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急性失代偿期心力衰竭的治疗进展

李　欢*，刘地川#

重庆医科大学附属第二医院心血管内科，重庆

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摘　要

急性失代偿期心力衰竭(ADHF)是急性心力衰竭(AHF)最常见的表现形式，随着医疗技术水平的不断进步，治疗心力衰竭的新药不断被批准上市、治疗方案不断优化调整。目前ADHF的治疗目的主要包括稳定血流动力学、缓解症状和预防短期发病率和死亡率，常见的治疗包括血管扩张剂、正性肌力药、醛固酮受体拮抗剂等相关药物及机械通气、血液净化等非药物辅助治疗方法。由于ADHF的病理生理机制尚未阐明，ADHF的标准治疗方案缺乏大规模临床试验、确切的证据等研究及报道，本文从药物及非药物治疗等方面综述了ADHF的治疗现状及研究进展。

关键词

急性失代偿期心力衰竭，治疗进展

Advances in Treatment of Acute Decompensated Heart Failure

Huan Li*, Dichuan Liu#

Department of Cardiovascular Medicine, The Second Hospital of Chongqing Medical University, Chongqing

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Abstract

Acute decompensated heart failure (ADHF) is the most common manifestation of acute heart failure (AHF), and with the continuous progress of medical technology, new drugs for heart failure continue to be approved and marketed, and treatment regimens continue to be optimized and adjusted. The common treatments include vasodilators, positive inotropic agents, aldosterone receptor antagonists and other related drugs, as well as non-pharmacological adjuvant therapies

*第一作者。
#通讯作者 E-mail: Idc670220@163.com

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such as mechanical ventilation and ultrafiltration, etc. Because the pathophysiological mechanisms of ADHF have not been elucidated, and the treatment protocols for ADHF lack large-scale clinical trials and precise evidence, this paper reviews the current status and research progress of ADHF treatment from the aspects of drug and non-drug treatments.

Keywords

Acute Decompensated Heart Failure, Treatment Progress

1. 引言

急性失代偿期心力衰竭(Acute decompensated heart failure, ADHF)是各种病因及诱因导致体容量负荷过重、肺循环淤血、重要组织脏器灌注不足、血流动力学失代偿、多器官功能级联效应、终末器官功能障碍等情况的急性演变[1]。研究指出，ADHF 在因心力衰竭原因住院患者中占 16.5% [2]，ADHF 病因多样，如缺血性心脏病、高血压、各种原因导致的心肌病(病毒、药物、遗传性、心律失常)、瓣膜性心脏病、感染性心内膜炎、内分泌代谢疾病相关的心肌病等，ADHF 可能由上述一种或多种病因共同导致。针对这些病因导致的 ADHF 不仅要迅速评估患者血流动力学、临床症状及液体潴留状况，而且要尽早确定病因、诱因及有无并发症的损害[3]。由于现对 ADHF 的治疗尚无明确的指南或专家共识，多数医务人员对 ADHF 治疗的认识较少，且若其临床管理不够、未得到充分的治疗可能导致再住院率、发病率、心血管死亡等终点复合事件的风险增加[4]，现对 ADHF 的治疗方面取得的进展做一综述。

2. 药物治疗

2.1. 正性肌力类药物

ADHF 患者心脏缺血时心内充盈压突然升高和(或)急性心肌功能障碍可导致外周灌注减少和肺水肿，治疗目的恢复心肌收缩功能、增加心肌供血血管的灌注[4]。作用机制及靶点不同的正性肌力药可能导致不同的获益-风险比。新型正性肌力药物左西孟旦通过钙离子依赖方式与心肌肌钙蛋白 C (Tn-C)结合以增强钙离子敏感性，增强心肌收缩力，同时并不影响心室舒张，且其可通过开放血管平滑肌的 ATP 敏感的钾离子通道，从而诱导全身动脉和冠状动脉阻力血管以及全身静脉容量血管舒张，降低心脏前、后负荷[5] [6]。多个研究证明[7] [8]，左西孟旦可有效改善 ADHF 患者心肌收缩功能降低、重要脏器灌注不足、肺水肿等情况，使相关临床症状得到有效缓解，还可使患者全因死亡率风险降低。但需警惕部分患者使用左西孟旦后出现心率增加、血压降低等情况可能导致低血压、头痛、心律失常等不良事件发生。Istaroxime 是雄烯二酮的衍生物，通过抑制钠钾 ATP 酶活性和激活肌钙网 SERCA2a 发挥正性肌力作用[9]，在急性失代偿性心衰动物模型中，Istaroxime 可显著改善血流动力学和超声心动图参数，不易导致心律失常[9] [10]，但仍需大样本试验探究其在 ADHF 的进一步作用。

2.2. 血管扩张剂类药物

ADHF 主要是心脏前后、负荷增加导致急性心力衰竭(AHF)的最常见表现形式。血管扩张剂主要有硝酸酯类、脑利钠肽类、尼可地尔等，尽管目前 ADHF 的病理生理机制尚未明确，但肾素－血管紧张素－

醛固酮系统(Renin-angiotensin-aldosterone system, RAAS)的激活导致全身血管收缩是导致 ADHF 患者病情加重的重要原因之一。脑利钠肽是由心室容积扩张和压力刺激从心室肌细胞分泌的一种激素，对 RAAS 系统具有天然拮抗作用，具有扩张动、静脉，增加心输出量，减轻心脏负荷超载，提高肾小球滤过率，增强钠的排泄，减少肾素和醛固酮的分泌，改善患者呼吸困难程度等相关临床不适症状的作用，且因其无正性肌力作用，不增加心肌耗氧[11] [12] [13]。奈西立肽的化学本质是重组人脑利钠肽，属于新型的血管扩张剂之一，研究发现，住院期间患者脑利钠肽水平下降至少 30%被认为预示着比没有变化或水平上升有着更好的预后[14]。另有研究发现，奈西立肽可使血流动力学指标和临床症状得到有效改善[15] [16]。应注意临床使用过程中应密切关注血压变化，对 ADHF 患者用药应个体化，不因担心其降压作用而不予应用，若出现低血压、头晕等不适表现应立即调整使用剂量。

2.3. 利尿剂类药物

研究发现，ADHF 患者的病程隐匿且伴有多种合并症，部分患者在入院前几天甚至几周就报告有充血症状，在极端情况下入院[1] [17]。患者入院后应尽快评估患者液体过载情况，不同类型利尿剂在肾脏不同位置作用从而缓解体内充血，ADHF 患者在严重容量超负荷的情况下，肾静脉充血引起的急性肾损伤可以通过利尿剂给药改善[14]。新型利尿剂托伐普坦是选择性的血管加压素 V2 受体拮抗剂，通过结合并阻断肾脏集合管上的 V2 受体活性，使水通道蛋白-2 表达下降并脱落，肾脏重吸收水下降，从而达到降低容量负荷的同时轻度增高血清钠浓度的目的。研究表明，托伐普坦可以在 48 小时内减轻液体负荷，特别是在限制液体、使用其他类型利尿剂仍无明显改善、症状性高容量低钠血症患者，尽管其在死亡率和再住院率方面没有明显改善[14]。还有部分研究指出[18] [19] [20]，托伐普坦在保钠、排水基础上，可不激活 RAAS 系统、不降低心衰患者血压、不导致肾功能恶化，维持患者肾脏血流循环。但在治疗 ADHF 过程中应注意利尿剂的不当使用会增加死亡率、发病率和再住院率，因此临床应用时需谨慎[3]。

2.4. 控制心率类药物

ADHF 患者可因神经内分泌过度激活导致心率代偿性增快，但心率过快会反向加重心衰的发展，而心率是评价患者预后的重要指标之一[21] [22]，所以对于 ADHF 患者应早期将心率控制在合适范围可改变患者的心功能和生活质量，降低患者心血管死亡风险[23] [24]。目前临床上控制心率类药物主要包括 β-受体阻滞剂、If 通道抑制剂等。β-受体阻滞因其降低心排血量及血压等不良反应或禁忌症而应用较少，伊伐布雷定是临床中治疗 ADHF 的新型药物，其通过选择性和特异性抑制心脏起搏 If 电流而呈剂量依赖性降低心率，而不影响心肌收缩和房室传导[25]。Sargento 等研究表明[21]，ADHF 患者应用伊伐布雷定可以有效减慢心率。还有研究指出，伊伐布雷定可减轻 AT1 受体的表达和血管紧张素 II 的水平进而减少心肌缺血的发生[26]，早期运用伊伐布雷定将心率控制在<70 次/分以下，可显著降低出院后 3 个月内 21%的再住院风险[27]。

3. 非药物治疗

3.1. 机械通气

ADHF 患者临床主要表现为血压下降、心源性肺水肿出现呼吸困难逐渐加重、持续性低氧血症，脑缺氧致意识障碍等。目前机械通气是纠正 ADHF 导致呼吸衰竭的有效方法之一[28]，机械通气通过外在机械提供大气与肺泡－肺毛细血管膜间的氧和二氧化碳运输，目的是维持 PO_2 和 PCO_2 在适当水平，减少呼吸肌做功，进而改善氧合，且机械通气可通过改变胸腔内压力及肺容积，直接影响患者血流动力学[29] [30]。机械通气可分为经气管插管的有创机械通气(IPPV)和无创机械通气(NPPV)，IPPV 因清醒患者

较难耐受，且其易造成气道损伤、人工气道梗阻、呼吸机相关肺炎、氧中毒等并发症在临床应用容易受到限制。NPPV 因操作较为简单、无创伤、呼吸机相关性肺部感染等并发症发生率较低，且患者对其有良好的依从性等特点，在实际临床中应用较为广泛。研究表明，NPPV 可降低急性心源性肺水肿患者有创机械通气比例和病死率，改善急性心力衰竭患者的血流动力学指标、动脉血气状况、运动耐量，对预后有一定的意义[31]。也有研究表明，NPPV 可缓解呼吸困难、纠正酸碱代谢失衡，但对患者的短期病死率不会产生显著影响[32]。

3.2. 血液净化

循环容量负荷过重、肺淤血是 ADHF 患者住院的主要原因。临床治疗需有效减轻液体负荷，利尿剂虽能部分缓解上述不适症状，但其不能充分纠正水钠储溜，且若利尿剂使用不当可能出现电解质代谢紊乱(低钠、低钾)、高尿酸血症、糖代谢障碍，甚至造成肾功能恶化。ADHF 患者如果在强化利尿剂策略治疗的情况下仍有体内液体超载，可选择血液净化治疗以缓解充血，同时保持血管内容量[14]。连续血液净化治疗不仅改善 ADHF 的容量状况，而且能改善心肾功能、缓解充血症状等[33]。ADHF 是全身炎症反应综合征的临床表现之一，使用血液净化治疗不仅能够清除体内多余的水分，维持电解质代谢平衡，降低血尿酸浓度，而且可以降低神经内分泌水平，有效清除血液循环中的炎性因子，保护受损的重要脏器，对心衰的缓解有重要意义[34]。部分研究表明，血液净化可使血浆中的部分肾上腺皮质类激素和儿茶酚胺类激素水平降低，并且可增加尿量，改善血流动力学指标[35]，可对改善心力衰竭患者的病情和生活质量有重要作用[36]，但目前仍无研究确切证实血液净化对 ADHF 患者长期预后的作用。血液净化为有创性操作，可能出现出血、感染等并发症，且由于其治疗花费较高，在临床上应用可能受到一定的局限性，但血液净化治疗可作为一种有效缓解 ADHF 患者症状的方法应用于临床，临床应充分评估患者病情，严格把握适应症，个体化合理选择治疗。

3.3. 机械辅助装置

随着医疗科学技术的不断发展，ADHF 患者在药物治疗方面效果不佳时，机械辅助装置已经成为治疗 ADHF 的重要手段之一，其中左心室辅助装置(LVAD)应用较为普及。LVAD 可代替部分心脏的做功，改善心肌供血和心脏泵血功能，提高心输出量，降低左室充盈压，维持重要器官的血液灌注[37] [38] [39]。ADHF 患者病情随时可能发生变化，临床应依据病情及植入 LVAD 后情况调整其治疗时间。研究表明，LVAD 与标准药物联合治疗较标准药物治疗终末期心力衰竭患者的死亡风险可降低到 48%左右，且其可明显改善患者生活质量[40]。LVAD 为有创性操作，植入费用较为昂贵，植入后需抗凝药物长期抗凝治疗，且植入 LVAD 后可能出现感染、出血、血栓形成等并发症，部分患者 LVAD 植入术后可能出现不同程度焦虑、抑郁等心理精神异常[41]，但 ADHF 患者在药物治疗效果不佳时可考虑将 LVAD 作为有效治疗手段。目前关于 LVAD 是否可改善 ADHF 患者的再住院率、发病率、心血管死亡风险等终点复合事件的研究仍较少，未来需更多大型、高质量的临床研究探索。

4. 小结

ADHF 是急性心力衰竭最常见的表现形式，随着医疗技术水平的不断进步，ADHF 治疗药物不断增加、治疗方案也在不断优化。目前 ADHF 紧急治疗的主要目的是控制液体过载和血流动力学损害，患者不适表现、短期病死率可改善，但血流动力学指标、临床症状、临床体征的恢复是否可降低患者长期死亡率和改善预后的研究仍较少。临床应加大研究力度，更加深入研究 ADHF 病理生理机制，不断使 ADHF 治疗方案更加多元、精准、有效，使 ADHF 患者得到充分的治疗，使更多的 ADHF 患者能够获益。

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