血液中有形成分在心房颤动血栓形成中的作用

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【摘要】 心房颤动（房颤）是较为常见的心律失常，以往研究多关注左心耳局部因素和血液中无形成分对房颤血栓形成的影响，但越来越多的研究发现，血液中各种有形成分，如血小板、单核细胞、巨噬细胞、淋巴细胞、红细胞、粒细胞、循环微粒等，对房颤血栓形成也起到重要的作用。

【关键词】 心房颤动；血栓形成；有形成分
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心房颤动（房颤）是较为常见的心律失常，在成年人中的发生率为 2%～4%[1]。房颤会造成血栓前状态及高凝状态，使患者有较高的血栓栓塞风险[2-4]。目前认为房颤血栓的形成主要与左心耳的血流淤滞、内皮损伤、血液中的无形成分（如凝血系统、纤溶系统、生长因子）变化等有关[5-6]。本文介绍血液中的各种有形成分，包括血小板、单核细胞、巨噬细胞、淋巴细胞、红细胞、粒细胞、循环微粒等对房颤血栓形成的作用。

1　血小板

血小板在血栓形成中发挥作用，但其在房颤血栓形成中的作用一直存在争议。1997 年，P 选择素和 CD63 被证实与非瓣膜性房颤患者的高凝状态和血栓形成有关[7]。2007 年 Choudhury 等[8]研究发现，房颤患者可溶性 P 选择素和血小板颗粒的水平较窦性心律的对照组明显升高，但与合并其他心血管疾病的患者相比无明显差异，表明血小板活化可能是由于合并的其他心血管疾病所致，而非房颤本身。Fu 等[9]研究发现孤立性房颤患者可溶性 P 选择素的水平较正常对照组明显升高。其他研究在严格排除可能影响血小板活化的疾病和因素后，也发现房颤患者血小板处于激活状态[10]。恢复窦性心律的孤立性房颤患者血小板活性降低，进一步证实房颤本身可以导致血小板活化，进而导致高凝状态和血栓形成。一项 meta 研究纳入了 59 篇相关文献共 5 412 例房颤患者，结果显示房颤组血小板活化相关物质如 P 选择素、β-血小板球蛋白、血小板因子 -4 的水平明显高于对照组[11]。

在对房颤患者平均血小板体积（MPV）的研究中发现，房颤患者恢复窦性心律时 MPV 较存在房颤心律时明显下降[12]。1 项对 352 例房颤患者的随访研究也发现，在 MPV 较大的房颤患者中左房血栓或脑卒中的发生比例较 MPV 较小的房颤患者更高，Cox 回归分析证实 MPV 是左房血栓形成的独立预测指标[13]。

目前房颤的抗血栓治疗以口服抗凝药为主，但口服抗凝药并不能减少血小板在房颤患者中的活化程度[14-15]。而抗血小板药物预防房颤血栓形成的效果不如抗凝药物[16]，间接否定了血小板在房颤血栓形成中的直接作用。

尽管目前没有明确证据显示血小板在房颤血栓形成中发挥直接作用，但是房颤会引起血小板活化，因此认为血小板可能间接地参与了房颤的血栓形成。

2　单核细胞

单核细胞的主要生理功能是介导固有免疫以及促进巨噬细胞和树突细胞发育，在血栓形成过程中也起到重要作用。单核细胞可以产生组织因子（TF），研究表明在活化的单核细胞中阻断 TF 信号通路可以减少血栓形成[17]。单核细胞 - 血小板计数（MPAs）是检测单核细胞和血小板激活情况的指标[18]。已有研究表明，MPAs 的升高与脑卒中不良预后有关[19]。Pfluecke 等[20]发现在房颤伴左房血栓患者中 MPAs 的数量增加，单核细胞表面的 CD11b 表达水平也显著高于房颤无左房血栓患者，且 MPAs 和 CD11b 与左心耳血流流速呈反比。以上研究结果提示房颤、血栓和单核细胞三者之间存在密切关系。

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3　巨噬细胞

研究证实巨噬细胞在房颤患者的心房中聚集[21]，通过引起心肌纤维化导致心房结构重构和电重构，促发和维持房颤[22]。在瓣膜性房颤患者中，M1 型巨噬细胞在房颤伴血栓患者中数量增加，而 M2 型巨噬细胞数量在正常对照组、房颤无血栓组、房颤有血栓组间无明显差别。利用原位末端转移酶标记技术（TUNEL）分析发现，在有血栓的房颤患者中，心房内皮细胞凋亡程度明显增加，巨噬细胞可能通过诱导内皮细胞凋亡，促使房颤血栓形成[21]。

4　淋巴细胞

研究发现 T 细胞与房颤的发生有关[23-24]。而 B 细胞可通过产生自身抗体介导心血管疾病如房颤的发生[25-26]。

目前尚无证据表明淋巴细胞在房颤血栓形成中的直接作用，但中性粒细胞 / 淋巴细胞比值（NLR）在许多疾病如血栓栓塞性卒中、急性冠脉综合征、主动脉狭窄中明显升高。Yalcin 等[27] 报道 NLR 与房颤左房血栓的形成有关。Kaya 等[28] 报道在二尖瓣狭窄患者中，NLR 与心房内自发性云雾状回声有关。一项队列研究也发现，在房颤合并脑卒中的患者中，NLR 比值显著增加，多元 Cox 比例回归模型证实 NLR 是房颤合并脑卒中的独立预测指标[29]。

5　红细胞

红细胞在房颤血栓形成中的研究多集中于红细胞分布宽度（RDW），该指标反映了红细胞形态大小和体积的异质性。一项纳入 117 例非瓣膜性房颤患者的研究证实，房颤组 RDW 水平明显增加，线性回归分析证实，RDW 是非瓣膜性房颤的独立预测指标[30]。另一研究发现 RDW 水平在房颤伴左房血栓患者中明显增加[31]。高 RDW 与卒中风险有直接关系，在无贫血的房颤患者中，RDW 增大的患者 CHA_2DS_2-VASc 评分也较高，说明 RDW 水平与房颤血栓事件存在一定关系[32]。

6　中性粒细胞

1993 年，Masawa 等[33] 在显微镜下观察到房颤患者的心内膜存在附壁血栓和水肿，并有中性粒细胞浸润。多形核中性粒细胞浸润心内膜后可以释放不同的细胞因子如白细胞介素 -6、肿瘤坏死因子、基质金属蛋白酶 -2、髓过氧化物酶、活性氧等，这些物质在心房重构中发挥重要作用[34-35]，而心房重构与房颤血栓形成相关，推测中性粒细胞可能在房颤血栓形成中起到一定的作用。

7　循环微粒

循环微粒（cMP）是从激活或凋亡细胞的细胞膜上脱落的囊泡，直径多在 100～1 000 nm 之间。cMP 被认为在凝血和血栓形成中发挥重要作用[36-37]。2006 年就有研究发现内皮细胞来源的微粒（EMP）对急性缺血性脑卒中的作用和影响[38]。研究证实有促凝作用的 cMP 在房颤患者中表达增加[39-40]。房颤本身可以导致左房血流淤滞、血流动力学紊乱、氧化应激、缺氧等病理生理反应，引起内皮细胞损伤和相关细胞活化，促进 cMP 释放，这提示 cMP 水平的升高可能会增加左房血栓和血栓栓塞的发生风险[41]。

近期的临床研究进一步证实 cMP 在房颤高凝状态中发挥重要作用[42]，尤其是磷脂酰丝氨酸（PS）阳性的 cMP，其在房颤伴左房血栓患者中的水平明显高于无血栓的房颤患者，PS 阳性的 cMP 会明显缩短房颤患者的凝血时间，促进凝血因子Ⅹ、凝血酶和纤维蛋白的生成[39]。

总之，既往研究提示血液中的无形成分对血栓形成起到了重要作用，近年来研究发现血液中相关有形成分对房颤患者的血栓形成也起到了一定作用。目前关于血液中有形成分对房颤血栓形成的研究较少，需更多更深入的研究以了解房颤血栓形成的机制，为临床预防房颤血栓形成提供可能的监测和干预手段。

参　考　文　献

[1] Benjamin EJ, Muntner P, Alonso AA, et al. Heart disease and stroke statistics—2019 update a report from the American Heart Association[J]. Circulation, 2019, 139(10):E56-E528.

[2] Wang CC, Lin CL, Gj W, et al. Atrial fibrillation associated with increased risk of venous thromboembolism. A population-based cohort study[J]. Thromb Haemost, 2015, 113(1):185-192.

[3] Sundbøll J, Hováth-Puhó E, Adelborg K, et al. Risk of arterial and venous thromboembolism in patients with atrial fibrillation or flutter: a nationwide population-based cohort study[J]. Int J Cardiol, 2017, 241:182-187.

[4] Enga KF, Rye-Holmboe I, Hald EM, et al. Atrial fibrillation and future risk of venous thromboembolism: the Tromsø study[J]. J Thromb Haemost, 2015, 13(1):10-16.

[5] Watson T, Shantsila E, Lip GY. Mechanisms of thrombogenesis in atrial fibrillation: Virchow's triad revisited[J]. Lancet, 2009, 373(9658):155-166.

[6] Khan AA, Lip GYH. The prothrombotic state in atrial fibrillation: pathophysiological and management implications[J]. Cardiovasc Res, 2019, 115(1):31-45.

[7] Pongratz G, Brandt-Pohlmann M, Henneke KH, et al. Platelet activation in embolic and preembolic status of patients with nonrheumatic atrial fibrillation[J]. Chest, 1997, 111(4):929-933.

[8] Choudhury A, Chung I, Blann AD, et al. Elevated platelet microparticle levels in nonvalvular atrial fibrillation: relationship to p-selectin and antithrombotic therapy[J]. Chest, 2007, 131(3):809-815.

[9] Fu R, Wu S, Wu P, et al. A study of blood soluble P-selectin, fibrinogen, and von Willebrand factor levels in idiopathic and lone atrial fibrillation[J]. Europace, 2011, 13(1):31-36.

[10] Makowski M, Smorąg I, Bissinger A, et al. Effect of sinus rhythm restoration on platelet function in patients with lone atrial fibrillation[J]. Int J Cardiol, 2014, 172(1):e22-e23.

[11] Wu N, Tong S, Xiang Y, et al. Association of hemostatic markers with atrial fibrillation: a meta-analysis and meta-regression[J]. PLoS One, 2015, 10(4):e0124716.

[12] Makowski M, Baj Z. Platelet reactivity and mean platelet volume as risk markers of thrombogenesis in atrial fibrillation[J]. Int J Cardiol, 2017, 244:204.

[13] Choi SW, Kim BB, Choi DH, et al. Stroke or left atrial thrombus prediction using antithrombin Ⅲ and mean platelet volume in patients with nonvalvular atrial fibrillation[J]. Clin Cardiol, 2017, 40(11):1013-1019.

[14] Martischnig AM, Mehilli J, Pollak J, et al. Impact of dabigatran versus phenprocoumon on ADP induced platelet aggregation in patients with atrial fibrillation with or without concomitant clopidogrel therapy (the Dabi-ADP-1 and Dabi-ADP-2 trials)[J]. Biomed Res Int, 2015, 2015:798486.

[15] Duzen IV, Oguz E, Cekici Y, et al. Effect of new oral anticoagulants on platelet indices in non-valvular atrial fibrillation patients[J]. Herz, 2021, 46(1):76-81.

[16] Voukalis C, Lip GYH, Shantsila E. Effects of antithrombotic drugs on the prothrombotic state in patients with atrial fibrillation: the west Birmingham atrial fibrillation project[J]. Thromb Res, 2021, 200:149-155.

[17] Peshkova AD, Le Minh G, Tutwiler V, et al. Activated monocytes enhance platelet-driven contraction of blood clots via tissue factor expression[J]. Sci Rep, 2017, 7(1):5149.

[18] Allen N, Barrett TJ, Guo Y, et al. Circulating monocyte-platelet aggregates are a robust marker of platelet activity in cardiovascular disease[J]. Atherosclerosis, 2019, 282:11-18.

[19] Lukasik M, Dworacki G, Kufel-Grabowska J, et al. Upregulation of CD40 ligand and enhanced monocyte-platelet aggregate formation are associated with worse clinical outcome after ischaemic stroke[J]. Thromb Haemost, 2012, 107(2):346-355.

[20] Pfluecke C, Tarnowski D, Plichta L, et al. Monocyte-platelet aggregates and CD11b expression as markers for thrombogenicity in atrial fibrillation[J]. Clin Res Cardiol, 2016, 105(4):314-322.

[21] He G, Tan W, Wang B, et al. Increased M1 macrophages infiltration is associated with thrombogenesis in rheumatic mitral stenosis patients with atrial fibrillation[J]. PLoS One, 2016, 11(3):e0149910.

[22] Liu Y, Shi Q, Ma Y, et al. The role of immune cells in atrial fibrillation[J]. J Mol Cell Cardiol, 2018, 123:198-208.

[23] Sulzgruber P, Thaler B, Koller L, et al. $CD4^{+}CD28^{null}$ T lymphocytes are associated with the development of atrial fibrillation after elective cardiac surgery[J]. Sci Rep, 2018, 8(1):9624.

[24] Kazem N, Sulzgruber P, Thaler B, et al. $CD8^{+}CD28^{null}$ T lymphocytes are associated with the development of atrial fibrillation after elective cardiac surgery[J]. Thromb Haemost, 2020, 120(8):1182-1187.

[25] Şimşek B, Altay S, Özbilgin N, et al. Autoimmune activation as a determinant of atrial fibrillation among Turks: a prospective evaluation[J]. Medicine (Baltimore), 2018, 97(31):e11779.

[26] Melduni RM, Cooper LT, Gersh BJ, et al. Association of autoimmune vasculitis and incident atrial fibrillation: a population-based case-control study[J]. J Am Heart Assoc, 2020, 9(18):e015977.

[27] Yalcin M, Aparci M, Uz O, et al. Neutrophil-lymphocyte ratio may predict left atrial thrombus in patients with nonvalvular atrial fibrillation[J]. Clin Appl Thromb Hemost, 2015, 21(2):166-171.

[28] Kaya MG, Akpek M, Elcik D, et al. Relation of left atrial spontaneous echocardiographic contrast in patients with mitral stenosis to inflammatory markers[J]. Am J Cardiol, 2012, 109(6):851-855.

[29] Saliba W, Barnett-Griness O, Elias M, et al. Neutrophil to lymphocyte ratio and risk of a first episode of stroke in patients with atrial fibrillation: a cohort study[J]. J Thromb Haemost, 2015, 13(11):1971-1979.

[30] Gungor B, Ozcan KS, Erdinler I, et al. Elevated levels of RDW is associated with non-valvular atrial fibrillation[J]. J Thromb Thrombolysis, 2014, 37(4):404-410.

[31] Zhao JP, Liu T, Korantzopoulos P, et al. Red blood cell distribution width and left atrial thrombus or spontaneous echo contrast in patients with non-valvular atrial fibrillation[J]. Int J Cardiol, 2015, 180:63-65.

[32] Kurt M, Tanboga IH, Buyukkaya E, et al. Relation of red cell distribution width with CHA_2DS_2-VASc score in patients with nonvalvular atrial fibrillation[J]. Clin Appl Thromb Hemost, 2014, 20(7):687-692.

[33] Masawa N, Yoshida Y, Yamada T, et al. Diagnosis of cardiac thrombosis in patients with atrial fibrillation in the absence of macroscopically visible thrombi[J]. Virchows Arch A Pathol Anat Histopathol, 1993, 422(1):67-71.

[34] Diao SL, Xu HP, Zhang B, et al. Associations of MMP-2, BAX, and Bcl-2 mRNA and protein expressions with development of atrial fibrillation[J]. Med Sci Monit, 2016, 22:1497-1507.

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outcomes[J]. Acta Radiol, 2021:284185120983977.
[10] Liu X, Mo X, Zhang H, et al. A 2-year investigation of the impact of the computed tomography-derived fractional flow reserve calculated using a deep learning algorithm on routine decision-making for coronary artery disease management[J]. Eur Radiol, 2021, 31(9):7039-7046.
[11] Tang CX, Guo BJ, Schoepf JU, et al. Feasibility and prognostic role of machine learning-based FFRCT in patients with stent implantation[J]. Eur Radiol, 2021, 31(9):6592-6604.
[12] Tesche C, Otani K, De Cecco CN, et al. Influence of coronary calcium on diagnostic performance of machine learning CT-FFR: results from MACHINE registry[J]. JACC Cardiovasc Imaging, 2020, 13(3):760-770.
[13] Han D, Lin A, Gransar H, et al. Influence of coronary artery calcium score on computed tomography-derived fractional flow reserve: a meta-analysis[J]. JACC Cardiovasc Imaging, 2021, 14(3):702-703.
[14] Modi BN, Sankaran S, Kim HJ, et al. Predicting the physiological effect of revascularization in serially diseased coronary arteries[J]. Circ Cardiovasc Interv, 2019, 12(2):e007577.
[15] Lee JM, Choi KH, Koo BK, et al. Prognostic implications of plaque characteristics and stenosis severity in patients with coronary artery disease[J]. J Am Coll Cardiol, 2019, 73(19):2413-2424.
[16] Kawasaki T, Kidoh M, Kido T, et al. Evaluation of significant coronary artery disease based on CT fractional flow reserve and plaque characteristics using random forest analysis in machine learning[J]. Acad Radiol, 2020, 27(12):1700-1708.
[17] Pontone G, Weir-McCall JR, Baggiano A, et al. Determinants of rejection rate for coronary CT angiography fractional flow reserve analysis[J]. Radiology, 2019, 292(3):597-605.
[18] Celeng C, Leiner T, Maurovich-Horvat P, et al. Anatomical and functional computed tomography for diagnosing hemodynamically significant coronary artery disease: a meta-analysis[J]. JACC Cardiovasc Imaging, 2019, 12(7 Pt 2): 1316-1325.
[19] Curzen N, Nicholas Z, Stuart B, et al. Fractional flow reserve derived from computed tomography coronary angiography in the assessment and management of stable chest pain: the FORECAST randomized trial[J]. Eur Heart J, 2021, 42(37):3844-3852.
[20] Moss AJ, Williams MC, Newby DE, et al. The updated NICE guidelines: cardiac CT as the first-line test for coronary artery disease[J]. Curr Cardiovasc Imaging Rep, 2017, 10(5):15.
[21] 中华医学会放射分学会质量控制与安全管理专业委员会，江苏省医学会放射分会智能影像与质量安全学组. 冠状动脉CT血流储备分数应用中国专家建议[J]. 中华放射学杂志, 2020, 54(10):925-933.
[22] Narula J, Chandrashekhar Y, Ahmadi A, et al. SCCT 2021 expert consensus document on coronary computed tomographic angiography: a report of the society of cardiovascular computed tomography[J]. J Cardiovasc Comput Tomogr, 2021, 15(3):192-217.
[23] Ihdayhid AR, Sakaguchi T, Kerrisk B, et al. Influence of operator expertise and coronary luminal segmentation technique on diagnostic performance, precision and reproducibility of reduced-order CT-derived fractional flow reserve technique[J]. J Cardiovasc Comput Tomogr, 2020, 14(4):356-362.

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[35] Wang P, Cheng M, Wang P, et al. SNP rs2243828 in MPO associated with myeloperoxidase level and atrial fibrillation risk in Chinese Han population[J]. J Cell Mol Med, 2020, 24(17):10263-10266.
[36] Ramacciotti E, Hawley AE, Farris DM, et al. Leukocyte-and platelet-derived microparticles correlate with thrombus weight and tissue factor activity in an experimental mouse model of venous thrombosis[J]. Thromb Haemost, 2009, 101(4):748-754.
[37] Mallat Z, Hugel B, Ohan J, et al. Shed membrane microparticles with procoagulant potential in human atherosclerotic plaques: a role for apoptosis in plaque thrombogenicity[J]. Circulation, 1999, 99(3):348-353.
[38] Simak J, Gelderman MP, Yu H, et al. Circulating endothelial microparticles in acute ischemic stroke: a link to severity, lesion volume and outcome[J]. J Thromb Haemost, 2006, 4(6):1296-1302.
[39] Wang L, Bi Y, Yu M, et al. Phosphatidylserine-exposing blood cells and microparticles induce procoagulant activity in non-valvular atrial fibrillation[J]. Int J Cardiol, 2018, 258:138-143.
[40] Siwaponanan P, Keawvichit R, Udompunturak S, et al. Altered profile of circulating microparticles in nonvalvular atrial fibrillation[J]. Clin Cardiol, 2019, 42(4):425-431.
[41] Liles J, Liles J, Wanderling C, et al. Increased level of thrombotic biomarkers in patients with atrial fibrillation despite traditional and new anticoagulant therapy[J]. Clin Appl Thromb Hemost, 2016, 22(8):743-748.
[42] Pourtau L, Sellal JM, Lacroix R, et al. Platelet function and microparticle levels in atrial fibrillation: changes during the acute episode[J]. Int J Cardiol, 2017, 243:216-222.

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