

综述

生物钟、生理稳态与疾病专辑



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心力衰竭的生物钟调控机制研究进展

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摘要: 生物钟是机体内源性节律调控系统, 通过整合环境和基因互作维持心血管稳态。心力衰竭(简称心衰)是以心脏结构和/或功能进行性恶化为特征的复杂临床综合征, 近年研究发现, 生物钟核心组分(如 BMAL1、REV-ERB α 等)可通过调控心肌能量代谢、参与神经-体液调节、炎症及氧化应激反应等, 影响心脏结构和代谢重构, 进而参与心衰的发生和发展。流行病学证据表明, 长期生物钟紊乱可显著增加心衰的发生风险, 而许多心衰相关治疗药物的时间依赖性疗效也提示基于昼夜节律的给药策略有助于改善心衰预后。本文将系统阐述生物钟, 尤其是核心生物钟基因, 在心衰中的多维调控机制, 并简要探讨时间疗法在心衰治疗中的应用, 为开发心衰的时间生物学个体化治疗提供理论依据。

关键词: 生物钟; 心力衰竭; 时间生物学

Research advances in the mechanisms of circadian regulation in heart failure

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Abstract: The circadian clock is an endogenous time-keeping system that maintains physiological homeostasis by integrating environmental and genetic interactions. Heart failure is a complex clinical syndrome characterized by structural abnormalities and/or functional impairment of the heart. Growing evidence suggests that core circadian components, such as BMAL1 and REV-ERB α , play important roles in modulating myocardial energy metabolism, inflammatory responses, and oxidative stress, contributing to myocardial structural and metabolic remodeling during heart failure progression. Notably, circadian disruption is closely associated with heart

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failure, with aberrant blood pressure rhythms and disturbances in the sleep-wake cycle in patients. The time-dependent efficacy of heart failure medications further supports the potential of chronotherapy-based strategies to improve clinical outcomes. Here, we summarize the multifaceted regulatory roles of the circadian clock, particularly core clock genes, in heart failure pathogenesis, providing a theoretical framework for developing personalized chronotherapeutic strategies for heart failure management.

Key words: circadian clock; heart failure; chronobiology

心力衰竭(简称心衰)作为大多数心血管疾病的终末阶段,是一种具有典型临床症状和体征的临床综合征,其主要表现为端坐呼吸、夜间阵发性呼吸困难、下肢水肿、颈静脉压升高、肺淤血和乏力等,这些症状严重损害患者的生活质量和日常活动能力。超声心动图是诊断心衰的核心检查,可准确评估左心室射血分数(left ventricular ejection fraction, LVEF),一般LVEF < 40%被诊断为心衰,但临床上也会出现射血分数保留型心衰(LVEF ≥ 50%)和射血分数中间值型心衰(LVEF在40%~49%之间)等。脑钠肽和N末端脑钠肽前体的检测对诊断心衰也具有重要价值。此外,胸部X线可显示心影增大和肺淤血表现,心电图可能发现心律失常或心肌缺血证据等^[1]。流行病学数据显示,全球心衰患病人数超5600万人^[2],从2012年到2030年,心衰患病率预计将增加46%^[3]。尽管近年来心衰治疗领域取得了显著进展,包括药物治疗、器械治疗和心脏移植等多种干预手段,但患者的远期预后仍不理想。

近年来,越来越多证据表明,生物钟在心血管生理功能稳态维持中发挥关键作用^[4]。例如,正常健康个体的血压一般表现为典型的“昼高夜低”(夜间血压下降超过10%,即杓型血压)模式,而生物钟紊乱(轮班工作、睡眠障碍或钟基因突变等)可导致血压呈现非杓型(夜间血压下降小于10%,部分患者夜间血压甚至高于日间血压,称为反杓型)^[5,6],这类患者发生心衰和其它终末器官损伤的风险也显著增加^[7]。除调控血压稳态之外,生物钟与心律失常、心肌代谢紊乱、内皮功能障碍以及心脏重构等多种参与心衰的病理过程密切相关^[8]。此外,很多急性心血管疾病如动脉瘤、心肌梗死、心源性猝死等的发病时间也具有昼夜节律性,多在清晨高发^[9]。因此,生物钟紊乱不仅是心衰的伴随现象,更可能是其重要的驱动因素,深入探讨生物钟调控心衰发生和发展的分子机制具有重要临床意义。本文将系统阐述生物钟基因网络调控心衰进展的分子机制,并对时间生物学疗法在心衰治疗中的应用前景进行简要综述。

1 生物钟系统组成及分子机制

生物钟是生物体内的内源性计时系统,由中枢生物钟(位于下丘脑视交叉上核)和外周组织(如心脏、血管、肝脏、肾脏等)的生物钟共同构成,通过分子振荡网络精确调控机体的多种生理和行为节律,如睡眠-觉醒周期、激素分泌、摄食行为、体温调节,以及心血管功能(如血压、心率、血管张力)的节律性调节等^[10,11]。在哺乳动物中,几乎所有的细胞和组织内都存在生物钟。当外界光信号通过视网膜感知时,视网膜神经节细胞能够将光刺激转化为神经体液信号^[12],传递到其他外周组织,从而调节自身时钟与外界环境同步,形成机体各种生理活动和行为的昼夜节律。

哺乳动物生物钟主要通过核心生物钟基因/蛋白及其调控的钟控基因/蛋白构成的转录-翻译反馈环路,实现约24 h的昼夜节律调控作用^[13]。简单来讲,BMAL1 (brain and muscle aryl-hydrocarbon receptor nuclear translocator-like 1) 与 CLOCK (circadian locomotor output cycles kaput)蛋白在细胞核内形成异源二聚体BMAL1/CLOCK,通过与 *Per* (period)和 *Cry* (cryptochrome)基因启动子区域的 E-box (CANNTG)结合,激活其在细胞核的转录^[14]。翻译产物PER和CRY蛋白在细胞质中积累,部分PER蛋白被酪蛋白激酶Iε/δ (casein kinase Iε/δ, CKIε/δ)磷酸化,并通过随后的蛋白酶体降解。未被降解的PER蛋白与积累的CRY蛋白形成稳定复合物,并移位到细胞核内抑制BMAL1/CLOCK异源二聚体的转录活性,形成第一个负反馈环路^[15]。多种生物钟基因如 *Rev-erbs* (reverse viral erythroblastosis oncogene product)、*Rors* (retinoic acid-related orphan receptors)和 *Dbp* (D-box binding protein)等均受异源二聚体BMAL1/CLOCK的转录调控,这些基因通过协调表达参与调控多种生理功能的昼夜节律性振荡^[16]。其中,核受体REV-ERBs和RORs是第二个反馈环路的核心组分。REV-ERBs是 *Bmal1* 转录的主要抑制因子,而RORα是其转录激活因子。两者表达后进

入细胞核竞争结合位于 *Bmal1* 基因启动子上的 RORE (ROR response element) 位点, 进而调控 *Bmal1* 的转录^[17]。除经典的 E-box 元件外, D-box 顺式元件在生物节律调控中也发挥重要作用。核心时钟基因(如 *Per* 和 *Rors*)及众多钟控基因的表达受到 D-box 元件的精细调控。转录因子 DBP (D-site binding protein) 和 E4BP4 (E4 promoter-binding protein 4) 作为 D-box 的特异性结合蛋白, 通过竞争性结合机制实现对下游基因的时序性调控, 其中 DBP 作为激活因子可显著增强基因转录, 而 E4BP4 则发挥抑制作用。这种拮抗调控模式不仅参与维持核心时钟基因的振荡表达, 还广泛影响代谢酶、离子通道等钟控基因的节律性表达, 从而将生物钟信号传递至全身各个组织器官^[18] (图 1)。

2 生物钟与心衰的临床联系

临床上, 心衰患者的生理节律异常主要体现在睡眠-觉醒周期紊乱、血压昼夜节律异常、心率变异性的昼夜波动减弱, 以及神经内分泌节律异常等方面。首先, 心衰患者的睡眠结构被破坏, 包括入睡困难(表现为睡眠潜伏期延长)、睡眠片段化(特征为频繁觉醒和深睡眠减少)以及昼夜节律失调(日间过度嗜睡伴夜间失眠)^[19]。此外, 心衰患者睡眠呼吸障碍高发, 约 50% 的心衰患者合并睡眠呼吸障碍, 主要表现为中枢性睡眠呼吸暂停伴特征性潮式呼吸, 以及阻塞性睡眠呼吸暂停^[20]。心衰合并睡眠呼吸障碍患者存在双向恶性循环: 心功能恶化加重睡眠呼吸障碍, 睡眠呼吸障碍又进一步损害心功能, 导致预后不良^[21]。机制研究表明, 心衰患者的睡眠障碍

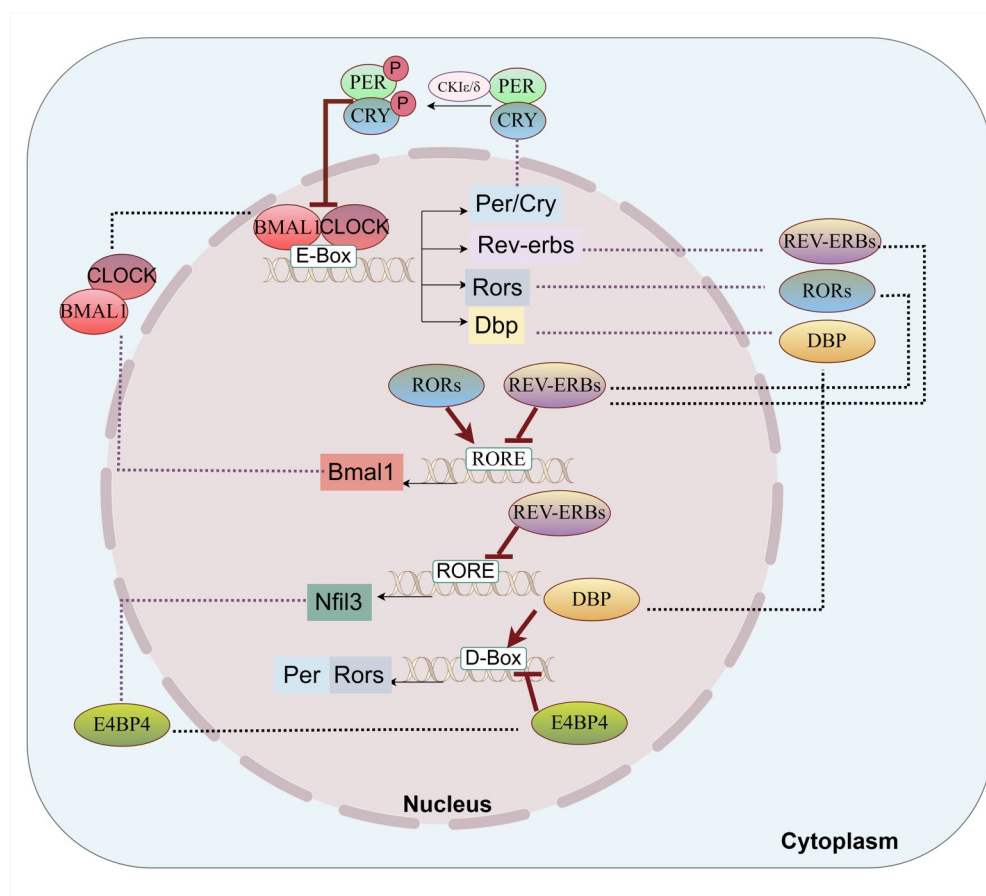


图 1. 哺乳动物生物钟调控的分子机制(本图由 Figdraw 绘制)

Fig. 1. Molecular mechanisms of circadian clock regulation in mammals (by figdraw.com). The mammalian circadian clock is governed by transcriptional-translational feedback loops. The core loop involves CLOCK/BMAL1 heterodimers activating *Per* and *Cry* gene expression, while PER/CRY proteins later inhibit CLOCK/BMAL1, creating an about 24-hour cycle. Auxiliary loops (e.g., REV-ERB/ROR) stabilize *Bmal1* expression. Post-translational modifications fine-tune timing. These mechanisms coordinate physiological oscillations. RORE: ROR response element; DBP: D-site binding protein; E4BP4: E4 promoter-binding protein 4.

与交感神经过度活跃密切相关,皮质醇等应激相关激素的上调对患者的心血管功能产生显著影响^[22]。其次,血压昼夜节律紊乱是心衰患者的显著特征^[23]。在生理状态下,人体血压昼夜节律一般表现为杓型血压^[24, 25],而心衰患者的血压呈非杓型模式的比例显著增加^[23]。研究表明异常的血压节律与心血管风险增加密切相关。在一项针对夜间工作的女性受试者的研究显示,轮班工作者表现出更高的收缩压和舒张压水平^[26]。异常的血压昼夜节律,尤其是夜间血压下降不显著,会使心脏在夜间承受着相对较高的压力负荷。再者,心率变异性作为评估心脏功能的重要指标,在心衰患者中表现出两个显著特征:一是整体心率变异性水平显著降低,二是正常的昼夜节律模式出现紊乱^[27, 28]。在健康人群中,心率变异性呈现规律的昼夜波动:白天低频成分(low frequency, LF)占优势,反映交感神经活性增强;而夜间高频成分(high frequency, HF)升高,显示迷走神经张力占优势。然而,心衰患者的这种节律模式发生明显改变,表现为夜间HF升高幅度减弱甚至反常性降低。更值得注意的是,心衰患者白天LF/HF比值持续升高,且夜间下降幅度明显减弱,这种特征性改变提示心衰患者存在显著的自主神经功能失调:交感神经过度活跃而迷走神经调节功能受损。这种自主神经平衡的破坏会显著增加心肌电不稳定性,从而大大增加发生恶性心律失常的风险^[27]。最后,心衰患者的神经内分泌节律异常是一个多系统、多层次调控的病理生理过程,主要表现为下丘脑-垂体-肾上腺轴功能紊乱,其特征是皮质醇昼夜分泌节律异常,正常晨高夜低的分泌模式被破坏,夜间皮质醇水平异常升高,这不仅加剧胰岛素抵抗,还促进全身炎症反应^[29]。同时,利钠肽系统节律失调表现为脑钠肽/AN末端前体脑钠肽昼夜波动幅度减小,失去正常的夜间下降趋势,反映心脏持续处于应激状态^[30]。褪黑素作为重要的时间信号分子,其夜间分泌峰值降低且时相延迟,这不仅影响睡眠质量,还减弱了其抗氧化和抗炎作用^[31, 32]。这些异常通过持续交感神经激活、炎症反应增强、能量代谢紊乱等多重机制,形成恶性循环,加速心衰进展。

近年来大量临床研究表明,生物钟紊乱与心衰的发生和发展之间存在密切关联。长期处于生物钟紊乱状态的人群,如轮班工作者、慢性睡眠障碍患者等,其心衰的发病率显著增高^[33],这一现象可能与生物钟失调导致的心血管系统多重病理生理改变

密切相关。随着现代工作模式的转变,轮班工作模式和跨时区差旅人群规模不断扩大。流行病学研究显示,这类特殊职业人群的心血管疾病发病风险及全因死亡率均显著高于常规作息人群^[34]。一项以中青年人群为研究对象的研究,通过系统记录其职业性轮班工作史发现,与正常作息人群相比,轮班工作时长不足5年者冠心病风险增加12%,时长5~9年者风险上升至19%,而长期(≥ 10 年)轮班工作者的冠心病风险增幅可高达27%,证实昼夜节律紊乱可对心血管系统产生渐进性损害^[35]。还有Meta分析结果显示,相较于日间工作者,轮班/夜班作业人员的心血管疾病发病风险具有显著升高趋势^[36]。此外,多种心衰相关心血管疾病或事件呈现出显著的昼夜节律特征,其发病高峰多集中于清晨时段,这一现象在急性心肌梗死、心源性猝死、缺血性卒中、腹主动脉瘤破裂以及恶性心律失常等急重症心血管事件中表现尤为突出^[37]。这种时间分布特征与人体昼夜节律调控下的神经内分泌变化密切相关,包括晨间交感神经系统活性骤增、皮质醇分泌高峰以及血小板聚集性增强等多重生理节律的协同作用。

3 核心生物钟基因与心衰

在分子生物钟方面,核心生物钟基因(包括*Bmal1*、*Clock*、*Rev-erb*、*Per*和*Cry*等)在心衰发生和发展中起关键调控作用(表1)。*Škrlec*研究团队通过一项病例对照研究(纳入200例心肌梗死住院患者及200例健康对照),重点分析了4个核心生物钟基因(*Bmal1*、*Clock*、*Cry2*和*Per2*)的单核苷酸多态性(single nucleotide polymorphisms, SNPs)分布特征。研究结果显示,*Cry2*和*Per2*基因的特定遗传变异可能与心肌梗死发病风险显著相关,提示生物节律在心肌梗死的发生和发展中可能发挥作用,但*Bmal1*和*Clock*基因的遗传变异与心肌梗死无直接关联^[38]。与之相悖的是,他们的另一项病例对照研究则发现*Bmal1*和*Clock*基因的多态性可能与心肌梗死有关^[39]。导致上述矛盾的可能原因包括两项研究的样本量差异、表型定义和分析方法的差异等。进一步扩大样本量,增加人群异质性分析,同时纳入环境因素(如光照周期等)对心肌梗死发生结果的影响分析将有助于得到更为准确的结果。此外,*Bmal1*的特异性SNPs也被证明与高血压发病风险显著相关^[40]。而*Clock*基因多态性可通过饮食调节影响2型糖尿病患者的心血管疾病发病率^[41]。有研究发现,*Per3*基因多态性与ST段抬高型心肌梗死患者更高

表1. 核心生物钟基因在心力衰竭中的病理生理作用
Table1. Pathophysiological effects of core clock genes in heart failure

Genes	Intervention strategies	Phenotypes	Mechanisms	Refs
<i>Bmal1</i>	Global <i>Bmal1</i> knockout	Thinning of the myocardial walls, dilation of the left ventricle, and decreased cardiac performance with age	Disruption of sarcomere structure	[45]
<i>Bmal1</i>	Heart-specific <i>Bmal1</i> knockout	Ventricular dilation, thinned myocardial walls, thrombosis in the ventricle, congestion of multiple organs and a short life span	Defects in mitochondrial function	[48]
<i>Bmal1</i>	<i>Bmal1</i> deficiency in human embryonic stem cell-derived cardiomyocytes	Attenuated contractility, calcium dysregulation, and disorganized myofilaments	Reduced BNIP3 protein level and compromised mitophagy and mitochondria dysfunction	[47]
<i>Bmal1</i>	Postnatal deletion of <i>Bmal1</i> in cardiomyocytes	Increased pressure overload induced cardiac hypertrophy and augmented fibrosis	Activation of PI3K/AKT signaling pathway	[49]
<i>Bmal1</i>	Inducible cardiomyocyte-specific <i>Bmal1</i> knockout	Abolished circadian variability in myocardial injury, diminished endogenous cardioprotection and reduced systolic function	Enhancing the transcriptional activity of HIF2A and stabilizing the HIF2A protein	[54]
<i>E4bp4</i>	Cardiomyocyte-specific <i>E4bp4</i> double knockout	Prevention of age-onset cardiomyopathy following clock disruption	Alterations in cardiac metabolism and electrophysiology	[46]
<i>Clock</i>	siRNA-mediated <i>clock</i> knock-down in H9c2 cardiomyocytes	Cardiomyocyte hypertrophy	Downregulation of the sGC-cGMP-PKG1 signaling	[55]
<i>Clock</i>	Cardiomyocyte-specific <i>Clock</i> mutant	Cardiac hypertrophy, and loss of the responsiveness of the heart to isoproterenol stimuli	/	[71]
<i>Clock</i>	<i>Clock</i> Δ19 mutant	Alteration in cardiac remodeling after myocardial infarction	Increased inflammatory cell infiltration into infarcted myocardium	[57]
<i>Clock</i>	<i>Clock</i> mutant	Blunting of deoxycorticosterone/salt-mediated cardiac inflammation and fibrosis and promoting cardiac hypertrophy	Enhancement of mineralocorticoid receptor-mediated transactivation of <i>per1</i>	[58]
<i>Rev-erb</i>	Cardiac-specific <i>rev-erba/β</i> knockout	Systolic dysfunction, progressive dilated cardiomyopathy and lethal heart failure with age	Dysfunction of fatty acid oxidation and excessive reliance on glycolysis	[60]
<i>Rev-erb</i>	Cardiac-specific <i>rev-erba/β</i> knockout	Lethal dilated cardiomyopathy with age	Downregulation of fatty acid oxidation genes, which was mediated by induction of <i>e4bp4</i>	[61]
<i>Rev-erb</i>	Cardiac-specific <i>rev-erba</i> knockout	Aggravated myocardial infarction after ischemia-reperfusion injury	Enhancing cardiac inflammatory response by increasing cardiotrophin-like cytokine factor 1	[33]
<i>Rev-erb</i>	Global <i>Rev-erba</i> knockout and platelet-specific <i>Rev-erba</i> knockout	Reduction of carotid arterial occlusive thrombosis, prevention of pulmonary thromboembolism, and protection of microvascular microthrombi obstruction and infarct expansion	Inhibition of platelet activation via oligophrenin-1-mediated RhoA/ERM (ezrin/radixin/moesin) pathway	[67]

的炎症指标和特定昼夜发作节律相关，尤其在男性患者中表现显著^[42]。

动物实验结果表明，*Bmal1*是唯一一个单基因敲除即可导致小鼠行为活动昼夜节律完全消失的核心生物钟基因。与对照组相比，无论是出生前还是出生后*Bmal1*基因全身敲除小鼠，其活动度、心率

和血压的24 h周期性昼夜节律变化均完全消失^[43, 44]。随着年龄的增长，全身*Bmal1*基因敲除小鼠会发展成扩张型心肌病，表现为心肌壁变薄、左心室扩张和心功能下降，最终导致心衰^[45, 46]。值得注意的是，这种年龄依赖性的心功能衰退可通过敲除钟控输出基因*E4bp4*得到显著改善^[46]。利用*Bmal1*缺失的人

胚胎干细胞来源的心肌细胞研究表明, BMAL1 可通过抑制 BNIP3 介导的线粒体自噬, 导致心肌细胞功能受损^[47]。此外, 心肌细胞特异性敲除 *Bmal1* 基因, 可通过抑制心脏中与脂肪酸氧化、三羧酸循环以及线粒体呼吸链相关的基因表达, 导致心脏代谢重塑, 这些代谢异常共同促进了年龄相关性心衰的发生和发展^[48]。我们课题组的研究发现, 心肌细胞中 *Bmal1* 的缺失也会通过激活 PI3K/AKT (phosphoinositide 3-kinase/protein kinase B) 信号通路促进压力过载诱导的心脏结构重塑, 进而参与心衰的发生和发展^[49]。也有研究显示, BMAL1 蛋白可通过直接调控 *Klf15* (kruppel-like factor 15) 的转录和表达节律进而发挥功能^[50], 而 KLF15 已被证实是心衰的一种保护性调节因子及潜在治疗靶点^[51–53]。值得一提的是, 最近刚刚发表在 *Nature* 杂志的文章发现 BMAL1 通过与缺氧诱导因子 2 α (hypoxia-inducible factor 2 α , HIF2A) 形成异源二聚体节律性调控双调蛋白 (amphiregulin, AREG) 表达, 从而控制心肌损伤的昼夜差异, 为缺血性心脏病的治疗提供了全新靶点^[54]。

Clock 基因表达异常与心衰同样密切相关。研究通过建立持续三个月时差紊乱诱导的心衰动物模型发现, 与正常昼夜节律对照组相比, 心衰模型组小鼠 *Bmal1* 和 *Clock* 的 mRNA 表达水平均出现显著下调。进一步机制研究发现, 敲除心肌细胞中的 *Clock* 可通过抑制 sGC-cGMP-PKG (soluble guanylate cyclase-cyclic guanosine monophosphate-protein kinase G) 信号通路诱导心肌细胞肥大^[55]。另有研究还发现 *Clock* 突变小鼠心肌梗死后心脏的炎症反应异常, 从而加剧非适应性心脏重塑, 导致心衰^[56, 57]。有趣的是, *Clock* 突变可保护醋酸脱氧皮质酮盐诱导的心脏炎症和纤维化, 同时促进心肌肥大^[58]。导致上述矛盾的可能原因包括实验模型的选择差异、细胞类型特异性效应, 以及心衰进程中炎症反应、纤维化与心肌肥大等病理过程可能涉及不同的调控通路或分子机制等。后续研究应着重探究 *Clock* 基因在不同病理生理条件下的特异性调控机制, 从而系统阐明其在心衰发生和发展中的多维度作用。

Rev-erbs 是执行转录抑制功能的核心生物钟基因, 包括 *Rev-erba* 和 *Rev-erbb*。二者是核受体超家族中的同源基因, 但具有组织特异性表达差异: REV-ERB α 广泛高表达于多种组织, 而 REV-ERB β 则选择性富集于大脑、甲状腺、子宫和垂体等特定部位^[59]。目前关于 *Rev-erbs* 参与心衰调控的研究大

部分通过利用 *Rev-erba*/ β 双敲除小鼠进行研究或集中于对 *Rev-erba* 进行研究, 关于 *Rev-erbb* 的独立研究相对较少。文献表明心肌细胞特异性 *Rev-erba*/ β 双敲除可导致小鼠发生扩张型心肌病而过早死亡^[60, 61]。在分子机制层面, 研究揭示 *Rev-erba*/ β 双敲除可通过调控转录抑制因子 E4BP4 的表达下调脂肪酸氧化基因表达, 进而导致小鼠随年龄增长发生扩张型心肌病, 并导致早发性死亡^[61]。此外, REV-ERB α 可与关键转录因子共定位, 抑制异常基因表达, 并防止心肌细胞肥大^[62]。与基因敲除相反, 短期使用靶向 REV-ERB α / β 的小分子激动剂 SR9009 可促进小鼠心肌缺血再灌注后的长期心脏修复, 且仅需一天的治疗即可抑制心脏炎症小体活化, 减少免疫细胞浸润, 从而促进脆弱梗死区的愈合^[63]。但也有研究表明, SR9009 在压力过载时呈现出 REV-ERBs 非依赖性的心脏保护作用^[64]。近几年, 我国科学家在 REV-ERB α 与心血管疾病研究领域取得重要突破, 揭示了该生物钟核心组分具有组织特异性的多效调控作用: 在心肌组织中, REV-ERB α /CLCF1 (cardiotrophin-like cytokine factor 1) 信号轴被认为是介导轮班工作加速心肌损伤的关键分子机制^[33]; 在血管系统中, REV-ERB α 可通过调控血管平滑肌细胞线粒体代谢影响腹主动脉瘤的发生和发展^[65], 也可通过调控巨噬细胞焦亡和炎症反应调控动脉粥样硬化的病程进展^[66]; 此外, 血小板特异表达的 REV-ERB α 被证明可作为血栓性心血管疾病的潜在治疗靶点^[67]。

Per 和 *Cry* 基因在心衰中的作用虽然没有直接研究, 但多项相关研究揭示了这些生物钟基因在心血管调控中的关键作用。研究发现, *Per2* 突变小鼠表现出夜间血压和心率降低的特征^[68]。遗传学研究表明, 同时敲除小鼠的 *Cry1* 和 *Cry2* 基因会诱发盐敏感性高血压^[69]。此外, 过表达 *Cry1* 可能通过调节 TLR/NF- κ B (Toll-like receptor/nuclear factor-kappa B) 通路缓解小鼠动脉粥样硬化的发展^[70]。这些发现提示了生物钟基因在心衰发生和发展中的多效性调控作用。

4 生物钟参与心衰调控的机制

4.1 生物钟与心肌细胞生理功能调控

心肌细胞作为心脏的基本功能单位, 其生理功能呈现显著的昼夜节律特征。在电生理方面, 离子通道表达和动作电位参数存在周期性波动; 收缩功能在光-暗周期中同样表现出明显的昼夜节律变

化^[72]。这些节律特性受神经-体液因素和细胞自主生物钟的双重调控，约10%~15%的心肌细胞蛋白编码基因的表达呈现昼夜振荡^[73]。研究表明，生物钟通过调节心肌细胞内钙循环关键蛋白的表达和活性，直接参与心衰的发生和发展。其中，肌浆/内质网钙-ATP酶2a (sarcoplasmic/endoplasmic reticulum calcium ATPase 2a, SERCA2a)是生物钟调控心肌细胞功能的核心靶点^[74]。昼夜节律紊乱可导致SERCA2a表达和活性显著降低，导致肌浆网对钙离子的摄取功能障碍，从而影响心肌收缩和舒张功能，加速心衰进程^[75]。分子机制研究揭示，*Per1*基因通过调节p38促分裂原活化蛋白激酶(mitogen-activated protein kinase, MAPK)的节律性活动参与SERCA2a的激活，从而在心衰的发生和发展中起到重要作用^[76]。此外，在主动脉缩窄术构建的慢性心衰小鼠模型中，BMAL1可直接结合到T型钙离子通道(T-type calcium channel, TTCC)启动子区域的E-box位点调控TTCC的转录，通过转录调控TTCC影响慢性心衰室性心律失常昼夜节律^[77]，提示生物钟可以通过直接调控钙通道来调节心肌细胞内的钙循环稳态从而影响心衰。BMAL1还可通过调控KLF15的节律性表达，进而介导钾通道辅助亚基Kv通道连接蛋白2(Kv channel-interacting protein 2, KChIP2)的周期性转录。这一调控通路的紊乱可导致心肌复极化异常，显著增加室性心律失常的易感性^[78]。此外，生物钟通过精细调控心肌收缩相关蛋白的表达节律，直接影响心肌细胞的收缩功能。研究表明，心肌细胞通过调节细胞内钠离子和钾离子水平的变化维持其兴奋性和收缩性的昼夜节律^[79]。有研究发现心肌细胞特异性敲除*Bmal1*会破坏心脏钠通道和钾通道基因表达的昼夜节律波动，导致动作电位时程紊乱，最终表现为显著升高的恶性心律失常及心源性猝死发生率^[80, 81]。且当生物钟发生紊乱时，心肌细胞表现为收缩蛋白功能异常、心肌收缩力下降，进而影响心脏的泵血功能^[72]。

4.2 生物钟与心血管神经-体液调节

交感神经系统在心衰的发生和发展中发挥着重要的作用。在生理情况下，生物钟通过调节交感神经活动的节律，防止其过度兴奋，避免对心脏的损伤^[82]。生物钟紊乱会导致交感神经节律消失及活性异常。临床研究证实，心脏交感神经过度兴奋与心律失常死亡风险显著相关^[83]。在分子机制方面， β 肾上腺素受体(β -adrenergic receptors, β -ARs)作为G

蛋白偶联受体超家族成员之一，是介导心脏交感神经活动的关键调节因子。研究表明心脏内源性生物钟能够直接影响 β 1-AR的表达和功能。具体来说，心脏中的BMAL1/CLOCK异源二聚体复合物可识别并结合到 β 1-AR基因*Adrb1*的启动子区域的E-box元件上，从而直接调控其转录和表达水平^[84]。此外，生物钟与肾素-血管紧张素-醛固酮系统(renin-angiotensin-aldosterone system, RAAS)的相互作用也备受关注。临床和动物研究均证实，在生理条件下，RAAS各组分均表现出显著的昼夜节律^[85, 86]。哺乳动物血浆肾素活性、血管紧张素转化酶、血管紧张素II(angiotensin II, AngII)和醛固酮水平呈昼夜节律变化，其中RAAS活性在活动期出现高峰，非活动期活性相对较低^[85]。生物钟紊乱会导致RAAS的异常激活，包括AngII和醛固酮的过度激活^[87, 88]，并通过诱导心脏重塑^[89]、加剧高血压^[90]及损害内皮细胞功能^[91]等促进心衰的发生和发展。生物钟也参与调节利钠肽系统的生理稳态。研究表明，大鼠心脏利钠肽系统的昼夜调控存在组织特异性差异，脑利钠肽的表达呈现显著的昼夜节律波动，而心房利钠肽(atrial natriuretic peptide, ANP)在基因转录水平未检测到明显节律性变化^[92]。然而，采用离体器官灌注技术进行的研究揭示，大鼠心房组织中ANP蛋白的分泌水平具有明显的昼夜节律特征^[93]。生物钟紊乱时，利钠肽系统功能发生失调，对RAAS的拮抗作用减弱，可进一步促进心衰发展。

4.3 生物钟与炎症反应和氧化应激

在心衰患者中，心脏的氧化损伤和炎症反应往往相互促进，并通过正反馈调节显著加速心肌损伤和心功能恶化的进程。研究表明核心生物钟基因可直接调控多种炎症因子的表达，如NLRP3(NOD-like receptor family, pyrin domain containing 3)炎症小体及其组成细胞因子IL-1 β (interleukin-1 β)受到生物钟核心组份BMAL1和REV-ERBs的转录调控^[94-96]。基因表达谱分析显示，心肌特异性敲除*Bmal1*可通过上调多种炎症反应和氧化应激相关基因[如谷胱甘肽过氧化物酶(glutathione peroxidases, *Gpx*)、超氧化物歧化酶(superoxide dismutase, *Sod*)和氧转运相关基因等]的表达水平参与心脏重塑过程，从而加剧心衰^[48]。此外，BMAL1蛋白缺失会加剧脂多糖诱导的脓毒症心肌细胞损伤，而过表达BMAL1则可通过激活sirtuin 1减轻心肌细胞炎症和氧化应激，改善心脏功能^[97]。REV-ERBs激动剂SR9009可通过抑

制炎症反应显著降低心肌梗死后的死亡率并改善心功能^[98]。有趣的是,生物钟系统也可通过精确调控中性粒细胞的迁移动态直接参与心肌梗死后的炎症反应过程。当特异性敲除中性粒细胞的核心生物钟基因 *Bmal1* 时,可导致中性粒细胞从骨髓向血液及靶组织迁移的时序性紊乱,并显著削弱其在疾病模型中的免疫应答能力^[99]。在 *Clock* 突变小鼠模型中,中性粒细胞向梗死区心肌组织的浸润速率明显减缓,且在心肌组织中的滞留时间显著延长^[57]。因此,内源性生物钟可通过调控中性粒细胞的趋化,在心肌梗死后的炎症反应过程中发挥着关键性调控作用。与此一致的是,有研究发现,与睡眠时段发生心肌梗死的小鼠相比,觉醒时段发生心肌梗死的小鼠表现出 CCR2 (C-C chemokine receptor type 2) 水平显著升高、CCL2 (C-C motif chemokine ligand 2) 蛋白表达量增加以及 Ly6C 高表达单核细胞向梗死心肌的募集更为显著^[100],提示单核细胞向梗死区心肌组织浸润的昼夜节律调控可能直接影响心脏修复效果和临床预后。值得注意的是,活性氧(reactive oxygen species, ROS)的产生和清除相关酶的编码基因表现出明显的昼夜节律性波动^[101]。有研究发现 *Per2* 基因表达的昼夜波动可通过调节 ROS 的生成影响心肌缺血再灌注损伤的严重程度^[102]。另有研究提示中枢 NADPH 氧化酶亚基 gp91^{phox} 介导的氧化应激也可能参与了心肌梗死后心衰小鼠血压和心率的昼夜节律异常变化^[103]。

4.4 生物钟与心血管代谢稳态调控

近年研究发现,生物钟可通过精细调控心脏能量代谢的动态平衡在维持心血管稳态中发挥核心作用,生物钟紊乱可导致心脏能量代谢稳态破坏,成为诱发心衰的重要机制之一。首先,心脏对脂肪酸的代谢调节具有昼夜节律特征,当血液中脂肪酸水平升高时,心肌细胞会启动氧化和非氧化代谢途径来维持稳态,这一调控过程包含急性(秒至分钟级)和慢性(小时至天级)两种机制:急性阶段主要依赖翻译后修饰,如通过腺苷酸活化蛋白激酶磷酸化快速抑制乙酰辅酶 A 羧化酶活性,即时调节脂肪酸氧化速率;慢性阶段则通过激活过氧化物酶体增殖物激活受体(peroxisome proliferator-activated receptor, PPAR)核转录通路,重构代谢网络^[104]。研究发现,大鼠心脏在静息期接触高脂肪酸环境时会出现心功能暂时性下降,但在活动期则无此现象^[105];相反,活

动期心脏能更有效地激活相关基因表达来应对脂肪酸刺激^[106]。这种差异源于心肌细胞生物钟对 PPAR α 、REV-ERB α 和 PPAR γ 共激活因子-1 α (PPAR γ coactivator 1- α , PGC1 α) 等核受体昼夜表达的调控作用^[107,108]。同时,有研究揭示 PGC1 α 可能通过调节代谢基因的昼夜节律,在生物钟介导的心脏功能损伤中发挥重要作用^[109]。其次,正常大鼠心脏中参与葡萄糖代谢、脂肪酸代谢及线粒体功能的基因呈现显著的昼夜节律性表达波动。然而,在心脏肥大状态下,这些关键代谢基因的整体表达水平显著下调,同时其原有的昼夜节律特征也出现明显紊乱^[110]。分子机制研究表明, BMAL1/REV-ERB α 昼夜节律回路的破坏与心衰大鼠脂肪过度消耗有关,表明稳定脂肪组织节律可能有助于对抗能量稳态的破坏,并减轻心衰情况下脂肪组织的过度消耗^[111]。此外,心肌细胞 *Bmal1* 基因特异性缺失会导致代谢适应性异常:在禁食状态下,脂肪酸氧化代谢持续亢进,而葡萄糖氧化利用、糖酵解及糖原合成通路则表现为持续性抑制,这种代谢紊乱不受摄食状态调节^[112]。更值得注意的是,持续的代谢紊乱会损害线粒体功能并加剧氧化应激反应,最终加速心功能失代偿^[48]。而 BMAL1 靶基因产物 KLF15 可能通过调控烟酰胺腺嘌呤二核苷酸代谢稳态,显著增强心肌对缺血再灌注损伤的易感性^[113]。研究证实 REV-ERB α 激动剂 SR9009 通过上调脂肪酸氧化关键调节因子——丙酮酸脱氢酶激酶 4 (pyruvate dehydrogenase kinase 4, PDK4) 的表达,显著改善心衰小鼠的代谢异常。ChIP-seq 结果显示 REV-ERB α 可通过直接结合 PDK4 基因增强子区域调控其转录活性,表明 PDK4 是 REV-ERB α 介导心脏代谢重构的重要效应分子^[62]。在小鼠心脏中, REV-ERB α/β 在日间促进脂肪酸氧化,在夜间抵消葡萄糖代谢^[60]。此外,心肌细胞特异性 *E4bp4* 敲除小鼠表现为白天油酸氧化率异常升高、脂肪酸代谢昼夜节律改变,提示 *E4bp4* 可能是维持心脏代谢功能稳态的关键负性调控因子^[46]。通过对野生型和心肌细胞特异性 *Clock* 突变小鼠心脏进行全基因组表达谱分析,研究发现大量调控甘油三酯代谢和糖原代谢的关键基因受到心肌细胞 *Clock* 的节律性调控^[114]。同时,研究人员通过构建显性负突变 *Clock* 过表达的小鼠模型,发现在禁食时脂肪酸响应基因的诱导严重受损,进一步证实 CLOCK 直接调控心肌脂肪酸代谢,

揭示了CLOCK在调节心肌对脂肪酸的急性转录反应性方面的关键作用^[108]。随后,该团队又发现心肌细胞自主的生物钟直接调控心肌甘油三酯的合成与分解,心肌细胞特异性Clock突变小鼠心肌甘油三酯水平的昼夜振荡显著减弱,机制研究表明心肌生物钟通过抑制激素敏感性脂肪酶的活性导致甘油三酯净合成增加,且这种调控在活动/清醒阶段尤为显著^[115]。这些研究充分证实,生物钟通过调控心脏代谢功能的昼夜稳态在维持心功能稳态中发挥核心作用,为开发基于时间生物学的心衰代谢调控策略提供了重要理论依据。

5 时间疗法在心衰治疗中的应用前景

时间疗法是一种基于昼夜节律的治疗方法,包括利用生理节律优化常规治疗方案(如调整药物给药时间)和靶向生物钟分子通路的干预手段等^[116]。值得注意的是,许多心衰治疗相关的药物呈现出显著的时间依赖性特征,这种特性与人体生物钟对药物代谢动力学、靶器官敏感性以及疾病病理生理过程的昼夜节律调控密切相关。有研究发现,仅在睡眠期给予血管紧张素转化酶抑制剂(angiotensin converting enzyme inhibitor, ACEI)有利于小鼠主动脉缩窄术压力过载时的血管重塑,而清醒期给药作用与安慰剂相同^[117]。这一现象可能与睡眠期间RAAS活性增强有关,提示睡前服用ACEI类药物对心衰患者更具临床意义。此外,与传统的早晨服药方式相比,睡前服用ACEI类药物也能更有效地控制心衰患者的夜间血压,从而优化整体治疗效果^[118, 119]。我们和他人的研究结果也提示,在高血压患者群体及高盐饮食诱导的高血压小鼠模型中,临睡前给予阿司匹林较晨起给药能产生更显著的降压效果^[120-122]。这一现象可能与阿司匹林对夜间血管紧张素系统活性的特异性调节作用有关。此外,钙通道阻滞剂硝苯地平采用睡前给药方案可改善非杓型高血压患者的血压节律异常,同时有效缓解药物引起的夜间外周水肿等不良反应^[123]。然而,也有研究认为ACEI等抗高血压药物的降压效果不存在晨间-晚间给药时间差异^[124]。尽管如此,从时间治疗学角度而言,合理把握用药时间有望提升药物疗效并降低不良反应。除临床用药之外,一项发表在Lancet上的临床研究发现,与上午接受主动脉瓣置换术的患者相比,下午接受手术对心脏有更好的保护及改

善患者的预后^[125],提示心血管系统的生物节律特性可能对各类治疗干预措施产生重要影响,这些发现为心衰的时间治疗学应用提供了重要依据。

褪黑素是由松果体昼夜节律性分泌的神经内分泌激素,作为生物钟系统的关键输出分子,可广泛调控睡眠-觉醒周期、核心体温及激素分泌等昼夜节律生理过程。临床研究表明,心衰患者褪黑素分子水平显著降低^[126]。最新研究提示,血清褪黑素水平可作为心衰患者的有效生物标志物^[127]。褪黑素治疗被认为是缺血性和高血压性心脏病的一种潜在辅助疗法^[128, 129]。研究表明,褪黑素给药可有效恢复血压昼夜节律,显著改善接受降压药物治疗患者的夜间高血压症状^[130, 131],且在高龄患者群体(≥ 80 岁)中仍表现出稳定的疗效^[132]。特别值得注意的是,褪黑素不仅能够优化心血管功能,还能显著改善患者的心理状态指标,表明其具有潜在的心衰辅助治疗价值,可作为新型治疗策略用于心衰患者的症状管理与临床干预^[133]。除褪黑素外,其它靶向生物钟的小分子药物在心衰治疗中也显示一定疗效。在主动脉缩窄术构建的小鼠模型中,REV-ERBs激动剂SR9009处理可阻止心肌细胞肥大,减少纤维化,从而抑制心衰的发生和发展^[62]。此外,有研究发现SR9009单次给药24 h内即能显著抑制NLRP3炎症小体活化,同时减少梗死区中性粒细胞浸润和巨噬细胞聚集^[63]。SR9009在改善压力负荷诱导的小鼠心功能障碍方面同样有效^[64]。另一种REV-ERBs激动剂GSK4112也被证明可抑制小鼠心肌细胞的肥大和细胞氧化应激标志物的表达^[62]。这些研究结果共同提示靶向生物钟的小分子药物研发有望成为心衰治疗的新思路。

最后,光照疗法在心衰防治中也可能发挥一定作用,有报道称强光可通过增强PER2的昼夜节律振幅发挥心脏保护作用^[134]。此外,持续光照抑制小鼠下丘脑视交叉上核的中枢生物钟功能,可显著改善心肌梗死后的心脏功能,减少纤维化并促进血管新生^[135]。同样,运动训练的心脏保护作用可能也与其对生物节律系统的正向调节作用密切相关^[136, 137]。

6 小结与展望

综上所述,生物钟是调节心血管系统功能稳态的重要内在机制,可通过调控心肌细胞生理功能、参与心血管系统神经-体液调节、影响炎症反应和氧化应激,及调控能量代谢昼夜稳态等多种途径参与心衰的病理生理学进程(图2)。深入解析生物钟调控

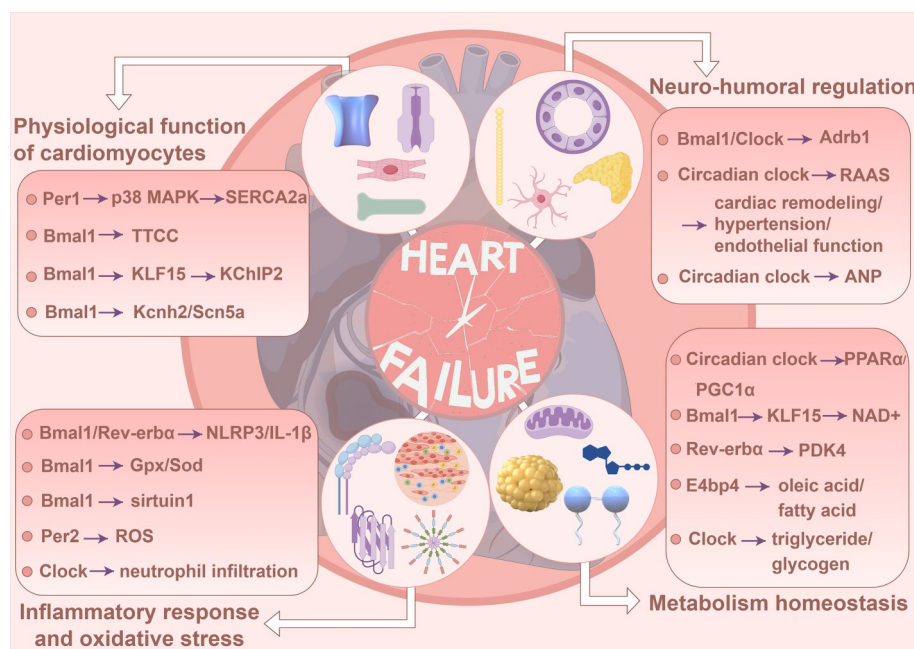


图 2. 生物钟调控心力衰竭的机制(本图由Figdraw绘制)

Fig. 2. The mechanism of circadian clock regulation of heart failure (by figdraw.com). The circadian clock serves as a critical intrinsic mechanism regulating cardiovascular homeostasis. It participates in the pathophysiological progression of heart failure through multiple pathways: modulating cardiomyocyte physiology, engaging in neuro-humoral regulation of the cardiovascular system, influencing inflammatory responses and oxidative stress, as well as maintaining circadian energy metabolism homeostasis. TTCC: T-type calcium channel; KLF15: kruppel-like factor 15; KChIP2: Kv channel-interacting protein 2; RAAS: renin-angiotensin-aldosterone system; ANP: atrial natriuretic peptide; NLRP3: NOD-like receptor family, pyrin domain containing 3; IL-1 β : interleukin-1 β ; ROS: reactive oxygen species; PPAR α : peroxisome proliferator-activated receptor α ; PGC1 α : PPAR γ coactivator 1- α ; PDK4: pyruvate dehydrogenase kinase 4.

心衰的分子机制，将不仅为理解心衰发病机制提供新视角，更为基于时间生物学的心衰防治提供重要理论依据。随着基因编辑、单细胞时空组学、人工智能等前沿技术的突破性进展，未来研究需进一步深入解析生物钟调控心衰的具体分子机制，尤其是生物钟在非心肌细胞(如成纤维细胞、内皮细胞、免疫细胞等)中的调节作用，并持续推动靶向生物钟核心组分的小分子药物研发和节律重置策略研究。最后，结合可穿戴设备动态监测患者昼夜表型，开展大规模临床研究验证不同时间疗法在心衰防治中的作用，实现从机制研究到时间精准医疗的跨越，将成为心衰患者管理的新方向。

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