心外膜脂肪组织：从解剖生理、临床评估到心血管疾病的干预靶点

赵松　张毅

张毅

赵松

引言

心血管疾病（cardiovascular diseases，CVD）是全球人类的主要死因之一[1]。据推算，我国CVD现有患病人数为3.3亿，给我国带来了严重的社会和经济负担[2]。心外膜脂肪组织（epicardial adipose tissue，EAT）是位于心肌表面和心外膜内脏层之间的独特的脂肪库[3]。EAT的独特性主要体现在两个方面，一是其独特的解剖结构，EAT和心脏无障碍紧密相连[4]；二是EAT拥有不同于其他内脏脂肪组织和皮下脂肪组织的信号转录系统[5]。自EAT有报道以来，EAT与CVD的相关研究引起了广泛的关注。由于其接近心脏，EAT被认为在CVD的发生和发展中发挥作用，特别是在冠状动脉疾病（coronary artery disease，CAD）、心房颤动和心力衰竭中。随着一些心血管药物被发现对EAT产生影响，EAT也被认为是CVD的潜在的治疗靶点[6]。

心外膜脂肪组织的解剖特点

EAT指心肌和心外膜内脏层（心包内脏层）之间的脂肪组织（图1），覆盖了心脏表面80%的区域，由冠状动脉的分支供血[7]。EAT在心肌表面分布不均匀，主要位于房室沟和室间沟，分为冠状动脉周围EAT和心肌EAT[8]。EAT主要由脂肪细胞组成，也包含神经细胞、炎症细胞（主要是巨噬细胞和肥大细胞）、基质细胞、内皮细胞和免疫细胞[4]。EAT是一种白色脂肪，但有类似棕色脂肪和米色脂肪的特征[9]。EAT和心肌之间不存在肌筋膜，因此和心肌有相同的微循环，并且这一特点仅在EAT与心肌之间存在，在其他内脏脂肪组织中未曾见到[4]。

心外膜脂肪组织的生理和病理

在正常生理情况下，EAT对心脏有保护作用。EAT能缓冲游离脂肪酸对邻近心肌的损害，保护心脏免受高浓度脂肪酸的伤害[10]。然而，与无代谢综合征的人相比，代谢综合征患者的EAT的脂肪酸结合蛋白-4分泌明显增加，使游离脂肪酸向心肌细胞内的转运增多[11]。EAT基因转录组中富含编码心脏保护性脂肪因子的基因，具有潜在的抗炎和抗动脉粥样硬化特性[12]。EAT可以释放多种炎症因子，并通过旁分泌的形式作用于心脏及冠状动脉[13]。EAT被认为在缺血或缺氧情况下为心肌提供直接热源，并保护心肌[14]。EAT中控制产热的过程相当复杂，目前其机制还未完全清晰。在新生儿中，EAT具有类似棕色脂肪的特性和功能[14]，随着年龄的增长，EAT的功能从产热转变为储能，并且棕色脂肪样的活动明显减少[14]，表明从棕色脂肪到米色脂肪的转

作者单位：上海市第十人民医院心内科 同济大学附属第十人民医院，上海 200072
通信作者：张毅，Email：yizshcn@gmail.com
基金项目：国家自然科学基金（82170388）
引用格式：赵松，张毅. 心外膜脂肪组织：从解剖生理、临床评估到心血管疾病的干预靶点[J/OL]. 中华心血管病杂志（网络版），2022，5：e1000111(2022-05-27). http://www.cvjc.org.cn/index.php/Column/columncon/article_id/289. DOI: 10.3760/cma.j.cn116031.2022.1000111.
本文编辑：史红
收稿日期：2022-04-05
录用日期：2022-05-12
DOI：10.3760/cma.j.cn116031.2022.1000111

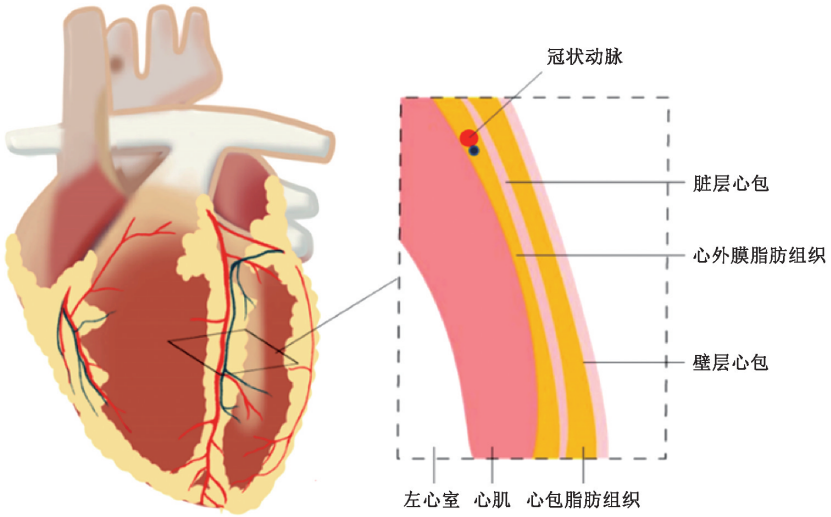

图1　心外膜脂肪组织的解剖位置

变是成人EAT的特点[14]。在高血压、肥胖、代谢综合征和糖尿病等炎症参与的代谢性疾病中，EAT成为脂肪发生紊乱的场所之一，此时EAT的棕色脂肪样的活动减少，影像学上表现为EAT的体积增加和(或)密度的改变，并分泌促炎因子对心脏产生不利影响[15]。另一方面，在慢性和长期的缺血状态下，与脂肪细胞褐变和产热激活相关的蛋白质的基因表达在EAT中下调，促炎细胞因子的基因表达增加[14]。值得关注的是，EAT可以被诱导恢复其棕色脂肪样功能，并对长期缺血患者的心脏产生有益影响[16]。

● 心外膜脂肪组织的影像学评估

EAT可以用多种影像学技术进行评估，我们将临床上常用的评估EAT的技术进行了优缺点总结(表1)。心脏超声是比较早期用于评估EAT的检查。EAT的厚度可以通过标准二维超声心动图进行测量。在心脏超声上，EAT指心肌外壁和心包内脏层之间的无回声空间，但当出现炎症或大量EAT时，EAT也可能出现回声密集的空间[17]。使用心脏超声测量EAT的优势主要体现在成本低、易获取和多次重复测量。但心脏超声是一项十分依赖于操作者熟练度的检测手段，对操作者有较高要求，且无法对局部的EAT和EAT的体积进行评估。心脏CT和MRI可以检测心脏超声无法检测到的深部区域的EAT，从而计算EAT的体积和评估EAT密度[18-19]。由于CT的高分辨率、测量可完全覆盖心脏以及可同时评估冠状动脉，所以CT测量EAT成为当下研究使用最多的方法[20]。CT主要的缺点是不易获取，费用较心脏超声高，且有电离辐射。MRI虽然被认为是脂肪组织成像的“金标准”，但部分图像上EAT与心包脂肪组织分界欠清，相对CT来说检查时间更长、更昂贵、更不易获得且不适用于有金属植入的患者。尽管正电子发射计算机体

表1　心外膜脂肪组织测量的成像技术

成像方式	优点	缺点
心脏超声	成本低，易获取，可多次重复测量	依赖操作者水平，无法测量局部的EAT和EAT的体积
CT	分辨率高，可以测量EAT的体积和密度，可以测量局部的EAT，可同时评估冠状动脉	不易获取，成本高，暴露于电离辐射
MRI	脂肪测量“金标准”，可以测量EAT的体积和密度，可以测量局部的EAT	不易获取，成本更高，测量时间长，部分图像上EAT与心包脂肪组织分界欠清，不适用于有金属植入的患者
PET/CT	可以评估EAT的炎症活动	不易获取，成本非常高
FAI	可以测量血管周围的脂肪炎症	不易获取，成本高，对局部EAT的测量有待进一步的研究
影像组学	人工智能处理，可详细说明图像	不易获取，成本高，有待进一步研究

注：EAT，心外膜脂肪组织；PET/CT，正电子发射计算机体层显像；FAI，脂肪衰减指数

层显像(positron emission tomography and computed tomography,PET/CT)可以检测EAT炎症活动,但囿于其费用高昂,难以广泛运用[21]。CT脂肪衰减指数(fat attenuation index,FAI)已被提出作为血管周围脂肪炎症的标志物[21],但FAI同样具有CT测量的缺点,且FAI对局部EAT的测量有待进一步的研究。人工智能结合影像组学也是未来评估EAT发展的方向[22-23]。

心外膜脂肪组织和冠状动脉疾病的关系

CAD的发病受多种因素的影响,其中炎症已被明确在动脉粥样硬化过程中扮演着关键的角色[24]。尽管EAT参与冠状动脉粥样硬化形成的机制很复杂,但炎症是CAD患者EAT的主要特征[25]。在CAD患者中,EAT分泌的脂联素减少,而瘦素水平升高[26-27],从而增加炎症和氧化应激,进一步加速动脉粥样硬化[28]。研究表明,无论血浆炎症生物标志物的水平如何,EAT促进炎症的特征均可在CAD患者中观察到[29]。

一、心外膜脂肪组织与冠状动脉钙化

与非糖尿病人群相比,糖尿病患者CT评估的EAT体积较高,并且与冠状动脉钙化评分成正相关[30]。Framingham心脏研究队列中,调整传统的心血管危险因素后,EAT和冠状动脉钙化之间仍有显著的相关性[31]。随后的队列研究再次证实了EAT与冠状动脉钙化的关联[32]。该研究纳入了3 367例(平均年龄53岁,53%为女性)无CAD的人群并随访5年,结果显示EAT与冠状动脉钙化的进展相关,特别是在年龄小于55岁、冠状动脉钙化评分为0~100分和体重指数小于25 kg/m^{2}的人群中[32]。同样,在一项针对可疑CAD患者的研究中发现,EAT与体重指数较低(小于27 kg/m^2)的患者的冠状动脉钙化严重程度成正相关,在体重指数较高的患者中无相关性[33]。另一项重度主动脉瓣狭窄患者的研究则显示EAT与冠状动脉钙化的性别差异[34],该研究发现男性中EAT与高冠状动脉钙化评分独立相关,而在女性中未发现这种相关性[34]。与该研究相反,在573名健康绝经后女性的研究中则发现,女性冠状动脉周围EAT越厚,冠状动脉钙化评分越高[35]。以上研究提示,EAT与冠状动脉钙化之间存在关联,但这种关联可能受到肥胖和性别等因素的影响。

二、心外膜脂肪组织与冠状动脉疾病严重程度

除了冠状动脉钙化,EAT也与冠状动脉狭窄的严重程度独立关联。研究显示,冠状动脉周围EAT的密度随着CT评估的冠状动脉管腔内狭窄严重程度的增加而增加[36]。通过血管内超声成像进一步对冠状动脉内斑块进行评估的研究显示,在CAD患者中,EAT体积越大,斑块的负荷越重[37]。随后,有研究在6~24个月内对EAT通过CT进行两次评估,将517例非肥胖的CAD患者分为EAT增加组、EAT减少组及EAT保持组,中位随访时间4.4年,结果发现EAT增加组具有高风险特征斑块的发生率显著高于EAT减少组和EAT保持组[38]。除了常用于评估的CT之外,另一项纳入32例男性稳定型心绞痛患者的研究则证实了MRI评估EAT也有助于早期非钙化不稳定斑块的识别[39]。另一方面,除了与高危斑块关联,EAT也与CAD病变血管数目及更为严重的CAD相关[40-41]。

三、心外膜脂肪组织与冠状动脉疾病事件

EAT不仅与冠状动脉钙化及CAD严重程度相关,队列研究中发现评估EAT可独立预测CAD事件的发生。病例对照研究中发现,EAT体积与主要心血管不良事件发生率之间独立相关[42]。一项纳入了4 093名无CVD的参与者(平均年龄59.4岁,53%为女性)平均随访8年的前瞻性队列研究发现,EAT体积每增加2倍,致命或非致命性冠状动脉事件的发生率增加1.5倍[43]。除了EAT的体积改变,FAI评估的EAT的炎症水平也可独立预测不良事件[44]。一项研究纳入了1 872例无先天性心脏病的患者(中位年龄62岁,37%为女性),中位随访72个月,结果发现右冠状动脉近端和左前降支动脉周围FAI都可以独立预测全因死亡和心血管死亡,并在验证队列中得到了一致的结果[44]。

因此,EAT评估有助于评判断脉粥样硬化斑块风险,以及预测主要冠状动脉事件的风险。除此之外,在无明显冠状动脉狭窄的CAD患者中,也有报道EAT与冠状动脉血流储备减少[45]、冠状动脉痉挛[46]和冠状动脉微循环障碍有关[47]。

心外膜脂肪组织和心房颤动的关系

心房颤动会增加心力衰竭、卒中和死亡的风险[48]。肥胖是心房颤动明确的危险因素,减肥和改变生活方式可以降低心房颤动发病的风险[48]。

EAT的厚度与体积均与肥胖严重程度相关[49]。在肥胖症患者中，EAT失去其对心脏的保护特性，成为具有促炎特性的组织[15]。但无论体重指数如何，都可观察到EAT炎症水平在心房颤动的患者中升高[50]。推测EAT可以通过释放细胞因子、脂肪因子和改变脂肪细胞的渗透性影响心脏电生理特征和离子电流，从而导致心脏的异常电活动[51]。EAT与心房颤动的发生率、持续性和心房颤动导管消融术后的复发有关联。在Framingham心脏研究队列中，在调整了其他风险因素后，EAT体积每增加一个标准差，心房颤动的发生率增加近40%[52]。慢性和持续性心房颤动患者的EAT厚度和体积比阵发性心房颤动或窦性心律患者大，并且与肥胖、年龄、性别、CAD、糖尿病、血脂异常或高血压无关[53]。有研究使用EAT测量来预测阵发性或持续性心房颤动导管消融后的心房颤动复发，EAT体积较大的患者消融后预后较差，心房颤动复发早[54]。在纳入102例首次进行心房颤动消融术患者的研究中，通过MRI测量的EAT体积独立于体重指数，与心房颤动消融术后的复发有关[55]。结合影像组学的左心房周围EAT体积和影像特征也对预测心房颤动消融术后复发有指导价值[56]。然而，一项采取倾向性评分控制混杂因素的回顾性研究发现，心房颤动消融术后复发的独立预测因子是EAT的密度，而不是EAT的体积[57]。这可能预示着EAT的功能改变与心房颤动的关系更密切。以上研究说明，EAT与心房颤动关系密切，为心房颤动的干预和预防消融术后心房颤动的复发提供了新思路。

● 心外膜脂肪组织和心力衰竭的关系

心力衰竭是一种复杂的临床常见疾病，主要表现为心脏收缩或舒张功能障碍。心力衰竭患者生活质量较差，死亡风险显著增加[58]。EAT被认为在心力衰竭中有一定作用，特别是在射血分数保留的心力衰竭（heart failure with preserved ejection fraction，HFpEF）中。HFpEF肥胖患者EAT厚度比HFpEF非肥胖患者高出20%，比无心力衰竭的非肥胖人群高50%[59]。EAT厚度的增加可能导致氧消耗增加、氧利用受损以及对脂肪酸氧化的依赖性增加，导致HFpEF患者的心脏供氧能力减弱[59]。但上述研究没有考虑肥胖等混杂因素。进一步的研究显示，尽管体重指数相似，HFpEF和射血分数中间值的心力衰竭（heart failure with mid-range ejection fraction，HFmrEF）患者（射血分数>40%）的总EAT体积和心室EAT体积均显著高于无心力衰竭的患者[60]，该研究说明了EAT独立于体重指数，与HFpEF和HFmrEF相关。然而，EAT可能在射血分数降低的心力衰竭（heart failure with reduced ejection fraction，HFrEF）患者中表现为增加、不变或者减少[61-62]。最近的一项荟萃分析则发现，EAT与无心力衰竭的患者相比，HFrEF患者的EAT较少，而HFpEF及HFmrEF患者的EAT较多[63]。更重要的是，EAT对HFpEF、HFrEF及HFmrEF患者发生不良事件的影响仍然存在差别。一项纳入了188例HFpEF患者（中位年龄73岁，52%为女性）及205例HFrEF患者（中位年龄55岁，35%为女性）中位随访21个月的研究发现，HFpEF患者EAT的厚度增加（>5 mm）与心力衰竭住院和心血管死亡的复合事件发生率增加显著相关，在HFrEF患者中EAT增加却是保护因素[64]。另一项纳入155例HFmrEF患者（平均年龄72岁，50%为女性），中位随访24个月的研究显示，EAT体积增大预示着预后不良[65]。尽管EAT与不同类型心力衰竭之间的关联存在差异，但最近一项纳入12个研究、1 983例心力衰竭患者的荟萃分析显示，EAT厚度的增加与脑利钠肽和脑利钠肽前体升高有明显关联，测量EAT厚度有可能作为诊断心力衰竭和对心力衰竭进行分层的补充指标[66]。综上所述，EAT可能与HFpEF及HFmrEF的关系更加密切，与HFrEF的关联还存在争议，加之EAT的评估不如脑利钠肽等方便，因此心力衰竭患者EAT评估的临床运用还需要更多研究支持。

● 心外膜脂肪组织与心血管疾病的治疗

由于EAT与CVD的密切关系，EAT有望成为CVD治疗的靶点之一。目前的治疗手段都不是专门为EAT开发的，但部分药物对EAT有间接的影响，如钠-葡萄糖协同转运蛋白-2（sodium-dependent glucose transporters-2，SGLT-2）抑制剂、胰高血糖素样肽-1受体（glucagon-like peptide-1 receptor，GLP-1R）激动剂和二肽基肽酶-4（dipeptidyl peptidase-4，DPP-4）抑制剂等药物。荟萃分析证实了SGLT-2抑制剂可减少EAT厚度或体积[67]。GLP-1R激动剂和DPP-4抑制剂也可以减少EAT的

厚度和体积[68-69]。此外，二甲双胍也可以降低EAT的体积[70]。他汀类药物已被证实可以用于治疗CVD，并能减少EAT的体积，但他汀类药物对EAT的影响弱于SGLT-2抑制剂和GLP-1R激动剂[71]。由于EAT在CVD中主要表现为炎症特性，上述药物对EAT的影响可能与这些药物有部分抗炎作用有关。因此，抗炎药物如卡纳基努单抗[72]、甲氨蝶呤[73]和秋水仙碱[74]也可能对EAT有间接影响，但还未见到相关的报道。总的来说，这些药物对EAT的间接影响可能是这些药物使CVD获益的潜在因素，但目前尚未有研究报道减少EAT与CVD结局之间的关系。

小结

EAT与心肌的无障碍接触决定了EAT在CVD中扮演着重要的角色。EAT的生理作用和病理生理改变与CVD的关系是一个重要研究领域。EAT评估结果可以通过心脏超声、CT和MRI等获得，这使得EAT评估具备辅助临床诊疗策略的巨大潜能。随着SGLT-2抑制剂等药物对EAT影响得到证实，EAT可能是解释这些药物治疗CVD获益的一个潜在因素。但我们也应该注意到，EAT的减少是否可以为CVD带来获益还需要进一步的研究。另外，促使EAT恢复对心脏的生理保护特性也是一个值得研究的方向。

参 考 文 献

[1] Roth GA, Mensah GA, Johnson CO, et al. Global burden of cardiovascular diseases and risk factors, 1990-2019: update from the GBD 2019 study[J]. J Am Coll Cardiol, 2020,76(25): 2982-3021. DOI: 10.1016/j.jacc.2020.11.010.

[2] 中国心血管健康与疾病报告编写组. 中国心血管健康与疾病报告2020概要[J]. 中国循环杂志，2021，36(6)：521-545. DOI: 10.3969/j.issn.1000-3614.2021.06.001.

[3] Iacobellis G, Ribaudo MC, Assael F, et al. Echocardiographic epicardial adipose tissue is related to anthropometric and clinical parameters of metabolic syndrome: a new indicator of cardiovascular risk[J]. J Clin Endocrinol Metab, 2003, 88 (11):5163-5168. DOI: 10.1210/jc.2003-030698.

[4] Iacobellis G, Corradi D, Sharma AM. Epicardial adipose tissue: anatomic, biomolecular and clinical relationships with the heart[J]. Nat Clin Pract Cardiovasc Med, 2005, 2(10): 536-543. DOI: 10.1038/ncpcardio0319.

[5] McAninch EA, Fonseca TL, Poggioli R, et al. Epicardial adipose tissue has a unique transcriptome modified in severe coronary artery disease[J]. Obesity (Silver Spring), 2015, 23 (6):1267-1278. DOI: 10.1002/oby.21059.

[6] Iacobellis G. Epicardial fat: a new cardiovascular therapeutic target[J]. Curr Opin Pharmacol, 2016, 27: 13-18. DOI: 10.1016/j.coph.2016.01.004.

[7] Monti CB, Codari M, De Cecco CN, et al. Novel imaging biomarkers: epicardial adipose tissue evaluation[J]. Br J Radiol, 2020, 93(1113): 20190770. DOI: 10.1259 / bjr.20190770.

[8] Corradi D, Maestri R, Callegari S, et al. The ventricular epicardial fat is related to the myocardial mass in normal, ischemic and hypertrophic hearts[J]. Cardiovasc Pathol, 2004, 13(6):313-316. DOI: 10.1016/j.carpath.2004.08.005.

[9] Sacks HS, Fain JN, Bahouth SW, et al. Adult epicardial fat exhibits beige features[J]. J Clin Endocrinol Metab, 2013,98 (9):E1448-E1455. DOI: 10.1210/jc.2013-1265.

[10] 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[J]. Int J Obes, 1990,14(12):1013-1022.

[11] Vural B, Atalar F, Ciftci C, et al. Presence of fatty-acid-binding protein 4 expression in human epicardial adipose tissue in metabolic syndrome[J]. Cardiovasc Pathol, 2008,17(6):392-398. DOI: 10.1016/j.carpath.2008.02.006.

[12] Iacobellis G, di Gioia CR, Cotesta D, et al. Epicardial adipose tissue adiponectin expression is related to intracoronary adiponectin levels[J]. Horm Metab Res, 2009,41(3):227-231. DOI: 10.1055/s-0028-1100412.

[13] Iacobellis G, Barbaro G. The double role of epicardial adipose tissue as pro-and anti-inflammatory organ[J]. Horm Metab Res, 2008, 40(7): 442-445. DOI: 10.1055 / s-2008-1062724.

[14] Fainberg HP, Birtwistle M, Alagal R, et al. Transcriptional analysis of adipose tissue during development reveals depot-specific responsiveness to maternal dietary supplementation[J]. Sci Rep, 2018,8(1):9628. DOI: 10.1038/ s41598-018-27376-3.

[15] Villasante Fricke AC, Iacobellis G. Epicardial adipose tissue: clinical biomarker of cardio-metabolic risk[J]. Int J Mol Sci, 2019,20(23): 5989. DOI: 10.3390/ijms20235989.

[16] Singh SP, McClung JA, Thompson E, et al. Cardioprotective heme oxygenase-1-PGC1α signaling in epicardial fat attenuates cardiovascular risk in humans as in obese mice[J]. Obesity (Silver Spring), 2019, 27(10): 1634-1643. DOI: 10.1002/oby.22608.

[17] Iacobellis G, Willens HJ. Echocardiographic epicardial fat: a review of research and clinical applications[J]. J Am Soc Echocardiogr, 2009, 22(12): 1311-1319, 1417-1418. DOI: 10.1016/j.echo.2009.10.013.

[18] Spearman JV, Renker M, Schoepf UJ, et al. Prognostic value of epicardial fat volume measurements by computed tomography: a systematic review of the literature[J]. Eur Radiol, 2015, 25(11): 3372-3381. DOI: 10.1007 / s00330-015-3765-5.

[19] Nelson AJ, Worthley MI, Psaltis PJ, et al. Validation of cardiovascular magnetic resonance assessment of pericardial adipose tissue volume[J]. J Cardiovasc Magn Reson, 2009,11: 15. DOI: 10.1186/1532-429X-11-15.

[20] Wong CX, Ganesan AN, Selvanayagam JB. Epicardial fat and atrial fibrillation: current evidence, potential mechanisms, clinical implications, and future directions[J]. Eur Heart J, 2017,38(17):1294-1302. DOI: 10.1093/eurheartj/

ehw045.

[21] Antonopoulos AS, Sanna F, Sabharwal N, et al. Detecting human coronary inflammation by imaging perivascular fat[J]. Sci Transl Med, 2017, 9(398): eaal2658. DOI: 10.1126 / scitranslmed.aal2658.

[22] Wen D, An R, Lin S, et al. Influence of different segmentations on the diagnostic performance of pericoronary adipose tissue[J]. Front Cardiovasc Med, 2022, 9: 773524. DOI: 10.3389/fcvm.2022.773524.

[23] Greco F, Salgado R, Van Hecke W, et al. Epicardial and pericardial fat analysis on CT images and artificial intelligence: a literature review[J]. Quant Imaging Med Surg, 2022,12(3):2075-2089. DOI: 10.21037/qims-21-945.

[24] Libby P. Inflammation in atherosclerosis-no longer a theory [J]. Clin Chem, 2021,67(1):131-142. DOI: 10.1093/clinchem/hvaa275.

[25] Hirata Y, Tabata M, Kurobe H, et al. Coronary atherosclerosis is associated with macrophage polarization in epicardial adipose tissue[J]. J Am Coll Cardiol, 2011, 58(3): 248-255. DOI: 10.1016/j.jacc.2011.01.048.

[26] Eiras S, Teijeira-Fernández E, Shamagian LG, et al. Extension of coronary artery disease is associated with increased IL-6 and decreased adiponectin gene expression in epicardial adipose tissue[J]. Cytokine, 2008, 43(2): 174-180. DOI: 10.1016/j.cyto.2008.05.006.

[27] Iacobellis G, Pistilli D, Gucciardo M, et al. Adiponectin expression in human epicardial adipose tissue in vivo is lower in patients with coronary artery disease[J]. Cytokine, 2005,29 (6):251-255. DOI: 10.1016/j.cyto.2004.11.002.

[28] Iacobellis G, Malavazos AE, Corsi MM. Epicardial fat: from the biomolecular aspects to the clinical practice[J]. Int J Biochem Cell Biol, 2011,43(12):1651-1654. DOI: 10.1016/j.biocel.2011.09.006.

[29] Mazurek T, Zhang L, Zalewski A, et al. Human epicardial adipose tissue is a source of inflammatory mediators[J]. Circulation, 2003, 108(20): 2460-2466. DOI: 10.1161 / 01.CIR.0000099542.57313.C5.

[30] Wang CP, Hsu HL, Hung WC, et al. Increased epicardial adipose tissue (EAT) volume in type 2 diabetes mellitus and association with metabolic syndrome and severity of coronary atherosclerosis[J]. Clin Endocrinol (Oxf), 2009, 70 (6):876-882. DOI: 10.1111/j.1365-2265.2008.03411.x.

[31] Rosito GA, Massaro JM, Hoffmann U, et al. Pericardial fat, visceral abdominal fat, cardiovascular disease risk factors, and vascular calcification in a community-based sample: the Framingham Heart Study[J]. Circulation, 2008, 117(5): 605-613. DOI: 10.1161/CIRCULATIONAHA.107.743062.

[32] Mahabadi AA, Lehmann N, Kälsch H, et al. 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 [J]. JACC Cardiovasc Imaging, 2014, 7(9): 909-916. DOI: 10.1016/j.jcmg.2014.07.002.

[33] Gorter PM, de Vos AM, van der Graaf Y, et al. Relation of epicardial and pericoronary fat to coronary atherosclerosis and coronary artery calcium in patients undergoing coronary angiography[J]. Am J Cardiol, 2008, 102(4): 380-385. DOI: 10.1016/j.amjcard.2008.04.002.

[34] Mancio J, Pinheiro M, Ferreira W, et al. Gender differences in the association of epicardial adipose tissue and coronary artery calcification: EPICHEART study: EAT and coronary calcification by gender[J]. Int J Cardiol, 2017, 249: 419-425. DOI: 10.1016/j.ijcard.2017.09.178.

[35] de Vos AM, Prokop M, Roos CJ, et al. Peri-coronary epicardial adipose tissue is related to cardiovascular risk factors and coronary artery calcification in post-menopausal women[J]. Eur Heart J, 2008, 29(6): 777-783. DOI: 10.1093 / eurheartj/ehm564.

[36] Ma R, van Assen M, Ties D, et al. Focal pericoronary adipose tissue attenuation is related to plaque presence, plaque type, and stenosis severity in coronary CTA[J]. Eur Radiol, 2021,31 (10):7251-7261. DOI: 10.1007/s00330-021-07882-1.

[37] Yamashita K, Yamamoto MH, Igawa W, et al. Association of epicardial adipose tissue volume and total coronary plaque burden in patients with coronary artery disease[J]. Int Heart J, 2018,59(6):1219-1226. DOI: 10.1536/ihj.17-709.

[38] Nakanishi K, Fukuda S, Tanaka A, et al. Persistent epicardial adipose tissue accumulation is associated with coronary plaque vulnerability and future acute coronary syndrome in non-obese subjects with coronary artery disease[J]. Atherosclerosis, 2014, 237(1): 353-360. DOI: 10.1016 / j.atherosclerosis.2014.09.015.

[39] Hassan M, Said K, Rizk H, et al. Segmental peri-coronary epicardial adipose tissue volume and coronary plaque characteristics[J]. Eur Heart J Cardiovasc Imaging, 2016, 17 (10):1169-1177. DOI: 10.1093/ehjci/jev298.

[40] Sun Y, Li XG, Xu K, et al. Relationship between epicardial fat volume on cardiac CT and atherosclerosis severity in three-vessel coronary artery disease: a single-center cross-sectional study[J]. BMC Cardiovasc Disord, 2022, 22 (1):76. DOI: 10.1186/s12872-022-02527-7.

[41] Mahabadi AA, Balcer B, Dykun I, et al. Cardiac computed tomography-derived epicardial fat volume and attenuation independently distinguish patients with and without myocardial infarction[J]. PLoS One, 2017, 12(8): e0183514. DOI: 10.1371/journal.pone.0183514.

[42] Ding J, Hsu FC, Harris TB, et al. The association of pericardial fat with incident coronary heart disease: the Multi-Ethnic Study of Atherosclerosis (MESA)[J]. Am J Clin Nutr, 2009,90(3):499-504. DOI: 10.3945/ajcn.2008.27358.

[43] Mahabadi AA, Berg MH, Lehmann N, et al. Association of epicardial fat with cardiovascular risk factors and incident myocardial infarction in the general population: the Heinz Nixdorf Recall Study[J]. J Am Coll Cardiol, 2013, 61(13): 1388-1395. DOI: 10.1016/j.jacc.2012.11.062.

[44] Oikonomou EK, Marwan M, Desai MY, et al. Non-invasive detection of coronary inflammation using computed tomography and prediction of residual cardiovascular risk (the CRISP CT study): a post-hoc analysis of prospective outcome data[J]. Lancet, 2018, 392(10151): 929-939. DOI: 10.1016/S0140-6736(18)31114-0.

[45] Pasqualetto MC, Tuttolomondo D, Cutruzzolà A, et al. Human coronary inflammation by computed tomography: Relationship with coronary microvascular dysfunction[J]. Int J Cardiol, 2021,336:8-13. DOI: 10.1016/j.ijcard.2021.05.040.

[46] Kataoka T, Harada K, Tanaka A, et al. Relationship between epicardial adipose tissue volume and coronary artery spasm [J]. Int J Cardiol, 2021, 324: 8-12. DOI: 10.1016 / j.

ijcard.2020.09.074.
[47] Huang S, Li Y, Jiang L, et al. Impact of type 2 diabetes mellitus on epicardial adipose tissue and myocardial microcirculation by MRI in postmenopausal women[J]. J Magn Reson Imaging, 2022,DOI: 10.1002/jmri.28121.
[48] Magnani JW, Rienstra M, Lin H, et al. Atrial fibrillation: current knowledge and future directions in epidemiology and genomics[J]. Circulation, 2011, 124(18): 1982-1993. DOI: 10.1161/CIRCULATIONAHA.111.039677.
[49] Iacobellis G, Willens HJ, Barbaro G, et al. Threshold values of high-risk echocardiographic epicardial fat thickness[J]. Obesity (Silver Spring), 2008,16(4):887-892. DOI: 10.1038/oby.2008.6.
[50] Mazurek T, Kiliszek M, Kobylecka M, et al. Relation of proinflammatory activity of epicardial adipose tissue to the occurrence of atrial fibrillation[J]. Am J Cardiol, 2014,113(9): 1505-1508. DOI: 10.1016/j.amjcard.2014.02.005.
[51] Zhou M, Wang H, Chen J, et al. Epicardial adipose tissue and atrial fibrillation: Possible mechanisms, potential therapies, and future directions[J]. Pacing Clin Electrophysiol, 2020,43(1):133-145. DOI: 10.1111/pace.13825.
[52] Thanassoulis G, Massaro JM, O′Donnell CJ, et al. Pericardial fat is associated with prevalent atrial fibrillation: the Framingham Heart Study[J]. Circ Arrhythm Electrophysiol, 2010,3(4):345-350. DOI: 10.1161/CIRCEP.109.912055.
[53] Jhuo SJ, Hsieh TJ, Tang WH, et al. The association of the amounts of epicardial fat, P wave duration, and PR interval in electrocardiogram[J]. J Electrocardiol, 2018, 51(4): 645-651. DOI: 10.1016/j.jelectrocard.2018.04.009.
[54] Masuda M, Mizuno H, Enchi Y, et al. Abundant epicardial adipose tissue surrounding the left atrium predicts early rather than late recurrence of atrial fibrillation after catheter ablation[J]. J Interv Card Electrophysiol, 2015, 44(1): 31-37. DOI: 10.1007/s10840-015-0031-3.
[55] Wong CX, Abed HS, Molaee P, et al. Pericardial fat is associated with atrial fibrillation severity and ablation outcome[J]. J Am Coll Cardiol, 2011, 57(17): 1745-1751. DOI: 10.1016/j.jacc.2010.11.045.
[56] Yang M, Cao Q, Xu Z, et al. Development and validation of a machine learning-based radiomics model on cardiac computed tomography of epicardial adipose tissue in predicting characteristics and recurrence of atrial fibrillation [J]. Front Cardiovasc Med, 2022, 9: 813085. DOI: 10.3389/fcvm.2022.813085.
[57] Yang M, Bao W, Xu Z, et al. Association between epicardial adipose tissue and recurrence of atrial fibrillation after ablation: a propensity score-matched analysis[J]. Int J Cardiovasc Imaging, 2022[Online ahead of print]. DOI: 10.1007/s10554-022-02557-4.
[58] Yancy CW, Jessup M, Bozkurt B, et al. 2017 ACC/AHA/HFSA focused update of the 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Failure Society of America[J]. J Am Coll Cardiol, 2017, 70(6): 776-803. DOI: 10.1016/j.jacc.2017.04.025.
[59] Obokata M, Reddy Y, Pislaru SV, et al. Evidence Supporting the existence of a distinct obese phenotype of heart failure with preserved ejection fraction[J]. Circulation, 2017,136(1): 6-19. DOI: 10.1161/CIRCULATIONAHA.116.026807.
[60] van Woerden G, Gorter TM, Westenbrink BD, et al. Epicardial fat in heart failure patients with mid-range and preserved ejection fraction[J]. Eur J Heart Fail, 2018,20(11): 1559-1566. DOI: 10.1002/ejhf.1283.
[61] Doesch C, Streitner F, Bellm S, et al. Epicardial adipose tissue assessed by cardiac magnetic resonance imaging in patients with heart failure due to dilated cardiomyopathy[J]. Obesity (Silver Spring), 2013, 21(3): E253-E261. DOI: 10.1002/oby.20149.
[62] Wang X, Butcher SC, Kuneman JH, et al. The quantity of epicardial adipose tissue in patients having ablation for atrial fibrillation with and without heart failure[J]. Am J Cardiol, 2022, 118(3): 625-633. DOI: 10.1016/j.amjcard.2022.02.021.
[63] Correia E, Barbetta L, Costa O, et al. Epicardial adipose tissue in heart failure phenotypes -a meta-analysis[J]. Arq Bras Cardiol, 2022, 118(3): 625-633. DOI: 10.36660/abc.20200755.
[64] Pugliese NR, Paneni F, Mazzola M, et al. Impact of epicardial adipose tissue on cardiovascular haemodynamics, metabolic profile, and prognosis in heart failure[J]. Eur J Heart Fail, 2021,23(11):1858-1871. DOI: 10.1002/ejhf.2337.
[65] van Woerden G, van Veldhuisen DJ, Manintveld OC, et al. Epicardial adipose tissue and outcome in heart failure with mid-range and preserved ejection fraction[J]. Circ Heart Fail, 2022,15(3):e009238. DOI: 10.1161/CIRCHEARTFAILURE.121.009238.
[66] Nyawo TA, Dludla PV, Mazibuko-Mbeje SE, et al. A systematic review exploring the significance of measuring epicardial fat thickness in correlation to B-type natriuretic peptide levels as prognostic and diagnostic markers in patients with or at risk of heart failure[J]. Heart Fail Rev, 2022,27(2):665-675. DOI: 10.1007/s10741-021-10160-3.
[67] Masson W, Lavalle-Cobo A, Nogueira JP. Effect of SGLT2-inhibitors on epicardial adipose tissue: a meta-analysis[J]. Cells, 2021, 10(8): 2150. DOI: 10.3390/cells10082150.
[68] Iacobellis G, Mohseni M, Bianco SD, et al. Liraglutide causes large and rapid epicardial fat reduction[J]. Obesity (Silver Spring), 2017, 25(2): 311-316. DOI: 10.1002/oby.21718.
[69] Dutour A, Abdesselam I, Ancel P, et al. Exenatide decreases liver fat content and epicardial adipose tissue in patients with obesity and type 2 diabetes: a prospective randomized clinical trial using magnetic resonance imaging and spectroscopy[J]. Diabetes Obes Metab, 2016,18(9): 882-891. DOI: 10.1111/dom.12680.
[70] Ziyrek M, Kahraman S, Ozdemir E, et al. Metformin monotherapy significantly decreases epicardial adipose tissue thickness in newly diagnosed type 2 diabetes patients[J]. Rev Port Cardiol (Engl Ed), 2019,38(6):419-423. DOI: 10.1016/j.repc.2018.08.010.
[71] Raggi P, Gadiyaram V, Zhang C, et al. Statins reduce epicardial adipose tissue attenuation independent of lipid lowering: a potential pleiotropic effect[J]. J Am Heart Assoc, 2019,8(12):e013104. DOI: 10.1161/JAHA.119.013104.
[72] Ridker PM, MacFadyen JG, Everett BM, et al. Relationship of C-reactive protein reduction to cardiovascular event reduction following treatment with canakinumab: a

secondary analysis from the CANTOS randomised controlled trial[J]. Lancet, 2018, 391(10118): 319-328. DOI: 10.1016/S0140-6736(17)32814-3.

[73] Micha R, Imamura F, Wyler von Ballmoos M, et al. Systematic review and meta-analysis of methotrexate use and risk of cardiovascular disease[J]. Am J Cardiol, 2011, 108(9): 1362-1370. DOI: 10.1016/j.amjcard.2011.06.054.

[74] Nidorf SM, Fiolet A, Mosterd A, et al. Colchicine in patients with chronic coronary disease[J]. N Engl J Med, 2020, 383(19):1838-1847. DOI: 10.1056/NEJMoa2021372.