Role of Epicardial Adipose Tissue in Health and Disease: A Matter of Fat?

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Comprehensive Physiology

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Abstract

Epicardial adipose tissue (EAT) is a small but very biologically active ectopic fat depot that surrounds the heart. Given its rapid metabolism, thermogenic capacity, unique transcriptome, secretory profile, and simply measurability, epicardial fat has drawn increasing attention among researchers attempting to elucidate its putative role in health and cardiovascular diseases. The cellular crosstalk between epicardial adipocytes and cells of the vascular wall or myocytes is high and suggests a local role for this tissue. The balance between protective and proinflammatory/profibrotic cytokines, chemokines, and adipokines released by EAT seem to be a key element in atherogenesis and could represent a future therapeutic target. EAT amount has been found to predict clinical coronary outcomes. EAT can also modulate cardiac structure and function. Its amount has been associated with atrial fribrillation, coronary artery disease, and sleep apnea syndrome. Conversely, a beiging fat profile of EAT has been identified. In this review, we describe the current state of knowledge regarding the anatomy, physiology and pathophysiological role of EAT, and the factors more globally leading to ectopic fat development. We will also highlight the most recent findings on the origin of this ectopic tissue, and its association with cardiac diseases.

Didactic synopsis

Major teaching points:" followed by a bulleted list of 5-10 summary statements.

- EAT is an ectopic fat depot located between myocardium and the visceral pericardium with no fascia separating the tissues, allowing local interaction and cellular cross-talk between myocytes and adipocytes
- Given the lack of standard terminology, it is necessary to make a distinction between epicardial and pericardial fat to avoid confusion in the use of terms. The pericardial fat refers to the combination of epicardial fat and paracardial fat (located on the external surface of the parietal pericardium)
- Imaging techniques such as echocardiography, computed tomography or magnetic resonance imaging are necessary to study EAT distribution in humans
- Very little amount of EAT is found in rodents compared to humans
- EAT displays high rate of fatty acids metabolism (lipogenesis and lipolysis), thermogenic (beiging features), and mechanical properties (protective framework for cardiac autonomic nerves and vessels)
- Compared to visceral fat, EAT is likely to have predominant local effects
- EAT secretes numerous bioactive factors including adipokines, fibrokines, growth factors and cytokines that could either be protective or harmful depending on the local microenvironement
- Human EAT has a unique transcriptome enriched in genes implicated in extracellular matrix remodeling, inflammation, immune signaling, beiging, thrombosis and apoptosis pathways
- Epicardial adipocytes have a mesothelial origin and derive mainly from epicardium. Cells originating from the Wt1+ mesothelial lineage, can differentiate into EAT and this "epicardium-to-fat transition" fate could be reactivated after myocardial infarction
- Factors leading to cardiac ectopic fat deposition may include dysfunctional subcutaneous adipose tissue, fibrosis, inflammation, hypoxia, and aging
- Periatrial EAT has a specific transcriptomic signature and its amount is associated with atrial fibrillation
- EAT is likely to play a role in the pathogenesis of cardiovascular disease and coronary artery disease
- EAT amount is a strong independent predictor of future coronary events
- EAT is increased in obesity, type 2 diabetes, hypertension, metabolic syndrome, non-alcoholic fatty liver disease, and obstructive sleep apnea (OSA)

- **Introduction**

Obesity and type 2 diabetes have become importantly prevalent in recent years, and are strongly associated with cardiovascular diseases, which remain a major contributor to total global mortality despite advances in research and clinical care (195). Organ-specific adiposity has renewed scientific interest in that it probably contributes to the pathophysiology of cardiometabolic diseases (63, 321). Better phenotyping obese individuals, increasing our knowledge on one's individual risk, and identifying new therapeutic targets is therefore decisive. Epicardial adipose tissue (EAT) is the visceral heart depot in direct contact with myocardium and coronary arteries. Its endocrine and metabolic activity is outstanding, and its key localization allows a singular cross talk with cardiomyocytes and cells of the vascular wall. Despite the little amount of EAT found in rodents, human EAT is readily measured using imaging methods. This has brought more than 1000 publications in the past decade. In this review, we discuss the recent basic and clinical research with regards to the EAT (i) anatomy, (ii) physiology, (iii) origin, and (iv) development, (v) clinical applications of EAT measurments, and (vi) its role in pathophysiology, in particular with atrial fribrillation, heart function, coronary artery disease (CAD) and obstructive sleep apnea syndrome.

Systematic review criteria

We searched MEDLINE and Pubmed for original articles published over the past ten years, focusing on epicardial adipose tissue. The search terms we used alone or in combination, were "cardiac ectopic fat", "cardiac adiposity", "fatty heart", "ectopic cardiovascular fat", "ectopic fat depots", "ectopic fat deposits", "epicardial fat" "epicardial adipose tissue", "pericardial fat", "pericardial adipose tissue". All articles identified were English-language, full-text papers. We also searched in the reference lists of identified articles, for further investigation.

EAT IN HEALTH

Anatomy of EAT

Definitions and distinction between pericardial and epicardial fat

Epicardial fat is the true visceral fat deposit over the heart (111, 253, 265). It is most commonly defined as adipose tissue surrounding the heart, located between the myocardium and the visceral pericardium (Figure 1). It should be distinguished from paracardial fat (adipose tissue located external to the parietal pericardium) and pericardial fat (often defined as paracardial fat plus epicardial fat) (84, 126). However, it should be noted that in the literature there is often some confusion in the use of the term pericardial instead of epicardial or conversely, so that it is prudent to carefully review the definition of adipose tissues measured by imaging used by authors in any individual study.

Distribution of EAT in humans and other species

Eventhough the adipose tissue of the heart was neglected for a long time, anatomists made early observations in humans that it varies in extent and distribution pattern. EAT constitutes in average 20% of heart weight in autopsy series (50, 253, 259). However, it has been shown to vary widely among individuals from 4% to 52% and to be preferentially distributed over the base of the heart, the left ventricular apex, the atrioventricular and interventricular grooves, along the coronary arteries and veins, and over the right ventricle (RV), in particular free wall (253). In our postmortem study, age, waist circumference and heart weight were the main determinants of EAT increase, the latter covering the entire epicardial surface of the heart in some cases (284). Importantly, a close functional and anatomical relationship exists between the EAT and the myocardium. Both share the same microcirculation, with no fascia separating the adipose tissue from myocardial layers, allowing cellular cross talk between adipose tissue and cardiac muscle (127). In other species than humans, such as pigs, rabbits or sheep, EAT is relatively abundant, which contrasts with the very small EAT amount found in rodents (Figure

2) (127). Initially, these findings did not support for a critical role of EAT in normal heart physiology and partly explain why EAT has been so poorly studied. However, there is a growing body of evidence that beyond the amount of EAT, its metabolic and endocrine activity is also crucial.

Physiology of EAT

The current understanding of EAT physiology is still in its infancy. The main anatomical and supposed physiological properties of epicardial fat are summarized in table 1. One of the major limitations in studying the physiology of EAT is that only patients with cardiac diseases undergo cardiac surgery. Sampling healthy volunteers would be unethical.

Histology

In humans, EAT has a smaller adipocyte size than subcutaneous or peritoneal adipose tissue (11). But EAT is composed of far more than simply adipocytes. It also contains inflammatory, stromal and immune cells but also nervous and nodal tissue (206). It has been suggested that EAT may serve as a protective framework for cardiac autonomic nerves and ganglionated plexi (GP). Accordingly, nerve growth factor β (NGF), which is essential for the development and survival of sensory neurons, is highly expressed in EAT (266). Atrial EAT is thus often the target of radiofrequency ablation for arrhythmias (see paragraph EAT and atrial fibrillation).

Metabolism

Up to now, our understanding of EAT physiology in humans remains quite limited, and data regarding lipid storage (lipogenesis) and release (lipolysis) come mainly from animal studies. In guinea pigs, Marchington et al., reported that EAT exhibits an approximately two-fold higher metabolic capacity for fatty acids incorporation, breakdown, and release relative to other intra-abdominal fat depots (198). Considering that free fatty acids (FFA) are the major

source of fuel for contracting heart muscle, EAT may act as a local energy supply, and an immediate ATP source for adjacent myocardium during time of energy restriction (199). Conversely, due to its high lipogenic activity, and high expression of fatty acid transporters specialized in intracellular lipid trafficking such as FABP4 (325), (fatty-acid-binding-protein 4), EAT could serve as a buffer against toxic levels of FFA during time of excess energy intake. How FFAs are transported from the EAT into the myocardium has however to be elucidated. One hypothesis is that FFAs could diffuse bidirectionally in interstitial fluid across concentration gradients (265).

Secretome

EAT is more than a fat storage depot. Indeed, it is now widely recognized to be an extremely active endocrine organ and a major source of adipokines, chemokines, cytokines that could either be protective or harmful depending on the local microenvironement (127, 206). The human secretome of EAT is wide and is described in Table 2. This richness probably reflects the complex cellularity and cross talk between EAT and neighboring structures. Interleukin (IL)-1β, IL6, IL8, IL10, tumor necrosis factor α (TNF-α), monocyte chemoattractive protein 1 (MCP-1), adiponectin, leptin, visfatin, resistin, phospholipase A2 (sPLA2), and plasminogen activator inhibitor 1 (PAI-1) are examples of bioactive molecules secreted by EAT (44, 74, 206, 268). Given the lack of anatomical barriers, adipokines produced by EAT are thought to interact with vascular cells or myocytes in two manners: paracrine and/or vasocrine. Interaction with cardiomyocytes is likely to be paracrine as close contact between epicardial adipocytes and myocytes exist and fatty infiltration into myocardium is not rare (50, 193, 308). Interactions with cells of the vascular wall seem to be paracrine or vasocrine. In paracrine signalling, it is hypothesized that EAT-derived adipokines could diffuse directly through the layers of the vessel wall via the interstitial fluid to interact with smooth muscle

cells, endothelium probably influencing the initiation of inflammation, and atherogenesis (see EAT and Coronary artery disease (CAD)). An alternative vasocrine signalling mechanism has been proposed, in which EAT-derived adipokines directly enter the lumen of closely opposed adventitial vasa vasorum, and thus are transported downstream into the arterial wall (126, 265). Apart from the classical endothelial and intima layers "inside–out" cross talk, this would suggest the opposite existence of an "outside-in" cellular cross talk (111, 124, 266).

Supposed Protective functions

Mechanical protective effects have been attributed to epicardial fat. EAT is supposed to act as a shock absorber to protect coronary arteries against torsion induced by the arterial pulse wave and cardiac contraction (253). A permissive role of EAT on vessel expansion and positive remodeling of coronary vessels, to maintain the arterial lumen has been reported (251). Given its high metabolic activity, EAT is likely to be involved in the regulation of fatty acids homeostasis in the coronary microcirculation (199). Some adipokines such as adiponectin, adrenomedullin and omentin, may have protective effects on vasculature, by regulating arterial vascular tone (vasodilation), reducing oxidative stress, improving endothelial function, and increasing insulinsensitivity (42, 76, 89, 283). EAT is also considered as an immunological tissue that serves to protect the myocardium and vessels against pathogens (76, 266). Hence, under physiological conditions EAT can exert cardioprotective actions through production of anti-atherogenic cytokines. However, the modification of EAT into a more pro-inflammatory or pro-fibrosing phenotype is susceptible to favor many pathophysiological states (see EAT in diseases). Determining the factors that regulate this fragile balance is a big challenge for next years.

Transcriptome

EAT has a unique transcriptomic signature when compared to subcutaneous fat (89, 188). Using a pangenomic approach we identified that EAT was particularly enriched in

extracellular matrix remodeling, inflammation, immune signaling, beiging, coagulation, thrombosis and apoptosis pathways (89). Omentin (ITLN1) was the most upregulated gene in EAT, as confirmed by others (76, 102), and network analysis revealed that its expression level was related with many other genes, supporting an important role for this cardioprotective adipokine (273). Remarkably, we observed a specific transcriptomic signature for EAT taken at different anatomical sites. EAT taken from the periventricular area overexpressed genes implicated in Notch/p53, inflammation, ABC transporters and glutathione metabolism. EAT taken from coronary arteries overexpressed genes implicated in proliferation, O-N glycan biosynthesis, and sphingolipid metabolism. Finally, EAT taken from atria overexpressed genes implicated in oxidative phosphorylation, cell adhesion, cardiac muscle contraction and intracellular calcium signalling pathway, suggesting a specific contribution of periatrial EAT to cardiac muscle activity. These findings further support the importance of the microenvironment on EAT gene profile. Likewise abdominal adipose tissue comprises many different depots there is not one but rather many epicardial adipose tissues.

Thermogenesis

The thermogenic and browning potential of epicardial fat has received increasing attention, and has been recently reviewed elsewhere (41). Brown adipose tissue generates heat in response to cold temperatures and activation of the autonomic nervous system. The heat generation is due to the expression of an uncoupling protein UCP-1, in the mitochondria of brown adipocytes (183). Until quite recently, BAT was thought to be of metabolic importance only in mammals during hibernation, and human newborns. However, recent studies using positron emission tomography (PET), have reported the presence of metabolically active BAT in human adults (56, 224). Interestingly, Sacks et al, reported that UCP-1 expression was fivefold higher in EAT than substernal fat, and undetectable in subcutaneous fat, suggesting that EAT could have «brown» fat properties to defend myocardium and coronary arteries

against hypothermia (40). The authors further demonstrated that the structure and architecture of EAT differs among the neonate, infant, and child with more genes implicated in the control of thermogenesis in EAT of neonates, and a shift towards lipogenesis through infancy (230). Further studies identified that EAT had beige or brite profile, with the expression of beige markers such as CD137 (267). Besides, we reported that periventricular EAT could be an EAT more sensitive to browning, as it expressed more UCP-1 than other epicardial fat stores (18). Furthermore, several genes upregulated in periventricular EAT encoded for enzymes of the glutathione metabolism pathway. Yet these enzymes have a specific signature in brown adipose tissue, due to the decoupling of the respiratory chain, and the increase in oxidative metabolism (246). The 'brite' (i.e. brown in white) or 'beige' adipocytes are multi-locular adipocytes located within white adipose tissue islets, which have the capacity to be recruited and to express UCP-1, mainly in case of cold exposure (52, 282, 339). It has been suggested that beige adipose tissue in EAT originates from the recruitment of white adipocytes that could produce UCP-1 in response to browning factors such as myokines like irisin, cardiac natriuretic peptides, or fibroblast growth factor 21 (FGF21) (24). Whether these factors have a direct beiging effect on EAT and can stimulate its thermogenic potential remains to be addressed. A recent study demonstrated that increased reactive oxygen species (ROS) production from epicardial fat of CAD patients was possibly associated with brown to white transdifferentiation of adipocytes within EAT (72). Accordingly, another study revealed that an increase in brown EAT was associated with the lack of progression of coronary atherosclerosis in humans (2). These results point to a beneficial role of EAT browning in CAD development. Whether these beige adipocytes within white epicardial adipocytes could serve, as a therapeutic target to improve cardiac health and metabolism remains to be explored.

The origin of epicardial adipose tissue

In the recent years, there has been growing interest in the distribution and function of adipocytes and the developmental origins of white adipose tissue (WAT) (20, 109, 168, 244). Since adipocytes are located close to microvasculature, it has been suggested that white adipocytes could have endothelial origin (307, 315). However, this hypothesis has been challenged by recent lineage tracing experiments that revealed epicardium as the origin of epicardial fat cells (39, 180, 343). Chau et al, used genetic lineage tracing to identify descendants of cells expressing the Wilms' tumor gene Wt1 (Wt1-Cre mice), and found a major ontogenetic difference between VAT and WAT (39). The authors observed that epicardial and five other visceral fat depots (gonadal, mesenteric, perirenal, retroperitoneal, and omental) appearing postnatally received a significant contribution from cells that once expressed Wt1 late in gestation. By contrast, Wt1-expressing cells did not contribute to the development of inguinal WAT or brown adipose tissue (BAT). Wt1 is a major regulator of mesenchymal progenitors in the developing heart. During development Wt1 expression is restricted mainly to the intermediate mesoderm, parts of the lateral plate mesoderm and tissues that derive from these and the mesothelial layer that lines the visceral organs and the peritoneum (201). Postnatally, in their experiments a subset of visceral WAT continued to arise from Wt1-expressing cells, consistent with the finding that Wt1 marks a proportion of cell populations enriched in WAT progenitors (39). Depending on the depot, Wt1+ cells comprised 4-40% of the adult progenitor population, being the most abundant in omental and epicardial fat. This suggested heterogeneity in the visceral WAT lineage. Finally, using FACS analysis the authors showed that Wt1-expressing mesothelial cells expressed accepted markers of adipose precursors (CD29, CD34, Sca1). Cultures of epididymal appendage explants in addition gave rise to adipocytes from Wt1+ cells, confirming that Wt1 expressing mesothelium can produce adipocytes (39). The concept of a mesothelial origin of epicardial

fat cells has been supported by contemporaneous lineage-tracing studies from Liu et al, using double transgenic mice line Wt1-CreER; Rosa26$^{RFP/+}$ tracing epicardium-derived cells (EDPCs), and adenovirus that expresses Cre under an epicardium-specific promoter Msln (180). They demonstrated that epicardial fat descends from embryonic epicardial progenitors expressing Wt1 and Msln. They referred to this as epicardium-to-fat transition (ETFT). Furthermore, cells of the epicardium in adult animals gave rise to epicardial adipocytes following myocardial infarction, but not during normal heart homeostasis (180). Another group confirmed these results and further established IGF1R signaling as a key pathway that governs EAT formation after myocardial injury by redirecting the fate of Wt1+ lineage cells (349). Taken together this suggested that while embryonic epicardial cells contribute to EAT, there is minima ETFT in normal adult heart, but this process can be reactivated after myocardial infarction or severe injury (Figure 3). This important discovery provides new insights into the treatment of cardiovascular diseases and regenerative medicine or stem cell therapy, as isolated human epicardial adipose derived stem cells (ADSCs) revealed the highest cardiomyogenic potential, as compared to the pericardial and omental subtypes (340). Further investigations are awaited in humans to decipher the mechanisms of ETFT reactivation in the setting of metabolic and cardiovascular diseases.

Another study clarified the discrepancy of EAT abundance among species in EAT development (343). The authors confirmed in mice that EAT originates from epicardium, that the adoption of the adipocyte fate in vivo requires the transcription factor PPARγ (peroxisome proliferator activated receptor gamma). By stimulation of PPARγ at times of epicardium–mesenchymal transformation, they were indeed able to induce this adipocyte fate ectopically in ventricular epicardium, in embryonic and adult mice (343). Human embryonic ventricular epicardial cells natively express PPARγ, which explains the abundant presence of fat seen in

human hearts at birth and throughout life, whereas in mice EAT remains small and located to the atrio-ventricular groove.

Whereas EAT seems to have epicardial origin, adipocytes present in myocardium could have a different one (Figure 3). Indeed infiltration of adipocytes interspersed with the right ventricular muscle fibres is commonly seen in necropsies (308). It is thought to reflect the normal physiological process of involution that occurs with ageing. This is different from the accumulation of triglycerides in cardiomyocytes (namely steatosis). A recent study identified endocardial origin of intramyocardial adipocytes during development (351). Nevertheless, the endocardium of the postnatal heart did not contribute to intramyocardial adipocytes during homeostasis or after myocardial infarction, suggesting that the endocardium-to-fat transition could not be recapitulated after myocardial infarction. It remains however unknown whether endocardial cells could give rise to excessive adipocytes in other types of cardiovascular diseases such as arrhythmogenic right ventricular cardiomyopathy. In this genetic disease, excessive adipose tissue replace myocardium of the right ventricle, leading to ventricular arrhythmias, and sudden death (182).

Taken together, further lineage studies are hence needed to better understand whether mesothelial progenitors contribute to epicardial adipocyte hyperplasia in obesity, type 2 diabetes or cardiovascular diseases.

What drives the development of ectopic fat in the heart?

It is likely that genetic, epigenetic and environmental factors are involved in this process. EAT has been found to vary among population of different ethnicities (7–13), EAT volume or thickness was reported to be lower in South Asians, Southeast and East Asians compared to Caucasians (13), higher in White, or Japanese versus Blacks or African Americans (8,9,11). In a genome-wide association analysis including 5,487 individuals of European ancestry from

the Framingham Heart Study (FHS) and the Multi-Ethnic Study of Atherosclerosis (MESA) a unique locus 10198628 near TRIB2 (Tribbles homolog 2 gene) was identified to be associated with cardiac ectopic fat deposition, reinforcing the concept that there are unique genetic underpinnings to ectopic fat distribution (14). Animal studies have also revealed the possible effects of fetal programming such as late gestation undernutrition on visceral adiposity predisposing (15). Other environmental factors such as aging, excess caloric intake, sedentary life style, pollutants, and microbiota may also modulate ectopic fat deposition (16,17). In obesity and type 2 diabetes, increased amount of ectopic fat stores have been consistently reported, but the mobilization of those ectopic fat depots seem to be site specific (18–20). Studying the cellular mechanisms that favors ectopic fat accumulation has become therefore an important focus of research.

Factors leading to ectopic fat development

Expandability hypothesis: dysfunctional subcutaneous fat

There are several potential mechanisms that might explain the tendency to deposit ectopic fat but one convincing hypothesis is that individual's capacity to store lipids in subcutaneous adipose tissue has a set maximal limit. When this limit is exceeded, increased import and storage of lipids in visceral adipose tissue and in non-adipose tissues occurs. This is the adipose tissue expandability hypothesis (323). The limited capacity of the subcutaneous adipose tissue to expand induces a “lipid spillover” to other cell types, leading to ectopic lipid deposition, which, in turn, are drivers of insulin resistance and the collective pathologies that encompass metabolic syndrome (319).

There is some intriguing evidence from human studies that supports the adipose tissue expansion hypothesis. In LMNA linked lipodystrophies, the lack of subcutaneous adipose tissue result in severe insulin resistance, hypertriglyceridemia and increased ectopic fat

deposition in the liver and the heart (19, 90). Data on animal studies have revealed that transplantation of SAT or removal of VAT in obese mice reversed adverse metabolic effects of obesity, improved glucose homeostasis, and hepatic steatosis (80, 117). These data replace the adipose tissue function at the center of ectopic lipids deposition.

Fibrosis

Adipocytes are surrounded by a network of extracellular matrix (ECM) proteins which represent a mechanical support and respond to various signaling events (151, 223). During adipogenesis, both the formation and expansion of the lipid droplet require dramatic morphological changes, involving both cellular and ECM remodeling (208). Throughout the progression from the lean to the obese state, adipose tissue has been reported to actively change its ECM to accommodate the growth (5, 65, 244). Moreover, it has been shown that metabolically dysfunctional adipose tissue exhibits a higher degree of fibrosis, characterized by abundant ECM proteins, and particularly abnormal collagen deposition (151). Therefore, as obesity progresses, ECM rigidity, composition and remodeling impact adipose tissue expandability by physically limiting adipocytes hypertrophy, thus promoting lipotoxicity and ectopic fat deposition. Indeed, genetic ablation of collagen VI (which is a highly enriched ECM constituent of adipose tissue (137)) in mouse model of genetic or dietary obesity, induced impaired ECM stability, reduced adipose tissue fibrosis and dramatically ameliorated glucose and lipid metabolism (151). In this mouse model, the lack of collagen VI allowed adipocytes to increase their size without ECM constraints, which favored lipid storage and minimized ectopic lipid accumulation in non adipose tissues. Such results suggest that adipose tissue fibrosis is likely to induce systemic metabolic alterations as fibrosis in the liver, heart or kidney. Moreover, it appears that maintaining a high degree of ECM elasticity allows adipose tissue to expand in a healthy manner, without adverse metabolic consequences (299). Though hypertrophic adipocytes exhibit a profibrotic transcriptome (114), the contribution and the identity of different cell types responsible for fibrotic deposits in adipose tissue is

difficult to determine. However, we and others have demonstrated that macrophages are the master regulators of fibrosis in adipose tissue (25, 150, 299). They produce high levels of transforming growth factor β1 (TGF- β1), and we and others demonstrated that they could directly activate preadipocytes (the so-called adipose progenitor cells) to differentiate towards a myofibroblast-like phenotype thus promoting fibrosis into adipose tissue during its unhealthy excessive development (25, 150). Importantly, it has recently been demonstrated that transcription factor interferon regulatory factor 5 (Irf5) known to polarize macrophages toward an inflammatory phenotype (162) represses directly TGF-β1 expression in macrophages thus directly controlling ECM deposition (59). Importantly, IRF5 expression in obese individuals is negatively associated with insulin sensitivity and collagen deposition in visceral adipose tissue (162).

It has been proposed that fibrosis development in adipose tissue promotes adipocyte necrosis which in turn induces the infiltration of immune cells in order to remove cell debris, thus leading to low-grade inflammation state. Whether fibrosis is a cause or a consequence of adipose tissue inflammation in obesity is still a matter of intense debate (258). That being said, it is undisputed that there is a close relationship between adipose tissue fibrosis and inflammation development in adipose tissue.

Inflammation

The link between obesity and adipose tissue inflammation was first suspected with the finding that proinflammatory cytokine TNF-α levels were increased in obese adipose tissue the blockade of which led to insulin sensitivity improvement (120, 121). Consequently, macrophages were found to infiltrate obese adipose tissue (329, 341), which led to the general concept that obesity is a chronic unmitigated inflammation with insidious results, where adipose tissue releases proinflammatory cytokines and adipokines which impairs insulin

sensitivity in metabolic tissues (47). Very importantly, of the various fat depots visceral adipose tissue has been shown to be the predominant source of chronic systemic inflammation (140). Under lean conditions adipose tissue houses a number of immune cells, mostly M2-like macrophages (with a 4:1 M2:M1 ratio(186)), as well as eosinophils and regulatory T cells which secrete Il-4/IL-13 and IL-10 respectively, polarizing macrophages toward an anti-inflammatory phenotype (185, 331). To note, the M2-like phenotype of macrophages has been reported to be maintained by both immune cells and adipocytes (203). Importantly, the polarization of macrophages from an M2 to a pro-inflammatory M1-like phenotype has been considered as a key event in the induction of obesity visceral adipose tissue inflammation (26, 34, 185, 240). However, the crucial trigger for such polarization as well as the increase of immune cells in adipose tissue is still unclear, but is likely to be derived from adipocytes. As already mentioned above, with adipose tissue mass increase several morphological changes occur leading to activation of several stress pathways such as endoplasmic reticulum stress, oxidative stress and inflammasome within adipose tissue (48,56). Meanwhile, adiponectin production drops, the one of leptin increases and adipose tissue produces inflammatory mediators including IL1-β, IL-6; IL-8, Il-10; TGF-β, TNF-α, MCP-1, plasminogen activating inhibitor-1 (PAI-I) macrophage migratory inhibitory, metallothionin, osteopontin, chemerin, and prostaglandin E2 (140, 196). Adiponectin drop results in decreased glucose uptake while leptin decrease affects satiety signals but also the immune system. Indeed, leptin receptor (LEP-R) is expressed on most immune cells (331) and increased leptin production by adipose tissue could dramatically promote immune cell increase (236). Mice that are leptin (ob/ob) or leptin receptor (db/db) deficient are obese and exhibit a strong reduction in functional immune cells (regulatory T cells, NK cells and dendritic cells (166, 214)). Paradoxically, very provocative recent data argue that a reduced ability for an adipocyte to sense and respond to proinflammatory stimuli decreases the capacity for healthy adipose tissue expansion and

remodeling. As for fibrosis, such inability would result in increased high fat diet induced ectopic fat accumulation and metabolic dysfunction. Moreover, the authors demonstrate that proinflammatory responses in adipose tissue are essential for both proper ECM remodeling and angiogenesis, two processes known to facilitate adipogenesis, thus favoring healthy adipose tissue expansion (332). Finally, new regulatory players in adipose tissue homeostasis have been identified: the innate lymphoid type 2 cells (ILC2s) and IL-33. ILC2 are a regulatory subtype of ILCs, which are immune cells that lack a specific antigen receptor and can produce a spectrum of effectors cytokines, which match T helper cell subsets (294). ILCs are activated by IL-33 and produce large amounts of type 2 cytokines IL-5 and IL-13 (217). Upon binding to its receptor (ST2), IL-33 induces the production of large amounts of antiinflammatory cytokines by adipose tissue ILC2s and also the polarization of macrophages toward a M2 phenotype, which results both in adipose tissue mass reduction and insulin resistance improvement (110).

Considerable changes in the composition and phenotype of immune cells occur in adipose tissue during the onset of obesity suggesting that they are actively involved in releasing secretory products along with adipocytes. Conversely to chronic systemic inflammation, which interferes with optimal metabolic fitness a potent acute adipose tissue inflammation is an adaptive response to stress-inducing conditions, which has beneficial effects since it enables healthy adipose tissue remodeling and expansion.

Hypoxia

In the attempt to identify the trigger of adipose dysfunction in obesity, the theory of insufficient angiogenesis to maintain normoxia in the developing fat pad during obesity has also been proposed (316, 345). Interestingly parallels exist between the excessive development of adipose tissue and tumors in that both situations are challenged to vascularize

growing tissue to provide sufficient O2 and nutrients (298). Various arguments strongly support the idea of "hypoxia in adipose tissue". First, white mature hypertrophic adipocytes can reach a diameter of up to 200 µm in obese patients (205, 286) and the normal diffusion distance of O2 across tissues is 100 to 200 µm (27). Second, although lean subjects exhibit a postprandial blood flow rise to adipose tissue obese individuals do not (98, 148), indicating that O2 delivery to adipose tissue is indeed impaired in obesity. Third, various works performed in different murine models of obesity have robustly shown that in obese mice, hypoxia-responsive genes expression is increased, increased number of hypoxic foci (using hydroxyprobes system, such as pimonidazole) is found as well as lower adipose tissue oxygen partial pressure (256, 344, 347). As a result of hypoxic state, hypoxia-inducible factor (HIF) 1α, which has been described as the "master regulator of oxygen homeostasis" (261, 274, 317) is induced in adipose tissue. The molecular and cellular responses of mature adipocytes to reduced O2 tension have been intensively investigated (336). Hypoxia has been shown to dramatically modify the expression and/or release of leptin (increase) and adiponectin (decrease) and inflammation related proteins (IL-6, IL1β, MCP-1), indicating the installation of an inflammatory state (336). For that reason, hypoxia is postulated to explain the development of inflammation and is considered as a major initiating factor for ECM production, thus triggering the subsequent metabolic dysfunction of adipose tissue in obesity (299, 317). Among the other functional changes that were described concern the rates of lipolysis and lipogenesis, where lipolysis seem to be increased (92) while both lipogenesis and the uptake of fatty acids are decreased (232) and the fact that hypoxia may directly impair adipocyte insulin sensitivity (257). Other cell types present in adipose tissue have been shown to respond to hypoxia. Indeed, it has been clearly demonstrated that hypoxia induces pro-inflammatory phenotype of macrophages (218). Moreover, macrophages have been localized within adipose tissue in hypoxic areas of obese mice thus augmenting their inflammatory

response (256). In addition to macrophages, preadipocytes have been demonstrated to largely increase both their production of VEGF and leptin under hypoxic culture conditions. Conversely, PPARγ expression was reported to be dramatically diminished thus reducing preadipocyte adipogenic abilities under hypoxic environment (153).

Aging

With aging, adipose tissue changes in abundance, distribution, cell composition and endocrine signaling. Indeed, through middle/early old age, body fat percentage increases in both, men and women (107, 165, 211), shifts from subcutaneous depots to intra-abdominal visceral depots (75, 235). Moreover, the aging process is accompanied by subsequent changes in adipose tissue metabolic functions such as decreased insulin responsiveness and altered lipolysis, which could cause excessive free fatty acids release with subsequent ectopic lipid deposition and lipotoxicity (61, 83, 287). In a metabolic point of view, the balance between fat storage and oxidation is disrupted with aging and the capacity of tissues to oxidize fat progressively decreases. Therefore, it is likely that adiposity increase with aging could be also due to positive energy balance, decreased physical activity and basal metabolic rate and maintained caloric intake (75, 245). Thus, fat aging is associated with age-related diseases, lipotoxicity, reduced longevity (216, 309). The aged adipose tissue is also characterized by reduced adipocyte size, fibrosis, endothelial dysfunction and diminished angiogenic capacity (69). Importantly, extensive changes in preadipocyte functions occur with aging (66, 154, 155). These include preadipocyte replication decrease (66), diminished adipogenic abilities (155), increased susceptibility to lipotoxicity (108), and increased pro-inflammatory cytokine, chemokine and ECM-modifying proteases (33, 310).

As in obesity, inflammation is a common feature of aging (215, 295). Associated to this low-grade inflammation state, macrophages have been reported to accumulate with age in

subcutaneous adipose tissue. Conversely, no significant change in the visceral one was observed, however, the ratio of pro-inflammatory M1 macrophages to anti-inflammatory M2 macrophages has been shown to increase with aging (91, 185, 187). Interestingly, T cells populations have also been reported to change with aging. Specifically, Treg cells which accumulate to unusually high levels as a function of age and exacerbate both the decline of adipose metabolic function as well as the rise in insulin resistance (12, 187). Aging is also linked with immune-senescence, a process leading to dysregulation of immunity or an adaptive response (106, 241). Notably, T cell dysfunction has been described and might also lead to systemic increases in TNF-α, IL-6 and acute phase proteins such as C-reactive protein and serum amyloid A (29, 270). The "redox stress hypothesis' is also proposed to explain that age-related redox imbalance activates various pro-inflammatory signaling pathways leading to tissue inflammaging and immune deregulation (288). To note, considerable accumulation of senescent cells has been reported in aging adipose tissue (309). Among the various changes, which occur in senescent cells, multiple cytokines, chemokines, growth factors, matrix metalloproteinases and senescence-associated secretory phenotype (SASP) proteins are secreted and were shown to induce or sustain the age-related inflammation state (49, 187, 235, 342). It was recently shown that removing senescent cells from older mice improves adipogenesis and metabolic function (342). The authors propose that senescent cell removal may facilitate healthy adipose tissue expansion, less ectopic fat formation and improved insulin sensitivity (235).

Circulating adipose stem/stromal cells

Ectopic fat deposition can also take the form of mature adipocytes, which "infiltrate" non adipose organs such as muscles, pancreas and heart. Conversely to ectopic lipid formation, the cause and mechanisms responsible for ectopic adipocyte formation are largely unknown (21),

neither their cellular origin nor the mechanisms controlling their metabolic activity (1, 248, 313). As already discussed in the present review, adipose tissue depots undergo active remodeling throughout adulthood. To enable such remodeling, the presence of precursor cells exhibiting adipogenic potential is necessary (272). A population of multipotent progenitors, the adipose-derived stem/stromal cells (ASCs) (long identified as preadipocytes) were identified by various studies including ours to exhibit such abilities (95, 204, 205, 262, 275, 352). ASCs, as their bone marrow counterpart the mesenchymal stem/stromal cells (MSCs) are endowed with multilineage mesodermal differentiation potentials as well as regenerative abilities, leading to their extensive investigation from a therapeutic and tissue engineering perspective (77, 96, 158). Adipose tissue remodeling is frequently reported to be associated with the infiltration of various cell populations (226, 329). However, adipose tissue is rarely seen as a reservoir of exportable cells.

Indeed, cell export, the so-called mobilization process, has been essentially studied in bone marrow (169). For instance, in response to stress or injury, hematopoietic stem/progenitor cells lose their anchorage in the bone marrow microenvironment and are increasingly mobilized into the circulation. Cell mobilization involves chemoattractants and adhesion molecules and among these factors, the chemokine CXCL12 and its receptor CXCR4 are dominant in controlling stem/progenitor cell trafficking (70, 170, 171). Interference with CXCL12/CXCR4-mediated retention is a fundamental mechanism of stem/progenitor cell mobilization. Such interferences can be obtained by inducing (i) a CXCL12 decrease in the microenvironment through proteolysis by protease dipeptidyl-peptidase 4 (DPP4, also known as CD26) (46), (ii) a CXCL12 destabilization with MMP9, or neutrophil elastase or cathepsin G (175), (iii) an increase in CXCL12 plasma levels, which favors CXCL12-induced migration of stem/progenitor cells into the circulation over their retention in the bone marrow (213) and (iv) CXCR4 antagonism, with AMD3100 for instance, which induces the fast release of

stem/progenitor cells from the bone marrow to the circulation (60). We and others have reported that both human and murine native ASCs (freshly harvested) express functional CXCR4 (94, 276). Moreover we have also demonstrated for the first time that the in vivo administration of AMD3100 (a CXCR4 antagonist) induces the rapid mobilization of ASCs from subcutaneous adipose tissue to the circulation (93, 94).

Interestingly, obesity has been associated with increased systemic circulation of MSCs, the tissue origin of which has not been identified (18). Moreover, while a reduction in CXCL12 level has been demonstrated in adipose tissue with obesity (227), CXCL12 plasmatic levels were demonstrated to dramatically increase in the context of type 2 diabetes (147, 181). Therefore one can speculate that since we showed that subcutaneous adipose tissue releases adipose progenitors via a CXCL12/CXCR4 dependant mechanism, the unhealthy development of subcutaneous adipose tissue might trigger the aberrant release of adipose progenitors into the circulation and their further infiltration into non adipose tissues leading to ectopic adipocyte formation (Figure 4).

To sum up, the mechanisms driving the development of ectopic fat deposition and its consequences are summarized in Figure 4. What drive the development of one ectopic fat among others remains unknown. This needs to be explored further in clinical and experimental settings.

EAT IMAGING

Noninvasive Imaging Quantification of EAT

EAT can be relatively easily assessed by a variety of different imaging techniques, whose characteristics are summarized in Table 3. Epicardial fat quantification is usually performed on an exam that was realized in a clinical work up for a condition other than fat repartition quantification. In research, set up quantification of EAT is of major interest in several cardiac and metabolic diseases. Pericardium is the anatomical limit between epicardial and

paracardial fat. As outlined earlier in this review, these two tissues have different embryonic origin (see paragraph EAT origin), different vascularization, and their hypertrophy has different origin and consequences (265). The main problem for quantification of epicardial fat is the precise definition of the anatomical limit of the pericardium. Normal pericardium is a very thin layer and required cardiac ultrasound, gated MRI sequences and synchronized CT acquisition to be depicted. Besides imaging acquisition that has to depict correctly the pericardium layer, manual quantification of epicardial fat volume is time consuming. Recent teams have developed software analysis allowing and semi-automatic quantification of epicardial fat (192, 222, 229). These tools are now available for research community and progress will be made to save time during analysis phase.

Echocardiography

Quantification of epicardial fat using trans thoracic echocardiography (TTE) is limited to measurements of fat thickness surrounding the right ventricle through one echoic window. Indeed, EAT is visible as an echo free space between the outer wall of the myocardium and the visceral layer of the pericardium (Figure 5). The thickness of this space is measured on the right ventricular free wall in the parasternal long and short axis views where EAT is thought to be thickest. This technique, which is the most accessible and affordable imaging modality has been described by the group of Iacobellis (125). Distinction of the pericardium in a normal patient using TTE is possible so distinction of epicardial or paracardial fat is feasible using TTE.

Computed Tomography (CT)

CT is widely used for thoracic or cardiac diseases. The majority of clinical studies to date examining associations of epicardial fat depots with cardiovascular disease have utilized CT.

With high spatial resolution, pericardial fat can be readily and reproducibly identified with CT (Figure 6). Pericardial fat quantification is possible on non synchronized images but motion artefacts might pertain clear depiction between epicardial and paracardial fat (28). Synchronized acquisitions such as calcium scoring and coronary CT angiography are now well-established exams in clinical practice with a large number of indications. Distinction of the pericardium layer is facilitated by excellent spatial definition and by the high contrast between chest-pericardium-EAT and heart. Synchronized images provide less artifact and more precise quantification of fat volume and should be considered as the standard of reference for fat volume quantification using CT (174). Iodine injection is not required for fat quantification and acquisition such as calcium scoring could be used for fat quantification (43). Technical progress has dramatically decreased the amount of radiation exposure for one standard acquisition for 10 years with the irradiation dose of less than 1msv for calcium score and coronary CT. Nevertheless irradiation exposure pertains broad use of CT for fat quantification. Recent studies suggested that epicardial fat quantification can be performed semi-automatically with good accuracy thus reducing the time required for the quantification to fewer than 2 min (43, 292).

Magnetic Resonance Imaging (MRI)

MRI offers excellent spatial resolution and is considered today as the standard of reference for epicardial fat quantification (192). Fat tissues have low T1 value and appear in high signal on most sequences. Usually cine Steady State Free Precession (SSFP) sequences are used to quantify fat volume. Contrast on SSFP images allow a precise distinction between paracardial and epicardial fat and coverage of whole ventricles is always performed on a standard cardiac MR acquisition (161). Recently novel 3D Dixon acquisition using cardiac synchronization

and respiratory triggering provide high accuracy and reproducibility for peri and epicardial fat quantification (118).

Furthermore MRI is a great tool to assess other cardiac parameters such as function, myocardial fibrosis or intramyocardial fat quantification using proton spectroscopy (86, 87). MRI image acquisition does not require irradiation and MRI is the ideal imaging method for follow-up. Usually, distinction of pericardium is well performed either on end diastolic or systolic phase (Figure 7). Areas obtained for each slice are summed together and multiplied by the slice thickness to yield epicardial fat volume. Consistency between measurements at two different time points required the definition of anatomical landmarks and by using the same imaging parameters (86). Recently software that provides an automatic quantification of epicardial fat was described with no difference compared to manual drawing and significant time saving but to date these tools are not broadly available (55).

What Should be Measured and How?

MRI was the only technique that was validated in vivo on animal models (192, 225). Mahajan et al., imaged at 1.5T, 10 merino sheep using cine steady state free precession sequences in short axis covering the whole heart. End diastolic images were used to quantify ventricular, atrial and total pericardial fat. Correlation between MRI and autopsies were strong with ICC>0.8 and Inter- observer 95% limits of agreement were 7.2% for total pericardial adipose tissue (192). No study validates CT against histologic quantification of adipose tissue but based on the current knowledge, one can assume that result might be similar to MRI. MRI and CT are the two techniques that could quantify the total amount of epicardial, paracardial and pericardial fat. Nevertheless MR should be preferred, if possible, due to the lack of irradiation. Ultrasound is limited to fat thickness assessment on one region. A recent study including 311 patients validated TTE against CT with the use of a High-Frequency Linear

Probe (r=0.714, p< 0.001) (116). By contrast, one recent paper found no correlation between epicardial fat thicknesses measured using TTE and volume of epicardial fat measured using MRI (281). This fact could be explained by the wide anatomical variability of cardiac fat repartition (16). Nevertheless, localized thickness of epicardial fat might be a measured of interest to assess clinical risk. A recent paper showed that EAT thickness localized at the left atrio-venticular groove assessed on CT performed for calcium scoring was the only parameter correlated with the number of vessels exhibiting stenosis ≥ 50% (338). Furthermore some investigators found that epicardial fat thickness measured at the left atrioventricular groove was the best predictor of obstructive coronary artery disease (116, 338). This finding was confirmed in a meta-analysis but confirmation is needed in other populations than Asians (337).

EAT IN DISEASES

EAT and atrial fibrillation

Atrial fibrillation (AF) is caused by an interaction between an initiating trigger and the underlying atrial substrate, the latter being structural or electrical. AF is the most prevalent cardiac arrhythmia seen in clinical practice, that is associated with increased morbidity and mortality such as stroke or heart failure (144, 160, 334). Previous studies have highlighted that obesity is an independent risk factor for the new onset of atrial fibrillation (AF) (311, 327). In the general population, obesity increases the risk of developing AF by 49%, and the risk escalates in parallel with increased BMI (326). Recently, there has been evolving evidence that EAT could be implicated in the pathogenesis of AF. Numerous studies have confirmed the association between EAT abundance and the AF risk, severity and post ablation or electrical cardioversion recurrence (3, 37, 45, 219, 221, 312, 335). This has been

particularly observed in patients with persistent compared to paroxysmal AF (3, 17, 280). This association was found to be independent of total adiposity or left atrial enlargement (3). In the Framingham Heart cohort including 3217 participants, CT measured pericardial fat (but not VAT) was an independent predictor of prevalent AF even after adjusting for established AF risk factors (age, sex, systolic blood pressure, PR interval, clinically significant valvular disease) and other measures of adiposity such as BMI or intrathoracic fat volume (312). Interestingly, several studies have shown that EAT surrounding the atria in particular, was linked to AF recurrence after catheter ablation (219, 221, 318). But what are the mechanisms involved in this association between EAT and AF? Does EAT modulate the trigger (initiation) or the substrate (maintenance) of AF?

Direct mechanisms

Histologically, there is no fascia boundaries separating EAT from myocardium. Hence a direct infiltration of adipocytes within the atrial myocardium is not rare as we observed in huma atria (Figure 8). This could contribute to a remodeled atrial substrate, and lead to conduction defects (conduction slowing or inhomogeneity) (112, 335). In a diet-induced obese sheep model, Mahajan et al, showed a major fatty infiltration in the atrial musculature (posterior left atrial wall) of obese sheep compared to controls (193). This sub-epicardial adipocyte infiltration interspersed between cardiac myocytes was associated with reduction in posterior left atrial voltage and increased voltage heterogeneity in this region, suggesting that EAT could be a unique feature of the AF substrate (193). This EAT infiltration could promote side-to-side cells connection loss and conduction abnormalities in a way similar to microfibrosis (291). In 30 patients in sinus rhythm, prior to AF ablation procedure, left atrial EAT was associated with lower bipolar voltage and electrogram fractionation (350). In the Framingam Heart study cohort, Friedman et al, showed that pericardial fat was significantly associated with several P wave indices such as P wave duration even after adjustment for

visceral and intrathoracic fat (82). P wave indices (PWI) represent indeed a summation of the electrical vectors of atrial depolarization reflecting the atrial activation sequence. These are also known as markers of atrial remodeling (249). Another small study using a unique 3D merge process, dominant frequency left atrial map, identified EAT locations to correspond to high dominant frequency during AF. High dominant frequency are key electrophysiological parameters reflecting microreentrant circuits or sites of focal-firing that drive AF (6, 302). Therefore, overlap between EAT locations and high dominant frequency sites implies that EAT is most likely to harbor high-frequency sites, producing a favorable condition for perpetuation of AF. In vitro incubation of isolated rabbit left atrial myocytes with EAT modulated the electrophysiological properties of the cells leading to higher arrhythmogenesis in left atrial myocytes (178). All together, these data suggest a possible role of EAT on AF electrophysiological substrate.

Another important point is that EAT is the anatomical site of intrinsic cardiac autonomic nervous system, namely ganglionated plexi (GP) and interconnecting nerves, especially in the posterior wall around pulmonary veins ostia (124). These ganglia are a critical element responsible for the initiation and maintenance of AF (51, 250). GP activation includes both parasympathetic and sympathetic stimulation of the atria/ pulmonary veins adjacent to the GP. Parasympathetic stimulation shortens the action potential duration, and sympathetic stimulation increases calcium loading and calcium release from the sarcoplasmic reticulum. The combination of the short action potential duration and longer calcium release induces triggered firing resulting from delayed after-depolarization of the atria/pulmonary veins, as manifested by the high dominant frequency sites. Pulmonary veins isolation and radiofrequency ablation target sites for substrate modification overlap most of the EAT sites (179, 250, 301). Whether EAT has a physiological role to protect these ganglia against mechanical forces due to cardiac contraction has been suggested (266). By contrast, recent

clinical data showed that periatrial EAT is an independent predictor of AF recurrence after ablation (157, 202, 219, 296), supporting that EAT may have a pro-arrhythmic influence. Furthermore, electrical conductivity of the fat being lower than that of the atrial tissue, EAT volume may directly decrease the chance of the procedure to succeed (297).

Finally, a mechanical effect of EAT on left atrial pressure stretch and wall stress, which is known to favor arrhythmias can not be excluded.

Indirect mechanisms

EAT is a endocrine organ and a source of pro-inflammatory cytokines (such as TNF-□, IL-1, IL-6, Monocyte Chemoattractant Protein-1 (MCP-1)) and profibrotic factors (such as TGFs and MMPs) acting in a paracrine way on the myocardium (111, 115, 206). These molecules are thought to diffuse in the pericardial sac and contribute to the structural remodeling of the atria. Indeed, using a unique organo-culture model, we showed that human EAT secretome, induced marked fibrosis of rat atrial myocardium and favored the differentiation of fibroblasts into myofibroblasts (322). This effect was mediated in part by Activin A, a member of the TGFβ family, and blocked by anti-activin A antibody (322). Constitutive TGF-ß1 overexpression in a transgenic mouse model produces increased atrial fibrosis and episodes of inducible AF while the ventricle remains normal (220, 231). This data suggest that EAT could interfere with cardiac electrical activity and with the electrophysiological remodeling of the atria. According this, we previously demonstrated using a transcriptomic approach that peri-atrial EAT had a unique signature, expressing genes implicated in cardiac muscle contraction and intracellular calcium signaling pathway. Fibrosis is a central process in the alteration of the functional and structural properties of the atrial myocardium (31, 172). It causes interstitial expansion between bundles of myocytes. Dense and disorganized collagen weave fibrils physically separate cardiomyocytes, and can create a barrier to impulse propagation

(285, 300). Other pro-fibrotic factors known to be secreted by EAT may also contribute to remodeling of the atrial myocardium. Matrix metalloproteinases (MMPs), key regulators of extra-cellular matrix turnover, are known to contribute to atrial fibrosis, are upregulated during AF, and their secretion is increased in EAT compared to SAT (22, 322).

Local inflammatory pathways may also influence structural changes in the left atrium, and occurrence of AF. EAT secretes a myriad of pro-inflammatory cytokines such as IL-6, IL-8, IL-1β, TNF-α, MCP-1 that may have local effects on the adjacent atrial myocardium, and may induce migration of monocytes and immune cells (146, 206). The pro-inflammatory activity of EAT, adjacent to left atrium, atrioventricular groove, and left main artery assessed with positron emission tomography (PET), was confirmed to be higher in AF compared with non AF patients. (207).

EAT is also an important source of reactive oxygen species (ROS) with a high oxidative stress activity that could be involved in the genesis of AF (271). Ascorbate, an antioxidant and peroxynitrite decomposition catalyst, has been shown to decrease atrial pacing-induced peroxynitrite formation in dogs, and the incidence of postoperative AF in humans (32). This point to a role of oxidative stress and cytokines produced by EAT on atrial remodeling and arrhythmogenesis.

Taken together, all these studies provide uncovered findings that EAT through mechanical, fibrotic, inflammation and oxidative stress mechanisms may exert an impact on the atrial susbtrate and triggering (summarized in Figure 9). An improved understanding of how EAT modifies atrial electrophysiology and struture may yield novel approaches towards preventing AF in obesity.

EAT and cardiac geometry and function:

EAT has local effects on the structure and function of the heart. Numerous clinical studies have unveiled the association between EAT volume and early defects in cardiac structure, volume and function (50, 57, 78, 87, 123, 128, 131, 143, 177, 328, 333). Increased amount of EAT has been associated with increased left ventricular (LV) mass and abnormal right ventricle geometry or subclinical dysfunction (97, 330). This is in accordance with initial necropsic and echographic studies showing an increase in LV mass to be strongly related to EAT, irrespective of CAD or hypertrophy (50, 128, 131). In a study of 208 non CAD patients evaluated by [^{15}O]H_2O hybrid positron emission tomography (PET)/CT imaging, EAT volume was associated with LV mass independently of BMI (10). EAT thickness and EAT volume were then associated with right and LV diastolic dysfunction, initially in severely obese patients and afterwards in various cohorts of subjects with impaired glucose tolerance, and no apparent heart disease (57, 87, 128, 143, 152, 177, 194, 228, 238, 328). In 75 men with or without metabolic syndrome, the amount of EAT correlated negatively with all parameters of LV diastolic function (LV mass-to-volume ratio, end-diastolic, end-systolic, and indexed stroke volumes) and was an independent determinant of LV early peak filling rate (228). After myocardial infarction, EAT volume was also associated with LV diastolic function after adjustment for classical risk factors and other adiposity parameters (9). By contrast, other studies have reported that myocardial fat, but not EAT, was independently associated with cardiac output and work (87, 134). Myocardial fat, which can be assessed by proton magnetic resonance spectroscopy (^{1}H-MRS) refers to the storage of triglyceride droplets within cardiomyocytes, which can generate toxic lipid intermediates ie ceramides, endoplasmic reticulum stress, mitochondrial dysfunction and lipotoxicity (209). In the physiologically aging male heart, myocardial triglyceride content increased in association with the decline in diastolic function and could be thus a potential confounding factor (133). Altough these

clinical studies do not infer causality, they point to possible early impact of cardiac adiposity on LV remodeling and function.

More recently, using newly innovative methods such as speckle tracking echocardiography (STE) or cardiovascular magnetic resonance (CMR) displacement encoded imaging, subtle changes in cardiac structure, contractile dysfunction and myocardial dyssynchrony were associated with EAT volume. Indeed, cardiac mechanics (strain, torsion, and synchrony of contraction) are more sensitive measures of heart function that may detect subtle abnormalities, preceding clinical manifestations. Using CMR in 41 obese children, Jing et al, showed that, early in life obese children develop contractile dysfunction with higher LV mass indexed to height compared to healthy weight children (139). In this study, EAT was linked to LV mass, peak longitudinal and circumferential strains and was a better indicator for cardiac remodeling and dysfunction than BMI z-score or VAT (139). Another study found a persistent association between regional EAT and LV function beyond serum levels of adipokines, which is in favor of a local EAT effect rather than a systemic VAT effect (122). Healthy men aged 19-94 were evaluated using STE echography, to study the profile of the healthy aging heart. EAT was associated with longitudinal STE LV-dyssynchrony, longitudinal strain, circumferential LV-dyssynchrony, and LV twist (54). Furthermore EAT and hepatic triglyceride content correlated negatively with peak circumferential systolic strain and diastolic strain rate in type 2 diabetes (174). However, this is not consistent with other studies reporting no link of geometry alterations and LV diastolic dysfunction with EAT (23, 100, 247, 252). EAT has been associated with myocardial and hepatic steatosis, which are confounding factors (133, 197). Whether EAT, VAT, hepatic fat or myocardial fat is the best predictor of LV function merits further evaluation and large population studies assessing each ectopic fat depot are needed.

The impact of EAT on cardiac function is less evident at a more advanced stage disease. Interestingly, reduced amount of EAT were found in patients with congestive heart failure (HF), compared to patients with preserved systolic function (67, 68, 132). Furthermore, EAT reduction was predictive of cardiac deaths in these patients (68). Reduction of EAT volume with the severity of right ventricular systolic dysfunction in patients with chronic obstructive pulmonary disease was also demonstrated (145). EAT reduction might reflect a global fat mass reduction due to disease (124). Burgeiro et al, found reduction of glucose uptake, lipid storage and inflammation-related gene expression in EAT of patients with heart failure compared to SAT (30). However, the triggering factors causing EAT diminution and phenotype modification in heart failure is still under investigation, yet.

How EAT can participate and initiate LV dysfunction? First, EAT could mechanically enhanced LV afterload that could lead to increase LV output and stroke volume to enable adequate myocardium perfusion. EAT may act as local energy supplier and/or as a buffer against toxic levels of free fatty acids in the myocardium (198). EAT was found to have an enhanced adrenergic activity with increased catecholamine levels and expression of catecholamine biosynthetic enzymes so that EAT could directly contribute to sympathetic nervous system hyperactivity in the heart that accompanies and fosters myocardial sympathetic denervation. Indeed, Parisi et al, studied the relationship between EAT and sympathetic nerve activity assessed by 123I-metaiodobenzylguanidine (^{123}I-MIBG) in patients with HF (237). They found that EAT thickness was correlated to cardiac sympathetic denervation and represented an important source of norepinephrine, whose levels were 2-fold higher than those found in plasma. Because of the EAT proximity to the myocardium, the increase in catecholamine content in this tissue could result in a negative feedback on cardiac sympathetic nerves, thus inducing a functional and anatomic denervation of the heart (237) . Alternatively, secretory products of EAT and an imbalance between anti-inflammatory and

proinflammatory adipocytokines could participate in myocardium remodeling (84). The contribution of EAT to cardiac fibrosis, a substratum widely recognized to impair cardiac function, has been recently demonstrated (see also above EAT and AF) (322). EAT, through its capacity to produce and secrete adipo-fibrokines and miRNA could be a main mechanism contributing to the excess deposition of extracellular matrix proteins which distort organ architecture, induce pathological signaling and impair mechano-electric coupling of cardiomyocytes. (163, 291). However, concomitant study of heart fibrosis and EAT molecular characteristics has never been simultaneously performed in humans. In vitro studies from the group of Eckel, have demonstrated in both guinea pigs and humans that secreted factors from EAT can affect contractile function and insulin signaling in cardiomyocytes (103, 104). High-fat feeding of guinea pigs induces qualitative alterations in the secretory profile of EAT, which contributes to the induction of impaired rat cardiomyocyte function, as illustrated by impairments in insulin signaling, sarcomere shortening, cytosolic Ca2+ metabolism and SERCA2a expression (104). Rat cardiomyocytes treated with secretome of EAT from diabetic patients showed reductions in sarcomere shortening, cytosolic Ca^{2+} fluxes, expression of sarcoplasmic endoplasmic reticulum ATPase 2a. This result suggests that EAT could contribute to the pathogenesis of cardiac dysfunction in type 2 diabetes, eventhough the development of cardiac dysfunction is likely to be multifactorial, insulinresistance, myocardial fibrosis, endothelial dysfunction, autonomic dysfunction and myocyte damage being probably implicated.

The reciprocal crosstalk between EAT, myocardium and epicardium is even more complex than what was first suggested. Indeed as described above in paragraph EAT origin, signals from necrotic cardiomyocytes could induce epicardium-to-fat transition, thay may increase EAT volume which may in turn modulate heart disease evolution.

All together, the available studies in humans do not imply causality but suggest that

accumulation of EAT is, at least an indirect marker of early cardiac dysfunction in selected stages of disease progression. Wide cohorts evaluating extensively all ectopic fat depots and comprehensively characterizing cardiac geometry and function across the lifespan are needed.

EAT and coronary artery disease

Histological and radiological evidence

Although our limited understanding of the physiological role of EAT, there has been a lot of studies published in recent years, underscoring the strong association of EAT with the onset and development of coronary artery disease (CAD) in humans (41, 48, 234). Initially, a plausible role of EAT in CAD was supported by the histological observations that segments of coronary arteries running in a myocardial bridge (ie free of any immediately adjacent epicardial fat) tended to be free from atherosclerosis (135, 260). Necropsic studies have then demonstrated that EAT was higher in patients dead from CAD, and correlated with CAD staging (284). Since then, and although correlations do not necessarily prove causation, a growing body of imaging studies using echocardiography (thickness), computed tomography (CT, reviewed elsewhere (293)) or magnetic resonance imaging (MRI) have confirmed the association of EAT with CAD (99, 101, 105, 156, 190, 212, 264, 305, 324). Initial large population studies, including the Framingham Heart Study and Multi-Ethnic Study of Atherosclerosis, identified pericardial fat as an independent predictor of cardiovascular risk (64, 191). Compared to the Framingham Risk Score, pericardial fat volume >300 cm^3 was by far the strongest predictor for coronary atherosclerosis (OR 4.1, 95% CI 3.63-4.33)(101). Other studies highlighted the add-on predictive value of EAT compared to CAD scores such as coronary calcium score (CAC) (113, 138, 173). EAT significantly correlated with the extent and severity of CAD, chest pain, unstable angina and coronary flow reserve (233, 269). In addition, case-control studies identified pericardial fat volume as a strong predictor of

myocardial ischemia (113, 305). By contrast, some studies did not find such an association between EAT and the extent of CAD in intermediate to high risk patients, suggesting that the relationship is not constant at more advanced stages (263, 306). Interestingly, in the positive studies linking EAT with CAD and developing high risk obstructive plaques, the association was independent of adiposity measures, BMI and the presence of coronary calcifications (128, 136). Recent studies indicated that EAT could also serve as a marker for the presence and severity of atherosclerosis burden in asymptomatic patients (8, 346), threshold EAT thickness identified at 2.4 mm (8). All these findings are highly suggestive of a role for EAT in promoting the early stages of atherosclerotic plaque formation. In highly selected healthy volunteers, we reported that a higher EAT volume was associated with a decrease in coronary microvascular response, likely suggesting that EAT could participate in endothelial dysfunction (88). By using intravascular ultrasound it could be demonstrated that plaques develop most frequently with a pericardial spatial orientation suggesting a permissive role of EAT (251).

EAT and Clinical outcomes

More recently, the Heinz Nixdorf Recall study including more 4000 patients from general population confirmed the predictive role of EAT on clinical outcomes within 8 years (189). In this prospective trial, EAT volume significantly predicted fatal and nonfatal coronary events independently of cardiovascular risk factors and CAC score. They observed that subjects in the highest EAT quartile had a 4 fold higher risk of coronary events when compared to subjects in the lowest quartile (0.9 versus 4.7 %, $p<0.001$, respectively). In addition, doubling EAT volume was associated with a 1.5 fold adjusted risk of coronary events [hazard ratio (HR), 1.54; 95% CI, 1.09-2.19] (189). A recent meta-analysis, evaluating 411 CT studies confirmed EAT as a prognostic metric for future clinical adverse events (binary cut-off of 125

mL) (293). This cut-off needs to be evaluated further in prospective cohorts in order to discuss the relevance of its introduction in clinical care. To date, there is a lack of agreement on EAT threshold value associated with increased CAD risk, as various methods are used for its assessment (see Imaging paragraph). In conclusion to all these clinical studies, EAT volume is a strong independent predictor of CAD. Nevertheless, whether a reduction in the amount of EAT could reduce CAD in humans remains to be established.

Pathophysiology of EAT in CAD

The mechanisms by which EAT can cause atherosclerosis are complex and not completely understood. Epicardial fat might alter the coronary arteries through multiple pathways, including oxidative stress, endothelial dysfunction, vascular remodeling, macrophage activation, innate inflammatory response, and plaque destabilization (124, 243)

***1/ EAT has a specific profile in coronary artery disease*:**

EAT in CAD displays a pro-inflammatory phenotype, high levels of ROS and a specific pattern of micro RNA. Epicardial adipocytes have intrinsic proinflammatory and atherogenic secretion profiles (9, 42). In 2003, Mazurek et al., first reported that, in CAD patients EAT exhibited significantly higher levels (gene expression and protein secretion) of chemokines such as monocyte chemotactic protein-1 (MCP-1) and several inflammatory cytokines IL-6, IL-1β, and TNF-α than SAT (206). They also observed the presence of inflammatory cells infiltrate including macrophages, lymphocytes and mast cells in EAT compared to SAT. The presence of these inflammatory mediators was hypothesized to accentuate vascular inflammation, plaque instability via apoptosis (TNF-α), and neovascularization (MCP-1). Peri-adventitial application of endotoxin, MCP-1, IL-1β, or oxidized LDL induces inflammatory cell influx into the arterial wall, coronary vasospasm, or intimal lesions, which suggests that bioactive molecules from the pericoronary tissues may alter arterial homeostasis (279). These observations tend to support the concept of "outside to-inside" cellular cross-talk

or “vasocrine/paracrine signaling”, in that inflammatory mediators or free fatty acids produced by EAT adjacent to the coronary artery, may have a locally toxic effect on the vasculature, in diffusing passively or in vasa vasorum through the arterial wall, as depicted in Figure 10 (38, 266, 348). Migration of immune cells between EAT and adjacent adventitia may also occur (133). Nevertheless, direct proofs that these mechanisms operate in vivo are lacking. Since then, other groups have confirmed that EAT is a veritable endocrine organ and a source of a myriad of bioactive locally acting molecules (266). EAT content and release of adiponectin were consistently found to be decreased in CAD patients, suggesting that an imbalance between antiatherogenic, insulinsensitizing and harmful adipocytokines secreted by EAT could initiate inflammation in the vascular wall (42, 129, 278). Innate immunity represents one of the potential pathways for proinflammatory cytokines release. Innate immunity can be activated via the toll-like receptors (TLRs), which recognize antigens such as lipopolysaccharide (LPS) (141). Activation of TLRs leads to the translocation of NFκB into the nucleus to initiate the transcription and the release of IL-6, TNF-α, and resistin (53, 164). Remarkably Baker et al, showed that NFκB was activated in EAT of CAD patients (9). TLR-2 and TLR-4 and TNF-α gene expression was higher in EAT of CAD patients, and was closely linked to the presence of activated macrophages in the EAT. In another study, EAT amount positively correlated with the CD68+ and CD11c+ cell numbers, NLRP3 inflammasome, IL-1β, and IL-1R expression. NLRP3 inflammasome is a sensor in the nod-like receptor family of the innate immune cell system that activates caspase-1 and mediates the processing and release of IL-1β, and thereby has a central role in the inflammatory response (14). Interestingly, the ratio of proinflammatory M1 macrophages and anti-inflammatory M2 macrophages in EAT was reported to be shifted toward the M1 phenotype in patients with CAD (115). More recently, Patel et al nicely demonstrated the implication of renin-angiotensin system in the inflammation of EAT (239). In a model of mice lacking

angiotensin converting enzyme 2 (ACE2) submitted to a HFD, loss of ACE2 resulted in decreased weight gain, but increased glucose intolerance, and EAT inflammation. Ang 1-7 treatment resulted in ameliorated EAT inflammation and reduced cardiac steatosis, function and lipotoxicity (239).

MicroRNAs could also be an important actor of this crosstalk between EAT and the coronary artery wall. Indeed miRNAs are small, non-coding RNAs acting as posttranscriptional regulators of gene expression, either interfering with protein translation or reducing transcript levels (176). A nice integrative miRNA and whole genome analyses of EAT identified the signature of miRNAs in EAT of CAD patients (320). The authors described that EAT in CAD displays affected metabolic pathways with suppression of lipid- and retinoid sensing nuclear receptors, transcriptional activities, increased inflammatory infiltrates, activation of innate and adaptive immune response enhanced chemokine signalling (CCL5, CCL13, and CCL5R) and decrease of miR-103-3p as prominent features (320).

Furthermore higher levels of reactive oxygen species (ROS) and lower expression of antioxidant enzymes (such as catalase), have been observed in EAT of individuals with CAD compared with SAT (Figure 10) (271). On the other hand, EAT might also contribute to the accumulation of oxidized lipids within atherosclerotic plaques, as we evidenced increased expression and secretion of Secretory type II phospholipase A2 (sPLA2-IIa) in EAT of CAD patients (74).

2/ *EAT plays a pivotal role in the initiation of atherosclerosis*

The negative impact of EAT secretome on adjacent coronary arteries in CAD has been clearly demonstrated. In vitro studies revealed that EAT secreted fatty acids, inflammatory, stress mediators and migrated immune cells may induce endothelial dysfunction and vascular remodeling. EAT can affect the endothelium by inducing cell-surface expression of adhesion molecules such as VCAM-1, and it enhances migration of monocytes to coronary artery

endothelial cells (146). Besides, it has been demonstrated that the permeability of endothelial cells in vitro was significantly increased after exposure to EAT supernatrant in patients with acute coronary syndrome, and this effect was normalized by anti-resistin antiserum (167). Payne et al, showed that perivascular EAT derived leptin electively impaired coronary endothelial-dependent dilation in Ossabaw swine with metabolic syndrome (242). Other in vitro studies support the role of perivascular adipose tissue on vascular remodeling (243). Conditioned medium of cultured perivascular adipocytes from HFD rats was found to significantly stimulate vascular smooth muscle cells proliferation (13). Other in vitro studies highlighted the role of peri-adventitial fat on neointimal formation after angioplasty (303, 304). Finally, in a recent study involving Ossabaw miniature swine, selective surgical excision of EAT surrounding the left anterior descending artery was shown to be associated with slower progression of coronary atherosclerosis over a period of 3 months with atherogenic diet (210). Athough this study was preliminary and without controls, these results support the hypothesis that EAT could locally contribute to the initiation of coronary atherosclerosis, and further suggest that targeting its reduction could reduce CAD progression.

To conlude, EAT is not simply a marker of CAD but seems to play a key role in the initiation of atherosclerosis, by secreting locally many bioactive molecules such as fatty acids, inflammatory, immune, and stress factors, cytokines or chemokines. Current investigations are done to comprehensively understand how factors produced by EAT are able to cross the vessel wall, and to what initiate or precede the change in EAT phenotype. An imbalance between the protective and the deleterious factors secreted by EAT, and between the pro and anti-inflammatory immune cells is likely to trigger CAD development. Despite all the described findings, the pathophysiological link between EAT and CAD needs to be elucidated

further, and we really need interventional studies to investigate whether EAT reduction could reduce clinical outcomes.

EAT and obstructive sleep apnea

Obstructive sleep apnea (OSA) is a sleep disorder characterized by repetitive episodes of upper airway obstruction during sleep, resulting in decreased oxygen saturation, disruption of sleep, and daytime somnolence (71). Repetitive apneic events disrupt the normal physiologic interactions between sleep and the cardiovascular system (289, 314). Such sleep fragmentation and cyclic upper airway obstruction may result in hypercapnia, chronic intermittent hypoxemia that have been linked to increased sympathetic activation, vascular endothelial dysfunction, increased oxidative stress, inflammation, decreased fibrinoloytic activity, and metabolic dysregulation (62, 142, 149, 255). Hence OSA could contribute to the initiation and progression of cardiac and vascular disease. Conclusive data implicate OSA in the development of hypertension, CAD, congestive heart failure, and cardiac arrhythmias (277, 290). We previously reported that EAT is sensitive to OSA status and that bariatric surgery had little effect on epicardial fat volume (EFV) loss in OSA patients (86). It is tempting to hypothesize that OSA-induced chronic intermittent hypoxia could modify the phenotypic features of EAT and may be an initiator of adipose tissue remodeling (fibrosis or inflammation). However, this has never been investigated in EAT yet.

Two recent studies have reported a relationship between epicardial fat thickness and OSA severity (184, 200). Mariani et al. reported a significant positive correlation between EFT and apnea/hypopnea inex (AHI), and EFT values were significantly higher in moderate and severe OSA groups comparing to mild OSA group (200). A similar study was conducted by Lubrano et al. in 171 obese patients with and without metabolic syndrome, in which EFT rather than BMI was the best predictor of OSA (184). Treatment of OSA with continuous positive airway

pressure (CPAP) during 24 weeks significantly reduced EFT in 28 symptomatic OSA patients with AHI > 15, without significant change in BMI or waist circumference (36). Shorter-term of CPAP treatment (3 months) in 25 compliant OSA patients also reduced EFT (159), but in another study EAT remained higher in CPAP treated OSA obese patients (n=19, mean BMI 38 ± 4 kg/m^2) compared to age-matched healthy subjects (n=12), and CPAP was not sufficient to alleviate left ventricular concentric hypertrophy, as assessed by mass-cavity ratio, the latter being independently correlated with EAT (15). These data are consistent with previous studies supporting a negative role of EAT on cardiac function (35, 57, 79, 128, 130, 143, 174, 238).

The prognostic impact of EAT reduction by CPAP therapy on cardiovascular outcomes need to be further explored by large prospective studies. In all, EAT is increased in OSA patients and is a correlate of OSA severity. Additionally, CPAP therapy can significantly reduce the amount of EAT. Further large prospective studies are needed to evaluate the effect of CPAP therapy on EAT quantity, phenotype, and secretome.

Conclusion and perspectives

To conclude, the unique anatomic location of epicardial adipose tissue likely translates into a unique physiological relevance and pathophysiological role for this cardiac ectopic depot. Far from being an inert and uniform tissue, EAT has been shown to be a dynamic organ with highly developed functions, and a unique trasncriptome that are determined by its developmental epicardial origin, its regenerative potential, and molecular structure. It was poorly studied during a long time because of the small amount of EAT found in rodents and because of the difficulties faced by the researchers for biological studies requiring open cardiac surgery. Since, imaging studies have provided new non invasive tools for EAT quantification, and recent studies have paved the way for identifying new cellular characteristics of EAT by measuring its radiodensity (7, 81, 85).

In addition, an increase of epicardial fat result in an increased propensity not only for the onset but also for the progression and severity of CAD or atrial fibrillation in humans. Many intervention studies have proven that EAT is flexible and is a modifiable factor with weight loss induced by diet, GLP-1 receptor agonists or bariatric surgery (73, 254). The type of intervention, in addition to the amount of weight loss achieved, is predictive of the amount of EAT reduction. Hence this depot represents a therapeutic target for the management of CAD, and should be further assessed to identify CAD risk. But whether its reduction will lead to the reduction of cardiac events or cardiac rhythm disorders needs to be addressed in randomized controlled studies. The effect of EAT on cardiac autonomic nerves and the cardiac conduction system also needs to be further explored.

Furthermore, EAT has a beige profile that decreases with age and CAD. In support of this hypothesis is evidence of brown-to-white differentiation trans-differentiation in CAD patients with a decrease in thermogenic genes and up-regulation of white adipogenesis (4, 72). The thermogenic potential of EAT may represent a useful beneficial property, and another unique

target for therapeutic interventions. This is an attractive way of research in that the understanding of EAT browning and factors able to induce the browning of fat is mounting daily. Further experimental research is hence warranted to enhance our understanding of EAT thermogenic and wholesome energy expenditure potential as well as its potential flexibility with life style, medical or surgical treatments.

Finally, additional research and understanding on adipose tissue biology in general and mechanisms responsible for ectopic fat formation are needed in the future. Whether epicardium-to-fat-transition reactivation exists in humans, and whether unhealthy subcutaneous adipose tissue could trigger the release of adipose progenitors such as adipose-derived stem/stromal cells into the circulation, and whether these adipogenic cells could reach the heart and give rise to new adipocyte development in EAT is a fascinating area of interest for next years.

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References

1. **Addison O**, **Marcus RL**, **Lastayo PC**, **Ryan AS**. Intermuscular Fat: A Review of the Consequences and Causes. *Int J Endocrinol* 2014: 309570, 2014.
2. **Ahmadi N**, **Nabavi V**, **Hajsadeghi F**, **Zeb I**, **Flores F**, **Ebrahimi R**, **Budoff M**. Aged garlic extract with supplement is associated with increase in brown adipose, decrease in white adipose tissue and predict lack of progression in coronary atherosclerosis. *Int J Cardiol* 168: 2310–2314, 2013.
3. **Al Chekakie MO**, **Welles CC**, **Metoyer R**, **Ibrahim A**, **Shapira AR**, **Cytron J**, **Santucci P**, **Wilber DJ**, **Akar JG**. Pericardial fat is independently associated with human atrial fibrillation. *J Am Coll Cardiol* 56: 784–788, 2010.
4. **Aldiss P**, **Davies G**, **Woods R**, **Budge H**, **Sacks HS**, **Symonds ME**. "Browning" the cardiac and peri-vascular adipose tissues to modulate cardiovascular risk. *Int J Cardiol* 228: 265–274, 2017.
5. **Alligier M**, **Meugnier E**, **Debard C**, **Lambert-Porcheron S**, **Chanseaume E**, **Sothier M**, **Loizon E**, **Hssain AA**, **Brozek J**, **Scoazec JYY**, **Morio B**, **Vidal H**, **Laville M**. Subcutaneous adipose tissue remodeling during the initial phase of weight gain induced by overfeeding in humans. *J Clin Endocrinol Metab* 97: 92, 2012.
6. **Atienza F**, **Calvo D**, **Almendral J**, **Zlochiver S**, **Grzeda KR**, **Martínez-Alzamora N**, **González-Torrecilla E**, **Arenal A**, **Fernández-Avilés F**, **Berenfeld O**. Mechanisms of fractionated electrograms formation in the posterior left atrium during paroxysmal atrial fibrillation in humans. *J Am Coll Cardiol* 57: 1081–1092, 2011.
7. **Baba S**, **Jacene HA**, **Engles JM**, **Honda H**, **Wahl RL**. CT Hounsfield units of brown adipose tissue increase with activation: preclinical and clinical studies. *J Nucl Med Off Publ Soc Nucl Med* 51: 246–250, 2010.
8. **Bachar GN**, **Dicker D**, **Kornowski R**, **Atar E**. Epicardial adipose tissue as a predictor of coronary artery disease in asymptomatic subjects. *Am J Cardiol* 110: 534–538, 2012.
9. **Baker AR**, **Harte AL**, **Howell N**, **Pritlove DC**, **Ranasinghe AM**, **da Silva NF**, **Youssef EM**, **Khunti K**, **Davies MJ**, **Bonser RS**, **Kumar S**, **Pagano D**, **McTernan PG**. Epicardial adipose tissue as a source of nuclear factor-kappaB and c-Jun N-terminal kinase mediated inflammation in patients with coronary artery disease. *J Clin Endocrinol Metab* 94: 261–267, 2009.
10. **Bakkum MJ**, **Danad I**, **Romijn M a. J**, **Stuijfzand WJA**, **Leonora RM**, **Tulevski II**, **Somsen GA**, **Lammertsma AA**, **van Kuijk C**, **van Rossum AC**, **Raijmakers PG**, **Knaapen P**. The impact of obesity on the relationship between epicardial adipose tissue, left ventricular mass and coronary microvascular function. *Eur J Nucl Med Mol Imaging* 42: 1562–1573, 2015.
11. **Bambace C**, **Telesca M**, **Zoico E**, **Sepe A**, **Olioso D**, **Rossi A**, **Corzato F**, **Di Francesco V**, **Mazzucco A**, **Santini F**, **Zamboni M**. Adiponectin gene expression and adipocyte diameter: a comparison between epicardial and subcutaneous adipose tissue in men. *Cardiovasc Pathol* 20: e153–e156, 2011.
12. **Bapat SP**, **Myoung Suh J**, **Fang S**, **Liu S**, **Zhang Y**, **Cheng A**, **Zhou C**, **Liang Y**, **LeBlanc M**, **Liddle C**, **Atkins AR**, **Yu RT**, **Downes M**, **Evans RM**, **Zheng YC**. Depletion of fat-resident Treg cells prevents age-associated insulin resistance. *Nature* 528: 137–141, 2015.
13. **Barandier C**, **Montani J-P**, **Yang Z**. Mature adipocytes and perivascular adipose tissue stimulate vascular smooth muscle cell proliferation: effects of aging and obesity. *Am J Physiol Heart Circ Physiol* 289: H1807-1813, 2005.

14. **Baroja-Mazo A**, **Martín-Sánchez F**, **Gomez AI**, **Martínez CM**, **Amores-Iniesta J**, **Compan V**, **Barberà-Cremades M**, **Yagüe J**, **Ruiz-Ortiz E**, **Antón J**, **Buján S**, **Couillin I**, **Brough D**, **Arostegui JI**, **Pelegrín P**. The NLRP3 inflammasome is released as a particulate danger signal that amplifies the inflammatory response. *Nat Immunol* 15: 738–748, 2014.
15. **Barone-Rochette G**, **Vivodtzev I**, **Tamisier R**, **Rodière M**, **Ormezzano O**, **Baguet JP**, **Grangier A**, **Wuyam B**, **Levy P**, **Pépin JL**. Left ventricular remodeling and epicardial fat volume in obese patients with severe obstructive sleep apnea treated by continuous positive airway pressure. *Int J Cardiol* 179: 218–219, 2015.
16. **Bastarrika G**, **Broncano J**, **Schoepf UJ**, **Schwarz F**, **Lee YS**, **Abro JA**, **Costello P**, **Zwerner PL**. Relationship between coronary artery disease and epicardial adipose tissue quantification at cardiac CT: comparison between automatic volumetric measurement and manual bidimensional estimation. *Acad Radiol* 17: 727–734, 2010.
17. **Batal O**, **Schoenhagen P**, **Shao M**, **Ayyad AE**, **Van Wagoner DR**, **Halliburton SS**, **Tchou PJ**, **Chung MK**. Left atrial epicardial adiposity and atrial fibrillation. *Circ Arrhythm Electrophysiol* 3: 230–236, 2010.
18. **Bellows CF**, **Zhang Y**, **Simmons PJ**, **Khalsa AS**, **Kolonin MG**. Influence of BMI on level of circulating progenitor cells. *Obes Silver Spring* 19: 1722–6, 2011.
19. **Bidault G**, **Vatier C**, **Capeau J**, **Vigouroux C**, **Béréziat V**. LMNA-linked lipodystrophies: from altered fat distribution to cellular alterations. *Biochem Soc Trans* 39: 1752–1757, 2011.
20. **Billon N**, **Dani C**. Developmental origins of the adipocyte lineage: new insights from genetics and genomics studies. *Stem Cell Rev* 8: 55–66, 2012.
21. **Bluher M**. Adipose tissue dysfunction in obesity. *Exp Clin Endocrinol Diabetes* 117: 241–50, 2009.
22. **Boixel C**, **Fontaine V**, **Rücker-Martin C**, **Milliez P**, **Louedec L**, **Michel JB**, **Jacob MP**, **Hatem SN**. Fibrosis of the left atria during progression of heart failure is associated with increased matrix metalloproteinases in the rat. *J Am Coll Cardiol* 42: 336–344, 2003.
23. **Bonapace S**, **Perseghin G**, **Molon G**, **Canali G**, **Bertolini L**, **Zoppini G**, **Barbieri E**, **Targher G**. Nonalcoholic fatty liver disease is associated with left ventricular diastolic dysfunction in patients with type 2 diabetes. *Diabetes Care* 35: 389–395, 2012.
24. **Bordicchia M**, **Liu D**, **Amri E-Z**, **Ailhaud G**, **Dessì-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 Invest* 122: 1022–1036, 2012.
25. **Bourlier V**, **Sengenes C**, **Zakaroff-Girard A**, **Decaunes P**, **Wdziekonski B**, **Galitzky J**, **Villageois P**, **Esteve D**, **Chiotasso P**, **Dani C**, **Bouloumie A**. TGFbeta family members are key mediators in the induction of myofibroblast phenotype of human adipose tissue progenitor cells by macrophages. *PLoS One* 7: e31274, 2012.
26. **Bourlier V**, **Zakaroff-Girard A**, **Miranville A**, **De Barros S**, **Maumus M**, **Sengenes C**, **Galitzky J**, **Lafontan M**, **Karpe F**, **Frayn KN**, **Bouloumie A**. Remodeling phenotype of human subcutaneous adipose tissue macrophages. *Circulation* 117: 806–15, 2008.
27. **Brahimi-Horn MC**, **PouyssÃ©gur J**. Oxygen, a source of life and stress. *FEBS Lett* 581: 3582–3591, 2007.
28. **Britton KA**, **Massaro JM**, **Murabito JM**, **Kreger BE**, **Hoffmann U**, **Fox CS**. Body fat distribution, incident cardiovascular disease, cancer, and all-cause mortality. *J Am Coll Cardiol* 62: 921–925, 2013.

29. **Bruunsgaard H**, **Pedersen BK**. Age-related inflammatory cytokines and disease. *Immunol Allergy Clin North Am* 23: 15–39, 2003.
30. **Burgeiro A**, **Fuhrmann A**, **Cherian S**, **Espinoza D**, **Jarak I**, **Carvalho RA**, **Loureiro M**, **Patrício M**, **Antunes M**, **Carvalho E**. Glucose uptake and lipid metabolism are impaired in epicardial adipose tissue from heart failure patients with or without diabetes. *Am J Physiol Endocrinol Metab* 310: E550-564, 2016.
31. **Burstein B**, **Nattel S**. Atrial fibrosis: mechanisms and clinical relevance in atrial fibrillation. *J Am Coll Cardiol* 51: 802–809, 2008.
32. **Carnes CA**, **Chung MK**, **Nakayama T**, **Nakayama H**, **Baliga RS**, **Piao S**, **Kanderian A**, **Pavia S**, **Hamlin RL**, **McCarthy PM**, **Bauer JA**, **Van Wagoner DR**. Ascorbate attenuates atrial pacing-induced peroxynitrite formation and electrical remodeling and decreases the incidence of postoperative atrial fibrillation. *Circ Res* 89: E32-38, 2001.
33. **Cartwright MJ**, **Schlauch K**, **Lenburg ME**, **Tchkonia T**, **Pirtskhalava T**, **Cartwright A**, **Thomou T**, **Kirkland JL**. Aging, depot origin, and preadipocyte gene expression. *J Gerontol Biol Sci Med Sci* 65: 242–51, 2010.
34. **Castoldi A**, **Naffah de Souza C**, **CÃ¢mara NO**, **Moraes-Vieira PM**. The Macrophage Switch in Obesity Development. *Front Immunol* 6: 637, 2015.
35. **Cavalcante JL**, **Tamarappoo BK**, **Hachamovitch R**, **Kwon DH**, **Alraies MC**, **Halliburton S**, **Schoenhagen P**, **Dey D**, **Berman DS**, **Marwick TH**. Association of epicardial fat, hypertension, subclinical coronary artery disease, and metabolic syndrome with left ventricular diastolic dysfunction. *Am J Cardiol* 110: 1793–1798, 2012.
36. **Çetin S**, **Vural MG**, **Gündüz H**, **Akdemir R**, **Fırat H**. Epicardial fat thickness regression with continuous positive airway pressure therapy in patients with obstructive sleep apnea: assessment by two-dimensional echocardiography. *Wien Klin Wochenschr* 128: 187–192, 2016.
37. **Chao T-F**, **Hung C-L**, **Tsao H-M**, **Lin Y-J**, **Yun C-H**, **Lai Y-H**, **Chang S-L**, **Lo L-W**, **Hu Y-F**, **Tuan T-C**, **Chang H-Y**, **Kuo J-Y**, **Yeh H-I**, **Wu T-J**, **Hsieh M-H**, **Yu W-C**, **Chen S-A**. Epicardial adipose tissue thickness and ablation outcome of atrial fibrillation. *PloS One* 8: e74926, 2013.
38. **Chaowalit N**, **Lopez-Jimenez F**. Epicardial adipose tissue: friendly companion or hazardous neighbour for adjacent coronary arteries? *Eur Heart J* 29: 695–697, 2008.
39. **Chau Y-Y**, **Bandiera R**, **Serrels A**, **Martínez-Estrada OM**, **Qing W**, **Lee M**, **Slight J**, **Thornburn A**, **Berry R**, **McHaffie S**, **Stimson RH**, **Walker BR**, **Chapuli RM**, **Schedl A**, **Hastie N**. Visceral and subcutaneous fat have different origins and evidence supports a mesothelial source. *Nat Cell Biol* 16: 367–375, 2014.
40. **Chechi K**, **Blanchard P-G**, **Mathieu P**, **Deshaies Y**, **Richard D**. Brown fat like gene expression in the epicardial fat depot correlates with circulating HDL-cholesterol and triglycerides in patients with coronary artery disease. *Int J Cardiol* 167: 2264–2270, 2013.
41. **Chechi K**, **Richard D**. Thermogenic potential and physiological relevance of human epicardial adipose tissue. *Int J Obes Suppl* 5: S28-34, 2015.
42. **Cheng K-H**, **Chu C-S**, **Lee K-T**, **Lin T-H**, **Hsieh C-C**, **Chiu C-C**, **Voon W-C**, **Sheu S-H**, **Lai W-T**. Adipocytokines and proinflammatory mediators from abdominal and epicardial adipose tissue in patients with coronary artery disease. *Int J Obes 2005* 32: 268–274, 2008.
43. **Cheng VY**, **Dey D**, **Tamarappoo B**, **Nakazato R**, **Gransar H**, **Miranda-Peats R**, **Ramesh A**, **Wong ND**, **Shaw LJ**, **Slomka PJ**, **Berman DS**. Pericardial fat burden on ECG-

gated noncontrast CT in asymptomatic patients who subsequently experience adverse cardiovascular events. *JACC Cardiovasc Imaging* 3: 352–360, 2010.
44. **Cherian S**, **Lopaschuk GD**, **Carvalho E**. Cellular cross-talk between epicardial adipose tissue and myocardium in relation to the pathogenesis of cardiovascular disease. *Am J Physiol Endocrinol Metab* 303: E937-949, 2012.
45. **Cho K-I**, **Kim B-J**, **Cha T-J**, **Heo J-H**, **Kim H-S**, **Lee J-W**. Impact of duration and dosage of statin treatment and epicardial fat thickness on the recurrence of atrial fibrillation after electrical cardioversion. *Heart Vessels* 30: 490–497, 2015.
46. **Christopherson KW 2nd**, **Cooper S**, **Broxmeyer HE**. Cell surface peptidase CD26/DPPIV mediates G-CSF mobilization of mouse progenitor cells. *Blood* 101: 4680–6, 2003.
47. **Cildir G**, **AkÄ±ncÄ±lar SC**, **Tergaonkar V**. Chronic adipose tissue inflammation: all immune cells on the stage. *Trends Mol Med* 19: 487–500, 2013.
48. **Clement K**, **Basdevant A**, **Dutour A**. Weight of Pericardial Fat on Coronaropathy. *Arterioscler Thromb Vasc Biol* 29: 615–616, 2009.
49. **Coppe JP**, **Patil CK**, **Rodier F**, **Sun Y**, **Munoz DP**, **Goldstein J**, **Nelson PS**, **Desprez PY**, **Campisi J**. Senescence-associated secretory phenotypes reveal cell-nonautonomous functions of oncogenic RAS and the p53 tumor suppressor. *PLoS Biol* 6: 2853–68, 2008.
50. **Corradi D**, **Maestri R**, **Callegari S**, **Pastori P**, **Goldoni M**, **Luong TV**, **Bordi C**. The ventricular epicardial fat is related to the myocardial mass in normal, ischemic and hypertrophic hearts. *Cardiovasc Pathol* 13: 313–316, 2004.
51. **Coumel P**. Paroxysmal atrial fibrillation: a disorder of autonomic tone? *Eur Heart J* 15 Suppl A: 9–16, 1994.
52. **Cousin B**, **Cinti S**, **Morroni M**, **Raimbault S**, **Ricquier D**, **Pénicaud L**, **Casteilla L**. Occurrence of brown adipocytes in rat white adipose tissue: molecular and morphological characterization. *J Cell Sci* 103 (Pt 4): 931–942, 1992.
53. **Creely SJ**, **McTernan PG**, **Kusminski CM**, **Fisher ff M**, **Da Silva NF**, **Khanolkar M**, **Evans M**, **Harte AL**, **Kumar S**. Lipopolysaccharide activates an innate immune system response in human adipose tissue in obesity and type 2 diabetes. *Am J Physiol Endocrinol Metab* 292: E740-747, 2007.
54. **Crendal E**, **Dutheil F**, **Naughton G**, **McDonald T**, **Obert P**. Increased myocardial dysfunction, dyssynchrony, and epicardial fat across the lifespan in healthy males. *BMC Cardiovasc Disord* 14: 95, 2014.
55. **Cristobal-Huerta A**, **Torrado-Carvajal A**, **Malpica N**, **Luaces M**, **Hernandez-Tamames JA**. Automated quantification of epicardial adipose tissue in cardiac magnetic resonance imaging. *Conf Proc Annu Int Conf IEEE Eng Med Biol Soc IEEE Eng Med Biol Soc Annu Conf* 2015: 7308–7311, 2015.
56. **Cypess AM**, **Lehman S**, **Williams G**, **Tal I**, **Rodman D**, **Goldfine AB**, **Kuo FC**, **Palmer EL**, **Tseng Y-H**, **Doria A**, **Kolodny GM**, **Kahn CR**. Identification and importance of brown adipose tissue in adult humans. *N Engl J Med* 360: 1509–1517, 2009.
57. **Dabbah S**, **Komarov H**, **Marmor A**, **Assy N**. Epicardial fat, rather than pericardial fat, is independently associated with diastolic filling in subjects without apparent heart disease. *Nutr Metab Cardiovasc Dis NMCD* 24: 877–882, 2014.
58. **Dabbah S**, **Komarov H**, **Marmor A**, **Assy N**. Epicardial fat, rather than pericardial fat, is independently associated with diastolic filling in subjects without apparent heart disease. *Nutr Metab Cardiovasc Dis NMCD* 24: 877–882, 2014.
59. **Dalmas E**, **Toubal A**, **Alzaid F**, **Blazek K**, **Eames HL**, **Lebozec K**, **Pini M**, **Hainault I**, **Montastier E**, **Denis RG**, **Ancel P**, **Lacombe A**, **Ling Y**, **Allatif O**, **Cruciani-**

Guglielmacci C, **AndrÃ© S**, **Viguerie N**, **Poitou C**, **Stich V**, **Torcivia A**, **Foufelle F**, **Luquet S**, **Aron-Wisnewsky J**, **Langin D**, **ClÃ©ment K**, **Udalova IA**, **Venteclef N**. Irf5 deficiency in macrophages promotes beneficial adipose tissue expansion and insulin sensitivity during obesity. *Nat. Med.* (2015). doi: 10.1038/nm.3829.
60. **Dar A**, **Schajnovitz A**, **Lapid K**, **Kalinkovich A**, **Itkin T**, **Ludin A**, **Kao WM**, **Battista M**, **Tesio M**, **Kollet O**, **Cohen NN**, **Margalit R**, **Buss EC**, **Baleux F**, **Oishi S**, **Fujii N**, **Larochelle A**, **Dunbar CE**, **Broxmeyer HE**, **Frenette PS**, **Lapidot T**. Rapid mobilization of hematopoietic progenitors by AMD3100 and catecholamines is mediated by CXCR4-dependent SDF-1 release from bone marrow stromal cells. *Leukemia* 25: 1286–96, 2011.
61. **Das M**, **Gabriely I**, **Barzilai N**. Caloric restriction, body fat and ageing in experimental models. *Obes. Rev.* (2004). doi: 10.1111/j.1467-789X.2004.00115.x.
62. **Dean RT**, **Wilcox I**. Possible atherogenic effects of hypoxia during obstructive sleep apnea. *Sleep* 16: S15-21-22, 1993.
63. **Despres J-P**. Body Fat Distribution and Risk of Cardiovascular Disease: An Update. *Circulation* 126: 1301–1313, 2012.
64. **Ding J**, **Hsu F-C**, **Harris TB**, **Liu Y**, **Kritchevsky SB**, **Szklo M**, **Ouyang P**, **Espeland MA**, **Lohman KK**, **Criqui MH**, **Allison M**, **Bluemke DA**, **Carr JJ**. The association of pericardial fat with incident coronary heart disease: the Multi-Ethnic Study of Atherosclerosis (MESA). *Am J Clin Nutr* 90: 499–504, 2009.
65. **Divoux A**, **ClÃ©ment K**. Architecture and the extracellular matrix: the still unappreciated components of the adipose tissue. *Obes Rev Off J Int Assoc Study Obes* 12: 503, 2011.
66. **Djian P**, **Roncari AK**, **Hollenberg CH**. Influence of anatomic site and age on the replication and differentiation of rat adipocyte precursors in culture. *J Clin Invest* 72: 1200–8, 1983.
67. **Doesch C**, **Haghi D**, **Flüchter S**, **Suselbeck T**, **Schoenberg SO**, **Michaely H**, **Borggrefe M**, **Papavassiliu T**. Epicardial adipose tissue in patients with heart failure. *J Cardiovasc Magn Reson Off J Soc Cardiovasc Magn Reson* 12: 40, 2010.
68. **Doesch C**, **Suselbeck T**, **Leweling H**, **Fluechter S**, **Haghi D**, **Schoenberg SO**, **Borggrefe M**, **Papavassiliu T**. Bioimpedance analysis parameters and epicardial adipose tissue assessed by cardiac magnetic resonance imaging in patients with heart failure. *Obes Silver Spring Md* 18: 2326–2332, 2010.
69. **Donato AJ**, **Henson GD**, **Hart CR**, **Layec G**, **Trinity JD**, **Bramwell CR**, **Enz RA**, **Morgan GR**, **Reihl KD**, **Hazra S**. The impact of ageing on adipose structure, function and vasculature in the B6D2F1 mouse: evidence of significant multisystem dysfunction. *J Physiol* 592: 4083–4096, 2014.
70. **Döring Y**, **Pawig L**, **Weber C**, **Noels H**. The CXCL12/CXCR4 chemokine ligand/receptor axis in cardiovascular disease. *Front Physiol* 5: 212, 2014.
71. **Douglas NJ**, **Polo O**. Pathogenesis of obstructive sleep apnoea/hypopnoea syndrome. *Lancet Lond Engl* 344: 653–655, 1994.
72. **Dozio E**, **Vianello E**, **Briganti S**, **Fink B**, **Malavazos AE**, **Scognamiglio ET**, **Dogliotti G**, **Sigrüener A**, **Schmitz G**, **Corsi Romanelli MM**. Increased reactive oxygen species production in epicardial adipose tissues from coronary artery disease patients is associated with brown-to-white adipocyte trans-differentiation. *Int J Cardiol* 174: 413–414, 2014.
73. **Dutour A**, **Abdesselam I**, **Ancel P**, **Kober F**, **Mrad G**, **Darmon P**, **Ronsin O**, **Pradel V**, **Lesavre N**, **Martin JC**, **Jacquier A**, **Lefur Y**, **Bernard M**, **Gaborit B**. Exenatide decreases Liver fat content and Epicardial Adipose Tissue in Patients with obesity and

Type 2 Diabetes: A prospective randomised clinical trial using Magnetic Resonance Imaging and Spectroscopy. *Diabetes Obes. Metab.* (April 23, 2016). doi: 10.1111/dom.12680.
74. **Dutour A**, **Achard V**, **Sell H**, **Naour N**, **Collart F**, **Gaborit B**, **Silaghi A**, **Eckel J**, **Alessi M-C**, **Henegar C**, **Clément K**. Secretory Type II Phospholipase A2 Is Produced and Secreted by Epicardial Adipose Tissue and Overexpressed in Patients with Coronary Artery Disease. *J Clin Endocrinol Metab* 95: 963–967, 2010.
75. **Enzi G**, **Gasparo M**, **Biondetti PR**, **Fiore D**, **Semisa M**, **Zurlo F**. Subcutaneous and visceral fat distribution according to sex, age, and overweight, evaluated by computed tomography. *Am J Clin Nutr* 44: 739–46, 1986.
76. **Fain JN**, **Sacks HS**, **Buehrer B**, **Bahouth SW**, **Garrett E**, **Wolf RY**, **Carter RA**, **Tichansky DS**, **Madan AK**. Identification of omentin mRNA in human epicardial adipose tissue: comparison to omentin in subcutaneous, internal mammary artery periadventitial and visceral abdominal depots. *Int J Obes 2005* 32: 810–815, 2008.
77. **Ferraro GA**, **Mizuno H**, **Pallua N**. Adipose Stem Cells: From Bench to Bedside. *Stem Cells Int* 2016: 6484038, 2016.
78. **Fontes-Carvalho R**, **Fontes-Oliveira M**, **Sampaio F**, **Mancio J**, **Bettencourt N**, **Teixeira M**, **Rocha Gonçalves F**, **Gama V**, **Leite-Moreira A**. Influence of epicardial and visceral fat on left ventricular diastolic and systolic functions in patients after myocardial infarction. *Am J Cardiol* 114: 1663–1669, 2014.
79. **Fontes-Carvalho R**, **Fontes-Oliveira M**, **Sampaio F**, **Mancio J**, **Bettencourt N**, **Teixeira M**, **Rocha Gonçalves F**, **Gama V**, **Leite-Moreira A**. Influence of epicardial and visceral fat on left ventricular diastolic and systolic functions in patients after myocardial infarction. *Am J Cardiol* 114: 1663–1669, 2014.
80. **Foster MT**, **Shi H**, **Seeley RJ**, **Woods SC**. Removal of intra-abdominal visceral adipose tissue improves glucose tolerance in rats: role of hepatic triglyceride storage. *Physiol Behav* 104: 845–854, 2011.
81. **Franssens BT**, **Nathoe HM**, **Leiner T**, **van der Graaf Y**, **Visseren FL**, **SMART study group**. Relation between cardiovascular disease risk factors and epicardial adipose tissue density on cardiac computed tomography in patients at high risk of cardiovascular events. *Eur. J. Prev. Cardiol.* (November 21, 2016). doi: 10.1177/2047487316679524.
82. **Friedman DJ**, **Wang N**, **Meigs JB**, **Hoffmann U**, **Massaro JM**, **Fox CS**, **Magnani JW**. Pericardial fat is associated with atrial conduction: the Framingham Heart Study. *J Am Heart Assoc* 3: e000477, 2014.
83. **Fukagawa NK**, **Kohrt WM**. Loss of skeletal muscle mass with aging: effect on glucose tolerance. *J. Â€¦* (1995). doi: 10.1093/gerona/50A.Special_Issue.68.
84. **Gaborit B**, **Abdesselam I**, **Dutour A**. Epicardial fat: more than just an “epi” phenomenon? *Horm Metab Res Horm Stoffwechselforschung Horm Métabolisme* 45: 991–1001, 2013.
85. **Gaborit B**, **Dutour A**. Looking beyond ectopic fat amount: A SMART method to quantify epicardial adipose tissue density. *Eur. J. Prev. Cardiol.* (January 1, 2017). doi: 10.1177/2047487317689976.
86. **Gaborit B**, **Jacquier A**, **Kober F**, **Abdesselam I**, **Cuisset T**, **Boullu-Ciocca S**, **Emungania O**, **Alessi M-C**, **Clément K**, **Bernard M**, **Dutour A**. Effects of bariatric surgery on cardiac ectopic fat: lesser decrease in epicardial fat compared to visceral fat loss and no change in myocardial triglyceride content. *J Am Coll Cardiol* 60: 1381–1389, 2012.
87. **Gaborit B**, **Kober F**, **Jacquier A**, **Moro PJ**, **Cuisset T**, **Boullu S**, **Dadoun F**, **Alessi**

M-C, **Morange P**, **Clément K**, **Bernard M**, **Dutour A**. Assessment of epicardial fat volume and myocardial triglyceride content in severely obese subjects: relationship to metabolic profile, cardiac function and visceral fat. *Int J Obes* 36: 422–430, 2012.
88. **Gaborit B**, **Kober F**, **Jacquier A**, **Moro PJ**, **Flavian A**, **Quilici J**, **Cuisset T**, **Simeoni U**, **Cozzone P**, **Alessi M-C**, **Clément K**, **Bernard M**, **Dutour A**. Epicardial fat volume is associated with coronary microvascular response in healthy subjects: a pilot study. *Obes Silver Spring Md* 20: 1200–1205, 2012.
89. **Gaborit B**, **Venteclef N**, **Ancel P**, **Pelloux V**, **Gariboldi V**, **Leprince P**, **Amour J**, **Hatem SN**, **Jouve E**, **Dutour A**, **Clément K**. Human epicardial adipose tissue has a specific transcriptomic signature depending on its anatomical peri-atrial, peri-ventricular, or peri-coronary location. *Cardiovasc Res* 108: 62–73, 2015.
90. **Galant D**, **Gaborit B**, **Desgrouas C**, **Abdesselam I**, **Bernard M**, **Levy N**, **Merono F**, **Coirault C**, **Roll P**, **Lagarde A**, **Bonello-Palot N**, **Bourgeois P**, **Dutour A**, **Badens C**. A Heterozygous ZMPSTE24 Mutation Associated with Severe Metabolic Syndrome, Ectopic Fat Accumulation, and Dilated Cardiomyopathy. *Cells* 5, 2016.
91. **Garg SK**, **Delaney C**, **Shi H**, **Yung R**. Changes in adipose tissue macrophages and T cells during aging. *Crit Rev Immunol* 34: 1–14, 2014.
92. **Geiger K**, **Leiherer A**, **Muendlein A**, **Stark N**, **Geller-Rhomberg S**, **Saely CH**, **Wabitsch M**, **Fraunberger P**, **Drexel H**. Identification of hypoxia-induced genes in human SGBS adipocytes by microarray analysis. *PLoS One* 6: e26465, 2011.
93. **Gil-Ortega M**, **Fernandez-Alfonso MS**, **Somoza B**, **Casteilla L**, **Sengenes C**. Ex vivo microperfusion system of the adipose organ: a new approach to studying the mobilization of adipose cell populations. *Int. J. Obes.* (December 20, 2013). doi: 10.1038/ijo.2013.243.
94. **Gil-Ortega M**, **Garidou L**, **Barreau C**, **Maumus M**, **Breasson L**, **Tavernier G**, **Garcia-Prieto CF**, **Bouloumie A**, **Casteilla L**, **Sengenes C**. Native adipose stromal cells egress from adipose tissue in vivo: evidence during lymph node activation. *Stem Cells* 31: 1309–20, 2013.
95. **Gimble J**, **Guilak F**. Adipose-derived adult stem cells: isolation, characterization, and differentiation potential. *Cytotherapy* 5: 362–9, 2003.
96. **Gimble JM**, **Bunnell BA**, **Guilak F**. Human adipose-derived cells: an update on the transition to clinical translation. *Regen Med* 7: 225–35, 2012.
97. **Gökdeniz T**, **Erkol A**, **Kalaycıoğlu E**, **Çağrı Aykan A**, **Gül İ**, **Boyacı F**, **Turan B**, **Ozkan M**. Relation of epicardial fat thickness to subclinical right ventricular dysfunction assessed by strain and strain rate imaging in subjects with metabolic syndrome: a two-dimensional speckle tracking echocardiography study. *Echocardiogr Mt Kisco N* 32: 248–256, 2015.
98. **Goossens GH**, **Bizzarri A**, **Venteclef N**, **Essers Y**, **Cleutjens JP**, **Konings E**, **Jocken JWE**, **Cajlakovic M**, **Ribitsch V**, **Clement K**, **Blaak EE**. Increased Adipose Tissue Oxygen Tension in Obese Compared With Lean Men Is Accompanied by Insulin Resistance, Impaired Adipose Tissue Capillarization, and Inflammation. *Circulation* 124: 67–76, 2011.
99. **Gorter PM**, **de Vos AM**, **van der Graaf Y**, **Stella PR**, **Doevendans PA**, **Meijs MFL**, **Prokop M**, **Visseren FLJ**. Relation of epicardial and pericoronary fat to coronary atherosclerosis and coronary artery calcium in patients undergoing coronary angiography. *Am J Cardiol* 102: 380–385, 2008.
100. **Granér M**, **Nyman K**, **Siren R**, **Pentikäinen MO**, **Lundbom J**, **Hakkarainen A**, **Lauerma K**, **Lundbom N**, **Nieminen MS**, **Taskinen M-R**. Ectopic fat depots and left ventricular function in nondiabetic men with nonalcoholic fatty liver disease. *Circ*

Cardiovasc Imaging 8, 2015.
101. **Greif M**, **Becker A**, **von Ziegler F**, **Lebherz C**, **Lehrke M**, **Broedl UC**, **Tittus J**, **Parhofer K**, **Becker C**, **Reiser M**, **Knez A**, **Leber AW**. Pericardial adipose tissue determined by dual source CT is a risk factor for coronary atherosclerosis. *Arterioscler Thromb Vasc Biol* 29: 781–786, 2009.
102. **Greulich S**, **Chen WJY**, **Maxhera B**, **Rijzewijk LJ**, **van der Meer RW**, **Jonker JT**, **Mueller H**, **de Wiza DH**, **Floerke R-R**, **Smiris K**, **Lamb HJ**, **de Roos A**, **Bax JJ**, **Romijn JA**, **Smit JWA**, **Akhyari P**, **Lichtenberg A**, **Eckel J**, **Diamant M**, **Ouwens DM**. Cardioprotective properties of omentin-1 in type 2 diabetes: evidence from clinical and in vitro studies. *PloS One* 8: e59697, 2013.
103. **Greulich S**, **Maxhera B**, **Vandenplas G**, **de Wiza DH**, **Smiris K**, **Mueller H**, **Heinrichs J**, **Blumensatt M**, **Cuvelier C**, **Akhyari P**, **Ruige JB**, **Ouwens DM**, **Eckel J**. Secretory products from epicardial adipose tissue of patients with type 2 diabetes mellitus induce cardiomyocyte dysfunction. *Circulation* 126: 2324–2334, 2012.
104. **Greulich S**, **de Wiza DH**, **Preilowski S**, **Ding Z**, **Mueller H**, **Langin D**, **Jaquet K**, **Ouwens DM**, **Eckel J**. Secretory products of guinea pig epicardial fat induce insulin resistance and impair primary adult rat cardiomyocyte function. *J Cell Mol Med* 15: 2399–2410, 2011.
105. **Groves EM**, **Erande AS**, **Le C**, **Salcedo J**, **Hoang KC**, **Kumar S**, **Mohar DS**, **Saremi F**, **Im J**, **Agrawal Y**, **Nadeswaran P**, **Naderi N**, **Malik S**. Comparison of epicardial adipose tissue volume and coronary artery disease severity in asymptomatic adults with versus without diabetes mellitus. *Am J Cardiol* 114: 686–691, 2014.
106. **Gruver AL**, **Hudson LL**, **Sempowski GD**. Immunosenescence of ageing. *J Pathol* 211: 144–156, 2007.
107. **Guo SS**, **Zeller C**, **Chumlea WC**, **Siervogel RM**. Aging, body composition, and lifestyle: the Fels Longitudinal Study. *Am J Clin Nutr* 70: 405–411, 1999.
108. **Guo W**, **Pirtskhalava T**, **Tchkonia T**, **Xie W**, **Thomou T**, **Han J**, **Wang T**, **Wong S**, **Cartwright A**, **Hegardt FG**, **Corkey BE**, **Kirkland JL**. Aging results in paradoxical susceptibility of fat cell progenitors to lipotoxicity. *Am J Physiol Endocrinol Metab* 292: E1041-51, 2007.
109. **Gupta OT**, **Gupta RK**. Visceral Adipose Tissue Mesothelial Cells: Living on the Edge or Just Taking Up Space? *Trends Endocrinol Metab TEM* 26: 515–523, 2015.
110. **Han JM**, **Wu D**, **Denroche HC**, **Yao Y**, **Verchere CB**, **Levings MK**. IL-33 Reverses an Obesity-Induced Deficit in Visceral Adipose Tissue ST2+ T Regulatory Cells and Ameliorates Adipose Tissue Inflammation and Insulin Resistance. *J Immunol* 194: 4777–83, 2015.
111. **Hassan M**, **Latif N**, **Yacoub M**. Adipose tissue: friend or foe? *Nat Rev Cardiol* 9: 689–702, 2012.
112. **Hatem SN**, **Redheuil A**, **Gandjbakhch E**. Cardiac adipose tissue and atrial fibrillation: the perils of adiposity. *Cardiovasc Res* 109: 502–509, 2016.
113. **Hell MM**, **Ding X**, **Rubeaux M**, **Slomka P**, **Gransar H**, **Terzopoulos D**, **Hayes S**, **Marwan M**, **Achenbach S**, **Berman DS**, **Dey D**. Epicardial adipose tissue volume but not density is an independent predictor for myocardial ischemia. *J Cardiovasc Comput Tomogr* 10: 141–149, 2016.
114. **Henegar C**, **Tordjman J**, **Achard V**, **Lacasa D**, **Cremer I**, **Guerre-Millo M**, **Poitou C**, **Basdevant A**, **Stich V**, **Viguerie N**, **Langin D**, **Bedossa P**, **Zucker J-DD**, **Clement KC**. Adipose tissue transcriptomic signature highlights the pathological relevance of extracellular matrix in human obesity. *Genome Biol* 9, 2008.
115. **Hirata Y**, **Tabata M**, **Kurobe H**, **Motoki T**, **Akaike M**, **Nishio C**, **Higashida M**,

Mikasa H, **Nakaya Y**, **Takanashi S**, **Igarashi T**, **Kitagawa T**, **Sata M**. Coronary atherosclerosis is associated with macrophage polarization in epicardial adipose tissue. *J Am Coll Cardiol* 58: 248–255, 2011.
116. **Hirata Y**, **Yamada H**, **Kusunose K**, **Iwase T**, **Nishio S**, **Hayashi S**, **Bando M**, **Amano R**, **Yamaguchi K**, **Soeki T**, **Wakatsuki T**, **Sata M**. Clinical Utility of Measuring Epicardial Adipose Tissue Thickness with Echocardiography Using a High-Frequency Linear Probe in Patients with Coronary Artery Disease. *J Am Soc Echocardiogr Off Publ Am Soc Echocardiogr* 28: 1240–1246.e1, 2015.
117. **Hocking SL**, **Stewart RL**, **Brandon AE**, **Suryana E**, **Stuart E**, **Baldwin EM**, **Kolumam GA**, **Modrusan Z**, **Junutula JR**, **Gunton JE**, **Medynskyj M**, **Blaber SP**, **Karsten E**, **Herbert BR**, **James DE**, **Cooney GJ**, **Swarbrick MM**. Subcutaneous fat transplantation alleviates diet-induced glucose intolerance and inflammation in mice. *Diabetologia* 58: 1587–1600, 2015.
118. **Homsi R**, **Meier-Schroers M**, **Gieseke J**, **Dabir D**, **Luetkens JA**, **Kuetting DL**, **Naehle CP**, **Marx C**, **Schild HH**, **Thomas DK**, **Sprinkart AM**. 3D-Dixon MRI based volumetry of peri- and epicardial fat. *Int J Cardiovasc Imaging* 32: 291–299, 2016.
119. **Hotamisligil GS**. Endoplasmic reticulum stress and the inflammatory basis of metabolic disease [Online]. *Cell*. C:\Mon Dossier\Banque Doc Sympas\Hotamisligil-2010-Cell.pdf http://www.sciencedirect.com/science/article/pii/S009286741000187X.
120. **Hotamisligil GS**, **Arner P**, **Caro JF**. Increased adipose tissue expression of tumor necrosis factor-alpha in human obesity and insulin resistance. *J. Clin. Â€¦* (1995). doi: 10.1172/jci117936.
121. **Hotamisligil GS**, **Shargill NS**, **Spiegelman BM**. Adipose expression of tumor necrosis factor-alpha: direct role in obesity-linked insulin resistance. *Science* 259: 87–91, 1993.
122. **Hua N**, **Chen Z**, **Phinikaridou A**, **Pham T**, **Qiao Y**, **LaValley MP**, **Bigornia SJ**, **Ruth MR**, **Apovian CM**, **Ruberg FL**, **Hamilton JA**. The influence of pericardial fat upon left ventricular function in obese females: evidence of a site-specific effect. *J Cardiovasc Magn Reson Off J Soc Cardiovasc Magn Reson* 16: 37, 2014.
123. **Iacobellis G**. Relation of epicardial fat thickness to right ventricular cavity size in obese subjects. *Am J Cardiol* 104: 1601–1602, 2009.
124. **Iacobellis G**. Local and systemic effects of the multifaceted epicardial adipose tissue depot. *Nat Rev Endocrinol* 11: 363–371, 2015.
125. **Iacobellis G**, **Assael F**, **Ribaudo MC**, **Zappaterreno A**, **Alessi G**, **Di Mario U**, **Leonetti F**. Epicardial fat from echocardiography: a new method for visceral adipose tissue prediction. *Obes Res* 11: 304–310, 2003.
126. **Iacobellis G**, **Bianco AC**. Epicardial adipose tissue: emerging physiological, pathophysiological and clinical features. *Trends Endocrinol Metab TEM* 22: 450–457, 2011.
127. **Iacobellis G**, **Corradi D**, **Sharma AM**. Epicardial adipose tissue: anatomic, biomolecular and clinical relationships with the heart. *Nat Clin Pract Cardiovasc Med* 2: 536–543, 2005.
128. **Iacobellis G**, **Leonetti F**, **Singh N**, **M Sharma A**. Relationship of epicardial adipose tissue with atrial dimensions and diastolic function in morbidly obese subjects. *Int J Cardiol* 115: 272–273, 2007.
129. **Iacobellis G**, **Pistilli D**, **Gucciardo M**, **Leonetti F**, **Miraldi F**, **Brancaccio G**, **Gallo P**, **di Gioia CRT**. Adiponectin expression in human epicardial adipose tissue in vivo is lower in patients with coronary artery disease. *Cytokine* 29: 251–255, 2005.
130. **Iacobellis G**, **Pond CM**, **Sharma AM**. Different “weight” of cardiac and general

adiposity in predicting left ventricle morphology. *Obes Silver Spring Md* 14: 1679–1684, 2006.
131. **Iacobellis G**, **Ribaudo MC**, **Zappaterreno A**, **Iannucci CV**, **Leonetti F**. Relation between epicardial adipose tissue and left ventricular mass. *Am J Cardiol* 94: 1084–1087, 2004.
132. **Iacobellis G**, **Zaki MC**, **Garcia D**, **Willens HJ**. Epicardial fat in atrial fibrillation and heart failure. *Horm Metab Res Horm Stoffwechselforschung Horm Métabolisme* 46: 587–590, 2014.
133. **Iozzo P**. Myocardial, Perivascular, and Epicardial Fat. *Diabetes Care* 34: S371–S379, 2011.
134. **Iozzo P**, **Lautamaki R**, **Borra R**, **Lehto H-R**, **Bucci M**, **Viljanen A**, **Parkka J**, **Lepomaki V**, **Maggio R**, **Parkkola R**, **Knuuti J**, **Nuutila P**. Contribution of glucose tolerance and gender to cardiac adiposity. *J Clin Endocrinol Metab* 94: 4472–4482, 2009.
135. **Ishikawa Y**, **Ishii T**, **Asuwa N**, **Masuda S**. Absence of atherosclerosis evolution in the coronary arterial segment covered by myocardial tissue in cholesterol-fed rabbits. *Virchows Arch Int J Pathol* 430: 163–171, 1997.
136. **Ito T**, **Suzuki Y**, **Ehara M**, **Matsuo H**, **Teramoto T**, **Terashima M**, **Nasu K**, **Kinoshita Y**, **Tsuchikane E**, **Suzuki T**, **Kimura G**. Impact of epicardial fat volume on coronary artery disease in symptomatic patients with a zero calcium score. *Int J Cardiol* 167: 2852–2858, 2013.
137. **Iyengar P**, **Espina V**, **Williams TW**, **Lin Y**, **Berry D**, **Jelicks LA**, **Lee H**, **Temple K**, **Graves R**, **Pollard J**, **Chopra N**, **Russell RG**, **Sasisekharan R**, **Trock BJ**, **Lippman M**, **Calvert VS**, **Petricoin EF**, **Liotta L**, **Dadachova E**, **Pestell RG**, **Lisanti MP**, **Bonaldo P**, **Scherer PEC**. Adipocyte-derived collagen VI affects early mammary tumor progression in vivo, demonstrating a critical interaction in the tumor/stroma microenvironment. *J Clin Invest* 115: 1163–1176, 2005.
138. **Janik M**, **Hartlage G**, **Alexopoulos N**, **Mirzoyev Z**, **McLean DS**, **Arepalli CD**, **Chen Z**, **Stillman AE**, **Raggi P**. Epicardial adipose tissue volume and coronary artery calcium to predict myocardial ischemia on positron emission tomography-computed tomography studies. *J Nucl Cardiol Off Publ Am Soc Nucl Cardiol* 17: 841–847, 2010.
139. **Jing L**, **Binkley CM**, **Suever JD**, **Umasankar N**, **Haggerty CM**, **Rich J**, **Wehner GJ**, **Hamlet SM**, **Powell DK**, **Radulescu A**, **Kirchner HL**, **Epstein FH**, **Fornwalt BK**. Cardiac remodeling and dysfunction in childhood obesity: a cardiovascular magnetic resonance study. *J Cardiovasc Magn Reson Off J Soc Cardiovasc Magn Reson* 18: 28, 2016.
140. **Johnson AR**, **Milner JJ**, **Makowski L**. The inflammation highway: metabolism accelerates inflammatory traffic in obesity. *Immunol Rev* 249: 218–238, 2012.
141. **Kaisho T**, **Akira S**. Toll-like receptors as adjuvant receptors. *Biochim Biophys Acta* 1589: 1–13, 2002.
142. **von Känel R**, **Loredo JS**, **Ancoli-Israel S**, **Mills PJ**, **Natarajan L**, **Dimsdale JE**. Association between polysomnographic measures of disrupted sleep and prothrombotic factors. *Chest* 131: 733–739, 2007.
143. **Kankaanpää M**, **Lehto H-R**, **Pärkkä JP**, **Komu M**, **Viljanen A**, **Ferrannini E**, **Knuuti J**, **Nuutila P**, **Parkkola R**, **Iozzo P**. Myocardial triglyceride content and epicardial fat mass in human obesity: relationship to left ventricular function and serum free fatty acid levels. *J Clin Endocrinol Metab* 91: 4689–4695, 2006.
144. **Kannel WB**, **Abbott RD**, **Savage DD**, **McNamara PM**. Epidemiologic features of chronic atrial fibrillation: the Framingham study. *N Engl J Med* 306: 1018–1022, 1982.
145. **Kaplan O**, **Kurtoglu E**, **Gozubuyuk G**, **Dogan C**, **Acar Z**, **EyupKoca F**, **Pekdemir H**. Epicardial adipose tissue thickness in patients with chronic obstructive pulmonary

disease having right ventricular systolic dysfunction. *Eur Rev Med Pharmacol Sci* 19: 2461–2467, 2015.
146. **Karastergiou K**, **Evans I**, **Ogston N**, **Miheisi N**, **Nair D**, **Kaski J-C**, **Jahangiri M**, **Mohamed-Ali V**. Epicardial adipokines in obesity and coronary artery disease induce atherogenic changes in monocytes and endothelial cells. *Arterioscler Thromb Vasc Biol* 30: 1340–1346, 2010.
147. **Karimabad MN**, **Hassanshahi G**. Significance of CXCL12 in type 2 diabetes mellitus and its associated complications. *Inflammation* 38: 710–717, 2015.
148. **Karpe F**, **Fielding BA**, **Ilic V**, **Macdonald IA**, **Summers LK**, **Frayn KN**. Impaired postprandial adipose tissue blood flow response is related to aspects of insulin sensitivity. *Diabetes* 51: 2467–73, 2002.
149. **Kato M**, **Roberts-Thomson P**, **Phillips BG**, **Haynes WG**, **Winnicki M**, **Accurso V**, **Somers VK**. Impairment of endothelium-dependent vasodilation of resistance vessels in patients with obstructive sleep apnea. *Circulation* 102: 2607–2610, 2000.
150. **Keophiphath M**, **Achard V**, **Henegar C**, **Rouault C**, **Clément K**, **Lacasa D**. Macrophage-secreted factors promote a profibrotic phenotype in human preadipocytes. *Mol Endocrinol* 23: 11–24, 2009.
151. **Khan T**, **Muise ES**, **Iyengar P**, **Wang ZV**, **Chandalia M**, **Abate N**, **Zhang BB**, **Bonaldo P**, **Chua S**, **Scherer PE**. Metabolic dysregulation and adipose tissue fibrosis: role of collagen VI. *Mol Cell Biol* 29: 1575–91, 2009.
152. **Kilicaslan B**, **Ozdogan O**, **Aydin M**, **Dursun H**, **Susam I**, **Ertas F**. Increased epicardial fat thickness is associated with cardiac functional changes in healthy women. *Tohoku J Exp Med* 228: 119–124, 2012.
153. **Kim KH**, **Song MJ**, **Chung J**, **Park H**, **Kim JB**. Hypoxia inhibits adipocyte differentiation in a HDAC-independent manner. *Biochem Biophys Res Commun* 333: 1178–84, 2005.
154. **Kirkland JL**, **Dobson DE**. Preadipocyte function and aging: links between age-related changes in cell dynamics and altered fat tissue function. *J Am Geriatr Soc* 45: 959–67, 1997.
155. **Kirkland JL**, **Hollenberg CH**, **Gillon WS**. Age, anatomic site, and the replication and differentiation of adipocyte precursors. *Am J Physiol* 258: C206-10, 1990.
156. **Kitagawa T**, **Yamamoto H**, **Sentani K**, **Takahashi S**, **Tsushima H**, **Senoo A**, **Yasui W**, **Sueda T**, **Kihara Y**. The relationship between inflammation and neoangiogenesis of epicardial adipose tissue and coronary atherosclerosis based on computed tomography analysis. *Atherosclerosis* 243: 293–299, 2015.
157. **Kocyigit D**, **Gurses KM**, **Yalcin MU**, **Turk G**, **Evranos B**, **Yorgun H**, **Sahiner ML**, **Kaya EB**, **Hazirolan T**, **Tokgozoglu L**, **Oto MA**, **Ozer N**, **Aytemir K**. Periatrial epicardial adipose tissue thickness is an independent predictor of atrial fibrillation recurrence after cryoballoon-based pulmonary vein isolation. *J Cardiovasc Comput Tomogr* 9: 295–302, 2015.
158. **Kolaparthy LK**, **Sanivarapu S**, **Moogla S**, **Kutcham RS**. Adipose Tissue - Adequate, Accessible Regenerative Material. *Int J Stem Cells* 8: 121–127, 2015.
159. **Kostopoulos K**, **Alhanatis E**, **Pampoukas K**, **Georgiopoulos G**, **Zourla A**, **Panoutsopoulos A**, **Kallianos A**, **Velentza L**, **Zarogoulidis P**, **Trakada G**. CPAP therapy induces favorable short-term changes in epicardial fat thickness and vascular and metabolic markers in apparently healthy subjects with obstructive sleep apnea-hypopnea syndrome (OSAHS). *Sleep Breath Schlaf Atm* 20: 483–493, 2016.
160. **Krahn AD**, **Manfreda J**, **Tate RB**, **Mathewson FA**, **Cuddy TE**. The natural history of atrial fibrillation: incidence, risk factors, and prognosis in the Manitoba Follow-Up

Study. *Am J Med* 98: 476–484, 1995.
161. **Kramer CM**, **Barkhausen J**, **Flamm SD**, **Kim RJ**, **Nagel E**, **Society for Cardiovascular Magnetic Resonance Board of Trustees Task Force on Standardized Protocols**. Standardized cardiovascular magnetic resonance (CMR) protocols 2013 update. *J Cardiovasc Magn Reson Off J Soc Cardiovasc Magn Reson* 15: 91, 2013.
162. **Krausgruber T**, **Blazek K**, **Smallie T**, **Alzabin S**, **Lockstone H**, **Sahgal N**, **Hussell T**, **Feldmann M**, **Udalova IA**. IRF5 promotes inflammatory macrophage polarization and TH1-TH17 responses. *Nat Immunol* 12: 231–8, 2011.
163. **Krenning G**, **Zeisberg EM**, **Kalluri R**. The Origin of Fibroblasts and Mechanism of Cardiac Fibrosis. *J Cell Physiol* 225: 631–637, 2010.
164. **Kusminski CM**, **da Silva NF**, **Creely SJ**, **Fisher FM**, **Harte AL**, **Baker AR**, **Kumar S**, **McTernan PG**. The in vitro effects of resistin on the innate immune signaling pathway in isolated human subcutaneous adipocytes. *J Clin Endocrinol Metab* 92: 270–276, 2007.
165. **Kyle UG**, **Genton L**, **Hans D**, **Karsegard L**, **Slosman DO**, **Pichard C**. Age-related differences in fat-free mass, skeletal muscle, body cell mass and fat mass between 18 and 94 years. *Eur J Clin Nutr* 55: 663–72, 2001.
166. **La Cava A**, **Matarese G**. The weight of leptin in immunity. *Nat Rev Immunol* 4: 371–379, 2004.
167. **Langheim S**, **Dreas L**, **Veschini L**, **Maisano F**, **Foglieni C**, **Ferrarello S**, **Sinagra G**, **Zingone B**, **Alfieri O**, **Ferrero E**, **Maseri A**, **Ruotolo G**. Increased expression and secretion of resistin in epicardial adipose tissue of patients with acute coronary syndrome. *Am J Physiol Heart Circ Physiol* 298: H746-753, 2010.
168. **Lansley SM**, **Searles RG**, **Hoi A**, **Thomas C**, **Moneta H**, **Herrick SE**, **Thompson PJ**, **Newman M**, **Sterrett GF**, **Prêle CM**, **Mutsaers SE**. Mesothelial cell differentiation into osteoblast- and adipocyte-like cells. *J Cell Mol Med* 15: 2095–2105, 2011.
169. **Lapidot T**, **Dar A**, **Kollet O**. How do stem cells find their way home? *Blood* 106: 1901–10, 2005.
170. **Lapidot T**, **Kollet O**. The essential roles of the chemokine SDF-1 and its receptor CXCR4 in human stem cell homing and repopulation of transplanted immune-deficient NOD/SCID and NOD/SCID/B2m(null) mice. *Leukemia* 16: 1992–2003, 2002.
171. **Lapidot T**, **Petit I**. Current understanding of stem cell mobilization: the roles of chemokines, proteolytic enzymes, adhesion molecules, cytokines, and stromal cells. *Exp Hematol* 30: 973–81, 2002.
172. **Lau DH**, **Schotten U**, **Mahajan R**, **Antic NA**, **Hatem SN**, **Pathak RK**, **Hendriks JML**, **Kalman JM**, **Sanders P**. Novel mechanisms in the pathogenesis of atrial fibrillation: practical applications. *Eur Heart J* 37: 1573–1581, 2016.
173. **Lee B-C**, **Lee W-J**, **Lo S-C**, **Hsu H-C**, **Chien K-L**, **Chang Y-C**, **Chen M-F**. The ratio of epicardial to body fat improves the prediction of coronary artery disease beyond calcium and Framingham risk scores. *Int J Cardiovasc Imaging* 32 Suppl 1: 117–127, 2016.
174. **Levelt E**, **Pavlides M**, **Banerjee R**, **Mahmod M**, **Kelly C**, **Sellwood J**, **Ariga R**, **Thomas S**, **Francis J**, **Rodgers C**, **Clarke W**, **Sabharwal N**, **Antoniades C**, **Schneider J**, **Robson M**, **Clarke K**, **Karamitsos T**, **Rider O**, **Neubauer S**. Ectopic and Visceral Fat Deposition in Lean and Obese Patients With Type 2 Diabetes. *J Am Coll Cardiol* 68: 53–63, 2016.
175. **Levesque JP**, **Hendy J**, **Takamatsu Y**, **Williams B**, **Winkler IG**, **Simmons PJ**. Mobilization by either cyclophosphamide or granulocyte colony-stimulating factor transforms the bone marrow into a highly proteolytic environment. *Exp Hematol* 30:

440–9, 2002.
176. **Lim LP**, **Lau NC**, **Garrett-Engele P**, **Grimson A**, **Schelter JM**, **Castle J**, **Bartel DP**, **Linsley PS**, **Johnson JM**. Microarray analysis shows that some microRNAs downregulate large numbers of target mRNAs. *Nature* 433: 769–773, 2005.
177. **Lin H-H**, **Lee J-K**, **Yang C-Y**, **Lien Y-C**, **Huang J-W**, **Wu C-K**. Accumulation of epicardial fat rather than visceral fat is an independent risk factor for left ventricular diastolic dysfunction in patients undergoing peritoneal dialysis. *Cardiovasc Diabetol* 12: 127, 2013.
178. **Lin Y-K**, **Chen Y-C**, **Chen J-H**, **Chen S-A**, **Chen Y-J**. Adipocytes modulate the electrophysiology of atrial myocytes: implications in obesity-induced atrial fibrillation. *Basic Res Cardiol* 107: 293, 2012.
179. **Liu Q**, **Chen D**, **Wang Y**, **Zhao X**, **Zheng Y**. Cardiac autonomic nerve distribution and arrhythmia. *Neural Regen Res* 7: 2834–2841, 2012.
180. **Liu Q**, **Huang X**, **Oh J-H**, **Lin R-Z**, **Duan S**, **Yu Y**, **Yang R**, **Qiu J**, **Melero-Martin JM**, **Pu WT**, **Zhou B**. Epicardium-to-fat transition in injured heart. *Cell Res* 24: 1367–1369, 2014.
181. **Loader B**, **Stokic D**, **Riedl M**, **Hickmann S**, **Katzinger M**, **Willinger U**, **Luger A**, **Thurner S**, **Wick N**. Combined analysis of audiologic performance and the plasma biomarker stromal cell-derived factor 1a in type 2 diabetic patients. *Otol Neurotol* 29: 739–44, 2008.
182. **Lombardi R**, **Dong J**, **Rodriguez G**, **Bell A**, **Leung TK**, **Schwartz RJ**, **Willerson JT**, **Brugada R**, **Marian AJ**. Genetic fate mapping identifies second heart field progenitor cells as a source of adipocytes in arrhythmogenic right ventricular cardiomyopathy. *Circ Res* 104: 1076–1084, 2009.
183. **Lowell BB**, **Spiegelman BM**. Towards a molecular understanding of adaptive thermogenesis. *Nature* 404: 652–660, 2000.
184. **Lubrano C**, **Saponara M**, **Barbaro G**, **Specchia P**, **Addessi E**, **Costantini D**, **Tenuta M**, **Di Lorenzo G**, **Genovesi G**, **Donini LM**, **Lenzi A**, **Gnessi L**. Relationships between body fat distribution, epicardial fat and obstructive sleep apnea in obese patients with and without metabolic syndrome. *PloS One* 7: e47059, 2012.
185. **Lumeng CN**, **Bodzin JL**, **Saltiel AR**. Obesity induces a phenotypic switch in adipose tissue macrophage polarization. *J Clin Invest* 117: 175–84, 2007.
186. **Lumeng CN**, **DelProposto JB**, **Westcott DJ**, **Saltiel AR**. Phenotypic switching of adipose tissue macrophages with obesity is generated by spatiotemporal differences in macrophage subtypes. *Diabetes* 57: 3239–46, 2008.
187. **Lumeng CN**, **Liu J**, **Geletka L**, **Delaney C**, **Delproposto J**, **Desai A**, **Oatmen K**, **Martinez-Santibanez G**, **Julius A**, **Garg S**, **Yung RL**. Aging is associated with an increase in T cells and inflammatory macrophages in visceral adipose tissue. *J Immunol* 187: 6208–16, 2011.
188. **Maghbooli Z**, **Hossein-Nezhad A**. Transcriptome and Molecular Endocrinology Aspects of Epicardial Adipose Tissue in Cardiovascular Diseases: A Systematic Review and Meta-Analysis of Observational Studies. *BioMed Res Int* 2015: 926567, 2015.
189. **Mahabadi AA**, **Berg MH**, **Lehmann N**, **Kälsch H**, **Bauer M**, **Kara K**, **Dragano N**, **Moebus S**, **Jöckel K-H**, **Erbel R**, **Möhlenkamp S**. 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* 61: 1388–1395, 2013.
190. **Mahabadi AA**, **Lehmann N**, **Kälsch H**, **Robens T**, **Bauer M**, **Dykun I**, **Budde T**, **Moebus S**, **Jöckel K-H**, **Erbel R**, **Möhlenkamp S**. Association of epicardial adipose tissue with progression of coronary artery calcification is more pronounced in the early phase

of atherosclerosis: results from the Heinz Nixdorf recall study. *JACC Cardiovasc Imaging* 7: 909–916, 2014.
191. **Mahabadi AA**, **Massaro JM**, **Rosito GA**, **Levy D**, **Murabito JM**, **Wolf PA**, **O'Donnell CJ**, **Fox CS**, **Hoffmann U**. Association of pericardial fat, intrathoracic fat, and visceral abdominal fat with cardiovascular disease burden: the Framingham Heart Study. *Eur Heart J* 30: 850–856, 2009.
192. **Mahajan R**, **Kuklik P**, **Grover S**, **Brooks AG**, **Wong CX**, **Sanders P**, **Selvanayagam JB**. Cardiovascular magnetic resonance of total and atrial pericardial adipose tissue: a validation study and development of a 3 dimensional pericardial adipose tissue model. *J Cardiovasc Magn Reson Off J Soc Cardiovasc Magn Reson* 15: 73, 2013.
193. **Mahajan R**, **Lau DH**, **Brooks AG**, **Shipp NJ**, **Manavis J**, **Wood JPM**, **Finnie JW**, **Samuel CS**, **Royce SG**, **Twomey DJ**, **Thanigaimani S**, **Kalman JM**, **Sanders P**. Electrophysiological, Electroanatomical, and Structural Remodeling of the Atria as Consequences of Sustained Obesity. *J Am Coll Cardiol* 66: 1–11, 2015.
194. **Mahfouz RA**, **Alzaiat A**, **Yousry A**. Relationship of epicardial fat thickness with endothelial and cardiac functions in children with family history of type 2 diabetes mellitus. *Echocardiogr Mt Kisco N* 32: 28–33, 2015.
195. **Main ML**, **Rao SC**, **O'Keefe JH**. Trends in obesity and extreme obesity among US adults. *Jama* 303: 1695; author reply 1695-6, 2010.
196. **Makki K**, **Froguel P**, **Wolowczuk I**. Adipose tissue in obesity-related inflammation and insulin resistance: cells, cytokines, and chemokines. *ISRN Inflamm* 2013: 139239, 2013.
197. **Malavazos AE**, **Di Leo G**, **Secchi F**, **Lupo EN**, **Dogliotti G**, **Coman C**, **Morricone L**, **Corsi MM**, **Sardanelli F**, **Iacobellis G**. Relation of echocardiographic epicardial fat thickness and myocardial fat. *Am J Cardiol* 105: 1831–1835, 2010.
198. **Marchington JM**, **Mattacks CA**, **Pond CM**. Adipose tissue in the mammalian heart and pericardium: structure, foetal development and biochemical properties. *Comp Biochem Physiol B* 94: 225–232, 1989.
199. **Marchington JM**, **Pond CM**. Site-specific properties of pericardial and epicardial adipose tissue: the effects of insulin and high-fat feeding on lipogenesis and the incorporation of fatty acids in vitro. *Int J Obes* 14: 1013–1022, 1990.
200. **Mariani S**, **Fiore D**, **Barbaro G**, **Basciani S**, **Saponara M**, **D'Arcangelo E**, **Ulisse S**, **Moretti C**, **Fabbri A**, **Gnessi L**. Association of epicardial fat thickness with the severity of obstructive sleep apnea in obese patients. *Int J Cardiol* 167: 2244–2249, 2013.
201. **Martínez-Estrada OM**, **Lettice LA**, **Essafi A**, **Guadix JA**, **Slight J**, **Velecela V**, **Hall E**, **Reichmann J**, **Devenney PS**, **Hohenstein P**, **Hosen N**, **Hill RE**, **Muñoz-Chapuli R**, **Hastie ND**. Wt1 is required for cardiovascular progenitor cell formation through transcriptional control of Snail and E-cadherin. *Nat Genet* 42: 89–93, 2010.
202. **Masuda M**, **Mizuno H**, **Enchi Y**, **Minamiguchi H**, **Konishi S**, **Ohtani T**, **Yamaguchi O**, **Okuyama Y**, **Nanto S**, **Sakata Y**. Abundant epicardial adipose tissue surrounding the left atrium predicts early rather than late recurrence of atrial fibrillation after catheter ablation. *J Interv Card Electrophysiol Int J Arrhythm Pacing* 44: 31–37, 2015.
203. **Mauer J**, **Chaurasia B**, **Goldau J**, **Vogt MC**, **Ruud J**, **Nguyen KD**, **Theurich S**, **Hausen AC**, **Schmitz J**, **BrÃ¶nneke HS**, **Estevez E**, **Allen TL**, **Mesaros A**, **Partridge L**, **Febbraio MA**, **Chawla A**, **Wunderlich FT**, **BrÃ¼ning JCC**. Signaling by IL-6 promotes alternative activation of macrophages to limit endotoxemia and obesity-associated resistance to insulin. *Nat Immunol* 15: 423–430, 2014.

204. **Maumus M**, **Peyrafitte JA**, **D'Angelo R**, **Fournier-Wirth C**, **Bouloumie A**, **Casteilla L**, **Sengenes C**, **Bourin P**. Native human adipose stromal cells: localization, morphology and phenotype [Online]. *Int. J. Obes.* http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=21266947.
205. **Maumus M**, **Sengenes C**, **Decaunes P**, **Zakaroff-Girard A**, **Bourlier V**, **Lafontan M**, **Galitzky J**, **Bouloumie A**. Evidence of in situ proliferation of adult adipose tissue-derived progenitor cells: influence of fat mass microenvironment and growth. *J Clin Endocrinol Metab* 93: 4098–106, 2008.
206. **Mazurek T**. Human Epicardial Adipose Tissue Is a Source of Inflammatory Mediators. *Circulation* 108: 2460–2466, 2003.
207. **Mazurek T**, **Kiliszek M**, **Kobylecka M**, **Skubisz-Głuchowska J**, **Kochman J**, **Filipiak K**, **Królicki L**, **Opolski G**. Relation of proinflammatory activity of epicardial adipose tissue to the occurrence of atrial fibrillation. *Am J Cardiol* 113: 1505–1508, 2014.
208. **McBeath R**, **Pirone DM**, **Nelson CM**, **Bhadriraju K**, **Chen CS**. Cell shape, cytoskeletal tension, and RhoA regulate stem cell lineage commitment. *Dev Cell* 6: 483–495, 2004.
209. **McGavock JM**, **Victor RG**, **Unger RH**, **Szczepaniak LS**, **American College of Physicians and the American Physiological Society**. Adiposity of the heart, revisited. *Ann Intern Med* 144: 517–524, 2006.
210. **McKenney ML**, **Schultz KA**, **Boyd JH**, **Byrd JP**, **Alloosh M**, **Teague SD**, **Arce-Esquivel AA**, **Fain JN**, **Laughlin MH**, **Sacks HS**, **others**. Epicardial adipose excision slows the progression of porcine coronary atherosclerosis. *J Cardiothorac Surg* 9: 1, 2014.
211. **Meunier P**, **Aaron J**, **Edouard C**, **Vignon G**. Osteoporosis and the replacement of cell populations of the marrow by adipose tissue. A quantitative study of 84 iliac bone biopsies. *Clin Orthop Relat Res* 80: 147–54, 1971.
212. **Mohar DS**, **Salcedo J**, **Hoang KC**, **Kumar S**, **Saremi F**, **Erande AS**, **Naderi N**, **Nadeswaran P**, **Le C**, **Malik S**. Epicardial adipose tissue volume as a marker of coronary artery disease severity in patients with diabetes independent of coronary artery calcium: findings from the CTRAD study. *Diabetes Res Clin Pract* 106: 228–235, 2014.
213. **Moore MA**, **Hattori K**, **Heissig B**, **Shieh JH**, **Dias S**, **Crystal RG**, **Rafii S**. Mobilization of endothelial and hematopoietic stem and progenitor cells by adenovector-mediated elevation of serum levels of SDF-1, VEGF, and angiopoietin-1. *Ann N Y Acad Sci* 938: 36, 2001.
214. **Moraes-Vieira P**, **Larocca RA**, **Bassi EJ**, **Peron JS**, **Andrade-Oliveira V**, **Wasinski F**, **Araujo R**, **Thornley T**, **Quintana FJ**, **Basso AS**, **Strom TB**, **CÃ¢mara N**. Leptin deficiency impairs maturation of dendritic cells and enhances induction of regulatory T and Th17 cells. *Eur J Immunol* 44: 794–806, 2014.
215. **Morin CL**, **Pagliassotti MJ**, **Windmiller D**, **Eckel RH**. Adipose tissue-derived tumor necrosis factor-alpha activity is elevated in older rats. *J Gerontol Biol Sci Med Sci* 52: B190-5, 1997.
216. **Morley JE**. The metabolic syndrome and aging. *J Gerontol A Biol Sci Med Sci* 59: 139–142, 2004.
217. **Moro K**, **Yamada T**, **Tanabe M**, **Takeuchi T**, **Ikawa T**, **Kawamoto H**, **Furusawa J**, **Ohtani M**, **Fujii H**, **Koyasu S**. Innate production of T(H)2 cytokines by adipose tissue-associated c-Kit(+)Sca-1(+) lymphoid cells. *Nature* 463: 540–4, 2010.
218. **Murdoch C**, **Muthana M**, **Lewis CE**. Hypoxia regulates macrophage functions in

inflammation. *J Immunol* 175: 6257–63, 2005.
219. **Nagashima K**, **Okumura Y**, **Watanabe I**, **Nakai T**, **Ohkubo K**, **Kofune T**, **Kofune M**, **Mano H**, **Sonoda K**, **Hirayama A**. Association between epicardial adipose tissue volumes on 3-dimensional reconstructed CT images and recurrence of atrial fibrillation after catheter ablation. *Circ J Off J Jpn Circ Soc* 75: 2559–2565, 2011.
220. **Nakajima H**, **Nakajima HO**, **Salcher O**, **Dittiè AS**, **Dembowsky K**, **Jing S**, **Field LJ**. Atrial but not ventricular fibrosis in mice expressing a mutant transforming growth factor-beta(1) transgene in the heart. *Circ Res* 86: 571–579, 2000.
221. **Nakanishi K**, **Fukuda S**, **Tanaka A**, **Otsuka K**, **Sakamoto M**, **Taguchi H**, **Yoshikawa J**, **Shimada K**, **Yoshiyama M**. Peri-atrial epicardial adipose tissue is associated with new-onset nonvalvular atrial fibrillation. *Circ J Off J Jpn Circ Soc* 76: 2748–2754, 2012.
222. **Nakazato R**, **Shmilovich H**, **Tamarappoo BK**, **Cheng VY**, **Slomka PJ**, **Berman DS**, **Dey D**. Interscan reproducibility of computer-aided epicardial and thoracic fat measurement from noncontrast cardiac CT. *J Cardiovasc Comput Tomogr* 5: 172–179, 2011.
223. **Napolitano LC**. THE DIFFERENTIATION OF WHITE ADIPOSE CELLS. AN ELECTRON MICROSCOPE STUDY. *J Cell Biol* 18: 663–679, 1963.
224. **Nedergaard J**, **Bengtsson T**, **Cannon B**. Unexpected evidence for active brown adipose tissue in adult humans. *Am J Physiol Endocrinol Metab* 293: E444-452, 2007.
225. **Nelson AJ**, **Worthley MI**, **Psaltis PJ**, **Carbone A**, **Dundon BK**, **Duncan RF**, **Piantadosi C**, **Lau DH**, **Sanders P**, **Wittert GA**, **Worthley SG**. Validation of cardiovascular magnetic resonance assessment of pericardial adipose tissue volume. *J Cardiovasc Magn Reson Off J Soc Cardiovasc Magn Reson* 11: 15, 2009.
226. **Nishimura S**, **Manabe I**, **Nagasaki M**, **Eto K**, **Yamashita H**, **Ohsugi M**, **Otsu M**, **Hara K**, **Ueki K**, **Sugiura S**, **Yoshimura K**, **Kadowaki T**, **Nagai R**. CD8+ effector T cells contribute to macrophage recruitment and adipose tissue inflammation in obesity. *Nat Med* 15: 914–20, 2009.
227. **Nishimura S**, **Manabe I**, **Takaki S**, **Nagasaki M**, **Otsu M**, **Yamashita H**, **Sugita J**, **Yoshimura K**, **Eto K**, **Komuro I**, **Kadowaki T**, **Nagai R**. Adipose Natural Regulatory B Cells Negatively Control Adipose Tissue Inflammation. *Cell Metab* (October 22, 2013). doi: 10.1016/j.cmet.2013.09.017.
228. **Nyman K**, **Granér M**, **Pentikäinen MO**, **Lundbom J**, **Hakkarainen A**, **Sirén R**, **Nieminen MS**, **Taskinen M-R**, **Lundbom N**, **Lauerma K**. Cardiac steatosis and left ventricular function in men with metabolic syndrome. *J Cardiovasc Magn Reson Off J Soc Cardiovasc Magn Reson* 15: 103, 2013.
229. **Oda S**, **Utsunomiya D**, **Funama Y**, **Yuki H**, **Kidoh M**, **Nakaura T**, **Takaoka H**, **Matsumura M**, **Katahira K**, **Noda K**, **Oshima S**, **Tokuyasu S**, **Yamashita Y**. Effect of iterative reconstruction on variability and reproducibility of epicardial fat volume quantification by cardiac CT. *J Cardiovasc Comput Tomogr* 10: 150–155, 2016.
230. **Ojha S**, **Fainberg HP**, **Wilson V**, **Pelella G**, **Castellanos M**, **May ST**, **Lotto AA**, **Sacks H**, **Symonds ME**, **Budge H**. Gene pathway development in human epicardial adipose tissue during early life. *JCI Insight* 1: e87460, 2016.
231. **Olgin JE**, **Verheule S**. Transgenic and knockout mouse models of atrial arrhythmias. *Cardiovasc Res* 54: 280–286, 2002.
232. **O'Rourke RW**, **Meyer KA**, **Gaston G**, **White AE**, **Lumeng CN**, **Marks DL**. Hexosamine biosynthesis is a possible mechanism underlying hypoxia's effects on lipid metabolism in human adipocytes. *PLoS One* 8: e71165, 2013.
233. **Otaki Y**, **Hell M**, **Slomka PJ**, **Schuhbaeck A**, **Gransar H**, **Huber B**, **Nakazato R**,

Germano G, **Hayes SW**, **Thomson LEJ**, **Friedman JD**, **Achenbach S**, **Berman DS**, **Dey D**. Relationship of epicardial fat volume from noncontrast CT with impaired myocardial flow reserve by positron emission tomography. *J Cardiovasc Comput Tomogr* 9: 303–309, 2015.
234. **Ouwens DM**, **Sell H**, **Greulich S**, **Eckel J**. The role of epicardial and perivascular adipose tissue in the pathophysiology of cardiovascular disease. *J Cell Mol Med* 14: 2223–2234, 2010.
235. **Palmer AK**, **Kirkland JL**. Aging and adipose tissue: potential interventions for diabetes and regenerative medicine. *Exp. Gerontol.* (2016). doi: 10.1016/j.exger.2016.02.013.
236. **Papathanassoglou E**, **El-Haschimi K**, **Li XC**, **Matarese G**, **Strom T**, **Mantzoros C**. Leptin receptor expression and signaling in lymphocytes: kinetics during lymphocyte activation, role in lymphocyte survival, and response to high fat diet in mice. *J Immunol Baltim Md 1950* 176: 7745–7752, 2006.
237. **Parisi V**, **Rengo G**, **Perrone-Filardi P**, **Pagano G**, **Femminella GD**, **Paolillo S**, **Petraglia L**, **Gambino G**, **Caruso A**, **Grimaldi MG**, **Baldascino F**, **Nolano M**, **Elia A**, **Cannavo A**, **De Bellis A**, **Coscioni E**, **Pellegrino T**, **Cuocolo A**, **Ferrara N**, **Leosco D**. Increased Epicardial Adipose Tissue Volume Correlates With Cardiac Sympathetic Denervation in Patients With Heart Failure. *Circ Res* 118: 1244–1253, 2016.
238. **Park HE**, **Choi S-Y**, **Kim M**. Association of epicardial fat with left ventricular diastolic function in subjects with metabolic syndrome: assessment using 2-dimensional echocardiography. *BMC Cardiovasc Disord* 14: 3, 2014.
239. **Patel VB**, **Mori J**, **McLean BA**, **Basu R**, **Das SK**, **Ramprasath T**, **Parajuli N**, **Penninger JM**, **Grant MB**, **Lopaschuk GD**, **Oudit GY**. ACE2 Deficiency Worsens Epicardial Adipose Tissue Inflammation and Cardiac Dysfunction in Response to Diet-Induced Obesity. *Diabetes* 65: 85–95, 2016.
240. **Patsouris D**, **Li P-PP**, **Thapar D**, **Chapman J**, **Olefsky JM**, **Neels JGC**. Ablation of CD11c-positive cells normalizes insulin sensitivity in obese insulin resistant animals. *Cell Metab* 8: 301–309, 2008.
241. **Pawelec G**. Hallmarks of human immunosenescence: adaptation or dysregulation? [Online]. *Immun. Ageing*. C:\Mon Dossier\Banque Doc Sympas\Pawelec-2012-Immunity Ageing.pdf http://immunityageing.biomedcentral.com/articles/10.1186/1742-4933-9-15.
242. **Payne GA**, **Borbouse L**, **Kumar S**, **Neeb Z**, **Alloosh M**, **Sturek M**, **Tune JD**. Epicardial perivascular adipose-derived leptin exacerbates coronary endothelial dysfunction in metabolic syndrome via a protein kinase C-beta pathway. *Arterioscler Thromb Vasc Biol* 30: 1711–1717, 2010.
243. **Payne GA**, **Kohr MC**, **Tune JD**. Epicardial perivascular adipose tissue as a therapeutic target in obesity-related coronary artery disease. *Br J Pharmacol* 165: 659–669, 2012.
244. **Pellegrinelli V**, **Carobbio S**, **Vidal-Puig A**. Adipose tissue plasticity: how fat depots respond differently to pathophysiological cues. *Diabetologia* 59: 1075–1088, 2016.
245. **Perez LM**, **Pareja-Galeano H**, **Sanchis-Gomar F**, **Emanuele E**, **Lucia A**, **GÃ¡lvez BG**. "Adipaging": Aging and obesity share biological hallmarks related to a dysfunctional adipose tissue. *J. Physiol.* (2016). doi: 10.1113/jp271691.
246. **Petrović V**, **Buzadzić B**, **Korać A**, **Vasilijević A**, **Janković A**, **Korać B**. Free radical equilibrium in interscapular brown adipose tissue: relationship between metabolic profile and antioxidative defense. *Comp Biochem Physiol Toxicol Pharmacol*

CBP 142: 60–65, 2006.
247. **Petta S**, **Argano C**, **Colomba D**, **Cammà C**, **Di Marco V**, **Cabibi D**, **Tuttolomondo A**, **Marchesini G**, **Pinto A**, **Licata G**, **Craxì A**. Epicardial fat, cardiac geometry and cardiac function in patients with non-alcoholic fatty liver disease: association with the severity of liver disease. *J Hepatol* 62: 928–933, 2015.
248. **Pinnick KE**, **Collins SC**, **Londos C**, **Gauguier D**, **Clark A**, **Fielding BA**. Pancreatic ectopic fat is characterized by adipocyte infiltration and altered lipid composition. *Obes Silver Spring* 16: 522–30, 2008.
249. **Platonov PG**. P-wave morphology: underlying mechanisms and clinical implications. *Ann Noninvasive Electrocardiol Off J Int Soc Holter Noninvasive Electrocardiol Inc* 17: 161–169, 2012.
250. **Po SS**, **Nakagawa H**, **Jackman WM**. Localization of left atrial ganglionated plexi in patients with atrial fibrillation. *J Cardiovasc Electrophysiol* 20: 1186–1189, 2009.
251. **Prati F**, **Arbustini E**, **Labellarte A**, **Sommariva L**, **Pawlowski T**, **Manzoli A**, **Pagano A**, **Motolese M**, **Boccanelli A**. Eccentric atherosclerotic plaques with positive remodelling have a pericardial distribution: a permissive role of epicardial fat? A three-dimensional intravascular ultrasound study of left anterior descending artery lesions. *Eur Heart J* 24: 329–336, 2003.
252. **Psychari SN**, **Rekleiti N**, **Papaioannou N**, **Varhalama E**, **Drakoulis C**, **Apostolou TS**, **Iliodromitis EK**. Epicardial Fat in Nonalcoholic Fatty Liver Disease: Properties and Relationships With Metabolic Factors, Cardiac Structure, and Cardiac Function. *Angiology* 67: 41–48, 2016.
253. **Rabkin SW**. Epicardial fat: properties, function and relationship to obesity. *Obes Rev* 8: 253–261, 2007.
254. **Rabkin SW**, **Campbell H**. Comparison of reducing epicardial fat by exercise, diet or bariatric surgery weight loss strategies: a systematic review and meta-analysis. *Obes Rev Off J Int Assoc Study Obes* 16: 406–415, 2015.
255. **Rångemark C**, **Hedner JA**, **Carlson JT**, **Gleerup G**, **Winther K**. Platelet function and fibrinolytic activity in hypertensive and normotensive sleep apnea patients. *Sleep* 18: 188–194, 1995.
256. **Rausch ME**, **Weisberg S**, **Vardhana P**, **Tortoriello DV**. Obesity in C57BL/6J mice is characterized by adipose tissue hypoxia and cytotoxic T-cell infiltration. *Int J Obes* 32: 451–63, 2008.
257. **Regazzetti C**, **Peraldi P**, **Gremeaux T**, **Najem-Lendom R**, **Ben-Sahra I**, **Cormont M**, **Bost F**, **Le Marchand-Brustel Y**, **Tanti JF**, **Giorgetti-Peraldi S**. Hypoxia decreases insulin signaling pathways in adipocytes. *Diabetes* 58: 95–103, 2009.
258. **Reggio S**, **Pellegrinelli V**, **ClÃ©ment K**, **Tordjman J**, **Tordjman JC**. Fibrosis as a Cause or a Consequence of White Adipose Tissue Inflammation in Obesity. *Curr. Obes. Rep.* (2013). doi: 10.1007/s13679-012-0037-4.
259. **Reiner L**, **Mazzoleni A**, **Rodriguez FL**. Statistical analysis of the epicardial fat weight in human hearts. *AMA Arch Pathol* 60: 369–373, 1955.
260. **Robicsek F**, **Thubrikar MJ**. The freedom from atherosclerosis of intramyocardial coronary arteries: reduction of mural stress--a key factor. *Eur J Cardio-Thorac Surg Off J Eur Assoc Cardio-Thorac Surg* 8: 228–235, 1994.
261. **Rocha S**. Gene regulation under low oxygen: holding your breath for transcription. *Trends Biochem Sci* 32: 389–97, 2007.
262. **Rodeheffer MS**, **Birsoy K**, **Friedman JM**. Identification of white adipocyte progenitor cells in vivo. *Cell* 135: 240–9, 2008.
263. **Rodriguez-Granillo GA**, **Carrascosa P**, **Deviggiano A**, **Capunay C**, **De Zan MC**,

Goldsmit A, **Campisi R**. Pericardial fat volume is related to atherosclerotic plaque burden rather than to lesion severity. *Eur. Heart J. Cardiovasc. Imaging* (July 1, 2016). doi: 10.1093/ehjci/jew139.
264. **Rosito GA**, **Massaro JM**, **Hoffmann U**, **Ruberg FL**, **Mahabadi AA**, **Vasan RS**, **O'Donnell CJ**, **Fox CS**. Pericardial Fat, Visceral Abdominal Fat, Cardiovascular Disease Risk Factors, and Vascular Calcification in a Community-Based Sample: The Framingham Heart Study. *Circulation* 117: 605–613, 2008.
265. **Sacks HS**, **Fain JN**. Human epicardial adipose tissue: A review. *Am Heart J* 153: 907–917, 2007.
266. **Sacks HS**, **Fain JN**. Human epicardial fat: what is new and what is missing?: Epicardial fat review. *Clin Exp Pharmacol Physiol* 38: 879–887, 2011.
267. **Sacks HS**, **Fain JN**, **Bahouth SW**, **Ojha S**, **Frontini A**, **Budge H**, **Cinti S**, **Symonds ME**. Adult epicardial fat exhibits beige features. *J Clin Endocrinol Metab* 98: E1448-1455, 2013.
268. **Sacks HS**, **Fain JN**, **Cheema P**, **Bahouth SW**, **Garrett E**, **Wolf RY**, **Wolford D**, **Samaha J**. Inflammatory genes in epicardial fat contiguous with coronary atherosclerosis in the metabolic syndrome and type 2 diabetes: changes associated with pioglitazone. *Diabetes Care* 34: 730–733, 2011.
269. **Sade LE**, **Eroglu S**, **Bozbaş H**, **Ozbiçer S**, **Hayran M**, **Haberal A**, **Müderrisoğlu H**. Relation between epicardial fat thickness and coronary flow reserve in women with chest pain and angiographically normal coronary arteries. *Atherosclerosis* 204: 580–585, 2009.
270. **Salam N**, **Rane S**, **Das R**, **Faulkner M**, **Gund R**, **Kandpal U**, **Lewis V**, **Mattoo H**, **Prabhu S**, **Ranganathan V**, **Durdik J**, **George A**, **Rath S**, **Bal V**. T cell ageing: effects of age on development, survival & function. *Indian J Med Res* 138: 595–608, 2013.
271. **Salgado-Somoza A**, **Teijeira-Fernández E**, **Fernández AL**, **González-Juanatey JR**, **Eiras S**. Proteomic analysis of epicardial and subcutaneous adipose tissue reveals differences in proteins involved in oxidative stress. *Am J Physiol Heart Circ Physiol* 299: H202-209, 2010.
272. **Sanchez-Gurmaches J**, **Hung C-MM**, **Guertin DAC**. Emerging Complexities in Adipocyte Origins and Identity. *Trends Cell Biol* 26: 313–326, 2016.
273. **Sawicka M**, **Janowska J**, **Chudek J**. Potential beneficial effect of some adipokines positively correlated with the adipose tissue content on the cardiovascular system. *Int J Cardiol* 222: 581–589, 2016.
274. **Semenza GL**. Targeting HIF-1 for cancer therapy. *Nat Rev Cancer* 3: 721–32, 2003.
275. **Sengenes C**, **Lolmede K**, **Zakaroff-Girard A**, **Busse R**, **Bouloumie A**. Preadipocytes in the human subcutaneous adipose tissue display distinct features from the adult mesenchymal and hematopoietic stem cells. *J Cell Physiol* 205: 114–22, 2005.
276. **Sengenes C**, **Miranville A**, **Maumus M**, **de Barros S**, **Busse R**, **Bouloumie A**. Chemotaxis and differentiation of human adipose tissue CD34+/CD31- progenitor cells: role of stromal derived factor-1 released by adipose tissue capillary endothelial cells. *Stem Cells* 25: 2269–76, 2007.
277. **Shamsuzzaman ASM**, **Gersh BJ**, **Somers VK**. Obstructive sleep apnea: implications for cardiac and vascular disease. *JAMA* 290: 1906–1914, 2003.
278. **Shimabukuro M**, **Hirata Y**, **Tabata M**, **Dagvasumberel M**, **Sato H**, **Kurobe H**, **Fukuda D**, **Soeki T**, **Kitagawa T**, **Takanashi S**, **Sata M**. Epicardial adipose tissue volume and adipocytokine imbalance are strongly linked to human coronary atherosclerosis. *Arterioscler Thromb Vasc Biol* 33: 1077–1084, 2013.

279. **Shimokawa H**, **Ito A**, **Fukumoto Y**, **Kadokami T**, **Nakaike R**, **Sakata M**, **Takayanagi T**, **Egashira K**, **Takeshita A**. Chronic treatment with interleukin-1 beta induces coronary intimal lesions and vasospastic responses in pigs in vivo. The role of platelet-derived growth factor. *J Clin Invest* 97: 769–776, 1996.
280. **Shin SY**, **Yong HS**, **Lim HE**, **Na JO**, **Choi CU**, **Choi JI**, **Kim SH**, **Kim JW**, **Kim EJ**, **Park SW**, **Rha S-W**, **Park CG**, **Seo HS**, **Oh DJ**, **Kim Y-H**. Total and interatrial epicardial adipose tissues are independently associated with left atrial remodeling in patients with atrial fibrillation. *J Cardiovasc Electrophysiol* 22: 647–655, 2011.
281. **Sicari R**, **Sironi AM**, **Petz R**, **Frassi F**, **Chubuchny V**, **De Marchi D**, **Positano V**, **Lombardi M**, **Picano E**, **Gastaldelli A**. Pericardial rather than epicardial fat is a cardiometabolic risk marker: an MRI vs echo study. *J Am Soc Echocardiogr Off Publ Am Soc Echocardiogr* 24: 1156–1162, 2011.
282. **Sidossis L**, **Kajimura S**. Brown and beige fat in humans: thermogenic adipocytes that control energy and glucose homeostasis. *J Clin Invest* 125: 478–486, 2015.
283. **Silaghi A**, **Achard V**, **Paulmyer-Lacroix O**, **Scridon T**, **Tassistro V**, **Duncea I**, **Clement K**, **Dutour A**, **Grino M**. Expression of adrenomedullin in human epicardial adipose tissue: role of coronary status. *AJP Endocrinol Metab* 293: E1443–E1450, 2007.
284. **Silaghi A**, **Piercecchi-Marti M-D**, **Grino M**, **Leonetti G**, **Alessi MC**, **Clement K**, **Dadoun F**, **Dutour A**. Epicardial Adipose Tissue Extent: Relationship With Age, Body Fat Distribution, and Coronaropathy. *Obesity* 16: 2424–2430, 2008.
285. **Silver MA**, **Pick R**, **Brilla CG**, **Jalil JE**, **Janicki JS**, **Weber KT**. Reactive and reparative fibrillar collagen remodelling in the hypertrophied rat left ventricle: two experimental models of myocardial fibrosis. *Cardiovasc Res* 24: 741–747, 1990.
286. **Skurk T**, **Alberti-Huber C**, **Herder C**, **Hauner H**. Relationship between adipocyte size and adipokine expression and secretion. *J Clin Endocrinol Metab* 92: 1023–33, 2007.
287. **Slawik M**, **Vidal-Puig AJ**. Lipotoxicity, overnutrition and energy metabolism in aging. *Ageing Res Rev* 5: 144–64, 2006.
288. **Sohal RS**, **Orr WC**. The redox stress hypothesis of aging. *Free Radic Biol Med* 52: 539–55, 2012.
289. **Somers VK**, **Dyken ME**, **Clary MP**, **Abboud FM**. Sympathetic neural mechanisms in obstructive sleep apnea. *J Clin Invest* 96: 1897–1904, 1995.
290. **Somers VK**, **White DP**, **Amin R**, **Abraham WT**, **Costa F**, **Culebras A**, **Daniels S**, **Floras JS**, **Hunt CE**, **Olson LJ**, **Pickering TG**, **Russell R**, **Woo M**, **Young T**, **American Heart Association Council for High Blood Pressure Research Professional Education Committee, Council on Clinical Cardiology**, **American Heart Association Stroke Council**, **American Heart Association Council on Cardiovascular Nursing**, **American College of Cardiology Foundation**. Sleep apnea and cardiovascular disease: an American Heart Association/american College Of Cardiology Foundation Scientific Statement from the American Heart Association Council for High Blood Pressure Research Professional Education Committee, Council on Clinical Cardiology, Stroke Council, and Council On Cardiovascular Nursing. In collaboration with the National Heart, Lung, and Blood Institute National Center on Sleep Disorders Research (National Institutes of Health). *Circulation* 118: 1080–1111, 2008.
291. **Spach MS**, **Boineau JP**. Microfibrosis produces electrical load variations due to loss of side-to-side cell connections: a major mechanism of structural heart disease arrhythmias. *Pacing Clin Electrophysiol PACE* 20: 397–413, 1997.
292. **Spearman JV**, **Meinel FG**, **Schoepf UJ**, **Apfaltrer P**, **Silverman JR**, **Krazinski AW**, **Canstein C**, **De Cecco CN**, **Costello P**, **Geyer LL**. Automated quantification of epicardial adipose tissue using CT angiography: evaluation of a prototype software. *Eur*

Radiol 24: 519–526, 2014.
293. **Spearman JV**, **Renker M**, **Schoepf UJ**, **Krazinski AW**, **Herbert TL**, **De Cecco CN**, **Nietert PJ**, **Meinel FG**. Prognostic value of epicardial fat volume measurements by computed tomography: a systematic review of the literature. *Eur Radiol* 25: 3372–3381, 2015.
294. **Spits H**, **Cupedo T**. Innate lymphoid cells: emerging insights in development, lineage relationships, and function. *Annu Rev Immunol* 30: 647–675, 2012.
295. **Starr ME**, **Evers BM**, **Saito H**. Age-associated increase in cytokine production during systemic inflammation: adipose tissue as a major source of IL-6. *J Gerontol Biol Sci Med Sci* 64: 723–30, 2009.
296. **Stojanovska J**, **Kazerooni EA**, **Sinno M**, **Gross BH**, **Watcharotone K**, **Patel S**, **Jacobson JA**, **Oral H**. Increased epicardial fat is independently associated with the presence and chronicity of atrial fibrillation and radiofrequency ablation outcome. *Eur Radiol* 25: 2298–2309, 2015.
297. **Suárez AG**, **Hornero F**, **Berjano EJ**. Mathematical modeling of epicardial RF ablation of atrial tissue with overlying epicardial fat. *Open Biomed Eng J* 4: 47–55, 2010.
298. **Sun K**, **Kusminski CM**, **Scherer PE**. Adipose tissue remodeling and obesity. *J Clin Invest* 121: 2094–101, 2011.
299. **Sun K**, **Tordjman J**, **ClÃ©ment K**, **Scherer PEC**. Fibrosis and adipose tissue dysfunction. *Cell Metab* 18: 470–477, 2013.
300. **Swynghedauw B**. Molecular mechanisms of myocardial remodeling. *Physiol Rev* 79: 215–262, 1999.
301. **Takahashi K**, **Okumura Y**, **Watanabe I**, **Nagashima K**, **Sonoda K**, **Sasaki N**, **Kogawa R**, **Iso K**, **Kurokawa S**, **Ohkubo K**, **Nakai T**, **Nakahara S**, **Hori Y**, **Nikaido M**, **Hirayama A**. Anatomical proximity between ganglionated plexi and epicardial adipose tissue in the left atrium: implication for 3D reconstructed epicardial adipose tissue-based ablation. *J. Interv. Card. Electrophysiol. Int. J. Arrhythm. Pacing* (April 12, 2016). doi: 10.1007/s10840-016-0130-9.
302. **Takahashi Y**, **Sanders P**, **Jaïs P**, **Hocini M**, **Dubois R**, **Rotter M**, **Rostock T**, **Nalliah CJ**, **Sacher F**, **Clémenty J**, **Haïssaguerre M**. Organization of frequency spectra of atrial fibrillation: relevance to radiofrequency catheter ablation. *J Cardiovasc Electrophysiol* 17: 382–388, 2006.
303. **Takaoka M**, **Nagata D**, **Kihara S**, **Shimomura I**, **Kimura Y**, **Tabata Y**, **Saito Y**, **Nagai R**, **Sata M**. Periadventitial adipose tissue plays a critical role in vascular remodeling. *Circ Res* 105: 906–911, 2009.
304. **Takaoka M**, **Suzuki H**, **Shioda S**, **Sekikawa K**, **Saito Y**, **Nagai R**, **Sata M**. Endovascular injury induces rapid phenotypic changes in perivascular adipose tissue. *Arterioscler Thromb Vasc Biol* 30: 1576–1582, 2010.
305. **Tamarappoo B**, **Dey D**, **Shmilovich H**, **Nakazato R**, **Gransar H**, **Cheng VY**, **Friedman JD**, **Hayes SW**, **Thomson LEJ**, **Slomka PJ**, **Rozanski A**, **Berman DS**. Increased pericardial fat volume measured from noncontrast CT predicts myocardial ischemia by SPECT. *JACC Cardiovasc Imaging* 3: 1104–1112, 2010.
306. **Tanami Y**, **Jinzaki M**, **Kishi S**, **Matheson M**, **Vavere AL**, **Rochitte CE**, **Dewey M**, **Chen MY**, **Clouse ME**, **Cox C**, **Kuribayashi S**, **Lima JAC**, **Arbab-Zadeh A**. 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* 8: e002676, 2015.
307. **Tang W**, **Zeve D**, **Suh JM**, **Bosnakovski D**, **Kyba M**, **Hammer RE**, **Tallquist MD**,

Graff JM. White fat progenitor cells reside in the adipose vasculature. *Science* 322: 583–586, 2008.
308. **Tansey DK**, **Aly Z**, **Sheppard MN**. Fat in the right ventricle of the normal heart. *Histopathology* 46: 98–104, 2005.
309. **Tchkonia T**, **Morbeck DE**, **Zglinicki T**, **Deursen J**, **Lustgarten J**, **Scrable H**, **Khosla S**, **Jensen MD**, **Kirkland JL**. Fat tissue, aging, and cellular senescence. *Aging Cell* 9: 667–684, 2010.
310. **Tchkonia T**, **Pirtskhalava T**, **Thomou T**, **Cartwright MJ**, **Wise B**, **Karagiannides I**, **Shpilman A**, **Lash TL**, **Becherer JD**, **Kirkland JL**. Increased TNFalpha and CCAAT/enhancer-binding protein homologous protein with aging predispose preadipocytes to resist adipogenesis. *Am J Physiol Endocrinol Metab* 293: E1810-9, 2007.
311. **Tedrow UB**, **Conen D**, **Ridker PM**, **Cook NR**, **Koplan BA**, **Manson JE**, **Buring JE**, **Albert CM**. The long- and short-term impact of elevated body mass index on the risk of new atrial fibrillation the WHS (women's health study). *J Am Coll Cardiol* 55: 2319–2327, 2010.
312. **Thanassoulis G**, **Massaro JM**, **O'Donnell CJ**, **Hoffmann U**, **Levy D**, **Ellinor PT**, **Wang TJ**, **Schnabel RB**, **Vasan RS**, **Fox CS**, **Benjamin EJ**. Pericardial fat is associated with prevalent atrial fibrillation: the Framingham Heart Study. *Circ Arrhythm Electrophysiol* 3: 345–350, 2010.
313. **Thomas EL**, **Fitzpatrick JA**, **Malik SJ**, **Taylor-Robinson SD**, **Bell JD**. Whole body fat: content and distribution. *Prog Nucl Magn Reson Spectrosc* 73: 56–80, 2013.
314. **Tilkian AG**, **Guilleminault C**, **Schroeder JS**, **Lehrman KL**, **Simmons FB**, **Dement WC**. Hemodynamics in sleep-induced apnea. Studies during wakefulness and sleep. *Ann Intern Med* 85: 714–719, 1976.
315. **Tran K-V**, **Gealekman O**, **Frontini A**, **Zingaretti MC**, **Morroni M**, **Giordano A**, **Smorlesi A**, **Perugini J**, **De Matteis R**, **Sbarbati A**, **Corvera S**, **Cinti S**. The vascular endothelium of the adipose tissue gives rise to both white and brown fat cells. *Cell Metab* 15: 222–229, 2012.
316. **Trayhurn P**. Hypoxia and adipocyte physiology: implications for adipose tissue dysfunction in obesity. *Annu Rev Nutr* 34: 207–236, 2014.
317. **Trayhurn P**, **Wang B**, **Wood IS**. Hypoxia in adipose tissue: a basis for the dysregulation of tissue function in obesity? *Br J Nutr* 100: 227–35, 2008.
318. **Tsao H-M**, **Hu W-C**, **Wu M-H**, **Tai C-T**, **Lin Y-J**, **Chang S-L**, **Lo L-W**, **Hu Y-F**, **Tuan T-C**, **Wu T-J**, **Sheu M-H**, **Chang C-Y**, **Chen S-A**. Quantitative analysis of quantity and distribution of epicardial adipose tissue surrounding the left atrium in patients with atrial fibrillation and effect of recurrence after ablation. *Am J Cardiol* 107: 1498–1503, 2011.
319. **Unger RH**, **Scherer PEC**. Gluttony, sloth and the metabolic syndrome: a roadmap to lipotoxicity. *Trends Endocrinol Metab TEM* 21: 345–352, 2010.
320. **Vacca M**, **Di Eusanio M**, **Cariello M**, **Graziano G**, **D'Amore S**, **Petridis FD**, **D'orazio A**, **Salvatore L**, **Tamburro A**, **Folesani G**, **Rutigliano D**, **Pellegrini F**, **Sabbà C**, **Palasciano G**, **Di Bartolomeo R**, **Moschetta A**. Integrative miRNA and whole-genome analyses of epicardial adipose tissue in patients with coronary atherosclerosis. *Cardiovasc Res* 109: 228–239, 2016.
321. **Vague J**. The degree of masculine differentiation of obesities: a factor determining predisposition to diabetes, atherosclerosis, gout, and uric calculous disease. *Am J Clin Nutr* 4: 20–34, 1956.
322. **Venteclef N**, **Guglielmi V**, **Balse E**, **Gaborit B**, **Cotillard A**, **Atassi F**, **Amour J**, **Leprince P**, **Dutour A**, **Clément K**, **Hatem SN**. Human epicardial adipose tissue induces

fibrosis of the atrial myocardium through the secretion of adipo-fibrokines. *Eur Heart J* 36: 795–805a, 2015.
323. **Virtue S**, **Vidal-Puig A**. Adipose tissue expandability, lipotoxicity and the Metabolic Syndrome--an allostatic perspective. *Biochim Biophys Acta* 1801: 338–49, 2010.
324. **de Vos AM**, **Prokop M**, **Roos CJ**, **Meijs MFL**, **van der Schouw YT**, **Rutten A**, **Gorter PM**, **Cramer M-J**, **Doevendans PA**, **Rensing BJ**, **Bartelink M-L**, **Velthuis BK**, **Mosterd A**, **Bots ML**. Peri-coronary epicardial adipose tissue is related to cardiovascular risk factors and coronary artery calcification in post-menopausal women. *Eur Heart J* 29: 777–783, 2008.
325. **Vural B**, **Atalar F**, **Ciftci C**, **Demirkan A**, **Susleyici-Duman B**, **Gunay D**, **Akpinar B**, **Sagbas E**, **Ozbek U**, **Buyukdevrim AS**. Presence of fatty-acid-binding protein 4 expression in human epicardial adipose tissue in metabolic syndrome. *Cardiovasc Pathol Off J Soc Cardiovasc Pathol* 17: 392–398, 2008.
326. **Wanahita N**, **Messerli FH**, **Bangalore S**, **Gami AS**, **Somers VK**, **Steinberg JS**. Atrial fibrillation and obesity--results of a meta-analysis. *Am Heart J* 155: 310–315, 2008.
327. **Wang TJ**, **Parise H**, **Levy D**, **D'Agostino RB**, **Wolf PA**, **Vasan RS**, **Benjamin EJ**. Obesity and the risk of new-onset atrial fibrillation. *JAMA* 292: 2471–2477, 2004.
328. **Watanabe K**, **Kishino T**, **Sano J**, **Ariga T**, **Okuyama S**, **Mori H**, **Matsushima S**, **Ohtsuka K**, **Ohnishi H**, **Watanabe T**. Relationship between epicardial adipose tissue thickness and early impairment of left ventricular systolic function in patients with preserved ejection fraction. *Heart Vessels* 31: 1010–1015, 2016.
329. **Weisberg SP**, **McCann D**, **Desai M**, **Rosenbaum M**, **Leibel RL**, **Ferrante AW Jr**. Obesity is associated with macrophage accumulation in adipose tissue. *J Clin Invest* 112: 1796–808, 2003.
330. **Wenger DS**, **Kawut SM**, **Ding J**, **Bluemke DA**, **Hough CL**, **Kronmal RA**, **Lima JA**, **Leary PJ**. Pericardial Fat and Right Ventricular Morphology: The Multi-Ethnic Study of Atherosclerosis- Right Ventricle Study (MESA-RV). *PloS One* 11: e0157654, 2016.
331. **Wensveen FM**, **ValentiÄ‡ S**, **Å estan M**, **Turk Wensveen T**, **PoliÄ‡ B**. The "Big Bang" in obese fat: Events initiating obesity-induced adipose tissue inflammation. *Eur J Immunol* 45: 2446–2456, 2015.
332. **Wernstedt Asterholm I**, **Tao C**, **Morley TS**, **Wang QA**, **Delgado-Lopez F**, **Wang ZV**, **Scherer PEC**. Adipocyte inflammation is essential for healthy adipose tissue expansion and remodeling. *Cell Metab* 20: 103–118, 2014.
333. **Wolf P**, **Winhofer Y**, **Smajis S**, **Jankovic D**, **Anderwald C-H**, **Trattnig S**, **Luger A**, **Krebs M**, **Kršš ák M**. Pericardial- Rather than Intramyocardial Fat Is Independently Associated with Left Ventricular Systolic Heart Function in Metabolically Healthy Humans. *PloS One* 11: e0151301, 2016.
334. **Wolf PA**, **Abbott RD**, **Kannel WB**. Atrial fibrillation as an independent risk factor for stroke: the Framingham Study. *Stroke J Cereb Circ* 22: 983–988, 1991.
335. **Wong CX**, **Abed HS**, **Molaee P**, **Nelson AJ**, **Brooks AG**, **Sharma G**, **Leong DP**, **Lau DH**, **Middeldorp ME**, **Roberts-Thomson KC**, **Wittert GA**, **Abhayaratna WP**, **Worthley SG**, **Sanders P**. Pericardial fat is associated with atrial fibrillation severity and ablation outcome. *J Am Coll Cardiol* 57: 1745–1751, 2011.
336. **Wood IS**, **Stezhka T**, **Trayhurn P**. Modulation of adipokine production, glucose uptake and lactate release in human adipocytes by small changes in oxygen tension. *Pflugers Arch* 462: 469–77, 2011.
337. **Wu F-Z**, **Chou K-J**, **Huang Y-L**, **Wu M-T**. The relation of location-specific

epicardial adipose tissue thickness and obstructive coronary artery disease: systemic review and meta-analysis of observational studies. *BMC Cardiovasc Disord* 14: 62, 2014.
338. **Wu F-Z**, **Huang Y-L**, **Wang Y-C**, **Lin H-S**, **Chen C-S**, **Ju Y-J**, **Chiou K-R**, **Cheng C-C**, **Wu M-T**. Impact of location of epicardial adipose tissue, measured by coronary artery calcium-scoring computed tomography on obstructive coronary artery disease. *Am J Cardiol* 112: 943–949, 2013.
339. **Wu J**, **Boström P**, **Sparks LM**, **Ye L**, **Choi JH**, **Giang A-H**, **Khandekar M**, **Virtanen KA**, **Nuutila P**, **Schaart G**, **Huang K**, **Tu H**, **van Marken Lichtenbelt WD**, **Hoeks J**, **Enerbäck S**, **Schrauwen P**, **Spiegelman BM**. Beige adipocytes are a distinct type of thermogenic fat cell in mouse and human. *Cell* 150: 366–376, 2012.
340. **Wystrychowski W**, **Patlolla B**, **Zhuge Y**, **Neofytou E**, **Robbins RC**, **Beygui RE**. Multipotency and cardiomyogenic potential of human adipose-derived stem cells from epicardium, pericardium, and omentum. *Stem Cell Res Ther* 7: 84, 2016.
341. **Xu H**, **Barnes GT**, **Yang Q**, **Tan G**, **Yang D**, **Chou CJ**, **Sole J**, **Nichols A**, **Ross JS**, **Tartaglia LA**, **Chen H**. Chronic inflammation in fat plays a crucial role in the development of obesity-related insulin resistance. *J Clin Invest* 112: 1821–30, 2003.
342. **Xu M**, **Palmer AK**, **Ding H**, **Weivoda MM**, **Pirtskhalava T**, **White TA**, **Sepe A**, **Johnson KO**, **Stout MB**, **Giorgadze N**, **Jensen MD**, **LeBrasseur NK**, **Tchkonia T**, **Kirkland JL**. Targeting senescent cells enhances adipogenesis and metabolic function in old age. *Elife* 4: e12997, 2015.
343. **Yamaguchi Y**, **Cavallero S**, **Patterson M**, **Shen H**, **Xu J**, **Kumar SR**, **Sucov HM**. Adipogenesis and epicardial adipose tissue: a novel fate of the epicardium induced by mesenchymal transformation and PPARγ activation. *Proc Natl Acad Sci U S A* 112: 2070–2075, 2015.
344. **Ye J**, **Gao Z**, **Yin J**, **He Q**. Hypoxia is a potential risk factor for chronic inflammation and adiponectin reduction in adipose tissue of ob/ob and dietary obese mice. *Am J Physiol Endocrinol Metab* 293: E1118-28, 2007.
345. **Ye JC**. Emerging role of adipose tissue hypoxia in obesity and insulin resistance. *Int J Obes 2005* 33: 54–66, 2009.
346. **Yerramasu A**, **Dey D**, **Venuraju S**, **Anand DV**, **Atwal S**, **Corder R**, **Berman DS**, **Lahiri A**. Increased volume of epicardial fat is an independent risk factor for accelerated progression of sub-clinical coronary atherosclerosis. *Atherosclerosis* 220: 223–230, 2012.
347. **Yin J**, **Gao Z**, **He Q**, **Zhou D**, **Guo Z**, **Ye J**. Role of hypoxia in obesity-induced disorders of glucose and lipid metabolism in adipose tissue. *Am J Physiol Endocrinol Metab* 296: E333-42, 2009.
348. **Yudkin JS**, **Eringa E**, **Stehouwer CDA**. "Vasocrine" signalling from perivascular fat: a mechanism linking insulin resistance to vascular disease. *Lancet Lond Engl* 365: 1817–1820, 2005.
349. **Zangi L**, **Oliveira MS**, **Ye LY**, **Ma Q**, **Sultana N**, **Hadas Y**, **Chepurko E**, **Später D**, **Zhou B**, **Chew WL**, **Ebina W**, **Abrial M**, **Wang Q-D**, **Pu WT**, **Chien KR**. Insulin-Like Growth Factor 1 Receptor-Dependent Pathway Drives Epicardial Adipose Tissue Formation After Myocardial Injury. *Circulation* 135: 59–72, 2017.
350. **Zghaib T**, **Ipek EG**, **Zahid S**, **Balouch MA**, **Misra S**, **Ashikaga H**, **Berger RD**, **Marine JE**, **Spragg DD**, **Zimmerman SL**, **Zipunnikov V**, **Trayanova N**, **Calkins H**, **Nazarian S**. Association of left atrial epicardial adipose tissue with electrogram bipolar voltage and fractionation: Electrophysiologic substrates for atrial fibrillation. *Heart Rhythm Off. J. Heart Rhythm Soc.* (August 18, 2016). doi: 10.1016/j.hrthm.2016.08.030.
351. **Zhang H**, **Pu W**, **Liu Q**, **He L**, **Huang X**, **Tian X**, **Zhang L**, **Nie Y**, **Hu S**, **Lui KO**,

Zhou B. Endocardium Contributes to Cardiac Fat. *Circ Res* 118: 254–265, 2016.
352. **Zuk PA**, **Zhu M**, **Mizuno H**, **Huang J**, **Futrell JW**, **Katz AJ**, **Benhaim P**, **Lorenz HP**, **Hedrick MH**. Multilineage cells from human adipose tissue: implications for cell-based therapies. *Tissue Eng* 7: 211–28, 2001.

Cross references

Ectopic lipid and inflammatory mechanisms of insulin resistance
Adiposity (legacy)
Beige adipose tissue in health and disease
Contribution of adipose tissue to development of cardiovascular disease
Perivascular adipose tissue in health and disease

Tables

Table 1. Main anatomical and physiological properties of EAT
Main anatomical and physiological properties of EAT

Localization	Between the myocardium and the visceral layer of the pericardium
Anatomical and functional proximity	Myocardium, coronary arteries, nerves and ganlionated plexi
Origin	Epicardium
Blood supply	Branches of the coronary arteries
Color	White and beige
Cells	Small adipocytes Mixed cellularity with stromal preadipocytes, fibroblasts, macrophages, mast cells, lymphocytes (immune cells)
Metabolism	High lipogenesis and lipolysis Thermogenesis
Secretome	Source of a myriad of adipocytokines, chemokines, growth factors, FFA
Way of action	Mainly local: paracrine and vasocrine
Transcriptome	Extracellular matrix remodeling, inflammation, immune signaling, coagulation, thrombosis, beiging and apoptosis enriched pathways
Protective actions	Arterial pulse wave, vasomotion Thermogenic potential Autonomic nervous system Immune defence Regeneration potential (epicardial-to-fat-transition)

Table 2. Human EAT bioactive molecules

Category	Biomarkers	Expression	Pathological state	References
Proinflammatory cytokines	α1-glycoprotein	mRNA	CAD	Fain *et al.*, 2010
	Chemerin	protein, mRNA	CAD	Spiroglou *et al.*, 2010
	CRP	secretion	CAD	Baker *et al.*, 2006
	Haptoglobin	mRNA	CAD	Fain *et al.*, 2010
	sICAM-1	mRNA	CAD	Karastergiou *et al.*, 2010
	IL-1β	protein, mRNA, secretion	CAD	Mazurek *et al.*, 2003
	IL-1Rα	secretion	CAD, obesity	Karastergiou *et al.*, 2010
	IL-6	protein, mRNA, secretion	CAD	Mazurek *et al.*, 2003 Kremen *et al.*, 2006

	sIL-6R	protein	Obesity	Malavazos *et al.*, 2011
	IL-8	mRNA	CAD	Fain *et al.*, 2010
	IL-10	mRNA	CAD	Eiras *et al.*, 2010
	IL-13	secretion	CAD, obesity	Karastergiou *et al.*, 2010
	IL-16	secretion	CAD, obesity	Karastergiou *et al.*, 2010
	JNK	mRNA, protein	Cardiac surgery	Baker *et al.*, 2009
	MCP-1	protein, mRNA, secretion	Cardiac surgery	Mazurek *et al.*, 2003 Kremen *et al.*, 2006
	MIF	mRNA	CAD	Langheim *et al.*, 2010
	PAI-1	mRNA	CAD	Baker *et al.*, 2006
	sPLA2-IIA	protein, mRNA, secretion	CAD	Dutour *et al.*, 2010
	PTGDS	mRNA	CAD	Guauque-Olarte *et al.*, 2011
	RANTES	secretion	CAD, obesity	Karastergiou *et al.*, 2010
	TNF-α	protein, mRNA, secretion	CAD, cardiac surgery	Mazurek *et al.*, 2003 Kremen *et al.*, 2006
Adipocytokines	Adiponectin	protein, mRNA	Hypertension, cardiac surgery	Baker *et al.*, 2006 Kremen *et al.*, 2006
	Leptin	protein, mRNA	CAD, cardiac surgery	Baker *et al.*, 2006 Kremen *et al.*, 2006
	Omentin	mRNA, protein	CAD, metabolic syndrome, T2DM	Gaborit *et al.*, 2015
	Resistin	mRNA, secretion	CAD, cardiac surgery	Baker *et al.*, 2006
	Serglycin	mRNA, protein	CAD	Imoto-Tsubakimoto *et al.*, 2013
	Vaspin	mRNA, protein	CAD	Spiroglou *et al.*, 2010
	Visfatin	protein, mRNA	CAD, metabolic syndrome, T2DM	Cheng *et al.*, 2008 Fain *et al.*, 2008
Growth and remodelling factors	Activin A	mRNA, protein	CAD	Venteclef *et al.*, 2013
	FLT1	mRNA	CAD	Fain *et al.*, 2010
	follistatin	mRNA, protein	CAD	Venteclef *et al.*, 2013
	GRO α	secretion	CAD, obesity	Karastergiou *et al.*, 2010
	MMP-1, -2, -3, -8, -9, -13	protein	CAD	Venteclef *et al.*, 2013
	NGF-β	mRNA	CAD	Fain *et al.*, 2010

	TGF - 1,-2,-3	mRNA, protein	CAD	Venteclef *et al.*, 2013
	FGF21	mRNA	Cardiac surgery	Kotulak *et al.*, 2011
Angiogenic and cardioprotective factors	Adrenomedullin	protein, mRNA	CAD	Iacobellis *et al.*, 2009
	Angiopoietin-2	protein	T2DM	Greulich *et al.*, 2012
	Angiotensin	protein, mRNA	CAD	Venteclef *et al.*, 2013
	Angiotensinogen	mRNA	Cardiac surgery	Roubicek *et al.*,2008
	CTRP9	mRNA, protein	CAD	Wang *et al.*, 2015
	Thrombospondin-2	protein	CAD	Venteclef *et al.*, 2013
	VEGF	protein	CAD	Venteclef *et al.*, 2013
Brown fat differentiation	PGC-1α	mRNA	Metabolic syndrome	Sacks *et al.*, 2009
	PRDM16	mRNA	Metabolic syndrome	Sacks *et al.*, 2009
	UCP-1	mRNA, protein	CAD	Gaborit *et al.*, 2015
Receptors	AT1 receptor	mRNA	Cardiac surgery	Roubicek *et al.*,2008
	GLUT-4	mRNA	CAD	Dozio *et al.*, 2016
	NPR-A	mRNA	CAD	Shibasaki *et al.*, 2010
	NPR-C	mRNA	CAD	Shibasaki *et al.*, 2010
	PPARγ	mRNA	CAD	Shibasaki *et al.*, 2010
	TLR	mRNA	CAD	Baker *et al.*, 2009
miR	10a-3p	miRNA	CAD	Vacca *et al.*, 2016
	18a-3p	miRNA	CAD	Vacca *et al.*, 2016
	196a-5p	miRNA	CAD	Vacca *et al.*, 2016
	196b-5p	miRNA	CAD	Vacca *et al.*, 2016
Immunocompetent cell markers	CD45	mRNA	Cardiac surgery	Kremen *et al.*, 2006
	CD68	protein, mRNA	Cardiac surgery	Kremen *et al.*, 2006
Lipids mediators	FABP4	mRNA	Metabolic syndrome	Vural *et al.*, 2008
	Free fatty acids	Lipids	CAD, metabolic syndrome, T2DM	Marchington *et al.*, 1989
	LRP1	mRNA	T2DM	Nasarre *et al.*, 2006

Table 3.
Imaging methods for epicardial fat assessment

Imaging modality	Spatial resolution	Cost	Possible measurements	Reproducibility	Strengths	Limitations
Echocardiography	+	+	• Thickness	• Moderately reproducible Inter and intra reader ICC 0.90 and 0.98 respectively	• No ionizing radiation • Non-invasive • Widely available • Often performed for other indications	• No volumetric quantification • Limited to one region (right ventricular free wall) • Poor image quality (limited acoustic windows, especially in obese individuals)
Cardiac computer Tomography (CT)	++	++	• Area • Thickness • Volume	• Highly reproducible Inter and intra scanner ICC , both r≥0.98	• Simultaneous coronary artery disease assessment • Volumetric quantification possible • Easy to perform and often for other indications	• Radiation exposure (especially problematic for serial studies) • Limited in separating pericardial/epicardial adipose tissue • Weight table limit for severely obese individuals
Cardiovascular magnetic resonance (CMR)	+++	+++	• Area • Thickness • Volume	• Highly reproducible Low intra and intraobserver variability ICC (both r>0.98) Volume reproducibility > thickness • Ex vivo validation in autopsies	• **Gold standard** for adipose tissue imaging • Volumetric quantification possible • No radiation or iodinated contrast required • Multi-parametric nature • Can be coupled with ^{1}H Spectroscopy	• Limited availability • Longer scan times and less tolerable • No accommodation for severely obese individuals • Bore magnet diameter limit for severely obese individuals

Figure legends

Figure 1: Layers of the heart and pericardium Scheme demonstrating epicardial fat between the visceral pericardium and myocardium, paracardial fat external to the parietal pericardium, and pericardial fat as the combination of epicardial and paracardial fat.

Figure 2: Epicardial adipose tissue among species – anterior and posterior heart photographic views in a 12-months-old rat (A), a 3-months-old swine (B) and a 50-years-old human (C).

Figure 3: The origin of epicardial adipose tissue. Epicardial adipocytes derived from embryonic epicardial progenitors by epicardium-to-fat transition (ETFT). After myocardial infarction in adult animals, reactivation of ETFT enables new epicardial adipocytes formation from epicardium cells.

Figure 4: Main factors leading to ectopic fat deposition in humans. FFA: free fatty acids; ASCs: adipose stem stromal cells; T2D: type 2 diabetes; CAD: coronary artery disease; MHO: metabolically healthy obesity

Figure 5: Echocardiography parasternal long axis view, thickness of paracardial and epicardial fat were measured on one anatomical point

Figure 6: CT scans in axial views, without iodine injection and with cardiac synchronization in A and with iodine injection and cardiac synchronization in B, C and D at different anatomical level. Pericardium was clearly depicted (white arrow) and allows the differentiation between epicardial fat (star in C) and paracardial fat (open arrow in C).

Figure 7: MR short axis cine sequences at the diastolic phase A, with contouring of the heart in B, contouring of the pericardium in C and contouring of the pericardial fat in D; each surface was multiplicated by slice thickness to obtain volumes. This contouring was repeated on the whole stack of images covering the entire heart to be able to quantify total fat volume. Volume of epicardial fat was measured as = volume in C minus volume B), and paracardial fat (volume D minus volume C)

Figure 8: Atrial EAT and myocardium. (A) Sirius red sections (B) Oil-red-O staining (C) Sirius red staining. At high magnification, adipocytes infiltration associated with important fibrosis within myocardium, impairing myocytes network (D) Haematoxylin and eosin staining

Figure 9: Role of epicardial fat in atrial fibrillation

Figure 10: Role of epicardial fat in coronary artery disease

Didactic Figure Legends

Figure 1. Teaching points: a variety of termes including “epicardial”, “pericardial”, “paracardial” and “intra-thoracic” have been used in the literature to describe ectopic fat depots in proximity to the heart or within mediastinum. The use of these terms appears to be a point of confusion, as there is varied use of definitions. Of particular confusion is the term used to define the adipose tissue located within the pericardial sac, between myocardium and visceral pericardium. This has previously been described in the literature as “pericardial fat”, while other groups have referred it as “epicardial fat”. As illustrated in Figure 1, the most accurate term for the adipose tissue fully enclosed in the pericardial sac that directly surrounds myocardium and coronary arteries is EAT. Pericardial fat (PeriF) refers to paracardial fat (ParaF) plus all adipose tissue located internal to the parietal pericardium. PeriF=ParaF+EAT.

Figure 2. This figure illustrates the relative amount of epicardial adipose tissue among species. Humans and swine have much more EAT than rodents.

Figure 3. This figure illustrates the origin of epicardial adipose tissue. Epicardial adipocytes have a mesothelial origin and derive mainly from epicardium. Cells originating from the (Wilms’ tumor gene Wt1) Wt1+ mesothelial lineage, can differentiate into EAT and this epicardium-to-fat transition (ETFT) fate can be reactivated after myocardial infarction.

Figure 4. This figures illustrates the mechanisms driving the development of ectopic fat deposition and its consequences. In an obesogenic environment and chronic positive energy balance, the ability of subcutaneous adipose tissue (SAT) to expand, and to store the free fatty acids in excess is crucial in preventing the accumulation of fat in ectopic sites, and the development of obesity complications. Healthy SAT and gynoid obesity are associated with a protective phenotype with less ectopic fat and metabolically healthy obesity, while dysfunctional SAT and android obesity are associated with more visceral fat and ectopic fat accumulation with an increased risk of type 2 diabetes, metabolic syndrome and coronary artery disease (CAD). Inflammation or profibrotic processes, hypoxia, and aging could also contribute to ectopic fat development. Mobilization and release of adipose progenitors adipose-derived stem/stromal cells (ASCs) into the circulation and their further infiltration into non adipose tissues leading to ectopic adipocyte formation also cannot be excluded.

Figure 5 to 7; These figures illustrate imaging techniques for EAT quantification. MRI remains the standard reference for adipose tissue quantification. The major advantage of this technique is its excellent spatial resolution and possible distinction between paracardial and epicardial fat. The major limitation of echocardiography is its 2D approach (thickness measurement). The major limitation of computed tomography remains its radiation exposure.

Figure 8. This figure illustrates microscopic images of human atrial epicardial adipose tissue and myocardium. One can observe fatty infiltration of myocardium with EAT, ie direct adipocytes infiltration into the underlying atrial myocardium, associated with fibrosis. Such direct adipocytes infiltration separating myocytes are supposed to induce remodeled atrial substrate, and lead to conduction defects (conduction slowing or inhomogeneity).

Figure 9. This figure summarizes the possible mechanisms that could link EAT with atrial fibrillation. EAT expansion-induced mechanical stress, direct adipocyte infiltration within atrial myocardium, inflammation, oxidative stress, and EAT producing adipofibrokines are thought to participate in structural and electrical remodeling of the atria, and in cardiac autonomous system activation, hence promoting arrhythmogenesis.

Figure 10. This figures illustrates a transversal and longitudinal view of EAT surrounding a coronary artery. As there is no fascia separating EAT from the vessel wall, free fatty acids or proinflammatory cytokines produced by EAT could diffuse passively or in vasa vasorum through the arterial wall and participate in the early stages of atherosclerosis plaque formation (endothelial dysfunction, ROS production, oxidized LDL uptake, monocyte transmigration, smooth muscle cells proliferation, macrophages transformation into foam cells). An imbalance between antiatherogenic, and harmful adipocytokines secreted by EAT could initiate inflammation in the intima. Innate immunity can be activated via the toll-like receptors (TLRs), which recognize antigens such as lipopolysaccharide (LPS). Activation of TLRs leads to the translocation of NFκB into the adipocyte nucleus to initiate the transcription and the release of proinfammatory molecules such as IL-6, TNF-α, and resistin. NLRP3 inflammasome is a sensor in the nod-like receptor family of the innate immune cell system that activates caspase-1, and mediates the processing and release of IL-1β by the adipocyte, and thereby has a central role in the EAT-induced inflammatory response.