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老年慢性心力衰竭合并心房颤动的病理生理学及治疗进展

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摘　要

心力衰竭(heart failure)是心脏结构和功能异常导致的进行性心脏泵功能障碍的一组临床综合征，是多种心脏疾病的终末阶段，现已经发展成为全球流行疾病，并且随着世界人口老龄化的加深，心力衰竭的发病率及死亡率也逐年上升，构成了重要的全球疾病负担之一。老龄化构比在慢性心力衰竭中呈持续上升趋势，由于其自身临床特点，若合并心房颤动可导致发病率升高、负担费用加大、生活质量降低、心脑血管意外及死亡率增加，且两者可互为因果又相互促进，因此现对老年慢性心力衰竭合并心房颤动的发病机制及诊治进展做进一步展述。

关键词

老年，心力衰竭，心房颤动，病理生理学，治疗进展

Pathophysiology and Treatment Progress of Elderly Patients with Chronic Heart Failure Complicated with Atrial Fibrillation

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Abstract

Heart failure is a group of clinical syndromes of progressive heart pump dysfunction caused by

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abnormal heart structure and function, and is the end stage of a variety of cardiac diseases that have developed into a global epidemic. As the world's population ages, the incidence and mortality of heart failure are also increasing year by year, constituting an important global burden of disease. The proportion of aging in chronic heart failure continues to rise. Due to its own clinical characteristics, if atrial fibrillation is combined, it can lead to increased morbidity, increased cost, decreased quality of life, increased cardiovascular and cerebrovascular accidents, and increased mortality. The two can cause and promote each other. Therefore, the pathogenesis, diagnosis and treatment progress of chronic heart failure combined with atrial fibrillation in the elderly are further described.

Keywords

The Elderly, Heart Failure, Atrial Fibrillation, Pathophysiology, Treatment Progress

1. 流行病学

心力衰竭(心衰)在全球广泛流行，2013 年至 2016 年期间，美国估计有 620 万人心衰，到 2030 年，美国将有超过 800 万人患有心衰，心衰发病率、症状负担随着人口老龄化持续上升[1] [2]，心衰患者合并房性和(或)室性心律失常可致预后较差，其中心房颤动(房颤)是心力衰竭最常见的心律失常，研究表明[3]在新发老年心衰中超过 57%的患者合并房颤，并随着心衰的严重程度加重而增加[4] [5]。

2. 老年慢性心衰合并房颤的病理生理学

2.1. 血管与心脏自身老化机制

房颤的发生率随年龄的增长而增加，老年心力衰竭患者更易合并房颤[6]，血管老化可导致心输出量下降、血管阻力增大、器官血流灌注减少，易发生心肌缺血、缺氧而诱发或加重心力衰竭，且老年心脏结构中最常见心肌肥大、心脏瓣膜退行性病变、心肌不均匀性纤维化、心肌延展性减低、脂肪组织增多、迷走神经张力增高、激动传导系统退变等易增加房颤发生风险。

2.2. 神经系统反应调节机制

2.2.1. 中枢神经系统

下丘脑室旁核(PVN)是大脑的主要心血管调节区，它包含了肾素、血管紧张素原、血管紧张素 II (AngII)、血管紧张素 1 受体(AT_1R)、血管紧张素(Ang)-(1-7)等成分，这些物质调节心脏交感传入反射(CSAR)，并在一定程度促进患者 CSAR 增强[7]，在建立心力衰竭小鼠动物实验中可以发现心力衰竭小鼠 PVN 区域的 AT_1R 和 AngII 水平升高，室旁核中的 AngII 通过激活 AT1 受体而增强 CSAR 和交感神经输出[8]，并导致 RASS 系统激活、醛固酮分泌增加，在神经激素刺激后导致心肌细胞增殖肥大，且易造成电解质代谢紊乱、心脏扩大、心房内压增高、心肌纤维化、心肌重构等心脏结构及功能改变，易导致合并房颤发生。

2.2.2. 心脏自主神经系统(ANS)

自主神经系统激活可引起心房电生理的异质性改变并诱发心律失常，心脏受其内、外在自主神经的

调节，内在自主神经对房颤发生密切相关[9]，心脏内在 ANS 由心房表面的神经丛(GP)和心外膜脂肪垫内心室组成，其中 GP 在肺静脉－左心房交界处分布较多，肺静脉具有较短的心房动作电位时程(ADP) [10]，当心衰发生时，出现肺静脉压及心室充盈压升高、心脏后负荷增加等致心房 ADP 缩短以及钙瞬变过长，从而易触发的房颤。

2.3. 氧化应激与炎症反应机制

氧化应激与炎症反应在房颤的发病机制中不断被提出，越来越多证据表明其导致了血管内皮的损伤，促进了血管硬化，是一系列心血管疾病的病理生理基础[11]。心脏结构重构与渐进性纤维化和炎症过程有关，炎症反应是房颤发生、维持和复发的重要因素[12]，研究发现房颤患者心房心肌广泛的氧化损伤[13]，房颤患者 C 反应蛋白(CRP)、超敏 C 反应蛋白(hs-CRP)、白介素-6 (IL-6)、肿瘤坏死因子-α (TNF-α)等炎性标志物指标表达均高于非房颤组[6]，当心衰发生时的心肌组织处于缺血、缺氧状态会降低抗氧自由基的能力并引起体内活性氧的堆积，从而形成氧化应激状态，诱发及加重心肌炎症反应，从而促进房颤发作。

2.4. 能量代谢失衡机制

细胞内能量耗尽可能导致心律失常的发生[11]，房颤患者心房心肌细胞普遍存在能量代谢异常，其中可见更高水平的甘油三酯、氧化物种和晚期糖化终末产物，且研究发现房颤患者的体外右心房组织样本中可观察到依赖起搏的线粒体呼吸损伤与线粒体的显著改变[13]。房颤患者的低密度脂蛋白较小，更容易被巨噬细胞摄取通过与血液中的活性氧物种和碳水化合物的相互作用，随着衰老、心功能减低的进展而糖化程度更高[14]。当心衰发生时，心肌组织缺乏足够的氧合、底物能量利用及 ATP 的合成减少、Ca^{2+}流通改变致 ATP 的生物利用度降低等造成心肌细胞脂肪酸氧化以及葡萄糖利用程度降低，线粒体呼吸功能受到限制、磷酸化水平降低、糖化程度增加，易导致房颤发生。

3. 老年慢性心力衰竭合并房颤的临床特点

3.1. 诱发因素多

老年慢性心衰患者年龄越大、病程越长，心脏的结构损伤、破坏、重构越严重，心脏储备功能逐渐下降，当出现情绪激动、饱餐、寒冷、生活方式改变、活动量增加、排便费力、甲亢、贫血、呼吸道感染、肾功能不全、血压控制不佳、液体入量过多、药物种类及剂量调整、心肌缺血加重等情况时，心脏负荷加重，心房组织中传导延迟、传导阻滞，易合并房颤。

3.2. 多病因参与

老年患者存在多种心血管危险因素、共病及伴有并发症多、多重用药、身体机能自然衰退等特点，老年人常见多病因致心衰，其中发生心衰合并房颤的病因可达数种，最常见的疾病是冠状动脉粥样硬化性心脏病、风湿性心脏病、先天性心脏病、肺源性心脏病、心脏瓣膜性疾病、心肌梗死、甲状腺功能亢进性心脏病等，上述又可分为单病因组、两病因组甚至多病因组。

3.3. 症状、体征不典型

由于老年患者日常活动量减少，部分老年慢性心衰合并房颤患者可表现为完全无症状，部分有症状者可出现心悸、胸闷、乏力、头晕、呼吸困难、活动耐量下降等典型症状发生比例显著降低，且由于老年人身体机能退化、反应迟钝、易合并其他系统疾病等可出现肺部及心脏听诊闻及杂音、脉律不齐、脉

搏短绌等典型体征不易被发现，常被漏诊而延误治疗。

3.4. 临床过程复杂

老年慢性心衰合并房颤患者可能通过多种机制相互作用、促进、发展及恶化，具体表现为其常合并多系统疾病、诱发因素多、症状体征不典型、临床表现复杂、病情不稳定及易反复、有相关的药代动力学和药效学改变、药物与疾病相互作用会随着年龄增长而增加、老年人对治疗的依从性差等可致老年慢性心衰合并房颤患者预后差、病死率高[15] [16] [17] [18]，上述可致老年慢性心衰合并房颤患者预后差、病死率高。

4. 老年慢性心衰合并房颤的治疗研究进展及治疗现状

老年慢性心衰患者合并房颤发作时，心肌收缩功能进一步下降，心脏充盈受损，房室失同步化，其左室射血分数、心输出量、每搏量、心脏指数、峰值运动耗氧量下降明显，心肌损伤不断加重，心力衰竭进程不断加剧恶化，患者生活质量及生存周期严重下降，其往往预后不良，目前针对老年慢性心衰合并房颤的研究较少，治疗上尚无相应指南建议，目前对老年慢性心衰合并房颤的治疗除常规抗心力衰竭治疗外，主要从心率及节律的控制两个方面进行，下面将对老年慢性心衰合并房颤的治疗进展进行展述。

4.1. 老年慢性心衰合并房颤药物治疗

4.1.1. 抗凝治疗

老年慢性心衰合并房颤患者由于其身体机能的退化、共病多、病情不稳定等可能导致血栓形成及出血发生的风险增加，但研究表明[19]在密切监测出凝血指标的情况下有效抗凝治疗可带来更大的获益。目前抗凝药物主要分为维生素 K 拮抗剂和新型口服抗凝药(New-oral anticoagulants, NOAC)两大类。维生素 K 拮抗剂代表药物华法林是抗凝治疗的基石，但其受食物、药物等因素影响，需严格监测国际标准化比值(INR)并根据结果调整口服剂量[20] [21]。新型口服抗凝剂因起效、清除快、不需监测 INR 等独特优势被广泛应用，包括达比加群酯、利伐沙班、阿哌沙班等。研究发现[22]低剂量新型口服抗凝剂在降低卒中风险或全身血栓事件方面与华法林作用相似，出血风险和死亡率明显降低。

4.1.2. 心室率控制

目前老年慢性心衰伴房颤患者心室率控制目标值尚不明确，欧洲心脏病学会(ESC)房颤管理指南推荐较为宽松的心率控制是可以接受的，静息状态下心室率 < 110 次/min 可以作为控制的起始目标[23] [24]。控制心室率的药物主要包括 β 受体阻滞剂、洋地黄类、非二氢吡啶类钙通道拮抗剂。Vamos M [25]研究提示房颤合并心衰患者中应用地高辛治疗组的死亡率增加。β 受体阻滞剂是心衰治疗的基石，可改善心衰症状及预后，且研究表明[26]心衰合并房颤患者使用 β 受体阻滞剂后全因死亡率可降低 28%，控制心室率建议选用 β 受体阻滞剂。

4.1.3. 节律控制

节律控制主要是在抗凝、控制心室率的基础上通过抗心律失常药物恢复并维持窦性节律，抗心律失常药物可使约一半的新发房颤患者转复为窦性心律[27]，其主要有胺碘酮、普罗帕酮、多非利特等药物，由于抗心律失常药物可能导致器官毒性作用、低血压、房室传导阻滞、其他类型致命性心律失常等不良反应，且老年慢性心衰伴房颤患者由于共病多、多重用药、身体机能自然衰退等特点，需密切行心电监测并定期随访肝肾功、血液药物浓度。目前欧洲心脏病学会(ESC)房颤管理指南[24]推荐胺碘酮和多非利特作为心衰合并房颤节律控制的药物。

4.2. 老年慢性心衰合并房颤非药物治疗

4.2.1. 电复律

同步直流电复律在心室率控制不佳、症状明显、血流动力学不稳定、严重心绞痛、心肌梗死的心衰合并房颤患者中具有一定的临床意义，其具有要间断、方便、有创性小及较为安全等特点，但电复律后仍易反复发作房颤，研究表明电复律前加用抗心律失常药物可以提高复律成功率[28]，且房颤复律过程中适当抗凝治疗可以减少栓塞风险[29] [30]。

4.2.2. 导管消融

当抗心律失常药物治疗方案无效、引起严重毒副作用或患者不愿长期口服抗心律失常药物时，导管消融是可选的治疗方案[31]。2019 美国心律学会(HRS)房颤管理指南中推荐导管消融治疗房颤合并心衰为 IIb 类推荐[32]，且多项研究表明[33] [34]心衰合并房颤患者行导管消融术后房颤复发率、死亡率及心衰恶化住院率均降低。部分研究表明导管消融联合抗心律失常药物或导管消融联合起搏器治疗对老年慢性心衰合并房颤患者有一定意义，但仍需要更多的临床大数据研究来支持。

4.2.3. 左心耳手术

部分老年慢性心衰合并房颤患者因药物代谢减退、药物蓄积及相互作用、肝肾功能不全、既往出血病史等可能导致口服抗凝剂后出血风险显著增加。房颤患者左心耳中血流速度减慢，易导致血栓形成，因此左心耳手术在这些患者栓塞的预防中具有一定地位。左心耳手术分为外科左心耳切除术以及内科经皮左心耳封堵术[35] [36]。内科经皮左心耳封堵术具有微创、无需心脏停搏、体循环栓塞发生率低等优势，且研究表明[37]左心耳封堵术较口服抗凝药相比严重卒中事件可减少近一半，但因左心耳封堵术手术费用较高，在临床应用上可能受到一定程度的限制。

4.2.4. 起搏治疗与植入型心律转复除颤器

Sulke N [38]研究证明起搏可减少房颤的发作次数及房颤负荷的积极作用，但增加了心房、心室起搏百分比数。目前心脏再同步化治疗(CRT)已经成为心衰合并房颤的重要治疗手段，CRT 可恢复房室、室间及室内的同步性，进一步降低死亡率、改善心脏功能状态，提高生活治疗[39]，2013 ACCF/AHA 心力衰竭管理指南建议 CRT 为心衰伴有房颤的 IIa 类推荐，近十分之一的心衰伴房颤患者中植入 CRT 可转复为窦性心律[40] [41]。老年慢性心衰合并房颤时易发生恶性心律失常导致心脏猝死可能，植入型心律转复除颤器可提高致命性心律失常患者的生存率[42]，但其不恰当放电等并发症发生率仍较高。

4.2.5. 机械循环支持装置与心脏移植

晚期心衰伴房颤患者强化药物后仍不能有效控制症状、生活质量及生存周期严重下降，需在药物治疗的基础上行机械循环支持装置或心脏移植进一步治疗。临床上使用的机械循环装置包括左心室辅助装置(LVAD)和全人工心脏，尽管有一些研究支持 LVAD 可提高患者的生存周期，但其生活质量尚不明确。心脏移植作为终末期心血管疾病的最终治疗方法，但因其供体少、易发生免疫排斥反应、移植后凝血功能障碍与炎症反应均会导致移植失败可能[43]。全人工心脏作为 LVAD 难以维系以及无法行心脏移植手术的晚期心衰伴房颤患者可以选择，但其治疗效果、可能出现并发症、不良反应等仍需大样本试验探究。

5. 小结

越来越多证据表明心衰与房颤互为因果，且两者具有共同的危险因素，导致心衰合并房颤十分常见，尤其易发生于老年人群中，对于心衰合并房颤患者除常规抗心衰外，抗心律失常及抗凝是改善症状的重要手段。对于优化药物治疗未能达到效果的老年慢性心衰合并房颤患者可采取非药物治疗，但仍需根据

患者病情轻重、个体差异、经济情况、依从性及患者个人意愿合理制定治疗方案。未来随着人们对老年心衰合并房颤的病理生理学机制的逐渐深入探究，治疗手段和选择越来越多，治疗方法不断改进、生活质量及生存率明显上升，可使患者获益最大化。

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