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极早产儿血流动力学显著的动脉导管未闭管理的研究进展

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摘　要

动脉导管未闭(patent ductus arteriosus, PDA)是早产儿、尤其极低出生体重儿中最常见的心血管问题之一，而血流动力学显著的动脉导管未闭(Hemodynamically significant patent ductus arteriosus, HsPDA)的存在或持续与早产儿多种严重并发症的发生密切相关，造成早期或晚期不良预后结局。尽管多年来，关于早产儿PDA的研究从未停止，但目前国内外对于HsPDA的评估、治疗仍存在争议，不同临床中心对于PDA的评估及实践管理仍存在较大的异质性，尤其在是否治疗以及治疗时机方面的选择显示出较大差异。故本文回顾现有的研究证据，对极早产儿HsPDA的病理生理、评估及干预管理进行综述。

关键词

早产儿，动脉导管未闭，评估，管理

Advance in Management of Hemodynamically Significant Patent Ductus Arteriosus for Extremely Preterm Infants

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Abstract

Patent ductus arteriosus (PDA) is one of the most common congenital cardiovascular anomalies

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in preterm infants, particularly those with very low birth weight (VLBW). The presence or persistence of Hemodynamically significant patent ductus arteriosus (HsPDA) is closely related to the occurrence of a variety of serious complications in preterm infants, resulting in early or late poor prognostic outcomes. Although extensive research on PDA in preterm infants has been conducted over recent decades, consensus remains lacking regarding standardized diagnostic criteria, risk stratification approaches, and therapeutic decision-making—including indications for pharmacologic or interventional closure and optimal timing of intervention. Moreover, considerable inter-center variability persists in the evaluation and management of PDA, especially concerning treatment initiation and timing. This review synthesizes current evidence to outline the pathophysiology, diagnostic assessment, and contemporary management strategies for HsPDA in extremely preterm infants.

Keywords

Preterm Infants, Patent Ductus Arteriosus, Evaluation, Management

1. 引言

动脉导管未闭是早产儿最常见的心血管疾病之一，占新生儿先天性心脏病的 10%左右，其发生率与出生胎龄呈负相关，胎龄越小，PDA 的发生率越高，尤其在<28 周的超早产儿中，PDA 的发生率可高达 80%以上[1]-[3]。近年来，流行病学证据表明 HsPDA 的持续暴露与早产儿的多种不良结局相关，包括死亡、支气管肺发育不良(bronchopulmonary dysplasia, BPD)、肺出血(pulmonary hemorrhage, PH)、新生儿坏死性小肠结肠炎(necrotizing enterocolitis, NEC)、早产儿视网膜病变(retinopathy of prematurity, ROP)、脑室内出血(intraventricular hemorrhage, IVH)等，并可能遗留长期的神经系统并发症[4]-[7]。自从 1972 年 Gupta 等人[8]早期报告了 PDA 的手术可行性及发现非甾体抗炎药对关闭 PDA 的有效性以来[9] [10]，目前已有近百项关于 PDA 治疗方案的随机对照研究，然而，这些研究未能证实 PDA 的治疗方案能减少早产儿不良结局的发生，并且相当一部分研究在评估 PDA 的血流动力学意义上具有显著的异质性。因此，目前国内外关于早产儿 PDA 的管理仍存在较大差异及争议，对于 HsPDA 的评估和诊断仍难以准确判断[11]-[13]。本文就极早产儿 HsPDA 的评估和管理进行回顾总结。

2. PDA 的病理生理学

动脉导管是胎儿期连接肺动脉主干与降主动脉近端的血管通道，其主要功能是使右心室血液绕过肺循环直接进入体循环，以维持胎儿期正常血液循环，大约 90%~95%的血液经该导管分流[14]。出生后，由于血氧分压的升高及激素水平的变化，正常足月新生儿动脉导管通常在生后 72 小时内发生功能性闭合，而在早产儿中，由于血管平滑肌的不成熟、前列腺素的高水平以及氧化应激等因素导致导管闭合失败[15]。在既往的认知中，若超过生后 3 天动脉导管仍持续开放则认为是病理性的，这种病理性的延迟开放被称为动脉导管未闭[16]-[18]。动脉导管的持续开放使血流从左向右由主动脉向肺动脉分流，引起肺循环血流增多，这一现象被称为“导管窃血”[13]。这种分流进一步引起显著的血流动力学改变时，被定义为 HsPDA，HsPDA 的持续导致肺循环充血、体循环低灌注，从而使得早产儿更易发生肺功能的恶化、脑及肠道等脏器的缺血及再灌注损伤[19] [20]。

3. HsPDA 的评估

3.1. HsPDA 的临床评估

近年来，尽管对 PDA 有了更进一步的认识，但对于血流动力学显著的 PDA 的评估标准仍具有不确定性，如何准确进行血流动力学评估对 HsPDA 的干预具有指导性意义。显著的血流动力学改变在临床上难以通过某单一指标进行量化，有学者[11]指出，明确 PDA 的血流动力学意义需考虑以下因素：(1) PDA 分流量的评估及其对肺循环和体循环的影响；(2) 心肌功能的评估；(3) 产前或围生期存在潜在危险因素，因此需要结合临床、影像学检查及实验室指标多维度、个体化评估。在临床上常常通过以下症状特征来帮助评估 HsPDA：(1) 可闻及的心脏杂音；(2) 持续的心动过速(心率 > 160 次/分)；(3) 心尖搏动过度活跃；(4) 需要使用血管活性药物的低血压；(5) 少尿(<1 ml/kg/h)；(6) 呼吸困难加重或呼吸暂停[21] [22]。然而这些临床表现往往是非特异性的，缺乏诊断 HsPDA 的准确性，需要结合其他辅助检查手段进一步帮助判断。

3.2. HsPDA 的影像学评估

超声心动图作为一种无创、简便的检查手段是目前国际上诊断 HsPDA 的金标准，能够早期评估 HsPDA 对肺循环及体循环的影响。Giesinger 等人[23]的研究指出，<26 周超早产儿在生后 18 小时内进行早期超声心动图筛查 HsPDA，并对其进行靶向治疗可将 BPD 或死亡的复合结局降低 2 倍，这表明超声心动图在 HsPDA 的评估及治疗中具有显著作用，为进一步标准化 HsPDA 的评估，David 等人[24]建议对早产儿进行全面的超声心动图检测，其中包括：(a) 描述 PDA 的特征：导管的直径、血流方向、收缩期和舒张期血流速度的比值等指标的测量；(b) 描述肺过度充血的表现：左心室输出量+左心容量负荷或左心压力负荷；(c) 描述体循环的分流效应。基于这些超声心动图指标，目前关于 HsPDA 的标准及严重程度评分系统主要包括“PARIS 标准”、“FLORENCE 标准”以及“El-Khuffash PDA 严重程度评分标准”[25]-[27]。Dani 等人[28]首次比较了不同标准下极早产儿 HsPDA 的诊断差异，发现 FLORENCE 标准、PARIS 标准和 PDA 严重程度评分检测到类似的 hsPDA 诊断率。然而目前新生儿重症超声技术的临床应用仍不成熟，不能作为评估血流动力学的唯一标准，应综合临床表现及其他辅助检查手段共同评估循环状态。

3.3. HsPDA 的生物标志物评估

3.3.1. 利钠肽

利钠肽家族是一组能对心脏容积及压力负荷变化迅速做出反应的标志物。在临床上，极早产儿疑诊 HsPDA 时，超声心动图是诊断的常规方法，但对于技术人员的操作要求较高，因此，利钠肽也常常被辅助用于早产儿 HsPDA 的早期诊断，尤其是 B 型利钠肽(BNP)及其无活性的 N 末端前体(NT-proBNP)，它们不仅有助于识别需要干预的 HsPDA，还能用于评估治疗效果。[29]一项观察性研究[30]明确指出，利钠肽水平在伴有 HsPDA 的早产儿中显著高于无 HsPDA 或无症状 PDA 的早产儿，尤其在出生后第一周，HsPDA 是导致 NT-proBNP 水平显著升高的主要因素，这强调了其在早期诊断中的指向性意义。同时，有研究[31]指出，NT-proBNP 的水平能较好地预测极早产儿 HsPDA 的临床结局。然而，最近的 Cochrane 研究[32]显示，BNP 和 NT-proBNP 对于极早产儿 HsPDA 的早期诊断意义为低确定性证据，但可以帮助新生儿重症监护室优先识别需要进行心脏超声的危重患儿。

3.3.2. 全身炎症指标

众所周知，动脉导管闭合的经典理论是由于低氧、前列腺素 E2 (PGE2)和前列腺素 I2 (PGI2)水平降低所引起的导管平滑肌收缩，从而进一步导致导管发生功能性闭合，而炎症状态下，环氧化酶(COX)会被进一步激活，从而合成更多的 PGE_2和前列环素，以维持导管的持续开放状态。此外，有研究显示，$CD71^+$

红细胞(CECs)作为炎症相关的免疫调节性细胞，其高水平被证实是重症 HsPDA 的独立预测因子，提示炎症细胞浸润亦参与导管持续开放的病理过程[33]。因此全身炎症状态是早产儿 HsPDA 发生和持续的重要影响因素。近年来，基于全血细胞计数衍生的全身炎症指数如全身免疫炎症指数(SII)、泛免疫炎症值(PIV)和全身炎症反应指数(SIRI)某些疾病的诊断和临床评估方面备受关注[34] [35]。一项大型回顾性研究[36]指出升高的 PIV 值是早期诊断 HsPDA 的独立显著因子，该研究纳入了 1228 例胎龄小于 32 的极早产儿，比较了 HsPDA 组与非 HsPDA 组的多项炎症指数，发现泛免疫炎症值(PIV)在 HsPDA 组中显著高于非 HsPDA 组，而 SII、SIR 在 HsPDA 组和非 HsPDA 组无显著差异。因此，将全身炎症指标，尤其是 PIV 等复合指数纳入临床评估系统，可经济高效地帮助床旁识别 HsPDA 高风险早产儿。但值得注意的是，该指标缺乏足够的特异性，仍需与临床表现、利钠肽水平等结合进行综合判断[37]。

3.4. 灌注指数

灌注指数(PI)是指周围组织(如指尖、耳垂等部位)搏动性血流与非搏动性血流的相对强度，该比值可反应动脉血灌注的强弱。一项前瞻性观察性研究[38]表明，HsPDA 患儿的导管前 PI、ΔPI (导管前平均 PI 与导管后平均 PI 的差值)相较非 HsPDA 患儿有显著升高，并且将 ΔPI 的临界值规定在 0.85 可能对生后 24 小时内 HsPDA 有较好的预测。另一项研究也观察到导管前后 PI 差值与早产儿 PDA 的血流动力学变化显著相关，且生后 1 周内 ΔPI > 1.05%能较好地检测出 HsPDA [39]。在未来极早产儿的管理中，灌注指数这项无创检查可能为早产儿 HsPDA 的早期评估提供参考和思路。

3.5. 近红外光谱

近红外光谱技术(near-infrared spectroscopy, NIRS)是一种无创、实时性地监测局部组织氧饱和度(区域氧饱和度，rSO_2)的技术。Huang 等人的一项前瞻性研究[40]通过近红外光谱技术连续性监测发现 HsPDA 对早产儿肠道组织供氧及肠道组织 rSO_2 有影响，当 NIRS 监测早产儿肠道组织 rSO_2 出现持续下降趋势时，提示可能存在需进一步进行临床干预的 HsPDA。此外，多项研究表明，NIRS 可以监测 HsPDA 患儿脑、肾及肠道等器官的血流情况，以辅助超声进行早期 HsPDA 的诊断，并帮助识别可能出现并发症的高危患儿，但不同器官对 HsPDA 所致血流动力学改变的反应存在差异，这将直接影响 NIRS 的敏感性和特异性[41]-[44]。

4. HsPDA 干预措施

4.1. 期待治疗

期待治疗是指对确诊 HsPDA 的极早产儿采取密切监测，通过液体限制等方法延迟干预的措施。由于极早产儿 PDA 自发闭合率与胎龄相关，部分 HsPDA 可随循环适应而改善[45]。近年来，国际上对 HsPDA 的管理理念已逐渐从积极干预转为期待治疗，一项大型 Cochrane 研究[46]显示，与早期药物治疗相比，期待管理在死亡、支气管肺发育不良(BPD)、坏死性小肠结肠炎(NEC)等关键复合结局尚未显示显著劣势，且证据提示期待策略可能降低感染相关死亡风险[47]。另一项荟萃分析进一步证实，在明确的 HsPDA 中，积极治疗组与期待治疗组之间的死亡或 BPD 发生率无明显差异，且期待治疗组生存率显著更高[48]。尽管目前临床上 HsPDA 的期待治疗主要采用液体限制、利尿剂等对症处理措施，但尚无有力证据支持液体限制及呋塞米等利尿剂对 HsPDA 的治疗效果[45]。有研究显示，生后一周的液体超负荷与 HsPDA 的持续时间有关，但似乎与需要治疗的 HsPDA 风险无显著关联[49] [50]。此外，需要警惕的是，HsPDA 的持续时间与 BPD 相关性肺动脉高压显著相关，这提示临床需对高呼吸支持、超低出生体重儿以及具有合并症的高危极早产儿设定干预阈值，优化个体化管理路径[51] [52]。

4.2. 药物干预

目前临床上，HsPDA 的治疗药物主要包括吲哚美辛、布洛芬以及扑热息痛。布洛芬是治疗 HsPDA 的一线药物，它是一种环氧化酶抑制剂(COX-I)，通过抑制前列腺素合成来促进导管闭合，但对极早产儿 BPD、NEC 等结局无显著改善[53]-[55]。一直以来，HsPDA 的药物治疗方案备受争议，治疗时机、给药策略在国际上尚无指南标准。近年来，多项高质量研究指出，预防性或生后 2 周内早期药物闭合未能带来临床获益，但对 2 周以上的 HsPDA 是否治疗尚不清晰[46]。此外，布洛芬的暴露–效应关系受胎龄、体重及药代动力学特征影响，需优化给药策略以提升闭合率[15]。有研究表明，与标准剂量静脉注射布洛芬或静脉注射吲哚美辛相比，高剂量口服布洛芬是 HsPDA 闭合的最佳药物治疗选择[56]。未来，需要建立更多高质量多中心研究，多模态评估 HsPDA 的治理效应，焦距近期与远期结局，通过联合机器学习推动 HsPDA 的个体化治疗发展。

4.3. 外科治疗

对于 HsPDA 患儿，当药物治疗无效或存在明显禁忌时，手术干预或成为关键。既往的外科治疗标准是传统手术结扎法，随着近年来微创技术的发展，经导管封堵术(transcatheter PDA closure, TCPC)在极低出生体重儿(VLBW)及超早产儿中应用日益增多，其优势在于避免开胸手术相关的创伤、出血及术后疼痛，同时能减少呼吸机相关依赖时间[57]。Brianna 等人[58]的研究表明，与手术治疗相比，接受经导管封堵术的极早产儿生存率更高，近期预后可能更佳。然而，有研究报道[59]，TCPC 治疗对封堵器微型及释放精度要求极高，且 TCPC 治疗的 HsPDA 患儿仍然存在导管再次开放的风险，尤其在胎龄小于 28 w 或出生体重小于 1000 g 的患儿中，此外，在极早产儿中，更易发生如肺动脉狭窄、出血性心包积液、死亡等不良事件。因此，有必要继续研究并改进导管封堵设备和输送系统，以最大限度地发挥其对极早产儿的治疗益处[60]。值得注意的是，手术干预的 HsPDA 极早产儿住院时间显著延长，且与 BPD、脑室内出血等不良结局独立相关。但当前证据仍存在局限性，多为观察性研究，缺乏大样本随机对照实验，同时，经导管技术在超低体重儿中的长期神经发育结局数据尚不充分，未来需要更多大规模随机对照研究来比较外科干预对 HsPDA 患儿的预后获益情况[57] [58]。

5. 讨论与展望

当前，极早产儿 HsPDA 的管理仍处于“证据与实践脱节”的困境，HsPDA 的诊断，尤其是对于血流动力学的评估仍是一个难题，尽管目前已经明确了 HsPDA 的超声心动图特征，但这些特征不能完全识别具有临床意义的 PDA，在未来的临床中，需进一步构建极早产儿 HsPDA 的预测模型，结合临床表现、血流动力学参数、炎症因子水平及机器学习算法，全面评估以早期识别高危人群。此外，HsPDA 的治疗选择及治疗时机仍不确定，多项高质量临床研究表明期待管理的优势并不亚于早期药物干预，但值得注意的是，过长时间的暴露与 HsPDA 与极早产儿 BPD 相关性肺高压、死亡风险的增加显著相关[51]。保守管理对极早产儿远期结局如心血管发育、神经系统发育等的影响目前尚不清楚。吲哚美辛和布洛芬仍然是目前主要的药物治疗方法，对乙酰氨基酚的治疗方式也在近年来逐渐被提及，手术治疗通常作为最后的手段提供，未来需要开展更多的多中心随机对照研究，以评估诸如保守管理、预防性/早期无症状或有症状治疗、以及不同治疗方式对长期心血管、呼吸和神经发育健康等策略的益处和风险。

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