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心房心肌病临床标志物的研究进展

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摘　要

心房心肌病是近年提出的新概念，是一个诸多临床因素损伤心房致其结构、电生理、功能改变的综合范畴。心房心肌病是发生心房颤动和卒中的心房基质，其与心房纤维化关系密切。早期识别心房心肌病患者并及早地进行综合治疗与管理，对于预防和控制房颤、卒中的发生至关重要。本文综合最新研究文献对心房心肌病相关标志物进行简要阐述。

关键词

心房心肌病，心房纤维化，心房颤动，标志物

Research Progress on Clinical Markers of Atrial Cardiomyopathy

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Abstract

Atrial cardiomyopathy is a new concept put forward in recent years. It is a comprehensive category of structure, electrophysiology and function changes caused by many clinical factors. Atrial cardiomyopathy is the atrial matrix in which atrial fibrillation and stroke occur, and it is closely related to atrial fibrosis. Early identification of patients with atrial cardiomyopathy and early comprehensive treatment and management are very important for preventing and controlling the occurrence of atrial fibrillation and stroke. In this paper, based on the latest research literature, the related markers of atrial cardiomyopathy were briefly described.

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Keywords

Atrial Cardiomyopathy, Atrial Fibrosis, Atrial Fibrillation, Biomarkers

1. 引言

2024 年欧洲心律协会(EHRA)、美国心律学会(HRA)、亚太心律学会(APHRS)以及拉丁美洲心脏起搏与电生理学会(SOLAECE)更新了心房心肌病的临床共识声明[1]将心房心肌病(Atrial Cardiomyopathy, ACM)定义为任何影响心房、并可能产生临床相关表现的心脏结构、收缩功能或电生理变化的疾病。ACM 是房性心律失常(房颤、房扑)、心房血栓形成和心脏重要功能–结构表现异常(如心房扩张继发的心衰、房室瓣膜功能障碍)的基础[2]。由于 ACM 病因复杂，致病机制多种多样，目前临床上对 ACM 的检测尚缺乏有效的手段。寻找可靠的临床标志物对早期识别、诊断 ACM 具有重要意义。

2. ACM 的病理生理学

多种因素如高血压、房颤、糖尿病、高龄、心衰等均可导致或加重 ACM [3] [4]。根据病理生理特点，将 ACM 分为四类(EHRAS 分类[1])：(1) 以心肌病变为主；(2) 以纤维化病变为主；(3) 同时存在心肌病变和纤维化；(4) 以非胶原纤维浸润为主(伴或不伴心肌改变)。ACM 的核心特征之一是心房结构的变化，包括心房扩张和纤维化。这些变化通常与长期的心房高压力负荷(如高血压、瓣膜病)、心房颤动和心力衰竭等疾病相关。

3. 血清标志物

3.1. 12,13-二羟基-9Z-十八烯酸(12,13-diHOME)

房颤患者队列代谢组学分析发现冠状静脉中 12,13-diHOME 水平与左心房重塑显著关联，房颤组冠状静脉 12,13-diHOME 水平明显低于非房颤对照组(84.32 ± 20.13 与 96.24 ± 23.56 pg/mL；$P < 0.01$) [5]。多变量回归分析进一步表明冠状静脉 12,13-diHOME 水平是房颤射频消融术后 1 年复发的独立预测因素[5]。12,13-DiHOME 是一种棕色脂肪细胞因子(batokines)，它会影响体内的信号脂质水平变化，如 ω-3 多不饱和脂肪酸(ω-3 PUFAs)的增加[6]。动物实验表明 ω-3PUFAs 可能通过预防丝裂原激活的蛋白激酶激活、减少基质金属蛋白酶活性和连接蛋白再分布逆转房颤介导的心房结构变化[7] [8]。但该房颤队列研究样本量较少且血液标本取自于冠状静脉，未来仍需在大样本临床研究及外周血样本中做进一步验证。

3.2. 基质金属蛋白酶(Matrix Metalloproteinase, MMPs)

胶原蛋白是心脏结构的主要组成部分，特别是在心脏的瓣膜和间隔中[9]。I 型及 III 型胶原蛋白分别占心肌细胞外基质(Extracellular matrix, ECM)胶原含量的 50%~80%和 10%~45% [10] [11]。心肌 ECM 胶原蛋白的降解是左心房重塑的特征之一，这一过程受到基质金属蛋白酶(MMPs)的调控[12]。房颤患者的心房胶原沉积增加已被活检所证实[13]。MMPs 参与了胶原纤维的降解途径，当心房发生多度胶原沉积时其表达水平也随之增加[14]。MMPs 作为非活性酶原由多种细胞类型分泌，包括成纤维细胞、内皮细胞和心肌细胞[15]。MMP-1、MMP-2 和 MMP-9 被认为在房颤相关心房重塑中发挥了重要作用[16] [17]。肺高压所

致右房显著扩大的大鼠模型中 MMP2、MMP9 水平上升明显[18]。较高的 MMP-2 水平可以预测消融术后房颤的复发[19] [20]。然而这一标志物尚处于临床探索阶段。因为关于 MMPs 与心房重构的研究其结果存在异质性，一部分研究并未观察到心房重构组 MMPs 水平的升高，这可能与研究人群混杂因素较多有关。

3.3. 糖基化终末产物受体(Receptor for Advanced Glycation End Products, RAGE)

RAGE 在高血压、动脉粥样硬化等多种心血管疾病发生发展中发挥重要作用[21]。高水平糖基化终末产物(advanced glycation end products, AGEs)与其受体相互作用，即 AGEs-RAGE 系统激活，能够介导炎症与氧化应激反应[22]。在动物模型中，还能引起组织纤维化、硬化及弹性蛋白消失等[22]。AGEs 能够上调结缔组织生长因子(connective tissue growth factor, CTGF)的表达，而 CTGF 是诱导细胞外基质中纤维连接蛋白表达的关键分子，能够促进心房肌纤维化的发生[23] [24]。AGEs 与其受体的相互作用一方面能够活化核因子 NF-κB，引起多种促炎因子的过度表达，促进了心房重构[24]。AGEs 加速了心房电重塑和细胞老化，通过激活 p16/Rb 通路增加了房颤的易感性[25]。AGEs 还可以诱导某些结构蛋白的交联，如细胞外基质中的 I 型胶原蛋白和弹力素，促进心房纤维化[26]。血清可溶性 RAGE (soluble form of receptor for advanced glycation end products, sRAGE)可能反映 AGEs-RAGE 轴的激活。Raposeiras-Roubín 等人发现血清中 AGEs 和 sRAGE 的水平与左房直径($r = 0.491$)和左房容积($r = 0.511$)呈显著正相关[27]。在二尖瓣心脏疾病患者中，RAGE 表达水平与心房纤维化程度独立相关(95%CI (4.76~14.2), $P < 0.001$) [28]。

3.4. Galectin-3

Galectin-3 是半乳糖凝集素家族中的一员。Galectin-3 参与了心肌纤维化和心脏重构，其表达水平反映了心力衰竭的进展和严重程度[29]。Galectin-3 的致纤维化作用是通过与基质蛋白如层粘连蛋白、纤连蛋白及胶原蛋白的结合来实现的，在这个过程中，Galectin-3 被激活，并且和其他 Galectin-3 的残基相结合成二聚体，形成网状结构，从而使细胞外基质堆积，组织僵硬度增加[30]。阵发性房颤患者冠状静脉中的 Galectin-3 水平与心房低电压面积呈正相关[31]。持续性房颤患者中 Galectin-3 的浓度与左心房壁的大小、收缩功能和顺应性显著负相关[32]。由于 Galectin-3 广泛分布在组织器官中且与肿瘤增殖、迁移密切相关，其对于诊断心房重构特异性较差，临床应用仍然受限。

4. 遗传学标志物

4.1. miR-21

miR-21 参与了 ACM 患者中心房 TASK-1 钾通道的表达调节，这导致了房颤易感性的增加[33]。在房颤大鼠模型中 miR-21 对心房纤维化重塑也起了关键作用[34]。血清 miR-21 水平与左心房低电压面积呈正相关并且是心房颤动患者射频消融术后复发的独立危险因素[35] [36]。然而也有研究发现合并阻塞性睡眠呼吸暂停(OSA)的患者，其血清 miR-21 水平越高的人群手术后发生房颤的风险反而越低[37]。长期缺氧状态会导致 miR-21 水平的升高[38]，OSA 患者缺氧程度的不同可能是影响该研究结果的重要因素之一。miR-21 与 ACM 的关系仍需进一步研究证实。

4.2. miR29b

全转录组测序提示相较对照组，miR29b 在心房纤维化大鼠模型组中下调[39]。在心房颤动患者中，血清 miR-29b 的表达较低，但经过射频消融治疗后，其表达较术前增加[40]。miR29b 可能通过靶向调节 TGFβR I 并抑制 Smad-2/3 通路来减轻 AF 大鼠的心房纤维化[41]。miR29b 同样也参与了心房 TASK-1 钾通道的表达调节[33]。

4.3. miR133a

miR133a 参与了心肌纤维化的调节[42] [43]。在房颤所致心房纤维化的大鼠中 miR133a 表达下调显著[44]。miR133a 可通过靶向调节胶原表达和 JNK 途径减弱缺氧诱导的心房纤维化[45]。miR-133a 抑制剂可以逆转 Ang II 诱导的人心房成纤维细胞增殖和迁移的抑制作用，从而促进了心房纤维化[23]。但目前 miR133a 与心房纤维化或心房重构的关系尚未得到临床研究的证实。

5. 电生理指标

5.1. P 波参数

心房胶原沉积和结构重塑导致传导减慢和电压降低[46]。心电图 P 波代表了心房除极过程。P 波时限、V1 导联 P 波终末电势(PTFV1)、P 波离散度等与心房事件(室上速、房颤、心房扩大)关系密切[47]。P 波时限 ≥ 120 ms 表明部分房间阻滞。下壁导联(II、III、aVF)中双相 P 波形态表明 Bachmann 束的完全阻滞，即高级别房间阻滞(advanced IAB) [48]。PTFV1 由其持续时间和绝对振幅的乘积计算得出。PTFV1 绝对值 > 4 mV·ms 被认为是病理性的。该传导异常由终末左房异常激动所致，这往往提示左房应变能力的降低[49]。P 波离散度是指 12 导联心电图上 P-P 最大时限与 P-P 最小时限之差。在隐源性卒中和植入循环记录仪的患者中，P 波离散度 > 40 ms 是房颤的预测指标[50]。

5.2. 心房电压

心内膜双极电压振幅降低，在电解剖标测图中表现为低电压区(low voltage area, LVA)，通常定义为双极电压 < 0.5 mV 的区域，这被视为心房心肌病的标志之一[51]。电解剖标测研究表明，心房双极电压降低是一个弥漫过程；而 LVA 是与组织学纤维化相关的弥漫性电压降低的局部反映[1]。首次消融的房颤患者中 LVAs 的存在及其程度与死亡、心力衰竭和卒中等长期复发终点有关[52]。目前尚无评价心房心肌病严重程度的标准化方法，LVA 可在一定程度上对心房心肌病进行量化指导后续治疗。但是有创、高成本等因素限制了其广泛应用。

6. 影像学标志

超声心动图、心脏磁共振(CMR)成像和心脏计算机断层扫描(CCT)是评估心房形态特征的常用手段。经食管超声心动图(TEE)和 CCT 可以具体地描述左房和右心耳的特征。基于 CT 的局部室壁变形能够更好地预测心房低电压区域。心脏磁共振特征追踪技术(cardiac magnetic resonance-feature tracking, CMR-FT)可在常规电影扫描序列中通过后处理软件探测心动周期中心肌长度随时间的变化情况，反映心肌在张力作用下发生形变的能力，从而获得反映心肌功能的应变和应变率[53]。心外膜脂肪组织 EAT 通过直接浸润或间接分泌细胞活性物质影响心房心肌重塑，CCT 或 CMR 可有效评估心房周围 EAT 的面积及浸润深度，有助于识别早期 ACM [54]。

7. 未来展望

影像学标志基于较好的特异性在 ACM 诊疗中的应用相对较多，电学参数在临床上往往作为诊断的次要参考标准。而血清标志物及遗传标志物受限于费用、研究证据不足等问题仍未广泛应用于 ACM 的诊疗。ACM 标志物的研究多数在特定类型患者(如房颤)或动物上进行，尤其是血清标志物及遗传标志物，由于样本的异质性仍需大规模临床研究证实标志物与 ACM 的关联。此外 ACM 病因复杂，涉及炎症、代谢紊乱、电生理重构等多种机制，单一标志物其敏感性、特异性可能较差。未来需探索多组学标志物的联合应用，以提高临床诊断准确性和预测能力。另外仍需不断结合新技术(如质谱分析、单细胞 RNA 测

序等)发现潜在的新型标志物，为 ACM 的诊疗提供有力工具。

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