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综 述

生物钟与心血管疾病联系的研究进展

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摘 要：昼夜节律广泛存在于生命体中，主要由生物钟调控，使生命活动呈现以24 h为周期的变化。越来越多的研究表明，生物钟与心血管的生理功能密切相关，比如基础血压和心率的日周期变化主要受控于生物钟而非行为。此外，心肌细胞的代谢、血管内皮的功能，以及血管的收缩和舒张均受到生物钟的调节。不仅如此，许多心血管事件的发生，如心肌梗死的发生也具有明显的昼夜节律特征。基于动物模型的研究显示，昼夜节律紊乱是心血管事件发生的重要风险因素之一。本文综述了有关生物钟与心血管疾病联系的最新研究进展，希望有助于根据生物钟理论优化心血管疾病治疗策略。

关键词：生物钟；昼夜节律；心血管疾病；心肌梗死；动脉粥样硬化；高血压
中图分类号：R852.6；R714.252

Research advances in relationship between biological clock and cardiovascular diseases

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Abstract: Circadian rhythms widely exist in living organisms, and they are regulated by the biological clock. Growing evidence has shown that circadian rhythms are tightly related to the physiological function of the cardiovascular system, including blood pressure, heart rate, metabolism of cardiomyocytes, function of endothelial cells, and vasoconstriction and vasodilation. In addition, disruption of circadian rhythms has been considered as one of the important risk factors for cardiovascular diseases, such as myocardial infarction. This review summarizes the recent research advances in the relationship between circadian clock and cardiovascular diseases, hoping to improve treatment strategies for patients with cardiovascular diseases according to the theory of biological clock.

Key words: biological clock; circadian rhythms; cardiovascular disease; myocardial infarction; atherosclerosis; hypertension

生物在生理和行为等方面表现出重复出现的特征，称为生物节律；产生和调节生物节律的内在机制则称为生物钟。生物节律包括年节律，季节律，月节律，昼夜节律等。昼夜节律广泛存在于自然界的生命体中，如动物、植物、细菌和真菌[1]。昼夜节律由内源性的生物钟所驱动，能够使生命体调整行为和生理活动以适应环境的变化。例如体温[2, 3]，睡眠 - 觉醒[4]，进食[5]，激素释放[5, 6]，营养物质代谢[5]，血压[7]，心率[8]等均具有周期性的变化[9–11]。本文重点综述 24 h 为周期的昼夜节律。

人体多种生理功能受生物钟的调节，心血管系统的功能也不例外[12]。在生理状态下，凌晨 3 点左

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右成年人的动脉血压最低，觉醒后迅速升高，形成晨峰，随后下降，但仍维持在较高水平，夜晚入睡后，血压持续下降至最低 [7]。脉搏和心率在一天中的变化也遵循一定的规律。前臂的血流量、血管阻力以及血管对酚妥拉明 (α- 肾上腺素能受体拮抗剂) 刺激下的舒张反应在一天中也存在规律变化 [13]。更为重要的是，临床上一些急性心血管事件，如急性心肌梗死、室性心动过速、缺血性和出血性脑卒中以及心源性猝死等均在凌晨达发病高峰 [8, 14]。轮班工人昼夜节律的紊乱增加了其发生急性心血管事件的风险 [15]。大量的证据表明昼夜节律在维持心血管正常生理功能中至关重要，而昼夜节律破坏成为心血管事件发生的风险因素之一，值得被关注。

1 生物钟调节的分子基础

生物钟系统由位于下丘脑视交叉上核 (suprachiasmatic nucleus, SCN) 的中央时钟和外周组织的外周时钟构成 [16]，中央时钟是控制哺乳动物产生昼夜节律的主振荡器，视网膜接受来自外界的光信号，将其转化为各种神经信号和体液信号，SCN 接收这些信号，通过自主神经系统、体液介质和未知因素调节生理活动节律的产生。除了中央时钟外，每个外周器官或细胞都有自己的内部时钟即外周时钟 [17, 18]。虽然中央时钟可以同步外周时钟，研究证明，位于各组织器官的外周时钟也能独立发挥作用 (图 1)，如 SCN 损伤的小鼠，外周器官仍表现出恒定的节律性 [19]，离体的小鼠肾脏仍具有时钟基因的节律性表达 [20]。

在哺乳动物中，核心时钟基因 (发挥主要作用的时钟基因) 包括 *bmal1* (brain and muscle aryl-hydrocarbon receptor nuclear translocator-like 1)、*clock* (circadian locomotor output cycles kaput)、*per* (Period) 和 *cry* (Cryptochrome) 等 (表 1)，它们共同组成一系列正负反馈通路 [21]。Bmal1 和 CLOCK 蛋白，或者和 CLOCK 蛋白的类似物 NPAS2 形成异源二聚体，与 *per* 和 *cry* 基因启动子区域的 E-box 元件结合，激活它们的转录和翻译。随着 *per* 和 *cry* 翻译出的蛋白质在细胞质中积聚，它们又转入细胞核中，抑制 Bmal1 与 CLOCK/NPAS2 二聚体的形成，从而抑制自身的转录翻译。这个核心的环路与其他的正负反馈环路相结合，如 RORα (RAR-related orphan receptor α)、REV-ERBα (NR1D1, nuclear receptor subfamily 1, group D, member 1) 和过氧化物酶体增殖物激活受体 (peroxisome proliferator-activated receptors, PPARs) 等蛋白参与的反馈环路，共同构成昼夜节律的调控通路。同时，这些时钟基因还调控一些下游基因 (也被称为钟控基因) 的表达，从而调节各种生理和生命活动的昼夜节律 [9, 22, 23](图 2)，

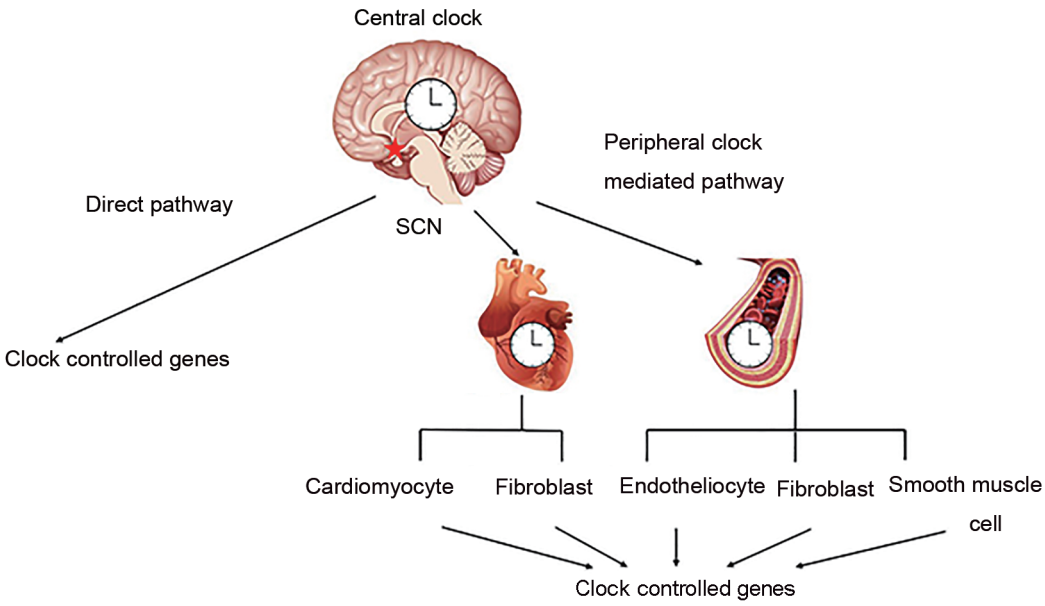

图 1. 中央时钟与外周时钟

Fig. 1. The circadian clock exists as the central clock in the suprachiasmatic nucleus (SCN) in the hypothalamus, and the peripheral tissues (e.g., heart, vasculature) serve as the peripheral clock. They all mediate through transcriptional and translational feedback loops.

表1. 哺乳动物核心时钟基因缺失后的心血管表型

Table 1. Cardiovascular phenotypes in core clock genes knock out mammals

Genes	Position	Cardiovascular phenotypes
bmal1	Global	Diabetic cardiomyopathy[29]
		Arterial thrombosis↑[30]
		Endothelial dysfunction↑[31]
		Age-associated DCM[32]
		Atherosclerosis↑[33] (conventional knock out)
		Atherosclerosis↓[26] (inducible knock out)
		Loss of diurnal variation in blood pressure[26, 34]
	Endothelial cells	Neointimal hyperplasia (Femoral artery)↑[35]
		Blood pressure↓[36]
	Smooth muscle cells	Blood pressure↓[37]
	Cardiomyocyte	Age-associated DCM[38]
		Heart rate↓[34]
	Macrophage	Atherosclerosis↑[39]
per1	Global	Blood pressure↓[40]
per2		
	Global	Cardiac function↓[41]
		Blood pressure↓[27]
		Endothelial dysfunction↑[27]
clock	Global	TTVO↑[36]
		Blood pressure↓[42]
		Atherosclerosis↑[43]
cry1/2	Global	Salt sensitive hypertension [44]

↑, aggravation; ↓, relief. DCM: dilated cardiomyopathy; TTVO: the time to thrombotic vascular occlusion.

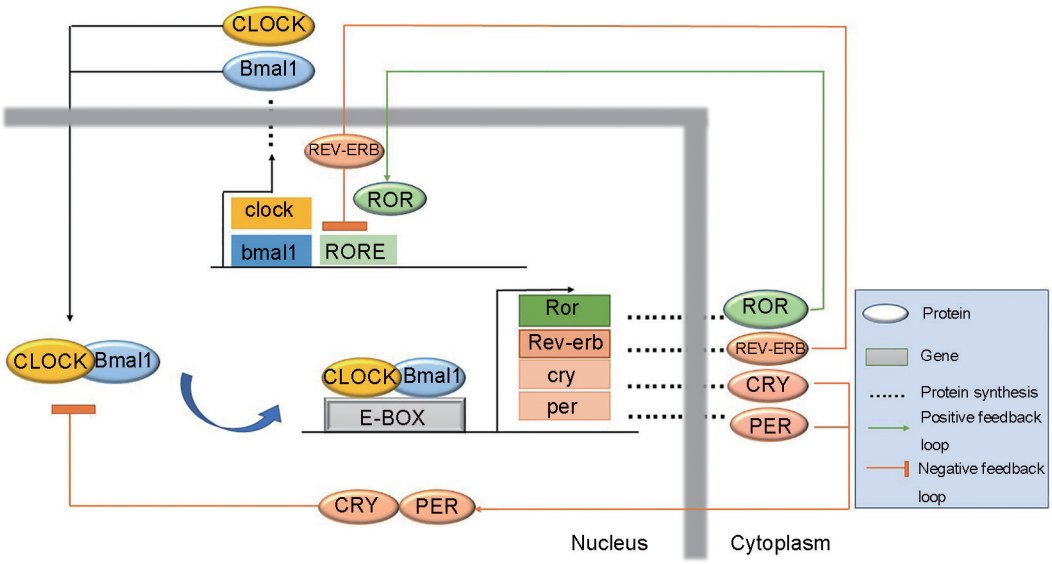

图 2. 哺乳动物生物钟的转录反馈回路

Fig. 2. Transcriptional feedback loops of the mammalian circadian clock. In the core loop, Bmal1/CLOCK heterodimer activates transcription of the *per* and *cry* genes via binding to the E-box elements in their promoter regions. The resulting PER and CRY proteins heterodimerize, are translocated into the nucleus and interact with the Bmal1/CLOCK complex to inhibit their own transcription. In addition, RAR-related orphan receptor (ROR) activates, whereas REV-ERB, also known as NR1D1 (nuclear receptor subfamily 1, group D, member 1), represses ROR response element (RORE)-mediated transcription, forming the secondary autoregulatory feedback loop.

例如 PPAR 是 Bmal1 的直接靶基因，其所有亚型都具有昼夜节律性，另外 PPARα 所调控的甾醇调节元件结合蛋白 (sterol regulatory element binding protein, SREBP)、脂肪酸合成酶 (fatty acid synthase, Fas) 以及 HMG-CoA 还原酶在肝脏中也呈现出昼夜节律，当 PPARα 缺失时，它们的振幅相应降低 [24, 25]。在核心时钟基因中，*bmal1* 是唯一一个基因单独缺失即可导致全身节律丧失的核心时钟基因，因此针对其和昼夜节律的相关研究也比较深入。研究显示，*bmal1* 等核心时钟基因的变异和缺失对包括血压、心率 [26]、活动度 [27, 28] 等多种重要生理活动的昼夜节律均可产生重要影响。此外，除调控昼夜节律功能外，*bmal1* 等还可能存在其它非节律相关功能 [26]，如何区分时钟基因的节律与非节律功能、明确其相关关系是目前研究的难点。

2001 年，研究者首次发现在小鼠心脏 [45] 和血管 [46] 中核心时钟基因的表达呈现节律性，并且通过 RNA 测序发现在主动脉和心脏中分别有 6% 和 4% 的编码蛋白的基因呈现节律性表达 [18]。在体外培养的心血管系统的细胞如心肌细胞 [47]、成纤维细胞 [48]、血管平滑肌细胞 [49] 以及内皮细胞 [50] 中也同样发现了核心时钟基因的节律性表达。因此，近年来有关昼夜节律与心血管功能和疾病的关系越来越受到关注，目前大多数研究使用基因修饰技术探讨时钟基因在疾病的发生、发展中的作用。

2 生物钟与心脏疾病

2.1 生物钟与心肌梗死(myocardial infarction, MI)

已知 MI 的发病时间具有明显的昼夜节律特点，与血压的昼夜变化相一致。清晨，收缩期血压和心率增加，心脏的能量和氧气需求增加，而冠状动脉的血管张力在清晨上升，导致冠状动脉血流量和氧供应减少，更易导致心肌缺血 [51]。据报道，MI 在早上的发病率是夜晚的 2~3 倍 [52]。急性 MI 的面积也与昼夜节律紧密相关 [53]。最新的研究表明，生物钟基因的遗传变异可能与 MI 患者的昼夜表型 (即时间型和白天嗜睡) 有关 [54]。Skrlec 等对 200 例因 MI 住院的患者和 200 名健康对照者进行了病例对照研究，根据其先前报道的与心血管危险因素的关联，选择分析了 MI 与 4 个核心时钟基因 (*bmal1*、*clock*、*cry2* 和 *per2*) 中单核苷酸多态性 (SNPs) 的关系，发现 *cry2* 和 *per2* 基因的遗传变异可能与 MI 有关 [55]。但是，时钟基因的变异是否造成了昼夜节律的改变，还需研究明确，而且 MI 的发生是否与昼夜节律的改变直接相关也需要进一步研究。另外，纤溶酶原激活物抑制物 -1[56] 和许多血小板表面活化标记物 (如血小板表面活化糖蛋白 Ib 和 P- 选择素)[57] 显示出明显的昼夜节律，这与血栓形成和血小板聚集的晨峰相一致 [58]，由此导致的血液高凝状态是发生 MI 的重要原因之一。研究证明，昼夜节律紊乱可明显恶化小鼠 MI 后的心室重塑过程，包括炎症浸润加重，细胞外基质沉积增多，梗死面积增大等 [59]。

2.2 生物钟与心律失常

正常状态下哺乳动物的心率表现出明显的昼夜节律特征，研究显示无论是出生前还是出生后敲除核心生物钟基因 *bmal1*，小鼠心率和血压的正常昼夜节律均完全消失 [26]，同时出生前敲除 *bmal1* 还伴随扩张型心肌病的发生 [34]，但 *bmal1* 或其它生物钟基因缺失是否伴随心律失常的发生及其与心率昼夜节律特征改变之间的关系尚需明确。Schroder 等发现在一种新的时钟依赖振荡器 Krüppel 样因子 15 (Klf15) 的控制下，心肌离子通道的表达和 QT 间期 (心肌复极指数) 表现出内源性昼夜节律性，而缺乏或过表达 Klf15 则导致 QT 间期节律的丧失，增加心律失常的发生几率 [34]，提示生物钟基因变异与人类心律失常易感性之间存在潜在的联系。

2.3 生物钟与糖尿病心肌病

糖尿病心肌病是常见的糖尿病的并发症，由代谢性疾病引起的心脏病变，即代谢性心脏病，引起多种结构异常，最终导致左心室肥厚和功能障碍 [60, 61]。高血糖是糖尿病患者心脏损伤的独立危险因素，糖尿病心肌病的发生和发展与高糖的持续时间和严重程度密切相关。对人体和动物模型的大量研究证实，内部时钟系统的紊乱构成肥胖、2 型糖尿病和心血管疾病等代谢相关疾病的危险因素 [62, 63]。*bmal1* 全身敲除小鼠昼夜节律消失，并且在链脲佐菌素诱导的糖尿病模型中，心脏活动的昼夜节律有所改变。*bmal1* 的基因破坏导致糖异生受损、高瘦素血症、葡萄糖不耐受和血脂异常 [29]。Rudic 等的研究显示，小鼠 Bmal1 和 CLOCK 的正常表达促进糖异生，有利于胰岛素低血糖反应的恢复，而 *bmal1* 的缺失抑制糖异生 [29]。另外，Harfmann 等研究显示，骨骼肌中生物钟核心基因 *bmal1* 的缺失导致糖代谢紊乱，表现为葡萄糖摄取受损，伴随着葡萄糖转运体 4 (glucose transporter 4, GLUT 4) 的减少和糖酵解关键消除酶活性的降低 [64]。Qiao 等进一步研究发现，

Bmal1 可通过 mTOR 信号通路调节自噬的正调节因子，保护心肌细胞免受高糖毒性，从而对糖尿病心肌病患者起到保护作用 [65]，但 Bmal1 对糖脂代谢的影响是否与其在昼夜节律中的功能直接相关尚需要进一步明确。

3 生物钟与血管疾病

3.1 生物钟与血压调节

哺乳动物的血压和心率具有一定的昼夜节律。人类的血压在觉醒时急剧上升，并在早上 10 点左右达到高峰。与此同时，许多心血管事件，如心源性猝死、心肌梗死和中风，都表现出日变化，早晨发病率增加 [66]。本研究组通过对出生后 *bmal1* 基因敲除小鼠的研究表明，基础血压的昼夜节律主要受控于生物钟而非行为 [67]。此外，本研究组研究显示，核受体 PPARγ 通过与 *bmal1* 基因的直接相互作用调节血压和心率的昼夜节律 [68, 69]。在小鼠体内全身缺失 *bmal1* 可消除血压的昼夜节律，同时引发低血压，其机制可能是儿茶酚胺的产生减少 [70]。研究显示，在血管内皮细胞和平滑肌细胞特异性敲除 *bmal1* 均能降低平均动脉压 [34, 36, 37]。其他几个核心时钟基因也被报道以不同的方式调节血压。例如 *clock* 基因敲除小鼠动脉压降低，平均动脉压、收缩压和舒张压相对于野生型小鼠降低 10 mmHg 左右 [42]。同样，*per1* 和 *per2* 缺失的小鼠也出现血压降低的现象 [40, 71, 72]。然而，小鼠 *cry1/2* 基因的双重缺失却导致盐敏感性高血压的发生 [44]。由此可知，核心时钟基因对于血压的影响是复杂的。需要注意的是，上述研究多数是通过对时钟基因进行突变或敲除而研究其对血压调节的影响，虽然时钟基因的突变或缺失同时伴随包括血压、心率、活动度等生理活动昼夜节律的改变，但血压调节与昼夜节律改变之间的直接相关性尚需要进一步探讨。

3.2 生物钟与动脉粥样硬化

有关小鼠核心时钟基因突变或缺失引起昼夜节律紊乱并参与动脉粥样硬化发生、发展的研究也有很多。Cheng 等将 *bmal1* 全身敲除小鼠的动脉移植至野生型小鼠体内，引发野生型小鼠明显的动脉硬化病变，表明血管内的生物钟在动脉硬化性疾病中作为一种自主的影响因子发挥着重要作用 [73]。Pan 等研究显示，Clockδ19/δ19 蛋白通过增加肠道胆固醇吸收，增加巨噬细胞对修饰脂蛋白的摄取，减少巨噬细胞胆固醇外流，促使动脉粥样硬化的发生，该研究建立了时钟基因 *clock* 与动脉粥样硬化的联系，表明动脉粥样硬化的形成可能与昼夜节律有关 [43]。Pan 等研究显示，*bmal1* 全身性和肝细胞特异性缺失均能诱导高脂血症并促进动脉粥样硬化，其原因在于 *bmal1* 调节 *shp* 和 *mtp* 基因以调节肝脂蛋白的生成，此外，*bmal1* 通过调节 Gata 4 的表达来调节胆固醇的分泌 [33]。Huo 等也发现，巨噬细胞中的 *bmal1* 缺乏可通过促进 $Ly6c^{hi}$ 单核细胞向动脉粥样硬化病变的聚集而促进动脉粥样硬化的发生 [39]。Yang 等研究显示，与传统的 *bmal1* 全身敲除小鼠 (胚胎期敲除) 不同，成年后敲除 *bmal1* 基因却可以延缓动脉粥样硬化的发生、发展 [26]，提示 *bmal1* 在发育过程中至关重要，其在动脉粥样硬化中的具体作用尚需要进一步明确。Winter 等最新的研究显示，动脉粥样硬化病变部位髓系细胞的募集具有明显节律，并且确定 CCR2-CCL2 轴为其调节因子，据此 Winter 等提出了在高峰期给药抑制髓系细胞募集从而缓解动脉粥样硬化的治疗策略 [74]。同时，动脉硬化与血压昼夜节律也有关，研究显示，夜间血压不降低的非杓型高血压与动脉硬化呈正相关 [75]。同样，上述研究多是生物钟基因突变或缺失对动脉粥样硬化发生、发展的影响，当基因缺失时，是否同时伴随昼夜节律改变，以及节律改变与心血管疾病之间的直接相关性尚需要进一步探讨。

3.3 生物钟与血栓形成

Westgate 等发现，核心时钟基因调控着机体对血栓形成刺激的反应，光化学损伤后血栓闭塞时间 (the time to thrombotic vascular occlusion, TTVO) 存在节律性的日变化，当核心时钟基因 *bmal1*、*clock* 和 *NPAS2* 发生突变或缺失时，这一模式被破坏或改变，时钟基因突变使 TTVO 的日变化消失，而 *NPAS2* 的缺失使 TTVO 延长 [36]。Somanath 等研究显示，无论是在肠系膜动脉血栓还是在颈动脉血栓的模型中，*bmal1* 缺失导致明显的剪切应力依赖性血栓前状态出现，加速血栓形成，这是由于血管性血友病内皮因子 (von Willebrand factor, vWF) 的表达具有昼夜节律，直接受生物钟转录复合体的调控，而这种调节在 *bmal1* 全身敲除小鼠的血管结构中受到损害 [30]。*bmal1* 全身敲除小鼠还具有纤维蛋白原和纤溶酶原激活物抑制剂 (PAI-1) 水平升高的特点 [30]。以上这些研究表明，核心时钟基因与血栓形成密切相关，*bmal1* 调控了凝血途径的几个关键分子的表达。

3.4 生物钟与血管损伤和重构

血管功能障碍被证明是诸多血管疾病的发生基础。血管内皮细胞可通过分泌 NO、前列腺素 I2 (prostacyclin I2, PGI2)、内皮素 1 (endothelin 1, ET-1) 等一系列血管活性物质发挥调节血管紧张性、抗血栓形成、抑制平滑肌细胞增殖及血管壁炎症反应等功能，维持正常的收缩和舒张。核心时钟基因 *bmal1* 和 *clock* 的缺失可导致类似代谢综合征的表型，如肥胖、血脂异常、高血压、胰岛素抵抗和高血糖等 [76]。这些危险因素可造成血管损伤，尤其是促进内皮功能障碍，导致心血管疾病的发生。*bmal1* 基因敲除和 *per2* 亚型突变的小鼠会出现内皮功能障碍，表现为对乙酰胆碱的内皮依赖性舒张作用减弱 [77, 78]。时钟基因 *clock* 突变小鼠出现 Akt 和内皮型一氧化氮合酶 (endothelial nitric oxide synthase, eNOS) 的失调，这在内皮张力调节中起着关键作用 [79]；Anea 等研究显示，*bmal1* 通过控制 eNOS 与其辅助因子四氢生物蝶呤 (tetrahydrobiopterin, BH4) 的耦联调节内皮超氧化物歧化酶 (superoxide dismutase, SOD) 的产生，从而维持血管正常功能 [31]。

Anea 等对 *bmal1* 和 *clock* 全身敲除小鼠行左颈总动脉结扎以及颈动脉导丝拉伤术，发现 *bmal1* 和 *clock* 的缺失使血管损伤和病理重构增加，这与 Akt 和下游的 NO 信号减弱而导致的血管功能障碍相关 [78]。Bhatwadekar 等研究显示，*bmal1* 在血管内皮细胞中的条件缺失可促进视网膜微血管和股动脉大血管的损伤，进一步证明了昼夜节律的破坏加速血管损伤进程 [35]。Mehta 等 [80] 研究显示，在平滑肌细胞中特异性缺失 *bmal1* 可改变动脉瘤的发生、发展，起到延缓动脉瘤发生的保护作用，其原因是平滑肌细胞 *bmal1* 的缺失选择性地上调了金属蛋白酶组织抑制因子 4 (metalloproteinase tissue inhibitor 4, TIMP4) 的表达，抑制了醋酸脱氧皮质酮盐诱导的基质金属蛋白酶 (matrix metalloproteinase, MMP) 激活和弹性蛋白断裂。上述研究表明，核心时钟基因在血管疾病的病理生理过程中发挥的作用是复杂的，需要更深入的研究和探讨。

4 生物钟在心血管疾病治疗中的应用

正常活动和休息的紊乱 (如睡眠剥夺或轮班工作) 会导致生理活动与内在时钟之间的失调，从而对心血管功能产生不利影响 [81]。由于急性心血管事件与节律的重大相关性，基于分子水平的研究显得尤为重要。除了发病机制的研究，在疾病的治疗方面，依据节律变化特点改进治疗方法是一个新的研究切入点。给药时间的选择，甚至心血管外科手术的时间选择都会影响组织的修复和疾病的转归。本研究组研究显示，阿司匹林的降压疗效具有明显的时效性，无论是高血压患者还是在高盐引起的高血压小鼠模型，临睡前给予阿司匹林，其降压效果明显优于晨起给药 [82]。同样，另一项研究也显示，硝苯地平睡前给药能使非杓型高血压患病率降低，缓解夜间外周浮肿 [83]。此外，Montaigne 等研究发现，在主动脉瓣置换术后 500 d 内，下午手术组的主要不良心脏事件发生率低于上午组 [84]，提示心血管外科手术的安排也要考虑时间因素。因此，更好地理解生物钟与心血管疾病之间的联系可能有助于为心血管疾病患者制定更有针对性和个性化的治疗策略。

5 结语

生物钟在心血管正常生理活动中发挥重要作用。同时，生物钟与心血管疾病的发生、发展又有着复杂的联系。诸多研究表明，当生物钟基因发生变化或缺失时，心血管疾病的发生、发展受到不同程度和方向的影响。日后的研究除了要探索生物钟基因的复杂生理功能外，更应关注生物钟基因改变引起的昼夜节律变化与心血管疾病的直接相关性，这有可能使生物钟基因以及昼夜节律成为心血管疾病治疗的新靶点。

参考文献

1 Harmer SL, Panda S, Kay SA. Molecular bases of circadian rhythms. Annu Rev Cell Dev Biol 2001; 17: 215–253.

2 Refinetti R, Menaker M. The circadian rhythm of body temperature. Physiol Behav 1992; 51(3): 613–637.

3 Refinetti R. The circadian rhythm of body temperature. Front Biosci (Landmark Ed) 2010; 15: 564–594.

4 Fisk AS, Tam SKE, Brown LA, Vyazovskiy VV, Bannerman DM, Peirson SN. Light and cognition: roles for circadian rhythms, sleep, and arousal. Front Neurol 2018; 9: 56.

5 Bass J, Takahashi JS. Circadian integration of metabolism and energetics. Science 2010; 330(6009): 1349–1354.

6 Serin Y, Acar Tek N. Effect of circadian rhythm on metabolic processes and the regulation of energy balance. Ann Nutr Metab 2019; 74(4): 322–330.

7 Polonia J, Amado P, Barbosa L, Nazare J, Silva JA, Bertoquini S, Martins L, Carmona J. Morning rise, morning surge and daytime variability of blood pressure and cardiovascular target organ damage. A cross-sectional study in 743

subjects. Rev Port Cardiol 2005; 24(1): 65–78.
8 Elliott WJ. Circadian variation in the timing of stroke onset. Stroke 1998; 29(5): 992–996.
9 Chen L, Yang G. Recent advances in circadian rhythms in cardiovascular system. Front Pharmacol 2015; 6: 71.
10 Feng D, Lazar MA. Clocks, metabolism, and the epigenome. Mol Cell 2012; 47(2): 158–167.
11 Kohsaka A, Waki H, Cui H, Gouraud SS, Maeda M. Integration of metabolic and cardiovascular diurnal rhythms by circadian clock. Endocr J 2012; 59(6): 447–456.
12 Paschos GK, FitzGerald GA. Circadian clocks and vascular function. Circ Res 2010; 106(5): 833–841.
13 Panza JA, Epstein SE, Quyyumi AA. Circadian variation in vascular tone and its relation to alpha-sympathetic vasoconstrictor activity. N Engl J Med 1991; 325(14): 986–990.
14 Cohen MC, Rohtla KM, Lavery CE, Muller JE, Mittleman MA. Meta-analysis of the morning excess of acute myocardial infarction and sudden cardiac death. Am J Cardiol 1997; 79(11): 1512–1516.
15 Knutsson A. Increased risk of ischaemic heart disease in shift workers. Occup Med (Lond) 1995; 45(1): 55.
16 Schibler U. The daily rhythms of genes, cells and organs. Biological clocks and circadian timing in cells. EMBO Rep 2005; 6 Spec No: S9–S13.
17 Takeda N, Maemura K. Circadian clock and vascular disease. Hypertens Res 2010; 33(7): 645–651.
18 Zhang R, Lahens NF, Ballance HI, Hughes ME, Hogenesch JB. A circadian gene expression atlas in mammals: implications for biology and medicine. Proc Natl Acad Sci U S A 2014; 111(45): 16219–16224.
19 Kowalska E, Brown SA. Peripheral clocks: keeping up with the master clock. Cold Spring Harb Symp Quant Biol 2007; 72: 301–305.
20 Myung J, Wu MY, Lee CY, Rahim AR, Truong VH, Wu D, Piggins HD, Wu MS. The kidney clock contributes to timekeeping by the master circadian clock. Int J Mol Sci 2019; 20(11). DOI: 10.3390/ijms20112765.
21 Yang G, Paschos G, Curtis AM, Musiek ES, McLoughlin SC, FitzGerald GA. Knitting up the raveled sleave of care. Sci Transl Med 2013; 5(212): 212rv3.
22 Dibner C, Schibler U, Albrecht U. The mammalian circadian timing system: organization and coordination of central and peripheral clocks. Annu Rev Physiol 2010; 72: 517–549.
23 Partch CL, Green CB, Takahashi JS. Molecular architecture of the mammalian circadian clock. Trends Cell Biol 2014; 24(2): 90–99.
24 Gibbons GF, Patel D, Wiggins D, Knight BL. The functional efficiency of lipogenic and cholesterogenic gene expression in normal mice and in mice lacking the peroxisomal proliferator-activated receptor-alpha (PPAR-α). Adv Enzyme Regul 2002; 42: 227–247.
25 Patel DD, Knight BL, Wiggins D, Humphreys SM, Gibbons GF. Disturbances in the normal regulation of SREBP-sensitive genes in PPAR alpha-deficient mice. J Lipid Res 2001; 42(3): 328–337.
26 Yang G, Chen L, Grant GR, Paschos G, Song WL, Musiek ES, Lee V, McLoughlin SC, Grosser T, Cotsarelis G, FitzGerald GA. Timing of expression of the core clock gene Bmal1 influences its effects on aging and survival. Sci Transl Med 2016; 8(324): 324ra316.
27 Zheng B, Larkin DW, Albrecht U, Sun ZS, Sage M, Eichele G, Lee CC, Bradley A. The mPer2 gene encodes a functional component of the mammalian circadian clock. Nature 1999; 400(6740): 169–173.
28 van der Horst GT, Muijtjens M, Kobayashi K, Takano R, Kanno S, Takao M, de Wit J, Verkerk A, Eker AP, van Leenen D, Buijs R, Bootsma D, Hoeijmakers JH, Yasui A. Mammalian Cry1 and Cry2 are essential for maintenance of circadian rhythms. Nature 1999; 398(6728): 627–630.
29 Rudic RD, McNamara P, Curtis AM, Boston RC, Panda S, Hogenesch JB, Fitzgerald GA. BMAL1 and CLOCK, two essential components of the circadian clock, are involved in glucose homeostasis. PLoS Biol 2004; 2(11): e377.
30 Somanath PR, Podrez EA, Chen J, Ma Y, Marchant K, Antoch M, Byzova TV. Deficiency in core circadian protein Bmal1 is associated with a prothrombotic and vascular phenotype. J Cell Physiol 2011; 226(1): 132–140.
31 Anea CB, Cheng B, Sharma S, Kumar S, Caldwell RW, Yao L, Ali MI, Merloiu AM, Stepp DW, Black SM, Fulton DJ, Rudic RD. Increased superoxide and endothelial NO synthase uncoupling in blood vessels of Bmal1-knockout mice. Circ Res 2012; 111(9): 1157–1165.
32 Lefta M, Campbell KS, Feng HZ, Jin JP, Esser KA. Development of dilated cardiomyopathy in Bmal1-deficient mice. Am J Physiol Heart Circ Physiol 2012; 303(4): H475–485.
33 Pan X, Bradfield CA, Hussain MM. Global and hepatocyte-specific ablation of Bmal1 induces hyperlipidaemia and enhances atherosclerosis. Nat Commun 2016; 7: 13011.
34 Schroder EA, Lefta M, Zhang X, Bartos DC, Feng HZ, Zhao Y, Patwardhan A, Jin JP, Esser KA, Delisle BP. The cardiomyocyte molecular clock, regulation of Scn5a, and arrhythmia susceptibility. Am J Physiol Cell Physiol 2013; 304(10): C954–C965.
35 Bhatwadekar AD, Beli E, Diao Y, Chen J, Luo Q, Alex A, Caballero S, Dominguez JM, Salazar TE, Busik JV, Segal MS, Grant MB. Conditional deletion of Bmal1 accentuates microvascular and macrovascular injury. Am J Pathol 2017; 187(6): 1426–1435.
36 Westgate EJ, Cheng Y, Reilly DF, Price TS, Walisser JA, Bradfield CA, FitzGerald GA. Genetic components of the

circadian clock regulate thrombogenesis *in vivo*. Circulation 2008; 117(16): 2087–2095.

37 Xie Z, Su W, Liu S, Zhao G, Esser K, Schroder EA, Lefta M, Stauss HM, Guo Z, Gong MC. Smooth-muscle BMAL1 participates in blood pressure circadian rhythm regulation. J Clin Invest 2014; 125(1): 324–336.

38 Ingle KA, Kain V, Goel M, Prabhu SD, Young ME, Halade GV. Cardiomyocyte-specific Bmal1 deletion in mice triggers diastolic dysfunction, extracellular matrix response, and impaired resolution of inflammation. Am J Physiol Heart Circ Physiol 2015; 309(11): H1827–H1836.

39 Huo M, Huang Y, Qu D, Zhang H, Wong WT, Chawla A, Huang Y, Tian XY. Myeloid Bmal1 deletion increases monocyte recruitment and worsens atherosclerosis. FASEB J 2017; 31(3): 1097–1106.

40 Solocinski K, Holzworth M, Wen X, Cheng KY, Lynch IJ, Cain BD, Wingo CS, Gumz ML. Desoxycorticosterone pivalate-salt treatment leads to non-dipping hypertension in Per1 knockout mice. Acta Physiol (Oxf) 2017; 220(1): 72–82.

41 Qin T, Sun YY, Bai WW, Wang B, Xing YF, Liu Y, Yang RX, Zhao YX, Li JM. Period2 deficiency blunts hypoxia-induced mobilization and function of endothelial progenitor cells. PLoS One 2014; 9(9): e108806.

42 Zuber AM, Centeno G, Pradervand S, Nikolaeva S, Maquelin L, Cardinaux L, Bonny O, Firsov D. Molecular clock is involved in predictive circadian adjustment of renal function. Proc Natl Acad Sci U S A 2009; 106(38): 16523–16528.

43 Pan XY, Jiang XC, Hussain MM. Impaired cholesterol metabolism and enhanced atherosclerosis in clock mutant mice. Circulation 2013; 128(16): 1758–1769.

44 Masuki S, Todo T, Nakano Y, Okamura H, Nose H. Reduced alpha-adrenoceptor responsiveness and enhanced baroreflex sensitivity in Cry-deficient mice lacking a biological clock. J Physiol 2005; 566(Pt 1): 213–224.

45 Young ME, Razeghi P, Taegtmeyer H. Clock genes in the heart: characterization and attenuation with hypertrophy. Circ Res 2001; 88(11): 1142–1150.

46 McNamara P, Seo SB, Rudic RD, Sehgal A, Chakravarti D, FitzGerald GA. Regulation of CLOCK and MOP4 by nuclear hormone receptors in the vasculature: a humoral mechanism to reset a peripheral clock. Cell 2001; 105(7): 877–889.

47 Durgan DJ, Hotze MA, Tomlin TM, Egbejimi O, Graveleau C, Abel ED, Shaw CA, Bray MS, Hardin PE, Young ME. The intrinsic circadian clock within the cardiomyocyte. Am J Physiol Heart Circ Physiol 2005; 289(4): H1530–H1541.

48 Welsh DK, Yoo SH, Liu AC, Takahashi JS, Kay SA. Bioluminescence imaging of individual fibroblasts reveals persistent, independently phased circadian rhythms of clock gene expression. Curr Biol 2004; 14(24): 2289–2295.

49 Nonaka H, Emoto N, Ikeda K, Fukuya H, Rohman MS, Raharjo SB, Yagita K, Okamura H, Yokoyama M. Angiotensin II induces circadian gene expression of clock genes in cultured vascular smooth muscle cells. Circulation 2001; 104(15): 1746–1748.

50 Takeda N, Maemura K, Horie S, Oishi K, Imai Y, Harada T, Saito T, Shiga T, Amiya E, Manabe I, Ishida N, Nagai R. Thrombomodulin is a clock-controlled gene in vascular endothelial cells. J Biol Chem 2007; 282(45): 32561–32567.

51 Mori H, Nakamura N, Tamura N, Sawai M, Tanno T, Narita T, Singh RB, Otsuka K. Circadian variation of basal total vascular tone and chronotherapy in patients with vasospastic angina pectoris. Biomed Pharmacother 2002; 56 Suppl 2: 339s–344s.

52 Culic V. Chronobiological rhythms of acute cardiovascular events and underlying mechanisms. Int J Cardiol 2014; 174(2): 417–419.

53 Bulluck H, Nicholas J, Crimi G, White SK, Ludman AJ, Pica S, Raineri C, Cabrera-Fuentes HA, Yellona D, Rodriguez-Palomares J, Garcia-Dorado D, Hausenloy DJ. Circadian variation in acute myocardial infarct size assessed by cardiovascular magnetic resonance in reperfused STEMI patients. Int J Cardiol 2017; 230: 149–154.

54 Skrlec I, Milic J, Heffer M, Wagner J, Peterlin B. Circadian clock genes and circadian phenotypes in patients with myocardial infarction. Adv Med Sci 2019; 64(2): 224–229.

55 Skrlec I, Milic J, Heffer M, Peterlin B, Wagner J. Genetic variations in circadian rhythm genes and susceptibility for myocardial infarction. Genet Mol Biol 2018; 41(2): 403–409.

56 Kurnik PB. Circadian variation in the efficacy of tissue-type plasminogen activator. Circulation 1995; 91(5): 1341–1346.

57 Scheer FA, Michelson AD, Frelinger AL 3rd, Evoniuk H, Kelly EE, McCarthy M, Doamekpor LA, Barnard MR, Shea SA. The human endogenous circadian system causes greatest platelet activation during the biological morning independent of behaviors. PLoS One 2011; 6(9): e24549.

58 Gum PA, Kottke-Marchant K, Poggio ED, Gurm H, Welsh PA, Brooks L, Sapp SK, Topol EJ. Profile and prevalence of aspirin resistance in patients with cardiovascular disease. Am J Cardiol 2001; 88(3): 230–235.

59 Alibhai FJ, Tsimakouridze EV, Chinnappareddy N, Wright DC, Billia F, O'Sullivan ML, Pyle WG, Sole MJ, Martino TA. Short-term disruption of diurnal rhythms after murine myocardial infarction adversely affects long-term myocardial structure and function. Circ Res 2014; 114(11): 1713–1722.

60 Bugger H, Abel ED. Molecular mechanisms of diabetic cardiomyopathy. Diabetologia 2014; 57(4): 660–671.

61 Huynh K, Bernardo BC, McMullen JR, Ritchie RH. Diabetic cardiomyopathy: mechanisms and new treatment strategies targeting antioxidant signaling pathways. Pharmacol Ther

2014; 142(3): 375–415.
62 Spiegel K, Tasali E, Leproult R, Van Cauter E. Effects of poor and short sleep on glucose metabolism and obesity risk. Nat Rev Endocrinol 2009; 5(5): 253–261.
63 Suwazono Y, Dochi M, Sakata K, Okubo Y, Oishi M, Tanaka K, Kobayashi E, Kido T, Nogawa K. A longitudinal study on the effect of shift work on weight gain in male Japanese workers. Obesity (Silver Spring) 2008; 16(8): 1887–1893.
64 Harfmann BD, Schroder EA, Kachman MT, Hodge BA, Zhang X, Esser KA. Muscle-specific loss of Bmal1 leads to disrupted tissue glucose metabolism and systemic glucose homeostasis. Skelet Muscle 2016; 6: 12.
65 Qiao L, Guo B, Zhang H, Yang R, Chang L, Wang Y, Jin X, Liu S, Li Y. The clock gene, brain and muscle Arnt-like 1, regulates autophagy in high glucose-induced cardiomyocyte injury. Oncotarget 2017; 8(46): 80612–80624.
66 Reavey M, Saner H, Paccaud F, Marques-Vidal P. Exploring the periodicity of cardiovascular events in Switzerland: variation in deaths and hospitalizations across seasons, day of the week and hour of the day. Int J Cardiol 2013; 168(3): 2195–2200.
67 Yang G, Chen L, Zhang J, Ren B, FitzGerald GA. Bmal1 deletion in mice facilitates adaptation to disrupted light/dark conditions. JCI Insight 2019; 5. pii: 125133.
68 Yang G, Jia Z, Aoyagi T, McClain D, Mortensen RM, Yang T. Systemic PPARgamma deletion impairs circadian rhythms of behavior and metabolism. PLoS One 2012; 7(8): e38117.
69 Wang N, Yang G, Jia Z, Zhang H, Aoyagi T, Soodvilai S, Symons JD, Schnermann JB, Gonzalez FJ, Litwin SE, Yang T. Vascular PPARgamma controls circadian variation in blood pressure and heart rate through Bmal1. Cell Metab 2008; 8(6): 482–491.
70 Curtis AM, Cheng Y, Kapoor S, Reilly D, Price TS, Fitzgerald GA. Circadian variation of blood pressure and the vascular response to asynchronous stress. Proc Natl Acad Sci U S A 2007; 104(9): 3450–3455.
71 Vukolic A, Antic V, Van Vliet BN, Yang Z, Albrecht U, Montani JP. Role of mutation of the circadian clock gene Per2 in cardiovascular circadian rhythms. Am J Physiol Regul Integr Comp Physiol 2010; 298(3): R627–R634.
72 Stow LR, Richards J, Cheng KY, Lynch IJ, Jeffers LA, Greenlee MM, Cain BD, Wingo CS, Gumz ML. The circadian protein period 1 contributes to blood pressure control and coordinately regulates renal sodium transport genes. Hypertension 2012; 59(6): 1151–1156.
73 Cheng B, Anea CB, Yao L, Chen F, Patel V, Merloiu A, Pati P, Caldwell RW, Fulton DJ, Rudic RD. Tissue-intrinsic dysfunction of circadian clock confers transplant arteriosclerosis. Proc Natl Acad Sci U S A 2011; 108(41): 17147–17152.
74 Winter C, Silvestre-Roig C, Ortega-Gomez A, Lemnitzer P, Poelman H, Schumski A, Winter J, Drechsler M, de Jong R, Immler R, Sperandio M, Hristov M, Zeller T, Nicolaes GAF, Weber C, Viola JR, Hidalgo A, Scheiermann C, Soehnlein O. Chrono-pharmacological targeting of the CCL2-CCR2 axis ameliorates atherosclerosis. Cell Metab 2018; 28(1): 175–182.e5
75 Park JS, Shin JH, Park JB, Choi DJ, Youn HJ, Park CG, Kwan J, Ahn Y, Kim DW, Rim SJ, Park SW, Sung J, Bae JH; Korean Hypertension Research Network. Relationship between arterial stiffness and circadian pattern of blood pressure. Medicine (Baltimore) 2019; 98(12): e14953.
76 Turek FW, Joshu C, Kohsaka A, Lin E, Ivanova G, McDearmon E, Laposky A, Losee-Olson S, Easton A, Jensen DR, Eckel RH, Takahashi JS, Bass J. Obesity and metabolic syndrome in circadian Clock mutant mice. Science 2005; 308(5724): 1043–1045.
77 Viswambharan H, Carvas JM, Antic V, Marecic A, Jud C, Zaugg CE, Ming XF, Montani JP, Albrecht U, Yang Z. Mutation of the circadian clock gene Per2 alters vascular endothelial function. Circulation 2007; 115(16): 2188–2195.
78 Anea CB, Zhang M, Stepp DW, Simkins GB, Reed G, Fulton DJ, Rudic RD. Vascular disease in mice with a dysfunctional circadian clock. Circulation 2009; 119(11): 1510–1517.
79 Ko ML, Jian KH, Shi LH, Ko GYP. Phosphatidylinositol 3 kinase-Akt signaling serves as a circadian output in the retina. J Neurochem 2009; 108(6): 1607–1620.
80 Mehta RH, Manfredini R, Hassan F, Sechtem U, Bossone E, Oh JK, Cooper JV, Smith DE, Portaluppi F, Penn M, Hutchison S, Nienaber CA, Isselbacher EM, Eagle KA, International Registry of Acute Aortic Dissection I. Chronobiological patterns of acute aortic dissection. Circulation 2002; 106(9): 1110–1115.
81 Morris CJ, Purvis TE, Hu K, Scheer FA. Circadian misalignment increases cardiovascular disease risk factors in humans. Proc Natl Acad Sci U S A 2016; 113(10): E1402–E1411.
82 Chen L, Yang G, Zhang J, Ren B, Tang S, Li X, FitzGerald GA. Time-dependent hypotensive effect of aspirin in mice. Arterioscler Thromb Vasc Biol 2018; 38(12): 2819–2826.
83 Hermida RC, Ayala DE, Mojon A, Fernandez JR. Chronotherapy with nifedipine GITS in hypertensive patients: improved efficacy and safety with bedtime dosing. Am J Hypertens 2008; 21(8): 948–954.
84 Montaigne D, Marechal X, Modine T, Coisne A, Mouton S, Fayad G, Ninni S, Klein C, Ortmans S, Seunes C, Potelle C, Berthier A, Gheeraert C, Piveteau C, Deprez R, Eeckhoute J, Duez H, Lacroix D, Deprez B, Jegou B, Koussa M, Edme JL, Lefebvre P, Staels B. Daytime variation of perioperative myocardial injury in cardiac surgery and its prevention by Rev-Erbα antagonism: a single-centre propensity-matched cohort study and a randomised study. Lancet 2018; 391(10115): 59–69.