Advances in Clinical Medicine 临床医学进展, 2025, 15(4), 3389-3396
Published Online April 2025 in Hans. https://www.hanspub.org/journal/acm
https://doi.org/10.12677/acm.2025.1541310

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大脑自动调节功能在非神经系统疾病中的研究与应用

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收稿日期：2025年3月28日；录用日期：2025年4月24日；发布日期：2025年4月30日

摘　要

大脑自动调节功能(Cerebral Autoregulation, CA)是颅脑自我保护机制，能在一定范围血压波动下通过调节脑小血管的收缩或舒张维持恒定的脑血流量以防止颅脑灌注不足及过度灌注。CA自提出以来广泛应用于神经重症患者，如创伤性脑损伤、出血性卒中、缺血性卒中等。随着对CA研究的深入及监测手段的更新，CA的临床应用范围不断扩展，特别是在脓毒症、围手术期、儿科等领域。本文就CA在非神经系统疾病的临床应用做一综述。

关键词

大脑自动调节功能，脓毒症，围手术期，儿科

Research and Application of Cerebral Autoregulation in Non-Neurological Diseases

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Received: Mar. 28th, 2025; accepted: Apr. 24th, 2025; published: Apr. 30th, 2025

Abstract

Cerebral autoregulation (CA) is a self-protective mechanism of the brain that maintains constant cerebral blood flow by regulating the constriction or dilation of cerebral microvessels within a certain range of blood pressure fluctuations, thereby preventing cerebral hypoperfusion or hyperperfusion. Since its proposal, CA has been widely applied in neurocritical care, including traumatic

文章引用: 朱学梁, 刘微丽. 大脑自动调节功能在非神经系统疾病中的研究与应用[J]. 临床医学进展, 2025, 15(4): 3389-3396. DOI: 10.12677/acm.2025.1541310

brain injury, hemorrhagic stroke, and ischemic stroke. With advancements in CA research and monitoring techniques, its clinical applications have expanded into non-neurological fields such as sepsis, perioperative care, and pediatrics. This article reviews the clinical applications of CA in non-neurological diseases.

Keywords

Cerebral Autoregulation, Sepsis, Perioperative Period, Pediatrics

1. 引言

CA 首次于 1959 年由 Lassen 首次提出[1]，其分为静态大脑自动调节功能(static Cerebral Autoregulation, sCA)和动态大脑自动调节功能(dynamic Cerebral Autoregulation, dCA)。sCA 是指大脑在缓慢变化的血压中，通过调节脑血管阻力，维持脑血流量(Cerebral Blood Flow, CBF)相对恒定的能力，其作用时间范围在数分钟至数小时之间。dCA 是指大脑在瞬时血压波动下，在几秒至数分钟内快速调节脑血管阻力以维持 CBF 的能力[2]。特别自经颅超声多普勒问世以来，dCA 临床应用价值在创伤性脑损伤、蛛网膜下腔出血、急性脑卒中等神经系统疾病领域积累了大量循证医学证据[3]-[5]。近年来研究发现，在非原发性神经系统疾病患者中也存在 CA 受损，且会引起继发性脑损伤，导致患者的不良结局[6]-[8]。在非神经系统疾病领域，部分研究通过 CA 的监测指导临床治疗，以改善 CBF 及减少神经系统并发症[9]-[11]，因此就 CA 的调节机制、监测方法及其在非神经系统疾病领域的临床应用做一综述，希望能为临床治疗提供参考。

2. CA 调节的生理机制

CA 调节的生理过程是复杂的，由多种因素介导，目前主流认为有以下四种调节机制参与，即肌源性调节机制、代谢性调节机制、神经源性调节机制、内皮机制。肌源性调节机制主要涉及脑血管平滑肌对跨壁压力的变化的反应，其能通过血管平滑肌收缩或舒张以调节 CBF。当动脉血压升高时，血管跨壁压力升高，脑血管收缩以增高血管阻力；当动脉血压降低时，血管跨壁压力降低，脑血管舒张以减少血管阻力。肌源性调节机制是一种负反馈调节，其由血管壁张力直接引发，而非动脉血压。该机制主要由电压门控钙通道参与，当血压升高时，钙离子内流至平滑肌细胞后，细胞膜去极化，激活肌球蛋白轻链激酶(Myosin Light Chain Kinase, MLCK)，后者进一步磷酸化肌球蛋白轻链，最终引起血管收缩[12]。代谢机制主要由二氧化碳分压、氧分压介导血管收缩或舒张维持 CBF。CBF 对二氧化碳分压的变化很敏感，但二氧化碳分压与 CBF 并非简单线性的关系。当高碳酸血症时，二氧化碳分压升高 1 mmHg，CBF 增加 6%，当低碳酸血症时，二氧化碳分压下降 1 mmHg，CBF 增加 3% [13]。正常情况下氧分压不会引起脑血管的收缩与舒张，但在低氧的情况下(氧分压 ＜60 mmHg)时，K^+通道激活，Ca^{2+}内流减少，脑血管会代偿性舒张以增加 CBF [14]-[16]。神经源性调节机制是指神经元或神经胶质细胞通过释放各种神经递质(如乙酰唑胺、一氧化氮、5-羟色胺、神经肽 Y 等)使脑血管收缩或舒张维持 CBF，其由交感神经及副交感神经共同参与[17] [18]。内皮机制是指脑血管内皮细胞通过旁分泌的方式调节血管收缩与舒张来维持 CBF。内皮细胞分泌可分泌血管收缩剂(如血栓素 A2、内皮素-1)及血管舒张剂(如一氧化氮)，其中一氧化氮是最重要的血管调节剂[19]。截至目前，人们对 CA 调节机制的认识仍不够深入。CA 的核心是通过各种机制介

导脑血管的收缩或舒张以调节脑血管的阻力，但目前对于不同血管区对血管阻力的贡献依然存在争议，Gould 等人认为供血小动脉(d < 10 μm)旁的毛细血管为主要贡献者[20]，Hadi Esfandi 等人认为穿支动脉和毛细血管前小动脉对 CBF 调节发挥主要的作用，而毛细血管直径的改变并非血管阻力改变的最重要因素[21]。CA 调节过程中对不同血管的血流动力学改变的研究或区分不同血管区的 CA 可能为未来临床治疗提供参考依据。

3. CA 的监测方法

由于目前临床应用及临床研究主要集中于 dCA，以下主要阐述 dCA 的临床常见监测方法。1989 年，Aaslid 等人首次使用下肢袖带释放试验定量 dCA [22]，随后出现各种监测方法用于评估 dCA，然而目前仍没有金标准用于评估 dCA。基于 CA 的定义，dCA 的监测需要同时记录 CBF 及动脉血压，若 CBF 随血压变化趋势波动，则提示 CA 受损，若 CBF 在血压波动时能维持稳定，则说明 CA 功能完好。临床上，经颅超声多普勒(Transcranial Doppler, TCD)是评估 dCA 最常用的工具，其能动态、实时、连续记录大脑中动脉血流速度间接反应 CBF。近年来，采用近红外光谱(Near Infrared Spectrum Instrument, NIRS)测量局部脑氧饱和度(Regional Cerebral Oxygen Saturation, $rScO_2$)也被应用于评估患者 CBF。目前主要通过主动诱发血压改变或自发血压变化两种方法评估 dCA。主动诱发血压变化的方法包括下肢袖带释放试验、蹲立位试验、倾斜床试验、瓦氏试验、压颈试验等[19]。其中压颈试验是通过短暂压迫颈动脉后解除压迫引起脑血管代偿性舒张，血流增快原理计算出瞬时充血反应比(Transient Hyperemic Response Ratio, THRR)进行量化 dCA，其计算为 THRR = 压迫前 5 个大脑中动脉收缩期血流速度的平均值/解除压迫后 2 个收缩期血流速度。相关研究表明当 THRR ≥ 1.09 时，大脑自动调节功能正常，当 THRR < 1.09 时，大脑自动调节功能受损[23] [24]。压颈试验通过压迫颈动脉降低脑灌注压，在假定颅内压不变的情况下也可归类为主动诱发血压变化。临床上常用量化 dCA 的参数包括平均流量指数(Mean Flow Index, Mx)、脑组织氧合反应指数(Tissue Oxygenation Reactivity Index, TO_X)、自动调节指数(Autoregulatory Index, ARI)等。Mx 是分析平均动脉压及 TCD 测得的大脑中动脉血流速度相关性所得的参数，其范围为−1 至+1，Mx 值 > 0.3 定义为 CA 受损[25]。TO_X 是反应动脉血压与 $rScO_2$ 之间关系的时间相关系数，范围从−1 到 1，负值或零附近的值表示完整的自动调节，而 $TO_X > 0.3$ 表示受损的自动调节[26] [27]。ARI 是描述动脉血压及脑血流速度关系的二阶微分方程所得整数值参数，其范围为 0 至 9，数值越高代表 dCA 越完好[28]。此外这些参数还能衍生出最佳血压及 CA 调节的上下限，如当 TO_X 处于最低值时的平均动脉压被定义为患者的最佳血压[29] [30]，当 $TO_X = 0.3$ 时血压的最高值及最低值定义为 CA 调节的上下限[31]。

4. 脓毒症与 CA

脓毒症引发的全身炎症反应可显著影响 CA，其病理机制涉及血脑屏障破坏、神经炎症因子释放、内皮损伤及脑微循环障碍等[32]-[34]。近年来 CA 的研究主要集中于脓毒症相关性脑病(Sepsis-Associated Encephalopathy, SAE)及脓毒症休克中的血压管理。SAE 是由脓毒症引起的全身炎症反应引起的弥漫性脑功能障碍，其临床症状缺乏特异性，较轻者可表现为轻度谵妄，症状严重者可表现为昏迷[35]。既往研究显示，SAE 患者普遍存在脑血流自动调节能力下降，其机制可能与 CA 受损导致脑灌注不足及神经元的损伤[36]。CA 受损是 SAE 发生的独立预测因素，同时 CA 受损往往与患者神经系统结局及死亡率相关。Patrick Schramm 等人纳入 30 名脓毒症患者研究中发现 60%患者在前两天内存在 CA 受损，且第 1 天 CA 受损与第 4 天谵妄的发生率相关[37]。Crippa IA 等人的一项前瞻性研究中采用 TCD 测量患者 Mx 值以评估 CA，100 名脓毒症患者中 50 人存在 CA 受损，57 名患者出现 SAE，CA 受损与 SAE 独立相关，且 Mx 越高 SAE 的发生的风险越高[36]。Bindra 等人采用 TO_X 评估脓毒症患者前三天 CA，研究发现 28 名患者

中 18 名患者死亡，幸存者第一天、第三天 TO_X 明显低于非幸存者，早期 CA 受损与 3 个月随访死亡率独立相关[38]。近年来，也有学者基于脓毒症患者的 CA 优化脓毒症患者血压的管理以减少相关神经系统并发症。Lucia Rivera-Lara、Rosenblatt 等人提出危重患者的 CA 血压调节上下限不同，基于 $rScO_2$ 确定 SAE 患者自我调节的血压范围，以此优化 SAE 患者的血压的管理可以改善脑灌注[39] [40]。随后张丽娜等人开展了共纳入 51 例感染性休克患者的前瞻性随机对照研究，实验组 26 人基于 TO_X 确定休克复苏过程中维持脑自动调节功能正常的最优血压，对照组按指南治疗，维持平均动脉压 ≥65 mmHg，结果表明实验组较对照组谵妄发生率明显降低(30.8% vs 60.0%, $P = 0.036$) [11]。目前脓毒症性休克指南推荐在液体复苏后维持平均动脉压在 65 mmHg 以上[41]，CA 的正常血压调节范围普遍认为在 60~150 mmHg。在 CA 正常的情况下 65 mmHg 能维持脑灌注，然而脓毒症患者普遍存在 CA 受损，血压调节的上下限改变，65 mmHg 这单一目标值似乎是不合理的。基于此理论，临床上改善脓毒症患者颅脑灌注可优化血压的管理或改善脓毒症患者 CA 功能。一氧化氮(Nitric Oxide, NO)由内皮细胞分泌，是调节脑血管舒张的重要因素。研究表明脓毒症患者内源性 NO 酶抑制剂，不对称二甲基精氨酸(Asymmetric Dimethylarginine, ADMA)显著升高[42] [43]，高水平 ADMA 可导致内皮细胞功能障碍[44]，进而损伤 CA。然而，动物脓毒症模型显示 NO 酶可诱导高水平 NO，血管舒张导致低血压[45]，组织灌注下降。所以，基于 NO 的代谢途径提高 NO 水平联合 CA 的监测优化血压管理可能是改善脓毒症脑灌注的潜在靶点。

5. 围手术期与 CA

术后神经系统并发症是常见的严重并发症，直接影响患者预后和生活质量[46] [47]。这些并发症包括急性脑卒中、认知功能障碍、谵妄、癫痫、脑出血等[48]。尤其在心脏手术、体外循环手术术后，患者常出现谵妄、认知功能障碍等，这与术中剧烈的血流动力学改变、缺血再灌注、低温与复温、患者自身因素等相关[49]-[51]。术中脑过度灌注或低灌注是术后神经系统并发症发生的重要因素，CA 能维持手中患者脑血流动力学的稳定，然而研究表明部分手术患者存在 CA 受损[52] [53]。CA 受损是术后谵妄的独立危险因素。Caldas 等人的一项前瞻性观察性研究中，体外循环下冠状动脉搭桥手术 67 名患者中，术后 24 h、术后 7 天分别有 55%和 20%患者发现 CA 受损，术后谵妄发生率为 25.4%，且术后 24 h CA 受损是谵妄发生的独立危险因素[54]。此外 CA 受损也与术后记忆减退相关。Greta Kasputyt 等人一项共纳入 83 名体外循环下冠状动脉搭桥手术患者研究中，通过 HVLT-R 评分量表评估患者记忆能力及 TCD 评估患者 CA，研究发现所以患者均存在短暂性 CA 受损及部分患者(30.1%)存在术后记忆障碍，单次最长 CA 受损持续时间是术后记忆障碍的预测因素[55]。目前现有研究表明基于 CA 设定的最佳血压管理可能减少术后神经系统并发症。Hori，D 等人一项共纳入 493 名接受体外循环手术患者的研究中通过 TO_X 评估 CA 及 CA 调节血压的上下限，研究发现手术期间血压高于 CA 调节上限是谵妄发生的危险因素，发生率是血压未超出上限患者的 4 倍[31]。Charles W 等人纳入 460 体外循环心脏手术患者中基于 CA 定义血压调节下限将患者分组自动调节组(手术期间维持血压高于 CA 调节下限)及常规组，研究发现两组患者术后卒中及新发脑缺血性损伤无统计学差异，但自动调节组谵妄发生率较常规组明显降低(8.2% vs 14.9%) [9]。

6. 儿科领域中的 CA

CA 的儿科领域临床应用主要集中于接受心脏手术的先天性心脏病儿科患者、接受体外膜肺氧合(Extracorporeal Membrane Oxygenation, ECMO)治疗儿童。心脏手术及术后神经系统并发症的关系我们已论述，但合并先天性心脏病的儿童病理生理基础有别与成人患者。患有先心病儿童大脑发育不成熟、脑血量减少、血管神经系统尚未成熟等可能是导致 CA 受损的病理生理基础，在手术期间可能更易受到颅脑过度灌注及低灌注的影响导致术后各种神经系统并发症甚至影响患者神经发育[56]-[58]。此外复杂的先

天性心脏病常需要多次手术，大脑多次受手术打击。目前已有相关研究表明，患者先天性心脏病的儿童患者存在 CA 受损[10] [59]，但仍缺乏 CA 受损对儿童术后神经系统并发症及大脑神经发育结局影响的相关研究。ECMO 可通过多种因素使患者 CA 受损，包括患者原发疾病对 CA 的影响、非搏动性血流介导的血管内皮功能障碍[60]-[62]、炎症反应[63] [64]等。越来越多证据表明儿童患者在接受 ECMO 治疗时 CA 受损[65]-[67]，这可能引起颅脑灌注的改变，导致各种神经系统并发症。ECMO 治疗期间 CA 受损可能与不良神经系统结局相关，Nicolas Joram 等人研究发现 ECMO 治疗前 24 h 内 CA 受损最为显著，且 CA 受损与急性神经系统并发症相关[66]。目前临床研究已证实部分危重患儿存在 CA 受损，但缺乏足够的临床数据描述 CA 受损对儿童神经系统结局的影响。

7. 小结

在传统神经系统疾病，如脑出血性疾病、脑缺血性疾病，人们非常重视脑保护。然而非神经系统疾病能通过各种机制产生继发性脑损伤，我们应该同样关注与重视这些患者的脑保护。已有临床证据证明 CA 受损与继发性损伤相关，同时基于 CA 的评估指导治疗可减少这些疾病的神经系统并发症，拓展 CA 临床应用的范围能为患者脑保护的个体化治疗提供临床参考依据。但目前 CA 的评估方法各异，缺乏统一的标准，通过 TCD 及 NIRS 评估 CA 均有其局限性。TCD 受检查者技术水平和经验的影响导致检查结果存在差异，同时受颅骨厚度密度的影响导致超声波不能穿透部分患者。NIRS 测量的信号可能受到头皮、颅骨和脑膜等浅层组织的影响，导致对大脑氧合和代谢的评估不够准确。临床上仍需开发出新的方法以统一 CA 评估的标准。

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