

心脏淀粉样变性：猝死

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摘要

轻链型心脏淀粉样变性(AL-CA)是心脏淀粉样变性中最具侵袭性的类型,其特点是疾病进展迅速,心源性猝死率异常高。其病理生理机制涉及双重途径:淀粉样纤维对心肌的机械性浸润,以及循环游离轻链对心肌细胞的直接细胞毒性作用。希氏束-浦肯野传导系统的优先受累,使患者易发生致命性心律失常和传导异常。尽管血液系统治疗取得了进展(包括基于达雷妥尤单抗的方案显著提高了缓解率),但即使采取预防性器械干预,猝死仍是患者的主要死亡原因。非特异性的临床表现导致诊断延迟,大多数患者就诊时已处于疾病晚期,且已发生不可逆的心脏损伤。通过系统性多器官评估、心脏生物标志物检测及先进影像学技术实现早期识别,对改善预后至关重要。目前的预防策略包括快速实现血液学缓解、合理使用心脏器械以及精细化血流动力学管理。然而,干预的最佳时机和患者选择标准仍未完全明确。本综述总结了目前对AL-CA猝死机制的认知,评估了循证预防策略,强调迫切需要建立早期诊断流程和个体化治疗方案,以降低心源性猝死对此类患者的严重影响。

关键词

心脏淀粉样变性, 淀粉样变性, 达雷妥尤单抗, 猝死, 预防

Cardiac Amyloidosis: Sudden Cardiac Death

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Abstract

Light-chain cardiac amyloidosis (AL-CA) represents the most aggressive form of cardiac amyloidosis, characterized by rapid disease progression and exceptionally high sudden cardiac death rates. The pathophysiology involves dual mechanisms: mechanical myocardial infiltration by amyloid fibrils

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and direct cytotoxic effects of circulating free light chains on cardiomyocytes. Preferential involvement of the His-Purkinje conduction system predisposes patients to fatal arrhythmias and conduction abnormalities. Despite advances in hematologic therapies, including daratumumab-based regimens achieving improved remission rates, sudden death remains the predominant cause of mortality even with prophylactic device interventions. The non-specific clinical presentation results in delayed diagnosis, with most patients presenting at advanced stages when irreversible cardiac damage has occurred. Early recognition through systematic multi-organ assessment, cardiac biomarkers, and advanced imaging techniques is crucial for improving outcomes. Current prevention strategies encompass rapid achievement of hematologic remission, judicious use of cardiac devices, and meticulous hemodynamic management. However, the optimal timing of interventions and patient selection criteria remain incompletely defined. This review synthesizes current understanding of sudden death mechanisms in AL-CA and evaluates evidence-based prevention strategies, highlighting the urgent need for early diagnostic algorithms and individualized treatment approaches to reduce the devastating impact of sudden cardiac death in this population.

Keywords

Cardiac Amyloidosis, Amyloidosis, Daratumumab, Sudden Cardiac Death, Prevention

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1. 引言

心脏淀粉样变性(Cardiac Amyloidosis, CA)是一种由异常折叠蛋白形成的淀粉样原纤维沉积于心肌细胞外空间中导致的浸润性心肌病[1][2]。根据前体蛋白类型,心脏淀粉样变性主要分为轻链型(AL-CA)、野生型转甲状腺素运载蛋白型(wtATTR-CA)、遗传性转甲状腺素运载蛋白型(hATTR-CA)等类型[3]-[5]。其中,AL型(轻链型)淀粉样变性是最常见且预后最差的类型,其心源性猝死风险显著高于其他类型[6]-[8]。

相较于其他类型,AL型淀粉样变性具有独特的病理生理特征:游离轻链(free light chains, FLC)不仅形成淀粉样原纤维造成心肌间质的机械性损伤,轻链蛋白本身还对心肌细胞具有直接的细胞毒性作用,导致心肌细胞功能障碍和细胞死亡[9]-[12]。此外,AL型淀粉样变性易累及His-Purkinje传导系统,常表现为各种程度的房室传导阻滞和心律失常,这与其高猝死率密切相关[13]-[15]。

然而AL型心脏淀粉样变性因其临床表现缺乏特异性,致使大多数患者在确诊时病情已进展至晚期阶段,此时心源性猝死风险显著增高。流行病学发现AL型淀粉样变性进展迅速,中位生存期仅6~15个月,早期准确诊断对改善预后至关重要。目前,AL型心脏淀粉样变性的诊断与治疗仍面临严峻挑战。由于早期症状隐匿且缺乏特异性,确诊时多已进展至心功能严重受损阶段,甚至需依赖尸检明确诊断[16][17]。更值得注意的是,即便患者接受规范化疗或植入埋藏式心脏转复除颤器(ICD),心脏起搏器等预防措施,其猝死发生率仍居高不下[7]。因此,深入理解AL型心脏淀粉样变性的猝死机制,并据此制定针对性的早期筛查及个体化干预策略,是改善患者预后的关键突破口。

本综述旨在系统阐述AL型心脏淀粉样变性致猝死的病理生理机制,并综合评述现有诊断及治疗策略的成效与局限性,为AL型心脏淀粉样变性相关猝死的预防和治疗提供新的理论依据和临床思路。

2. 心源性猝死机制

了解淀粉样变性猝死的病理生理机制对于疾病的诊断、治疗及预防具有关键意义。AL型淀粉样变性

患者表现出空间异质性传导和复极化异常, 这些电生理改变是心律失常和心力衰竭风险增加的重要标志, 并与猝死密切相关[18]。一些尸检病理学报告显示, 淀粉样原纤维和轻链的毒性浸润心脏传导系统是引发猝死最可能的机制。淀粉样蛋白优先浸润希氏-浦肯野系统, 导致传导速度异质性和传导阻滞, 当传导系统广泛受累时, 可发生完全性房室传导阻滞, 成为心脏停搏的关键机制, 而浸润传导系统引起的严重心动过速也是心脏终末期表现[13][19][20]。同时, 窦房结的淀粉样蛋白浸润是房性心律失常如心房颤动的重要原因, 淀粉样蛋白沉积导致心房电机械功能解耦联, 当心房功能障碍时, 心脏整体循环灌注受到影响[14]。在心室功能层面, 淀粉样原纤维在心脏的不均匀沉积导致左右心室收缩不同步和心室内传导延迟的空间异质性, 血流动力学效能降低, 最终可能导致猝死, 而严重的淀粉样蛋白浸润可引起急性机电分离, 表现为有电活动但无有效机械收缩, 这是猝死的直接机制之一[21]。此外, 血管周围淀粉样蛋白沉积导致壁增厚和管腔阻塞影响心肌灌注, 可能加重传导系统的血供障碍, 瓣膜组织的淀粉样蛋白浸润同样可能影响心脏整体的血流动力学稳定性[22][23]。

3. 早期识别是预防猝死的关键

鉴于 AL 型心脏淀粉样变性临床表现缺乏特异性且疾病进展迅速, 建立系统性早期识别框架对改善患者预后具有重要意义[1]。多系统受累征象往往早于心脏症状出现, 是提高诊断敏感性的关键切入点[24]。

AL 型淀粉样变性的早期识别依赖于多系统受累征象和基础检查的综合评估[25][26]。心外表现包括皮肤紫癜和瘀斑、巨舌症、周围神经病变、肾病综合征、消化系统症状及凝血功能异常, 这些表现为疾病怀疑提供重要线索。心电图检查可发现 QRS 波群低电压与心室壁厚度增加形成的“电-机械分离”现象、伪梗死型 Q 波、房室传导阻滞及心房颤动等特征性改变[13][27][28]。血清生物标志物方面, NT-proBNP 与心肌肌钙蛋白的不成比例升高具有重要诊断提示意义[29][30], 而血清游离轻链 κ/λ 比值异常是筛查单克隆免疫球蛋白病的核心指标[31]。

当基础检查提示可能的 AL 型心脏淀粉样变性时, 影像学检查提供进一步的诊断依据[32]。超声心动图显示心肌颗粒状闪光回声、室壁增厚、舒张功能异常, 二维斑点追踪成像评估的整体纵向应变减低伴心尖保留模式对早期诊断具有较高敏感性[33]-[35]。多参数超声心动图评分系统整合多个指标, 诊断准确性 AUC 达 0.90 [36]。核素心肌显像中, 99mTc-PYP 等骨扫描剂在 AL 型中仅 20%~30% 患者呈轻度摄取, 主要用于排除 ATTR 型[37]。心脏磁共振成像提供最精确的组织特征化信息, 原生 T1 弛豫时间延长和细胞外容积分数增加是淀粉样沉积的早期表现, 延迟钆增强呈心内膜下环周性分布, 钆对比剂清除异常为典型征象[38][39]。

综合多种无创性检查能够在大多数情况下建立 AL 型心脏淀粉样变性的高可能性诊断[40]。这种基于无创检查的综合诊断策略避免有创操作风险, 满足早期识别需求。然而, 在临床表现不典型或无创检查结果不确定的疑难病例中, 组织学检查仍具有确诊价值[41]。心外组织活检包括腹壁脂肪垫穿刺、直肠黏膜活检或唾液腺活检, 相对心内膜活检风险较低, 但仍存在并发症风险, 特别是凝血功能异常的 AL 型患者。刚果红染色显示苹果绿双折射现象, 激光显微切割质谱分析确定淀粉样蛋白具体类型[42]。临床实践中应优先采用无创性综合诊断策略, 必要时谨慎选择组织学检查作为补充手段。

4. 治疗策略

预防策略需要针对这些机制采取综合性治疗措施, 核心包括快速达到血液学缓解以阻止疾病进展, 以及积极管理心脏并发症[1]。早期诊断、快速达到完全缓解、合理选择器械治疗以及个体化的风险评估是提高患者生存率、降低猝死风险的关键措施。治疗决策需在获益与风险间平衡, 充分考虑疾病分期、

心功能状态和预期生存期。

4.1. 猝死预防的根本策略

血液学缓解是预防心源性猝死的关键,通过抑制异常浆细胞克隆减少致病性轻链产生,阻止淀粉样物质进一步沉积,是逆转心肌损伤、降低 AL-CA 猝死风险的核心,不同治疗方案的心脏反应特征及缓解深度直接决定预后差异。以达雷妥尤单抗为基础的 D-VCd 方案(达雷妥尤单抗、硼替佐米、环磷酰胺和地塞米松)已成为新诊断 AL 型淀粉样变性的标准治疗,并且在 IIIb 患者仍有显著的缓解效果[43] [44]。Bellofiore 等人在 2025 年发表的匹配病例对照研究显示。对于 AL 淀粉样变性 IIIb 期心脏受累患者人群,达雷妥尤单抗联合方案组的中位总生存期为 10.3 个月,显著高于 CyBorD 方案(硼替佐米、环磷酰胺和地塞米松)组的 4.0 个月,主要器官恶化无进展生存期中位数为 10.2 个月,远超 CyBorD 组的 3.2 个月,而达雷妥尤单抗联合方案组在治疗开始后 3 个月时的总血液学缓解率达到 50%,显著高于 CyBorD 组的 21%。更重要的是,达雷妥尤单抗组在 3 个月时实现了 25%的心脏反应率,显著优于对照组的 3%,这表明即使在具有较高克隆负荷的晚期 IIIb 期患者中,达雷妥尤单抗的加入也能带来更深层次的血液学和心脏缓解,从而延长患者的 OS [44]。自体造血干细胞移植(ASCT)的策略正在重新定义,当前倾向于先使用新型药物诱导治疗后评估是否需要 ASCT。达到完全缓解的患者可继续维持治疗或选择 ASCT,而达到部分缓解的合适患者仍可从 ASCT 获得缓解深化和生存获益。自体造血干细胞移植仍是符合条件的 AL 淀粉样变性患者的首选治疗方案之一,主要适用于年龄 < 65 岁、且心功能储备较好的患者。D'Souza 等 2015 年的研究证实,ASCT 能够带来长期的深度缓解,患者在 5 年时的血液学完全缓解率约为 37%。虽然心脏反应的出现通常延迟至治疗后 6~12 个月,但其缓解持续时间长,显著优于传统药物治疗方案。然而,ASCT 预处理阶段的心脏毒性风险是巨大的挑战,因此需要全程严密监测和支持[45]。

血液学缓解的深度与患者的猝死风险及长期预后量化关联目前尚不明确,Palladini 等人于 2012 年制定的标准,完全缓解要求血清 FLC 比值正常,且血清和尿液中无单克隆蛋白;而非常好部分缓解则要求受累和非受累 FLC 之间的差值(ΔFLC) $\leq 40 \text{ mg/L}$ 。然而需要注意的是,心脏反应的判定需基于心肌生物标志物(如 NT-proBNP)的下降幅度(如 $\geq 30\%$ 且 $\geq 300 \text{ pg/mL}$ 的下降)来单独评估,不应与血液学缓解标准混用[31]。动态监测 NT-proBNP、肌钙蛋白等指标对心脏反应进行,以便及时调整治疗策略,才是能最大化降低患者的猝死风险并争取器官功能保护的窗口。

4.2. 直接预防心源性猝死

心律失常是 AL 型心脏淀粉样变性最直接的猝死原因。传导系统受累常导致症状性心动过缓和房室传导阻滞,起搏器植入适应症包括症状性心动过缓、二度 II 型或三度房室传导阻滞、以及伴症状的窦房结功能障碍[46]。

对于室性心律失常,植入型心律转复除颤器(ICD)的应用仍存争议。2019 年 HRS 专家共识推荐持续性室速或室颤幸存者接受 ICD 治疗,对于预期生存期 > 1 年且非持续性室速的患者可考虑 ICD 植入[47]。一些研究也证明了轻链淀粉样变性患者预防性植入心律转复除颤器可有效成功治疗这些患者的持续性 VA [48]。

预防血流动力学崩溃

AL 型心脏淀粉样变性表现为限制性心肌病,心输出量高度依赖前负荷。容量管理构成治疗核心,需在缓解充血症状与维持足够心输出量间达到平衡。过度利尿可导致心输出量急剧下降,诱发低血压性晕厥甚至心源性休克。

药物选择需格外谨慎。钙通道阻滞剂因与淀粉样纤维高亲和力结合可诱发严重心功能恶化,地高辛

可因心肌局部浓度升高出现毒性反应, 正性肌力药物易诱发室性心律失常, 均应避免使用[11]。 β 受体阻滞剂的使用存在争议, 但对于合并快速房颤且血压可耐受的患者, 小剂量使用可能改善血流动力学状态[12]。

4.3. 降低栓塞性猝死风险

AL 型心脏淀粉样变性患者血栓栓塞风险增加, 不仅因房颤, 还因心房功能障碍和血液高凝状态。抗凝决策应个体化评估而非严格依据 CHA₂DS₂-VASc 评分。建议房颤患者均应抗凝除非有绝对禁忌症, 窦性心律但有心房功能障碍或既往栓塞史者应考虑抗凝。新型口服抗凝药可能优于华法林, 大出血风险更低[13]。

5. 展望

AL 型心脏淀粉样变性因其快速进展和较差预后, 特别是猝死这一致命并发症, 给临床管理带来巨大挑战。构建有效的预防策略体系是当前研究的重点和临床实践的迫切需求。基于 AL 型心脏淀粉样变性从病理生理机制到临床表现的全程认识, 后续可结合 AL-CA 病理生理特征与临床实践, 在 Mayo 分期(基于肌钙蛋白、NT-proBNP)基础上, 整合心脏磁共振(CMR)细胞外容积分数(ECV)、超声整体纵向应变(GLS)等影像学参数, 尝试建立“临床-生物标志物-影像学”三维风险分层模型, 实现个体化预防干预, 目前可进行分层递进的预防策略: 在疾病早期, 关键在于提高识别能力, 通过优化诊断流程和生物标志物筛查实现早期发现; 在治疗层面, 以血液学治疗为核心, 控制轻链产生和淀粉样蛋白沉积, 目前对于 AL 淀粉样变性血液方面治疗处于完善阶段, 达雷妥尤单抗这种新兴药物的出现, 明显改善了疾病的缓解程度; 当心脏功能受损时, 需要根据具体的病理生理机制, 个体化选择心律管理设备如 ICD 或起搏器。尽管现有证据显示器械治疗对总体生存期的改善有限, 但这主要反映了疾病的晚期特征——患者更多死于心力衰竭而非猝死。因此, 这些干预措施在提高生活质量和预防猝死方面仍具有重要价值。未来研究应聚焦于早期诊断, 制定个体化的综合治疗策略, 最终实现从被动治疗向主动预防的转变。

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