Myocardial fat as a part of Cardiac Visceral Adipose Tissue: Physiological and Pathophysiological view

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Source / Izvornik: **Journal of Endocrinological Investigation, 2015, 38, 933 - 939**

Journal article, Published version
Rad u časopisu, Objavljena verzija rada (izdavačev PDF)

https://doi.org/10.1007/s40618-015-0258-y

Permanent link / Trajna poveznica: https://urn.nsk.hr/urn:nbn:hr:239:735129

J Endocrinol Invest (2015) 38:933–939
DOI 10.1007/s40618-015-0258-y

REVIEW

Myocardial fat as a part of cardiac visceral adipose tissue: physiological and pathophysiological view

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Received: 23 November 2014 / Accepted: 8 February 2015 / Published online: 15 March 2015

Abstract Thoracic fat includes extra-pericardial (outside the visceral pericardium) and intra-pericardial (inside the visceral pericardium) adipose tissue. It is called ectopic adipose tissue although it is a normal anatomical structure. Intra-pericardial adipose tissue, which is predominantly composed of epicardial and pericoronary adipose tissue, has a significant role in cardiovascular system function. It provides metabolic-mechanical support to the heart and blood vessels in physiological conditions, while it represents metabolic-cardiovascular risk in case of qualitative and quantitative structural changes in the tissue: it correlates with coronary atherosclerotic disease, left ventricular mass, left atrium enlargement and atrial fibrillation presence. In the last decade there has been mounting evidence of fat cells presence in the myocardium of healthy (non-diseased) persons as well as in persons with both cardiovascular and non-cardiovascular diseases. Thus, it is necessary to clarify the incidence, aetiology, physiological role of fat cells in the myocardium, as well as the clinical significance of pathological fatty infiltration of the myocardium.

Keywords Cardiometabolic disease · Cardiac visceral adipose tissue · Epicardial fat · Myocardial fat · Myocardial fat aetiology · Obesity

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Introduction

Thoracic fat: extra/intra-pericardial adipose tissue

Adipose tissue within the thoracic cavity is divided into extra-pericardial and intra-pericardial adipose tissue (AT) (Fig. 1). Extra-pericardial AT is found outside the visceral pericardium [1]. It has no direct contact with the myocardium and it consists of mediastinal adipose tissue [2] and thoracic periaortic adipose tissue [3]. Intra-pericardial AT is located between the myocardium and the visceral pericardium [4–7]. The fat located on the outer surface of the fibrous pericardium differs from the intra-pericardial fat in biochemical, molecular and vascular nutrition properties [4]. Total amount of extra-pericardial and intra-pericardial fat in healthy eutrophic persons is about 100 g, while in type 2 diabetic patients it is about 400 g, in some persons even up to 800–900 g, and have weak correlation to body mass index (BMI) but strong correlation with waist circumference [8, 9].

Intra-pericardial fat: cardiac visceral adipose tissue

Cardiac visceral adipose tissue (CVAT) represents fat inside of the visceral pericardium:

(a) *Epicardial adipose tissue (EAT)* A fat tissue accumulated between visceral pericardium and the myocardium, without structure or fascia separating it from the myocardium and the epicardial vessels [4];
(b) *Pericoronary adipose tissue (PCAT)* A part of epicardial fat tissue which surrounds coronary arteries and arterioles [5, 10];
(c) *Myocardial fat (MF)* Individual or clusters of fat cells or fatty infiltration within the myocardium, appearing

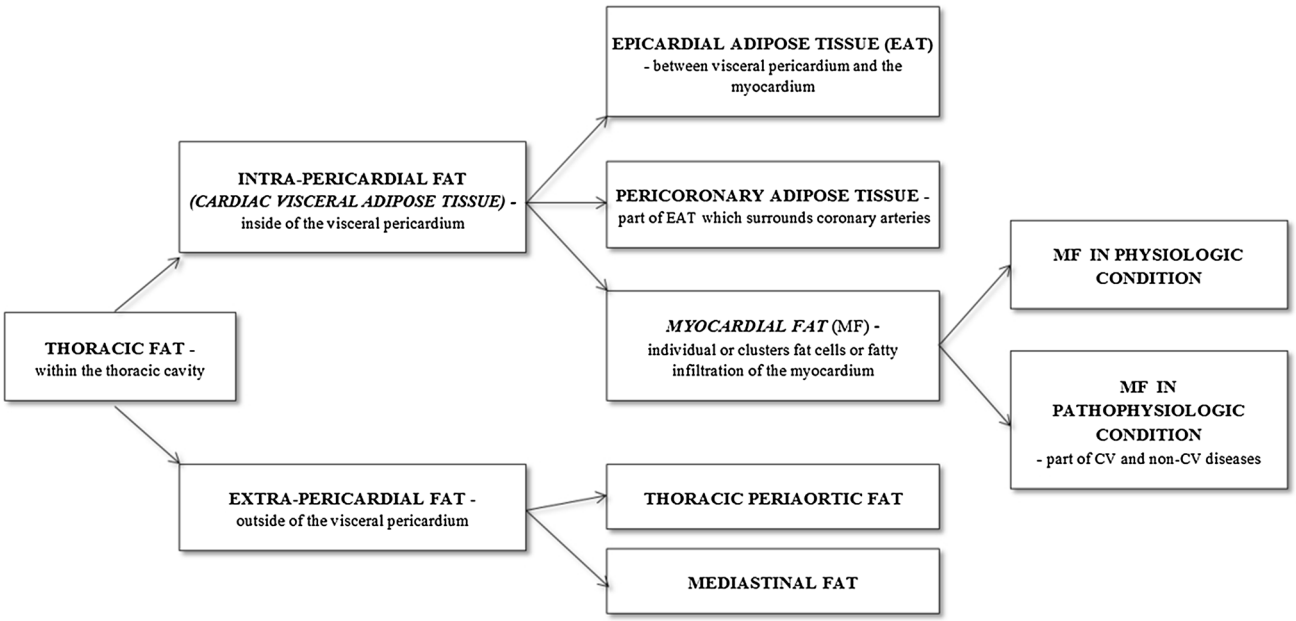

Fig. 1 Algorithm of intra-pericardial and extra-pericardial adipose tissue. *EAT* epicardial adipose tissue, *MF* myocardial fat, *CV* cardiovascular

in physiological condition and as a part of cardiovascular (CV) and non-CV diseases [6, 7].

CVAT is composed of adipocytes, stromal cells, macrophages and neuronal network, all nourished by a rich microcirculation. It plays an important role in maintaining intra-thoracic homeostasis: preserves contractile function of the heart and blood vessels by providing mechanical support; energy storage with ability to retain/release fatty acids as required, simultaneously avoiding lipotoxicity; protective vasocrine function since there is no muscular fascia, which enables both migration of fat cells and diffusion of synthesised molecules [8]. In case of CVAT expansion (up to now due to unknown trigger factors and mechanisms), local hypoxia develops causing dysfunction of adipose tissue endocrine mechanisms, which is expressed by reduced numbers of protective cells and increased numbers of detrimental adipocytokines. This promotes inflammation, macrophages infiltration, vasoconstriction, plaque neoangiogenesis and prothrombotic effects via local paracrine effect [11–14]. From clinical point of view, CVAT is linked, not independently, with increased cardiac mass and remodelling, left atrium (LA) enlargement, left ventricle (LV) diastolic dysfunction development, lower ejection fraction (EF), vascular ageing, increased peripheral vascular resistance and subclinical atherosclerosis [15–17]. CVAT in diseased and non-diseased heart represents additional cardiovascular risk factor regardless of conventional risk factors [18].

Epicardial adipose tissue (EAT)

EAT evolves from brown adipose tissue during embryogenesis [19], as a regular anatomical structure in all persons regardless of their body weight. Its total amount is linked with the level of obesity, race, gender and age [20, 21]. It has direct contact with the myocardium and coronary blood vessels, providing support and protecting them mechanically from tension and torsion, metabolically is a source and storage of energy, provides thermogenic protection, represents a source of antiatherogenic and anti-inflammatory adipokines in normal condition [19]. Physiology of EAT is different than subcutaneous adipose tissue, it has a higher rate of lipolysis and insulin-induced lipogenesis, richer in saturated fatty acids, higher rates of free fatty acids synthesis, incorporation and breakdown, act as a buffering system against toxic levels of fatty acids [22].

In the adult heart, EAT is found in the atrioventricular and interventricular grooves extending to the apex along the coronary arteries and surrounding them, while their branches bring blood supply [23–25]. EAT is located over both ventricles and it constitutes around 20 % of the total ventricular weight in the human heart. The absolute amount of EAT is similar between the right and left ventricle, while the ratio of fat to myocardium weight for the right side of the heart is more than three times that of the left side [26].

From clinical point of view, EAT exerts local effect on the atrial mechanical and electrical remodelling [27] due to mechanical infiltration of conductive system and cardiomyocytes degeneration, which leads to separation of

intracellular cardiomyocytes communication [6]. Thus, it is associated with paroxysmal/persistent atrial fibrillation (AF) and poorer outcome after AF ablation; LA enlargement and remodelling [28, 29], cardiac hypertrophy, increased LV mass [30]. In persons with reduced systolic function of LV, EAT thickness is reduced, which can be a part of complex pathogenetic mechanisms in development of cardiac cachexia (cardioprotective role of EAT) [31].

Pericoronary adipose tissue (PCAT)

PCAT, as EAT, evolves from brown adipose tissue during embryogenesis [19] and have the same blood supply from coronary arteries [4]. In normal human heart PCAT (part of EAT) follows the adventitia of coronary arteries [4, 5, 22]. PCAT thickness, volume distribution and structure depend on a blood vessel type and also on the location on blood vessel [20, 32, 33]. Local pathogenic effect of PCAT is achieved either by a direct compression on a blood vessel or by changes within the tissue that are linked with obesity, hypertension, hyperglycaemia and metabolic syndrome via pathways that includes numbers of adipokines. Their metabolic, vascular, immunologic and inflammatory effects [19, 34] has influence on vascular function, smooth muscle cell and immune cell migration into the vascular wall, modulation of insulin effect on the vasculature, alterations in nitric oxide signalling and lower microvascular coronary response [35–38], with direct relation to coronary atherosclerotic plaque thickness and severity of coronary artery disease [39].

Myocardial fat (MF)

According to recent findings, incidence and role of MF can no longer be considered a random autopsy finding and needs to be further investigated [40, 41]. Development of modern cardio-imaging techniques (echocardiography, computed tomography and magnetic resonance) made it possible to identify MF ante mortem. It has been recognised that the incidence of fat cells within the myocardium plays a significant role, not only as a part of regular heart structure in healthy persons, in obese/non-obese, but also as a part of heart ageing process as well as a part of pathohistological findings in both, CV and non-CV diseases [6, 7]. There are many issues regarding MF that need to be explained: incidence, aetiology, localisation, amount and distribution of fat, as well as its clinical significance and influence on the function of the myocardium [42].

Myocardial fat in physiologic condition

Most adults with non-diseased hearts contain varying amounts of physiologic MF, more often elderly people, woman and persons with more visceral adipose tissue independently of BMI [43].

MF is predominantly found in the right ventricle (RV), especially in the anterolateral and apical walls, RV outflow tract and trabeculae, while only a small amount is found in LV wall, in its apical part [29, 40, 41]. MF infiltration in the RV starts in the epicardium (external part of the myocardium) gradually expanding to the endocardium, depending on the infiltration level. In cases of slight fatty infiltration, MF is typically located in perivascular connective tissue [7, 41, 44]. Increased amount of MF is noticed in persons with increased amount of EAT [42]. Fat cells within the myocardium are usually interspersed among myocardial fibres without cardiomyocytes replacement, fibrosis or signs of inflammation [40, 41, 44–46], RV walls remain equally thick or become even thinner, while RV size stays normal [29].

Myocardial fat in pathophysiological conditions

The differentiation of pathologic from physiologic myocardial fat is very important for diagnosis and prognosis. MF within the myocardium is a regular pathohistological finding in primary diseases of myocardium and coronary blood vessels, as well as secondary finding in some systemic diseases and diseases of other organ system [7]. CV and non-CV diseases with myocardial fat infiltration are:

(a) *MF in healed myocardium* a regular finding in persons with history of myocardial infarction (MI). MF occurs in the area surrounding the infarcted coronary artery, correlates with infarcted area volume and extends into the sub-endocardium. There is no difference in amounts of fat according to location of MI [5]. LV wall thickness does not change, while LV dilation depends on the percentage of affected myocardium area and the scar size [7]. Percentage of MF within the LV increases with time elapsed since MI [6, 47], but does not correlate with gender, age and standard risk factors for coronary artery disease [48, 49].
(b) *Arrhythmogenic right ventricular dysplasia (ARVD)* hereditary progressive disease affecting the myocardium that is characterised first by segmental and then by diffuse fibro-fatty replacement (FFR) in the myocardium. It develops predominantly in the RV free wall, but its incidence is also reported in LV wall as well as in interventricular septum [50, 51]. The nature of clinical manifestation of the disease depend on anatomical location and the extent of the disease, which influences myocardium function and electrical excitability, often resulting in development of malignant arrhythmias that cause sudden cardiac death [52].
(c) *Lipomatous hypertrophy of the interatrial septum (LHIS)* is benign, excessive fat deposition in the intera-

trial septum, histologically characterised by mature fat with varying quantity of foetal fat, inflammation and fibrosis. It correlates with age and level of obesity and develops more often in women, increases the risk of mostly benign arrhythmias that can rarely become malignant [6, 53].

(d) *Dilatative cardiomyopathy (DCM)* is characterised by linear accumulations of MF in the middle layer of the LV myocardium with myocardial fibrosis, dilated LV and reduced LV EF [7, 48].

(e) *Cardiac lipoma* is a benign, encapsulated neoplasm, composed of mature adipose tissue. It can occur within any heart cavity or pericardial space at any age, but without myocardial fatty infiltration [54].

(f) *Tuberous sclerosis complex* is a high variable, multisystem, genetic disorder that causes non-malignant tumours to form in many organs including the heart. It is characterised by numerous well-circumscribed fatty deposits, mostly within the interventricular septum and LV wall, as well as by multiple intra-myocardial lipomas [55].

(g) *Muscular dystrophies* are X-linked recessive disorders that lead to degeneration of both skeletal muscles and myocardium, with fibrosis, degeneration and fatty infiltration of the myocardium [56] and development of DCM with reduced EF [57].

Myocardial fat: role and aetiology

Despite the growing number of publications in the field of modern imaging methods on the incidence of fat cells within the myocardium, there is still question why fat cells exist in the myocardium, except its developmental/physiological role. According to research, these are the mechanisms that lead to the presence of myocardial fat infiltration.

(a) *Embryonic basis/physiologic role* Fat cells possess an important physiologic role as a source of energy [8], as connective [58] and supportive tissue [36] in homeostasis of myocardium and associated cardiac structures, according to available data embryonic development leads to connective tissue development [59].

(b) *Storage of triglyceride droplets* If energy exchange in the heart muscle is disturbed (unhealthy myocardium, disturbed metabolic processes, diabetes mellitus type 2, obesity) free fatty acids are excessively released and form endogenous triglyceride depots [60] that depending on infiltration level progress into cardiac steatosis with potential cardiotoxic effect [9] and functional damage to the heart, especially diastolic dysfunction [8].

(c) *Over-accumulation* Surplus fat cells migrate from EAT to the myocardium (especially to the RV) due to absence of muscular fascia towards myocardium, while visceral pericardium is a barrier for intra-thoracic spread of adipose tissue. This confirms positive correlation between the macroscopic grading of EAT and the microscopic myocardial fatty infiltrative degree [61, 62].

(d) *Healing process* Numerous studies on both humans and animals have proven that acute post-infarction cardiomyocytes apoptosis occurs resulting in scarring as a part of a healing process, but continues in post-acute phase in the border area to the viable myocardium [63]. Pathogenesis of fat formation is unclear, it may result from: (a) inability of ischaemic myocytes to metabolise free fatty acids [64]; (b) reperfusion therapy for coronary artery disease which promotes cells transdifferentiation [45]; (c) consequence of adipose tissue deposition in infarcted area where myocytes have been replaced by fibrous tissue (active inflammatory response, angiogenesis, fibroblast proliferation and collagen deposition) [7, 64].

(e) *Pluripotent cells migration* There is very little data on potential hypothesis. Hypothesis is based on the fact that the heart is of mesenchymal origin, while cardiac outflow tract cells originate from neural crest, an ectoderm-derived structure that produces connective-supportive tissue, also containing stem cells. During migration pluripotent possibilities become limited, cells stay behind and their potential depends on growth factor and they can influence heart development. It is not clear when and where cells development potential will be realised [65, 66].

(f) *Trans-differentiation of cardiac myocytes into adipocytes* ARVD is an example of genetic autosomal dominant disease in which fibrofatty replacement of cardiomyocytes takes place, primarily in the RV [67, 68].

(g) *Ageing process* Cardiac biology is characterised by little capacity for self-regeneration [68]. Process of regeneration and degeneration of the myocardium has not been completely explained yet, but it is known that number and functional ability of cardiomyocytes decreases with ageing, while percentage of MF increases [41, 69, 70]. The changes are based on necrosis and apoptosis with reduced regenerative possibilities of cardiac progenitor cells [71, 72] or accumulated lipids influence cardiomyocytes metabolism causing hypoxia with activation of a series of proinflammatory and proatherogenic cytokines with increased oxidative stress resulting in interstitial and perivascular fibrosis [73].

Conclusion

According to data from post/ante mortal analysis, molecular and clinical researches, it can be concluded that: (a)

MF is essential for maintaining myocardial physiological homeostasis in metabolic and thermogenic processes, as a mechanical support; (b) it is still unclear which mechanisms lead to accumulation of fat cells that results in activation of pathophysiologic mechanisms and subsequent changes in the structure and function of up to then non-diseased myocardium; (c) depending on the degree of infiltration and the presence of CV/non-CV diseases, MF can affect diastolic and/or systolic function of the myocardium with cardiomyopathy development; (d) MF represents an important structural part and significant diagnostic and prognostic factor.

Acknowledgments This research received no grant from any funding agency in the public, commercial or not-for-profit sectors.

Conflict of interest The authors declare that there is no conflict of interest.

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

Informed consent No informed consent.

References

1. Dey D, Nakazato R, Li D, Berman DS (2012) Epicardial and thoracic fat-noninvasive measurement and clinical implications. Cardiovasc Diagn Ther 2(2):85–93
2. Yun KH, Rhee SJ, Yoo NJ, Oh SK, Kim NH, Jeong JW et al (2009) Relationship between the echocardiographic epicardial adipose tissue thickness and serum adiponectin in patients with angina. J Cardiovac Ultrasond 17(4):121–126
3. Britton KA, Wang N, Palmisano J, Corsini E, Schlett CL, Hoffmann U et al (2013) Thoracic periaortic and visceral adipose tissue and their cross-sectional associations with measures of vascular function. Obesity (Silver Spring) 21(7):1496–1503
4. Bertaso AG, Bertol D, Duncan BB, Foppa M (2013) Epicardial fat: definition, measurements and systematic review of main outcomes. Arq Bras Cardiol 101(1):e18–e28
5. Sacks HS, Fain JN (2007) Human epicardial adipose tissue: a review. Am Heart J 153:907–917
6. Pananowitz L (2001) Fat infiltration in the heart. Heart 85:253
7. Kimura F, Matsuo Y, Nakajima T, Nishikawa T, Kawamura S, Sannohe S et al (2010) Myocardial fat at cardiac imaging: how can we differentiate pathologic from physiologic fatty infiltration? Radiographics 30:1587–1602
8. Iozzo P (2011) Myocardial, perivascular and epicardial fat. Diab Care 34:S371–S379
9. Iozzo P, Lautamaki R, Borra R, Lehto HR, Bucci M, Viljanen A et al (2009) Contribution of glucose tolerance and sex to cardiac adiposity. J Clin Endocrinol Metab 94:4472–4482
10. Fitzgibbons TP, Cezch MP (2014) Epicardial and perivascular adipose tissues and their influence on cardiovascular disease: basic mechanisms and clinical associations. J Am Heart Assoc 3:e000582
11. Iacobellis G, Pistilli D, Gucciardo M, Leonetti F, Miraldi F, Brancaccio G et al (2005) Adiponectin expression in human epicardial adipose tissue in vivo is lower in patients with coronary artery disease. Cytokine 29:251–255
12. Mahabadi AA, Massaro JM, Rosito GA, Levy D, Murabito JM, Wolf PA et al (2009) Association of pericardial fat, intrathoracic fat, and visceral abdominal fat with cardiovascular disease burden: the Framingham Heart Study. Eur Heart J 30:850–856
13. Greenstein AS, Khavandi K, Wihers SB, Sonoyama K, Clancy O, Jeziorska M et al (2009) Local inflammation and hypoxia abolish the protective anticontractile properties of perivascular fat in obese patients. Circulation 119:1661–1670
14. Zhang H, Zhang C (2009) Regulation of microvascular function by adipose tissue in obesity and type 2 diabetes: evidence of adipose-vascular loop. Am J Biomed Sci 1:133–142
15. Iacobellis G, Willens HJ (2009) Echocardiographic epicardial fat: a review of research and clinical applications. J Am Soc Echocardiogr 22:1311–1319
16. Fox CS, Gona P, Hoffmann U, Porter SA, Salton CJ, Massaro JM et al (2009) Pericardial fat, intrathoracic fat, and measures of left ventricular structure and function: the Framingham Heart Study. Circulaton 119:1586–1591
17. Natale F, Tedesco MA, Mocerino R, de Simone V, Di Marco GM, Aronne L et al (2009) Visceral adiposity and arterial stiffness: echocardiographic epicardial fat thickness reflects, better than waist circumference, carotid arterial stiffness in a large population of hypertensives. Eur J Echocardiogr 10:549–555
18. Britton KA, Pedley A, Massaro JM, Corsini EM, Murabito JM, Hoffmann U et al (2012) Prevalence, distribution, and ris factor correlates of high thoracic periaortic fat in the Framingham heart study. J Am Heart Assoc 1(6):e004200
19. Marchington JM, Mattacks CA, Pond CM (1989) Adipose tissue in the mammalian heart and pericardium: structure, foetal development and biochemical properties. Comp Biochem Physiol B 94:225–232
20. Alexopoulos N, McLean DS, Janik M, Arepalli CD, Stillman AE, Raggi P (2010) Epicardial adipose tissue and coronary artery plaque characteristics. Atherosclerosis 210:150–154
21. Iacobellis G, Ribaudo MC, Assael F, Vecci E, Tiberti C, Zappaterreno A et al (2003) Echocardiographic epicardial adipose tissue is related to anthropometric and clinical parameters of metabolic syndrome: a new indicator of cardiovascular risk. J Clin Endocrinol Metab 88:5163–5168
22. Echavarría-Pinto M, Hernando L, Alfonso F (2013) From the epicardial adipose tissue to vulnerable coronary plaques. World J Cardiol 5(4):68–74
23. Montani JP, Carroll JF, Dwyer TM, Antic V, Yang Z, Dulloo AF (2004) Ectopic fat storage, blood vessels and kidneys in the pathogenesis of cardiovascular diseases. Int J Obes Relat Metab Disord 28:S58–S65
24. Rosito GA, Massaro JM, Hoffmann U, Ruberg FL, Mahabadi AA, Vasan RS et al (2008) Pericardial fat, visceral abdominal fat, cardiovascular disease risk factors, and vascular calcifications in a community-based sample: the Framingham Heart Study. Circulation 117:605–613
25. Savks HS, Fain JN, Bahouth SW, Ojha S, Frontini A, Budge H et al (2013) Adult epicardial fat exhibits beige features. J Clin Endocrinol Metab 98:E1448–E1455
26. Corradi D, Maestri R, Callegari S, Pastori P, Goldoni M, Luong TV et al (2004) The ventricular epicardial fat is related to the myocardial mass in normal, ischemic and hypertrophic hearts. Cardiovasc Pathol 13:313–316
27. Venteclef N, Guglielmi V, Balse E, Gaborit B, Cotillard A, Atassi F et al (2013) Human epicardial adipose tissue induces fibrosis of the atrial myocardium through the secretion of adipo-fibrokines. Eur Heart J. doi:10.1093/eurheartj/eht099
28. Wong CX, Abed HS, Molaee P, Nelson AJ, Brooks AG, Sharma G et al (2011) Pericardial fat is associated with atrial fibrillation severity and ablation outcome. J Am Coll Cardiol 57:1745–1751
29. Kim E, Choe YH, Han BK, Kim SM, Kim JS, Park SW et al (2007) Right ventricular fat infiltration in asymptomatic subjects:

observation from ECG gated 16 slice multidetector CT. J Comput Assist Tomogr 31:22–28
30. Iacobellis G, Ribaudo MC, Zapaterrano A, Iannucci CV, Leonetti F (2004) Relation between epicardial adipose tissue and left ventricular mass. Am J Cardiol 94:1084–1087
31. Khawaja T, Greer C, Chokshi A, Chavarria N, Thadani S, Jones M et al (2011) Epicardial fat volume in patients with left ventricular systolic dysfunction. Am J Cardiol 108:397–401
32. Enriga EC, Bakker W, Smulders YM, Serné EH, Yudkin JS, Stehouwer CDA (2007) Regulation of vascular function and insulin sensitivity by adipose tissue: focus on perivascular adipose tissue. Microcirculation 14:389–402
33. Vela D, Buja LM, Madjid M, Burke A, Naghavi M, Willerson JT, Casscells SW et al (2007) The role of periadventitial fat in atherosclerosis. Arch Pathol Lab Med 131:481–487
34. Lohn M, Dubrovska G, Lauterbach B, Luft FC, Gollasch M, Sharma AM (2002) Periadventitial fat releases a vascular relaxing factor. FASEB J 16:1057–1063
35. Baker AR, Silva NF, Quinn DW, Harte AL, Pagano D, Bonser RS et al (2006) Human epicardial adipose tissue expresses a pathogenic profile of adipocytokines in patients with cardiovascular disease. Cardiovasc Diabetol 5:1
36. Yudkin JS, Eringa E, Stehouwer CD (2005) "Vasocrine" signalling from perivascular fat: a mechanism linking insulin resistance to vascular disease. Lancet 365:1817–1820
37. Gaborit B, Kober F, Jacquier A, Moro PJ, Flavian A, Quilici J et al (2012) Epicardial fat volume is associated with coronary microvascular response in healthy subjects: a pilot study. Obesity (Silver Spring) 20:1200–1205
38. Britton KA, Fox CS (2011) Perivascular adipose tissue and vascular disease. Clin Lipidol 6:79–91
39. Demircelik MB, Yilmaz OC, Gurem OM, Selcoki Y, Atlar IA, Bozkurt A et al (2014) Epicardial adipose tissue and pericoronary fat thickness measured with 64-multidetector computed tomography: potential predictors of the severity of coronary artery disease. Clinics 69(6):388–392
40. Basso C, Thiene G (2005) Adipositas cordis, fatty infiltration of the right ventricle, and arrhythmogenic right ventricular cardiomyopathy: just a matter of fat? Cardiovasc Pathol 14:37–41
41. Tansey DK, Aly Z, Sheppard MN (2005) Fat in the right ventricle of the normal heart. Histopathology 46:98–104
42. Kellman P, Hernando D, Arai AE (2010) Myocardial fat imaging. Curr Cardiovasc Imaging Rep 3:83–91
43. Litwin SE (2012) Normal weight obesity: is bigger really badder? Circ Cardiovasc Imaging 5:286–288
44. de la Grandmaison LG, Le Bihan C, Duringon M (2001) Assessment of right ventricular lipomatosis by histomorphometry in control adult autopsy cases. Int J Legal Med 115:105–108
45. Fontaine G, Fontaliran F, Zenati O, Guzman CE, Rigoulet J, Berthier JL et al (1999) Fat in the heart: a feature unique to the human species? Observational reflections on an unsolved problem. Acta Cardiol 54:189–194
46. Goldfarb JW, Arnold S, Roth M, Han J (2007) T1-weighted magnetic resonance imaging shows fatty depositions after myocardial infarction. Magn Reson Med 57:828–834
47. Ahn SS, Kim YJ, Hur J, Lee HJ, Kim TH, Choe KO et al (2009) CT detection, of subendocardial fat in myocardial infarction. Am J Roentgenol 192:532–537
48. Minjie L, An J, Gang J, Shiliang J, Qiong L, Ning M et al (2012) Myocardial fat deposition in dilatated cardiomyopathy-assessment by using MR water-fat separation imaging. Heart 98:E249–E250
49. Ichikawa Y, Kitagawa W, Chino S, Ishida M, Matsuoka K, Tanigawa T et al (2009) Adipose tissue detected by multislice computed tomography in patients after myocardial infarction. JACC Cardiovasc Imaging 2:548–555
50. Basso C, Ronco F, Marcus F, Abudureheman A, Rizzo S, Frigo AC et al (2008) Quantitative assessment of endomyocardial biopsy in arrhythmogenic right ventricular cardiomyopathy/dysplasia: an in vitro validation of diagnostic criteria. Eur Heart J 29:2760–2771
51. Marcus F, McKenna WJ, Sherill D, Basso C, Bauce B, Bluemke DA et al (2010) Diagnosis of arrhythmogenic right ventricular cardiomyopathy/dysplasia: proposed modification of the Task force criteria. Circulation 121:1533–1541
52. Kimura F, Sakai F, Sakomura Y, Fujimura M, Ueno E, Matsuda N et al (2002) Helical CT features of arrhythmogenic right ventricular cardiomyopathy. Radiographics 22:1111–1124
53. Heyer CM, Kagel T, Lemburg SP, Bauer TT, Nicolas V (2003) Lipomatous hypertrophy of the interatrial septum: a prospective study of incidence, imaging findings, and clinical symptoms. Chest 124:2068–2073
54. Araoz PA, Mulvagh SL, Tazelaar HD, Julsrud PR, Breen JF (2000) CT and MR imaging of benign primary cardiac neoplasms with echocardiographic correlation. Radiographics 20:1303–1319
55. Shaaya EA, Hirshberg JS, Rabe OT, Thibert RL, Inglessis I, Sharma A et al (2013) Cardiac-fat containing lesions are common in tuberous sclerosis complex. AM J Med Genet A 161:1662–1665
56. Nishimura T, Yanagisawa A, Sakata H, Sakata K, Shimoyama K, Ishihara T et al (2001) Thallium-201 single photon emission computed tomography (SPECT) in patients with Duchenne's progressive muscular dystrophy: a histopathologic correlation study. Jpn Circ J 65:99–105
57. Puchalski MD, Williams RV, Askovich B, Sower CT, Hor KH, Su JT et al (2009) Late gadolinium enhancement: precursor to cardiomyopathy in Duchenne muscular dystrophy? Int J Cardiovasc Imaging 25:57–63
58. Iacobellis G, Corradi D, Sharma AM (2005) Epicardial adipose tissue: anatomic, biomolecular and clinical relation to the heart. Nat Clin Pract Cardiovasc Med 2:536–543
59. Hartung H, Feldman B, Lovec H, Coulier F, Birnbaum D, Goldfarb M (1997) Murine FGF-12 and FGF-13: expression in embryonic nervous system, connective tissue and heart. Mech Dev 64(1–2):31–39
60. Van der Meer RW, Smit JW, Hammer S, Schär M, Bax JJ, Smit JW et al (2008) The ageing male heart: myocardial triglyceride contents as independent predictor of diastolic dysfunction. Eur Heart J 29:1516–1522
61. Lou BT, Jiang HG, Zhao YH, Chen XY (2010) Pathology of myocardial fatty infiltration: an autopsy report from 117 cases. Zhonghua Xin Guan Bing Za Zhi 38:350–353
62. Malavazos AE, Di Leo G, Secchi F, Lupo EN, Dogliotti G, Coman C et al (2010) Relation of echocardiographic epicardial fat thickness and myocardial fat. Am J Cardiol 105(12):1831–1835
63. Palojoki E, Saraste A, Eriksson A, Pulkki K, Kallajoki M, Voipio-Pulkki LM et al (2001) Cardiomyocyte apoptosis and ventricular remodeling after myocardial infarction in rats. Am J Physiol Heart Circ Physiol 280:H2726–H2731
64. Su L, Siegel JE, Fishbein MC (2004) Adipose tissue in myocardial infarction. Cardiovasc Pathol 13:98–102
65. Sieber-Blum M (2004) Cardiac neural crest stem cells. Anat Rec A Discov Mol Cell Evol Biol 276:34–42
66. D'Amati G, di Gioia CRT, Giordano C, Gallo P (2000) Myocyte transdifferentiation. A possible pathogenic mechanism for arrhythmogenic right ventricular cardiomyopathy. Arch Pathol Lab Med 124:287–290
67. Chellamuthu S, Smith AM, Thomas SM, Hill C, Brown PW, Al-Mohammad A (2014) Is cardiac MRI an effective test for arrhythmogenic right ventricular cardiomyopathy diagnosis? World J Cardiol 26(6):675–681
68. Feng Y, Wang Y, Cao N, Yang H, Wang Y (2012) Progenitor/stem cell transplantation for repair of myocardial infarction: Hype or hope? Ann Palliat Med 1:65–77

69. Selthofer-Relatić K (2014) Cardiac visceral adiposity and right ventricle apex remodelling—locus minoris resistentiae. Med Hypo 82:404
70. Selthofer-Relatić K, Rajc J, Belovari T, Bošnjak I, Dumenčić B (2014) Fatty infiltration of the right heart—histopathological human analysis. Cardiologia Croatica 9(9–10):444
71. Lazzarini V, Mentz RJ, Fiuzat M, Metra M, O'Connor CM (2013) Heart failure in elderly patients: distinctive features and unresolved issues. Eur J Heart Fail 15:717–723
72. Wong LS, van der Harst P, de Boer RA, Huzen J, van Gilst WH, van Veldhuisen DJ (2010) Aging, telomeres and heart failure. Heart Fail Rev 15:479–486
73. Crendal E, Dutheil F, Naughton G, McDonald T, Obert P (2014) Increased myocardial dysfunction, dyssynchrony, and epicardial fat across the lifespan in healthy males. BMC Cardiovasc Disord 14:95