PJCCPVD May 2019，Vol.27 No.5 http：//www.syxnf.net

·综述·

可溶性 ST2 与心血管疾病关系的研究进展

曾艳，谭华清，唐湘宇，颜迪华

【摘要】 ST2 属白介素 1 受体（IL-1R）家族，主要分为可溶性 ST2（sST2）和跨膜型 ST2（ST2L）两种类型，其中 sST2 与白介素 33（IL-33）结合后可通过阻断 IL-33/ST2 信号传导而抑制核因子 -κB、丝裂原活化蛋白激酶激活，进而减弱心肌保护作用、促进心脏损伤及重塑。本文主要综述了 sST2 与心力衰竭、冠心病、心房颤动、主动脉瓣狭窄、心肌病等心血管疾病的关系，以期为心血管疾病的诊断、治疗及预后评估等提供参考。

【关键词】 心血管疾病；可溶性 ST2；冠心病；心力衰竭；心房颤动；心肌病；主动脉瓣狭窄；综述

【中图分类号】 R 54 【文献标识码】 A DOI：10.3969/j.issn.1008-5971.2019.05.023

曾艳，谭华清，唐湘宇，等 . 可溶性 ST2 与心血管疾病关系的研究进展[J]. 实用心脑肺血管病杂志，2019，27(5)：112-116. [www.syxnf.net]

ZENG Y，TAN H Q，TANG X Y，et al.Progress on relationship between soluble ST2 and cardiovascular disease [J]. Practical Journal of Cardiac Cerebral Pneumal and Vascular Disease，2019，27（5）：112-116.

Progress on Relationship between Soluble ST2 and Cardiovascular Disease *ZENG Yan*，*TAN Huaqing*，*TANG Xiangyu*，*YAN Dihua*

Department of Cardiology，*Loudi Hospital Affiliated to Nanhua University*，*Loudi 417000*，*China*

Corresponding author：*TAN Huaqing*，*E-mail*：*Ldrythq@aliyun.com*

【**Abstract**】 ST2，as a member of interleukin 1 receptor family，mainly includes two types，that is soluble ST2（sST2）and transmembrane ST2（ST2L）. Researches show that，sST2 may inhibit the activation of NF-κb and mitogen activated protein kinase by combination of interleukin 33 and inhibiting the signal transduction of interleukin 33/ST2，and then reduce the cardioprotective effects，promote the heart injury and remodeling. This paper mainly reviewed the relationship between sST2 and cardiovascular disease，such as heart failure，coronary heart disease，atrial fibrillation，aortic valve stenosis and myocardiopathy，in order to provide a reference for the diagnosis，treatment and prognosis assessment.

【**Key words**】 Cardiovascular diseases；Soluble ST2；Coronary heart disease；Heart failure；Atrial fibrillation；Cardiomyopathy；Aortic valve stenosis；Review

近年有研究表明，ST2 是特异性细胞标志物，属于白介素 1 受体（IL-1R）家族，其与炎症性肠病[1]、糖尿病[2]、心力衰竭[3]、冠心病[4]等有关，并参与炎性反应、促进肥大细胞活化。ST2 主要类型有可溶性 ST2（sST2）和跨膜型 ST2（ST2L），均与心血管有关。sST2 是一种诱骗受体，与白介素 33（IL-33）结合后阻断 IL-33/ST2 信号传导，进而抑制核因子 -κB（NF-κB）和丝裂原活化蛋白激酶（MAPK）激活[5]，减弱心肌保护作用，促进心脏损伤和重塑[6]。本文主要综述了 sST2 与心力衰竭、冠心病、心房颤动、主动脉瓣狭窄、心肌病等心血管疾病的关系，以期为心血管疾病的诊断、治疗及预后评估等提供参考。

1 sST2 与心力衰竭

据统计，我国心力衰竭发病率为 0.7‰~0.9‰，每年新发心力衰竭患者约 50 万例[7]。心力衰竭的临床症状不典型，病情变化多端，其诊断易受医师经验等影响[8]。目前，对于心力衰竭并没有独立的诊断试验，其主要诊断依据为患者病史和体征[9]。而随着心力衰竭发病率上升，生物标志物逐渐应用于心力衰竭的早期诊断、治疗和预后评估[10]。

sST2 作为心力衰竭的新型生物标志物在炎性反应、纤维化和心脏应激中的作用引起广泛关注[11-13]。有研究表明，sST2 可有效诊断心力衰竭[14-15]。PRIDE 研究[14]通过分析急性心力衰竭呼吸困难患者的 sST2 和氨基末端脑钠肽前体（NT-proBNP）水平发现，急性心力衰竭呼吸困难患者 sST2 水平高于急性心力衰竭无呼吸困难患者，在诊断急性心力衰竭方面 NT-proBNP 优于 sST2，但 sST2 与心力衰竭心功能（如左心室射血分数、心功能分级）存在依赖性关系。HUANG 等[16]经荟萃分析发现，sST2 对心力衰竭具有诊断价值。目前关于 NT-proBNP 诊断心力衰竭及预测其预后的报道较多，研究发现无论是新发的心力衰竭还是慢性心力衰竭急性发作患者，NT-proBNP 水平和心功能分级均成正比，其为诊断心力衰竭的独立预测因素，并被国内外指南推荐为心力衰竭诊断及预后评估的重要指标[17-19]。sST2 在体内 $t_{1/2}$ 及反应过程尚不清楚，

417000 湖南省娄底市，南华大学附属娄底医院心内科

通信作者：谭华清，E-mail：Ldrythq@aliyun.com

但在炎性反应及免疫性疾病中缺乏特异度，导致 sST2 诊断心力衰竭受到限制，但与其他生物标志物〔如脑钠肽（BNP）〕相比，sST2 水平不受年龄、肾功能或体质指数影响[20]。

WU 等[21]研究发现，健康受试者 sST2 具有较低的生物变异性，故相比其他生物标志物（如 BNP）其更适用于监测心力衰竭的病情变化。PIPER 等[22]通过检测 50 例慢性心力衰竭患者 1 h、1 个月、3 个月、6 个月 sST2 水平发现，sST2 生物变异性低于 NT-proBNP。既往研究表明，植入左心室装置、有急性心脏同种异体移植排斥反应及植入肺动脉导管的终末期心力衰竭患者及使用 β-受体阻滞剂、血管紧张素转换酶抑制剂（ACEIs）、血管紧张素受体拮抗剂（ARBs）、盐皮质激素受体拮抗剂的慢性心力衰竭患者 sST2 水平较低，说明 sST2 水平可预测心力衰竭治疗效果[12，23-24]。因此，理论上连续测量 sST2 可辅助决策心力衰竭患者的治疗方案，但在个体化治疗上仍需更多的基础研究和临床研究制定最佳方案。

PRIDE 研究[14]显示，NT-proBNP 联合 sST2 预测心力衰竭死亡风险优于单独 NT-proBNP。GAGGIN 等[25]研究了 151 例左心室收缩功能障碍（左心室射血分数 <40%）导致心力衰竭患者的 sST2 水平发现，sST2 是心力衰竭的影响因素〔*OR*=3.64，95%*CI*（1.37，9.67），*P*=0.009〕。在基于社区低风险人群中，sST2 水平可预测心力衰竭患者预后[12，26-27]。一项纳入 167 例心功能Ⅰ～Ⅲ级且左心室射血分数 <45%的慢性收缩性心力衰竭患者的研究结果显示，sST2 水平与心功能分级、慢性心力衰竭恶化住院、死亡等呈正相关[28]。一项分析 10 篇 sST2 对急性心力衰竭患者预测价值的研究共包括 4 835 例患者，随访中位时间为 13.5 个月，结果显示在入院时或出院时检测 sST2 水平可对心力衰竭加重、再次入院、死亡有一定预测价值[29]。一项有关 sST2 水平对心力衰竭患者预后影响的研究结果显示，sST2 预测心力衰竭患者发生心血管事件的曲线下面积为 0.750，NT-proBNP 为 0.790，两者间无统计学差异，说明 sST2 水平可有效预测心力衰竭患者心血管事件发生风险[30]，且 sST2 联合 NT-proBNP 检测可识别心血管事件高危人群[31-33]。

2　sST2 与冠心病

冠心病是冠状动脉粥样硬化导致器质性病变的最常见类型，也是严重危害人类健康的常见病。Th1 免疫应答与动脉粥样硬化有关，而 IL-33/ST2L 可通过诱导免疫应答的 Th1 转换为 Th2 而缓解动脉粥样硬化。在高脂饮食诱导载脂蛋白 E（ApoE）基因敲除小鼠动脉粥样硬化模型中发现，IL-33 可消融动脉粥样硬化斑块，抑制主动脉窦中巨噬细胞、T 细胞聚集，诱导血清及淋巴结中 Th2 细胞因子和低氧密度脂蛋白特异性抗体，且 sST2 水平与增大的动脉粥样硬化斑块和 Th1 反应增加有关[34]。PFETSCH 等[35]对 1 081 例冠心病患者随访 13 年发现，sST2 水平与炎性反应标志物〔超敏 C 反应蛋白（hs-CRP）、白介素（IL-6）〕呈正相关，提示 sST2 也参与了动脉粥样硬化过程。

在冠心病所有类型中急性冠脉综合征的危害最大，而 ST 抬高型心肌梗死（STEMI）是最危急的急性冠脉综合征。尽管近年来 STEMI 患者预后得到改善，但 STEMI 患者不良事件发生率仍居高不下[36]，因此早期预测 STEMI 不良事件发生风险具有重要意义[37-39]。一项纳入 1 258 例急性心肌梗死患者的研究显示，NT-proBNP、中段心房利尿钠肽前体（MR-proANP）、sST2、肌钙蛋白 T、髓过氧化物酶（MPO）、hs-CRP 和妊娠相关血浆蛋白是急性心肌梗死预后标志物，与 30 d 内心血管死亡或慢性心力衰竭发生风险有关[40]。有研究表明，sST2 与急性冠脉综合征的诊断及其预后有关[41-43]；且 sST2 水平反映受损组织情况，NT-proBNP 与心脏机械应激有关，提示 sST2 和 NT-proBNP 作用互补[37]。YU 等[44]通过 323 例接受直接经皮冠状动脉介入治疗（PCI）的 STEMI 患者与 sST2、NT-proBNP 相关性的研究显示，sST2 或 NT-proBNP 升高可独立预测患者 1 年内心脑血管不良事件发生风险，但其具体机制仍需大量研究证实。

3　sST2 与心房颤动

心房颤动是一种室上性快速性心律失常，其发病率随着我国老年人口数量增加而升高。心房颤动在临床上较常见，并与心力衰竭有关[45]。心房颤动患者并发症发生率较高，包括脑梗死、充血性心力衰竭、认知障碍和死亡等，故预测心房颤动发作具有重要的临床意义。但有研究显示，sST2 可能是心房颤动发生严重后果的标志物，但不能预测心房颤动的发生[46]。MA 等[47]通过检测 194 例心房颤动患者及 60 例健康人群的 sST2 水平发现，心房颤动患者 sST2 水平高于健康人群，持续性心房颤动患者 sST2 水平高于阵发性心房颤动，提示 sST2 可能是预测心房颤动预后和进展的生物标志物。

4　sST2 与主动脉瓣狭窄

由于人口老龄化进程加剧，主动脉瓣狭窄发病率呈上升趋势[48]。主动脉瓣狭窄使左心室后负荷增加，引起左心室壁厚度增加及 BNP 合成、释放[49-50]。有研究表明，非严重和严重主动脉瓣狭窄患者 NT-proBNP 水平均升高，且 NT-proBNP 水平与心功能分级呈正相关[51]。SAWADA 等[52]研究结果显示，主动脉瓣狭窄患者 sST2 较高提示 IL-33/ST2 通路可能参与主动脉瓣狭窄的病理生理过程。LANCELLOTTI 等[53]研究显示，sST2 与左心房大小、左心室肥厚、主动脉瓣狭窄严重程度及左心室收缩功能有关，并证实 sST2>23 ng/ml 可准确识别无症状主动脉瓣狭窄。一项纳入 345 例严重主动脉瓣狭窄患者的研究结果显示，sST2 对患者选择不同手术方法具有临床意义[54]。但 SOBCZAK 等[55]通过检测 69 例退行性主动脉瓣狭窄且射血分数保留患者的 NT-proBNP、sST2 水平发现，NT-proBNP 和 sST2 水平均不能区分主动脉瓣狭窄严重程度。提示 sST2 与主动脉狭窄的发生发展及治疗方法有关，但 sST2 在判断主动脉狭窄严重程度上仍需大量研究证实。

5　sST2 与心肌病

心肌病是一组异质性心肌疾病，由不同病因（遗传性病因较多见）引起的心肌病变导致心肌机械和/或心电功能障碍，常表现为心室肥厚或心室扩张，其中致心律失常性右心室心肌病（ARVC）患者的猝死率高，但对 ARVC 的诊断和预后评估指标较少[56]。有研究表明，sST2 水平可以反映左心功能及肺动脉高压患者右心功能[57-61]。BROCH 等[62]通过检测 44 例 ARVC 患者 sST2 水平发现，sST2 与 ARVC 患者右心功

能及心律失常有关，表明 sST2 可评估 ARVC 患者疾病严重程度。

6 小结

随着国内外学者对 sST2 的深入研究，sST2 不仅对心力衰竭诊断、治疗和预后评估价值较高，其在急性心肌梗死、心房颤动、主动脉瓣狭窄、心肌病中的诊断及预测价值比传统生物标志物更具有优势，但 sST2 与心血管组织的生物学效应及机制仍需进一步深入研究，尤其是与心肌细胞功能的关系。

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(收稿日期: 2019-01-04; 修回日期: 2019-04-19)
(本文编辑: 刘新蒙)