

• 综 述 •

心搏骤停后脑损伤的病理生理改变的研究进展

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心搏骤停后脑损伤(Post-cardiac arrest brain injury, PCABI)是心搏骤停(Cardiac arrest, CA)后心肺复苏(Cardiopulmonary resuscitation, CPR)成功患者死亡和长期功能障碍的首要原因^[1-6]。目前对于PCABI缺乏有效的治疗措施,且没有任何干预方法被证明可以有效地提高CA/CPR后的生存率并改善神经功能结局^[5-6]。因此,需要加深对PCABI病理生理改变的认识,以更好地指导临床实践和今后的临床及基础研究。本研究对PCABI的病理生理改变做出详细描述,以期今后的进一步研究提供理论基础和可能研究方向。

1 心搏骤停后综合征的重要病理生理组成部分

CA指心脏有效泵功能丧失,导致全身有效血液循环中断。根据心电图表现,可将CA时的心律分为两大类:可电击心律(可除颤心律)和不可电击心律(不可除颤心律);前者包含心室颤动和无脉性室性心动过速,后者包括无脉性电活动和心室停搏。尽管CA的发病率和存活率在不同国家和地区存在差异^[7],但其仍是世界范围内死亡的重要原因之一^[8]。成功的CPR可以实现自主循环的恢复(Return of spontaneous circulation, ROSC),全身恢复再灌注。即使ROSC恢复,患者的病死率和神经功能障碍率仍然很高,这是由一系列的病理生理过程所导致的,我们将其称之为心搏骤停后综合征(Post-cardiac arrest syndrome, PCAS)^[1]。PCAS的严重程度受多种因素影响,包括CA前因素、CA相关因素、复苏相关因素、复苏后治疗相关因素和康复相关因素等。如果在CA后迅速复苏实现ROSC,那么PCAS则不会发生^[1]。

PCAS的病理生理机制包含4个主要组成部分:PCABI、心搏骤停后心肌功能障碍(Post-cardiac arrest myocardial dysfunction, PCAMD)、全身性缺血/再灌注反应(Systemic ischemia/reperfusion response, SIRR)和持续存在病理损伤(Persistent precipitating pathology, PPP)^[1-2]。此外,还有其它的病理生理机制参与了PCAS的进展。PCABI的病理生理机制将在下一节详细讨论,我们在这里对PCAS的其它主要病理生理机制进行简要阐释,以期PCABI的发病机制提供整体观的全面认识。

1.1 PCAMD

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PCAMD引起的心血管衰竭是PCAS患者早期死亡的主要原因^[3,9-10]。除特殊心脏原因引起的CA(如急性冠脉综合征),大部分PCAMD的病理生理表现为心肌顿抑,其临床表现为低血压和心脏收缩/舒张功能障碍^[1-2]。绝大多数心肌顿抑性PCAMD对治疗有反应且其病理生理过程可逆^[11-13],其特征是心肌缺血/再灌注损伤(Ischemia/reperfusion injury, IRI)中氧化应激和胞内钙超载导致的持久性心肌收缩功能障碍^[11-12,14-17]。PCAMD导致的低心排量会严重损害脑和其它器官/组织的氧输送和能量底物输送,并可能导致继发性缺血缺氧性损伤。

1.2 SIRR

CA代表最严重的休克状态^[1],全身的血液循环彻底停止(无血流状态)。CPR仅可恢复部分血流(低血流状态),但仍不足以满足最低代谢需求。实现ROSC后全身血液灌流恢复,产生严重的IRI和一系列病理反应,我们将其称之为SIRR^[1]。SIRR导致严重的全身性炎症反应和应激反应,包括血管内低血容量、氧输送和利用受损、血管麻痹、免疫通路激活、细胞因子水平升高、内皮细胞活化、凝血系统激活/抗凝血系统抑制、纤溶系统充分活化/抗纤溶系统抑制、内毒素血症、肾上腺功能不全、高血糖和感染风险增加等^[1-2,18-23]。由于SIRR和脓毒症(Sepsis)的病理生理表现有诸多相似之处,故有学者将其称为“脓毒症样综合征”^[20]。SIRR可导致严重的全身炎症反应综合征、多器官功能障碍综合征甚至死亡^[2]。故而SIRR引起的全身性炎症反应可通过血液循环来加重PCABI损伤,继而影响神经功能结局和生存率。

1.3 PPP

PPP代表引起CA的病因在ROSC后仍未消除而造成的持续性损伤^[1]。在复苏后未能及时识别和纠正CA病因将会使患者面临持续性损伤和CA复发的风险。PPP及其并发症是PCAS异质性的来源之一。引起CA的病因可分为心源性因素和非心源性因素两大类;前者包括缺血性心脏病、致死性心律失常、心肌病、瓣膜性心脏病和先天性心脏病等,后者包括但不限于创伤、失血、恶性肿瘤、窒息和缺氧、低钾血症和高钾血症、低血糖、低体温、低血容量、营养不良、毒素、癫痫和脓毒症等^[24]。因此,不同的PPP会对PCABI进展造成不同程度的影响,在临床实践中需要具体分析,并采取具体措施防止PPP加剧PCABI造成的不良结局。

1.4 颅外多器官功能障碍对PCABI的影响

在 CA/CPR 后颅外多器官功能障碍是常见的且与病死率显著相关,其可能主要由复苏后的全身血流动力学异常和氧合障碍引起^[25]。考虑到几乎所有器官之间均存在相互作用(Crosstalk),包括结构和功能上的联系。因此,颅外的多器官功能障碍会通过各自与脑的结构和功能联系而引起脑功能障碍。阐明 PCAS 中 PCABI 和颅外器官功能障碍之间的相互作用机制,不仅使我们能够开发新的治疗策略来改善 PCABI 治疗结局,而且还可以利用这一双向相互作用设计安全有效的 PCABI 临床干预措施。鉴于此,优化心肺功能和内脏主要器官灌注是复苏后重症监护治疗的重要组成部分和脑复苏的基础且重要的措施^[26]。早期预防、早期识别和及时治疗颅外多器官功能障碍,防止因其而加重 PCABI 对脑复苏有重要意义。

2 PCABI 的病理生理机制

PCABI 是一种急性缺氧缺血性脑损伤,由严重的脑 IRI 引起并由其它损伤因素导致持续性进展,导致较高病死率和神经功能缺损率。PCABI 中不同脑区的神经元亚群易受损性不同,海马、大脑皮层、小脑、纹状体和丘脑中的神经元更易受损^[1-2]。PCABI 的临床表现包括括昏迷、癫痫发作、肌阵挛、脑水肿、交感神经亢进、神经行为障碍和脑死亡等^[1-2,6]。既往研究将 PCABI 的病理生理机制形象地概括为“二次打击模型”,其特征是 CA 时的原发性缺血损伤和复苏后的继发性损伤^[27]。

2.1 原发性缺血损伤

CA 时全脑血流中断,脑的氧气和能量底物供应完全丧失。大脑具有很高的能量代谢率,虽然只占体重的 2% 却消耗全身约 20% 的氧气和 25% 的葡萄糖^[28]。由于代谢高且能量储存低,CA 后脑极易发生缺氧和缺血损伤。

脑血流供应的中断使有氧氧化的底物(氧气和葡萄糖)供应完全中断。脑中有氧氧化产生的能量底物(如三磷酸腺苷)对于维持脑的正常生理活动必不可少^[29],且三磷酸腺苷等能量底物的耗竭导致线粒体膜电位去极化^[30],而线粒体膜电位保持正常是合成能量底物的重要条件,因此形成了能量生成受损的恶性循环^[31]。有氧氧化过程的损伤使脑转向无氧氧化供能,但作用极其有限。脑缺血损伤和能量供应丧失导致离子泵功能紊乱,进一步导致细胞内离子稳态紊乱。离子通过离子泵跨细胞膜运输并产生相应化学梯度,调节 pH 值或细胞生长^[32]。这些能量依赖的初级离子泵(如 Na⁺、K⁺-ATP 酶)通过水解能量底物产生的能量将离子进行跨细胞膜转运,而次级离子泵利用储存在离子电化学梯度中的能量,通过耦合这些离子的运动来驱动另一种离子的跨细胞膜转运^[33]。缺氧导致细胞内 Na⁺、H⁺ 和 Ca²⁺ 离子聚积,进而导致细胞内酸化和细胞肿胀。离子失衡导致神经元和神经胶质细胞的缺氧性去极化,这被认为是缺血性脑损伤的标志和引发因素,也是神经元缺氧性永久性损伤的主要因素,并进一步导致电压门控离子通道打开和兴奋性神经递质释放^[34-35]。当神经元继续去极化达到阈值电位时电压门控 Na⁺ 通道打开,产生动作电位^[36]。随着动作突触前电位的传播,Ca²⁺ 通过电压门控通道并导致囊泡内神经递质释

放^[37]。在脑缺血期谷氨酸等兴奋性神经递质被释放并引发兴奋性毒性造成的损伤^[38]。谷氨酸与突触后膜结合和相应的配体门控离子通道结合,导致其过度激活,促进 Na⁺ 和 Ca²⁺ 的过量胞内转运。此外,谷氨酸可与代谢性谷氨酸受体结合,促进胞内信号转导并刺激内质网释放储存的 Ca²⁺。缺氧去极化和兴奋毒性共同导致胞质钙超载。细胞内钙进入线粒体,破坏电子传递链,激活线粒体通透性转换孔,导致活性氧的产生和细胞凋亡^[39]。此外,钙可以激活裂解酶和促进活性氧产生,导致细胞损伤和死亡。细胞死亡和损伤可能引起局部无菌性炎症。

CA 后若长期没有恢复再灌注会导致神经元缺血坏死。氧和葡萄糖的剥夺、离子稳态失衡、缺氧去极化、兴奋毒性、钙超载和细胞肿胀等病理生理过程共同介导了无血流期脑细胞的损伤和死亡。

2.2 继发性脑损伤

继发性脑损伤始于 CPR 启动后并可持续数天^[6]。CPR 仅使脑血流部分恢复(约 25%),全脑仍处于低血流阶段。ROSC 后全脑实现完全再灌注。虽然及时的恢复再灌注可以防止不可逆性脑死亡,但也可以导致进一步的脑损伤。

由于继发性脑损伤存在多种病理生理改变和分子机制以及各种病理生理机制之间相互作用的复杂性,因此很难构建出统一的病理生理机制框架^[6,40]。继发性脑损伤的关键损伤机制是脑氧输送和氧利用之间的不平衡^[27]。多种病理生理改变参与了继发性脑损伤的进展,包括炎症(无菌性/全身性)、氧化应激、细胞内钙超载、线粒体功能障碍和细胞死亡信号通路的激活、血脑屏障破坏、微循环障碍、脑自身调节障碍、低血压、低氧血症/高氧、高热、高血糖、癫痫发作和肌痉挛、谵妄、脑水肿和颅内压升高以及电解质紊乱等^[3-6,26-27]。此外,医源性治疗因素(如药物、机械通气等)对 PCABI 进展的影响也需要评估。

多种病理生理机制均与 PCABI 的严重程度相关。完整的血脑屏障对于建立和维持 1 个允许大脑正常运作的微环境至关重要,当其受到损伤而使紧密连接被破坏和/或运输过程受损时会导致免疫细胞外渗增加,各种离子和分子异常跨屏障转运,并最终导致神经元功能障碍、神经炎症和神经元变性^[41]。PCAS 患者早期出现微循环障碍^[42],脑再灌注后常出现无血流现象,加重脑损伤^[43]。肾上腺素复苏可增强即时脑血流灌注,但也可能造成微血管功能障碍^[44]。ROSC 后脑灌注表现为 3 个阶段:早期充血阶段(0~20 min)、低灌注阶段(20 min~12 h)和恢复正常血流(12~72 h)^[45]。脑自动调节是指平均动脉压在一定范围内波动,脑血流可维持在 1 个相对稳定的阶段;在 PCABI 中这一变化曲线可能出现调节范围变窄和右移^[27,46]。脑灌注压(即平均动脉压和颅内压之间的差值)对于维持局部脑组织氧气压非常重要。因此,当平均动脉压降低(如低血压)或颅内压升高(如脑水肿和脑充血)时脑的氧输送可能受到损害^[46]。高氧血症和低氧血症均与病死率和神经功能预后不良有关^[47-48]。高氧血症可能导致血流动力学异常(外周和冠状血管收缩)、再吸收性肺扩张不全和氧化应激损伤(活性氧产生增加)等不利影响^[49-50]。低氧血症会加剧脑缺氧性损伤,并

与神经胶质细胞损伤和促炎状态有关,但与脑内皮或糖萼损伤无关^[51]。CA 后高热的原因需要谨慎评估,可能的因素包括 IRI、神经性发热和感染等^[3]。CA 后由于严重应激可引起高血糖和胰岛素抵抗等现象,并与病死率增高相关^[52]。癫痫发作是严重缺氧、缺血性脑损伤的表现,并可能进一步加剧脑损伤^[3]。在大多数 PCAS 病例中急性期肌阵挛^[53-54]和谵妄^[55]与病死率升高神经功能预后不良相关。

3 PCABI 病理生理机制的异质性

PCABI 患者在临床表现、神经生理、影像学 and 分子表型上具有很大的异质性^[40],且在 PCABI 患者的不同脑区神经元易受损性也存在差异^[56]。从脑氧合的角度看,PCABI 患者在氧输送、氧扩散和氧利用等方面存在差异,因此对于单一优化脑氧合的治疗措施的反应也不一致^[46]。这种异质性已被认为是区分 PCABI 亚型并进一步制定相应治疗措施的障碍。

尽管经过数十年的研究,PCABI 复杂的病理生理机制仍未被很好地理解,PCABI 相关的知识缺口仍然存在,包括机制、时间进程、作用和每个组成部分的意义等^[1]。在宏观层面上治疗、预后和康复方面的进展均需要了解 PCABI 病理生理机制,需要具体分析不同情况作为治疗的理论基础和支持。在具体的临床研究中应考虑 PCABI 的异质性,以进一步区分不同亚型并指导新型治疗措施的开发。

4 PCABI 病理生理机制的转化研究

我们对 PCABI 病理生理机制的认识有许多来源于动物实验研究结果。虽然动物实验与临床实际情况之间的相关性仍然存在争议^[57-60],但这仍是我们加深对 PCABI 发病机制认识的重要途径。常用的动物 CA 模型的建模方法包括窒息法、电刺激法、高钾法和失血法^[58,61]。不同的建模方法对应不同的 CA 病因,且具有不同的病理生理特征。窒息法诱导的 CA 动物具有更明显的心肌损伤,而窒息法诱导的 CA 动物脑损伤更为严重,这一现象与临床研究得出的结论一致^[40]。高钾法诱导的 CA 动物模型较为常用,该法几乎可以立即引起 CA、不需要任何设备且可以一定程度上提高复苏后生存率^[62]。小鼠、大鼠、猪和狗等模型动物均被用于 CA/CPR 研究^[57,61]。造模术中/术后监测指标包括脑电图、平均动脉压和体温等。

从方法学角度来讲,目前对于 PCABI 病理生理机制的基础研究存在较高的偏倚风险^[59]。因此,有必要采用标准的动物研究报告准则^[63]并详细地充分报告动物的基线特征和标准手术方案。毫无疑问,相关基础研究可以促进对 PCABI 发病机制的理解和临床治疗。但是,为了促进相关的临床转化,我们必须细化基础研究细节,从宏观到微观维度进行进一步探索 PCABI 的病理生理改变和发病机制。

5 总结与展望

PCABI 的病理生理机制非常复杂,颅内和颅外多种因素共同参与了 PCABI 的进展。PCABI 的病理生理机制可概

括为“二次打击模型”,包括原发性缺血性损伤和继发性脑损伤。目前对于 PCABI 的病理生理机制仍有诸多不明之处,这需要临床研究和基础研究的进一步探索,以期开发新型脑保护策略并促进脑复苏的进步。

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(上接第 297 页)

迟钝,同时美多芭冲击试验阳性,要警惕亨廷顿病的可能,同时要想到可能是非单纯 *HTT* 基因突变。尽早做出正确诊断,合理治疗,对确诊患者提供遗传和优生优育咨询。

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