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沙库巴曲缬沙坦治疗心房颤动合并心力衰竭的研究进展

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摘　要

心房颤动和心力衰竭是两种常见的心血管疾病，两者具有很多相同的危险因素，常合并存在并相互促进，且房颤合并心衰时较任一疾病预后更差。本文旨在总结近年来沙库巴曲缬沙坦在治疗房颤合并心衰方面的研究进展，探讨沙库巴曲缬沙坦能否成为治疗房颤合并心衰的一线用药。

关键词

沙库巴曲缬沙坦，心房颤动，心力衰竭

Research Progress of Sacubitril/Valsartan in the Treatment of Patients with Atrial Fibrillation Complicated with Heart Failure

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Abstract

Atrial fibrillation and heart failure are two common cardiovascular diseases. They have many of the same risk factors, often coexist and promote each other, and the prognosis of atrial fibrillation combined with heart failure is worse than either disease. This article aims to summarize the research

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progress of sacubitril/valsartan in the treatment of atrial fibrillation complicated with heart failure in recent years, and to explore whether sacubitril/valsartan can be the first-line drug for the treatment of atrial fibrillation complicated with heart failure.

Keywords

Sacubitril/Valsartan, Atrial Fibrillation, Heart Failure

1. 引言

心房颤动(Atrial Fibrillation，房颤)是最常见的心律失常之一，与心力衰竭、脑卒中及血栓栓塞、认知功能下降和痴呆的风险增加有关[1]-[4]，心悸、乏力等症状也严重影响了患者的生活质量[5] [6]。心力衰竭(Heart Failure，心衰)是各种心血管疾病的严重表现。房颤与心衰同时存在时比任一疾病单独存在时预后更差，死亡风险更高[7]。沙库巴曲缬沙坦(Sacubitril/Valsartan)已成为治疗心衰的一线药物，但在治疗房颤方面研究较少，本文旨在总结沙库巴曲缬沙坦在房颤合并心衰中的研究进展。

2. 房颤和心衰的流行病学

有荟萃分析显示，与没有房颤的患者相比，房颤患者发生心衰的相对危险度增加 4~5 倍[1] [2]。Framingham 心脏研究显示，37%的新发房颤患者合并心衰，57%的新发心衰患者合并房颤[7]。心衰有时是部分房颤患者就诊的首发表现，同时也是房颤患者发生卒中的高危因素之一[8]。有研究发现，在房颤发生前已有心衰的患者死亡率更高[9]。房颤是心衰患者最常发生的心律失常，而心衰也是房颤患者最常见的非致死性危害，随着年龄的增加，大约有一半的房颤患者会发生心衰[10]。一项涉及 7 项随机试验、9 项观察性研究，分别包括 30,248 名和 23,721 患者的荟萃分析表明，房颤增加了慢性心衰患者死亡的风险[11]。随着高血压、糖尿病和冠心病等慢性病发病率上升、人口老龄化的加剧，房颤和心衰将会给社会和医疗系统带来沉重负担[8] [12]。目前迫切需要一种不良反应小的药物来改善房颤合并心衰患者的预后，减少心脏射频消融术后房性心律失常的复发。

3. 房颤合并心衰的病理生理机制

房颤与心衰具有很多相同的易患因素如糖尿病、高血压、缺血性心脏病和心脏瓣膜病等，两者常合并存在，相互促进[13] [14]。

心房电重构和结构重构促进了房颤的发生和维持。心房肌细胞内向 L 型钙电流(I_{CaL})减少导致心房肌细胞不应期缩短，外向钾电流(I_{K1})增加引起心房肌细胞加速复极化，两者均可诱发房颤发生[15] [16]。钙调神经磷酸酶/活化 T 细胞核因子(Calcineurin/Nuclear Factor of Activated T Cell, CaN-NFAT)信号通路可使内向 I_{CaL} 密度降低、动作电位时程缩短，促进房颤的发生[17]。钙/钙调蛋白依赖性蛋白激酶 II (CaMK II)介导雷诺丁受体 2 (RyR2)过度磷酸化，增加 RyR2 通道开放概率，促进舒张期 Ca^{2+}释放，导致细胞内 Ca^{2+}超载，Na^{+}-Ca^{2+}交换体(Sodium-Calcium Exchanger, NCX)激活，形成延迟后除极，从而诱发房颤的发生[18] [19]。心衰患者心房肌细胞 I_{CaL} 表达减少，导致心房肌细胞去极化时钙离子内流减少，从而导致频繁发生延迟后除极和增加对心律失常的易感性，最终诱发房颤的发生[20]。缝隙连接蛋白的异常表达和分

布、纤维化区域细胞间耦联的丧失是心房电重构的主要原因之一，可以导致折返回路产生并使心房激动变得无序，促进房颤的发生和维持[21]-[23]。

房颤患者心脏结构重构的主要原因之一是心肌纤维化的形成，而心房纤维化是由细胞和神经激素之间相互作用引起的[24]。心衰基础上发生房颤的关键因素就是心房纤维化[25]。心衰患者左心房压力升高引起左心房扩张，从而导致心房纤维化和瘢痕形成，使传导速度减慢，动作电位时程和有效不应期缩短，促进折返的产生和房颤的维持[13] [14] [26]。肺静脉在房颤的发生和维持中至关重要，左心房压力升高导致肺静脉发放快速冲动，从而促进房颤的发生[20] [27]。心衰使肾素－血管紧张素－醛固酮系统(Renin Angiotensin Aldosterone System, RAAS)激活，继而可激活成纤维细胞，诱导心房结构重构，促进房颤的发生和维持[20] [28]。

导致房颤患者发生心衰的机制包括心房收缩功能丧失、心率不规律、持续性心动过速、神经体液激活和心肌结构改变等。快速型房颤患者因心室率增加和心律不齐可导致心房有效收缩减少和舒张期充盈时间缩短，使左心室充盈减少，从而导致每搏心输出量减少和左心房压力升高，同 RAAS 和交感－肾上腺素髓质系统激活，促进心肌细胞肥大、凋亡，心脏发生重构，引起心衰[29]。另外，房颤导致的左心房扩张和心肌纤维化可直接导致心衰[30]。房颤还可以通过心律失常性心肌病直接诱发左心室功能障碍，导致心室功能迅速下降，并伴有心力衰竭[31]。

4. 房颤合并心衰的治疗方案

房颤合并心衰的治疗策略有诱因治疗、心衰的优化治疗、预防血栓栓塞、控制心室率、转复并维持窦律，其中转复并维持窦律包括应用抗心律失常药物、进行心脏电复律及心脏导管消融治疗[8] [10] [32]。长期应用抗心律失常药物会发生很多不良反应，如抗心律失常药物的致心律失常作用及心脏外毒性[33] [34]。目前国内外相关指南推荐对于合并射血分数降低的心衰(Heart Failure with Reduced Ejection Fraction, HFrEF)的房颤患者行导管消融治疗，可以改善患者的预后[8] [32]。

CABANA 试验[35]发现，房颤合并心衰患者行心脏射频消融术或药物治疗，1 年时消融组的房颤负荷平均为 7%，药物治疗组为 18%；5 年时，分别为 17%和 26%。导管消融术后有一定的复发率，可能需要多次消融，甚至发生肺静脉狭窄、心房食管瘘等相关并发症[36]。而房颤导管消融术后复发的高危因素包括左心房大小、心房纤维化程度等[8]。

防止心房电重构和结构重构来降低房颤首次发作和复发的可能性称为上游治疗。沙库巴曲缬沙坦被推荐为治疗心功能 II/III 级(NYHA 分级) HFrEF 患者的一线治疗药物[12] [37] [38]，可以减少 HFrEF 患者的发病率和死亡率，改善患者的症状和生活质量[39] [40]。沙库巴曲缬沙坦可以改善心室重构，或许可以减少心房重构并预防房颤的发生，改善房颤合并心衰患者的预后，减少心脏射频消融术后的复发率。

5. 沙库巴曲缬沙坦的药理作用

沙库巴曲缬沙坦是全球第一种治疗心衰的血管紧张素受体－脑啡肽酶抑制剂(Angiotensin Receptor Neprilysin Inhibitor, ARNI)，由血管紧张素受体阻拮抗剂缬沙坦和脑啡肽酶抑制剂前药沙库巴曲按 1:1 组成的化合物[41]。缬沙坦通过阻断血管紧张素 1 型受体(Angiotensin Receptor 1, AT_1R)，减轻血管收缩和抑制醛固酮释放，降低交感神经活性，并减少水钠潴留，缬沙坦还可以抑制血管紧张素 II (Angiotensin II, Ang II)所介导的心肌细胞肥大和纤维化作用，减轻心血管重构[41] [42]。脑啡肽酶可以降解利尿钠肽和许多其他血管活性肽，沙库巴曲通过羧酸酯酶转化为 LBQ 657，LBQ 657 可以抑制脑啡肽酶的活性，减少利尿钠肽、Ang I 及缓激肽的降解，从而产生排钠利尿、舒血管、减轻心血管重构的作用[40] [41]。综上所述，沙库巴曲缬沙坦具有抑制心肌纤维化、改善心肌重构的作用，可能是治疗房颤合并心衰患者的新型药物。

6. 沙库巴曲缬沙坦在房颤合并心衰患者中的应用

在 Li 等[17]的一项研究中，家兔接受快速心房起搏模拟房颤，并随机分为沙库巴曲缬沙坦组和对照组。对照组家兔的心房有效不应期缩短，心房和右心室明显增大，心肌纤维化程度较重，房颤诱发率明显升高。而沙库巴曲缬沙坦组的家兔心肌重构和纤维化相对减少，心房不应期较长，房颤易感性下降。本研究表明沙库巴曲缬沙坦可以降低 I_{CaL} 的电流密度的减少和细胞内钙超载来减轻心房电重构，其机制可能是沙库巴曲缬沙坦抑制 CaN-NFAT 信号通路。这项研究说明沙库巴曲缬沙坦可以减轻房颤患者的左房电重构和结构重构，改善左心功能，为沙库巴曲缬沙坦在房颤患者中的临床应用奠定了基础。在另一项动物试验中，结果表明沙库巴曲缬沙坦可以逆转 RyR2 通道和 NCX 通道的重塑，使房颤发生风险降低[43]。

在一项回顾性对照研究中，显示与口服 ACEI 或 ARB 相比，沙库巴曲缬沙坦更能降低慢性心衰患者房颤复发风险[44]。本研究中提到的心房纵向应变峰值(Peak Atrial Longitudinal Strain, PALS)主要是反映心房储库功能的指标。这项研究纳入了 80 名既往至少发作过一次房颤且心功能 II/III 级(NYHA 分级)慢性心衰患者，将 40 名接受沙库巴曲缬沙坦治疗的患者与 40 名接受 ACEI 或 ARB 治疗的患者进行了比较，随访 1 年，结果显示沙库巴曲缬沙坦组 PALS 增加更高($P < 0.001$)，提示其改善房颤伴心衰患者的心房储备功能的效果更好。沙库巴曲缬沙坦组房颤复发风险显著降低($P = 0.001$)，有 1 名患者发生 1 次房颤，4 名患者发生了 2 次房颤。通过本研究可以推断沙库巴曲缬沙坦可以降低房颤合并心衰患者房颤复发的风险，考虑与沙库巴曲缬沙坦抑制脑啡肽酶有关。但本研究是一项来自两个中心的回顾性研究，纳入的样本量少，本身存在偏倚风险，随访时间短，未来仍需多中心大样本的前瞻性随机试验来验证沙库巴曲缬沙坦预防房颤复发的作用。另一项回顾性队列研究首次探讨了沙库巴曲缬沙坦对阵发性房颤患者的疗效。结果发现，与缬沙坦组相比，沙库巴曲缬沙坦组显著降低了阵发性房颤向持续性房颤发展的风险[45]。

Wang 等[46]将 143 名接受导管射频消融的持续性房颤患者随机分为沙库巴曲缬沙坦组或缬沙坦组，干预持续 12 个月，每 3 个月随访 1 次，主要结局包括 3 个月空白期后持续 ≥ 30 s 的任何房性心律失常(房颤、房扑或房性心动过速)发作，次要结局包括任何持续 ≥24 小时或在 3 个月空白期后需要心脏复律的房性心律失常发作。除 5 名患者未能随访，两组各 69 名患者，沙库巴曲缬沙坦组 21.7%的患者和缬沙坦组 42%的患者达到主要终点($P < 0.001$)。沙库巴曲缬沙坦组 10.1%的患者和缬沙坦组 37.7%的患者达到次要终点($P < 0.001$)。沙库巴曲缬沙坦组患者的左房内径、左房容积指数、NT-proBNP 显著降低，6 分钟步行距离显著延长。本研究表明沙库巴曲缬沙坦可以减少持续性房颤患者导管消融术后 1 年的房颤复发，提高患者术后生活质量。在本研究中，沙库巴曲缬沙坦组建立剂量稳定后，9 例(13.0%)沙库巴曲缬沙坦剂量为 25 mg，2 次/天；22 例(31.9%)患者沙库巴曲缬沙坦剂量为 50 mg，2 次/天；38 例(55.1%)患者沙库巴曲缬沙坦剂量为 100 mg，2 次/天。缬沙坦组所有患者均口服 80 mg，2 次/天。沙库巴曲缬沙坦组患者所能耐受的药物最大剂量不同，未来的研究或许可进一步研究不同剂量的沙库巴曲缬沙坦对房颤射频消融术后复发的影响。而 Dong 等[47]进行了一项回顾性队列研究，发现沙库巴曲缬沙坦可以降低房颤患者首次导管射频消融术后房颤的复发风险。一项小样本临床试验显示，沙库巴曲缬沙坦在减轻房颤患者导管消融术后的心房结构重构方面优于缬沙坦[48]。

汪建兵等[49]报告了 3 例口服沙库巴曲缬沙坦治疗房颤合并心衰的临床病例，3 例病人均诊断为持续性房颤合并慢性心衰，在将血管紧张素转换酶抑制剂(Angiotensin Converting Enzyme Inhibitor, ACEI)或血管紧张素 II 受体阻滞剂(Angiotensin II Receptor Blocker, ARB)更换为沙库巴曲缬沙坦片治疗后均转为窦性心律，并且相关指标如射血分数、左房容积指数和 NT-proBNP 都得到改善。本报道提示沙库巴曲缬沙坦可能具有逆转左房重构，转复并维持窦律的功能。

赵玉清等[50]的前瞻性研究纳入了 170 名老年性阵发性房颤合并心衰患者，观察组和对照组均予以常规抗心衰和胺碘酮治疗，观察组在此基础上加用沙库巴曲缬沙坦治疗 1 年，比较两组的窦律维持率、左心房内径和左心室射血分数等。结果观察组第 6、9、12 个月窦律维持率均高于对照组($P < 0.05$)，观察组左心房内径小于对照组($P < 0.05$)，观察组左心室射血分数高于对照组($P < 0.05$)。本研究提示沙库巴曲缬沙坦可能有助于提高老年性阵发性房颤合并心衰的窦律维持率，并改善心功能和心肌重构。

宫士坤等[51]进行了一项小样本前瞻性研究，80 名房颤合并心衰患者均予以抗心衰、心脏射频消融及术后口服胺碘酮治疗。根据合并阵发性房颤或持续性房颤，以及是否口服沙库巴曲缬沙坦，分为 4 组，每组各 20 名患者，随访 1 年。结果显示口服沙库巴曲缬沙坦治疗的亚组，左心房内径均较术前减小(均 $P < 0.05$)，窦性心律维持率、左室射血分数改善方面均更好($P < 0.05$)。本研究表明沙库巴曲缬沙坦能更好地减少房颤合并心衰患者心脏射频消融术后的复发、改善左室射血分数及左心房重构。

PARAMOUNT II 期试验是一项双盲、随机、对照、多中心试验，该试验表明沙库巴曲缬沙坦与缬沙坦相比，对逆转左心房重构有一定作用，更能减小 NT-proBNP 和左心房内径[52]。另一项入组了 464 名 HFrEF 受试者的随机、双盲临床试验，结果提示沙库巴曲缬沙坦可以改善左房重构[53]。

PARADIGM-HF 试验也是一项双盲、随机、对照、多中心试验，将 844 名心功能 II/III/IV 级(NYHA 分级)的 HFrEF 患者在常规基础治疗上，随机分配为沙库巴曲缬沙坦组(剂量为 200 mg，每日两次)或依那普利组(剂量为 10 mg，每日两次)，结果显示沙库巴曲缬沙坦在降低死亡和因心力衰竭住院的风险方面优于依那普利[40]。同时也显示沙库巴曲缬沙坦在 HFrEF 患者伴或不伴房颤的情况下同样有效。

在 PARAGON-HF 试验中，发现新发房颤和既往房颤病史均与较高的心衰住院和心血管死亡的风险有关[54]。然而，沙库巴曲缬沙坦在房颤和非房颤患者中的治疗效果无差异。而且，沙库巴曲缬沙坦也未能改善射血分数保留的心衰(Heart Failure with Preserved Ejection Fraction, HFpEF)患者新发房颤。可能抑制脑啡肽酶对阻断血管紧张素受体治疗的递增影响不足以引起房颤的减少，因为作为对照组的血管紧张素受体阻滞剂可减少房颤的复发[55]。

在一项荟萃分析中，共纳入 6 个试验，包括 15,512 名患者(7750 名随机分配至沙库巴曲缬沙坦组，7762 名随机分配至对照组)，所有试验均为随机、双盲、对照。结果显示沙库巴曲缬沙坦组与对照组依那普利或缬沙坦在预防心衰患者发生房颤方面无明显差异[56]。

7. 小结

房颤和心衰是两种常见的心血管疾病，两者合并存在时预后更差，死亡风险更高。以上大部分研究表明，沙库巴曲缬沙坦可以减轻心房纤维化、降低房颤的易感性及改善心房重构，以减少房颤的发生和发展。但多为单中心、小样本研究，未来还需进行更多的多中心、大样本、前瞻性的研究，来进一步验证沙库巴曲缬沙坦在房颤合并心衰患者中的疗效。12 导联心电图和 24 小时动态心电图可能在随访中会丢失部分患者房颤复发的数据，心电手表、心电贴等家庭用的可穿戴设备在房颤诊断和负荷评价等方面具有广泛的应用前景。综上所述，虽然对房颤和心衰以及沙库巴曲缬沙坦有了越来越多的认识，但沙库巴曲缬沙坦在治疗房颤合并心衰的研究较少，需要更多的研究来提高我们对房颤合并心衰的诊断、发病机制、药物治疗和安全性等方面的认识，以改善发病率迅速增高的房颤合并心衰患者的生活质量和预后。

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