·泛血管医学时代：脑心共病诊断与治疗·

脑与心脏的关联性及其共病的潜在机制

卓钰昕　叶晨　秦岭　姜帅　吴波

【摘要】 心脏与脑在遗传、结构和功能等方面具有极大的关联性，阐明二者之间关联性及其共病的潜在机制对心脑血管疾病的预防与治疗具有重要意义。本文综述心脏与脑的遗传、结构和功能关联性，并基于临床常见的心脏疾病和脑部疾病探讨二者之间关联性的潜在机制，以为脑心共病的预防与治疗提供理论依据。

【关键词】 心脏病；　脑疾病；　综述

Brain and heart connection and the potential mechanisms in brain and heart comorbidity

ZHUO Yu-xin[1], YE Chen[1,2], QIN Ling[3], JIANG Shuai[1], WU Bo[1,2]

[1]Department of Neurology, [2]Center of Cerebrovascular Diseases, [3]Department of Clinic, West China Hospital, Sichuan University, Chengdu 610041, Sichuan, China

Corresponding author: WU Bo (Email: dr.bowu@hotmail.com)

【Abstract】 The heart and brain are important organs of human body, which are closely related in genetic, structural and functional aspects. It is of great significance to elucidate the correlation between heart and brain and its mechanism for prevention and treatment of cardiovascular and cerebrovascular diseases. This paper reviews the genetic, structural and functional correlations between heart and brain, and discusses mechanisms of correlations from the perspective of common clinical heart diseases and brain diseases, so as to provide theoretical basis for the research and treatment of brain and heart comorbidity.

【Key words】 Heart diseases;　Brain diseases;　Review

This study was supported by the National Natural Science Foundation of China (No. 82271328, 82071320), and 1·3·5 Clinical Incubation Project of West China Hospital, Sichuan University (No. 2020HXFH012).

Conflicts of interest: none declared

心脑血管疾病是世界范围内的主要死因，属重大公共卫生问题，疾病负担严重[1]。心血管病和脑血管病存在共同的危险因素如高血压、糖尿病、血脂异常等，同时受全身炎症反应、动脉粥样硬化、血管痉挛、微栓子形成和神经内分泌紊乱等的影响[2]。心脏与脑在遗传、结构和功能等方面具有极大的关联性[3-4]。明确心脏与脑之间关联性及其共病的潜在机制对心脑血管疾病的预防与治疗具有重要意义。本文拟综述心脏与脑的遗传、结构和功能关联性，并从临床常见的心脏和脑部疾病层面探讨二者关联性的潜在机制，以为脑心共病的预防与治疗提供理论依据。

一、心脏与脑的关联性

1. 遗传关联性　遗传物质决定生物表型，一项基于40 000名健康人群的全基因组关联分析（GWAS）揭示了心脑连接的遗传关联性，发现心脏与脑的MRI特征之间具有共同的遗传效应，心脏MRI特征与80个基因座相关，如左心室舒张末期容积（LVEDV）与基因座10q26.11、12q24.12和2q31.2相关，以及与多个脑部MRI复杂特征（如灰质形态、脑功能连通性、白质微结构、脑默认网络和眶额情感网络等）和脑部疾病（如脑卒中、颅内动脉瘤、烟雾病和精神分裂症等）存在遗传多效性；同时阐明这些复杂特征之间的共定位，例如，降主动脉最小面积与颅内动脉瘤、冠状动脉疾病和烟雾病共享基

doi：10.3969/j.issn.1672-6731.2024.02.002

基金项目：国家自然科学基金资助项目（项目编号：82271328）；国家自然科学基金资助项目（项目编号：82071320）；四川大学华西医院1·3·5临床研究孵化项目（项目编号：2020HXFH012）

作者单位：610041 成都，四川大学华西医院神经内科（卓钰昕、叶晨、姜帅、吴波），脑血管病中心（叶晨、吴波），门诊部（秦岭）

通讯作者：吴波，Email：dr.bowu@hotmail.com

因座7p21.1,降主动脉最大面积和功能脑网络与基因座15q21.1相关联,舒张末期局部心肌壁厚度和双相情感障碍与基因座15q25.2有关,脑白质微结构和右心室收缩末期容积与基因座11q24.3和12q24.12有关;还通过已知疾病的遗传基础检测心脏与脑部MRI特征之间的因果关系,发现伴有特定主动脉特征遗传风险的受试者更易患有神经系统疾病[5]。该项研究提示心脏与脑的遗传关联性可为脑心共病提供新的治疗靶点。

2.结构关联性 虽然心脏与脑的血管发育形成存在差异,但二者的血管解剖结构存在相似之处,如动脉导管位于器官表面,通过穿支动脉供血深部组织以维持氧气和营养供应[1]。心脏和脑的共同病理改变是动脉粥样硬化,临床主要表现为心肌梗死或缺血性卒中[6]。左心室与扩散张量成像(DTI)测量的脑白质纤维束部分各向异性(FA)和平均扩散率(MD)具有最强的关联性[5]。一项影像学研究发现,在广泛的白质网络和特定的灰质网络中较高水平的脑游离水与血液中心血管标志物例如高敏肌钙蛋白T(hs-cTnT)、氨基末端B型利尿钠肽前体(NT-proBNP)和生长分化因子15(GDF-15)水平升高相关[7]。探究心脏与脑结构关联性的意义在于,通过早期发现心脏或脑的结构改变以预防或早期诊断严重心脑血管疾病。脑结构改变是脑小血管病(CSVD)的主要表现[8],其诊断主要依靠脑白质高信号(WMH)或腔隙等MRI特征,但这些是脑小血管病病理改变导致脑损伤后才出现的影像学改变,目前尚缺乏可靠的早期生物学标志物[9],基于心脏与脑的结构关联性开发出更早期的心脏生物学标志物以辅助临床识别脑小血管病高危人群,有助于脑小血管病的早期诊断与治疗。

3.功能关联性 结构决定功能,心脏与脑之间存在诸多功能关联性。心脏具有“泵”的功能,为全身器官供应充足的血液和氧气并维持脑灌注,进而维持机体正常功能。应激状态下,脑通过调节相关神经回路使心率加快,并通过交感神经和副交感神经影响心脏功能,交感神经过度兴奋对心血管病的发生具有重要作用[10]。研究发现,心脏功能正常的急性缺血性卒中患者右侧岛叶及周围脑区、左侧顶叶皮质损伤与左心室应变损伤有关,提示此类患者虽无原发性心脏疾病,但因脑卒中引起脑结构和功能损伤,进而引起心脏自主神经功能失调,导致左心室射血分数(LVEF)降低,使左心室功能受损[4]。心脏功能异常亦可影响脑功能,无短暂性脑缺血发作(TIA)或缺血性卒中病史的脑小血管病患者左心房结构和功能改变如心脏增大、应变减少、频繁的房性期前收缩和间歇性房颤均与MRI上脑小血管病生物学标记,包括灰质体积减少、白质微结构完整性破坏和微出血增加相关,表明对左心房结构和功能的详细评估有助于早期识别脑小血管病高危人群[11]。

二、临床常见的心脏疾病与脑部疾病的关联性

1.心力衰竭与神经功能障碍 心力衰竭是一种复杂的心脏疾病,其主要特征为心脏充盈或者射血分数结构性或功能性损害,可引起多种并发症,累及全身各系统和器官,与神经功能障碍之间存在多种相互作用[12-13]。心力衰竭对脑的最显著影响是导致脑低灌注,进而使血脑屏障通透性增加、炎症反应增强,损伤脑白质纤维束,导致神经功能障碍[14]。(1)心力衰竭与脑卒中:脑卒中是临床常见的引起神经功能障碍的严重神经系统疾病[15-16],心力衰竭患者脑卒中风险极高[17-18]。对比分析射血分数降低的心力衰竭(HFrEF)与射血分数保留的心力衰竭(HFpEF)发现,无论射血分数如何变化,既往有脑卒中病史的心力衰竭患者的血管并发症更多、心力衰竭更严重[19-20]。心力衰竭患者发生慢性脑低灌注(CCH)表现为灰质和白质损伤[21]。大脑皮质微梗死是一项新的血管损伤影像学标记,约17%的心力衰竭患者伴大脑皮质微梗死,与血管危险因素谱和心功能障碍严重程度相关[21]。心力衰竭患者发生脑卒中的机制尚未阐明,目前广泛认可的机制是心力衰竭诱发高凝状态,包括血流速度减慢、血小板聚集增强、纤溶减弱、血管内皮功能障碍、炎症反应激活和脑血流自动调节障碍[12-13];此外,心力衰竭患者还伴有小动脉闭塞(SAO)和大动脉粥样硬化(LAA),导致缺血性卒中风险增加,尤其在缺血性心力衰竭患者中十分常见[12]。(2)心力衰竭与认知功能障碍:有14%~70%的心力衰竭患者存在一定程度的认知功能障碍,并随心力衰竭严重程度的增加而加重[22]。荷兰一项多中心临床试验显示,约18%的心力衰竭患者存在认知功能障碍,尤其是记忆和注意认知域[23]。日本一项前瞻性多中心临床试验显示,约23%的老年心力衰竭患者存在认知功能障碍[24]。研究显示,脑低灌注、脑血流自动调节障碍、神经激素激活(包括肾上腺素能系统和肾素-血管紧张素-醛固酮系统激活、副交感神经张力丧失、对利

钠肽抵抗力增加[25])、氧化应激和炎症反应增强、神经胶质细胞激活、树突棘丢失及神经细胞程序性死亡均是心力衰竭患者发生认知功能障碍的危险因素[26-28]。MRI研究显示,心力衰竭患者发生认知功能障碍还可能与脑萎缩相关[29]。

2.脑卒中与心血管病 脑卒中除遗留严重神经功能障碍外,还可导致各种继发性脑损伤和心血管病如心律失常、心肌梗死等[30-31]。脑卒中后心血管病发生率显著增加[32-33]。一项前瞻性队列研究显示,急性缺血性卒中患者心力衰竭发生率在随访期间逐渐增加[34]。神经源性应激性心肌病(NSC)是急性脑卒中的严重心脏并发症,可引起致死性室性心律失常[35]。尸检发现,脑卒中患者冠状动脉粥样硬化和心肌梗死发生率极高,即使既往无心脏疾病病史,脑卒中后同样可发生心肌损伤[36-37]。脑卒中后出现的心功能障碍称为脑心综合征(CCS)[38],即脑卒中患者并发心脏疾病是由于共同的血管危险因素导致脑和心脏同时出现缺血症状[39],其发病机制还包括岛叶皮质损害、自主神经功能障碍、血浆儿茶酚胺水平激增、免疫炎症反应等[38],导致心肌细胞发生病理改变、微循环障碍和微血管损伤,进而引起心律失常、心功能障碍、心肌梗死和心肌纤维化。岛叶皮质损害常见于缺血性卒中患者,可导致自主神经功能障碍,引起心律失常和神经源性心肌损伤,高达88%的岛叶缺血性损伤患者数周内可能出现心肌损伤[38];儿茶酚胺峰是脑心综合征的最常见假说,下丘脑-垂体-肾上腺(HPA)轴和交感神经系统是儿茶酚胺的主要来源,缺血性卒中发病后上述两个通路即被激活[38],心脏和外周血儿茶酚胺水平升高与缺血性卒中后心律失常、心肌损伤密切相关[40];免疫炎症反应是脑卒中和心血管病的共同危险因素[33],缺血性卒中患者心脏单核细胞和巨噬细胞数目增加,炎症反应增强,导致心肌损伤[41],抑制炎症反应已被证实是减轻脑心综合征患者心肌损伤的有效方法[33]。

3.抑郁症与心血管病 抑郁症可使脑卒中风险增加1.13倍,心肌梗死风险增加1.28倍,心力衰竭风险增加1.04倍[42]。抑郁症可促进交感-肾上腺髓质(SAM)系统激活,使血浆儿茶酚胺水平升高,导致血小板激活、血管收缩、高血压和心律失常[11]。肾素-血管紧张素系统(RAS)参与抑郁症并发心血管病的发生发展过程,一方面,心血管病可导致RAS过度激活,影响神经递质水平,导致抑郁症;另一方面,抑郁症可通过影响RAS,减弱交感神经活性和改善动脉压力感受器反射能力,干扰心血管收缩和血压维持的调节[43]。抑郁症患者下丘脑-垂体-肾上腺轴过度激活,使皮质醇水平升高,导致高血压、向心性肥胖、胰岛素抵抗等不良反应,促进动脉粥样硬化,导致心功能障碍;以及脑脊液和血浆去甲肾上腺素水平显著升高,导致心肌收缩、兴奋性和耗氧量增加,导致心血管不良事件如室性心动过速、室颤、心力衰竭和急性冠脉综合征(ACS)等[44]。抑郁症患者心率变异性和压力反射敏感性降低,心率变异性降低可导致多种心血管病如心律失常、心力衰竭和急性冠脉综合征等[45]。炎症作为抑郁症与心血管病之间的中介具有重要意义[46],炎性因子如白细胞介素-6(IL-6)和C-反应蛋白(CRP)是抑郁症和冠心病的共同危险因素[43];抑郁症患者还表现为CRP水平升高及其他免疫功能障碍,导致血管内皮功能障碍、血小板聚集和活化、血栓形成,从而使血管收缩、斑块不稳定,最终引起心血管事件[47]。

4.房颤与认知功能障碍 房颤是最常见的持续性心律失常,全球疾病负担持续加重[48-49]。房颤作为脑卒中的主要危险因素,是导致脑卒中后认知功能障碍(PSCI)的主要原因,但二者之间的关联性和潜在作用机制尚不十分明确[50-51]。Meta分析显示,房颤患者发生认知功能障碍的风险极高[52],且可显著增加血管性痴呆和阿尔茨海默病的风险[53]。房颤导致认知功能障碍的发病机制复杂,包括脑低灌注、脑微出血、微栓子形成、脑小血管病、血管炎症和遗传因素等[54-57]。既往研究显示,房颤使脑卒中风险增加5倍,而脑卒中与认知功能障碍之间显著相关,因此认为心源性栓塞是房颤患者发生认知功能障碍的主要原因[54]。最新研究显示,脑卒中患者痴呆发生率约为18.4%[58];此外,流行病学调查发现,无论是否伴有脑卒中、心力衰竭或心肌梗死,房颤均是认知功能障碍的独立危险因素[59-60]。一项纳入11项研究共5317例无脑卒中病史的房颤患者的Meta分析显示,房颤使隐匿性缺血性卒中风险增加2.6倍[54],虽然多数隐匿性缺血性卒中无明显症状,但与认知功能障碍相关[61]。一项来自瑞士的房颤队列研究共纳入1737例房颤患者,1390例无脑卒中或短暂性脑缺血发作病史,其中201例(14.46%)存在较大面积的非皮质或皮质梗死,245例(17.63%)存在较小面积的非皮质梗死,且无症状性房颤患者存在大量未发现的脑损伤;此外,所有患者均存在

不同程度的脑白质损伤，约53.43%（928/1737）存在中度脑白质高信号（Fazekas评分≥2分）[62]。广泛性脑白质病变与痴呆相关[63]，表明房颤可以通过脑白质损伤引起认知功能障碍。研究显示，房颤负荷与认知功能障碍相关[64]，房颤患者心输出量降低可以导致局部脑血流量减少，且房颤期间脑血流量改变可以引起血脑屏障破坏，外周血炎性因子透过血脑屏障，启动神经炎症反应，进而增加痴呆风险[65]。炎症反应和遗传因素也在房颤导致认知功能障碍的发生发展中发挥重要作用，房颤可促进CRP和炎性因子释放，引起慢性炎症，导致脑血流自动调节失调，进而引起认知功能减退[56,65-66]。

5.癫痫与心功能障碍　癫痫是临床常见的慢性神经系统疾病，尽管既往25年间癫痫疾病负担有所减轻，但其发病率、病残率和病死率仍较高[67]。癫痫患者病死率较高的重要原因是部分患者伴有心功能障碍[68]，尤以心律失常最为常见。癫痫患者发生心律失常的风险显著增加[69]，并表现出广泛的心脏症状，发作期可以引起各种短暂性心脏效应如心率变异性和血压改变，诱发心律失常，导致神经源性应激性心肌病[68]。大多数难治性癫痫患者存在发作期心律失常和心率改变[70]，且心肌梗死、心律失常和心源性猝死风险较高[71]。这是由于癫痫与心律失常具有共同的遗传易感性[72]，心脏和脑共表达的基因变异可导致癫痫与心脏疾病共病风险增加[73]。发作间期心律失常是癫痫引起自主神经功能障碍的结果，其发生机制为交感神经激活和副交感神经抑制[74]。慢性癫痫可导致低氧血症和血浆儿茶酚胺水平激增，引起心脏和血管损伤，导致心肌纤维化、动脉粥样硬化、收缩期和舒张期功能障碍、心律失常[75-77]，而心肌纤维化和血管损伤可以改变心脏传导和复极，进一步促进心律失常进展[78]。

综上所述，越来越多的研究业已证实心脏与脑之间存在紧密关联性，从而为临床医师提供了新的治疗思路，即心功能损害并非一定是原发性心脏疾病引起，也可能是脑损伤所致。研究脑心共病的潜在发生机制，有助于加深对心脏疾病和脑部疾病关联性的认识和理解。针对脑心共病进行共同管理和治疗有助于促进心脏和脑的共同健康。

利益冲突　无

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（收稿日期：2023-12-12）
（本文编辑：彭一帆）

·小词典·

中英文对照名词词汇（一）

氨基末端B型利尿钠肽前体
N-terminal pro-B-type natriuretic peptide（NT-proBNP）
白细胞介素-6 interleukin-6（IL-6）
不明原因 stroke of undetermined etiology（SUE）
肠二醇葡萄糖醛酸 enterodiol glucuronide（EDG）
肠内酯葡萄糖醛酸 enterolactone glucuronide（ELG）
成本-效益比 cost-benefit ratio（CBR）
出血性转化 hemorrhagic transformation（HT）
大动脉粥样硬化 large artery atherosclerosis（LAA）
大脑后动脉 posterior cerebral artery（PCA）
大脑前动脉 anterior cerebral artery（ACA）
单不饱和脂肪酸 monounsaturated fatty acid（MUFA）
单侧选择性顺行脑灌注
unilateral antegrade cerebral perfusion（uACP）
低密度脂蛋白胆固醇
low-density lipoprotein cholesterol（LDL-C）
低温停循环时间 hypothermic circulatory arrest（HCA）
地中海饮食 Mediterranean diet（MD）
动脉粥样硬化性心血管病
atherosclerotic cardiovascular disease（ASCVD）
短暂性脑缺血发作 transient ischemic attack（TIA）
多学科诊疗模式 multi-disciplinary team（MDT）
二氧化碳分压 partial pressure of carbon dioxide（$PaCO_2$）
C-反应蛋白 C-reactive protein（CRP）
非瓣膜性房颤 non-valvular atrial fibrillation（NVAF）
非体外循环下冠状动脉旁路移植术
off-pump coronary artery bypass grafting（OPCABG）
改良Rankin量表 modified Rankin Scale（mRS）
感染性心内膜炎 infective endocarditis（IE）
高敏肌钙蛋白T
high-sensitivity cardiac troponin T（hs-cTnT）
冠心病 coronary heart disease（CHD）
冠状动脉旁路移植术
coronary artery bypass grafting（CABG）
国际标准化比值 international normalized ratio（INR）
国际卒中试验 International Stroke Trial（IST）
核因子-κB nuclear factor-κB（NF-κB）
活化部分凝血活酶时间
activated partial thromboplastin time（APTT）
急性冠脉综合征 acute coronary syndrome（ACS）
急性A型主动脉夹层
acute type A aortic dissection（aTAAD）
简易智能状态检查量表
Mini-Mental State Examination（MMSE）
交感-肾上腺髓质 sympathetico-adrenomedullary（SAM）
近红外光谱 near infrared spectroscopy（NIRS）
经导管主动脉瓣置换术
transcatheter aortic valve replacement（TAVR）
经颅多普勒超声 transcranial Doppler ultrasonography（TCD）