Advances in Clinical Medicine 临床医学进展, 2023, 13(7), 11410-11415
Published Online July 2023 in Hans. https://www.hanspub.org/journal/acm
https://doi.org/10.12677/acm.2023.1371595

Hans汉斯

心外膜脂肪组织及其与房颤关系的研究进展

杨雪松[1,2]，李　展[2]，张玉娇[2]，任满意[2]，侯应龙[1,2*]

[1]山东大学齐鲁医学院，山东　济南
[2]山东第一医科大学第一附属医院(山东省千佛山医院)心内科，山东　济南

收稿日期：2023年6月18日；录用日期：2023年7月13日；发布日期：2023年7月20日

摘　要

心外膜脂肪组织(EAT)是位于心肌与心包脏层之间的代谢活跃的脂肪库。相比于人体其他内脏脂肪库，EAT不仅具有产热、机械保护的共同特性，还兼有独特分泌功能。研究证实，EAT与房颤的发生及射频消融术后复发相关。EAT导致房颤的机制尚未完全阐明，可能的机制涉及心肌纤维化、脂肪细胞浸润、神经调节失衡等。近年来，EAT受到高度关注，或许会成为预测房颤发生及房颤射频术后复发的一项危险因素。

关键词

房颤，心外膜脂肪组织，射频消融

Research Progress on Epicardial Adipose Tissue and Its Relationship with Atrial Fibrillation

Xuesong Yang[1], Zhan Li[2], Yujiao Zhang[2], Manyi Ren[2], Yinglong Hou[1,2*]

[1]Cheeloo College of Medicine, Shandong University, Jinan Shandong
[2]Department of Cardiology, The First Affiliated Hospital of Shandong First Medical University (Shandong Provincial Qianfoshan Hospital), Jinan Shandong

Received: Jun. 18th, 2023; accepted: Jul. 13th, 2023; published: Jul. 20th, 2023

*通讯作者。

文章引用: 杨雪松, 李展, 张玉娇, 任满意, 侯应龙. 心外膜脂肪组织及其与房颤关系的研究进展[J]. 临床医学进展, 2023, 13(7): 11410-11415. DOI: 10.12677/acm.2023.1371595

Abstract

Epicardial adipose tissue (EAT) is an active metabolic fat reservoir located between the myocardium and the visceral layer of the pericardium. Compared to other visceral fat reservoirs in the human body, EAT not only has common characteristics of heat production and mechanical protection, but also has unique secretion functions. Research has confirmed that EAT is associated with the occurrence of atrial fibrillation and recurrence after radiofrequency ablation. The mechanism of EAT leading to atrial fibrillation has not been fully clarified, and the possible mechanism involves myocardial fibrosis, adipocyte infiltration, neuromodulation imbalance, etc. In recent years, EAT has received high attention and may become a risk factor for predicting the occurrence and recurrence of atrial fibrillation after radiofrequency surgery.

Keywords

Atrial Fibrillation, Epicardial Adipose Tissue, Radiofrequency Ablation

1. 引言

心房颤动是临床上最常见的快速性心律失常，具有较高的致死率与致残率[1]。近年来，人群中肥胖群体的比例越来越高，房颤的发病率也呈现上升趋势。研究表明，肥胖是仅次于高血压的第二大房颤的可归因风险[2]；而心外膜脂肪组织(Epicardial Adipose Tissue, EAT)与腹部或者全身其他脂肪组织相比，其与房颤之间则具有更强的相关性[3] [4] [5]。本文将从 EAT 的定义、解剖与生理学、EAT 与房颤关系研究进展等作一综述。

2. EAT 的解剖与生理作用

我们通常把心外膜脂肪组织(Epicardial Adipose Tissue, EAT)定义为心脏周围脂肪组织，是内脏脂肪的重要组成部分[6]。EAT 位于心肌和心包内脏层之间，主要位于房室沟和室间沟，沿冠状动脉主要分支分布。不同的文献对心脏周围脂肪组织的命名不尽相同。在心脏内，EAT 有时会根据不同的位置命名，如心房周围、心室周围和冠状动脉周围脂肪组织等[7]。从胚胎学层面来看，EAT 是从横隔迁移到心脏表面的一组间皮细胞，它与肠系膜脂肪及网膜脂肪起源相同，均起源于内脏胸膜中胚层。EAT 位于心肌和心包之间，环绕冠状动脉分布，与心肌细胞共享一套血液微循环。80%的心脏表面由 EAT 覆盖，EAT 约占心脏总重量的 20%左右，覆盖心脏周长的 56%~100% [8] [9]。心旁脂肪借助心包与心肌组织分离，而 EAT 和心肌组织之间没有筋膜分隔，这为生理条件下正常成人 EAT 滋养心脏提供了有力的客观条件。

EAT 与心肌之间的代谢是畅通的，EAT 是一个代谢活跃的脂肪库，也是真正意义上的内脏脂肪组织[6]。首先，EAT 具有机械保护作用，表现为在心肌收缩与心脏脉搏波传播期间，对 EAT 包裹的冠状动脉起到机械缓冲作用以防止动脉波的离散或扭转，也可以在受到意外冲击时减轻胸骨对心肌的机械损伤[10]。这种机械保护还可包含心外膜脂肪所包绕的神经丛等。其次，在机体代谢处于应激状态时，EAT 可充当局部的甘油三酯储存库，通过吸收心肌周围过多的脂肪酸来保护心脏免受高脂肪酸环境的影响

[11]。第三，健康人的 EAT 犹如一个分泌体，释放保护性抗炎、抗动脉粥样硬化的脂肪因子；EAT 分泌的脂联素、大网膜素等脂肪因子可以减少心肌的炎症和纤维化，分泌的瘦素对心肌起到保护作用；EAT 还可以分泌血管生成因子(血管紧张素、内皮抑素、血管内皮生长因子-1、血栓反应素-2、血管生成素)、生长和重塑因子等，对正常的心血管内环境平衡起到调节作用[12] [13]。此外，有文献报道健康人的心外膜脂肪组织中高表达线粒体解偶联蛋白-1 (UCP-1)，而 UCP-1 是被认为是棕色脂肪组织的标志物，所以健康人的 EAT 具有棕色脂肪的作用，表明心外膜脂肪组织可能以与棕色脂肪相同的方式发挥作用，帮助保护心肌和冠状动脉抵御低温[13] [14]。

3. EAT 导致房颤可能的病理机制

EAT 覆盖于心脏表面，心外膜的脂肪细胞、成纤维细胞、心肌细胞互相接触，三者在化学、电学以及代谢功能上具有十分密切的联系与交流。

3.1. 促炎反应介导心肌细胞纤维化

心房扩张并伴有心肌纤维化是房颤最重要的发生与维持机制。心房的正常运转依赖相邻心肌细胞彼此有序的电脉冲传导，而心肌细胞间成纤维细胞的浸润改变了心房组织的组成与功能，可使电信号传导中断[15]。机体处于肥胖或者血脂代谢异常时，EAT 易于合成促炎性脂肪因子，促进巨噬细胞浸润，破坏血管微循环，此时激活促纤维化途径，来自心外膜的间充质干细胞转换为成纤维细胞[12] [16]，一般情况下，心肌连续性的电传导是通过心肌细胞间特殊连接蛋白所形成的缝隙连接完成的，而在成纤维细胞和心肌细胞共同存在的系统中，二者能够形成低电阻的电连接，导致局部传导减慢，增加传导异质性[17] [18]。

另有研究显示，在病理条件下，成纤维细胞可从几个细胞系分化进而显著增加，包括单核细胞、内皮细胞、骨髓循环祖细胞和周细胞等[19]。在一项病例对照研究中，观察者发现相对于窦性心律者，有心脏基础疾病且易患房颤的患者，EAT 中促炎性和促纤维化的脂肪因子的表达增加，同时抗炎和抗纤维化的脂肪因子的表达下降[20]。这表明 EAT 在抗纤维化与促纤维化、抗炎与促炎的平衡中可能发挥了重要作用。YKL-40 是成纤维细胞增殖和基质形成的关键因子，它参与了心肌炎症、纤维化、组织重构以及心血管疾病的过程[21]。Wang 等研究冠状动脉搭桥术房颤患者($n = 28$)和窦性心律患者($n = 36$)的心房肌与 EAT 发现，房颤患者 EAT 中 YKL-40mRNA 及蛋白质水平显著高于窦律组($P < 0.001$)，而且 Masson 染色显示房颤患者心房纤维化水平明显高于窦律组($P < 0.001$)。基于上述研究结果 Wang 等人认为 YKL-40 可能通过促进心房纤维化诱发房颤发生，但 YKL-40 激活心房纤维化的具体机制有待进一步研究[22]。

3.2. 脂肪细胞浸润介导心肌重构

如前所述，心外膜脂肪组织、心肌内的肌细胞与成纤维细胞彼此连接，在化学、电学与代谢功能上具有高度的关联性与整合性。心外膜脂肪组织浸润心肌改变心肌结构，减缓或破坏心肌细胞动作电位的正常传导并产生电异质性，从而导致心律失常[23]。研究表明，脂肪浸润可通过旁分泌机制促进心房肌纤维化，后者则是房颤发生与维持的基质[24]。研究表明，血浆游离脂肪酸(FFAs)水平异常与多种心肌疾病风险增加有关。肥胖状态时脂肪细胞沉积增多，心外膜脂肪广泛浸润心肌和游离脂肪酸释放增加，后者通过旁分泌或血管分泌信号通路导致心脏电重构与结构重构[25]。一项关于在仓鼠的 EAT 研究中，EAT 表面或者脂肪浸润的相邻细胞间可以形成缝隙连接，进而破坏了心肌内正常动作电位的传导模式，这为房颤的发生提供了异质性电环境，而在人体中是否存在上述机制仍需要证实[26]。

3.3. 神经调节失衡激活炎症反应

心脏内自主神经系统在房颤的发生与维持过程中起着重要作用，这一点在实验室动物模型和房颤患

者中均已得到证实。心房表面的神经丛在心外膜脂肪的包裹之下，这些神经丛包含各类传入与传出神经元，其中既有胆碱能神经元，也有肾上腺素能神经元。这些神经元的激活可以分别引发副交感神经和交感神经兴奋性增高，后者分别导致心房肌动作电位时程缩短以及钙流升高[27]。进一步的研究表明，位于神经丛的胆碱能神经和肾上腺素能神经释放乙酰胆碱与儿茶酚胺失衡时，可能会促进脂肪生成与炎症反应；同时，心外膜脂肪分泌活性增强，也可能会增强心外膜脂肪组织中的有害作用，并对心肌细胞产生不良影响[28]。

4. EAT 对房颤射频消融预后的影响

目前，房颤的治疗原则主要是控制心室率、抗凝、转复并维持窦性心律。研究证实，导管消融在维持窦性心律、改善患者的心功能、减少心血管事件与提高生活质量方面优于传统抗心律失常药物。然而，射频消融术后房颤高复发率是影响房颤消融患者远期预后的主要因素[29]。

如何预测房颤患者射频消融术后复发，对于房颤患者术后管理显然具有重要的意义。根据目前研究，心外膜脂肪组织体积(EATV)是导管消融后房颤复发的独立预测因子，较高的 EATV 值可能有助于预测导管消融后的房颤复发。研究表明，无心衰的阵发性房颤患者导管消融后的晚期复发与左心房内径和总 EAT 体积之比独立相关[11] [12] [30]。Kim 等人研究发现，EAT 对不同类型房颤消融术后复发的预测价值存在差异，他们的研究表明 EAT 在持续性房颤亚组中对房颤预后具有良好的预测价值，而在阵发性房颤亚组中则不具备预测价值。Nefissa 等人的研究结果也得出了与上述相同的结论，表明不同的房颤亚型，EAT 在房颤发生与导管消融术后复发中的贡献比可能存在某种差异[31] [32]。尽管之前的研究一致认为 EATV 在评估房颤消融后复发方面要比一般性肥胖指标优越，但 EATV 预测消融术后房颤复发的价值仍需进一步挖掘与细化。

综上所述，局部区域脂肪分布在病理性代谢与心血管疾病风险中占据重要地位，心外膜脂肪组织作为一个代谢活跃的特殊分泌体，不但起着保护心脏的功能，在病理条件下则可成为心血管疾病的风险因素[33]。EAT 是近年研究的热点，其在房颤的发生与发展中扮演重要角色，阐明其中的确切机制或许是未来研究中一个有意义的方向，并可望为揭示房颤防治的新靶点提供线索与启示。

参考文献

[1] Chugh, S.S., Havmoeller, R., Narayanan, K., *et al*. (2014) Worldwide Epidemiology of Atrial Fibrillation: A Global Burden of Disease 2010 Study. *Circulation*, **129**, 837-847. https://doi.org/10.1161/CIRCULATIONAHA.113.005119

[2] Middeldorp, M.E., Kamsani, S.H. and Sanders, P. (2023) Obesity and Atrial Fibrillation: Prevalence, Pathogenesis, and Prognosis. *Progress in Cardiovascular Diseases*, **78**, 34-42. https://doi.org/10.1016/j.pcad.2023.04.010

[3] Kondo, H., Abe, I., Gotoh, K., *et al*. (2018) Interleukin 10 Treatment Ameliorates High-Fat Diet-Induced Inflammatory Atrial Remodeling and Fibrillation. *Circulation*: *Arrhythmia and Electrophysiology*, **11**, e006040. https://doi.org/10.1161/CIRCEP.117.006040

[4] Dybkova, N., Ahmad, S., Pabel, S., *et al*. (2018) Differential Regulation of Sodium Channels as a Novel Proarrhythmic Mechanism in the Human Failing Heart. *Cardiovascular Research*, **114**, 1728-1737. https://doi.org/10.1093/cvr/cvy152

[5] Packer, M. (2018) Epicardial Adipose Tissue May Mediate Deleterious Effects of Obesity and Inflammation on the Myocardium. *Journal of the American College of Cardiology*, **71**, 2360-2372. https://doi.org/10.1016/j.jacc.2018.03.509

[6] Iacobellis, G. (2022) Epicardial Adipose Tissue in Contemporary Cardiology. *Nature Reviews Cardiology*, **19**, 593-606. https://doi.org/10.1038/s41569-022-00679-9

[7] Sacks, H.S., Fain, J.N., Holman, B., *et al*. (2009) Uncoupling Protein-1 and Related Messenger Ribonucleic Acids in Human Epicardial and Other Adipose Tissues: Epicardial Fat Functioning as Brown Fat. *The Journal of Clinical Endocrinology & Metabolism*, **94**, 3611-3615. https://doi.org/10.1210/jc.2009-0571

[8] Nagy, E., Jermendy, A.L., Merkely, B. and Maurovich-Horvat, P. (2017) Clinical Importance of Epicardial Adipose

Tissue. *Archives of Medical Science*, **13**, 864-874. https://doi.org/10.5114/aoms.2016.63259

[9] Aldiss, P., Davies, G., Woods, R., *et al*. (2017) 'Browning' the Cardiac and Peri-Vascular Adipose Tissues to Modulate Cardiovascular Risk. *International Journal of Cardiology*, **228**, 265-274. https://doi.org/10.1016/j.ijcard.2016.11.074

[10] Aeddula, N.R., Cheungpasitporn, W., Thongprayoon, C. and Pathireddy, S. (2019) Epicardial Adipose Tissue and Renal Disease. *Journal of Clinical Medicine*, **8**, Article No. 299. https://doi.org/10.3390/jcm8030299

[11] Wong, C.X., Stiles, M.K., John, B., *et al*. (2010) Direction-Dependent Conduction in Lone Atrial Fibrillation. *Heart Rhythm*, **7**, 1192-1199. https://doi.org/10.1016/j.hrthm.2010.05.037

[12] Couselo-Seijas, M., Rodríguez-Mañero, M., González-Juanatey, J.R. and Eiras, S. (2021) Updates on Epicardial Adipose Tissue Mechanisms on Atrial Fibrillation. *Obesity Reviews*, **22**, e13277. https://doi.org/10.1111/obr.13277

[13] Shimabukuro, M. (2009) Cardiac Adiposity and Global Cardiometabolic Risk: New Concept and Clinical Implication. *Circulation Journal*, **73**, 27-34. https://doi.org/10.1253/circj.CJ-08-1012

[14] Marchington, J.M., Mattacks, C.A. and Pond, C.M. (1989) Adipose Tissue in the Mammalian Heart and Pericardium: Structure, Foetal Development and Biochemical Properties. *Comparative Biochemistry and Physiology Part B*: *Comparative Biochemistry*, **94**, 225-232. https://doi.org/10.1016/0305-0491(89)90337-4

[15] Dzeshka, M.S., Lip, G.Y., Snezhitskiy, V. and Shantsila, E. (2015) Cardiac Fibrosis in Patients with Atrial Fibrillation: Mechanisms and Clinical Implications. *Journal of the American College of Cardiology*, **66**, 943-959. https://doi.org/10.1016/j.jacc.2015.06.1313

[16] Uceda, D.E., Zhu, X.Y., Woollard, J.R., *et al*. (2020) Accumulation of Pericardial Fat Is Associated with Alterations in Heart Rate Variability Patterns in Hypercholesterolemic Pigs. *Circulation*: *Arrhythmia and Electrophysiology*, **13**, e007614. https://doi.org/10.1161/CIRCEP.119.007614

[17] Burstein, B. and Nattel, S. (2008) Atrial Fibrosis: Mechanisms and Clinical Relevance in Atrial Fibrillation. *Journal of the American College of Cardiology*, **51**, 802-809. https://doi.org/10.1016/j.jacc.2007.09.064

[18] Krishnan, A., Chilton, E., Raman, J., *et al*. (2021) Are Interactions between Epicardial Adipose Tissue, Cardiac Fibroblasts and Cardiac Myocytes Instrumental in Atrial Fibrosis and Atrial Fibrillation? *Cells*, **10**, Article No. 2501. https://doi.org/10.3390/cells10092501

[19] Lajiness, J.D. and Conway, S.J. (2012) The Dynamic Role of Cardiac Fibroblasts in Development and Disease. *Journal of Cardiovascular Translational Research*, **5**, 739-748. https://doi.org/10.1007/s12265-012-9394-3

[20] Smekal, A. and Vaclavik, J. (2017) Adipokines and Cardiovascular Disease: A Comprehensive Review. *Biomedical Papers*: *A Journal of Palacký University Olomouc*, *Faculty of Medicine and Dentistry*, *Olomouc*, *Czech Republic*, **161**, 31-40. https://doi.org/10.5507/bp.2017.002

[21] Marott, S.C., Benn, M., Johansen, J.S., *et al*. (2013) YKL-40 Levels and Atrial Fibrillation in the General Population. *International Journal of Cardiology*, **167**, 1354-1359. https://doi.org/10.1016/j.ijcard.2012.04.006

[22] Wang, Q., Shen, H., Min, J., *et al*. (2018) YKL-40 Is Highly Expressed in the Epicardial Adipose Tissue of Patients with Atrial Fibrillation and Associated with Atrial Fibrosis. *Journal of Translational Medicine*, **16**, Article No. 229. https://doi.org/10.1186/s12967-018-1598-0

[23] Abe, I., Teshima, Y., Kondo, H., *et al*. (2018) Association of Fibrotic Remodeling and Cytokines/Chemokines Content in Epicardial Adipose Tissue with Atrial Myocardial Fibrosis in Patients with Atrial Fibrillation. *Heart Rhythm*, **15**, 1717-1727. https://doi.org/10.1016/j.hrthm.2018.06.025

[24] Mahajan, R., Lau, D.H., Brooks, A.G., *et al*. (2015) Electrophysiological, Electroanatomical, and Structural Remodeling of the Atria as Consequences of Sustained Obesity. *Journal of the American College of Cardiology*, **66**, 1-11. https://doi.org/10.1016/j.jacc.2015.04.058

[25] O'Connell, R.P., Musa, H., Gomez, M.S., *et al*. (2015) Free Fatty Acid Effects on the Atrial Myocardium: Membrane Ionic Currents Are Remodeled by the Disruption of T-Tubular Architecture. *PLOS ONE*, **10**, e0133052. https://doi.org/10.1371/journal.pone.0133052

[26] Lau, D.H., Linz, D. and Sanders, P. (2019) New Findings in Atrial Fibrillation Mechanisms. *Cardiac Electrophysiology Clinics*, **11**, 563-571. https://doi.org/10.1016/j.ccep.2019.08.007

[27] Nakagawa, H., Scherlag, B.J., Patterson, E., *et al*. (2009) Pathophysiologic Basis of Autonomic Ganglionated Plexus Ablation in Patients with Atrial Fibrillation. *Heart Rhythm*, **6**, S26-S34. https://doi.org/10.1016/j.hrthm.2009.07.029

[28] Couselo-Seijas, M., Lopez-Canoa, J.N., Fernandez, Á.L., *et al*. (2020) Inflammatory and Lipid Regulation by Cholinergic Activity in Epicardial Stromal Cells from Patients Who Underwent Open-Heart Surgery. *Journal of Cellular and Molecular Medicine*, **24**, 10958-10969. https://doi.org/10.1111/jcmm.15727

[29] 孙恒, 周畅. 心房颤动导管消融术后复发风险预测模型研究进展[J]. 实用心脑肺血管病杂志, 2021, 29(7): 136-140.

[30] Maeda, M., Oba, K., Yamaguchi, S., *et al*. (2018) Usefulness of Epicardial Adipose Tissue Volume to Predict Recurrent Atrial Fibrillation after Radiofrequency Catheter Ablation. *The American Journal of Cardiology*, **122**, 1694-1700. https://doi.org/10.1016/j.amjcard.2018.08.005

[31] Kim, T.-H., Park, J., Park, J.-K., *et al*. (2014) Pericardial Fat Volume Is Associated with Clinical Recurrence after Catheter Ablation for Persistent Atrial Fibrillation, but Not Paroxysmal Atrial Fibrillation: An Analysis of over 600-Patients. *International Journal of Cardiology*, **176**, 841-846. https://doi.org/10.1016/j.ijcard.2014.08.008

[32] Hammache, N., Pegorer-Sfes, H., Benali, K., *et al*. (2021) Is There an Association between Epicardial Adipose Tissue and Outcomes after Paroxysmal Atrial Fibrillation Catheter Ablation? *Journal of Clinical Medicine*, **10**, Article No. 3037. https://doi.org/10.3390/jcm10143037

[33] Iacobellis, G., Corradi, D. and Sharma, A.M. (2005) Epicardial Adipose Tissue: Anatomic, Biomolecular and Clinical Relationships with the Heart. *Nature Clinical Practice Cardiovascular Medicine*, **2**, 536-543. https://doi.org/10.1038/ncpcardio0319