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热量限制与心血管老化的研究进展*

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摘要 热量限制（caloric restriction，CR）是指在不减少必需营养素摄入的情况下减少20%～40%的热量摄入. CR可通过由各种分子介导的氧化应激、炎症、程序性死亡、端粒体等机制，通过调节人及其他动物心血管老化的危险因素，进而减缓生理和病理状态下心血管老化进程. 本文通过对CR与心血管老化研究进展的系统阐述，探寻人类预防心血管老化的解决之道.

关键词 热量限制，老化，心血管
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根据《中国心血管病报告2017》概要[1]，2015年中国心血管病（CVD）死亡率仍居首位，高于肿瘤及其他疾病，中国CVD患病率也处于持续上升阶段，患者人数达2.9亿. 同时，中国已进入老龄化时代[2]，截至2015年底，中国60岁以上人口达到2.22亿，占人口总数的16.1%. 衰老是导致CVD患病率和死亡率增加的一个重要因素[3]，心血管老化过程与人体衰老过程也几乎是同步的[3]. 因此，在人口老龄化背景下如何能够延缓心血管老化从而减少CVD患病率和死亡率是目前普遍关注的问题.

热量限制（caloric restriction，CR）可通过调节氧化应激、自噬、炎症反应延缓心脏老化进程，然而国内外对CR的年龄、时长及作用强度等影响CR调节心血管老化的因素仍存在较大争议. 其CR预防心血管老化的各个生物化学分子之间的相互作用目前研究得也不是很清楚，例如在CR过程中，eNOS和Sirt1可能形成一个心血管保护网络[4]，AMPK、ULK1、Akt2和mTOR共同组成了自噬调节级联信号通路. 因此，研究这些分子之间的相互关系也显得尤为重要. 此外，有必要探讨一下热量限制在临床的应用前景. 通过对这些机制和分子及影响CR调节心血管老化的因素研究及CR临床应用前景的系统综述，有助于探寻预防心血管老化的新方法，针对心血管老化进行靶向治疗，以减轻或逆转心血管老化进程.

1 CR的定义及与心血管老化关系

CR是指在不减少必要营养素摄入的情况下减少20%～40%的热量摄入，而其他营养素的摄入维持在可以避免营养不良的水平[5]. 伴随着心血管老化，虽然老年人的心脏并没有表现出与终末期心力衰竭完全相同的表型，但在功能表现和代谢蛋白质上的伴随变化是明显的. 衰老的心肌会出现舒张功能减退、收缩速度减慢、β-肾上腺素能反应减少及纤维化[6]，血管也会出现内皮功能受损、动脉僵硬度增加[7]及收缩功能减弱，参与心肌细胞线粒体功能、电子传递链、柠檬酸循环和脂肪酸代谢的蛋白质丰度会随年龄增长而降低，参与糖酵解和氧化应激反应的蛋白质丰度会增加[8]，从而对心血管系统产生不利影响. 而CR通过调节心血管的氧化应激和炎症反应、诱导心血管自噬和防止心肌凋亡、维护线粒体和端粒酶的功能和活性，能够延缓心脏老化[9]、调节心脏和血管内皮功能[10]、降低年龄相关性左室舒张功能损害、动脉弹性和心率变

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异性[11]及心肌肥厚和纤维化[6，12]。

2　影响CR调节心血管老化的因素

2.1　年龄

目前，CR与心血管老化的研究多集中在小鼠和大鼠模型上。CR能改善中老年小鼠血管内皮功能和减少心肌细胞凋亡，延缓心血管老化的发生，这点在针对健康非肥胖小鼠[1，13]、肥胖型小鼠[14]、心肌梗死的小鼠模型[15]亦或中老年大鼠[16]的研究中均得到证实，但是CR可能会对幼龄鼠产生不利影响。Sheng等[13]针对年轻（3月龄）非肥胖小鼠进行3个月的研究发现，CR加速了年轻小鼠的衰老，诱发年轻小鼠心脏收缩功能障碍及心肌纤维化，甚至心脏重量下降了20%；Nutter等[17]针对年轻（14周大）的大鼠的研究也发现，CR下内皮功能和收缩压恢复不明显；Sheng等[13]通过透射电镜观察，发现CR在幼龄小鼠线粒体中电子密度下降、脂滴浸润增加，而相似的CR在中老年小鼠中显著改善与年龄相关的线粒体损伤，减少脂质积累（与心脏收缩功能障碍有关，同时脂质积累可能通过刺激促炎介质而加重衰老，减缓心肌愈合[18]）。但Melo等[19]给予刚出生的Wistar大鼠50% CR限制3个月却发现了CR降低大鼠的收缩压、心衰指数、基础代谢率和动脉粥样硬化指数等，这可能与这种状态的小鼠从一出生起适应了CR有关。

2.2　时长

以往的研究多针对CR与心血管老化的长期研究，例如：De等[20]研究发现CR一年可导致正常老年大鼠体重、心脏重量和心脏重量/胫骨长度比显著降低，心衰大鼠的左心室重塑及心肌收缩力储备也在CR饮食下得到了显著改善。甚至终身热量限制可防止与年龄相关的心脏改变，使得收缩压增加，防止与心血管老化相关的动脉硬化和内皮细胞功能障碍[21-22]。而最近的研究发现，CR的有益影响可能在起始时迅速发生[23-24]。仅针对小鼠的心肌梗死模型每天进行30%的CR，7天后该小鼠便出现了梗死面积变小、心脏功能的改善[16]；Dai等[24]针对小鼠进行为期10周的短期CR研究，也发现逆转了许多已存在的心脏老化的功能性缺陷，包括年龄依赖的心脏肥大、心脏舒张功能障碍和心肌损伤。同时定量的蛋白酶分析显示，年龄依赖性的心脏蛋白质组重构也能被短期的CR显著逆转，蛋白质组半衰期显著增加、年龄依赖性蛋白质氧化损伤和泛素化减弱，产生了一系列对心脏生理的有益影响[24]。

2.3　强度

Melo等[25]给予刚出生的Wistar大鼠50% CR的热量限制，发现尽管经过50% CR的体重和心脏重量较低，但与未经CR的正常大鼠相比，CR50大鼠的心脏-体重比增加。甚至Nutter等[17]曾发现，在70%热量限制6周后，年轻（2.5个月）雄性大鼠的心脏/体重比增加，这可能与CR下心肌收缩力增加和心肌纤维化减少有关；同时，这种状态下的大鼠有氧运动增加，磷酸化AKT水平升高。Broderick等[26]也曾报道，受到45%卡路里限制8周的3个月月龄大鼠在缺血再灌注后心脏/体重比增加和心脏功能改善，从出生到老年的50% CR可降低心血管的危险因素，增加基础心脏功能并保护心脏免受缺血再灌注的影响。可见，大鼠对CR的耐受能力较强。而针对小鼠的研究，热量限制多在30%左右[27]。Makino等[14]选取15周龄到20周龄的野生型小鼠分成随机饮食组和限制30% CR摄入组。热量限制组与正常饮食组相比，室间隔壁厚度（IVST）和后壁厚度（PWT）明显降低。Oellerich等[28]也观察到CR能显著降低CR组小鼠左心室舒张末期内径和左心室舒张末期容积。热量限制超过50%往往会发生严重不良反应引起受试小鼠死亡[14]。Mitchell等[29]的研究更是表明，CR对心血管的健康和生存益处由延长的每日禁食强度所赋予，与饮食构成无关，对人类健康和临床适用性具有重要意义。

2.4　影响CR与心血管老化的其他因素

虽然Mraovic等[30]研究发现含有相同量营养素的不同CR饮食中，对改善心脏代谢因子、降低促炎性超敏C反应蛋白（hypersensitive C-reactive protein，hs-CRP）水平具有同等的效果。但同样值得注意的是，针对CR的研究所使用的实验动物模型的品种和性别不同，对实验结果都会产生重大影响，需要进一步研究。例如：Harbison等[31]观察到，在CR条件下C57BL/6Nnia型小鼠对心血管老化的预防作用要好于DBA/6Nnia型小鼠；Colom等[32]研究发现，在CR下雌性比雄性大鼠有更低的患心血管疾病的几率。此外，针对人类的CR研究中，CR的同时总是伴随着体重下降，这使得很难区分是体重下降还是CR产生了对心血管老化效

应影响.

3　CR与预防心血管老化的机制

3.1　CR与氧化应激

3.1.1　氧化应激和心血管病

目前，氧化应激和抗氧化机制受损被认为是导致心血管老化的主要因素[33]. 氧化应激的产生是由于活性氧（reactive oxygen species，ROS）的过度生成，在心血管老化过程中产生的过量ROS与NO结合会形成强氧化剂过氧亚硝酸盐. 在血管壁，大部分细胞ROS是由线粒体氧化磷酸化产生的；在衰老的心脏，大部分ROS来源于NADPH氧化酶和线粒体电子传递链[34]. 诱导型一氧化氮合酶（inducible nitric oxide synthase，iNOS）、黄嘌呤氧化酶和超氧化物歧化酶（superoxide dismutase，SOD）过度表达[35]，SIRT活性的降低[36]，自身抗氧化应激调节因子Nrf2诱导的参与抗氧化和自由基胁迫的亲铁蛋白（谷胱甘肽转移酶、NADPH醌氧化还原酶1、血红素氧合酶1）表达减弱[37]，通过调控参与抗氧化防御和ROS生成的基因来调控细胞的生长和存活的JunD信号活性的降低[38]，都被认为与氧化应激和抗氧化机制受损有关. 衰老心肌中氧化应激升高会导致蛋白质氧化/硝化增强、生物利用度降低、脂褐素生成、细胞凋亡和内质网应激[17]，从而出现血管扩张受损、血管僵硬增加、心室肥厚和心脏舒张功能障碍[3].

3.1.2　减少氧化应激

CR可抑制氧化应激反应（图1），有选择性地减少ROS产生[39]和iNOS表达[40]，增加eNOS表达[41]. 上调Thr495去磷酸化，增加总eNOS蛋白质水平和eNOS的活性[41]，逆转改变的iNOS/eNOS比值[18]. 研究表明，SIRT1参与了CR增加eNOS表达的作用，Sirt1去乙酰化eNOS，从而刺激eNOS活性并增加内皮细胞的NO生成量，而eNOS的解耦连导致Sirt1的表达减少，进而加速内皮祖细胞衰老. 在CR过程中，eNOS和Sirt1可能形成一个心血管保护网络，两者都是开发CR诱导心血管保护的必要条件[3]，CR促进Sirt1-eNOS通路的活性，这有助于改善与年龄相关血管顺应性[42]. 此外，研究表明Sirt1可通过去乙酰化eNOS，从而刺激eNOS活性并增加内皮细胞的NO生成量，eNOS - NO上调辅助激活因子1α（PPARγcoactivator-1α，PGC-1α）发挥内皮细胞保护作用[43]，并降低老年心脏的蛋白质氧化损伤和ROS生成，而SIRT1敲除可减弱CR介导的ROS生成的减少[30].

心肌细胞是人体中最需要能量的细胞，心肌细胞氧消耗过程伴随着大量的游离脂肪酸和葡萄糖在线粒体产生乙酰辅酶a并释放能量[44]，促进了活性氧（ROS）的生成和线粒体蛋白质翻译后再修饰，诱发了ROS介导的氧化应激及增加线粒体蛋白质的代谢压力，而CR可借助线粒体sirtuins蛋白通过脱乙酰基作用缓解线粒体蛋白质的代谢压力[45]，减少线粒体H_2O_2[46]和ROS[11]的生成，降低线粒体膜电位[47-48]，改变线粒体膜的饱和/不饱和指数，从而维持线粒体膜的流动性[49]. 此外，CR还可以通过心磷脂过氧化的衰减来维护线粒体膜的活性[50].

3.1.3　增加抗氧化应激

CR会使过氧亚硝酸盐的形成减少[12]. 线粒体ROS产生和NADPH氧化酶活性及线粒体丙二醛和8-羟基-2'-脱氧鸟嘌呤这些氧化应激指标在CR条件

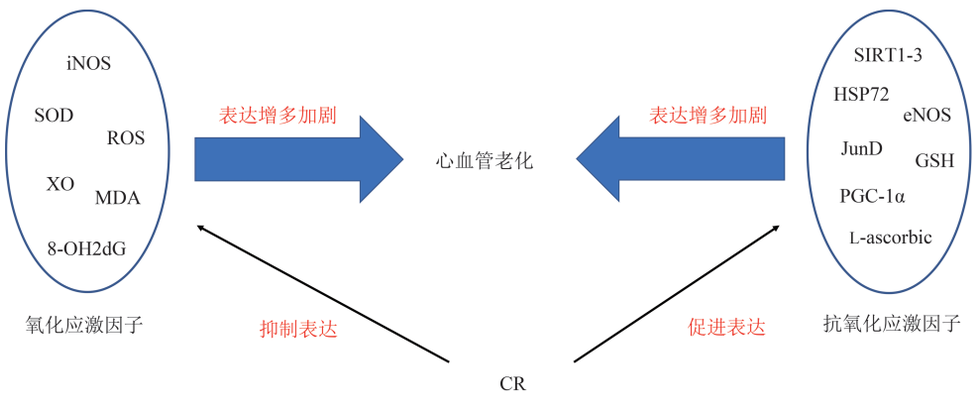

Fig. 1　A schematic diagram of CR regulates oxidative stress

图1　CR调节氧化应激示意图

下均降低[43，51]。CR条件下也发现了主动脉内源性抗氧化剂谷胱甘肽和抗坏血酸的水平增加[52]。心肌谷胱甘肽过氧化物酶和超氧化物歧化酶SOD活性增强，SOD将超氧自由基转化成过氧化氢[53]，谷胱甘肽过氧化物酶去除H_2O_2，以防止H_2O_2的毒性作用[13]。此外，SIRT3减少细胞ROS水平正是依赖去乙酰化SOD2上的2个关键赖氨酸残基实现的[54]，SIRT3直接去乙酰化并激活线粒体异柠檬酸脱氢酶2，导致线粒体中NADPH水平升高，还原性-氧化谷胱甘肽比例升高，蛋白质泛素化（蛋白酶体降解的限速步骤）减少[55]，从而增强线粒体谷胱甘肽抗氧化防御系统的抗氧化能力[56]。

3.2　CR与炎症反应

炎症反应是心血管衰老过程中的普遍现象，伴随着心血管系统的老化，促炎因子如TNF-α、E-选择素、CAM-1、VCAM-1、TGF-β、IL-1β在心血管系统内部的表达会相应增多[57]。CR可以通过NF-κB调节IL-1β、IL-6、TNFα、环氧合酶2和iNOS等相关炎性因子的活性[58-59]，降低心肌结缔组织积累和减轻心肌纤维化，促进左心室功能的恢复[60]，从而延缓心血管老化。TNF-α可激活内皮细胞中的促炎基因表达，促进单核细胞的黏附及其向内皮下层的迁移。E-选择素介导白细胞滚动，而趋化因子导致白细胞活化，而细胞间黏附分子1（cell adhesion molecule，CAM-1）和血管细胞黏附分子1（vascular cell adhesion molecule-1，VCAM-1）有助于白细胞黏附[61]。在脉管系统中，单核细胞经历转化为巨噬细胞，内化修饰的脂蛋白并产生泡沫细胞；在内膜中，动脉平滑肌细胞（smooth muscle cells，SMC）在各种生长因子的作用下增殖并分泌细胞外基质蛋白，包括间质胶原，尤其是响应转化生长因子β（TGF-β）和血小板衍生的生长因子[62-63]。SMC通过细胞外基质的降解从中膜迁移到内膜，细胞外基质由MMP-9以及其他蛋白酶介导。这些分子过程导致病变从富含脂质的斑块演变为金色斑块，然后是钙化斑块，这可能会造成血管的狭窄[63]。

心肌血管衰老中NF-κB信号调节与炎症相关。NF-κB是一种重要的转录因子，被认为是炎症通路的分子开关。它负责调节控制细胞黏附、增殖、形成、氧化还原状态和组织特异性酶的因子的基因表达[64]。CR可以增强SIRT1的表达来阻止TNFa诱导的NF-κB活化和NF-κB激活有关的IκB KYNA的磷酸化[30]，并使其亚基RelA / p65去乙酰化而抑制NFκB介导的转录，从而降低其DNA结合能力[65]，借助于依赖组蛋白去乙酰酶抑制剂激活SIRT6防止NF-κB核易位，从而阻止NF-κB进入细胞核以促进炎症因子转录[66]，以及内皮分泌体中与年龄相关的促炎转移[67]。CR减弱了与年龄相关的血管黏附分子表达[31]，CR的这种作用似乎是通过预防NF-κB抑制复合物中年龄相关的减少而起的。

3.3　CR与程序性死亡

3.3.1　CR与自噬

自噬是细胞内蛋白质和细胞器降解的一种保守途径，在CR条件下，自噬能保持机体的能量供应。体内的自噬机制可以防止长时间的CR导致心脏几何结构和功能的改变[68]。CR使得与自噬体形成有关的标志物的增加，如LC3B-Ⅱ（LC3B-Ⅱ/LC3B-Ⅰ比值）、Atg7和Beclin-1[69]。自噬调节级联信号包括AMPK、ULK1、Akt2和mTOR（图2）。Akt2基因的有效作用与促进自噬有关，特别是改善了心脏的自噬[70]。长期CR摄入后心脏Akt信号减弱[18]。Akt 2基因敲除可以改善CR引起的心脏重构和心输出量的改变及心脏质量损失[71]，机制可能是在CR下启动SERCA2a与SERCA2a结合，显著降低SERCA2a的磷酸化水平[72]，并上调磷酸盐的水平[38]。此外，Akt的信号减弱与CR下AMPK的激活有关[73]，正常饮食的小鼠中未发现AMPK激活，CR可直接促进AMPK激活，促使小鼠循环中抗老化因子高相对分子质量（high molecular weight，HMW）、脂联素的提高，AMPK的抑制会逆转CR导致的自噬和自噬信号的变化[74]。mTOR作为自噬的主要抑制剂，受到Akt和AMPK的双重调控。Akt直接刺激mTOR，AMPK磷酸化抑制mTOR[75]，ULK1可能被mTOR磷酸化和负调控。较高的mTOR活性阻碍ULK1在Ser757处的磷酸化，干扰ULK1和AMPK之间的相互作用[51]。

线粒体的周转率也主要与自噬有关，自噬随着年龄的增长而下降，伴随着人体的衰老心脏自噬作用会减弱，促使老化线粒体的积累和线粒体功能下降，进一步加速氧化应激和硝酸盐应激，而CR可以通过调节自噬来调节衰老心肌的线粒体功能和心肌功能[76]。

3.3.2　CR与凋亡

心血管老化是一个复杂的生理过程，是由分子、细胞和器官水平的损伤积累造成的，凋亡也起着至关重要的作用。CR通过抑制凋亡基因激活来

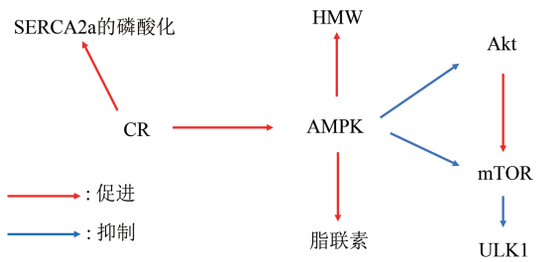

Fig. 2　The cascade signaling pathway regulated by CR autophagy

图2　CR自噬调节的级联信号通路

调节CR的心脏保护作用[75]，提高胰岛素的敏感性进而提高衰老内皮细胞的活性[76-77]，防止心肌细胞凋亡[78]，对衰老心肌起到保护作用. CR降低衰老大鼠心肌细胞凋亡激活信号：胞浆细胞色素C、caspase 9裂解产物、核糖体DNA片段[42]，凋亡抑制信号Bcl-xS和线粒体Bax蛋白增加.

3.4　CR与端粒酶活性

端粒的长度是细胞衰老的标志，其损耗与细胞功能的减退和增殖潜能降低有关. 端粒长度的缩短会导致心脏疾病的发展，而心脏端粒酶在防止端粒缩短、维持正常心脏功能中发挥重要作用[14]. Foxo 1被认为是没有端粒酶活性的端粒酶阳性调节因子，在调控人体器官老化中发挥重要作用，CR能够通过Foxo 1因子调节端粒酶的活性，减少端粒的缩短[79].

3.5　其他调节机制

CR除可以通过调节心血管的氧化应激和炎症反应、诱导心血管自噬和防止心肌凋亡、维护线粒体和端粒酶的功能和活性外，CR还可以通过对胰岛素生长因子1（IGF-1）受体调控来影响心肌细胞老化[80-81]，借助于Sirt1通过抑制局部补体系统激活来调节CR的心脏保护作用[82]，提高胰岛素的敏感性进而提高衰老内皮细胞的活性[83-84]. 此外，Foxo 1除了被认为是没有端粒酶活性的端粒酶阳性调节因子外，还被认为影响Akt信号转导相关目标基因的核定位[85]，并与eNOS和Sirt 1水平密切相关. CR可减弱心肌Akt信号，增加eNOS和Sirt 1水平和端粒酶的活性，而这些作用在FoxO 1敲除的小鼠中均未发现[14]，因此FoxO 1分子在CR抑制氧化应激和维护端粒酶活性的过程中都起着重要作用. p66Shc在防止老年性内皮功能障碍发挥积极作用，被认为是NADPH的上游调节分子和哺乳动物雷帕霉素（mTOR）通路的靶点[86]，因此p66Shc分子在CR抑制氧化应激和细胞凋亡的过程中都起着关键作用.

4　热量限制的临床应用前景

针对CR在临床的研究，Fontana等[87]通过6年时间评价了CR对延缓正常肥胖衰老的个体动脉粥样硬化危险因素的影响，CR组血清总胆固醇、低密度脂蛋白胆固醇（LDL-C）、甘油三酯、空腹血糖、收缩压和舒张压均明显低于正常饮食组. Ravussin等[88]对218名21～51岁健康非肥胖人群进行为期两年研究，受试人群被限制每天热量摄入量减少25%，两年后的研究结果表明，CR组体重下降达10.4%，总胆固醇浓度下降100 mg/L、甘油三酯浓度下降250 mg/L、平均血压下降3 mm Hg和血糖控制指数HOMA-IR减少0.3，而高密度脂蛋白（HDL）升高. Meyer等[89]对25名受试者进行了6.5年的CR，同样发现25名受试者血压、血清c反应蛋白、转化生长因子1水平明显下降，而这些都是造成心血管老化作用的重要危险因素. 针对人类长期CR的可行性还需进一步评价，因为伴随的体重减轻及肌肉和骨质量的减少将对老年人产生负面影响[90]，CR对防治心血管老化的作用毋庸置疑的，但要兼顾对其他脏器的影响.

而针对人类短期CR的研究：Lefevre等[91]一项临床随机试验评估25%CR对受试者心血管危险因素的影响，并估计了健康非肥胖男性和女性10年心血管疾病风险. 6个月后，受试者体重减轻10%，低密度脂蛋白胆固醇降低58 mg/L，甘油三酯降低103 mg/L和高密度脂蛋白胆固醇升高27 mg/L，10年心血管疾病风险率降低32%，证实了短期CR同样对心血管系统产生有益的影响. 短期CR同样对健康人和肥胖患者心血管老化防治产生积极影响. 很遗憾的是，目前文献中缺乏短期CR的具体定义，需要进一步研究界定短期CR的持续时间.

当今，肥胖是老年人的国家和全球流行病，在美国超过35%的美国人口被认为是肥胖，超过69%被认为是超重或肥胖[92]. 肥胖与高财务负担有关. 仅在美国，与肥胖相关的人均医疗费用从2005年的2 741美元增加到2011年的6 899美元[93]，在中国形势也不容乐观. 研究表明，即使是中度肥胖也存在明显的内皮功能障碍[94]. 胖人与瘦人相比，从肥胖受试者中分离出来的皮下动脉中

乙酰胆碱诱导的神经内皮细胞依赖性舒张功能受损[95]，肥胖引起的微血管内皮功能障碍损害器官灌注，与老年血管内皮功能受损、动脉僵硬度增加有关，并加剧衰老过程中的认知功能下降[96]. Csipo等[97]研究表明：食用低碳水化合物低热量饮食（大约每天减少30%热量摄入）所导致的短期体重减轻可以逆转与肥胖相关的微血管内皮功能障碍，肥胖个体的体重减轻会带来重要的心血管益处. 因此，针对热量限制与心血管老化展开基础机制和分子水平的研究及临床研究显得尤其重要，有助于探寻预防心血管老化的新方法，针对心血管老化进行靶向治疗，以减轻或逆转心血管老化进程.

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The Research Progress of Calorie Restriction and Prevention of Cardiovascular Aging*

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Abstract　Caloric restriction (CR) refers to a 20%－40% reduction in caloric intake without reducing essential nutrient intake. CR can alleviate the cardiovascular aging process under physiological and pathological conditions by mainly mechanisms including oxidative stress, inflammation, programmed death and telomerewhich are mediated by sundry molecules as well as regulating the risk factors of cardiovascular aging in human and other animals. This paper systematically elaborates the research progress of CR and cardiovascular aging and explore the solution to prevent cardiovascular aging in humans.

Key words　caloric restriction, aging, cardiovascular
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