

早产与高血压的关系

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[摘要] 近年来, 全球早产儿数量呈上升趋势, 其长期预后, 特别是早产儿成年后心血管的预后, 日益受到关注。早产儿成年后心血管疾病风险较高, 其可能与心血管结构改变、肾脏结构改变、身体成分改变、下丘脑-垂体-肾上腺轴过度激活等因素有关。为改善早产儿预后, 需进行长期随访监测并采取有效的防治措施。该文旨在回顾相关文献, 总结早产儿在儿童期及成年期发生高血压的风险、相关机制等, 以提高对早产儿成年后高血压风险的重视及认识。

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[关键词] 高血压; 机制; 预后; 早产儿

The association between preterm birth and hypertension

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Abstract: In recent years, the number of premature births worldwide has been increasing, and their long-term prognoses, particularly the cardiovascular outcomes of preterm individuals in adulthood, have become a growing concern. Adults who were born prematurely are at a higher risk for cardiovascular diseases, which may be related to changes in cardiovascular structure, renal structure alterations, changes in body composition, and overactivation of the hypothalamic-pituitary-adrenal axis. To improve the outcomes for preterm individuals, long-term follow-up monitoring and effective prevention and treatment measures are necessary. This article aims to review the relevant literature, summarize the risks and mechanisms of hypertension during childhood and adulthood in those born prematurely, and enhance awareness and understanding of the risk of hypertension in adults who were born prematurely.

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Key words: Hypertension; Mechanism; Prognosis; Preterm infant

近年来, 全球早产儿数量呈上升趋势。据世界卫生组织报告, 2014年全球早产儿的发生率约为10.6%, 每年影响近1 500万新生儿^[1]。随着医学技术的不断进步, 早产儿的生存率得到了显著提高, 超过95%的早产儿和大多数极早产儿都能活到成年^[2]。然而, 随之而来的长期健康问题也日益受到关注。大量研究表明, 早产儿成年幸存者患有慢性疾病的风险较高, 涵盖心血管、内分泌/代谢、呼吸、肾脏、神经发育和精神疾病等多个器官系统^[3-4]。与足月出生者相比, 这些疾病会导致早产出生者死亡风险增加30%~50%, 相关的

死亡风险甚至可持续至青春期及青年期^[4]。

高血压是心血管疾病、脑卒中和慢性肾脏疾病的主要危险因素, 也是世界上导致因死亡或残疾而失去的生命年的主要原因。随着围产期管理的改进和更多关于早产儿数据的积累, 早产与儿童及成年后高血压的关系日益凸显^[3-5]。

从怀孕开始的最初1 000 d被称为“健康编程的机遇窗口”, 胎儿编程指的是发育中的器官为面对外界环境而进行的结构和功能适应^[6]。根据流行病学观察, 有研究者提出“胎儿起源的成年疾病”的假说, 胎儿对不利的环境产生适应性反应,

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保证了短期内的生存,但代价是启动了导致成年疾病的病理过程^[6-7]。在生命早期(发育的关键时期)暴露于不利的环境,可能导致胎儿结构、功能和代谢的重新编程,可增加生后患心血管疾病、肾脏疾病、代谢性疾病的风险^[7-8]。

为改善早产儿的预后,需要妇产科医生、新生儿科医生、儿科医生、成人心血管医生等的共同协作,从生命的早期开始关注,进行长期随访监测,并采取有效的防治措施。本文旨在回顾相关文献,从发育发展的角度,就早产儿在儿童期及成年期发生高血压的风险、相关机制等,针对早产对心血管系统的重塑^[9-10]、肾脏发育的改变^[11]、身体成分的改变^[12-13]、下丘脑-垂体-肾上腺(hypothalamic-pituitary-adrenal, HPA)轴的过度激活^[14]等方面,进行综述和总结,以提高对早产成年后高血压风险的重视及认识。

1 流行病学特点

一项队列研究从早产儿出生随访至25~27岁,发现早产会导致成年后使用抗高血压药物的概率增加,这种增加与早产的胎龄呈反比^[15]。也有研究报道,早产出生的青少年和青年人较足月出生的同龄人的收缩压高3.4~4.2 mmHg,舒张压高2.1~2.3 mmHg,且女性似乎比男性更易受影响,特别是胎龄<32周的早产女性,其成年后妊娠期高血压疾病的风险显著增加^[16-18]。

一项在瑞典进行的大规模的高血压研究中,纳入了40年间出生的400多万单胎婴儿,随访至最大年龄43岁,与足月出生相比,早产与后期高血压风险增加有关(调整后的风险比 $HR=1.17$, 95% CI : 1.08~1.27, $P<0.001$);与足月出生相比,在18~29岁人群中发现早产和极早产出生与新发高血压的相关性(调整后的风险比分别为 $HR=1.28$, 95% CI : 1.21~1.36 和 $HR=2.45$, 95% CI : 1.82~3.31),而在30~43岁人群中调整后的风险比分别为 $HR=1.25$, 95% CI : 1.18~1.31 和 $HR=1.68$, 95% CI : 1.12~2.53^[5]。另一项研究比较了18~25岁间,极早产幸存者和正常体重对照组的血压及其年度变化,发现极早产儿在成年期可能有更高的血压水平和加速增长的血压轨迹。研究参与者包括1991—1992年在澳大利亚维多利亚州出生的297例极早产幸存者(极早产组)和260例正常出生体重的对照组。在25岁时,极早产组151例、对照

组119例完成了动态血压测量,结果显示,极早产组胎龄<28周/出生体重<1 000 g者在24 h内的收缩压(均数差4.5 mmHg, 95% CI : 1.2~7.7 mmHg)、舒张压(均数差3.4 mmHg, 95% CI : 1.5~5.2 mmHg)和平均血压(均数差3.6 mmHg, 95% CI : 1.4~5.8 mmHg)均高于对照组。在18~25岁期间,极早产组睡眠动态血压的增加幅度比对照组更大(每年增加收缩压0.56 mmHg,舒张压0.41 mmHg,平均血压0.41 mmHg; $P<0.05$)^[19]。国内有关研究也表明低出生体重有增加青春期或成年期高血压风险的可能^[20],同时有学者开始关注早产与其后期高血压的风险及机制^[21]。

2 早产与远期高血压发生的机制

2.1 心血管重塑

极早产儿具有独特的心脏表型,可持续到青少年期及成年期,有一定的风险出现血压升高并伴随着左右心室和主动脉尺寸的缩小,左右心室舒张功能的减低,右心室射血分数的减低^[22-24]。

早产可能会干扰甚至过早地终止血管的发育,影响血管结构和器官生成,因此早产后出现的高血压在很大程度上可归因于早产儿出生后血管结构的变化^[25]。与宫内的发育相比,早产儿生后的主动脉生长明显受限。有研究通过磁共振成像发现,胎龄30周以内的早产儿较足月儿,在成年后的升主动脉腔直径更小,但颈部和肱动脉直径相似,且尽管颈动脉直径大小相似,但早产儿成年后的颈动脉脉搏波动速度增加,颈动脉可扩张性降低^[26]。另外,在最近的一项横断面研究中,通过动态血压监测评估血压状况和颈-股动脉脉搏波动速度评估动脉硬化程度,研究发现早产与儿童/青少年的夜间血压升高及动脉硬化程度增加有关,其中早产出生的超重儿童其夜间收缩压和动脉脉搏波动速度最高^[27]。在人类,动脉壁中弹性蛋白的合成在妊娠末期达到高峰,生后急剧下降,围产期是一个与早产儿主动脉发育密切相关的窗口期^[28]。因此,可以推测早产可能导致血管床发育的中断或受限,导致内皮功能障碍,同时改变了早期主动脉弹性蛋白和胶原蛋白的发育,使动脉硬化程度增加,发生动脉高血压^[28]。此外,其他围产期干预和并发症(如围产期感染、肠外营养、产前和产后类固醇的使用等)也与血管硬化程度增加有关,可能参与长期的心血管重塑^[29]。

在微血管水平上,发现极早产出生的儿童和成年人的视网膜血管的直径和分布密度有下降^[30]。一项国内的纳入9 230例研究对象的大型研究,通过5年的随访,发现较高的高血压发病率与较窄的视网膜动脉直径相关^[31]。此外,有研究在早产儿后期的随访中发现,皮肤微血管的灌注和分布密度已被证实有减少,并与高血压和抗血管生成因子的增加相关^[32]。微血管分布密度下降和毛细血管生成能力受损是增加血管阻力的主要原因之一,并与高血压的发展有关,将高血压与毛细血管分布密度下降联系起来的机制包括内皮细胞产生的氧化应激(oxidative stress, OS)、血管紧张素Ⅱ及抗血管生成因子的增多,使血管的增殖和再生能力受损^[33]。

妊娠高血压作为早产分娩的高危因素之一,似乎对早产儿的血管和心脏生理有独特的长远的影响,也有增加早产儿成年后高血压的风险^[34-35]。其机制可能为局部子宫-胎盘肾素-血管紧张素系统(renin-angiotensin system, RAS)的过度激活^[36]。有研究证实,妊娠高血压孕母分娩的早产儿在20岁时发生高血压的风险可能会增加3倍^[37]。局部子宫-胎盘RAS在参与调节胎盘发育、调节胎盘内分泌、免疫功能和营养的转运中起关键作用^[38]。在缺氧条件下,由于胎盘血管发育所需的促血管生成因子的产生增加,使血管紧张素Ⅱ受体类型1(angiotensin II receptor type 1, AT₁R)的表达上调。然而,长时间的缺氧会过度激活AT₁R,导致抗血管生成因子的优势和胎盘生长因子的表达减少,两者都导致胎盘灌注损伤。AT₁R驱动的OS也被认为是子痫前期孕妇血管功能障碍发病机制及其后代心血管风险的主要因素,其在动物试验中也有证实,给正常妊娠大鼠注射选择性AT₁R激动剂会导致胎盘和肾脏中线粒体活性氧的产生增加^[39]。

对于早产儿,从宫内环境到宫外环境的过渡发生在心血管系统发育的关键阶段,生后暴露于高氧环境,使心脏结构及功能发生重塑^[40]。早产儿生后常合并危重情况,常需吸氧,甚至机械辅助通气,因此增加了暴露于富氧环境的风险^[41]。有证据表明,新生儿高氧暴露会增加活性氧的产生,改变全身血管内弹性蛋白和胶原的分布,导致内皮功能受损,动脉直径和弹性降低^[42-43]。同时有研究发现,与足月儿相比,胎龄<30周的早产儿的右心室质量较大,右心室体积较小,且右心室收缩功能参数显著降低;而这些早产儿在成年时,左心室质量较大,左心室体积较小,左心室

收缩和舒张功能参数显著降低^[44]。心脏发育从早产儿到成年后的明显改变,可能与胎儿期、新生儿期和环境因素等多种因素有关^[45]。在一些早产出生模型的动物实验研究中已证实,新生儿高氧暴露与心脏结构和功能改变有关,且心肌细胞肥大、纤维化和早期衰老标志物出现增加,最终导致成人心脏衰竭^[46]。在暴露于高氧的新生大鼠中,观察到RAS的早期激活,其特征为AT₁R表达显著增加,与血管紧张素Ⅱ2型受体的表达相比呈现失衡状态,且这种失衡状态持续到成年期。此外,有研究发现,对新生儿AT₁R的短暂阻断可防止心脏改变的发展,进一步证明了RAS在新生儿OS相关的心脏功能障碍发育编程中的关键作用^[46]。因此,早产儿较足月儿成年后的高血压发病率更高,高血压程度更重,且随着时间的推移,可能会因早产儿心脏对高血压的敏感性更大而进一步加速疾病进展。

2.2 肾脏结构的改变

肾单位是肾脏的功能单位,其形成始于第9周孕期,大多数肾单位在孕晚期时发育,在孕34~36周完成^[47]。出生体重与肾小球数量相关,估计每增加1 kg出生体重,每个肾脏就会额外增加232 217个肾小球,而出生时达到的肾小球数量将是个体生命中所拥有的数量^[48]。

大多数肾小球在孕晚期发育,因此早产或限制宫内生长的因素(微量营养素缺乏、感染、缺氧、药物、糖皮质激素、吸烟、产铅暴露等)都可能影响肾小球的生成,导致肾小球数量减少^[47, 49]。铅是常见的肾毒性物质,妊娠期和幼儿期是肾毒性金属的潜在易感窗口期。有研究发现,早产加上产前较高浓度的铅暴露会增加生后4~6岁时收缩压升高的风险,且肾小球数量减少^[49]。由此推测围产期暴露于肾毒性与较短的妊娠期相结合可能改变肾脏生长/发育轨迹并规划肾脏源性成人疾病,早产儿宫内的铅暴露可能会影响整个生命周期。

早产的个体,其肾单位数量少,通过剩余肾单位的补偿性滤过,来减少整体的功能丧失^[47-48]。根据Brenner等^[50]的高滤过理论,肾脏发育程序的改变可能会减少肾单位的数量,拥有减少肾小球的个体可通过肾小球的代偿性肥大以增加用于肾工作代谢的总表面积,以及增加肾小球内压,从而维持正常的肾小球滤过率(glomerular filtration rate, GFR)。但这些血流动力学的改变,可导致足细胞破坏、炎症介质释放和纤维化,并导致蛋白尿和肾小球硬化^[51]。此外,在早产儿中,肾盐消耗和容

量消耗诱导RAS过度激活,以减轻钠不足并恢复钠水平^[52]。血管紧张素Ⅱ在肾小球内的形成增加,局部RAS的促炎臂(血管紧张素Ⅱ-AT₁R轴)被激活,相比抗炎的血管扩张剂ACE2-Ang(1~7)-MasR通路的表达增加,这种失衡可能导致血管紧张素Ⅱ介导的输出小动脉血管收缩,肾小球内压升高,并维持肾小球的高滤过^[6]。激活肾素-血管紧张素Ⅱ-AT₁R通路,直接或间接通过超氧化物的产生,增强了氧化还原敏感的不对称二甲基精氨酸(内皮功能障碍的标志)积累,且血管紧张素Ⅱ介导的内皮功能障碍似乎在出生后持续存在,并导致生命后期心血管疾病的发生^[53]。因此,随着时间的推移这种适应性反应变得有害,肾小球过度滤过破坏了肾的自主调节机制,最终,过度滤过导致蛋白尿、继发性局灶性肾小球硬化和GFR逐渐下降,进一步减少了肾小球数量,进一步增加高血压的风险和程度^[11, 54]。

据报道,全球早产儿和低出生体重儿在活产新生儿中的发生率分别约为11%和15%,因此数百万人出生时就存在慢性肾病的风险^[54]。与足月儿相比,早产儿的肾单位数量明显减少,随着年龄的增长,早产儿更容易发生慢性肾病^[54-55],成年后出现慢性肾病的风险增加70%,因此高血压的风险也增加。一项Meta分析发现,低出生体重的早产儿与足月儿相比,GFR降低的OR为1.79(95%CI: 1.31~2.45),蛋白尿的OR为1.81(95%CI: 1.19~2.77)^[56]。据报道,在早产出生的儿童和青年人中,出现蛋白尿的概率增加^[57]。一项研究对96例14岁的极低出生体重早产儿和43例14岁的足月儿进行了横断面分析,结果发现,与足月儿相比,早产儿青少年时期的收缩压和舒张压较高、GFR较低、ln(x)尿白蛋白/肌酐比值较高^[58]。

肾小管钠重吸收的增加也被认为有增加早产儿在成年期发生盐敏感性高血压的风险。低出生体重早产儿的肾脏发育不成熟会导致肾脏盐损耗、高钠排泄率、Na⁺/H⁺交换明显减少^[59],以及上皮Na通道(ENaC)的mRNA的低表达^[60]。低出生体重早产儿在生命的最初几周内钠的消耗可能会引发反调节反应,以恢复他们的钠平衡,当这些反应持续存在时,可能导致水钠潴留的持续,造成长期的心血管和肾脏的不良影响^[54]。

肾脏数量的减少(严重的除外)并不一定会导致肾功能的障碍,但再次发生重度打击,肾脏

剩余的少量肾单位不能有效地应对功能需求,临床可出现明显的肾脏疾病进展,因此Brenner等^[50]提出“多重发育打击”的理论。第一个打击由不利的宫内环境引起,可能包括早产、宫内生长受限、低出生体重、孕母因素等。第二个打击与早产儿生后的危重病情,包括营养不平衡、暴露于肾毒性药物及感染或休克等所致肾脏缺血/再灌注等有关^[55]。怀孕也可能成为早产女婴在成年后面临的二重打击。有研究发现,早产的女婴较足月女婴在成年后怀孕的并发症(子痫前期、妊娠糖尿病、高血压、甲状腺和肝肾疾病)的风险有增加^[11, 61-62]。

因此,对早产儿进行长期的肾脏功能监测和保护至关重要,以降低慢性肾病和高血压的发生风险。围产期保健和儿科医生应密切关注早产儿的肾脏发育,采取有效的防治措施,从而改善患者的生活质量和预后。

2.3 身体成分改变

早产儿出生体重和脂肪含量通常低于足月儿,但在校正胎龄足月时,其体脂含量(fat mass, FM)较高,这增加了成年后患代谢综合征和晚年心血管疾病的风险^[12-13, 63]。研究早产儿的身体成分和生长模式有助于理解身体各部分、代谢-内分泌途径与心血管疾病的关系^[64]。传统使用的体重指数(body mass index, BMI)在衡量身体成分时过于简单,限制了对早产、体重与高血压复杂关系的理解^[65]。因此,评估FM等其他身体成分指标可能更全面地揭示身体成分变化与高血压的潜在联系。

由于早产破坏了正常的母体-胎盘的代谢和内分泌,在宫内胎儿生长期营养供应出现中断,早产儿出生后对宫外生活的适应导致脂肪量的增加,但早产儿在生后逐渐表现为身体脂肪含量增多,肌肉含量减低^[12]。

一项Meta分析显示,在校正胎龄足月时,早产儿的FM占总体重的百分比(FM%)比足月婴儿高6.3%(95%CI: 5.36%~7.32%)^[66]。一项意大利队列研究发现,早产儿的平均FM%显著高于足月新生儿,FM与胎龄呈负相关,而与出生后体重增加呈正相关^[67]。Gianni等^[68]的研究也表明,极早产儿在校正胎龄足月时,与足月新生儿相比,体重更轻,身高更矮,并且具有更高的FM%和更低的无脂质量(fat-free mass, FFM);随访到5岁时,早产出生的儿童与足月出生的儿童相比,体重明显

较轻,身高明显较矮,FM%较高,FFM较低。

在发育的关键阶段,营养过剩和营养不足都可能对早产儿产生不良影响。虽然体重增加速度减慢可能会影响智力的发育进程,但体重增加速度过快也会增加肥胖、血脂异常、高血压、胰岛素抵抗和2型糖尿病的风险^[11, 69]。这种快速而显著的脂肪积累改善了体温调节,增加了身体能量储存,从而更好地适应宫外生活,并受内分泌因子和早期生命营养的调节,早期的追赶似乎更有益,而后来的追赶似乎更有害^[70]。多项研究显示,极早产儿和极低出生体重儿体重的快速增长与血压升高之间存在正相关^[71]。其中有研究发现,在极早产儿中,随访到2~25岁之间的BMI上升速度越快,血压越高^[13]。

过多的身体脂肪,尤其是内脏脂肪,会导致心血管功能障碍和血压升高,其可能的机制包括脂肪因子失衡及验证、血管内皮功能障碍、钠排泄减少、胰岛素抵抗、RAS或交感神经激活等^[8, 13]。此外,在早产儿中观察到的肌肉量减少可进一步加剧高血压的风险。骨骼肌在葡萄糖和脂质代谢中起着至关重要的作用,胎儿时期肌肉发育受损会导致以后的胰岛素抵抗和代谢功能障碍^[72]。有关肥胖与高血压的关系已得到许多研究的证实。其中有研究发现,早产儿在校正胎龄足月至4个月间的FM增加与4岁时较高的收缩压和舒张压相关,从出院到校正胎龄4岁,较高的体重和FFM增加速率相关,而同一时间内较高的FM增加与4岁时血压呈正相关^[73]。一项多中心研究发现,中国及美国的儿童和青少年的高血压疾病负担很大,美国更明显,而肥胖对高血压的影响在美国也明显高于中国,提高身体肌肉质量的比例组成成分在两个人群中对高血压都具有保护作用,优化身体成分对改善儿童和青少年的血压有积极的影响^[74]。

2.4 HPA轴的过度激活

在生命早期,极早产儿HPA轴的特点是无法分泌足够的糖皮质激素来适应应激或疾病的程度。研究表明,随着年龄的增长,该轴变得过度活跃,而糖皮质激素的过度分泌,可导致血压的升高等,这可能与早产儿HPA轴受损有关^[14, 75]。同时一些研究也已经探讨了早产对HPA轴活性的长期影响,发现早产较足月儿后期有更高的皮质类固醇生成率^[76],并且观察到早产受试者在清晨、最低点或全天的血清或唾液皮质醇浓度升高^[77]。

3 总结及展望

总之,早产与成年期高血压的关系是明确的,可能的机制包括心血管重塑、肾脏结构改变、身体成分改变、HPA轴的过度激活等。此外,遗传因素是否增加了早产儿在成年期发生高血压的风险,还需要进一步研究。为更好地改善早产儿预后,有必要进一步研究早期的生活干预或药物防治对早产儿的长期影响^[19]。

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