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心脏类器官在心血管疾病建模与中医药研究中的应用进展

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摘要 心血管疾病是全球首位致死致残原因，传统二维细胞培养与动物模型在模拟人类心脏复杂微环境方面存在局限。心脏类器官作为源自多能干细胞的体外 3D 自组织“微型心脏”，是更接近人类心脏生理与病理状态的人源性平台。本文梳理了心脏类器官的现有平台谱系，其在心肌梗死、心肌病、心律失常、先天性心脏病、心力衰竭、心肌纤维化、糖尿病相关的心血管并发症、杜氏肌营养不良症及药物心脏毒性等各类心血管相关疾病的建模方法；以及在中医药研究中的应用，包括药效评价与机制解析、中药活性成分筛选与靶点发现以及药物心脏安全性评估等方面，以期为相关研究提供参考。

关键词 心脏类器官;心血管疾病;疾病建模;中医药

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Advances in the application of cardiac organoids in cardiovascular disease modeling and traditional Chinese medicine research

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Abstract Cardiovascular diseases represent the leading cause of global mortality and disability. However, traditional two-dimensional cell culture systems and animal models exhibit inherent limitations in recapitulating the intricate microenvironment of the human heart. As three- dimensional self-organized “miniature hearts” derived from pluripotent stem cells, cardiac organoids offer a human-derived experimental platform that more closely approximates the physiological and pathological states of the human heart. This review systematically outlines the current spectrum of cardiac organoid platforms, as well as their application in modeling a diverse array of cardiovascular-related disorders, including myocardial infarction, cardiomyopathy, arrhythmias, congenital heart disease, heart failure, myocardial fibrosis, diabetes-associated cardiovascular complications, Duchenne muscular dystrophy, and drug-induced cardiotoxicity. Additionally, the utility of cardiac organoids in traditional Chinese medicine (TCM) research is discussed, encompassing efficacy evaluation and mechanistic analysis, screening of TCM active ingredients and target discovery, and assessment of cardiac safety of TCM-derived drugs. This review aims to provide a reference for relevant research endeavors.

Key words cardiac organoids; cardiovascular diseases; disease modeling; traditional Chinese medicine

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心血管疾病（cardiovascular disease，CVD）作为全球发病率和病死率最高的疾病类别之一，严重威胁人类生命健康[1]。传统细胞和动物模型在 CVD 研究中发挥重要作用，但在模拟人类心脏复杂的生理结构和病理过程方面存在局限[2]。细胞模型缺乏 3D 空间中细胞间的相互作用，难以真实再现心肌细胞（cardiomyocytes，CMs）的电生理和机械特性[3]；动物模型因物种差异限制了临床转化性。心脏类器官作为新兴模型，可以体外重现心脏的组织结构和细胞多样性，展现多细胞的空间组织和功能协同[4]，适合模拟人类心脏组织的病理生理特征[5]。其不仅具备自主收缩和电生理活动，还能模拟心脏的发育过程及病理状态，为研究心脏疾病的发生机制、筛选治疗药物提供了更为人性化的平台[4]。随着人诱导多能干细胞（human induced pluripotent stem cells，hiPSCs）技术的成熟，可利用患者来源细胞构建具有个体遗传背景的心脏类器官，为精准医疗和个体化药物筛选奠定了基础[6-8]。心脏类器官构建方法主要包括自组装、组织工程、3D 及 4D 打印和微流控[9-11]，现已用于心肌梗死（myocardial infarction，MI）、心肌病、心律失常、先天性心脏病、心力衰竭（heart failure，HF）、心肌纤维化（myocardial fibrosis，MF）、糖尿病相关的心血管并发症、杜氏肌营养不良症（duchenne muscular dystrophy，DMD）及药物心脏毒性等多种 CVD 建模[12-14]。并具有较好的临床转化前景，如 4D 生理适应性心脏贴片治疗 MI，心脏类器官移植治疗缺血再灌注损伤（ischemia/reperfusion injury，I/R）等[15,16]。

中医药防治 CVD 具有多成分、多靶点、多通路协同调控的特点。现有研究提示，部分中药单体及经典复方可通过调控氧化应激、炎症反应、线粒体稳态、Ca^{2+}稳态、自噬/铁死亡、细胞凋亡以及血管生成等过程，发挥改善心肌缺血、减轻心肌损伤、抑制心室重构和保护心功能等作用[17-22]；但其疗效与安全性仍受药物组成、剂量、给药方式、制剂工艺及个体差异等因素影响，相关结论需更多高质量临床研究加以验证。心脏类器官为中医药现代化研究提供了更接近人源生理和病理状态的体外平台[17,23]。该平台有助于降低种属差异带来的外推偏倚，并为活性成分筛选、复方配伍优化、药效-毒性并行评价及作用机制解析提供更具可重复性和可量化的实验基础[24-26]。本文旨在系统综述心脏类器官疾病模型构建方法及其在中医药领域的应用，以期为相关研究提供参考。

1.心脏类器官的平台谱系

1.1 自组装/自组织

自组织法依托干细胞内在分化程序与细胞间相互作用，在 3D 空间中形成多细胞层次和结构，模拟心脏发育与组织结构[27]。以人胚胎干细胞（human embryonic stem cells，hESCs）为例，通过激活素 A、骨形态发生蛋白 4（bone morphogenetic protein 4，BMP4）、成纤维细胞生长因子 2（fibroblast growth factor 2，FGF2）及 Wnt 通路等分步诱导分化，可获得节律收缩、含平滑肌与内皮细胞（endothelial cells，ECs）的心脏类器官[28]。自组织的心脏类器官能较好地再现胚胎期心脏的多细胞相互作用及空间构型，展现心房和心室腔室的分布、前心包器官形成及视黄酸（retinoic acid，RA）介导的空间模式化等关键发育过程[29]。优势为可最低限度减轻外部干预，细胞自发地完成组织分化和空间重构[9]。但存在如类器官规模受限、中心区域可能发生坏死、功能成熟度不足以及难以实现长期传代等问题[28,30]。

1.2 组织工程法

组织工程法是指利用组织工程技术和生物材料来创建 3D 组织和器官模型的一种方法，其核心逻辑为依托人造骨架，实现心脏组织的工程化构建[31]。利用组织工程法构建的工程化心脏组织(engineered cardiac tissue，EHT)，具有良好的生物可降解性和可控的物理性能[32]。EHT 类型包括带

状、环形、贴片、薄膜、球状体、空心球形室和管状[33]。工程心脏类器官为通过宏观空间控制和可调材料特性研究心脏发育和疾病提供了极佳平台，但也存在局限：细胞种类单一难以还原真实心脏细胞网络；微观结构仿生精度不足，生理功能还原度有限；部分模型存在血管化缺失、营养运输不足等问题[27]。可通过多细胞模块精准组装、血管化网络构建及微观结构仿生设计，提升模型的生理相关性与应用价值。

1.3 3D 及 4D 生物打印技术

生物打印是一种多功能技术，结合活细胞和生物材料，制造类似原生组织的多维活体结构[34]。3D 生物打印可利用 hiPSCs 分化的心肌细胞（human induced pluripotent stem cell-derived cardiomyocytes，hiPSC-CMs）、ECs 与基质细胞，结合脱细胞化细胞外基质（extracellular matrix，ECM）、明胶/海藻酸盐及微凝胶等生物墨水构建心脏类器官[35-38]。4D 生物打印是从静态制造向动态响应性的转变，实现了可编程的形状变形、机械调校和功能变换，赋予支架自形变、选择性收缩与生理自适应能力[38,39]。基于聚乳酸-乙醇酸共聚物纳米-微纤维气凝胶、光固化弹性水凝胶及 ECM-聚(N-异丙基丙烯酰胺)温敏复合架，分别利用其形状记忆、光编程刚度调控和温敏收缩补偿功能，为层级血管网络的构建提供多材料策略[15,40,41]。生物打印通过精准调控材料微环境、空间结构与动态行为，提升了心脏类器官的生理仿真度与功能完整性，为心脏疾病机制解析、个性化药物筛选与再生修复移植提供了创新平台。但也存在血管化、细胞成熟度、打印精度与规模化矛盾、材料性能及临床转化壁垒等方面的不足。

1.4 微流控器官芯片

微流控器官芯片是融合微流控技术与类器官培养的新型平台，核心特征是通过微米级通道网络模拟体内生理微环境，实现对培养条件的精准调控[42,43]。通过微尺度通道网络构建可控灌流系统，使流体剪切力、周期性牵张、氧/营养梯度及代谢交换能够被精确调节[44-46]。可实时监测心肌收缩、电生理活动和药物反应，也便于纳入辅助细胞，从而更完整地重建心脏组织的细胞异质性与病理反应[47]。局限性包括芯片制造对设备要求、技术门槛与成本较高，推广难度较大[48]。平台谱系图见图 1。

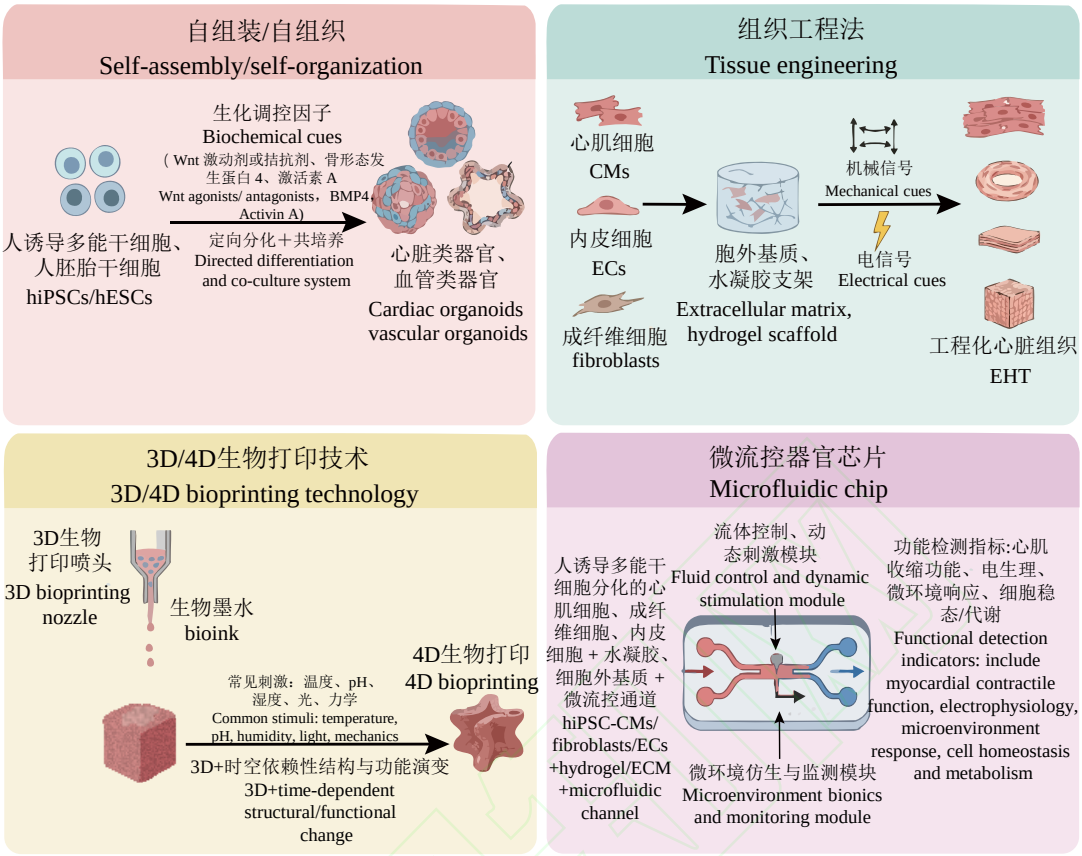

图 1 心脏类器官的平台谱系
Figure1 Cardiovascular organoids platform lineage

2.心脏类器官在疾病建模中的应用

2.1 心肌梗死

MI 是全球范围内导致 CVD 相关死亡的首要原因之一。传统造模方式有冠脉结扎、I/R 诱导等动物模型，及原代 CMs 缺氧复氧、氧糖剥夺/复氧等细胞模型[49]。类器官模型构建方法如下：Richards 等[50]用缺氧环境联合去甲肾上腺素（norepinephrine，NE）持续处理构建 MI 复合病理模型；Song 等[51]用氯化钴（$CoCl_2$）联合葡萄糖剥夺模拟急性心梗（acute myocardial infarction，AMI）缺血缺氧微环境；Khalil 等[52]将微流控共培养体系中的心脏细胞置于局部缺氧环境，并结合缺氧成纤维细胞（fibroblasts，FBs）与常氧 CMs 的旁分泌互作，构建 MI 边界区炎症与纤维化复合模型；Rexius-Hall 等[53]通过微流控芯片对工程化心肌组织线性氧梯度处理，模拟 MI 后缺氧-常氧交界的边界区微环境。

2.2 心肌病

心肌病是以心肌结构与功能异常为特征的异质性疾病[54,55]。传统造模以多柔比星（doxorubicin，DOX）、压力负荷、基因修饰等动物模型，以及氧化应激、药物损伤、基因干预等细胞模型为主。类器官模型构建方法如下：Li 等[56]通过 *C10orf71* 突变的 hiPSCs 定向分化并自组装，构建模拟扩张型心肌病模型；Wang 等[57]将 *TAFAZZIN* 突变患者的 CMs 定向分化后纯化，自组装形成层状心肌组织片，构建心肌芯片模型，构建 Barth 综合征线粒体心肌病模型；Pocock 等[58]将携带桥粒斑蛋白（desmoplakin，DSP）突变的患者来源 hiPSCs 定向分化后自组装成心脏类器官，构建模拟 DSP 心肌病模型；Filippo 等[59]将 *MYH7 R719Q* 突变患者来源 hiPSCs 分化后与人心脏微血管内皮细胞（human cardiac microvascular endothelial cells，HCMECs）/人心脏成纤维细胞（human cardiac fibroblasts，HCFs）共培养自组装，构建模拟肥厚型心肌病的模型。

2.3 心律失常

心律失常是指心脏冲动频率、节律、起始点、传导速度或兴奋顺序的异常[27]。动物模型构建方式有程序性电刺激/快速起搏、药理诱导和基因编辑；细胞模型常用急性分离原代 CMs 进行膜片钳记录，或借助异源表达体系评估单一离子通道的药理学效应。类器官模型构建方法如下：Pocock 等[58]将人多能干细胞（human pluripotent stem cells，hPSCs）敲除 *CASQ*2 后分化为心脏类器官，构建模拟儿茶酚胺敏感性多形性室速相关肌浆网 Ca^{2+}处理缺陷的心律失常模型，适用于单基因遗传性心律失常的基础机制研究；Williams 等[60]将健康人 hiPSC-CMs 与 HCFs 复合纤维蛋白水凝胶接种于类器官芯片，经甲基-β-环糊精（Methyl-β-cyclodextrin，MBCD）诱导，构建模拟获得性心律失常模型，适用于获得性复杂性心律失常的病理生理研究；Ghosheh 等[61]将 hiPSCs-CMs 与大鼠原代心脏微血管内皮细胞（primary rat cardiac microvascular endothelial cells，rCMECs）混于基质胶中，自组织后结合芯片实时监测，通过抑制线粒体钙单向转运体（mitochondrial calcium uniporter、MCU）、CRISPR/Cas9 敲低 MCU 及米托蒽醌诱导，构建心律失常模型，适用于代谢-电活动耦联机制研究；Goldfracht 等[62]将 hESCs 分化为纯化心房肌或心室肌细胞，包埋于胶原水凝胶，构建模拟心房颤动模型，适用于房颤的折返性心律失常机制研究，以及心房选择性抗心律失常药物的药效与安全性评价；O'hern 等[63]将基线心脏类器官分次整合同源卵黄囊样 $CD14^+$ 单核细胞，分化成人心脏-巨噬细胞组装体，慢性促炎刺激诱导，构建模拟慢性炎症驱动房颤样心律失常模型，适用于炎症驱动房颤的免疫-心脏互作机制研究。

2.4 先天性心脏病

先天性心脏缺陷是人类最常见的先天缺陷类型[64]。传统造模主要依赖基因编辑动物、药物诱导致畸及原代 CMs 培养。类器官模型构建方法如下：Kostina 等[64]将 hiPSCs 通过 Wnt 调控自组装构建心脏类器官，采用高糖高胰岛素（insulin，Ins）培养基，构建先天性心脏病模型；Drakhlis 等[65]将 hPSCs 聚集体包埋于基质胶中，经 Wnt 通路调控自组织形成心脏类器官，并通过 *NKX*2.5 基因敲除，构建复现心肌致密化障碍、肌节排列紊乱及 CMs 肥大等表型的先天性心脏畸形模型；Feng 等[66]调控 Wnt/RA 信号将 hiPSCs 分化为心房/心室型心脏类器官，通过基因编辑技术引入 *NKX2*-5 c.673C>A 相关变异，结合单细胞转录组与机器学习标签迁移，构建先天性心脏病模型。Meier 等[67]用携带 *PTPN*11 突变的努南综合征患者来源 hiPSCs 构建心外膜类器官，构建复现 CMs 过度增殖、早期间质纤维化及肌成纤维细胞激活的先天性心肌肥厚模型。

2.5 心力衰竭

HF 是一种病因多样的 CVD，是全球主要的死亡原因之一[68]。心衰的传统模型主要包括压力负荷、缺血损伤、药物诱导、转基因等动物模型及血管紧张素 II（Angiotensin Ⅱ，AngⅡ）、缺氧等刺激的细胞模型。类器官模型构建方法如下：Haim 等[69]将健康人来源的 hiPSCs 分化为 CMs 并自组装形成心脏类器官，在成熟培养基中，联合施加高糖+Ins 剥夺、AngⅡ+内皮素-1（endothelin-1，ET-1）以及白细胞介素-1β（interleukin-1β，IL-1β）+干扰素-γ（interferon-γ，IFN-γ），构建模拟射血分数保留型心力衰竭（heart failure with preserved ejection fraction，HFpEF）模型；Yao 等[70]将健康人来源的 hiPSCs 经分化自组装成心脏类器官，加以 DOX 处理，构建心肌损伤、炎症、凋亡及纤维化的 HF 模型；Tiburcy 等[71]将 hESCs/hiPSCs 来源的 CMs 与人包皮成纤维细胞（human foreskin fibroblasts，HFFs）混合，在柔性硅胶柱上构建工程化心脏类器官并加以 NE 处理，构建 HF 模型。

2.6 心肌纤维化

MF 是一种由多种疾病诱发的病理，是最常见的心脏异常之一[72]。传统造模以主动脉缩窄、冠状动脉左前降支结扎、异丙肾上腺素诱导等动物模型，以及转化生长因子-β1（transforming growth factor-beta 1，TGF-β1）、AngⅡ等刺激 FBs 的体外模型。类器官模型构建方法如下：Song 等[51]用心脏类器官模拟 AMI 的缺氧缺血微环境，并用 TGF-β1 诱导，构建 I/R 后继发性 MF 模型；Burrello 等[73]通过共培养构建心脏类器官，用原发性醛固酮增多症（primary aldosteronism，PA）患者血清或醛固酮干预，构建模拟醛固酮介导 MF 模型；Hua 等[74]将 hiPSCs 经拟胚体阶段定向分化为心脏类器

官，以白细胞介素-17A（interleukin-17A，IL-17A）诱导建立炎症性 MF 模型；Yang 等[75]将 hiPSCs 分步诱导为血管球体与 CMs 共组装，通过药物驱动血管化形成血管化腔室心脏类器官，以预冷针头进行局部冷冻损伤模拟 MI，并用卡托普利处理，构建可模拟 MI 后纤维化的模型；Basara 等[76]利用 hiPSCs 来源的衰老 CMs、FBs、ECs 与肌成纤维细胞，结合生物墨水，通过 3D 生物打印构建心梗后 MF 模型。

2.7 杜氏肌营养不良症

DMD 以进行性肌无力和肌肉退变为特征，累及骨骼肌和心肌[77, 78]。DMD 传统模型主要包括基因编辑小鼠以及大型动物/转化模型；体外常用 DMD 患者来源 hiPSCs 分化的骨骼肌细胞和 CMs。类器官模型构建方法如下：Kim 等[79]通过将 DMD 患者来源的 hiPSCs，自组装成心脏类器官，将其负载于集成可变形微电极阵列中进行长期功能表征，构建 DMD 相关扩张型心肌病心脏类器官模型；Marini 等[36]将 DMD 患者来源的 hiPSCs 在琼脂糖微孔模具中定向分化、自组装成心脏类器官，并采用 3D 生物打印技术包埋于复合水凝胶中制备成可融合的结构化构建体，构建模拟 DMD 相关 CMs 凋亡、ECM 纤维化沉积等表型。

2.8 糖尿病相关的心血管并发症

糖尿病相关的心血管并发症是指长期高血糖及 Ins 抵抗导致的心脏和血管系统损伤，主要包括冠状动脉粥样硬化性心脏病、心肌病、高血压、HF 及周围血管病变，是糖尿病患者致死、致残的首要原因[80]。糖尿病心血管并发症的传统造模以链脲佐菌素诱导、高脂饮食及遗传动物模型，以及联合高糖、棕榈酸酯或缺氧/复氧处理的细胞模型。类器官模型构建方法如下：Liu 等[81]将 hPSCs 定向分化为交感神经节类器官与心脏形成类器官，通过物理融合构建具有功能性交感神经支配的交感-心脏组装类器官，以高糖培养基诱导模拟糖尿病环境，构建复现心脏自主神经纤维退变、神经元凋亡及心肌调控异常的体外糖尿病性心脏自主神经病变模型；Mellor 等[82]以 hiPSCs 定向分化为 CMs，自组装成工程化心脏类器官，以高糖诱导构建糖尿病心肌病体外模型。

2.9 其他疾病

除上述疾病模型外，心脏类器官亦被广泛用于药物心脏毒性、肌强直性营养不良 1 型（myotonic dystrophy type 1，DM1）、I/R 以及获得性心肌肥厚等多种疾病建模。例如，Yang 等[75]以梯度浓度的 DOX 处理血管化腔室心脏类器官，构建可检测临床前药物剂量与时间依赖性心脏毒性的体外筛查平台；Liang 等[83]通过悬滴法形成拟胚体，自组织构建出腔室样血管化心脏类器官，并用替莫唑胺进行梯度浓度与时间依赖性毒性诱导，构建可模拟化疗药物心脏毒性及评估药物安全性风险的体外模型；Jajkiewicz 等[84]将 DM1 患者来源 hiPSCs 经腔室特异性定向分化方案，分别自组装成左心室和心房类器官，构建 DM1 心脏类器官模型；并将 DM1 左心室与心房类器官共培养，复现了心腔间电-机械整合障碍；Parker 等[85]将心脏类器官于无糖、低 pH 缺氧培养基中，并缺氧复氧处理，构建 I/R 模型；Meier 等[67]通过时序信号调控 RA 诱导 hPSCs 构建心外膜类器官，并以 ET-1 持续处理，构建心肌肥大模型。上述研究充分体现心脏类器官在药物毒性筛查、遗传多系统疾病、I/R 模拟及获得性心肌肥厚建模等多元化疾病场景中的适用性。

心脏类器官可在 3D 多细胞结构中重现部分 CVD 相关病理表型，并在一定程度上保留心肌组织的代谢、收缩、舒张及电生理等生理特征，具有较高的人源化程度和可控的遗传背景；但同时也存在细胞成熟度不足、免疫-血管-神经微环境及循环血流动力学缺失、长期慢性病程和复杂共病模拟不足、以及批次差异和通量有限，不能完全覆盖疾病的完整病理网络等问题。心脏类器官在心血管疾病建模中的应用概览见表 1。

表1 心脏类器官在心血管疾病建模中的应用概览

Table 1 Overview of cardiac organoids in cardiovascular disease modeling applications

疾病 Disease	培养体系/平台 Culture system/Culture platform	类器官构建策略 Organoid construction strategy	疾病建模方法 Disease modeling method	优势 Advantages	局限 Limitations
心肌梗死[50] MI	自组装/自组织 Self-assembly/self-	人源多细胞共培养，非黏附水凝胶模具自组装	10%缺氧环境+1 μmol/L 去甲肾上腺素处理 10 d	基于 3D 营养梯度；具有重现心梗核心病理	缺乏免疫、炎症细胞；细胞成熟度低

疾病 Disease	培养体系/平台 Culture system/Culture platform	类器官构建策略 Organoid construction strategy	疾病建模方法 Disease modeling method	优势 Advantages	局限 Limitations
	organization	Human multicellular co-culture, self-assembly in non-adhesive hydrogel molds	Treated with 10% hypoxia combined with 1 μmol/L NE for 10 d	Based on three-dimensional nutrient gradient; it can recapitulate the core pathological features of myocardial infarction	Lack of immune and inflammatory cells; low cellular maturity
心肌梗死[52] MI	微流控芯片 Microfluidic chip	微流控芯片+三腔室分区共培养 Microfluidic chip+three-chamber compartmentalized co-culture	调控氧梯度 Regulate oxygen gradient	时空精准控制氧梯度；高度重现心梗边界区旁分泌互作 Spatio-temporally precise control of oxygen gradient	细胞组分单一；仅模拟急性期 Single cell component; only simulates the acute phase
心肌梗死[53] MI	组织工程+微流控芯片 Tissue engineering+microfluidic chip	大鼠工程化心肌组织+微流控芯片 Rat engineered cardiac tissue+microfluidic chip	0%~20%线性氧梯度持续处理 4 h Continuous treatment with a linear oxygen gradient of 0%~20% for 4 h	时空精准调控氧梯度，真实模拟心梗边界区微环境 Spatio-temporally precise regulation of oxygen gradient; authentically mimics the microenvironment of myocardial infarction border zone	物种差异；细胞组分单一 Species differences; single cell component
心肌梗死/心肌纤维化[51] MI/MF	自组装/自组织 Self-assembly/self-organization	中胚层诱导联合多谱系分化策略 Mesoderm induction combined with multi-lineage differentiation strategy	50 μmol/L 氯化钴+葡萄糖剥夺，再转化生长因子-β1 诱导 7 d 50 μmol/L $CoCl_2$ plus glucose deprivation, followed by TGF-β1 induction for 7 d	多细胞谱系，可复现缺血再灌注的连续病理过程 Multicellular lineages and recapitulating the continuous pathological process of I/R	细胞组分不完整：细胞成熟度低 Incomplete cellular components; low cell maturity
心肌梗死/心肌纤维化[75] MI/MF	自组装/自组织 Self-assembly/self-organization	纯化心肌细胞包裹血管谱系球，经梯度诱导血管网络自组织 Purified CMs encapsulating vascular lineage spheroids undergo gradient-induced self-organization of vascular networks	局部冷冻损伤，再卡托普利（20 mmol/L）处理 3 d Local cryoinjury, followed by treatment with captopril (20 mmol/L) for 3 d	具有血管化腔室结构，多细胞互作 Possesses vascularized chamber structure and multicellular interactions	缺免疫细胞；细胞成熟度低 Lack of immune cells; low cell maturity
扩张型心肌病[56] Dilated cardiomyopathy	自组装/自组织 Self-assembly/self-organization	时序化心肌定向分化自组装 Temporally sequential directed differentiation and self-assembly of cardiomyocytes	*C10orf*71 纯合/杂合突变人诱导多能干细胞定向分化 *C10orf*71 homozygous/heterozygous mutant hiPSCs directed differentiation	遗传精准性高；患者来源；多功能表征 High genetic precision;patient-derived; multifunctional characterization	细胞组分单一；无循环微环境 Single cell component; no circulating microenvironment
Barth 综合征线粒体心肌病[57] Barth syndrome-related mitochondrial cardiomyopathyv	组织工程+微流控芯片 Tissue engineering+microfluidic chip	*TAFAZZIN* 突变心肌细胞经磁分选富集后自组装 Self-assembly of *TAFAZZIN* mutant cardiomyocytes enriched by magnetic cell sorting	*TAFAZZIN* 突变患者人诱导多能干细胞遗传模型 Genetic model of *TAFAZZIN*-mutant patient-derived hiPSCs	遗传精准性高；患者来源；多功能表征 High genetic accuracy; patient-derived; multifunctional characterization	细胞成熟度有限；组织组分单一 Limited cell maturity; simple tissue composition
桥粒斑蛋白心肌病[58] DSP cardiomyopathy	自组装/自组织＋组织工程 Self-assembly/self-organization＋tissue engineering	桥粒斑蛋白突变患者人诱导多能干细胞定向分化+胶原 I/基质胶+代谢成熟+定向成熟 Directed differentiation of DSP mutant patient-derived hiPSCs+collagen I/matrigel+metabolic maturation+directed maturation	患者来源的人诱导多能干细胞遗传模型 Patient-derived hiPSCs genetic model	高通量与可重复性；患者来源 High throughput and reproducibility; patient-derived	成熟度低；仅反映早期表型 Low maturity; only reflects early phenotypes
肥厚型心肌病[59] Hypertrophic cardiomyopathy	自组装/自组织 Self-assembly/self-organization	人诱导多能干细胞分化的心肌细胞/人心脏微血管内皮细胞/人心脏成纤维细胞（3:5:2）悬滴共培养 hiPSC-CMs/HCMECs/HCFs (3:5:2) co-cultured via hanging drop	患者人诱导多能干细胞分化的心肌细胞遗传模型 Genetic model of patient-derived hiPSC-CMs	三细胞互作；患者来源 Three-cell interaction; patient-derived	细胞成熟度低；细胞组分单一且异源 Low cell maturity; single and heterogeneous cell composition
心律失常[58] Arrhythmia	自组装/自组织＋组织工程 Self-assembly/self-organization＋tissue engineering	基因编辑敲除 *CASQ2* 或敲入 *RYR2*-*R*74*Q* 的人多能干细胞（健康人）+胶原 I/基质胶+代谢成熟+定向成熟 Gene-edited healthy human hPSCs with *CASQ*2 knockout or *RYR*2-*R*74*Q* knock-in,	基因编辑 Gene editing	功能性肌浆网成熟度高；表型明确；人源化 High functional sarcoplasmic reticulum maturity; well-defined phenotype; humanized	仅反映早期表型；遗传背景单一 Only reflects early phenotypes; single genetic background

疾病 Disease	培养体系/平台 Culture system/Culture platform	类器官构建策略 Organoid construction strategy	疾病建模方法 Disease modeling method	优势 Advantages	局限 Limitations
		collagen I/matrigel+metabolic maturation +directed maturation			
心律失常[60] Arrhythmia	组织工程+微流控芯片 Tissue engineering+microfluidic chip	人诱导多能干细胞分化的心肌细胞/人心脏成纤维细胞（3:1）于纤维蛋白水凝胶+芯片微孔体系 hiPSC-CMs/HCFs (3:1) encapsulated in fibrin hydrogel+microfluidic chip microwell system	甲基-β-环糊精连续处理 5 d Continuous MBCD treatment for 5 d	功能评估全面且表型可逆；复现进展性复杂性心率失常 Comprehensive functional evaluation with reversible phenotypes; recapitulation of progressive complex arrhythmia	缺乏腔室与细胞类型特异性；心率失常类型单一 Lack of chamber and cell type specificity; single type of arrhythmia
心律失常[61] Arrhythmia	自组装/自组织 Self-assembly/self-organization	人诱导多能干细胞分化的心肌细胞+大鼠原代心脏微血管内皮细胞+基质胶注入微孔阵列 hiPSC-CMs+rCMECs+matrigel injected into microwell array	线粒体钙单向转运体药理学抑制或基因敲除 Pharmacological inhibition or genetic knockout of MCU	多腔室结构；电-代谢-机械同步检测 Multichamber structure; simultaneous detection of electrophysiology-metabolism-mechanics	跨物种细胞组成；腔室形成可控性不足；缺免疫细胞 Cross-species cellular composition; insufficient controllability of chamber formation; lack of immune cells
心律失常[62] Arrhythmia	自组装/自组织＋组织工程 Self-assembly/self-organization+tissue engineering	人胚胎干细胞定向分化+胶原水凝胶注入环形模具 Directed differentiation of hESCs+collagen hydrogel injected into annular mold	心房工程化心脏组织自发折返性心律失常 Atrial EHT spontaneous reentrant arrhythmia	自发房颤模型：具备机械功能评估能力 Spontaneous atrial fibrillation model; Capable of mechanical function evaluation	心肌细胞缺 T 管；电复律后易复发 CMs lack T-tubules; high recurrence susceptibility after electrical cardioversion
心律失常[63] Arrhythmia	自组装/自组织 Self-assembly/self-organization	时序整合自体巨噬细胞到基线类器官 Temporally integrate autologous macrophages into baseline organoids	慢性炎症刺激 Chronic inflammatory stimulation	首纳入组织驻留巨噬细胞；发育时序与体内胚胎心脏一致 First incorporation of tissue-resident macrophages; developmental timeline consistent with that of the in vivo embryonic heart	缺乏募集型巨噬细胞和其他免疫细胞；无灌注血管网络 Lack of recruited macrophages and other immune cells; absence of perfused vascular network
先天性心脏病[64] Congenital heart disease	自组装/自组织 Self-assembly/self-organization	Wnt 通路时序调控定向分化 Temporal regulation of directed differentiation via Wnt signaling pathway	11.1 mmol/L 葡萄糖+高 Ins 处理 14 d 11.1 mmol/Lglucose combined with high insulin treatment for 14 d	多细胞类型；临床相关浓度建模 Multicellular composition; modeling at clinically relevant concentrations	发育阶段偏早期；缺乏母体-胎儿交互环境 Early-biased developmental stage; lack of maternal-fetal interactive microenvironment
先天性心脏病[65] Congenital heart disease	自组装/自组织 Self-assembly/self-organization	基质胶液滴包埋+Wnt 通路调控 Matrigel droplet embedding+Wnt pathway regulation	*NKX*2.5 基因敲除 *NKX*2.5 gene knockout	具有血管化与心内膜前体；高度模拟早期胚胎心脏与内胚层的共发育 Possessing vascularized and endocardial progenitors; highly mimicking the co-development of the early embryonic heart and endoderm	发育阶段早；前后轴发育不完善 Early developmental stage; imperfect anteroposterior axis development
先天性心脏病[66] Congenital heart disease	自组装/自组织 Self-assembly/self-organization	Wnt+视黄酸腔室特异性分化 Wnt+RA chamber-specific differentiation	*NKX2.5* c.673C>A 点突变 *NKX*2.5 c.673C>A point mutation	腔室特异性；高通量自组织腔室 Chamber specificity; high-throughput self-organized chambers	心肌成熟度低；结构异质性 Low cardiomyocyte maturity; structural heterogeneity
先天性心肌肥厚[67] Congenital myocardial hypertrophy	自组装/自组织 Self-assembly/self-organization	拟胚体＋阶段式定向分化 Embryoid body+staged directed differentiation	努南综合征 *PTPN*11 突变患者人诱导多能干细胞 Noonan syndrome *PTPN*11-mutant patient-derived hiPSCs	患者特异性；含间皮和间充质双层的心外膜室 Patient-specific; epicardial chamber containing mesothelial and mesenchymal bilayer	腔室结构不明显；内皮血管化不足 Poorly defined chamber structure; insufficient endothelial vascularization
射血分数保留型心力衰竭[69] HFpEF	自组装/自组织＋组织工程 Self-assembly/self-organization+tissue engineering	人诱导多能干细胞分化的心肌细胞＋牛胶原＋环形磨具 hiPSC-CMs+bovine collagen+annular mold	高糖 11.1 mmol/L+Ins 剥夺（糖尿病）、血管紧张素 II+内皮素-1 各 10 ng/mL（高血压）、白细胞介素-1β10 ng/mL+干扰素-γ 100 ng/mL（肥胖相关炎症），持续处理 7 d High glucose (11.1 mmol/L) combined with	多因素复合建模；关键表型复现 Multifactorial combined modeling; recapitulation of key phenotypes	细胞成熟度有限；无免疫细胞 Limited cellular maturity; absence of immune cells

疾病 Disease	培养体系/平台 Culture system/Culture platform	类器官构建策略 Organoid construction strategy	疾病建模方法 Disease modeling method	优势 Advantages	局限 Limitations
			insulin deprivation (diabetic condition); Ang Ⅱ and ET-1 each at 10 ng/mL (hypertensive condition); IL-1β at 10 ng/mL plus IFN-γ at 100 ng/mL (obesity-associated inflammation), with continuous treatment for 7 d		
心力衰竭[70] HF	自组装/自组织 Self-assembly/self-organization	U 形板拟胚体＋阶段式定向分化 U-shaped plate embryoid body+staged directed differentiation	多柔比星 10 μmol/L 处理 24 h DOX treatment at 10 μmol/L for 24 h	多细胞类型；表型全面 Multicellular composition; comprehensive phenotypes	无免疫细胞；暴露短；无血流动力学负荷 Absence of immune cells; short exposure duration; lack of hemodynamic load
心力衰竭[71] HF	组织工程 Tissue engineering	人诱导多能干细胞分化的心肌细胞/人包皮成纤维细胞 1:1，聚二甲基硅氧烷被动拉伸成熟 hiPSC-CMs/HFFs 1:1, polydimethylsiloxane passive stretch maturation	去甲肾上腺素处理 7 d NE treatment for 7 d	成熟度超过婴幼儿；表型全面 Exceeding infant maturity; comprehensive phenotypes	无血管网络；缺乏免疫细胞 Absence of vascular network; lack of immune cells
心肌纤维化[73] MF	自组装/自组织 Self-assembly/self-organization	人诱导多能干细胞分化的心肌细胞/人心脏成纤维细胞/人主动脉内皮细胞（hAECs，70:15:15）共培养 hiPSC-CMs/HCFs/ human aortic endothelial cells（hAECs，70:15:15) co-culture	醛固酮或原发性醛固酮增多症患者血清（10%）处理 7 d Aldosterone or serum from PA patients (10%) treatment for 7 d	人源化与多细胞组分；明确的病理表型 Humanized and multicellular components; distinct pathological phenotypes	先天免疫组分;处理周期短 Innate immune components; short treatment duration
心肌纤维化[74] MF	自组装/自组织 Self-assembly/self-organization	拟胚体＋阶段式定向分化 Embryoid body+staged directed differentiation	白细胞介素-17A 50 ng/ml 处理 7 d IL-17A treatment at 50 ng/mL for 7 d	复现炎症-纤维化耦联；人源化 Recapitulate inflammation-fibrosis coupling; humanized	诱导因素单一；缺乏免疫细胞组分 Single inducing factor; lack of immune cell components
心肌纤维化[76] MF	3D 生物打印 3D bioprinting	人诱导多能干细胞定向分化+挤出式 3D 生物打印 Directed differentiation of hiPSCs+extrusion-based 3D bioprinting	区域化细胞比例＋基质刚度＋细胞外基质梯度＋matrix stiffness＋ECM gradient Regional cell proportion	首现三区一体化老化心梗后模型；区域特异性表型 First establishment of a three-region integrated aged post-myocardial infarction model with region-specific phenotypes	缺乏免疫细胞；搏动成熟度低 Lack of immune cells; low beating maturity
杜氏肌营养不良症[79] DMD	自组装/自组织 Self-assembly/self-organization	上皮细胞重编程+阶段式分化 Epithelial cell reprogramming+staged differentiation	患者来源人诱导多能干细胞遗传模型 Patient-derived hiPSCs genetic model	患者个体化；精准表型复现 Patient individualization; precise phenotypic recapitulation	无免疫细胞；无法反映杜氏肌营养不良症多系统病理全貌 Absence of immune cells; unable to reflect the full multisystem pathological spectrum of DMD
杜氏肌营养不良症[36] DMD	自组装/自组织+3D 生物打印 Self-assembly/self-organization +3D bioprinting	琼脂糖模具自组装＋藻酸盐-明胶打印 Agarose mold self-assembly+alginate-gelatin bioprinting	患者来源人诱导多能干细胞遗传模型 Patient-derived hiPSC genetic model	严格遗传对照；均一性 Strict genetic control; homogeneity	无腔室/血管/神经；细胞成熟度低 No chambers/vessels/nerves; low cellular maturity
糖尿病性心脏自主神经病变[81] Diabetic cardiac autonomic neuropathy	自组装/自组织 Self-assembly/self-organization	交感神经节类器官与心脏类器共组装 Sympathetic ganglion organoids co-assembled with cardiac organoids	高糖培养基 High-glucose medium	体外交感-心脏双向支配；人缘性 Ex vivo sympathetic-cardiac bidirectional innervation; human relevance	发育阶段早；缺少副交感神经/免疫细胞 Early developmental stage; lack of parasympathetic nerves/immune cells
糖尿病心肌病[82]	组织工程	人诱导多能干细胞分化的心	高葡萄糖环境	表型模拟精准；人源化	细胞组分单一；病理因

疾病 Disease	培养体系/平台 Culture system/Culture platform	类器官构建策略 Organoid construction strategy	疾病建模方法 Disease modeling method	优势 Advantages	局限 Limitations
Diabetic cardiomyopathy	Tissue engineering	肌细胞自组装 hiPSC-CMs self-assembly	High-glucose environment	Precise phenotypic simulation; humanization	素简化 Single cell component; simplified pathological factors
药物心脏毒性[75] Drug-induced cardiotoxicity	自组装/自组织 Self-assembly/self-organization	定向分化+血管谱系诱导+共培养+梯度诱导 Directed differentiation+vascular lineage induction+co-culture+gradient induction	多柔比星 0.1~50 μmol/L 处理 24-72 h DOX treatment at 0.1-50 μmol/L for 24~72 h	腔室与血管化仿生；搏动率高 Chambered and vascularized biomimicry; high beating rate	微环境缺失；细胞构成偏离 Loss of microenvironment; deviation in cellular composition
化疗药物心脏毒性[83] Chemotherapy-induced cardiotoxicity	自组装/自组织 Self-assembly/self-organization	拟胚体＋阶段式定向分化 Embryoid body+staged directed differentiation	替莫唑胺 0.2~2 μg/mL 梯度处理＋时间梯度处理 Temozolomide gradient treatment at 0.2~2 μg/mL combined with time-gradient treatment	心肌细胞/心脏内皮细胞共分化；具有一定的腔室结构 CMs/cardiac endothelial cells（CECs）co-differentiation; with rudimentary chamber structure	心脏内皮细胞成熟度低；细胞组分单一 Low maturity of CECs; single cellular component
肌强直性营养不良 1 型[84] DM1	自组装/自组织 Self-assembly/self-organization	人诱导多能干细胞腔室特异性定向分化 Chamber-specific directed differentiation of hiPSCs	患者来源人诱导多能干细胞遗传模型 Patient-derived hiPSCs genetic model	腔室特异性建模；心室/心房类器官共培养 Chamber-specific modeling; co-culture of atrial and ventricular organoids	无血流动力学负荷；病理表型不全面 No hemodynamic load; incomplete pathological phenotype
缺血再灌注损伤[85] I/R	自组装/自组织 Self-assembly/self-organization	时序调控＋悬浮自组装 Temporal regulation+suspension self-assembly	无糖、低 pH 培养基＋缺氧 6 h 后复氧 Sugar-free, low pH medium+6 h of hypoxia followed by reoxygenation	患者来源：重复性好 Patient-derived; good reproducibility	成熟度低；无免疫细胞 Low maturity; absence of immune cells
获得性左心室肥厚[67] Acquired left ventricular hypertrophy	自组装/自组织 Self-assembly/self-organization	拟胚体＋阶段式定向分化 Embryoid body+staged directed differentiation	内皮素-1 25~50 nmol/L 处理 6 d ET-1 treatment at 25~50 nmol/L for 6 d	患者特异性；含间皮和间充质双层的心外膜室 Patient-specific; epicardial chamber containing mesothelial and mesenchymal double layers	腔室结构不明显；内皮血管化不足 Indistinct chamber structure; insufficient endothelial vascularization

3.心脏类器官在中医药领域的应用

中医药历史悠久，中药复方有多成分、多靶点、多通路的整体调节特性，难以通过单靶点、单机制的还原论评价体系加以验证。因此，现代中医药研究面临成分复杂、筛选模型不足、安全性评估难度较高、与化学药物相互作用研究不深等问题。现有模型具有一定局限性，而类器官平台可模拟人体微环境，为中医药研发提供创新平台[17]。类器官平台既保留了人源生理相关性，又具备高通量、可量化的技术特征，正逐步成为连接中医药传统整体观与现代精准评价的技术纽带。当前，基于类器官的中医药研究主要围绕药效评价与机制解析、活性成分筛选与靶点发现、药物心脏安全性评估 3 个方向展开。

3.1 药效评价与机制解析

心脏类器官在中药药效评价中的应用已从概念验证迈入实质性应用阶段。Fan 等[86,87]将新生大鼠心脏细胞自组装为心脏类器官，采用冠心宁注射液预处理后以苯肾上腺素损伤的建模方式，证实该药可抑制肥大、减少凋亡并保护线粒体功能，并结合 TAC 小鼠模型 RNA 测序锁定相关通路；该团队后续采用芪参益气滴丸与 AngⅡ共处理的建模方式，证实该药可抑制肥大、减轻纤维化，并结合动物 RNA 测序锁定并验证了骨膜蛋白及其下游通路。两项研究均以类器官作为药效评价工具和机制验证平台，形成宏观疗效、组学线索、微观机制验证、宏观确认的证据闭环。上述研究表明心脏类器官有望发展为中药心血管药效物质辨识与作用机制解析的重要实验平台。

3.2 中药活性成分筛选与靶点发现

心脏类器官具有细胞组成复杂性和功能可读出性，适用于复杂天然产物和中药复方中候选活性成分的筛选[88]。已有研究构建的 hiPSCs 来源心脏类器官可包含 CMs、心内膜/心外膜细胞及 FBs，并可自主搏动，从而更真实地反映药物对心脏组织整体功能的影响[24]。这类模型不仅适用于评价候选成分对收缩功能、节律稳定性和细胞存活的影响，也有助于发现细胞类型特异性的响应差异，为中药拆方

-组方-验证的研究路径提供支持[30,89]。如 Yao 等[70]将人 hiPSCs 定向分化为心脏类器官，以 DOX 诱导 HF 模型，通过网络药理学预测参附香芍汤的潜在活性成分及核心靶点，并在类器官中进行验证。该研究实现了虚拟筛选-湿实验验证的闭环，展示了类器官模型用于中药活性成分高效筛选与靶点发现的可行性。

3.3 药物心脏安全性评估

中药药物心脏毒性评价是制约其国际化应用的关键环节。传统模型由于物种差异和离子通道表达谱差异，往往难以准确预测人类心脏反应。hiPSCs 来源的心脏类器官可重现人源心肌的电生理活动，并结合多电极阵列对场电位时程、传导速度等指标进行连续监测，从而实现对潜在致心律失常风险的定量评估[89-91]。CiPA 等综合评估框架将离子通道实验、hiPSC-CMs 电生理测试与计算模型相结合，提高了风险预测可靠性；患者特异性 hiPSCs 的有助于比较不同遗传背景下的药物反应差异，为中药药物心脏毒性的个体化分层评价提供依据[92-95]。Liang 等[96]将 hESCs 定向分化为心脏类器官，以白花丹素处理建立心脏毒性模型，证实该成分可剂量依赖性地降低细胞活力、导致心肌结构蛋白丢失，并直接在人源模型中验证了毒性机制，呈现了毒性级联反应。其为中药活性成分的心血管安全性评估提供了从分子靶点到人源类器官再到整体动物的多层次评价范式。

相较于传统模型，心脏类器官具有更高的人源相关性，使中医药研究从经验描述迈向体外实证。但是心脏类器官在中医药研究中的应用仍处于早期阶段，且中医证候特征的表型尚未纳入建模体系[97]。心脏类器官在中医药研究中的应用主要集中于中药心脏毒性、药效及现代药理机制评价，尚缺乏以规范化临床辨证为基础、经多组学和方药反应性验证的中医证候相关心肌病理表型模型。未来应以临床证候特征为锚点，建立“临床证候解析-类器官表型重构-多维一致性验证-方药干预评价”的研究框架，推动心脏类器官在中医药“病-证-方药”关联研究中的应用。并应突破模型标准化、成熟度优化、功能性血管化及多器官串联等关键技术，推动高通量检测与多组学分析的深度融合，加速其在中医药现代化研究中的系统化应用与临床转化。

4.心脏类器官在再生领域中的应用

在再生医学领域，心脏类器官同样展现出广阔的应用前景。心脏类器官的临床转化核心方向之一是作为细胞移植载体。相较于传统单细胞悬液注射，类器官移植具有显著优势：细胞存活率更高、组织整合更好、移植细胞极化更可控。且心脏类器官可以提供原发 CMs 和心脏组织的很多生理、结构和遗传特性[98]。该策略有望缓解游离 CMs 移植后细胞滞留率低、失巢凋亡、成熟度不足以及局部组织整合有限等问题[16]。

Cui 等[15]利用光束扫描立体光刻技术制备了具有形态自适应能力的 4D 心脏贴片。该贴片由具有各向异性结构的水凝胶支架及 hiPSC-CMs、HCMECs 和间充质基质细胞构成，可在动态力学环境下与心脏表面贴合；在 MI 小鼠模型中，该构建体表现出改善细胞滞留、促进血管化及支持 CMs 成熟的作用；Tan 等[16]将心脏类器官心肌内注射到心肌 I/R 损伤大鼠梗死周边区，可增强 hPSC-CMs 治疗梗死心脏的疗效,其中多细胞支持组分可提高构建体的缺血耐受性，而导电纳米材料可能通过增强电刺激响应和细胞间电信号传递，进一步提高移植心肌组织的修复效能；Tiburcy 等[71]在无血清、成分明确条件下实现了可扩展、力产生型人类心肌补片的工程化制造，并在大鼠模型中证实了植入存活、宿主血管浸润、结构成熟和长期保留等方面的可行性，并显示出面向疾病建模、药物评价和心脏修复的可扩展制造潜力，为心肌组织构建体的标准化制备和临床级工艺开发提供了重要基础，但其长期移植疗效与临床可重复性仍需进一步验证；Miyagawa 等[99]将临床级 hiPSC-CMs 贴片移植于猪 MI 模型心外膜表面，证实心肌贴片可通过旁分泌促血管新生效应改善梗死区域心脏功能，并同时开展了肿瘤形成、遗传稳定性和心律失常风险评估，未观察到致死性心律失常，具备临床转化安全性与有效性。

这一技术的建立可以为心脏修复的临床转化提供坚实的实验基础和标准化产品平台。作为可植入的心肌修复产品，虽已取得重要临床前进展，并出现早期临床探索，但仍需解决血管化、成熟化、免疫相容性、电机械整合、致心律失常风险、规模化制造及长期随访等关键问题。随着多细胞构建、灌

流培养、智能生物材料、基因编辑和制造体系的发展，心脏类器官有望逐步成为心脏再生治疗的重要组成部分，而非单纯的体外研究模型[100]。

5.结语与展望

心脏类器官已成为 CVD 体外研究的重要平台，能够较好重现人源心肌的多细胞互作、自主搏动以及电生理、代谢与机械耦联特征，并已广泛用于疾病机制解析、药物筛选和毒性评价[101-103]。其构建思路也由早期单纯自组装逐步发展为融合发育信号诱导、基质/支架调控、组织工程、器官芯片及 3D 生物打印的复合路线，从而不断提高模型的生理相关性与应用深度[3,104,105]。但其仍普遍存在胎儿样成熟不足、批间差异明显、血管化和免疫/神经微环境缺失、长期稳定培养能力有限等问题，这些因素共同限制了其在标准化药物评价和临床转化中的进一步应用[106]。

未来研究应围绕多谱系自组织、工程化微环境以及多器官耦联 3 条主线展开：一方面，通过代谢与激素时序调控、电刺激和机械加载等方式促进结构与功能成熟；另一方面，借助共分化、微流控灌注和生物打印等策略构建可灌流的血管网络，并进一步发展心脏-肝脏、心脏-肾脏等多器官系统，以更真实地模拟系统性药代动力学、药效学及器官间互作[58,81,107,108]。与此同时，AI 辅助质控与多组学整合分析有望推动建立统一、可重复、可放大的评价体系，提升类器官平台的标准化与可比性[109,110]。总体而言，心脏类器官正由疾病模拟工具向“机制研究-药物筛选-个体化评估-再生医学”一体化平台演进；未来若能进一步整合证候相关分子表型与多模态智能分析，亦有望为中医药机制阐明与精准医学研究提供新的实验基础。

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