turk Kardiyol. Dern. Ars.* **2021**, *49*, 430–438. [[CrossRef](#)] [[PubMed](#)]
179. Zencirci, E.; Zencirci, A.E.; Degirmencioglu, A.; Karakus, G.; Ugurlucan, M.; Ozden, K.; Erdem, A.; Gullu, A.U.; Ekmekci, A.; Velibey, Y.; et al. The relationship between epicardial adipose tissue and ST-segment resolution in patients with acute ST-segment elevation myocardial infarction undergoing primary percutaneous coronary intervention. *Heart Vessel.* **2015**, *30*, 147–153. [[CrossRef](#)] [[PubMed](#)]
180. Sen, F.; Yilmaz, S.; Sen, O.; Balc, K.G.; Duman, I.; Topaloglu, S.; Temizhan, A.; Aras, D. Epicardial adipose tissue is related to coronary collateral vessel formation in patients with acute coronary syndrome. *Scand Cardiovasc. J.* **2015**, *49*, 130–135. [[CrossRef](#)]
181. Mohamed, A. Predicting mortality and no-reflow in STEMI patients using epicardial adipose tissue. *Clin. Cardiol.* **2021**, *44*, 1371–1376. [[CrossRef](#)] [[PubMed](#)]
182. Comert, N.; Yucel, O.; Ege, M.R.; Yaylak, B.; Erdogan, G.; Yilmaz, M.B. Echocardiographic epicardial adipose tissue predicts subclinical atherosclerosis: Epicardial adipose tissue and atherosclerosis. *Angiology* **2012**, *63*, 586–590. [[CrossRef](#)] [[PubMed](#)]
183. Harada, K.; Amano, T.; Uetani, T.; Tokuda, Y.; Kitagawa, K.; Shimbo, Y.; Kunimura, A.; Kumagai, S.; Yoshida, T.; Kato, B.; et al. Cardiac 64-multislice computed tomography reveals increased epicardial fat volume in patients with acute coronary syndrome. *Am. J. Cardiol.* **2011**, *108*, 1119–1123. [[CrossRef](#)]
184. Ito, T.; Nasu, K.; Terashima, M.; Ehara, M.; Kinoshita, Y.; Ito, T.; Kimura, M.; Tanaka, N.; Habara, M.; Tsuchikane, E.; et al. The impact of epicardial fat volume on coronary plaque vulnerability: Insight from optical coherence tomography analysis. *Eur. Heart J. Cardiovasc. Imaging* **2012**, *13*, 408–415. [[CrossRef](#)]



185. Schlett, C.L.; Ferencik, M.; Kriegel, M.F.; Bamberg, F.; Ghoshhajra, B.B.; Joshi, S.B.; Nagurney, J.T.; Fox, C.S.; Truong, Q.A.; Hoffmann, U. Association of pericardial fat and coronary high-risk lesions as determined by cardiac CT. *Atherosclerosis* **2012**, *222*, 129–134. [[CrossRef](#)]
186. Lu, M.T.; Park, J.; Ghemigian, K.; Mayrhofer, T.; Puchner, S.B.; Liu, T.; Fleg, J.L.; Udelson, J.E.; Truong, Q.A.; Ferencik, M.; et al. Epicardial and paracardial adipose tissue volume and attenuation—Association with high-risk coronary plaque on computed tomographic angiography in the ROMICAT II trial. *Atherosclerosis* **2016**, *251*, 47–54. [[CrossRef](#)]
187. Sarin, S.; Wenger, C.; Marwaha, A.; Qureshi, A.; Go, B.D.; Woomert, C.A.; Clark, K.; Nassef, L.A.; Shirani, J. Clinical significance of epicardial fat measured using cardiac multislice computed tomography. *Am. J. Cardiol.* **2008**, *102*, 767–771. [[CrossRef](#)] [[PubMed](#)]
188. Nakanishi, R.; Rajani, R.; Cheng, V.Y.; Gransar, H.; Nakazato, R.; Shmilovich, H.; Otaki, Y.; Hayes, S.W.; Thomson, L.E.; Friedman, J.D.; et al. Increase in epicardial fat volume is associated with greater coronary artery calcification progression in subjects at intermediate risk by coronary calcium score: A serial study using non-contrast cardiac CT. *Atherosclerosis* **2011**, *218*, 363–368. [[CrossRef](#)]
189. Bettencourt, N.; Toschke, A.M.; Leite, D.; Rocha, J.; Carvalho, M.; Sampaio, F.; Xara, S.; Leite-Moreira, A.; Nagel, E.; Gama, V. Epicardial adipose tissue is an independent predictor of coronary atherosclerotic burden. *Int. J. Cardiol.* **2012**, *158*, 26–32. [[CrossRef](#)]
190. Yu, W.; Chen, Y.; Zhang, F.; Liu, B.; Wang, J.; Shao, X.; Yang, X.; Shi, Y.; Wang, Y. Association of epicardial adipose tissue volume with increased risk of hemodynamically significant coronary artery disease. *Quant. Imaging Med. Surg.* **2023**, *13*, 2582–2593. [[CrossRef](#)]
191. Nakazato, R.; Dey, D.; Cheng, V.Y.; Gransar, H.; Slomka, P.J.; Hayes, S.W.; Thomson, L.E.; Friedman, J.D.; Min, J.K.; Berman, D.S. Epicardial fat volume and concurrent presence of both myocardial ischemia and obstructive coronary artery disease. *Atherosclerosis* **2012**, *221*, 422–426. [[CrossRef](#)]
192. den Dekker, M.A.; Takashima, R.; van den Heuvel, E.R.; van den Dungen, J.J.; Tio, R.A.; Oudkerk, M.; Vliedgenhart, R. Relationship between epicardial adipose tissue and subclinical coronary artery disease in patients with extra-cardiac arterial disease. *Obesity* **2014**, *22*, 72–78. [[CrossRef](#)]
193. Yerramasu, A.; Dey, D.; Venuraju, S.; Anand, D.V.; Atwal, S.; Corder, R.; Berman, D.S.; Lahiri, A. Increased volume of epicardial fat is an independent risk factor for accelerated progression of sub-clinical coronary atherosclerosis. *Atherosclerosis* **2012**, *220*, 223–230. [[CrossRef](#)]
194. Orlando, G.; Guaraldi, G.; Zona, S.; Carli, F.; Bagni, P.; Menozzi, M.; Cocchi, S.; Scaglioni, R.; Ligabue, G.; Raggi, P. Ectopic fat is linked to prior cardiovascular events in men with HIV. *J. Acquir. Immune Defic. Syndr.* **2012**, *59*, 494–497. [[CrossRef](#)] [[PubMed](#)]
195. Lin, A.; Wong, N.D.; Razipour, A.; McElhinney, P.A.; Commandeur, F.; Cadet, S.J.; Gransar, H.; Chen, X.; Cantu, S.; Miller, R.J.H.; et al. Metabolic syndrome, fatty liver, and artificial intelligence-based epicardial adipose tissue measures predict long-term risk of cardiac events: A prospective study. *Cardiovasc. Diabetol.* **2021**, *20*, 27. [[CrossRef](#)] [[PubMed](#)]
196. Lin, A.; Nerlekar, N.; Yuvaraj, J.; Fernandes, K.; Jiang, C.; Nicholls, S.J.; Dey, D.; Wong, D.T.L. Pericoronary adipose tissue computed tomography attenuation distinguishes different stages of coronary artery disease: A cross-sectional study. *Eur. Heart J. Cardiovasc. Imaging* **2021**, *22*, 298–306. [[CrossRef](#)]
197. Romijn, M.A.; Danad, I.; Bakkum, M.J.; Stuijzand, W.J.; Tulevski, I.I.; Somsen, G.A.; Lammertsma, A.A.; van Kuijk, C.; van de Ven, P.M.; Min, J.K.; et al. Incremental diagnostic value of epicardial adipose tissue for the detection of functionally relevant coronary artery disease. *Atherosclerosis* **2015**, *242*, 161–166. [[CrossRef](#)] [[PubMed](#)]
198. Milanese, G.; Silva, M.; Ledda, R.E.; Goldoni, M.; Nayak, S.; Bruno, L.; Rossi, E.; Maffei, E.; Cademartiri, F.; Sverzellati, N. Validity of epicardial fat volume as biomarker of coronary artery disease in symptomatic individuals: Results from the ALTER-BIO registry. *Int. J. Cardiol.* **2020**, *314*, 20–24. [[CrossRef](#)]
199. Mahabadi, A.A.; Berg, M.H.; Lehmann, N.; Kalsch, H.; Bauer, M.; Kara, K.; Dragano, N.; Moebus, S.; Jockel, K.H.; Erbel, R.; 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. [[CrossRef](#)]
200. Hajsadeghi, F.; Nabavi, V.; Bhandari, A.; Choi, A.; Vincent, H.; Flores, F.; Budoff, M.; Ahmadi, N. Increased epicardial adipose tissue is associated with coronary artery disease and major adverse cardiovascular events. *Atherosclerosis* **2014**, *237*, 486–489. [[CrossRef](#)]
201. Kunita, E.; Yamamoto, H.; Kitagawa, T.; Ohashi, N.; Oka, T.; Utsunomiya, H.; Urabe, Y.; Tsushima, H.; Awai, K.; Budoff, M.J.; et al. Prognostic value of coronary artery calcium and epicardial adipose tissue assessed by non-contrast cardiac computed tomography. *Atherosclerosis* **2014**, *233*, 447–453. [[CrossRef](#)] [[PubMed](#)]
202. Mahabadi, A.A.; Balcer, B.; Dykun, I.; Forsting, M.; Schlosser, T.; Heusch, G.; Rassaf, T. Cardiac computed tomography-derived epicardial fat volume and attenuation independently distinguish patients with and without myocardial infarction. *PLoS ONE* **2017**, *12*, e0183514. [[CrossRef](#)] [[PubMed](#)]
203. Massalha, S.; Walpot, J.; Dey, D.; Guler, E.C.; Clarkin, O.; Godkin, L.; Ratnayake, I.; Jayasinghe, P.; Hossain, A.; Crean, A.; et al. Epicardial Adipose Tissue: An Independent Predictor of Post-Operative Adverse Cardiovascular Events (CTA VISION Substudy). *JACC Cardiovasc. Imaging* **2020**, *13*, 882–884. [[CrossRef](#)] [[PubMed](#)]
204. Uygur, B.; Celik, O.; Demir, A.R.; Karakayali, M.; Arslan, C.; Otcu Temur, H.; Alis, D.; Yildirim, C.; Corekcioglu, B.; Erturk, M. Epicardial adipose tissue volume predicts long term major adverse cardiovascular events in patients with Type 2 diabetes. *Turk Kardiyol. Dern. Ars.* **2021**, *49*, 127–134. [[CrossRef](#)] [[PubMed](#)]

205. Raggi, P.; Zona, S.; Scaglioni, R.; Stentarelli, C.; Ligabue, G.; Besutti, G.; Menozzi, M.; Santoro, A.; Malagoli, A.; Bellasi, A.; et al. Epicardial adipose tissue and coronary artery calcium predict incident myocardial infarction and death in HIV-infected patients. *J. Cardiovasc. Comput. Tomogr.* **2015**, *9*, 553–558. [[CrossRef](#)]
206. Cosson, E.; Nguyen, M.T.; Rezgani, I.; Berkane, N.; Pinto, S.; Bihan, H.; Tatulashvili, S.; Taher, M.; Sal, M.; Soussan, M.; et al. Epicardial adipose tissue volume and myocardial ischemia in asymptomatic people living with diabetes: A cross-sectional study. *Cardiovasc. Diabetol.* **2021**, *20*, 224. [[CrossRef](#)]
207. Janik, M.; Hartlage, G.; Alexopoulos, N.; Mirzoyev, Z.; McLean, D.S.; Arepalli, C.D.; Chen, Z.; Stillman, A.E.; Raggi, P. Epicardial adipose tissue volume and coronary artery calcium to predict myocardial ischemia on positron emission tomography-computed tomography studies. *J. Nucl. Cardiol.* **2010**, *17*, 841–847. [[CrossRef](#)] [[PubMed](#)]
208. Hell, M.M.; Ding, X.; Rubeaux, M.; Slomka, P.; Gransar, H.; Terzopoulos, D.; Hayes, S.; Marwan, M.; Achenbach, S.; Berman, D.S.; et al. Epicardial adipose tissue volume but not density is an independent predictor for myocardial ischemia. *J. Cardiovasc. Comput. Tomogr.* **2016**, *10*, 141–149. [[CrossRef](#)]
209. Tong, J.; Bei, G.G.; Zhang, L.B.; Sun, Y.; Qi, M.; Yang, B.Q. Relationship between quantitative epicardial adipose tissue based on coronary computed tomography angiography and coronary slow flow. *BMC Cardiovasc. Disord.* **2023**, *23*, 500. [[CrossRef](#)]
210. Shan, D.; Wang, X.; Dou, G.; Zhang, W.; Jing, J.; He, B.; Li, Y.; Chen, Y.; Yang, J. Vascular-specific epicardial adipose tissue in predicting functional myocardial ischemia for patients with stable chest pain. *J. Thromb. Thrombolysis* **2021**, *51*, 915–923. [[CrossRef](#)]
211. Muthalaly, R.G.; Nerlekar, N.; Wong, D.T.; Cameron, J.D.; Seneviratne, S.K.; Ko, B.S. Epicardial adipose tissue and myocardial ischemia assessed by computed tomography perfusion imaging and invasive fractional flow reserve. *J. Cardiovasc. Comput. Tomogr.* **2017**, *11*, 46–53. [[CrossRef](#)] [[PubMed](#)]
212. Amisha; Malik, P.; Pathania, M.; Rathaur, V.K. Overview of artificial intelligence in medicine. *J. Fam. Med. Prim. Care* **2019**, *8*, 2328–2331. [[CrossRef](#)] [[PubMed](#)]
213. Koulaouzidis, G.; Jadczyk, T.; Iakovidis, D.K.; Koulaouzidis, A.; Bisnaire, M.; Charisopoulou, D. Artificial Intelligence in Cardiology-A Narrative Review of Current Status. *J. Clin. Med.* **2022**, *11*, 3910. [[CrossRef](#)] [[PubMed](#)]
214. Commandeur, F.; Slomka, P.J.; Goeller, M.; Chen, X.; Cadet, S.; Razipour, A.; McElhinney, P.; Gransar, H.; Cantu, S.; Miller, R.J.H.; et al. Machine learning to predict the long-term risk of myocardial infarction and cardiac death based on clinical risk, coronary calcium, and epicardial adipose tissue: A prospective study. *Cardiovasc. Res.* **2020**, *116*, 2216–2225. [[CrossRef](#)] [[PubMed](#)]
215. Tamarappoo, B.K.; Lin, A.; Commandeur, F.; McElhinney, P.A.; Cadet, S.; Goeller, M.; Razipour, A.; Chen, X.; Gransar, H.; Cantu, S.; et al. Machine learning integration of circulating and imaging biomarkers for explainable patient-specific prediction of cardiac events: A prospective study. *Atherosclerosis* **2021**, *318*, 76–82. [[CrossRef](#)] [[PubMed](#)]
216. Fisser, C.; Colling, S.; Debl, K.; Hetzenecker, A.; Sterz, U.; Hamer, O.W.; Fellner, C.; Maier, L.S.; Buchner, S.; Arzt, M. The impact of epicardial adipose tissue in patients with acute myocardial infarction. *Clin. Res. Cardiol.* **2021**, *110*, 1637–1646. [[CrossRef](#)]
217. Biere, L.; Behaghel, V.; Mateus, V.; Assuncao, A., Jr.; Grani, C.; Ouerghi, K.; Grall, S.; Willoteaux, S.; Prunier, F.; Kwong, R.; et al. Relation of Quantity of Subepicardial Adipose Tissue to Infarct Size in Patients with ST-Elevation Myocardial Infarction. *Am. J. Cardiol.* **2017**, *119*, 1972–1978. [[CrossRef](#)]
218. Gohbara, M.; Iwahashi, N.; Akiyama, E.; Maejima, N.; Tsukahara, K.; Hibi, K.; Kosuge, M.; Ebina, T.; Umemura, S.; Kimura, K. Association between epicardial adipose tissue volume and myocardial salvage in patients with a first ST-segment elevation myocardial infarction: An epicardial adipose tissue paradox. *J. Cardiol.* **2016**, *68*, 399–405. [[CrossRef](#)]
219. van Meijeren, A.R.; Ties, D.; de Koning, M.L.Y.; van Dijk, R.; van Blokland, I.V.; Lizana Veloz, P.; van Woerden, G.; Vliegthart, R.; Pundziute, G.; Westenbrink, D.B.; et al. Association of epicardial adipose tissue with different stages of coronary artery disease: A cross-sectional UK Biobank cardiovascular magnetic resonance imaging substudy. *Int. J. Cardiol. Heart Vasc.* **2022**, *40*, 101006. [[CrossRef](#)]
220. Homsí, R.; Sprinkart, A.M.; Gieseke, J.; Yuecel, S.; Meier-Schroers, M.; Luetkens, J.; Dabir, D.; Kuetting, D.; Marx, C.; Nadal, J.; et al. 3D-Dixon cardiac magnetic resonance detects an increased epicardial fat volume in hypertensive men with myocardial infarction. *Eur. J. Radiol.* **2016**, *85*, 936–942. [[CrossRef](#)] [[PubMed](#)]
221. Franssens, B.T.; Nathoe, H.M.; Visseren, F.L.; van der Graaf, Y.; Leiner, T.; Group, S.S. Relation of Epicardial Adipose Tissue Radiodensity to Coronary Artery Calcium on Cardiac Computed Tomography in Patients at High Risk for Cardiovascular Disease. *Am. J. Cardiol.* **2017**, *119*, 1359–1365. [[CrossRef](#)]
222. Du, Y.; Yang, L.; Liu, Y.; Yang, B.; Lv, S.; Hu, C.; Zhu, Y.; Zhang, H.; Ma, Q.; Wang, Z.; et al. Relation between quantity and quality of peri-coronary epicardial adipose tissue and its underlying hemodynamically significant coronary stenosis. *BMC Cardiovasc. Disord.* **2020**, *20*, 226. [[CrossRef](#)]
223. Fluchter, S.; Haghi, D.; Dinter, D.; Heberlein, W.; Kuhl, H.P.; Neff, W.; Sueselbeck, T.; Borggreffe, M.; Papavassiliu, T. Volumetric assessment of epicardial adipose tissue with cardiovascular magnetic resonance imaging. *Obesity* **2007**, *15*, 870–878. [[CrossRef](#)]
224. Doesch, C.; Suselbeck, T.; Haghi, D.; Streitner, F.; Schoenberg, S.O.; Borggreffe, M.; Papavassiliu, T. The relationship between the severity of coronary artery disease and epicardial adipose tissue depends on the left ventricular function. *PLoS ONE* **2012**, *7*, e48330. [[CrossRef](#)]
225. Doesch, C.; Suselbeck, T.; Leweling, H.; Fluechter, S.; Haghi, D.; Schoenberg, S.O.; Borggreffe, M.; Papavassiliu, T. Bioimpedance analysis parameters and epicardial adipose tissue assessed by cardiac magnetic resonance imaging in patients with heart failure. *Obesity* **2010**, *18*, 2326–2332. [[CrossRef](#)] [[PubMed](#)]

226. Goeller, M.; Achenbach, S.; Duncker, H.; Dey, D.; Marwan, M. Imaging of the Pericoronary Adipose Tissue (PCAT) Using Cardiac Computed Tomography: Modern Clinical Implications. *J. Thorac. Imaging* **2021**, *36*, 149–161. [[CrossRef](#)] [[PubMed](#)]
227. Oikonomou, E.K.; Marwan, M.; Desai, M.Y.; Mancio, J.; Alashi, A.; Hutt Centeno, E.; Thomas, S.; Herdman, L.; Kotanidis, C.P.; Thomas, K.E.; et al. Non-invasive detection of coronary inflammation using computed tomography and prediction of residual cardiovascular risk (the CRISP CT study): A post-hoc analysis of prospective outcome data. *Lancet* **2018**, *392*, 929–939. [[CrossRef](#)]
228. Wang, Z.; Zhang, J.; Zhang, A.; Sun, Y.; Su, M.; You, H.; Zhang, R.; Jin, Q.; Shi, J.; Zhao, D.; et al. The role of epicardial and pericoronary adipose tissue radiomics in identifying patients with non-ST-segment elevation myocardial infarction from unstable angina. *Heliyon* **2023**, *9*, e15738. [[CrossRef](#)]
229. Kuno, T.; Arce, J.; Fattouh, M.; Sarkar, S.; Skendelas, J.P.; Daich, J.; Schenone, A.L.; Zhang, L.; Rodriguez, C.J.; Virani, S.S.; et al. Cardiometabolic predictors of high-risk CCTA phenotype in a diverse patient population. *Am. J. Prev. Cardiol.* **2023**, *15*, 100578. [[CrossRef](#)] [[PubMed](#)]
230. Balcer, B.; Dykun, I.; Schlosser, T.; Forsting, M.; Rassaf, T.; Mahabadi, A.A. Pericoronary fat volume but not attenuation differentiates culprit lesions in patients with myocardial infarction. *Atherosclerosis* **2018**, *276*, 182–188. [[CrossRef](#)]
231. Duncker, H.; Achenbach, S.; Moshage, M.; Dey, D.; Bittner, D.O.; Ammon, F.; Marwan, M.; Goeller, M. Computed Tomography-derived Characterization of Pericoronary, Epicardial, and Paracardial Adipose Tissue and Its Association with Myocardial Ischemia as Assessed by Computed Fractional Flow Reserve. *J. Thorac. Imaging* **2023**, *38*, 46–53. [[CrossRef](#)] [[PubMed](#)]
232. Zhou, K.; Shang, J.; Guo, Y.; Ma, S.; Lv, B.; Zhao, N.; Liu, H.; Zhang, J.; Xu, L.; Wang, Y.; et al. Incremental diagnostic value of radiomics signature of pericoronary adipose tissue for detecting functional myocardial ischemia: A multicenter study. *Eur. Radiol.* **2023**, *33*, 3007–3019. [[CrossRef](#)] [[PubMed](#)]
233. Toya, T.; Corban, M.T.; Imamura, K.; Bois, J.P.; Gulati, R.; Oh, J.K.; Lerman, L.O.; Lerman, A. Coronary perivascular epicardial adipose tissue and major adverse cardiovascular events after ST segment-elevation myocardial infarction. *Atherosclerosis* **2020**, *302*, 27–35. [[CrossRef](#)] [[PubMed](#)]
234. Ma, Y.; Ma, Q.; Wang, X.; Yu, T.; Dang, Y.; Shang, J.; Li, G.; Hou, Y. Incremental Prognostic Value of Pericoronary Adipose Tissue Thickness Measured Using Cardiac Magnetic Resonance Imaging after Revascularization in Patients with ST-Elevation Myocardial Infarction. *Front. Cardiovasc. Med.* **2022**, *9*, 781402. [[CrossRef](#)]
235. Mazurek, T.; Kobylecka, M.; Zielenkiewicz, M.; Kurek, A.; Kochman, J.; Filipiak, K.J.; Mazurek, K.; Huczek, Z.; Krolicki, L.; Opolski, G. PET/CT evaluation of (18)F-FDG uptake in pericoronary adipose tissue in patients with stable coronary artery disease: Independent predictor of atherosclerotic lesions' formation? *J. Nucl. Cardiol.* **2017**, *24*, 1075–1084. [[CrossRef](#)]
236. Ohyama, K.; Matsumoto, Y.; Takamami, K.; Ota, H.; Nishimiya, K.; Sugisawa, J.; Tsuchiya, S.; Amamizu, H.; Uzuka, H.; Suda, A.; et al. Coronary Adventitial and Perivascular Adipose Tissue Inflammation in Patients with Vasospastic Angina. *J. Am. Coll. Cardiol.* **2018**, *71*, 414–425. [[CrossRef](#)]

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