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综 述

烟酰胺腺嘌呤二核苷酸在心血管疾病中的研究进展

文赵之[1]，杨怿航[1]，刘 东[1,2]，施冲旭[1,*]

[1]南通大学生命科学学院，南通市发育与疾病重点实验室，南通 226000；[2]神经再生协同创新中心，南通大学江苏省神经再生重点实验室，南通 226000

摘 要：心血管疾病(cardiovascular disease, CVD)是造成全球性死亡率升高的主要原因。烟酰胺腺嘌呤二核苷酸(nicotinamide adenine dinucleotide, NAD^+)是一种多功能的辅酶，参与多种生物学过程，如细胞能量代谢、细胞信号传导、DNA修复和蛋白质修饰等。许多研究表明，NAD^+水平随着年龄、肥胖和高血压等CVD的风险因素而降低。此外，提高机体NAD^+水平还可以减轻慢性炎症反应、重新激活自噬和线粒体的生物功能。在患有血管疾病的人类中，提高NAD^+水平还能增强细胞的抗氧化和代谢能力。动物模型研究发现，NAD^+水平的提高还能降低血压、增加寿命、预防代谢相关疾病。最近有研究揭示，通过基因手段、药物或日常饮食提升NAD^+水平，能有效改善动物和人类心血管健康的病理生理状况。在本综述中，我们首先详细阐述了NAD^+在维持血管健康方面的作用，然后总结了其与血管功能和疾病相关的最新研究进展，包括高血压、动脉粥样硬化和冠状动脉疾病等。此外，本综述还评估了各种NAD^+前体在提升NAD^+水平方面的效率，以及这些NAD^+前体对预防或治疗CVD的临床效果，旨在为新的治疗策略提供潜在参考。

关键词：烟酰胺腺嘌呤二核苷酸；心血管疾病；炎症；血管健康

NAD^+ metabolism in cardiovascular diseases

WEN Zhao-Zhi[1], YANG Yi-Hang[1], LIU Dong[1,2], SHI Chong-Xu[1,*]

[1]*Nantong Laboratory of Development and Diseases, School of Life Science, Nantong University, Nantong 226000, China;* [2]*Co-Innovation Center of Neuroregeneration, Key Laboratory of Neuroregeneration of Jiangsu and Ministry of Education, Nantong University, Nantong 226000, China*

Abstract: Cardiovascular diseases (CVDs) are the leading cause of death worldwide. Nicotinamide adenine dinucleotide (NAD^+) is a central and pleiotropic metabolite involved in multiple cellular energy metabolism, such as cell signaling, DNA repair, protein modifications, and so on. Evidence suggests that NAD^+ levels decline with age, obesity, and hypertension, which are all significant CVD risk factors. In addition, the therapeutic elevation of NAD^+ levels reduces chronic low-grade inflammation, reactivates autophagy and mitochondrial biogenesis, and enhances antioxidation and metabolism in vascular cells of humans with vascular disorders. In preclinical animal models, NAD^+ boosting also extends the health span, prevents metabolic syndrome, and decreases blood pressure. Moreover, NAD^+ storage by genetic, pharmacological, or natural dietary NAD^+-increasing strategies has recently been shown to be effective in improving the pathophysiology of cardiac and vascular health in different animal models and humans. Here, we discuss NAD^+-related mechanisms pivotal for vascular health and summarize recent research on NAD^+ and its association with vascular health and disease, including hypertension, atherosclerosis, and coronary artery disease. This review also assesses various NAD^+ precursors for their clinical efficacy and the efficiency of NAD^+ elevation in the prevention or treatment of major CVDs, potentially guiding new therapeutic strategies.

Key words: nicotinamide adenine dinucleotide; cardiovascular diseases; inflammation; vascular health

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*Corresponding author. E-mail: shichongxu@outlook.com

心血管疾病(cardiovascular disease, CVD)是一类严重威胁人类健康和寿命的重要疾病，年龄是许多CVD的主要风险因素，随着老龄化程度增加，CVD的患病率也会上升[1]。然而目前，大部分CVD的发病机制尚不清楚，因此揭示相关CVD的病理生理机制尤为重要。最近的临床前研究表明，烟酰胺腺嘌呤二核苷酸(nicotinamide adenine dinucleotide, NAD^+)水平的变化对细胞代谢和能量转化有重要影响。NAD^+水平随着年龄的增长而下降，并且在与年龄相关的疾病(例如癌症、CVD、糖尿病、神经变性以及代谢疾病)中都观察到NAD^+代谢的改变[2–8]。NAD^+是氧化还原反应的必需辅酶，最先是在酵母提取物中发现，它在细胞能量转化、代谢和线粒体功能中有着至关重要的作用。除此之外，NAD^+还可以作为非还原性NAD^+依赖性酶的辅因子，在细胞内的很多生物学过程中发挥重要作用，例如DNA修复、炎症、细胞内运输、衰老以及细胞死亡和存活[2–4, 9, 10]。本文综述了在健康状态下NAD^+主要生物合成和降解途径，讨论了NAD^+的血管保护机制以及NAD^+水平降低对血管功能和健康的影响，总结了NAD^+水平降低与CVD发病机制的关系，回顾了最近的临床前研究，探讨了应用NAD^+前体和促进NAD^+生物合成的小分子药物提升NAD^+水平对血管疾病的治疗效果。

1 NAD^+的代谢

在真核细胞中，NAD^+主要参与调节线粒体内膜的能量代谢过程[11]。在线粒体氧化还原反应中，NAD^+能够携带质子变成还原型烟酰胺腺嘌呤二核苷酸[nicotinamide adenine dinucleotide (hydrogen), NADH]，随后，NADH在电子传递链中被氧化，将电子传递至氧分子，同时驱动质子泵的运作，从而促使线粒体氧化磷酸化过程生成ATP。在分解代谢过程中，NAD^+可被转化为NADH或者通过NAD^+激酶的磷酸化生成烟酰胺腺嘌呤二核苷酸磷酸(nicotinamide adenine dinucleotide phosphate, $NADP^+$)。此外，NAD^+还可作为许多酶的重要辅酶，比如Sirtuins类蛋白酶(SIRTs)、多聚腺苷二磷酸核糖聚合酶[(poly(ADP-ribose) polymerases, PARPs]和环状ADP-核糖(cyclic adenosine diphosphate ribose, cADPR)合成酶(CD38和CD157)等[2]。目前报道的与NAD^+代谢有关的蛋白酶超过了400种[5, 12–15]。作为细胞代谢的重要辅酶，NAD^+和$NADP^+$参与细胞的多种生物学过程，比如DNA修复、线粒体生物发生、基因表达、细胞周期、细胞应激反应和细胞通讯等[10, 16–20]。

1.1 NAD^+的生物合成

在生物体内，NAD^+的生物合成有三种途径：从头生物合成途径、Preiss-Handler途径和补救途径(图1*A*)。补救途径是NAD^+的主要合成途径，该途径主要通过二次利用NAD^+分解过程中生成的烟酰胺(nicotinamide, NAM)来重新合成NAD^+。作为合成NAD^+的前体，NAM在限速酶烟酰胺磷酸核糖转移酶(nicotinamide phosphoribosyltransferase, NAMPT)作用下被转化为单核苷酸(nicotinamide mononucleotide, NMN)，然后NMN在细胞质中被单核苷酸腺苷基转移酶(nicotinamide mononucleotide adenylyltransferase, NMNAT)转化为NAD^+[21]。另外，NMN也可在细胞外被CD73转化为烟酰胺核苷(nicotinamide riboside, NR)，随后NR进入细胞内被烟酰胺核糖激酶转化成NMN，胞质内的NMN经NMNAT最终被转变为NAD^+[22]。值得注意的是，NR还可从日常饮食中摄取。

从头合成途径主要依赖色氨酸(Trp)，并且Trp不能在人体内合成，只能通过饮食中获得。从头合成途径包括两个关键步骤：第一步是通过吲哚胺2,3-双加氧酶或色氨酸2,3-双加氧将Trp转化为N-甲酰基金脲(FK)，最终FK被转化为2-氨基-3-羧酸盐半醛(ACMS)。第二个关键步骤是ACMS自发聚合为喹啉酸(Qa)，随后Qa转化为烟酸单核苷酸(nicotinic acid mononucleotide, NAMN)，然后NAMN经Preiss-Handler途径最终生成NAD^+[2]。

在Preiss-Handler合成途径中，烟酸(nicotinic acid, NA)是NAD^+的另一个重要前体，主要从食物中获得。首先来自食物中的NA通过烟酸磷酸核糖基转移酶转化为NAMN，然后NAMN通NMNAT转化为烟酸腺嘌呤二核苷酸(nicotinic acid adenine dinucleotide, NAAD)，最后NAAD通过NAD^+合成酶直接转化为NAD^+[23]。NMNAT是该途径中的关键限速酶。

1.2 NAD^+的消耗

NAD^+通过作为许多酶的重要辅酶参与多种生物学过程(图1*B*)。例如在糖酵解过程中，NAD^+被还原为氢离子载体NADH，NADH经线粒体的电子传输链释放能量帮助合成ATP。一方面，NAD^+也可以被磷酸化为$NADP^+$，$NADP^+$及其还原形式NADPH

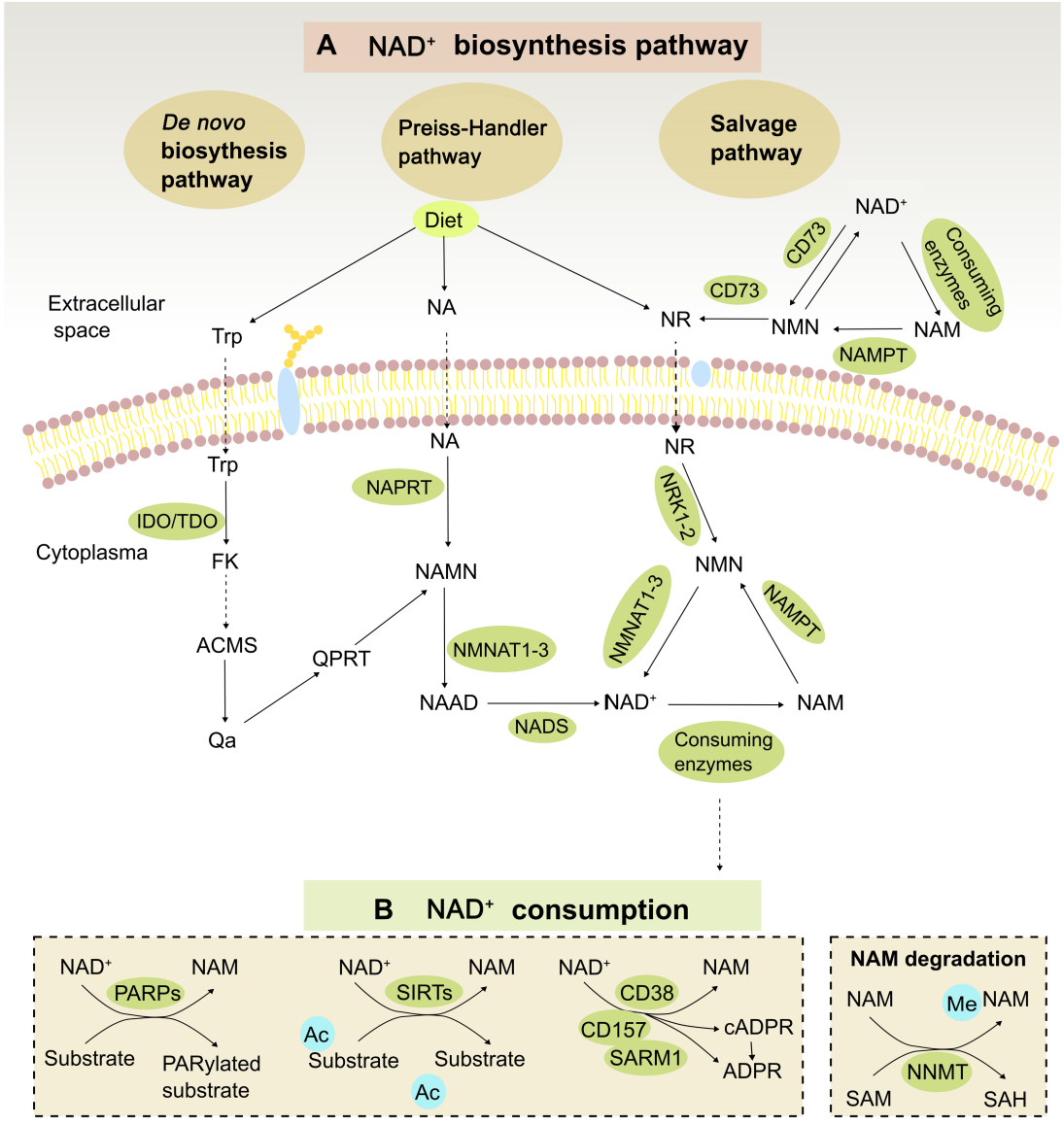

图 1. NAD⁺在机体的代谢

Fig. 1. NAD⁺ metabolism in the body. *A*: NAD⁺ biosynthetic pathway. *B*: NAD⁺ consumption. NAD⁺, nicotinamide adenine dinucleotide; IDO, indoleamine 2,3-dioxygenase; TDO, tryptophan 2,3-dioxygenase; Qa, quinolinic acid; NAMN, nicotinate mononucleotide; QPRT, quinolinate phosphoribosyl-transferase; NAPRT, nicotinic acid phosphoribosyltransferase; NMNATs, nicotinamide mononucleotide adenylyl transferases; NR, nicotinamide riboside; Trp, tryptophan; PARPs, poly(ADP-ribose) polymerases; SIRTs, Sirtuins; cADPR, cyclic adenosine diphosphate ribose; ADPR, adenosine diphosphate ribose; NNMT, nicotinamide N-methyltransferase; SAM, S-adenosyl-methionine; SAH, S-adenosyl-homocysteine; NMN, nicotinamide mononucleotide; NAM, nicotinamide; NA, nicotinic acid; NAMPT, nicotinamide phosphoribosyltransferase; Ac, acetyl; Me, methyl.

参与许多重要的氧化还原反应。另一方面NADP⁺和NADPH还作为谷胱甘肽还原酶的辅因子，保护细胞免受氧化应激损伤。

SIRTs是调节细胞代谢的能量传感器，NAD⁺主要作为SIRTs蛋白的底物被利用，在生理条件下SIRTs对NAD⁺的消耗约占总NAD⁺消耗的1/3 [24]。哺乳动物的SIRTs蛋白家族有七个成员(SIRT1~7)，它们在不同的细胞器中表达。SIRT1、SIRT6和SIRT7位于细胞核，SIRT2位于细胞质，SIRT3~5位于线粒体。研究表明，核SIRT1、SIRT6和SIRT7主要参与调节DNA修复和基因组稳定性，线粒体中的SIRT3~5和核SIRT1参与调节线粒体稳态和代谢过程[25]。SIRT1蛋白被广泛认为是调节寿命、衰老和代谢健康的关键因子，其在代谢综合征、CVD、神

经退行性疾病等方面发挥重要作用。在NAD^+的参与下，SIRT1会催化蛋白质的去乙酰化，产生NAM和ADP核糖。临床研究表明，SIRT1水平低的成年人发生微血管功能障碍和CVD的风险都比较高[26]。动物实验也证实了*SIRT1*敲除小鼠表现出明显的内皮功能障碍，并且有较高的风险发生微血管功能障碍和血管疾病并发症[27]。

PARPs蛋白家族在人类中由17种蛋白质组成，但只有PARP1、PARP2和PARP3位于细胞核中，这三种蛋白主要参与DNA损伤的早期反应，进而改善DNA损伤修复的过程[28–30]，上述过程会消耗大量的NAD^+。PARP1消耗NAD^+的过程中会产生NAM和ADP-核糖的副产物，即核糖基的复合物，该复合物主要是作为其他DNA修复酶的信号分子发挥作用[31, 32]。值得注意的是，DNA发生不可控的损伤会导致PARPs的过度激活，PARPs将一直持续激活状态直至NAD^+被耗尽，上述过程导致糖酵解速率降低、线粒体电子传输链受损和ATP产生减少，最终引发内皮细胞死亡[33, 34]。在高脂饮食(high-fat diet, HFD)小鼠模型上的研究显示，抑制PARP1可以提高NAD^+水平，增加SIRT1活性，最终改善线粒体功能[35, 36]。由此可见，PARP1可以调节胞内NAD^+代谢，因此通过PARP1来提高机体NAD^+水平的治疗策略非常有前景。

腺苷二磷酸核糖(adenosine diphosphate ribose, ADPR)蛋白发挥功能也依赖于NAD^+，ADPR消耗NAD^+生成NAM和ADP-核糖，后者在ADP-核糖环化酶的作用下生成cADPR。CD38和CD157是ADPR蛋白家族的重要成员，具有核糖苷水解酶和ADP-核糖环化酶的活性。在酸性条件下CD38进行碱交换反应将$NAD(P)^+$的NAM交换为NA，生成烟酸腺嘌呤二核苷酸(磷酸)[37]。除了NAD^+或$NADP^+$，CD38还可以将NMN作为可替代的底物[38, 39]，而CD157则利用NR作为替代底物，NMN和NR的水平与NAD^+水平密切相关[40, 41]。因此，CD38和CD157的小分子抑制剂在恢复机体NAD^+水平方面也可能有潜在应用价值。

2 NAD^+与血管功能

血管内皮在维持机体内稳态中发挥重要作用，如血液过滤、血管张力调节、免疫反应调节、激素运输和血管生成等过程[42]。NAD^+通过调节线粒体功能、自噬、炎症反应、氧化应激反应、蛋白质修饰等生物学过程参与调节血管功能，进而影响CVD的进程[43](图2)。

2.1 NAD^+与线粒体氧化应激

许多研究已经证实氧化应激与血管功能密切相关，并可能进一步促进血管疾病的发生及发展[43]。在正常生理条件下，细胞内活性氧(reactive oxygen species, ROS)的水平由抗氧化防御系统控制，而这些系统一旦失衡则会导致氧化应激损伤。病理条件下细胞会产生大量ROS (如超氧化物阴离子和一氧化氮自由基)，当ROS的量超过了细胞的抗氧化防御能力，过剩的ROS就会导致器官功能障碍[44–48]。老化的血管系统也会产生大量的ROS、超氧化物和过氧化氢，这些ROS产物损害血管扩张活性，并加速有毒自由基过氧亚硝酸盐的形成。线粒体是细胞内能量合成的主要场所，线粒体功能依赖于电子传递链的有效运行。在这一过程中，包括NAD^+在内的多种电子受体都参与了能量代谢过程中的三羧酸循环和氧化磷酸化。已知线粒体功能障碍与氧化应激密切相关[49]。在衰老过程中，ROS主要通过抑制三羧酸循环酶和ATP合成酶的活性，以及破坏线粒体DNA的结构，导致线粒体功能障碍和脂质过氧化；而线粒体损伤、脂质过氧化又进一步促进了ROS的产生，该过程最终诱发细胞凋亡[50]。

NAD^+的耗竭可能会影响线粒体氧化还原的平衡，增加线粒体氧化应激压力，从而增加发生血管疾病的风险。研究表明，补充NAD^+前体可以减轻血管的氧化应激反应、改善线粒体和血管功能障碍[51, 52]。例如补充NMN可以减少老年小鼠体内超氧化物的产生，从而逆转老年小鼠动脉中的氧化应激反应[51]，并改善线粒体膜电位和线粒体功能[53]。此外，补充NMN还可促进老年小鼠的线粒体生物能量转换，对神经血管功能具有保护作用[54]。研究显示，在老年小鼠中上调SIRT1可减少ROS的产生，并且激活小鼠体内抗氧化防御系统，进而改善线粒体氧化应激调节功能[55, 56]。除了SIRT1，NMN还会以SIRT3依赖的方式使多种线粒体蛋白(如超氧化物歧化酶2)脱乙酰化，进而减轻血管的氧化应激反应[57]。恢复细胞内NAD^+水平的另一种方法是下调NAD^+消耗酶的表达，减少对NAD^+的消耗[3]，研究显示，抑制体外培养的心脏内皮细胞中cADPR合成酶CD38的活性，可恢复细胞内NAD^+水平[58]，CD38基因敲除小鼠组织内NAD^+水平显著升高[59]。因此，补充NAD^+前体或抑制NAD^+消耗酶的活性可

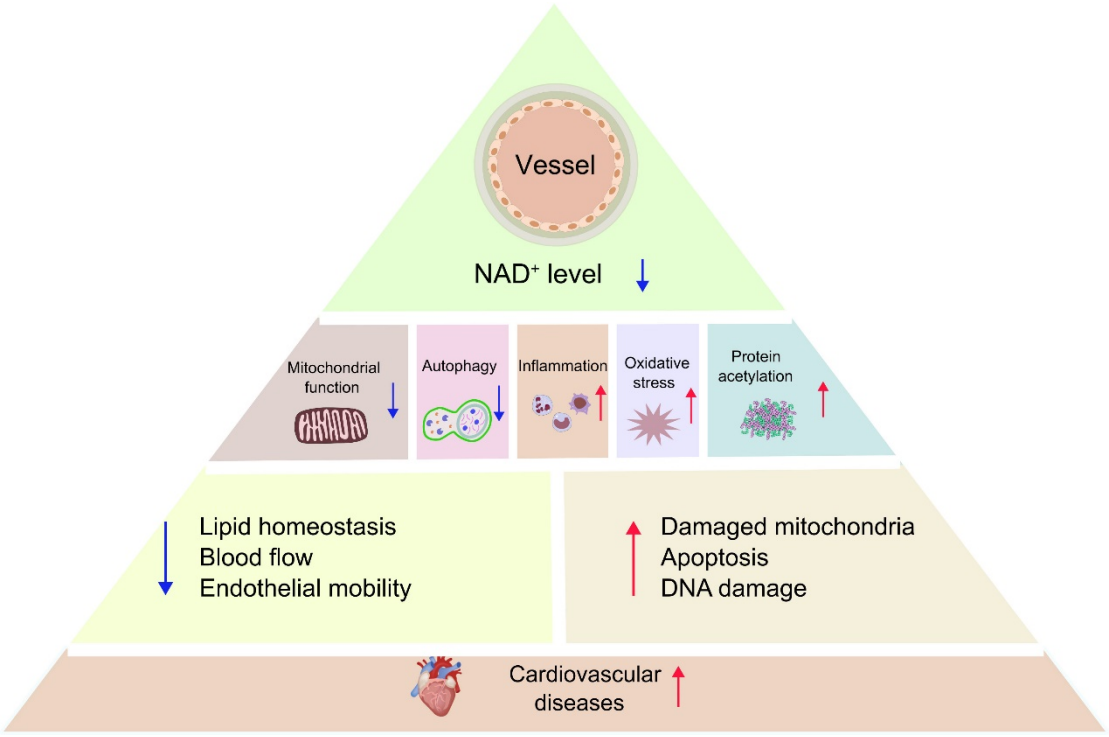

图 2. NAD⁺对血管健康和功能的影响

Fig. 2. NAD⁺ in vascular health and function. A decline in NAD⁺ levels leads to impaired mitochondrial function, increased oxidative stress, inflammation, and protein acetylation, ultimately contributing to endothelial dysfunction and cardiovascular diseases. NAD⁺, nicotinamide adenine dinucleotide.

有效缓解氧化应激、改善线粒体功能，并对血管健康产生保护作用。

2.2 NAD⁺与炎症

机体的慢性炎症随着年龄的增长而逐渐增强，这一过程与血管疾病的发展密切相关[60, 61]。炎症会导致血管内皮细胞功能障碍，表现为血管舒张因子如NO的产生减少，而促炎因子如白细胞介素-1β (interleukin-1β, IL-1β)、IL-6、肿瘤坏死因子α (tumor necrosis factor α, TNF-α)以及细胞黏附分子[如血管细胞黏附分子-1 (vascular cell adhesion molecule-1, VCAM-1)和细胞间黏附分子-1 (intercellular adhesion molecule-1, ICAM-1)]表达上调，促炎因子和细胞黏附分子促进了白细胞的黏附和迁移，这些过程都会进一步加剧炎症反应，进而导致血管舒张功能受损，血管重塑，甚至引发动脉粥样硬化斑块形成[62, 63]。另外，炎症因子也可以提高血液中的促凝血因子水平，如纤维蛋白原和C反应蛋白，使血小板活化，促进血栓的形成[64]。

衰老过程中的慢性炎症与NAD⁺水平的降低密切关联[65]。CD38是哺乳动物细胞内NAD⁺水平的主要调节因子之一。研究显示，老年小鼠体内与炎症相关的巨噬细胞数量增加，并且这些巨噬细胞都高表达CD38，而这些高表达CD38的巨噬细胞在肝脏和脂肪组织中的积累可降低NAD⁺水平[65]。在炎症条件下，人巨噬细胞和单核细胞中CD38水平提高[66]；老年人的血液样本中CD38水平也出现升高[67]。而补充NAD⁺前体物质可通过提高NAD⁺的水平来显著降低炎症反应，NAM是NAD⁺的主要前体之一，补充NAM可促进NAD⁺的合成，并显著降低小鼠的炎症反应[68]。在HFD饮食的小鼠中长期补充NAM可显著降低炎症反应，提高小鼠的健康状况[69]。另外，补充NMN和NR还会抑制IL-1β和TNF-α诱导的内皮细胞炎症，改善小鼠主动脉的血管舒张[70]。因此，提高血管内皮的NAD⁺水平可能是预防炎症导致的内皮功能障碍和血管疾病的有效策略。

2.3 NAD⁺与自噬

自噬是细胞内自修复的动态过程，自噬可以减轻氧化应激反应，提高NO的生物利用率，在动脉内皮上有抗炎作用。因此，细胞自噬在维持血管内

皮功能方面有着重要作用。自噬障碍是血管衰老及相关疾病发生的常见原因。研究显示，下调小鼠血管内皮中自噬基因的表达，或者完全阻断细胞自噬可导致动脉壁增厚、血管僵硬及内皮依赖性血管舒张功能受损[71]。Osonoi等研究显示，平滑肌细胞中*Atg7*基因(参与自噬体形成)的缺失会导致血管功能异常和平滑肌细胞收缩力降低[72]。正常的自噬反应对维持血管健康很重要，增强细胞自噬可改善血管内皮功能障碍[73]。Zhang等在对大鼠心脏微血管病变的研究中发现，补充NAD^+可恢复细胞的自噬能力，减少微血管损伤，维持大鼠心脏微血管的密度和完整性[74]。另外，NAD^+通过激活SIRT1的去乙酰化酶活性，调节自噬相关蛋白的乙酰化状态，进而直接或间接促进自噬体的形成和自噬过程的进行[75]。因此，通过提高细胞内NAD^+水平增强细胞的自噬能力具有作为血管疾病治疗方法的潜力。

3 NAD^+与CVD：基于动物模型的研究

衰老和慢性炎症是血管功能障碍及其相关疾病的主要原因，系统性的NAD^+水平下降与衰老和炎症密切相关。学者们在血管疾病中也观察到NAD^+的代谢紊乱，这些疾病包括动脉粥样硬化、高血压、心肌梗死以及心肌缺血/再灌注(ischemia/reperfusion, I/R)、心肌肥大及心力衰竭等。目前，用药物恢复机体NAD^+水平的疗法已被应用于CVD动物模型上，具体情况总结于表1。

3.1 动脉粥样硬化

研究表明，动脉壁中的慢性炎症最终会导致动脉粥样硬化，血液中过载的胆固醇会激活内皮细胞，随后通过招募M1型巨噬细胞引发炎症反应[76–78]。研究表明SIRTs蛋白参与上述所有过程。SIRT1通过调节肝脏中胆固醇的合成，降低血脂水平[79]。脂肪酸、胆固醇和葡萄糖的代谢受肝脏X受体(liver X receptor, LXR)蛋白的调节，SIRT1会以

表1. 药物恢复NAD^+稳态的动物模型研究

Table 1. Animal model studies on supplementing drugs to restore NAD^+ homeostasis

Vascular diseases	Experiment design	Vascular-related outcomes	Reference
Atherosclerosis	Supplementing NAM in *ApoE*$^{-/-}$ mice	Prevented the development of atherosclerosis	[81]
	Specific knockdown of NAMPT in *ApoE*$^{-/-}$ mouse	Reduced the area of arterial plaques, the number of macrophages and cell apoptosis	[85]
Acute myocardial infarction	Pig AMI model with external aid NAD^+ administration	Reduced myocardial necrosis and promoted cardiac function recovery	[91]
	Supplementing NMN in elderly AMI rats	Restored the NAD^+/NADH ratio of the myocardium	[92]
Myocardial ischemia/reperfusion	Overexpressing SUR 2A mice or mice on a nicotinamide rich diet	Increased the resistance of the heart to ischemia/reperfusion	[94]
	Overexpression of NAMPT in ischemia/reperfusion mice	Reduced myocardial infarction area and myocardial cell apoptosis	[95]
Cardiac hypertrophy	PARP inhibitor rucaparib treatment in mice with myocardial hypertrophy	Improved symptoms of myocardial hypertrophy and decreased myocardial contractility in mice	[100]
	Overexpression of SIRT3 in rats with myocardial hypertrophy	Reduced the acetylation level and activity of PARP-1, and exerted protective effects on myocardial hypertrophy	[101]
Heart failure	Short-term supplementation of NMN in a mouse model of heart failure	Protected mice from stress-induced heart failure	[104]
	Supplementing NAD^+ precursor NR in the diet of mice with heart failure model	Improved mitochondrial function and symptoms of heart failure	[102]
Hypertension	Supplementing NAM in hypertensive mice	Lowered arterial blood pressure	[109]

NAD^+, nicotinamide adenine dinucleotide; NADH, nicotinamide adenine dinucleotide (hydrogen); NAM, nicotinamide; SUR 2A, sulfonylurea receptor 2A; NAMPT, nicotinamide phosphoribosyltransferase; NMN, nicotinamide mononucleotide; NR, nicotinamide riboside; AMI, acute myocardial infarction; PARP, poly(ADP-ribose) polymerase.

NAD^+依赖的方式促进LXR的脱乙酰化，进而调节胆固醇的合成；此外，SIRT1还会抑制泡沫细胞的形成[80]。值得注意的是，对*ApoE*$^{-/-}$小鼠给予NAM处理可抑制脂蛋白氧化和主动脉的炎症，预防动脉粥样硬化的形成[81]。一项随机对照研究表明，甲基NAM会以NO依赖的方式促进内皮细胞NO生成增强、氧化应激下NO/O_2^-平衡恢复、血管舒张能力提高[82]。同样地，在*ApoE*-和*Ldlr*-缺陷小鼠中，甲基NAM能减少动脉粥样硬化斑块面积、斑块炎症和胆固醇含量，改善内皮功能障碍[83]。Jiang等研究显示，在*ApoE*$^{-/-}$小鼠中甲基NAM对内皮依赖性血管舒张也具有类似的保护作用[84]。

NAMPT是NAD^+补救生物合成途径中的限速酶，参与动脉粥样硬化的发展，在*ApoE*$^{-/-}$小鼠肝脏中特异性下调NAMPT的表达可显著抑制动脉粥样硬化的形成，减少斑块面积、巨噬细胞数量和细胞凋亡[85]，提示NAMPT可能有促炎的作用。而Bermudez等研究提示NAMPT可能有抑制炎症的作用，他们发现在*Ldlr*$^{-/-}$小鼠白细胞中特异性过表达NAMPT可通过调节单核细胞的分化和功能降低炎症反应，减小*Ldlr*$^{-/-}$小鼠动脉粥样硬化斑块[86]。

3.2 心肌梗死与心肌I/R

急性心肌梗死(acute myocardial infarction, AMI)与心肌I/R都与NAD^+水平降低密切相关[87–89]。Zhang等研究显示，NAD^+会以剂量依赖的方式减少大鼠心肌I/R模型中心肌细胞凋亡和心脏梗死面积[90]。在猪AMI模型中，补充NAD^+可显著减少心肌细胞坏死，增强葡萄糖代谢，降低心脏的炎症反应和纤维化程度[91]。NMN给药对老年大鼠AMI也有显著减轻作用，恢复心肌NAD^+/NADH比率，降低心肌的氧化应激反应和线粒体ROS水平[92]。另外，体外培养的内皮细胞在模拟I/R处理后，NAD^+水平下降，并与内皮细胞中CD38活性的升高密切相关[59]，另一项研究发现，小鼠心脏I/R模型中CD38的NAD^+水解酶活性导致缺血后小鼠心脏中NAD^+的耗竭，抑制血管舒张功能[93]。因此，抑制CD38可能成为预防心肌I/R诱导的内皮功能障碍的重要策略。在小鼠I/R模型中，富含NR的饮食可以上调小鼠I/R后磺酰脲受体2A (sulfonylurea receptor 2A, SUR 2A)的表达，并显著减少梗死的面积[94]。NAMPT在小鼠心脏特异性过表达能提高NAD^+水平，减少I/R后心肌梗死面积和心肌细胞凋亡[95]。

3.3 心肌肥大与心力衰竭

病理性心肌肥大往往伴随不良心血管事件，包括心力衰竭、心律失常等[96]。NAD^+是SIRT1必需的辅因子，并且SIRT1在心肌肥大的发生和进展中具有保护作用。SIRT1可激活过氧化物酶体增殖物激活受体γ辅激活因子1-α (peroxisome proliferator-activated receptor γ coactivator 1-α, PGC-1α)/过氧化物酶体增殖物激活受体α (peroxisome proliferator-activated receptor α, PPARα)信号通路，该通路可上调与能量代谢相关的线粒体功能基因的表达[97, 98]，最终延缓心肌肥大的病理进程。溴结构域蛋白4 (bromodomain-containing protein 4, BRD4)是溴结构域和额外末端家族成员，可通过与乙酰化染色质结合来诱导肥大基因的表达，导致心肌肥大。研究显示，BRD4可通过激活PARP-1来促进心肌肥大，下调BRD4的表达能抑制PRAP-1表达，减轻心肌肥大[99]。PARP抑制剂rucaparib可抑制PARP-1活性，改善小鼠心肌肥大和心肌收缩力降低的症状[100]。Feng等研究显示，过表达SIRT3可降低PARP-1乙酰化水平和活性，对心肌肥大也有减轻作用[101]。在临床上，Tong等在心力衰竭患者中观察到心肌细胞线粒体功能受损，并且参与NAD^+生物合成的基因表达也受到抑制[102]。Walker等在心力衰竭动物模型上的研究显示，提高细胞NAD^+水平能够预防心脏功能障碍，缓解心力衰竭[103]。Zhang等研究显示，短期给予NAD^+前体NMN可保护小鼠免受压力过载诱导的心力衰竭，而NMN可减轻线粒体超微结构的改变，降低心肌细胞中ROS水平，减少心肌细胞凋亡[104]。Tong等研究显示，在心力衰竭模型小鼠的食物中补充NAD^+前体NR可改善线粒体脂肪酸氧化功能和心力衰竭症状[102]。

3.4 高血压

高血压极大地增加了中风、心脏病、慢性肾脏疾病和认知能力下降的风险，全世界范围内高血压的患病率超过30% [105]。高血压的发病机制复杂，目前还不完全清楚。已知内皮功能障碍与高血压密切相关，肾功能变化也可能导致高血压的发生[106]。Zhou等研究显示，患有高血压的人类和小鼠体内NAD^+生物合成限速酶NAMPT表达下调[107]，提示提高NAD^+水平可能具有降压作用；在血管紧张素II诱导的高血压小鼠模型中，系统性过表达NAMPT通过抑制主动脉壁中ROS的产生和降低氧化应激水平显著减轻高血压和血管损伤[107]。Gao等

研究显示，血管平滑肌细胞中特异性过表达SIRT1能预防血管紧张素II诱导的小鼠高血压[108]。在内皮NO合酶功能障碍小鼠中，通过饮用水给药NAM可有效抑制血压的升高，降低炎症反应[109]。在患有慢性肾脏病的小鼠中，口服给药NA可降低血压、氧化应激和炎症反应[110]。一项I期临床研究结果显示，长期口服补充NR能有效刺激NAD^+的生物合成，降低中老年人的血压，减轻主动脉硬化[111]。此外，Gan等研究显示，通过抑制CD38活性来提高机体NAD^+水平可显著改善血管紧张素II诱导的小鼠高血压[112]。

4 NAD^+作为改善心血管健康的靶点：从实验室到临床

流行病学和临床前研究表明，机体各种组织细胞内NAD^+水平与CVD密切相关[39, 65, 112–117]。目前，已有许多临床和临床前研究通过药物恢复机体NAD^+水平的方式来治疗CVD，具体情况总结于表2。

4.1 白藜芦醇

白藜芦醇是一种非特异性化合物，可与细胞内的许多蛋白质相互作用[118]。白藜芦醇是ROS自由基清除剂，具有抗氧化的特性[119, 120]，还有抗癌作用[121–123]，还能有效调节机体NAD^+水平。动物实验结果显示，白藜芦醇能减轻HFD喂食小鼠体重的增加，减少胰腺和心脏损伤，改善葡萄糖代谢；白藜芦醇的保护作用与线粒体数量和功能增加有关；在正常饮食组中，白藜芦醇可显著降低血管内皮的炎症反应和凋亡[124, 125]。然而，白藜芦醇作用的机制仍存在争议。一些研究表明，白藜芦醇首先激活腺苷酸活化蛋白激酶(AMP-activated protein kinase, AMPK)，然后通过增加细胞内NAD^+水平间接激活SIRT1，从而改善血管功能状态[126, 127]。Price等研究表明，白藜芦醇可能首先激活SIRT1，然后使AMPK激酶脱乙酰化，启动AMPK通路，最终导致细胞内NAD^+水平的提高[128–130]。值得注意的是，白藜芦醇的作用有剂量依赖性，低剂量(25 μmol/L)白藜芦醇通过SIRT1依赖的方式激活AMPK，提高

表2. NAD^+补充剂的临床研究

Table 2. Clinical studies on NAD^+ supplements

Supplements	Time frame	Conditions of participants	No. of recruited participants	Vascular-related outcomes	Clinical Trial Number/reference
Resveratrol	24 months	Postmenopausal women aged 45 to 85	146	Improvement of cerebrovascular function	ACTRN1261600067-9482p
	30 d	Obese patients	150	Energy metabolism and changes in systolic blood pressure	[123]
NMN	60 d	Healthy subjects between the ages of 40 and 65	66	Changes in serum NAD^+/NADH levels and blood pressure	NCT04228640
	28 d	Healthy volunteers aged 30 to 60	20	Changes in arterial blood pressure, heart rate, and blood lipids	NCT04862338
NR	6 weeks	Healthy middle-aged people	30	Changes in blood pressure	NCT02921659
	6 weeks	Elderly people with hypertension	49	Changes in systolic blood pressure and arterial stiffness	NCT04112043
	3 months	Patients with moderate to severe chronic kidney disease	118	Changes in aortic stiffness and arterial blood pressure	NCT04040959
NA	1 year	Patients with atherosclerosis and low HDL-C (<40 mg/dL) (mean age 65 years)	71	Changes in carotid artery area and plaque size	NCT0023253
NAM	48 h	Women with early-onset preeclampsia	25	Changes in average blood pressure	NCT03419364

NMN, nicotinamide mononucleotide; NAM, nicotinamide; NR, nicotinamide riboside; NA, nicotinic acid; HDL-C, high density lipoprotein cholesterol.

NAD^+水平，促进线粒体生物合成，诱导肌肉纤维向更氧化型转变，而高剂量(50 μmol/L或更高)对线粒体功能的改善不显著，甚至可能表现出毒性作用[131]。因此，白藜芦醇在血管功能及其相关疾病中的保护机制仍然有待研究。在一项随机双盲临床研究中，健康肥胖男性接受白藜芦醇(150 mg/天)或安慰剂治疗30 d后，白藜芦醇治疗组基础代谢率和血压显著降低；此外，白藜芦醇可激活AMPK通路，上调SIRT1和PGC-1α蛋白的表达，并增加肌肉中的线粒体活性[132]。然而，另一项针对非肥胖男性的临床试验结果则显示，白藜芦醇治疗4周后药物组中未能观察到任何可测量的生理功能改善[133]。此外，白藜芦醇能够通过调节多种生物学参数改善肾脏衰老，包括降低氧化应激标志物(如丙二醛)和促炎因子(如TNF-α、IL-6)水平，提高抗氧化酶(如超氧化物歧化酶、谷胱甘肽过氧化物酶)活性[134]。白藜芦醇还能通过下调NADH氧化酶表达来改善动脉血管壁增厚，弹性降低，以及血管功能的退化[135, 136]。

4.2 NAD^+前体

大量研究表明，膳食中补充NAD^+前体，如NA、NAM、NR和NMN，可以有效提高动物和人机体的NAD^+水平[4, 51]。

4.2.1 NR

NR是NAD^+的主要前体物质之一，也是第一个用于临床试验评估人体药代动力学的前体[111]。口服NR在临床试验中以剂量依赖的方式提高血液NAD^+的水平，并且表现出良好的耐受性，无副作用[137, 138]。Zhou等在心力衰竭患者的临床试验中发现，口服NR可抑制免疫细胞的激活，改善线粒体适应性[139]。另一项随机双盲试验结果显示，与安慰剂对照组相比，给健康中老年人补充NR 6周后明显降低了I期高血压和主动脉硬化发生率[140]。这些临床试验表明，补充NR可以降低CVD发生率。然而，并非所有研究都支持NR补充剂在临床上的治疗效果。Martens等研究显示，NR补充剂不能改善中老年人的内皮功能障碍[111]。此外，尽管口服NR补充剂降低了70至80岁男性的炎症细胞因子水平，但是并没有改善其血流量、线粒体生物功能或骨骼肌代谢[141]。为了评估NR的有效性，由法国国家研究机构(Agence Nationale de la Recherche, ANR)资助的项目开展了NR用于治疗心力衰竭患者的II期临床试验(项目编号：ANR-17-CE17-0015)。为了评估NR的安全性和耐受性，一项包括30名收缩性心力衰竭患者的介入性临床试验也在进行中[142]。另一项研究招募了左心室有辅助装置的受试者，旨在揭示NR对心肌NAD^+水平、线粒体功能和炎症反应的影响(项目编号：NCT04528004)。为揭示NR的治疗效果，还有多项临床试验正在进行中(项目编号NCT03151239、NCT03432871、NCT03501433、NCT02835664)。

4.2.2 NAM

NAM也是NAD^+合成的前体之一，NAM可能对动脉粥样硬化患者没有显著影响，因为它不能决定性地降低患者的血脂水平[143]。相反，NAM具有抗氧化和抗炎能力[69, 81]。鉴于NAD^+耗竭与心脏炎症的发病机制密切相关，因此NAM可能对心肌炎患者有益处，给予NAD^+前体可能是治疗病毒性心肌炎的一种有前景的方法。临床上，在严重急性呼吸系统综合征冠状病毒2型(SARS-CoV-2)感染的受试者中观察到心肌炎[144, 145]。值得注意的是，SARS-CoV-2感染会激活NAD^+消耗酶(SIRT1和PARP)，并直接参与细胞内免疫反应；反之，SIRT1和PARP的激活可能继发性地诱导NAD^+耗竭[144, 145]。因为SARS-CoV-2感染还会引发呼吸系统以外的其他系统疾病，因此NAM治疗可以有效减少新冠肺炎综合征的副作用[146]。这一证据也提示，NAM或其他NAD^+前体可能对预防新冠肺炎感染造成的心肌炎具有积极的保护作用。然而，值得注意的是，有研究显示，在食物中补充0.5% NAM会导致大鼠肝脏脂肪酸含量增加，而且当在食物中补充1% NAM会导致大鼠生长受到抑制，但是后续没有研究确认，因此将NAM作为NAD^+前体用于治疗仍需要进一步研究验证其安全性[147]。

4.2.3 NMN

动物模型已经证实口服补充NMN可以有效提高机体NAD^+水平并改善各种生理功能[19, 54]。Liao等研究显示，NMN给药6周结合运动训练提高中年业余跑步者的肺活量和耗氧量，提示NMN可能会增加骨骼肌而不是心肌的耗氧量[148]。尽管这项研究没有分析心脏功能，但最近的一项研究表明运动训练会改善老年小鼠HFD引起的脂毒性心肌病[149]。因此，我们猜测NMN给药可能会进一步增强机体对HFD诱导的心脏病的运动抵抗力。然而仍需要进一步的研究来证实这一假设，以在未来的临床试验中验证NMN对心脏健康的潜在积极影响。

总的来说，关于NAD^+在CVD中的作用已经进

行了大量且广泛的研究，但关于NAD^+前体的使用仍然存在许多问题。这些问题包括给药方式、时间和安全剂量，同时还要考虑NAD^+在不同组织中的分布，上述因素都会对NAD^+前体的治疗效果有影响[6, 51]。因此，通过改善NAD^+代谢来治疗人类血管疾病仍有许多挑战需要克服。

5 总结与展望

CVD每年导致全球约30%的死亡，因此，改善心血管健康意义重大，其可能在很大程度上降低CVD的发病率，尤其是对老年群体而言。许多临床研究都提示，靶向提高机体的NAD^+水平在临床预防和治疗CVD方面有巨大潜力。将NAD^+前体与小分子药物结合使用以恢复细胞内NAD^+水平是治疗CVD的一种有前途的治疗方法。因此，许多临床前研究都集中在参与NAD^+前体代谢的转运蛋白和受体上，这些研究将有助于我们更好地了解NAD^+代谢参与CVD的分子机制。此外，NAD^+还可以调节血管炎症和自噬，体内补充NAD^+前体对这些生理功能的作用还有待研究。动物模型和临床研究都已经证明，NAD^+在CVD细胞代谢稳态和健康中发挥着至关重要的作用。在血管疾病的背景下，NAD^+增强策略可以提高血管健康，并改善老年人的心脑血管状况。为评估NAD^+前体的安全性和有效性，许多临床试验正在积极进行中。重要的是，早期试验已经证明，短期NR/NMN给药能提高健康受试者机体的NAD^+水平，并且没有副作用，是安全的。尽管已有多项有希望的初步试验结果，但长期补充NAD^+前体是否对机体有副作用仍然是未知的。我们需要进一步研究NAD^+补充疗法对CVD的治疗机制及效果。

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