



泛血管衰老与老年心血管共病: 现状、展望与中西医结合防治策略

漆仲文^{1,2,3}, 刘艳飞^{1,2,3}, 张艳虹^{1,2,3}, 张颖^{1,2,3}, 刘玥^{1,2,3*}, 徐凤芹^{1,2,3*}

1. 中国中医科学院西苑医院老年二科, 中国中医科学院老年医学研究所, 北京 100091

2. 国家中医药管理局病证结合防治血管衰老重点研究室, 北京 100091

3. 国家中医心血管病临床医学研究中心, 北京 100091

* 联系人, E-mail: 18800021979@163.com; liuyueheart@hotmail.com

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摘要 泛血管衰老理念的提出为老年心血管共病的防治以及老年共病机制研究提供理论依据和转化研究思路。泛血管衰老存在时间维度的时序性衰退与空间维度的多器官血管损伤双重特征, 其受到泛血管微环境的复杂动态网络调控。本文首先对泛血管衰老的内涵及多重典型特征进行了概述, 然后重点阐述了泛血管微环境(残余风险、易损因素、炎症状态等)对血管衰老的主要研究进展, 并围绕“心脑血管共病、心-肾-代谢综合征、心-外周血管共病、心肺血管共病”的泛血管衰老机制及转化应用面临的瓶颈问题进行了论述, 提出建立泛血管衰老危险分层预警模型、中西医数智融合泛血管衰老早期识别体系、多学科交叉泛血管衰老老年心血管共病防治一体化平台, 最后展望了整合时空多组学技术, 绘制泛血管衰老时空图谱, 揭示跨器官血管衰老调控靶点, 研发针对泛血管衰老共病靶点的新型药物为未来研究方向与应用前景。

关键词 泛血管衰老, 老年, 心血管共病, 防治策略, 多器官衰老

泛血管衰老(panvascular aging)是指随着年龄增长而发生的全身血管网络(包括动脉、静脉及微循环系统)结构与功能的渐进性退化过程。这一病理生理改变以内皮功能障碍、血管重构、慢性低度炎症及细胞衰老等为特征性表现^[1~3]。在全球人口老龄化日益加剧的背景下, 血管系统的退行性改变已成为老年人群心血管共病(如冠心病、糖尿病、高血压及外周血管疾病等)高发病率与死亡率的重要病理基础。从概念内涵来看, 泛血管疾病特指为以血管病变为共同病理特征的系统性血管疾病群, 其中动脉粥样硬化(atherosclerosis, AS)约占95%, 其病变范围可同时累及大、中、微血管系统, 导致心、脑、肺、肾、四肢等多个

重要靶器官损害^[1]。值得注意的是, 在老年共病人群中, 多系统血管病变的共存现象十分普遍, 而泛血管衰老与泛血管疾病并非孤立进程, 二者通过复杂的“衰老-疾病轴”机制形成动态互作的病理网络。本文系统梳理了泛血管衰老影响老年心血管共病稳态调控的最新研究现状, 创新性提出从“时序性生理衰退(时间维度)”与“泛血管病理性损伤(空间维度)”的双重视角, 深入解析泛血管衰老调控老年心血管共病的共性分子机制, 并探讨靶向干预血管衰老进展以阻断“衰老-疾病轴”恶性循环的治疗新策略, 旨在为泛血管衰老相关心血管共病的精准防治提供理论依据和转化研究思路。

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1 泛血管衰老的内涵及特征

1.1 泛血管衰老驱动多血管损伤重塑

泛血管是由人体动脉、静脉、淋巴管等共同构成的复杂网络体系。早在20世纪末,医学界便提出了“血管树”和“血管网络”的概念,强调应采用系统生物学方法研究血管性疾病^[4,5]。而“泛血管衰老”这一新兴概念的提出,则基于近年来对多血管病理衰老机制的系统性研究^[6-8],其核心在于强调衰老对全身多血管床的协同影响,而非局限于单一血管病变。血管衰老涵盖动脉、静脉及微循环的病理生理变化,其中动脉衰老则以粥样硬化斑块形成、弹性纤维降解及血管顺应性降低为核心,伴随脂蛋白沉积与炎症因子驱动的内皮功能障碍;静脉衰老以血管壁结构重塑、瓣膜功能退化及血流动力学异常为特征;微循环衰老表现为毛细血管密度减少、基底膜增厚及血流灌注不均,常累及组织氧供与代谢物质交换,三者共同构成血管系统衰老的多维病理图景。衰老作为心血管疾病(cardiovascular diseases, CVDs)的独立危险因素,通过泛血管衰老这一系统性病理过程,重塑多血管系统疾病的发展轨迹。值得注意的是,衰老对于泛血管系统的影响呈现明显的时序性特征。流行病学研究证实,即使在控制传统危险因素(如高血压、高脂血症、糖尿病)后,年龄的增加仍与AS、心力衰竭及微血管病变的风险呈显著正相关^[9,10]。Framingham心脏研究的重要发现表明,血管僵硬(动脉衰老的核心标志)每增加1个标准差,心血管事件风险将显著升高40%~60%^[10]。这一发现提示,泛血管衰老可能通过独特的分子途径驱动血管系统疾病的病程进展,即形成所谓的“衰老-疾病轴”。

从病理生理学角度看,血管衰老过程主要表现为血管弹性下降、血管壁增厚、内皮功能障碍及血管周围脂肪组织(perivascular adipose tissue deposition, PVAT)功能改变^[11]。研究表明,在衰老早期即可出现血管壁中细胞微环境的稳态失调和内皮功能障碍,影响大小动脉的生理功能,导致不同血流动力学的改变,包括大动脉和阻力动脉的张力增加、振荡剪切应力增强以及大动脉硬度增加等^[12,13]。进入老年阶段(衰老进展期),血管系统的退行性改变更为显著。与年轻血管相比,衰老血管系统以弹性蛋白降解和胶原蛋白沉积为特征性改变,大动脉可见AS相关的内膜增厚,血管腔直径明显扩张,外膜明显的脂肪沉积,而颈动脉则表现为全层(内膜、中膜和外膜)增厚^[11]。此外,老化的大动

脉还常见内膜和中膜钙化。这些变化在细胞层面上与血管平滑肌细胞(vascular smooth muscle cell, VSMC)功能障碍和内皮细胞的肥大、衰老和凋亡密切相关^[11]。VSMC数量随着年龄增长而减少,且在衰老和AS中均可观察到VSMC表型转化,表现为收缩蛋白表达减少,促增殖和迁移物质表达增加,VSMC从中膜向内膜迁移的现象反映了早期AS的病理改变,也提示老年人血管僵硬和斑块形成的共同机制^[14]。值得关注的是,PVAT在血管衰老过程中扮演重要角色。人体大多数血管被PVAT层包绕,随着年龄增长,血管周围PVAT沉积增加、脂肪细胞增殖及促炎性巨噬细胞浸润,这些变化通过血管外膜与血管壁形成双向通讯^[11]。研究表明,人主动脉PVAT的改变与衰老、主动脉僵硬、心血管风险升高密切相关,其中,PVAT密度增加与AS、罪犯病变及脑血管事件的高发生率相关^[15]。动物模型研究进一步证实,不同血管床周围的PVAT可诱导动脉僵硬、血管收缩、动脉舒张受损和AS^[16,17]。微血管网络的改变是泛血管衰老的另一重要特征。微血管网络包括小动脉和毛细血管,衰老可导致脑小动脉稀疏和毛细血管网密度降低,进而减少脑血流量并影响神经元信号传导的代谢途径^[18];同时也会引起冠状动脉微血管稀疏,导致动脉硬化和内皮功能障碍,最终导致靶器官损伤和心血管事件的发生^[19,20]。

泛血管衰老与AS迅速进展密切相关,尤其是在老年人群中,AS斑块的形成和破裂风险显著增加。AS作为系统性血管疾病,其病变分布可表现为单血管床受累(如孤立性冠状动脉病变)或多血管床联合受累(如冠状动脉、颈动脉及外周动脉同时病变)^[21]。外周动脉疾病往往与冠状动脉和颈动脉疾病并存,随着一个血管床中AS的进展,其他区域的AS风险增加,且不良心血管事件的发生率随着病变血管床的数量增多而显著增加^[22]。对68例冠状动脉病变患者和93例外周动脉病变患者进行血管内超声成像,发现在所有动脉中均观察到不同程度的斑块破裂(冠状动脉13%,颈动脉7%,肾动脉6%,髂动脉7%)和厚帽纤维粥样硬化(冠状动脉37%,颈动脉24%,肾动脉16%,髂动脉7%),与冠状动脉相比,肾动脉和髂动脉中观察到纤维粥样硬化较少,与中度或负性重构的病变相比,正性重构的病变在冠状动脉、颈动脉和肾动脉中表现出更多的纤维粥样硬化特征^[23]。研究发现,与来自同龄个体的健康动脉相比,AS血管含有更高比例的衰老内皮细胞和VSMC,而不稳定斑块中存在的衰老终末分化CD8⁺ T细胞,可作

为预测老年人全因死亡率的独立指标^[24,25]。从分子机制来看,氧化应激、端粒功能障碍、表观遗传及衰老相关分泌表型(senescence associated secretory phenotype, SASP)的激活与衰老进程密切相关。泛血管衰老通过血管内皮屏障破坏、VSMC表型转化及周细胞丢失,为泛血管疾病的进展提供了微环境基础^[7];反过来,泛血管疾病相关的血流动力学紊乱、代谢毒性物质蓄积及病理性血管重塑,又进一步加剧局部及远端血管床的衰老进程,形成“衰老促进疾病,疾病加剧衰老”的恶性循环^[26]。

1.2 血管微环境加速泛血管衰老过程

泛血管衰老作为机体衰老的关键驱动因素,其病理生理级联反应始于特定血管区域的脆弱性改变,并受到多种心血管危险因素的动态调控。高血压、高脂血症、糖尿病、吸烟及慢性炎症等易损因素可显著加速泛血管衰老的进展过程。研究表明,在这些易损因素的影响下,泛血管系统的不同解剖部位(包括冠状动脉、脑动脉、肾动脉及外周动脉等)呈现明显的异质性衰老特征,最终导致心脏、大脑、肺、肾脏和四肢等重要靶器官的功能损害^[2,27]。

从分子机制来看,高血压、高血糖及血脂异常可通过氧化应激介导的基质金属蛋白酶激活,优先导致动脉重塑,包括内膜-中膜增厚、AS、纤维化、钙化和动脉瘤形成等特征性改变^[28,29]。AS作为最主要的动脉疾病,在斑块形成和扩张过程中,平滑肌细胞异常增殖和内皮一氧化氮合酶水平下降可导致端粒缩短和氧化应激,这些改变均为细胞衰老的重要诱导因素^[30-32]。衰老的VSMC、内皮细胞与斑块中招募的免疫细胞之间存在着复杂的细胞通讯和空间维度的信号传导。在斑块形成起始阶段,衰老内皮细胞通过分泌SASP和表面受体介导循环单核细胞向血管壁的浸润^[33]。同时,衰老内皮细胞更易发生凋亡,导致内皮屏障功能破坏和血管通透性增加^[34]。在斑块进展期,SASP中的趋化因子(如促AS因子单核细胞趋化蛋白1和白细胞介素)发挥关键调控作用^[35]。最后,衰老细胞可导致斑块不稳定和易损斑块的形成,引发各种泛血管事件,如冠心病、严重肢体动脉缺血和血栓形成,增加中风和心肌梗死风险^[36],从而构建了从微观(细胞、分子水平)到宏观(组织、器官水平)的泛血管衰老空间关联网络。

炎症衰老(inflammaging)在泛血管衰老进程中扮演核心角色,是相关性CVDs的重要中介机制,在空间上

累及血管、心脏、大脑等多个器官^[37]。炎症衰老指老年机体出现的慢性低度无菌性炎症状态,参与多种与年龄相关的慢性疾病的发展。其特征是促炎细胞因子如肿瘤坏死因子 α 、白细胞介素(interleukin, 家族的IL-1 β 、IL-6)和C反应蛋白等促炎因子循环水平升高,涉及核苷酸寡聚化结构域样受体家族含吡林结构域3(nucleotide oligomerization domain-like receptor family pyrin domain-containing 3, NLRP 3)、基质金属蛋白酶的激活、细胞衰老、免疫衰老、线粒体功能障碍及肠道微生物群生态失调等多种病理生理机制,共同加剧老年心血管共病如高血压和AS的发生发展^[38,39]。在衰老过程中,错误折叠和异常定位的蛋白质逐渐累积,可作为损伤相关的分子模式(damage-associated molecular patterns, DAMPs)加剧炎症衰老反应,同时促进老年CVDs和脑血管疾病(如AS、动脉血栓形成、痴呆)的发生^[40]。临床研究显示,即使经过他汀类药物治疗,CVDs患者仍存在残余胆固醇和残余炎症的风险,二者的协同作用可显著增加全因死亡率^[41]。因此,在衰老过程中,即使传统风险因素(如高胆固醇、高血压)得到有效控制,泛血管衰老仍与持续的残余炎症和炎症衰老状态密切相关,通过影响代谢紊乱、免疫系统失调和细胞衰老等途径,持续加剧泛血管衰老进程,最终导致泛血管事件的发生^[38]。这一发现强调了针对炎症衰老干预策略在防治老年心血管共病中的潜在价值。

2 泛血管衰老对常见老年心血管共病稳态调控的研究现状

2.1 心-脑血管共病

心血管与脑血管系统通过共同的病理生理过程相互关联,形成复杂的“心脑血管轴”调控网络。这一轴系的异常与CVDs和阿尔茨海默病(Alzheimer's disease, AD)密切相关。有研究提出了“心脑血管环路”学说,认为心脏和大脑从空间上虽归属不同脏腑,但两者疾病的发展都受到全身炎症、AS和神经内分泌系统功能紊乱的影响^[42,43]。血脉和利是“心脑血管环路”运行的基础^[43]。《灵枢·平人绝谷》云:“血脉和利,精神乃居”。《素问·五脏生成篇》:“诸血者,皆属于心”,“脉为血之府”,老年心脑血管常见共病与泛血管衰老存在显著关联^[44]。AS和动脉硬化是泛血管衰老的典型特征,在分子水平上与内皮功能障碍、缺氧、炎症、氧化应激和晚期糖基化终

产物的积累等病理过程密切相关, 这些改变共同导致淀粉样蛋白 β (amyloid beta, A β)清除和降解失衡^[44,45], 部分解释了临床前AD中血浆A β 水平的升高. 流行病学研究证实, 冠状动脉、颈动脉、股动脉的亚临床AS与痴呆及AD的发病率呈正相关^[46,47]. 特别值得注意的是, 合并心功能不全和颈AS的老年受试者表现出更高的脑实质损伤风险, 提示心脑血管轴的累积性病变可能加速脑萎缩进程^[48]. 在CVDs的发展过程中, 促炎细胞因子的激活在高血压、慢性心力衰竭、代谢综合征和卒中的共病中发挥着作用^[49,50]. 炎症衰老相关因子(如IL-6、肿瘤坏死因子 α 和C反应蛋白)在CVD患者中水平较高, 可同时进入中枢神经系统, 影响交感神经活动并损害大脑功能^[51]. 值得注意的是, 炎症衰老对心脏和大脑的影响呈现显著的空间异质性, 在心脏组织中, 促炎细胞因子通过诱导氧化应激导致心肌细胞功能障碍, 最终促进心脏纤维化; 而在大脑中, 小胶质细胞作为主要的免疫调节细胞, 通过产生和释放促炎因子抑制神经元突触功能和信号传导, 促进AD特征性蛋白聚集^[52]. 这种双向调控机制表明, 大脑或心脏的损伤可以通过炎症衰老这一共同通路相互影响, 而泛血管衰老是心脑血管相关老年心血管共病的病理基础.

上述发现不仅深化了我们对心脑血管共病机制的理解, 也为开发针对泛血管衰老的干预策略提供了新的理论依据. 通过靶向调控炎症衰老等关键环节, 可能为老年心脑血管共病的防治开辟新的途径. 一项研究通过双样本孟德尔随机化发现了与冠状动脉疾病和认知障碍有显著因果关系的血液代谢物^[53], 结果表明, 大颗粒极低密度脂蛋白中游离胆固醇与总脂质的比率是与冠状动脉疾病显著相关的关键血液代谢产物, 小颗粒极低密度脂蛋白中的胆固醇酯与总脂质的比率成为与路易体痴呆有显著因果关系的主要血液代谢物. 此外, 肾虚血瘀是该类心脑血管共病患者的常见证型^[54], 也进一步佐证了衰老是老年心脑血管共病的影响因素. 在老年血管衰老的进程中, 肾虚血瘀的存在加速了血管的衰老和病变, 《素问·四时刺逆从论》云: “血气在中, 内著骨髓, 通于五藏”, 肾藏精主骨生髓, 肾精亏虚可影响血液生成和运行, 进而影响五脏功能, 若血液运行不畅则可致血瘀, 与血管衰老病变有一定联系.

2.2 心-肾-代谢综合征

随着老龄化进展, 2型糖尿病、CVDs和肾功能不全是老年患者中常见的共病, 这一疾病群已被定义为

心-肾-代谢(cardiovascular-kidney-metabolic, CKM)综合征. 流行病学研究表明, 心血管、肾脏和代谢疾病通常在同一患者中重叠并共存^[55]. 泛血管衰老可加速糖尿病性泛血管病变, 累及心、脑、肾、眼和外周系统中不同大小的血管(大血管和微血管), 病理表现为大血管粥样硬化、微血管内皮功能损害、基底膜增厚和微血栓形成^[56]. 糖尿病是细胞衰老的结果, 也是风险因素. 胰腺 β 细胞衰老已被证明在1型和2型和单基因糖尿病的发病机制中发挥作用^[57]. 高血糖诱导的超氧化物激活聚二磷酸腺苷(aenosine diphosphate, ADP)-核糖聚合酶(poly(ADP-ribose) polymerase, PARP), 导致ADP-核糖聚合物的积累, 进而抑制关键的糖酵解酶甘油醛-3磷酸脱氢酶^[58]. 这一关键步骤已被证明可诱导高血糖介导的组织损伤. 血压和血糖水平升高, 即使在正常范围内, 也预示着脉搏波速度(pulse wave velocity, PWV; 反映血管衰老的动脉僵硬度的指标)速度的增加^[57,59]. 主动脉PWV是2型糖尿病死亡率的独立预测因子, 其增加可导致压力变化更大程度地传递到肾脏和大脑微循环, 这些血管床暴露于破坏性动脉压力, 成为高血压与加速肾脏和认知功能下降的关键因素^[57,60]. 另外, 在糖尿病环境中, 肾细胞也呈现出衰老表型, 例如, 在体外肾小管上皮细胞中, 由于内质网应激, p21^{Cip1}激活导致p21^{Cip1}介导的过早衰老^[57]. 衰老细胞表型SASP也会导致慢性肾病中细胞外基质聚集和肾间质纤维化^[61]. 2型糖尿病患者, 由于血管衰老进程的加速, 会促使AS程度进一步加剧. 在冠心病患者群体中, 这一病理变化尤为凸显, 常表现为较为严重且广泛的多支血管病变.

上述发现揭示心血管-肾脏-代谢综合征过程中不同器官之间复杂且紧密的联系, 以及泛血管衰老在其中所扮演的关键角色. 有研究针对糖尿病泛血管并发症这一临床防治难题, 首次构建了跨器官血管单细胞图谱, 整合了8个不同组织的单细胞RNA测序数据, 构建了包含63种细胞类型的器官型血管系统单细胞图谱, 研究发现内皮细胞是血管系统细胞间通讯的核心枢纽, 同时揭示了不同器官中内皮细胞的高度异质性及其组织特异性分布规律, 建立了糖尿病跨器官并发症的细胞互作理论框架, 进一步通过跨器官血管细胞间通讯分析发现, 骨形态发生蛋白(bone morphogenetic protein, BMP)信号通路是介导糖尿病心肾共病的关键通路, 其中BMP6及其受体Bmpr1a在糖尿病心肾组织显著上调, 这为糖尿病心肾并发症的精准治疗提供了全新靶点,

这一研究从分子层面上揭示了中医“心肾不交”的生物内涵,为糖尿病泛血管疾病的早期预警、靶向干预及新药研发提供了重要的科学依据^[62]。

2.3 心-外周血管共病

在脉管系统中,血管老化表现为内皮功能受损、血管弹性降低和硬度增加。泛血管衰老除了累及心、脑、肾,外周血管衰老也会因风险因素的累积而加速,这些风险因素包括血压、葡萄糖稳态受损、肥胖等^[63-65]。空间上,在衰老过程中,外周动脉硬化的发生沿着动脉树的长度,在髂动脉-髂动脉通路、中央动脉的高弹性段和靠近心脏段中最为明显^[66]。动脉僵硬度与血压存在双向关系^[66]。随着动脉僵硬度的增加,血流动力学发生变化,以中心舒张压为代价,中心收缩压增加,并扩大了中心脉压^[67],从而影响心脏的功能。研究发现莲心碱可降低腹主动脉缩窄模型大鼠的血压,并改善心肌肥厚^[68]。另外,PWV是评估动脉硬度最常用的方法,测量两个动脉部位之间向前行进的脉搏波的传输时间。其中颈动脉-股动脉脉搏波速度(carotid-femoral pulse wave velocity, cfPWV)是一种基于颈动脉和股动脉的血压的测量值,被认为是评估中心动脉硬度的参考标准。一项研究测量了3789名男性和1383名女性的cfPWV,基线平均年龄为65.5岁,发现cfPWV在5年的时间进展中存在梯度^[69],在基线55~59岁的研究受试者中,cfPWV的5年变化为0.18 m/s,基线60~64岁的受试者增加至0.36 m/s,基线65~69岁的受试者增加至0.80 m/s,最后70岁或以上的受试者增加至0.99 m/s^[66]。而在10年的随访期间,基线60岁的AS患者主动脉弓的中位PWV从6.7 m/s增加到8.1 m/s^[63]。高血压也加速了动脉衰老,可累及全身体循环系统及靶器官。高血压患者动脉僵硬度高于血压正常者^[63],且较高基线的收缩压、舒张压和平均动脉压与随访10年内的主动脉PWV进展相关^[63]。当基线血压从 ≥ 140 mmHg降至10年随访时 < 140 mmHg,与收缩压持续升高的参与者相比,主动脉PWV进展较少。颈动脉作为全身血管病变的风向标,其衰老同样影响老年心血管共病的发生。对17项纵向研究的综述和荟萃分析发现,cfPWV增加1 m/s与心血管事件(心血管死亡和非致死性事件)风险增加14%、心血管死亡风险增加15%和全因死亡风险增加15%相关^[65,70]。血管硬度已被证明是老年心血管共病心血管事件和死亡率的长期预测因子^[66]。研究表明,在 > 60 岁的冠心病患者中,颈动脉AS与年龄、性

别、空腹血糖受损、高血压和高敏C反应蛋白相关^[71]。一项前瞻性的基于社区的观察性研究,评估了2型糖尿病患者外周动脉疾病与心源性死亡的风险,结果表明踝肱指数 ≤ 0.90 与心源性死亡风险增加67%独立相关^[72]。

综上,泛血管衰老累及多器官,外周血管受多种因素影响加速衰老,动脉僵硬度与血压具有双向作用,PWV可评估动脉硬度且与心血管事件相关,颈动脉等指标也提示泛血管病变及心源性死亡风险。

2.4 心-肺血管共病

泛血管衰老是心-肺血管共病的主要风险因素,随着年龄增长,衰老导致大动脉基质成分改变、小动脉血管张力的改变以及微血管稀疏,这些变化不仅对心脏造成损害,还会导致循环系统终末器官的损伤^[73,74]。值得注意的是,泛血管衰老这一概念同样适用于肺血管系统,受衰老的循环系统的影响,肺血管系统的组成部分发生重塑,可造成肺血管系统出现血管硬化、压力升高以及高脉动流等病理状态^[75]。在基础研究领域,有研究记录了年轻小鼠和老年小鼠在博莱霉素肺损伤后的不同表现。年轻小鼠能够从博莱霉素肺损伤中恢复,表现为毛细血管密度增加并实现修复;而老年小鼠则呈现出毛细血管稀疏以及非消退性肺纤维化的特征^[76]。临床研究发现,平均肺动脉收缩压与年龄呈现出线性相关关系,并且肺动脉压升高与体循环中所观察到的压力升高存在紧密联系^[77]。此外,收缩压和肺动脉平均压会随着年龄的增长而升高^[78]。肺作为终末器官,其血管同样展现出诸多与衰老相关的表型^[75],同时影响心血管衰老过程。在体循环动脉中,血管壁随着年龄的增长逐渐增厚,弹性蛋白逐渐丢失,传导动脉的直径增大^[79],与之类似,老化的肺血管系统也呈现出衰老依赖性改变,如弹性蛋白降解以及纤维解体^[80]。这些变化会导致血管壁中胶原蛋白过早加载,肺血管树的波传播特性发生改变,进而增加右心室压力,最终导致右心室肥大^[81]。在心血管衰老过程中,组织顺应性丧失是一个常见的病理途径,主要通过舒张功能障碍、间质纤维化以及血管重塑等方面表现出来^[73,82]。在肺动脉高压的病理过程中,同样可以观察到肺血管顺应性丧失所引发的类似结果。衰老机制涉及与衰老、炎症、线粒体功能障碍以及内皮功能障碍的相互作用,这些机制共同对肺血管生物学产生影响^[75]。这些机制与机械生物学因素相互作用,共同驱动肺血管系统的结构和

功能改变,包括细胞外基质重塑、血管张力增加和微血管功能障碍等方面^[75]。

由上可知,泛血管衰老对心-肺系统影响深远且机制复杂。其引发心、肺血管结构与功能改变,增加心脏与右心室压力负荷。未来应深入研究衰老机制及各因素间相互作用,寻找延缓泛血管衰老、改善心-肺血管共病的有效干预靶点与措施。

3 泛血管衰老中西医结合防治策略构建

3.1 建立泛血管衰老危险分层预警模型,推动疾病防治关口前移

泛血管衰老作为全身血管网络在结构与功能上呈现渐进性退化的复杂生理病理过程,与AS性心血管疾病、脑血管疾病等多种严重疾病的发生发展紧密相关。因此,建立泛血管衰老危险分层预警模型具有重要意义。该模型可以通过整合多维度、多层次的数据信息,涵盖血管结构参数(如血管壁厚度、管腔直径等)、内皮功能指标(如一氧化氮合酶活性、内皮素水平等)、炎症因子水平(如C反应蛋白、肿瘤坏死因子- α 等)^[83,84]以及细胞衰老标志物(如端粒长度、衰老相关 β -半乳糖苷酶活性等),借助大数据分析技术与先进的机器学习算法,能够对个体泛血管衰老的程度进行精准量化评估,并预测其未来发生相关疾病的风险概率。基于危险分层的结果,可将目标人群科学地划分为低、中、高风险组,针对不同风险组人群的特点和需求,实施差异化、个体化的干预策略,从而提高防治措施的针对性和有效性。为有效应对泛血管衰老带来的健康挑战,中西医整合的“五位一体”防治策略被提出,该策略融合了中西医药物治疗、中医非药物疗法、运动锻炼及中医传统功法、膳食调理以及情志调节等多个方面。在泛血管衰老的早期阶段,借鉴中医“治未病”的先进理念,积极调整生活方式是维持血管健康的重要基石^[85]。例如,遵循合理的膳食结构,增加富含膳食纤维、维生素和抗氧化物质的食物摄入,减少饱和脂肪酸和胆固醇的摄取^[86],保持适量的运动锻炼,如有氧运动、力量训练等,促进血液循环和新陈代谢^[87]。这些措施有助于维持血管内皮细胞的正常生理功能,增强血管的弹性和稳定性,从而有效延缓血管衰老的进程。此外,对于患有高血压、糖尿病等CVD危险因素的人群,应尽早采取药物干预手段,精准控制血压和血糖水平,最大程度地减少对血管的损伤,降低CVDs的发生风

险。在泛血管衰老进展期,在持续严格控制危险因素的同时,还需针对血管结构和功能的进行性改变采取积极的治疗措施。研究表明,多支血管床受累的高危患者在接受利伐沙班和阿司匹林的联合治疗后,其获益远大于单支血管受累的患者^[88]。通过临床研究发现,补肾益精中成药八子补肾胶囊可以显著改善老年患者的早衰症状、虚弱评分和生活质量,提高运动耐力,改善老年患者的握力、平衡、及肌肉质量,增强端粒酶活性^[89],延缓衰老。此外,风险评估工具筛查泛血管衰老的高危人群具有重要意义,对于老年心脑血管共病,一项对于400名冠心病患者的临床数据研究,开发了预测冠心病患者并发轻度认知障碍的多变量预测模型^[90],包含载脂蛋白E基因分型、年龄、教育、甘油三酯-葡萄糖指数、N末端B型脑钠肽前体、C反应蛋白和职业7个预测变量,从而预测冠心病患者发生轻度认知障碍的风险。通过开展空间多组学研究,包括空间转录组学、空间代谢组学、基因组学、蛋白质组学等前沿技术,深入挖掘和筛查与泛血管衰老相关的生物标志物,有利于对老年CVD共病的早期发生进行全面的风险评估^[91]。

3.2 中西医数智融合泛血管衰老早期识别体系,实现疾病早期诊断

在空间维度的医学视野中,泛血管衰老的防治策略不仅需聚焦于衰老血管在结构与功能层面的动态变化,更应着重考量血管系统各组成部分之间复杂的相互关系,以及多个器官间的协同作用机制,尤其是对心、脑、肾、外周等多靶器官的系统性衰老进程^[92],需开展早期预测评估工作,这对于把握疾病发展态势、制定有效干预措施具有重要意义。西医诊疗模式在血管病变评估方面具有一定优势,例如,通过血管造影、超声检查等手段,能够清晰呈现血管的形态结构,准确判断血管狭窄程度与斑块特征。而中医理论体系强调整体观念与辨证论治,注重从宏观角度把握人体生理病理状态,在疾病早期阶段,能够基于个体的体质、症状等信息进行综合评估,展现出独特的个体化诊疗特色^[93]。基于中西医各自的优势与特点,构建中西医数智融合的泛血管早期识别体系具有重要的临床价值。该体系旨在整合中西医在血管疾病诊疗方面的优势,借助现代数字技术,实现对泛血管疾病的精准、早期识别,多模态数据采集技术是构建该体系的基础^[94]。AS和炎症衰老是泛血管衰老的核心病理基础,与泛血管

事件的发生密切相关。通过侵入和非侵入性检查技术,评估斑块钙化情况、大分支动脉的狭窄程度及病变所累及的器官范围。例如,借助影像学技术检测血管内残余炎症指标,有助于识别易损斑块破裂早期的不稳定因素,为临床干预提供关键时机。中医传统的望、闻、问、切四诊信息蕴含着丰富的人体生理病理信息,通过现代图像识别技术,可以对患者的面色、舌象进行客观化分析,结合机器学习算法对不同的舌象特征进行分类和识别,以判断患者的气血、脏腑功能状态。此外,充分利用大数据和人工智能等前沿信息技术,整合中医证候及证候要素与泛血管衰老微观特征的关联,构建以数智融合为核心的泛血管衰老预测平台^[95]。在该预测平台中,决策树算法能够依据多源数据的特征,建立泛血管衰老的分类模型,实现对患者泛血管衰老程度的分层评估,并对相关疾病的严重程度进行预测。这一模型对于泛血管衰老相关疾病的早期诊断、危险分层治疗,以及血管稳态及代谢途径的调控十分重要。

3.3 多学科交叉助力泛血管衰老驱动的老年心血管共病防治一体化平台

泛血管衰老作为驱动老年心血管共病发生与发展的关键病理基础,广泛涉及多器官、多系统的血管病变,其复杂的病理机制对老年群体的健康构成了重大威胁。从系统论与整体论的宏观视角出发,运用辩证思维深入剖析泛血管病变的病证演变规律,通过多学科间的深度交叉融合,全面开展泛血管衰老引发多器官损害的并病规律研究。整合心血管病学、老年医学、影像学、生物信息学以及中医学等多学科的优势力量,构建一个集预防、精准筛查、综合评估、个体化治疗、长期随访、功能康复于一体的“病-证-症结合”全方位平台^[91]。这一平台的构建,促使研究模式从传统的以孤立靶器官为研究对象的条块式模式,向以“泛血管”为核心的交融式模式转变,充分融合了中医学“异病同治、同病异治”的先进理念,实现了对泛血管衰老相关老年心血管共病的统一、高效管理。在这一全方位平台的搭建基础之上,还需进一步深化多学科间的协同创新机制。借助生物信息学领域的前沿算法与技术,深度挖掘海量临床数据中潜藏的疾病特征、内在关联及演变趋势,为临床的精准诊断与个性化治疗方案的制定提供有力的数据支撑与科学依据。通过高分

辨率、动态化的影像学技术,对泛血管的结构与功能变化进行实时、精准监测,及时掌握病变的进展情况及治疗干预的效果反馈。同时,紧密结合中医学的辨证论治理论体系,依据患者不同的中医证候特点,制定个体化的综合干预策略,以调节机体的整体功能平衡,增强机体的自我修复与抗病能力。此外,构建完善且系统的患者教育体系至关重要,通过多样化的教育方式,提升患者对泛血管衰老及心血管共病的认知水平,增强其自我管理意识与能力。持续优化平台的随访机制,依据患者的康复进程与病情变化,及时调整防治策略,实现对泛血管衰老相关老年心血管共病的全生命周期、精细化管理,最终达到显著改善患者预后、提升其生活质量的目的。

4 总结与展望

随着人口老龄化,泛血管衰老相关的老年心血管共病已成为重要的健康挑战,时空视角为其稳态调控与管理策略的优化提供了新方向,未来研究存在广阔的发展空间。从时间维度看,泛血管衰老的渐进性与阶段性特点为老年心血管共病的全程管理提供了明确的时间线索,深入探究泛血管衰老随年龄增长的动态演变进程,精确捕捉不同时间节点关键分子机制与细胞功能改变,是实现早期精准预警与干预的关键。借助纵向队列研究和先进分子影像技术,建立泛血管衰老的时间序列图谱,有助于识别疾病发生发展的时间窗,为分层、分时的个性化干预提供依据。在空间层面,泛血管衰老所涉及的多组织、多器官间的相互作用错综复杂。此外,通过时空解析能够清晰识别不同器官血管衰老的异质性及其相互作用机制,明确各器官血管衰老对心血管共病的影响权重,是制定精准治疗策略的基础(图1)。

然而,目前对于泛血管衰老时空机制的研究仍有待深入探索。如衰老过程中不同时间点和空间位置的关键调控靶点尚未完全明确,多器官血管衰老的交互作用网络仍需进一步完善。整合空间多组学技术,绘制泛血管衰老的时空图谱,能够发现潜在的跨器官血管衰老调控靶点。同时,加强基础研究向临床应用的转化,研发针对泛血管衰老关键靶点的新型药物,制定符合老年人群特点的泛血管疾病防治指南,提高老年心血管共病的防治水平,改善患者的生活质量和预后。

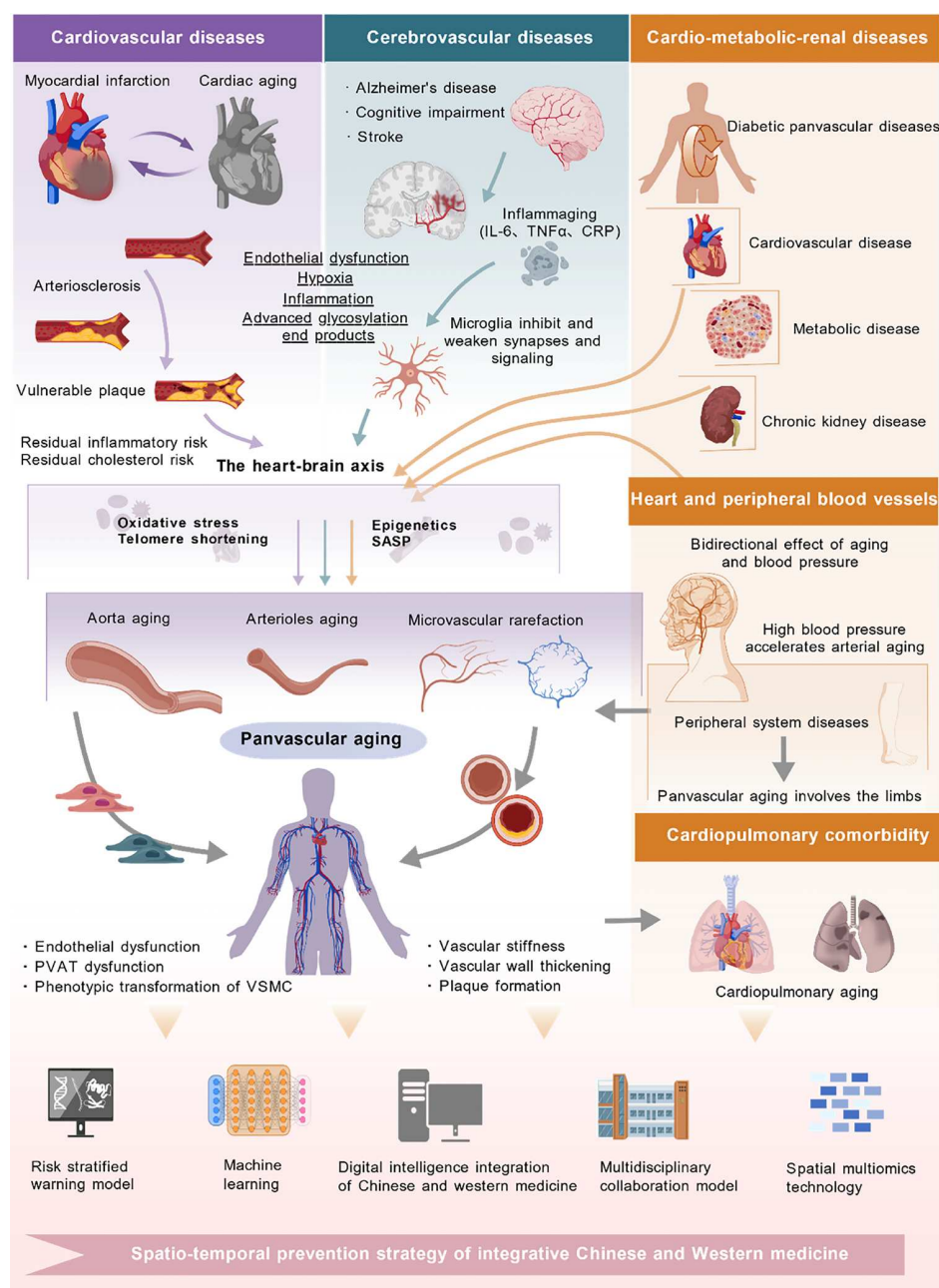


图 1 泛血管衰老与老年心血管共病的概述与中西医整合防治策略。泛血管微环境所涵盖的残余风险、易损因素以及炎症衰老等要素,显著加速了血管衰老进程。从时间维度剖析,在此过程中血管在结构与功能层面均发生了特征性改变,而从空间维度考量,血管衰老引发了多器官的损伤,主要累及心脏、大脑、肺脏、肾脏以及四肢等重要器官与部位,具体表现为心脑血管共病、心-肾-代谢综合征、心与外周血管共病,以及心肺血管共病等复杂病症,提出了建立泛血管衰老危险分层预警模型、中西医数智融合泛血管衰老早期识别体系和多学科交叉泛血管衰老老年心血管共病防治的一体化平台(使用BioGDP.com绘制^[96])

Figure 1 Overview of panvascular aging and geriatric cardiovascular comorbidities and integrative prevention and treatment strategies of traditional Chinese and Western medicine. The elements of the panvascular microenvironment, including residual risk, vulnerable factors, and inflammaging, significantly accelerate the process of vascular aging. From a temporal dimension, characteristic structural and functional changes occur in blood vessels during this process, while from a spatial perspective, vascular aging induces multi-organ damage, primarily involving vital organs and regions such as the heart, brain, lungs, kidneys, and extremities. This manifests as complex disorders, including cardiovascular and cerebrovascular comorbidities, cardio-metabolic-renal syndrome, cardiac and peripheral vascular comorbidities, and cardio-pulmonary vascular comorbidities, etc. It is proposed to establish a panvascular aging risk stratification early-warning model, an integrative digital-intelligent early identification system of traditional Chinese medicine and western medicine, and a multidisciplinary integrated platform for the prevention and treatment of geriatric cardiovascular comorbidities associated with panvascular aging (drawn using BioGDP.com^[93])

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Summary for “泛血管衰老与老年心血管共病: 现状、展望与中西医结合防治策略”

Panvascular aging and geriatric cardiovascular multimorbidity: current status, prospects, and integrated prevention and treatment strategies of traditional Chinese and Western medicine

Zhongwen Qi^{1,2,3}, Yanfei Liu^{1,2,3}, Yanhong Zhang^{1,2,3}, Ying Zhang^{1,2,3},
Yue Liu^{1,2,3*} & Fengqin Xu^{1,2,3*}

¹ The Second Department of Geriatrics, Xiyuan Hospital, Institute of Gerontology, China Academy of Chinese Medical Sciences, Beijing 100091, China

² Laboratory of Combining Diseases and Evidence to Prevent Vascular Aging, National Administration of Traditional Chinese Medicine, Beijing 100091, China

³ National Clinical Research Center for Traditional Chinese Medicine Cardiology, Beijing 100091, China

* Corresponding authors, E-mail: 18800021979@163.com; liuyueheart@hotmail.com

Panvascular aging offers a pivotal theoretical basis that accelerates the translation of basic scientific research into clinical practice, specifically for the prevention and treatment of cardiovascular comorbidities in the elderly. This biological process is distinguished by two core, interdependent features. In the temporal dimension, it presents as a gradual, age-associated decline in vascular structure and functional integrity. In the spatial dimension, it manifests as synchronous vascular damage across multiple organ systems, including the heart, brain, lungs, kidneys, and peripheral vessels. Critically, the progression of panvascular aging is not a passive process but is tightly modulated by a complex, dynamic regulatory network within the panvascular microenvironment, where various molecular and cellular factors interact to shape vascular aging trajectories. This paper begins with a systematic overview of the fundamental connotation of panvascular aging, clarifying its theoretical framework, and then elaborates on its multiple typical manifestations that collectively contribute to its pathological phenotype. Subsequently, the study focuses on the latest research progress regarding the role of the panvascular microenvironment in driving vascular aging, with particular emphasis on key regulatory elements (residual cardiovascular risk, intrinsic vulnerability factors, and chronic inflammatory responses). Concurrently, it dissects the pathological links between panvascular aging and major cardiovascular comorbidities, including cardio-cerebral comorbidities (e.g., coronary heart disease combined with ischemic stroke), cardio-metabolic-renal syndrome (interactions between cardiac dysfunction, metabolic disorders, and renal impairment), cardio-peripheral vascular comorbidities (e.g., heart failure with peripheral arterial disease), and cardio-pulmonary comorbidities (e.g., coronary artery disease with chronic obstructive pulmonary disease). Furthermore, the paper identifies and discusses current bottlenecks in the field: limitations in fully elucidating the cross-organ regulatory mechanisms of panvascular aging, and challenges in translating mechanistic findings into effective clinical interventions. To address these gaps, it proposes three targeted strategies: establishing a panvascular aging risk stratification and early warning model to enable precise risk assessment in elderly populations; developing an integrated early identification system for panvascular aging that combines principles of traditional Chinese medicine, Western medicine, and digital intelligence; and constructing a multidisciplinary integrated platform for the prevention and treatment of panvascular aging, and data scientists to optimize care for elderly patients with cardiovascular comorbidities. Looking forward, future research in this domain will focus on three core objectives: integrating spatial and temporal mapping techniques to visualize the dynamic, organ-specific progression of panvascular aging; identifying and validating cross-organ regulatory targets that govern vascular aging; and developing novel, targeted therapeutic agents that address the root causes of panvascular aging-related comorbidities, ultimately providing more effective, personalized strategies for managing cardiovascular diseases in the elderly.

panvascular aging, elderly, cardiovascular comorbidities, prevention and treatment strategy, multi-organ aging

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