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基于氧化应激探讨热量限制及其模拟物改善心血管疾病的研究进展

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摘 要：氧化应激能够导致心血管系统氧化与抗氧化的失衡，引起细胞化学损害，从而导致疾病的发生和发展。热量限制 (caloric restriction, CR) 通过改善机体氧化应激状态，可以降低心血管疾病风险。本文介绍了氧化应激与心血管疾病的关系，概括了 CR 对氧化应激的各方面调控机制，并探讨了几种常见热量限制模拟物 (caloric restriction mimetics, CRM) 调节氧化应激水平的主要通路，以期深入了解心血管疾病的发病机制，探求更科学有效的药物靶点。

关键词：氧化应激；热量限制；饮食限制；心血管
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Research progress on roles of caloric restriction and its mimics in improving cardiovascular diseases based on oxidative stress

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Abstract: Oxidative stress can induce imbalance between oxidation and antioxidants in the cardiovascular system and then cause chemical damage to cells, playing a role in the occurrence and development of diseases. Caloric restriction (CR) can reduce the risk of cardiovascular diseases by improving the body's oxidative stress state. This article briefly discusses the relationship between oxidative stress and cardiovascular diseases, and reviews the regulation mechanism of CR on oxidative stress in various aspects. In addition, this article also introduces several common caloric restriction mimics and explains the main pathways through which they regulate the level of oxidative stress. In this way, we can gain an in-depth understanding of the pathogenesis of cardiovascular diseases, and explore more scientific and effective drug targets.

Key words: oxidative stress; calorie restriction; dietary restriction; cardiovascular

众所周知，氧化应激在疾病的发生发展和病理改变中具有重要作用 [1]。活性氧 (reactive oxygen species, ROS) 的产生与爆发和抗氧化防御系统之间的不平衡密切相关，ROS 清除酶功能受损可导致氧化应激水平升高 [2]。过度产生的 ROS 在生物系统中对生物大分子，如脂质，蛋白质和 DNA 具有有害作用，还充当细胞信号转导第二信使，通过靶向调节途径，导致细胞炎症信号激活或程序性细胞死亡 [3]。

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心血管疾病是全球死亡的首要原因[4]。有证据表明，氧化应激在动脉粥样硬化、心脏衰竭、心律失常和缺血再灌注等多种心血管疾病的进展中起重要作用[5-6]。尽管人们在心血管疾病治疗领域已经取得了重大进展，但其发病率和死亡率仍然居高不下，因此，有必要评估其他治疗方案——如热量限制——以防治与氧化应激相关的心血管疾病。

热量限制 (caloric restriction, CR) 又称为饮食限制，是指在不造成营养不良的前提下，限制机体摄入的总热量，将食物摄入量减少每日能量需求的25%~30% 的饮食方式[7-8]。早在 20 世纪 30 年代，就已经有研究证明 CR 能够显著延长寿命，实验受体从酵母菌到与人类基因相似度极高的猩猩，均证明了 CR 的有益作用[7]。饮食限制通过调节饮食习惯改善人体状况，不仅绿色简单，且效果明显，已作为一种新型治疗方案应用于临床[9]。

在本综述中，我们将基于氧化应激探讨热量限制及其模拟物在心血管疾病中的治疗意义，探讨其作用机制，将 CR 作为一种绿色无害的治疗手段推广到临床，为心血管疾病的治疗提供新的思路。

1 热量限制

CR 的有益作用由美国康奈尔大学的 McCay 教授[10]于 1933 年首次发现，被称为衰老研究领域最重大的突破。大量实验已验证 CR 是延缓衰老的有效方法，CR 已经成为衰老机制及干预措施研究的一个重要模型[7]，并且已有不少研究探索了 CR 在临床中的应用。除此之外，CR 能够降低体重、血压、血脂等，并通过调整代谢来预防心血管疾病、2 型糖尿病、代谢综合征等常见疾病[11-15]。令人意想不到的是，CR 还能够治疗贫血[16]、神经退行性疾病[17]、体弱综合征[18]、癫痫[19]、癌症[20-21]并降低放射治疗癌症的副作用[22]，提高免疫力[23]。已有大量研究证明它可以延缓啮齿动物和非人灵长类动物衰老，延长健康寿命[24]，并改善各种疾病[25-26]。

Mitchell 等[27]的研究表明，CR 对心血管的改善与限食强度和持续时间相关，与饮食构成无关，CR 强度越大，持续时间越长，效果越明显。30% CR 干预 6 周的结果表明，CR 通过腺苷酸活化蛋白激酶 (AMP-activated protein kinase, AMPK) / 沉默信息调节因子 1 (sirtuin1, SIRT1)/ 过氧化物酶体增殖物激活受体 -γ 共激活因子 -1α (peroxisome proliferators activated receptor γ co-activator 1 α, PGC-1α) 通路改变心肌底物能量代谢，促进糖酵解，并恢复老龄鼠的心肌葡萄糖摄取，减少心肌缺血再灌注损伤后的梗死面积[28]。从上述结果可以看出，随着 CR 的强度和作用时间的增加，CR 对人体各个部位的作用也会更加显著。短期的饮食干预可能仅对一些特殊的疾病类型存在明显的影响，而随着干预强度的加大，干预时间的延长，CR 的效益从改善体重拓展到心血管系统，乃至机体的各个部分。

但 CR 并非百利而无一害，随着近年来对 CR 研究的愈发深入，发现接受 CR 的动物除了具备脂肪含量较低且寿命较长的益处之外，还存在体型缩小、繁殖力低下、发育较慢的副作用[29]，并且伴随着行为模式的转变[30]。因此在对体型较小、营养不良的患者实施 CR 时要谨慎。此外，CR 应当循序渐进且限制在每日能量需求的 70%~75%，即 25%~30% 的 CR 是适宜的。过度的 CR 损害了肌质网 (SR) 中肌浆网钙离子 ATP 酶 2a (SERCA2a) 的活性，降低了 L 型 Ca^{2+} 通道的表达，对心脏收缩功能产生了负面影响[31]；仅 2 周 60% 的 CR 就会导致肠系膜动脉内皮功能障碍以及缺血再灌注，从而诱发心律失常和心脏病变[32]；过度的 CR (60%，14 天) 还会导致肌原纤维紊乱伴收缩、心肌细胞溶解，心律失常的概率比正常饮食组增加了 1.7 倍[32]。有研究者还提出 CR 仅对幼年动物有益，对老龄动物采用 CR 可能不会延长寿命[33]。除了年龄差异外，CR 对机体的影响还可能存在基因差异和性别差异，较低的 CR 水平可能会延长对 CR 无应答或应答消极基因型的寿命，且雌性小鼠对 CR 较雄性小鼠更敏感[34]。由此可见，CR 对年轻患者、女性患者更加有益，但 CR 的实施应当控制在适宜范围之内，并注意副作用的影响。

2 氧化应激与心血管疾病

氧化应激是机体产生 ROS 干扰内源性抗氧化防御系统平衡，导致机体性质改变和功能障碍的重要病理过程[35]，是心血管疾病的主要致病因素[36]。CR 可以改善动物各组织和器官中的氧化损伤[37]，调节氧化应激水平[38]，从而降低心血管疾病的发生率和死亡率。

1956 年，英国学者 Harmna 首次提出自由基衰老学说；1990 年，美国衰老研究权威 Sohal 教授[39]等指出了自由基衰老学说的种种缺陷，并首先提出了氧化应激的概念。衰老、饮食等因素都能够引起氧化应激[40-41]，心脏缺血更会导致 ROS 增加 250%[42]。及时再灌注是治疗心肌缺血的方案，但这

个过程极有可能导致氧化应激和炎症反应，最终导致心肌细胞或内皮细胞死亡[43]。氧化应激水平失衡存在于病理状态下，与细胞毒性密切相关，直接参与心脏组织的发病机制，这可以在分子水平上解释心脏重塑和心功能障碍的发生。

转录激活因子 3 (STAT3) 是心脏微血管损伤和线粒体氧化应激之间的介质[44]，SIRT3~5 可通过氧化应激介导心脏损伤。当血管内皮细胞损伤时，辣椒素受体 (TRPV1) 抑制 SIRT1 的表达[45]，细胞质中下调的 SIRT1 继而阻断了 SIRT3 脱乙酰化，增加了炎症和氧化应激[46]。此外，细胞内钙离子浓度降低，PGC-1α 的异常激活导致 SIRT3 失调，从而诱导视神经萎缩蛋白 1 (OPA1) 介导的线粒体动态重塑，引发氧化应激[47]。据报道，Ⅲ型磷脂酰肌醇 3-磷酸 5- 激酶 (PIKfyve) 等脂质激酶是心脏代谢状态和线粒体完整性的关键调节器，能诱导线粒体 ROS 的产生和凋亡，并通过 SIRT3 依赖的通路减轻心脏肥大并改善心脏功能[48]。故而抑制 PIKfyve 即可抑制氧化应激、细胞凋亡和线粒体损伤。

线粒体是细胞动力源，是 ROS 与心衰重塑的关键，在维持细胞氧化还原平衡方面起着重要作用[49]。电子传递链中线粒体复合物 I 和 III 是 ROS 的主要来源，ROS 在正常生理状态下会被抗氧化防御系统抵消[38]。研究发现，G 蛋白偶联受体激活可导致 ROS 产生[38]，ROS 又能反过来刺激 G 蛋白，以促进心肌细胞增生[50]。ROS 还刺激细胞凋亡，当凋亡信号调节激酶 1 (ASK1) 过度表达时，通过特异性相关的基因表达抑制核因子 -κB (nuclear transcription factor-kappa B, NF-κB) 诱导的肥大[50]。当缺血性损伤发生时，线粒体产生过多的 ROS 对其作出应答，导致能量代谢异常和线粒体功能障碍[51]。

AMPK 是脂质代谢的中心调节器，也是介导氧化应激的关键分子，通过激活叉头转录因子 O1 (forkhead box O1, FOXO1)、抑制哺乳动物雷帕霉素靶蛋白 (mammalian target of rapamycin, mTOR) 信号来维持氧化还原平衡[52]。在肥胖诱导的心脏肥大中，脂肪代谢相关基因的敲除会导致 AMPK 磷酸化降低，而 mTOR 磷酸化升高[53]，加剧了心脏肥大、纤维化、内质网应激引发的细胞凋亡和氧化应激；它还可以通过 NF-κB/ 衰老相关分泌表型 (SASP)/STAT3 信号通路来防止氧化应激诱导的衰老[54]。此外，另一个脂质调节器脂滴包被蛋白 5 (PLIN5) 也参与脂滴的代谢，在心脏中高表达，在抑制 ROS 产生和减少氧化应激方面起着积极作用[55]。在压力过载的情况下，缺乏 PLIN5 的小鼠表现出心脏肥大和功能障碍的加重；并随着心脏脂质积累的减少，线粒体脂肪酸氧化增加，氧化应激加剧[56]。AMPK 还调节线粒体来源的 PGC-1α/ 缺氧诱导因子 -1α (HIF-1α) 信号转导，从而抑制 ROS 的产生[57]。Wang 等[58] 研究表明，高血糖可以以 AMPK 依赖的方式诱导烟酰胺腺嘌呤二核苷酸磷酸氧化酶 (NADPH oxidase, NOX) 相关的氧化应激。NOX2 主要在吞噬细胞中表达，是吞噬细胞 NADPH 氧化酶的催化亚基，其生物学功能是产生 ROS，常见于心衰和癌症等疾病[59-60]。高脂饮食小鼠即表现出 NOX2 水平升高，伴随心肌细胞增大、氧化应激增加以及异常的氧化还原信号[61]。

尽管大多数内源性氧化应激由线粒体所致，但无可争议的是，许多其他细胞结构也与氧化应激直接或间接相关。细胞外基质 (ECM) 是 ROS 有害作用的潜在靶标。ECM 是由细胞分泌到细胞外间质中的大分子物质所构成的复杂网络动态结构，为细胞和组织提供结构支持，并在健康和疾病中发挥重要作用[62]。ROS 可通过刺激心脏成纤维细胞的增殖来影响 ECM[50]，导致纤维化和基质重塑；同时，ROS 可刺激转录因子，如 NF-κB 和转录因子激活蛋白 -1 (AP-1)，以激活基质金属蛋白酶 (MMP) 表达[38]，MMP 参与细胞迁移、侵袭、增殖和凋亡，在正常的组织重塑过程中起着关键作用[62]。过量 ROS 引起的另一种有害作用发生在兰尼碱受体 (RyRs)[51]，它位于 SR 中，负责在横纹肌细胞兴奋 - 收缩耦联期间释放钙离子[63]。ROS 促进 RyRs 活性并抑制 SERCA2a 的活性，使钙过载和肌丝钙敏感性降低，导致收缩功能障碍[51]。

虽然不同细胞结构中的氧化应激对心血管的损害不同，但不可否认氧化应激是心脏重塑过程的重要调节剂，上述产生氧化应激的通路见图 2，但对某些分子的定位及其调节氧化应激的精确机制仍然知之甚少[64]。简而言之，氧化应激是一个复杂而动态的过程，其对心脏损伤的机制尚不清楚，需要进一步研究。

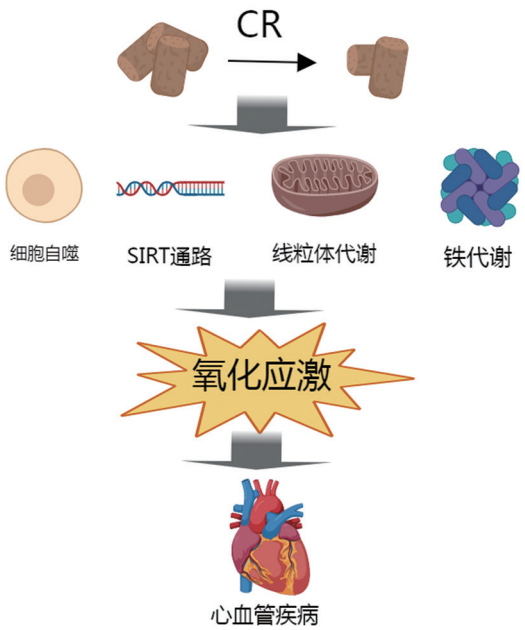
3　热量限制对心血管疾病中氧化应激的作用

氧化应激会导致心脏肥大和心力衰竭，少量 ROS 的形成可能不足以产生氧化应激，但可能激活氧化还原敏感信号导致心肌肥大，而长期高水平 ROS 的病理刺激可直接导致氧化应激、不良心脏重塑、心功能障碍和心力衰竭[65]。CR 是一种安全且

依从性良好的干预措施[66]，通过调控细胞自噬、SIRT 通路、线粒体代谢、铁代谢等减轻体重、减少脂肪量和腰围[12]，改善总体健康状况，使 10 年心血管疾病的发病风险降低 30%[67](图 1)。

在心肌中，基础水平的自噬对于维持组织稳态具有重要意义。自噬体形成或清除的缺陷可能导致心功能不全，甚至导致心力衰竭[68]。从机制上讲，CR 的有益效果与自噬密切相关，自噬是心血管稳态必不可少的细胞循环过程[69]。ROS 参与 HIF-1α 的活化，HIF-1α 可能通过激活下游蛋白 B 淋巴细胞瘤 -2/ 腺病毒 E1B19kDa 相互作用蛋白 3 (BCL-2/BNIP3) 并诱导线粒体自噬来维持细胞的正常生理状态[70]。研究表明，BNIP3 作为自噬的标志物通过与微管相关蛋白 1 轻链 3 (LC3) 直接结合诱导自噬[68]。由此可见，氧化应激可能会影响细胞中的自噬活性，这对于维持心血管稳态和功能至关重要[71]。CR 能够通过抑制 mTOR 通路平衡氧化应激水平，从而抑制过度自噬减轻心肌损伤，对缺血条件下的心肌产生保护作用[72]。

CR 还通过增加 SIRT1 和 PGC-1α 的活性来介导对心脏的积极影响，从而减少 ROS 的数量，减轻纤维化和炎症[73]。CR 导致 SIRT1 和 FOXO1 的蛋白表达增加，SIRT1 通过去乙酰化组蛋白和非组蛋白来调节存活、代谢、衰老和凋亡等至关重要的细胞过程[74]。而 SIRT3 是线粒体烟碱腺嘌呤二核苷酸 (nicotinamide adenine dinucleotide, NAD^+) 依赖的去乙酰化蛋白，是调节线粒体代谢的关键酶，其缺失可引起线粒体代谢异常和细胞损伤，甚至导致细胞凋亡[75]。



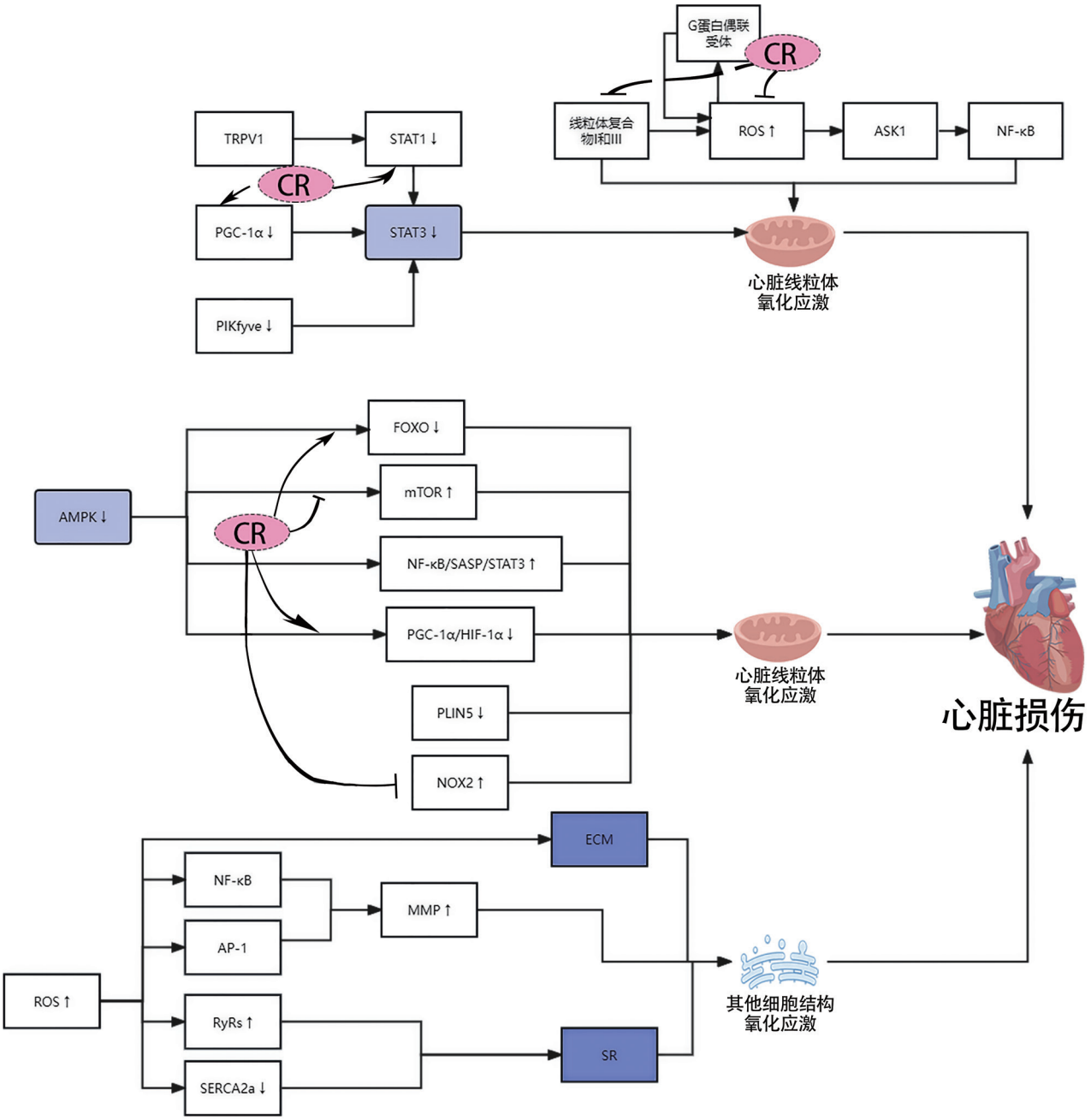
CR能够通过细胞自噬、SIRT通路、线粒体代谢、铁代谢等方面调控氧化应激，减少心血管疾病发生发展。

图1 CR对心血管疾病中氧化应激的作用

CR 通过激活线粒体改善细胞内的氧化还原平衡，从而减轻心脏肥大[76-77]。线粒体功能障碍已经成为心脏代谢紊乱的核心病理机制，CR 通过诱导心血管的保护机制，调节心脏的钙离子平衡和心脏线粒体功能的恢复[78]，减少 ROS 的产生，从而改善心脏和血管功能。研究显示，CR 对线粒体及其功能有积极影响，对 ROS 的产生有保护作用，能够增加抗氧化酶的水平和活性，并增加氧化物的转运[79]。ROS 主要由电子传递链中线粒体复合物 I 和 III 调节产生[38]，当电子滞留在这些复合物中时将导致 ROS 的生成增加。有报道称 CR 后的 NADH 脱氢酶乙酰化修饰减少[80]，抑制了 NADH 氧化呼吸链；用琥珀酸刺激线粒体的代谢后，ROS 生成减少，而 CR 能够限制 ROS 的产生[81] 也是由于促进电子通过 FADH 进入呼吸链，绕过了复合物 I，而复合物 I 是 ROS 产生的主要部位之一[38]。因此，CR 或抑制 NADH 氧化呼吸链或增强 FADH 氧化呼吸链以减少 ROS 的产生。有研究发现，CR 后心肌线粒体的最大呼吸速率与 H_2O_2 释放速率都下降，但呼吸控制率没有变化，即代谢速率不变[82]。线粒体活性的增加也许是生物体的一种适应机制，减少 ROS 的生成而无须降低细胞的呼吸作用[83]。

此外，CR 通过并激活超氧化物歧化酶 (superoxide dismutase, SOD) 和 NADPH 氧化酶并增加内皮一氧化氮合酶 (endothelial nitric oxide synthase, eNOS) 的表达来降低心脏和脉管系统中的氧化应激[84]。在代谢综合征模型中，CR 降低心脏重量，伴随着舒张功能障碍的改善，CR 后 NADPH 氧化酶 NOX 家族的活性下降，基因表达下调[85]。在心血管系统中，CR 能够改善血管内皮依赖性松弛，减少心脏肥大，并激活抗凋亡的信号级联[86-87]。在肥胖型糖尿病大鼠模型中，13 周的 CR 显著降低了体重、内脏脂肪沉积、血压，并改善了胰岛素敏感性[78]。除此之外，CR 还能改善心脏的左心室舒张功能[78]，抵抗心肌老化造成的收缩力下降[88]，益于健康和抗衰老[89]，从而在糖尿病和动脉硬化等老化相关疾病中起重要作用[90]。

CR 还能够通过调节铁代谢来减轻氧化应激和炎症，从而预防糖尿病和肥胖模型的不良心脏重塑[85]。CR 的益处在于激活核因子 E2 相关因子 2/



CR主要调控心脏线粒体的氧化应激，关键蛋白为STAT3与AMPK。CR通过促进STAT1与PGC-1α的表达来提高STAT3的活性。此外，CR调控AMPK下游蛋白减轻氧化应激，包括激活并促进FOXO表达，激活PGC-1α/HIF-1α通路；抑制mTOR通路，降低NOX2表达。在氧化呼吸过程中，线粒体复合物I和III是产生ROS的主要部分，CR的干预可以绕过复合物I和III而产生能量，减少了ROS的产生，减轻氧化应激，降低心脏损伤的概率。

图2　CR调控各途径减少氧化应激与心血管疾病

抗氧化反应元件 (Nrf2/ARE) 通路[91-92]，并提高关键的解毒和抗氧化酶的表达[92]。通过限制热量摄入或进餐频率，CR 驱动的 Nrf2 的激活对氧化应激有缓解作用[93]，这对中枢神经系统疾病的管理可能至关重要[92]。此外，Nrf2 调控的抗氧化因子 (HO-1) 和 NAD(P)H 醌脱氢酶 1 (NQO1) 表达的下降也证明了氧化应激水平的降低[94]。

虽然 CR 抵抗心脏肥大机制尚未确定，但 CR 已被证实可以有效地降低氧化应激水平[95]。在临床研究中也观察到 CR 的有益作用，如减少非肥胖者的多种心脏代谢危险因素[67, 96]，并减少临床上病情稳定的射血功能保留的心力衰竭 (HFpEF) 老年患者

的左心室质量和厚度[97]。然而，CR也可能对免疫力、生育能力和骨密度造成不利的副作用[29]。因此，需要进一步研究以开发更合适的饮食模式或药理学替代方案，以重现CR的健康益处。

4 热量限制模拟物对心血管疾病中氧化应激的作用

虽然CR对心血管疾病有一定的改善作用，但可能在老年人中有潜在的不良反应或存在依从性差的问题[98]，因此热量限制模拟物(caloric restriction mimetics, CRM)应运而生。二甲双胍、白藜芦醇、雷帕霉素、亚精胺以及漆黄素，都可以作为实现CR保护作用的有效替代品[20]。

4.1 二甲双胍

二甲双胍是一种用于糖尿病临床治疗的药物[99]，可降低心血管事件的发生率以及心血管疾病死亡率[98]。它能够明显降低收缩压、体重和氧化应激[100]，通过稳定葡萄糖摄取率来减缓心血管疾病早期的心肌葡萄糖利用率下降，从而改善心脏功能[101]。最近，一项包含16项研究和近200万参与者的荟萃分析显示，二甲双胍降低了糖尿病患者的整体心血管风险[102]。

二甲双胍对心血管系统有多种直接有益作用，归因于AMPK和mTOR信号通路的正常化[103]，以及脂肪酸氧化的增强和氧化应激水平的下降[99]。二甲双胍可通过增加细胞中的AMP/ATP比值来激活AMPK[104]，这抑制了线粒体复合体I的活性并减少氧化应激[105]。AMPK活性的增加改善了葡萄糖和脂肪酸的氧化，上调抗氧化酶SOD以减少心肌损伤[106]。心肌缺血再灌注模型经二甲双胍干预后，随着治疗时间的延长，大鼠血清SOD和谷胱甘肽过氧化物酶(GSH-Px)水平逐渐升高，丙二醛(MDA)含量逐渐降低[99]。此外，在心室肥厚大鼠模型中二甲双胍还可能增加AMPK和eNOS磷酸化以及升高一氧化氮(NO)水平[107]，改善内皮功能和血管舒张，从而在压力超负荷大鼠模型中有效防止心脏肥大。综上所述，二甲双胍可以增强抗氧化酶的活性，维持心肌损伤后的线粒体稳态，调节心脏代谢异常，改善心血管疾病的预后[108]。

4.2 白藜芦醇

在体内外条件下，白藜芦醇都可以激活益于心血管系统的多个相互关联的信号通路，对17个随机临床试验所做的Meta分析证实了白藜芦醇具有降低血压的效果[109]。

白藜芦醇对心血管的积极作用是通过心肌细胞和内皮细胞中的SIRT1和AMPK来实现的[110]，从而推动心脏保护[111]。白藜芦醇作为SIRT1的激活剂，能够上调抗氧化酶和线粒体蛋白的去乙酰化，从而维持心脏线粒体的功能和平衡[112]。在大鼠实验中，应用白藜芦醇可以上调心脏SIRT1的表达水平，显著上调SOD的活性，下调心肌MDA的水平，降低氧化应激，明显改善心肌梗死大鼠的心脏重塑，缓解收缩功能障碍[113]。

白藜芦醇还通过多种机制保护血管功能，包括抑制氧化应激和炎症反应、促进NO的合成等[114]。它通过上调eNOS的活性和表达，抑制eNOS的解耦，促进内皮细胞产生NO，缓解氧化应激，抑制心脏重塑的进展[115]。研究报告称，白藜芦醇可抑制NF-κB通路，减轻血管氧化应激，从而通过增加NO的生物利用度来改善内皮依赖性血管舒张[116]。综上所述，可以认为白藜芦醇诱导的心血管保护机制受细胞应激抵抗、氧化还原稳态和细胞能量代谢控制，因此白藜芦醇通过减少氧化应激可以改善心脏重塑和功能障碍。

4.3 雷帕霉素

雷帕霉素是美国FDA批准的药物，可直接抑制mTOR复合物I (C1)。抑制mTORC1在体内具有广泛作用，包括改变蛋白质合成、抑制细胞生长以及刺激应激反应和自噬[117]。在心脏方面，CR和雷帕霉素均可改善衰老过程中的心脏肥厚和心力衰竭以及心脏压力超负荷心衰[118]。

雷帕霉素长期治疗3个月可减轻老龄鼠的心功能障碍，并增加抗肥大和抗炎基因的表达[119]；10周的治疗亦可降低心脏氧化应激和泛素化[118]，并且可以恢复和逆转心脏衰老[118]；短期4周的雷帕霉素治疗能够改善心力衰竭的收缩功能并减轻左室纤维化[120]；低至1周干预即可抑制和消退主动脉弓缩窄诱导的心肌肥厚[121]。其机制可能是调节mTORC1的一个靶点——真核细胞翻译起始因子4E结合蛋白1 (4EBP1)的磷酸化，来抑制蛋白质翻译，改善衰老和心力衰竭患者的心功能[122]。综上所述，雷帕霉素可以通过mTOR通路减轻氧化应激，从而实现对心脏的保护作用。

4.4 亚精胺

亚精胺是一种存在于所有生物体中的天然多胺[123]，在哺乳动物细胞中含量很高，也存在于许多食物中，具有明显的抗氧化效果[124]，能够诱导不同模式生物体的自噬并参与维持细胞稳态。

亚精胺刺激线粒体自噬和线粒体生物发生，可使老年心肌中的线粒体数量及其形态正常化[125]，对与年龄有关的心脏功能障碍具有心脏保护作用[126]，能改善心脏功能，延长寿命。此外，亚精胺还能够预防糖尿病小鼠宫内缺氧引起的新生儿心脏损伤[127]。亚精胺还能增强线粒体中电子传递链复合物的活性，这证明了其在线粒体水平上的抗氧化潜力[128]。但比起年轻小鼠，老龄鼠左心室的线粒体的数量和超微结构更容易受亚精胺的影响[125]。亚精胺还可以充当自由基清除剂，启动端粒保护免受氧化应激，从而保护 DNA 免受氧化损伤[129]。并且，亚精胺能够促进恢复 NO 相关的内皮依赖性扩张，并通过自噬减少氧化应激来逆转动脉衰老[130]。

亚精胺通过调节自噬、抗氧化剂水平来对抗衰老诱导的氧化应激[131]，补充亚精胺可通过增强自噬和线粒体呼吸来缓解小鼠和大鼠的心脏老化[132-133]。由此可见，亚精胺可减少炎症介质，增加抗氧化酶活性，改善心肌细胞活力，已成为治疗人类心血管疾病的主要候选药物。

4.5　漆黄素

漆黄素又称为非瑟酮、非瑟素，是在许多可食用植物中提取的类黄酮植物雌激素[134]，能够通过抑制线粒体的氧化应激和线粒体功能障碍[135]，减轻心脏功能障碍、改善心肌纤维化、减轻心脏肥大[136]。

糖原合酶激酶 3β (GSK3β) 对线粒体具有调节作用[137]，漆黄素通过激活磷酸肌醇 3- 激酶 / 蛋白激酶 B (PI3K/Akt) 途径从而抑制下游 GSK3β 或通过与 GSK3β 直接相互作用而减轻心肌缺血[138]。漆黄素能够直接与线粒体复合体 I 结合，向黄素单核苷酸 (FMN) 传递电子，促使受损心脏中线粒体产生 ATP[137]。漆黄素还依赖 p62 消除受损线粒体来抑制 Toll 样受体 4/ 髓样分化蛋白 2 (TLR4/MD2) 介导的 Nod 样受体蛋白 3 (NLRP3) 炎性小体的活化[139]。

此外，漆黄素通过逆转 GSH-Px 水平来减轻心肌细胞的铁死亡和氧化应激[136]。漆黄素还可通过清除 ROS、减少脂质过氧化物和降低铁死亡标志物过氧化物合酶 2 (PTGS2) 的表达来保护细胞免受铁死亡诱导剂的影响，规避铁死亡的发生[140]。因此，漆黄素能够激活线粒体自噬，有效对抗氧化应激、铁死亡，这可能是治疗心肌梗死的有效候选者。

目前大多数药物都特异性地针对一种疾病，而 CR 与 CRM 打破了这一传统，能够同时作用于多个通路[141]，或能够提高治疗效果，甚至同时治疗多种疾病，减少多种疾病联合用药所导致的药物毒性作用。

5　结论和展望

显然，氧化应激在 CR 改善心脏代谢的过程中扮演着重要的角色，许多心血管疾病的危险因素可以通过调节氧化应激水平得到控制和逆转。CR 虽然对机体有一定益处，但 CR 的最适强度、饮食构成以及持续时间还没有确切的定论；且不佳的 CR 可能存在副作用，仍需要研究者探究更优的饮食方案；CRM 虽然部分解决了 CR 存在的副作用与依从性差的问题，但其最佳剂量还不明确。

综上所述，利用 CR 或 CRM 来降低心血管风险和心血管疾病的负担，是一种有效易行的预防途径，但需要更多高质量研究来确定不同形式的 CR 和 CRM 方案如何进一步降低心血管疾病患者的氧化应激水平。

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