·应激与心身疾病专题·

童年期创伤与静息态血压、心率及心血管疾病的相关性研究进展

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【摘要】 童年期创伤与静息态血压及心率存在着一定的关联性,是预测心血管疾病的重要风险因素。本文通过总结童年期创伤与静息态血压、心率和心血管疾病之间的相关性以及童年期创伤影响静息态血压、心率及心血管疾病的潜在机制,包括表观遗传学、神经内分泌、氧化应激、炎性反应、不良生活方式、心理应激等,明确童年期创伤对心血管系统的潜在影响,旨在为早期防治心血管疾病提供理论依据。

【关键词】 心血管疾病; 童年期创伤; 静息态血压; 静息心率; 心率变异性; 综述
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Research progress in the correlation between childhood trauma and resting blood pressure, resting heart rate, and cardiovascular disease

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【Abstract】 Childhood trauma has a certain correlation with resting blood pressure and resting heart rate, which is an important risk factor for predicting cardiovascular disease. This review summarizes the correlation between childhood trauma and resting blood pressure and resting heart rate and cardiovascular disease, as well as the potential mechanisms of childhood trauma affecting resting blood pressure, resting

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heart rate and cardiovascular disease, including epigenetics, neuroendocrine, oxidative stress, inflammation, adverse lifestyle, psychological stress etc. The aim is to clarify the potential impact of childhood trauma on the cardiovascular system, and provide a theoretical basis for the prevention and treatment of cardiovascular disease.

【**Key words**】 Cardiovascular diseases; Childhood trauma; Resting blood pressure; Resting heart rate; Heart rate variability; Review

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心血管疾病(cardiovascular disease, CVD)是全球疾病死亡和致残的主要原因。在我国城市居民死因调查中, CVD的死亡率位居首位。目前, 中国CVD患病人数达3.3亿, 正处于持续上升阶段[1]。静息态血压和心率是反映心功能的客观指标, 与CVD的发生、发展及预后密切相关[2-3]。有研究显示, 控制高血压可显著降低CVD的发生风险[3]。Zhang等[2]的荟萃分析提示, 静息心率每增加10次/min, CVD死亡率增加8%。因此, 探究影响静息态血压及心率的相关因素有利于早期预防CVD的发生。

童年期创伤是指早年生命周期中的逆境经历, 包括躯体虐待、情感虐待、性虐待、躯体忽视和情感忽视。既往研究数据表明, 一半以上的成年人都曾经历过童年期创伤[4]。童年期创伤的影响可能贯穿于整个生命周期, 与未经历创伤的人群相比, 暴露于童年期创伤的人罹患CVD的风险显著增加[5]。在明确CVD诊断之前, 存在童年期创伤的个体的前驱表现为静息态血压及心率的异常改变[6-7], 其可能通过多种机制增加CVD的风险。本文就表观遗传学、神经内分泌、氧化应激、炎性反应、不良生活方式、心理应激等相关机制进行综述, 旨在为CVD的早期干预提供思路。

一、童年期创伤与静息态血压、心率及CVD的关系

Godoy等[5]的研究表明, 有童年期创伤经历的成年人是CVD的高风险人群, 且童年期创伤与CVD之间存在剂量反应关系。Jakubowski等[8]的荟萃分析显示, 童年期创伤的累积效应与CVD的风险密切相关。静息态血压及心率异常是CVD发生风险的标志物, Kapur等[9]通过收集受试者不同时期的童年期创伤暴露情况, 发现7岁和19岁时的童年期创伤经历与血压升高有关。Nguyen等[10]报道了童年期创伤的不同类型与血压变化的关系, 发现任何形式的童年期创伤均与高血压相关, 并通过酒精使用、抑郁情绪、急性应激反应介导血压升高。心率变异性(heart rate variability, HRV)与CVD的发生呈负相关[11], Bussone等[12]考查了55名健康大学生的HRV水平及童年期创伤暴露情况, 发现情感虐待、情感忽视和性虐待与低HRV水平相关。一项关于创伤后应激障碍(posttraumatic stress disorder, PTSD)的荟萃分析发现, 严重的精神创伤常显示低HRV水平, 使PTSD患者罹患CVD的风险增加[11]。目前一项纳入超过15万名受试者的研究发现, 童年期创伤与心律失常密切相关, 其中躯体虐待与心律失常的关联性最强[13]。

二、童年期创伤影响静息态血压、心率及CVD的潜在机制

1.表观遗传学: 随着基因测序技术的发展, 研究发现下丘脑-垂体-肾上腺(hypothalamic-pituitary-adrenal, HPA)轴相关基因的甲基化[14]与遭受童年期创伤个体的静息态血压及心率变化有一定关联。糖皮质激素受体(glucocorticoid receptor, GR)是调控HPA轴的关键受体, 可与糖皮质激素结合通过负反馈机制调节HPA轴的功能。GR的表达受到糖皮质激素受体基因(glucocorticoid receptor nuclear receptor subfamily 3, *NR3C1*)的调节, 而*NR3C1*甲基化水平与静息血压呈显著正相关[15]。Lewis等[16]发现, 躯体虐待(如打屁股)可导致*NR3C1*甲基化增加, 且NR3C1甲基化水平与日间皮质醇浓度升高密切相关。FK506结合蛋白5基因(FK506-binding protein 5, *FKBP5*)可编码GR配体蛋白, 调节GR敏感性。暴露于躯体虐待与*FKBP5*甲基化水平降低相关, 这一改变诱导静息态血压、糖化血红蛋白、炎性反应增加, 增加成年期CVD的发生风险[17]。Ramo-Fernández等[18]检测了经历童年期创伤的母亲及其子代的基因序列, 发现童年期创伤与母亲的*FKBP5*低甲基化水平相关, 但其子代未发现上述基因改变, 表明基因甲基化水平可能不会遗传给下一代。DNA甲基化表达也可能发生在免疫炎症反应中, 在一项34名受试者的小型研究中, Janusek等[19]发现童年期创伤与IL-6启动子甲基化水平降低有关, 当个体面对急性应激时, 其体内IL-6水平异常升高。上述

结果提示童年期创伤会放大应激的炎性反应，并通过促进全身的炎性反应损害血管内皮功能，导致心血管系统疾病的发生。

2.神经内分泌：(1)自主神经系统。童年期创伤可能破坏了交感神经和副交感神经的节律平衡，导致副交感神经活性下降[12]。HRV指两次心跳间隔(RR间期)或瞬时心率的微小变化，是副交感神经系统张力的生理学标志[20]。HRV分析方法包括两种，分别为时域分析和频域分析。时域分析通常包括窦性心搏间隔的标准差(standard deviation of normal to normal interval，SDNN)和窦性心搏间隔差值的均方根(root mean square of successive differences，RMSSD)，其中SDNN反映测量期间的总体HRV水平；RMSSD反映窦性心律下副交感神经的控制能力，较少受到呼吸运动的影响，常用于反映迷走神经活跃程度。频域分析指标通常包括低频(low frequency，LF)、高频(high frequency，HF)以及LF/HF比例，其中LF可作为心脏交感神经活性的可靠指标，HF反映副交感神经活动，LF/HF反映心脏交感和副交感神经的平衡性。Bussone等[12]评估了55名大学生童年期创伤经历与HRV的关联性，发现情感虐待、性虐待和情感忽视与HRV水平呈负相关。Thurston等[21]研究了受试者的童年期创伤经历与HF的关系，发现童年期创伤暴露与清醒和睡眠期间的HF水平降低有关。童年期创伤导致自主神经张力的强度变化是CVD的风险因素之一。(2)HPA轴。当个体面对应激事件时，HPA轴通过不同的信号激活激素级联释放，HPA轴适当的应激反应有利于人体健康，而过度或慢性应激反应均会对机体生理、心理产生不良影响，特别是心血管系统，其对应激反应尤为敏感。童年期创伤经历可能与HPA轴功能失调以及皮质醇浓度异常变化有关。Nikkheslat等[22]收集了163例抑郁症患者和55名健康人群的唾液进行皮质醇测定，发现存在糖皮质激素抵抗个体的抑郁症患者童年期创伤经历与成年期昼夜皮质醇水平呈正相关，高浓度的皮质醇可通过水钠潴留、重吸收增强及激活肾素-血管紧张素-醛固酮系统(renin angiotensin aldosterone system，RAAS)等方式引起血压升高，最终增加个体罹患CVD的风险。Schalinski等[23]收集并测量了应激相关疾病的43例受试者与12名健康对照组的头发皮质醇浓度，发现受试者童年期创伤经历的严重程度与头发皮质醇浓度呈正相关。Bryson等[24]总结8 370名受试者在内的35项队列研究，其中24%的研究显示童年期创伤经历与头发皮质醇浓度呈正相关。童年期创伤对HPA轴的影响可能与创伤经历的持续时间有关[25]，White等[26]研究发现受虐待的儿童在3～7岁时表现为头发皮质醇浓度升高，9～10岁时表现为头发皮质醇浓度降低。Niwa等[27]在基础研究中证实了童年期创伤与高糖皮质激素水平有关。综上所述，童年期创伤的类型、强度及持续时间均会对HPA轴产生长期影响，诱导内环境如皮质醇水平的改变，久而久之导致CVD的发生。(3)RAAS。RAAS是机体调节血压与电解质平衡的重要系统，对急性或慢性应激原的应激反应起着调节作用。童年期创伤与RAAS的不同变化有关，一项包含2 038名社区样本的研究发现，童年期遭受创伤与受试者的醛固酮浓度增加有关[28]。另一项相关研究也表明，童年期创伤与醛固酮浓度升高有关，但与肾素浓度无明显相关性[29]。Nishimi等[30]的研究发现，与未暴露于创伤的女性相比，患有慢性PTSD的女性平均醛固酮浓度显著降低。Terock等[28]报道，尽管发现童年期创伤受试者的醛固酮浓度升高，但受试者并未出现高血压，这表明还有其他系统参与血压的调节。长期慢性应激与RASS分泌失调相关，由此产生的生理功能改变可能会影响心血管的健康水平。(4)内皮素。内皮素是活性最强的缩血管因子并具有促炎作用，可引起血管平滑肌的强烈收缩，引发心肌组织缺血缺氧、冠状动脉痉挛、心肌缺血性损伤等一系列反应[31]。Fox等[32]研究认为，急性应激反应诱导了内皮素的释放，内皮素途径的激活是急性心理应激导致血压变化的新介质，可直接引起血管收缩。Loria等[33]通过动物试验证实，母体分离会诱导成年大鼠体内循环内皮素水平升高，并通过内皮素途径诱导血压升高。血清内皮素水平与机体静息态收缩压水平呈正相关，Rogers等[34]发现，8周的系统性运动训练可有效降低童年期创伤受试者的血清内皮素水平和静息态收缩压。上述研究初步证明，内皮素可能是童年期创伤导致静息态血压升高及后期CVD发生的基础。(5)瘦素。瘦素是脂肪细胞合成与分泌的一种激素，主要通过中枢系统抑制食欲和增加能量消耗以调节能量平衡。瘦素可通过诱发氧化应激反应、炎性反应及激活RASS引起内皮功能障碍等，进而导致血压升高[35]。一项横断面研究发现，童年期创伤与瘦素分泌增加直接相关[36]。Daniels等[37]在200名健康人群中发现，童年期创伤与高水平的瘦素浓度显著相关。这些研究结果提示童年期创伤可影响机体瘦素水平，成为后续发生心脏代谢疾病的相关因

素。综上所述，童年期创伤会损害神经内分泌系统多个通路，并对全生命周期持续产生不良效应，增加CVD的易感性。

3.氧化应激反应：在正常情况下活性氧的产生和消除处于动态平衡状态，当自由基、活性氧及抗氧化剂浓度出现异常，即可通过氧化应激反应导致血管重构、血管紧张度增加、血管内皮舒张功能损害等，进而对心血管系统产生一定影响[38]。Moraes等[39]比较了68例双相障碍患者、37例重性抑郁障碍患者及66名健康对照者体内的抗氧化酶、还原酶及一氧化氮代谢产物水平，发现重度抑郁障碍患者躯体忽视与氧化应激反应增强有关。沉默信息调节因子1(silent information regulator sirtuin 1，SIRT1)可通过激活内皮的一氧化氮合酶抑制内皮氧化应激反应。Jenkins等[40]的研究发现，童年期创伤通过减少体内SIRT1的浓度，增强氧化应激反应引起内皮功能障碍，进而增加个体罹患高血压和CVD的易感性。在经历童年期创伤模型的小鼠中，研究人员观察到还原型辅酶Ⅱ氧化酶(reduced nicotinamide adenine dinucleotide phosphate oxidase，NOX)的基因表达增加，过度激活的NOX会引起活性氧的过度生成[41]。暴露于童年期不良经历可通过氧化应激机制诱发内皮功能障碍，对心血管内皮细胞造成损伤。

4.炎性反应：研究证实，遭受童年期创伤的人较未经历创伤的人表现出更高的炎性水平[42]。Chen等[43]的荟萃分析发现，炎症及免疫功能变化可能是童年期创伤引发CVD的潜在机制，炎性因子如IL-6、TNF-α、C反应蛋白、纤维蛋白原等可能介导了童年期创伤与CVD的关联。Rasmussen等[44]调查了1 391名受试者童年期创伤暴露情况，收集并检测了C反应蛋白、IL-6和可溶性尿激酶纤溶酶原激活受体(soluble urokinase-type plasminogen activator receptor，suPAR)浓度，结果显示童年期创伤与suPAR、IL-6水平升高有关，其中suPAR与童年期创伤的相关性最强。suPAR是慢性炎症的新型生物标志物，可促进炎性反应与内皮损伤，导致CVD的发生和发展，有望成为童年期创伤引起心血管系统损害的早期识别炎性因子。童年期创伤诱导机体高炎症表达是发生CVD的重要生理基础。

5.不良的生活方式：童年期创伤通过不良生活方式间接影响心血管系统，包括不健康的饮食习惯，如创伤介导过度进食与成年早期超重和肥胖有关[45]。Rienecke等[46]统计了1 061例进食障碍患者童年期创伤暴露情况，发现每一种进食障碍都与童年期创伤相关，其中暴食障碍最为显著。存在早年应激的人群更易发展为糖尿病[47]、代谢综合征[48]，与后续CVD风险增加显著相关[1]。不同程度的童年期创伤均会导致运动行为减少[49]，少运动或无运动者的CVD死亡风险增加[1]。童年期创伤还会导致物质滥用，包括酒精、大麻、药物、烟草等[50]。Islam等[51]调查了116 032名成年受访者的烟酒使用情况，发现童年期创伤增加了酗酒、吸烟等不良行为，导致心血管系统的早期损伤。这些不良生活方式增加了远期发生CVD的风险。

6.精神障碍：童年期创伤与精神障碍如急性应激障碍、PTSD、抑郁症、焦虑障碍、睡眠障碍等密切相关。Godoy等[5]认为，这些精神障碍自身介导了童年期创伤与成人CVD之间的关联。Petrov等[52]的研究证实了睡眠障碍是童年期创伤受试者发生高血压的重要中介因素，同时可能产生一系列生理心理改变。研究证明，精神药物也会导致静息态血压、心率异常变化及心脏功能损害[53]，特别是Q-T间期延长和心律失常。

三、总结与展望

综上所述，本文总结了童年期创伤与静息态血压、心率及CVD的关系，提示童年期创伤暴露的持续时间，创伤的强度、频率、类型与个体静息态血压、心率及心血管系统功能有一定关联。通过早年精神创伤介导的神经生物学变化以及不良的生活方式等因素对静息态血压和心率产生远期影响，最终发展为CVD。目前，童年期创伤与CVD关联的详细机制并不十分明确，且大多数为横断面研究，不能明确因果关系和疾病发生的潜在机制。此外，由于童年期创伤经历是回顾性的，可能存在回忆偏倚，未来需构建更为客观的测量工具，进一步研究童年期创伤对心血管系统的长期影响，为预防与治疗静息态血压、心率早期异常变化以及CVD提供理论依据。

利益冲突 文章所有作者共同认可文章无相关利益冲突

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