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弥漫性心肌纤维化诊治进展

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摘　要

在许多慢性心脏病中，由于胶原纤维在整个心肌过度沉积而导致弥漫性心肌纤维化。这种损伤是由于成纤维细胞对原纤维胶原周转调节的改变，促进心肌间质和心肌内血管周围I型和III型胶原纤维的过度沉积。现有证据表明，除了纤维沉积的程度外，胶原成分和纤维的物理化学性质也与弥漫性心肌纤维化对心力衰竭患者心脏功能和临床结果的有害影响有关。研究结果表明，心力衰竭患者存在弥漫性心肌纤维化的各种临床病理表型。本篇综述中，主要总结了目前关于心力衰竭中弥漫性心肌纤维化的机制、目前可用的和潜在的未来治疗策略，旨在个性化地预防和逆转心力衰竭患者弥漫性心肌纤维化。

关键词

弥漫性心肌纤维化，心力衰竭，诊断，治疗

Progress in Diagnosis and Treatment of Diffuse Myocardial Fibrosis

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Abstract

In many chronic heart diseases, diffuse myocardial fibrosis is caused by excessive deposition of collagen fibers throughout the heart muscle. This injury is due to the altered regulation of collagen turnover by fibroblasts, which promotes excessive deposition of type I and III collagen fibers in

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the myocardial interstitium and perivascular myocardium. The available evidence suggests that in addition to the extent of fiber deposition, collagen composition and the physicochemical properties of fibers are also associated with the detrimental effects of diffuse myocardial fibrosis on cardiac function and clinical outcomes in patients with heart failure. The results show that patients with heart failure have various clinicopathological phenotypes of diffuse myocardial fibrosis. In many chronic heart diseases, diffuse myocardial fibrosis is caused by excessive deposition of collagen fibers throughout the heart muscle. In this review, we summarize the current mechanisms of diffuse myocardial fibrosis in heart failure, current available and potential future treatment strategies, and aim to personalize the prevention and reversal of diffuse myocardial fibrosis in patients with heart failure.

Keywords

Diffuse Myocardial Fibrosis, Heart Failure, Diagnosis, Treatment

1. 引言

心肌梗死(Myocardial infarction (MI))后坏死心肌形成的宏观局灶性纤维化瘢痕，以及在非缺血性心肌病或 MI 后存活心肌中观察到的纤维化组织的弥漫性间质和血管周围沉积，称为弥漫性心肌纤维化[1]。首先，弥漫性心肌纤维化可在许多慢性心脏病和随着心力衰竭(HF) [2]而发展的许多全身性临床条件中检测到。第二，由于弥漫性心肌纤维化改变了细胞外基质(Extracellular matrix (ECM))的生物学作用，并扭曲了心肌结构和生理学，这种损伤损害了心脏功能，从而在 HF 的发展中发挥了关键作用，并导致 HF [3]患者的不良临床结果。在这方面，弥漫性心肌纤维化可被视为与 HF 负担增加相关的公共健康问题，尤其是老年人。因此，在精准心血管医学时代，了解弥漫性心肌纤维的发展和临床后果是一个真正的挑战。在这篇综述中，我们总结了导致弥漫性心肌纤维化机制的现有证据。

2. 心脏纤维化的机制

2.1. 心脏成纤维细胞的作用

弥漫性心肌纤维化过程的特征是存在活化的心脏成纤维细胞，其分泌大量 ECM 结构蛋白、酶、生长因子和细胞因子，进而导致原纤维胶原的细胞外加工发生变化，从而导致胶原纤维[4]的过度沉积。在这种情况下，常驻心脏成纤维细胞在纤维化过程中起着不可或缺的作用[5]。2016 年发表的一项研究表明，驻留的外膜成纤维细胞(心内脉管系统外膜中的成纤维细胞)和间质成纤维细胞约占小鼠心脏中非肌细胞的 20% [6]。值得注意的是，心脏成纤维细胞并不构成同一细胞群，其位置和胚胎起源存在差异[7]。

心脏成纤维细胞的激活包括大量变化，包括增殖和骨膜蛋白表达增加，内质网的广泛形成(合成活性成纤维细胞特征)和分化为肌成纤维细胞，其具有通过收缩聚合应力纤维的形成和 α 平滑肌肌动蛋白[8]的从头表达获得的平滑肌细胞的超微结构和表型特征。

2.2. 其他心脏细胞的作用

存在于心肌中的其他细胞类型，如心肌细胞、白细胞和内皮细胞(来自血管和淋巴管)，可通过分泌生

长因子、细胞因子、胶原和酶来促进弥漫性心肌纤维化，这些细胞可激活心肌成纤维细胞和/或影响胶原的转化和沉积[9] [10]。

2.3. 心脏成纤维细胞的活化

许多趋化因子、细胞因子和生长因子在受损心肌中分泌，并通过多种信号途径(例如 DAMP 依赖途径、炎症级联、机械敏感性机制和神经体液途径)刺激心脏成纤维细胞的活化[11]。

体外研究表明，血管紧张素 II 通过 1 型血管紧张素 II 受体激活心脏成纤维细胞增殖和分化为肌成纤维细胞，并增加胶原和生长因子的表达和分泌[12]。通过盐皮质受体的醛固酮信号传导也可促进弥漫性心肌纤维化[13]。除了驱动巨噬细胞向促纤维化表型[14]和诱导心肌细胞释放促纤维化介质外，醛固酮还直接刺激成纤维细胞增殖和胶原生成[15]。

2.4. 胶原周转的变化

活化的成纤维细胞还分泌因子，如血管紧张素 II [16]和 IL-11，这些因子以自分泌和旁分泌的方式起作用，以诱导心脏成纤维细胞增殖和分化为肌成纤维细胞，从而维持它们在促进受损心肌纤维化中的作用。

3. 心脏纤维化的有害影响

弥漫性心肌纤维化的发展导致心力衰竭和其他心脏并发症，最终导致心力衰竭进展和不良结局[17]。

4. 临床表现和预后

通过胶原沉积评估的弥漫性心肌纤维化程度与临床症状的严重程度、激素水平以及 HF 的收缩和/或舒张成像参数有关，而不考虑 HF [18] [19] [20] [21]的病因和类型。

此外，高水平的胶原沉积与 HF [22]患者住院、心脏事件和/或死亡的风险增加有关，胶原交联也被发现与 HF 患者的临床方面和预后有关。高水平的胶原交联与高血压病因的 HF 患者左心室舒张和收缩功能障碍的严重程度增加以及 HF 住院的风险增加相关[23]。严重胶原沉积和高交联的存在与心脏功能进一步受损以及这些患者因心衰住院和死亡的风险增加相关[24]。

5. 心脏纤维化的无创诊断

EMB 样本的组织病理学分析是诊断弥漫性心肌纤维化的金标准方法，但弥漫性心肌纤维的斑片状分布意味着 EMB 的主要局限性是代表性低，因此需要从不同的心室位置分析以提高诊断准确性。此外，其他原因(如操作员的经验、心脏病理学专业知识的可用性以及 EMB 结果对治疗的可疑影响)妨碍了心脏病患者常规实施 EMB。因此，尽管 EMB [25]相关的并发症发生率较低，但在临床实践中，这种侵入性手术并不是诊断弥漫性心肌纤维化的一种选择，已经开发出了替代的非侵入性方法。

5.1. 心血管磁共振

心血管磁共振(CMR)已被提出作为检测弥漫性心肌纤维化的成像方法。CMR 允许通过晚期钆增强技术表征局灶性替代性纤维化(主要是 MI 后的巨大病灶)。CMR 还允许通过使用根据患者红细胞压积调整的天然和对比后 T1 标测技术来确定细胞外体积分数(ECV)来表征弥漫性心肌纤维化[26]。

5.2. 心脏 CT

心脏 CT 的 ECV 成像依赖于与 CMR [26]的 ECV 图像相同的原理。在两项针对严重主动脉狭窄患者

的研究中，ECV-CT 显示与胶原沉积直接相关[27] [28]。

5.3. 超声心动图

斑点追踪超声心动图可以在节段和整体水平上评估心肌变形，从而可以对心肌组织进行表征。在这方面，胶原沉积与晚期 HF [29]和严重主动脉狭窄患者的心肌整体纵向应变的变化程度以及严重主动脉狭窄[30]患者的节段纵向应变变化程度有关。

5.4. 纤维胶原衍生肽

在许多提出的 HF 患者弥漫性心肌纤维化的循环生物标志物中，只有少数与细胞外胶原转换相关并通过特异性免疫测定评估的分子符合生物标志物的标准，包括生物标志物与组织学评估的心肌胶原沉积或胶原交联之间的关联的证明[31] [32]。例如，两种胶原衍生肽(I 型前胶原羧基端前肽(PICP)和 III 型前胶原氨基端前肽，PIIINP)的血清浓度与各种病因的 HF 患者心肌中胶原纤维的沉积直接相关[31]。

5.5. 蛋白质组生物标志物

使用蛋白质组学来表征与心脏疾病特异相关的纤维化亚蛋白质组，以及开发多组蛋白质组来捕获纤维化途径，将为弥漫性心肌纤维化的复杂性提供更全面的诊断观点。在这方面，2020 年发表的数据表明，具有不同心血管表型的患者具有不同的血浆蛋白质组谱[33]，这可能是与弥漫性心肌纤维化相关的不同生物学途径的基础。

6. HF 疗法的抗纤维化作用

6.1. 临床证据

临床研究的组织学证据表明，某些 HF 疗法具有抗纤维化作用(TABlE 2)。在患有或不患有 HF 的患者中，使用血管紧张素转换酶抑制剂(如赖诺普利) [34]、血管紧张素 II 受体阻断剂(如氯沙坦) [35]或盐皮质激素受体拮抗剂(如螺内酯) [36]治疗可减少胶原沉积，降低左心室硬度并改善左心室舒张功能。

6.2. 实验证据

已在弥漫性心肌纤维化动物模型中研究了用于治疗 HF 患者的多种药物。尼泊尔赖氨酸抑制剂－血管紧张素受体阻断剂 sacubiril-缬沙坦减少了梗死心肌远端和边缘区域的胶原沉积，并改善了 MI [37]后心衰大鼠的左心室收缩功能障碍。盐皮质激素受体拮抗剂依普利酮完全阻止了心房利钠肽缺乏的小鼠因压力过载而导致的胶原沉积增加和左心室收缩功能障碍[38]，β 受体阻滞剂美托洛尔治疗犬冠状动脉内微栓子诱导的 HFrEF 与胶原沉积减少和 LVEF [39]增加相关。

7. 总结

心衰是世界范围内日益普遍的健康问题，尤其是老年人。HF 对心脏本身和其他器官的有害影响突出了 HF 的医学重要性，尽管目前有可用的治疗方法，但这些患者的发病率和死亡率随后较高。越来越多的证据表明，弥漫性心肌纤维化对心力衰竭患者的临床演变产生不利影响，并代表了这些患者护理中未满足的公共卫生需求。事实上，过去 20 年发表的研究表明，弥漫性心肌纤维化是由心脏病特异性细胞生物学和病理生理学引起的复杂实体，表现为多种临床病理表型[17]。因此，弥漫性心肌纤维化的预防和治疗应基于对这种异质性的识别，并旨在实施 HF 患者的个性化治疗。需要进一步的研究来考虑这种基于精确医学的方法，以从心肌肌成纤维细胞特异性改变发展为针对 HF 和弥漫性心力衰竭患者的定制生物标志物和治疗心肌纤维化。

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