

心房颤动相关心肌纤维化生物学标志物研究进展

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摘 要

心房颤动是临床上最常见类型心律失常, 随着老龄化社会到来, 其发病率日益增加, 社会、经济负担随之加重。心房颤动导管消融治疗虽已取得巨大成功, 但术后复发率仍较高。目前认为心肌纤维化尤其是心房肌纤维化与心房颤动的发生及消融术后房颤的复发密切相关。心肌纤维化生物学标志物检测作为一种更为便捷、经济的评估心肌纤维化方法, 有望在心房颤动治疗方式选择、预后评估中发挥重要作用。

关键词

心房颤动, 心肌纤维化, 生物学标志物

Advances in the Biomarkers of Myocardial Fibrosis Related to Atrial Fibrillation

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Abstract

Atrial fibrillation is the most common type of arrhythmia in clinical practice. With the coming of the aging society, its incidence is increasing, and the social and economic burden is increasing. Although catheter ablation of atrial fibrillation has achieved great success, the postoperative recurrence rate is still high. Currently, it is believed that myocardial fibrosis, especially atrial fibrosis, is closely related to the occurrence of atrial fibrillation and the recurrence of atrial fibrillation after ablation. As a more convenient and economical method to evaluate myocardial fibrosis, biomark-

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er detection of myocardial fibrosis is expected to play an important role in the treatment choice and prognosis evaluation of atrial fibrillation.

Keywords

Atrial Fibrillation, Myocardial Fibrosis, Biomarkers

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1. 引言

心房颤动(房颤)是临床上最常见的心律失常,其患病率随着年龄的增加而增加[1]。不仅严重影响患者的生活质量,还伴随着不良心血管事件的发生,例如中风、心力衰竭、认知功能障碍极大地增加了医疗负担[2] [3]。导管消融作为一种有效的节律控制手段,能显著改善房颤患者的生活质量,因而被全球各大指南推荐作为一种重要的治疗手段[4] [5]。尽管导管消融术在房颤节律控制方面取得了较大的成功,但远期的复发率仍然较高[6]。虽然房颤潜在的病理生理机制已被广泛研究,但确切机制尚不明确,目前认为房颤与心肌纤维化关系密切[7] [8],特别是心房纤维化,目前已证实广泛的左心房纤维化易于导致房颤的发生、持续和复发[9] [10] [11] [12]。房颤发生及维持的机制可能包括异位触发活动、折返等,异位触发灶及折返环的形成与左心房的纤维化相关[13]。因此心房纤维化引起的房颤需引起我们的重视。目前,检测心房纤维化的手段有限,尚未找到一种简单、可行的方法识别心房纤维化。近年来生物学标志物的提出,为疾病的诊断、预后评估提供了巨大帮助。现将近年来关于房颤发生的相关机制,以及心肌纤维化生物学标志物的相关文章作一综述,有望通过本文,对房颤心肌纤维化生物学标志物做进一步的了解,为临床上房颤的早期诊断、治疗及预后判断提供帮助。

2. 心肌纤维化与心房颤动

心肌纤维化是由于细胞外基质(Extracellular matrix, ECM)蛋白的净积累而导致的心脏间质扩张,是大多数心脏疾病的常见病理生理变化[14]。纤维化的过程会导致心脏的心室和心房显著变化。心室纤维化主要引起泵血功能障碍,导致心力衰竭和室性心律失常的发生,而心房纤维化则可导致心房的传导异常,易于导致房颤的发生。在动物实验中,来自肺静脉内的兴奋灶能触发房颤[15]。此外,房颤的维持、发展与折返相关,而异位触发灶及折返的形成均与心房纤维化后心肌的各向异性传导相关[13]。

临床上,各类心血管疾病发展到终末阶段都可以引起心肌纤维化,包括心肌缺血、冠心病、高血压、各种心肌炎及心肌病。除了器质性心脏病,炎症、应激、年龄也与心肌纤维化的形成相关,炎症是导致房颤发生病理生理过程中的关键组成部分,炎症通路的放大可触发房颤,同时,房颤的发生将导致炎症反应加重[7] [16]。在这些共同作用下,使心肌细胞产生凋亡、坏死、能量代谢变化、氧化应激、成纤维细胞增殖和细胞外基质(ECM)激活[17],导致心房扩张及纤维化过程。

3. 房颤相关心肌纤维化相关生物学标志物

3.1. 胶原合成、降解相关标志物

心肌胶原分 5 种,心脏的细胞外基质(ECM)主要由 I、III 型胶原纤维组成,胶原代谢的循环生物学标

志物水平被认为是 I、III 型胶原合成的间接标志。目前循环中可测定的胶原肽段成分包括, I 型前胶原氨基端肽(PINP), I 型前胶原羧基端肽(PICP), I 型胶原羧基端肽(ICTP), III 型前胶原氨基端肽(PIIINP)等。Swartz 等[18]观察到心脏手术后房颤的发生与胶原前肽 PICP 和 PIIINP 的升高有关, 其中 PICP 与左心房纤维化的程度成线性相关。Sonmez 等[19]用左心房容积指数(LAVi)评估心房心肌纤维化程度, 发现非瓣膜性房颤组血清 PINP 水平显著高于窦性心律组, 且血清 PIIINP 水平与左房容积指数(LAVi)呈强正相关。Begg 等[20]发现房颤患者的循环 ICTP 水平高于匹配的非房颤对照组, 且 PIIINP 的水平与房颤持续时间相关, 但 ICTP、PIIINP 与左心房电压标测提示的纤维化程度无关, 不能预测导管消融术后房颤的复发[21]。Duprez 等[22]研究了没有明显心血管疾病患者的血浆基线 PIIINP 和 ICTP 水平, 并随访十年后与房颤发生的关系, 结果显示较高的 PIIINP 和 ICTP 水平与房颤的风险相关。最近的研究也表明 PINP 和 PIIINP 浓度的增加与左心房心肌纤维化的严重程度相关, 并可增加代谢综合征患者发生房颤的风险[23]。

能够降解胶原的基质金属蛋白酶(MMPs)及其抑制剂(TIMPs)可直接参与心肌纤维化的形成, 分为 TIMP-1、TIMP-2、TIMP-3、TIMP-4。Ravassa 等[24]发现 CCL+ (心肌 I 型胶原交联过量, 即 C1TP/MMP-1 比值降低)和 CD+ (心肌 I 型胶原沉积过多, 即 PICP 增加)的生物学标志物组合与较高的房颤患病率、发生率和消融后复发相关。同时, 也有研究显示较高的血浆 PICP/ICTP 和 MMP-2/TIMP-1 比值是肥厚性心脏病患者房颤的独立预测因子[25]。

3.2. 胶原代谢细胞因子

转化生长因子 β (TGF- β)是心脏成纤维细胞合成胶原的最重要的因子之一。TGF- β 的表达受到缺氧诱导因子(HIF-1 α)的调控, 该因子也参与了心房纤维化过程和房颤发展的发病机制。Su 等[26]显示 HIF-1 α 的表达与心肌纤维化程度呈正相关, 提示 HIF-1 α 可促进 TGF- β 的表达, 从而诱导心房纤维化。Xiao 等[27]得出心房组织中 TGF- β 1 的表达与房颤的纤维化程度呈正比, 并与房颤的类型有关。Tian 等[28]研究发现, TGF- β 1 是房颤复发的独立预测因子。

半乳糖凝集素 3 (gal-3)具有调节细胞增殖及凋亡, 并参与心肌纤维化、细胞外基质胶原蛋白的产生及心室重构。Ho JE 等[29]在分析中指出持续性房颤患者的 gal-3 明显高于阵发性房颤患者, 并且房颤射频消融术前 gal-3 浓度较高与术后房颤复发有关[30]。最近的研究也表明 gal-3 浓度的增加与左心房心肌纤维化的严重程度相关[23]。

此外, 成纤维细胞生长因子 23 (FGF-23)通过介导 STAT3 和 SMAD3 途径调节心房颤动中的心房纤维化[31]。Mizia-Stec K 等[32]研究中得出血清 FGF-23 浓度梯度是房颤复发的有效预测指标。

3.3. 胶原基因转录相关的 miRNA

miRNA 是负责基因表达调控的短的非编码 RNA 分子。许多分子和信号通路参与了心肌纤维化过程, 受到 miRNA 的调控[33]。一系列研究表明, 多种病理生理条件下心脏 miRNA 的表达异常会导致心房纤维化[34], 进而促进房颤的发生和发展。da Silva AMG 等[35]在新发房颤患者中观察到 miR-133b, miR-328 和 miR-499 的表达增加。Lu 等[36]发现小鼠心脏中 miR-328 超表达会导致心房纤维化和房颤的发生。另一方面, 一些 miRNA 可以通过负调控抑制心房纤维化过程。有研究发现术前较低的 miR-29 水平, 与心房纤维化程度相关[37]。QIAO 等[38]研究中观察到, 在人类和动物模型中, 在房颤过程中心房结构重构过程中, miR-132 表达降低, CTGF 蛋白表达水平升高。这些证据都表明 miRNA 参与心房重构的过程, 其表达水平与房颤发生相关, miRNA 的检测可能用于心房纤维化的评价。

3.4. 炎症因子

c 反应蛋白(CRP), 广泛用于预测心血管疾病风险的炎症标志物。一项研究炎症在房颤中的作用中指

出在非术后的房颤患者中 CRP 升高, 反映了房颤持续存在的炎症状态[39]。这一发现后来在一项更大的研究中得到证实, 对 5806 名受试者随访了 7 年, CRP 与房颤的存在相关, 也可以预测未来房颤的发展[40]。Marott 等[41]在 47,000 名受试者的大队列研究中观察到血浆 CRP 的升高与房颤风险的显著增加相关。另外, 一些研究报道了持续性房颤患者与阵发性房颤患者的 CRP 水平的差异。一项对 96 例新发房颤患者的研究得出结论, 阵发性房颤患者的 CRP 水平高于持续性房颤患者, 而有结构性心脏病史也与较高的 CRP 水平相关[42]。但一项包括房颤消融患者的研究得出结论, 只有在房颤发作时进行采血, 才观察到房颤与炎症独立相关, 而既往有房颤病史和 CRP 的水平无关[43]。另外一些研究还观察了循环炎症生物学标志物的水平是否可以预测消融术后房颤的复发。一项对 44 例接受初始肺静脉隔离的房颤患者的研究结果显示, 基质金属蛋白酶 2 (MMP-2) 和肿瘤坏死因子- α (TNF- α) 水平可能对预防房颤复发有一定的价值, 但并未发现 hsCRP 的具有预测房颤复发的作用[44]。但在另一项包括 202 名接受房颤导管消融的患者中, 经过 6 个月的随访证实消融前 hsCRP 水平与复发风险显著相关[45]。

TNF- α 是一种糖蛋白激素, 主要由单核细胞和巨噬细胞合成, 已在多种心血管疾病中进行了深入的研究。在一项风湿性心脏病引起的慢性房颤患者在内的研究中, 血浆和心房组织 TNF- α 水平均与左心房直径增加相关[46]。左心房心肌中蛋白浓度分析表明, 左心房心肌总胶原蛋白与 TNF- α 水平呈正相关[47]。提示 TNF- α 具有潜在的预测心肌纤维化及房颤导管消融术后复发的作用。

白细胞介素是参与炎症过程最重要的细胞因子, 包括白细胞介素 2 (IL-2)、白细胞介素 6 (IL-6)、白细胞介素 8 (IL-8) 等。许多研究已经探索了这些白细胞介素对房颤的影响[47] [48]。一项研究报道, 冠状动脉旁路移植术(CABG)后 IL-2 水平的升高与术后早期发生房颤的较高概率相关[49]。关于 IL-6 的研究更为广泛。在一项对 971 名参与者进行的大型研究中, IL-6 水平的升高与 AF 发病率的增加有关[50]。在发生房颤的冠脉搭桥(CABG)患者中也有心内 IL-6 水平升高的报道[51]。但 IL-8 在房颤中作用的存在争议。据报道, 永久性房颤患者的 IL-8 水平高于阵发性房颤患者[52]。然而, 在另的一项研究中显示, 房颤持续时间 < 6 个月的患者 IL-8 水平高于房颤持续 > 6 个月的患者[53]。

以上将目前房颤中较为热门的生物学标志物做详细阐述; 另外, 还有很多关于细胞因子、炎症因子与房颤的关系的研究仍有重大意义, 需更多的临床研究进一步证实。

4. 结语与展望

心肌纤维化的细胞和分子机制非常复杂, 涉及多种分子化合物, 各类细胞因子、炎症因子和氧化应激均可能促进成纤维细胞增殖、合成大量胶原, 导致纤维化的过程。生物学标志物的研究有望进一步扩大我们对房颤发病机制的知识, 并完善风险预测。

虽然目前房颤相关生物学标志物的研究仍待大量临床研究进一步证实, 但目前采集血浆标本均为外周静脉血液, 反应的是整体循环中的标志物水平。如能收集冠状静脉的血液, 乃至心房静脉的血液进行胶原代谢产物和纤维化生物标志物的检测, 则有可能更为准确和特异地评估房颤患者心房纤维化的程度。随着技术的进步及相关研究的完善, 相信在不久的将来生物学标志物可以在房颤患者的术前评估、术中指导消融、评价预后等方面发挥重要作用。

参考文献

- [1] Wang, L., Ze, F., Li, J., *et al.* (2021) Trends of Global Burden of Atrial Fibrillation/Flutter from Global Burden of Disease Study 2017. *Heart*, **107**, 881-887. <https://doi.org/10.1136/heartjnl-2020-317656>
- [2] Iwasaki, Y., Nishida, K., Kato, T., *et al.* (2011) Atrial Fibrillation Pathophysiology. *Circulation*, **124**, 2264-2274. <https://doi.org/10.1161/CIRCULATIONAHA.111.019893>
- [3] Schotten, U., Greiser, M., Benke, D., *et al.* (2002) Atrial Fibrillation-Induced Atrial Contractile Dysfunction: A Ta-

- chycardiomyopathy of a Different Sort. *Cardiovascular Research*, **53**, 192-201. [https://doi.org/10.1016/S0008-6363\(01\)00453-9](https://doi.org/10.1016/S0008-6363(01)00453-9)
- [4] Hindricks, G., Potpara, T., Dagres, N., *et al.* (2021) 2020 ESC Guidelines for the Diagnosis and Management of Atrial fibrillation Developed in Collaboration with the European Association for Cardio-Thoracic Surgery (EACTS). *European Heart Journal*, **42**, 373-498. <https://doi.org/10.1093/eurheartj/ehaa612>
 - [5] Calkins, H., Hindricks, G., Cappato, R., *et al.* (2017) 2017 HRS/EHRA/ECAS/APHRS/SOLAECE Expert Consensus Statement on Catheter and Surgical Ablation of Atrial Fibrillation. *Heart Rhythm*, **14**, e275-e444. <https://doi.org/10.1016/j.hrthm.2017.05.012>
 - [6] Hartono, B., Lo, L., Cheng, C., *et al.* (2012) A Novel Finding of the Atrial Substrate Properties and Long-Term Results of Catheter Ablation in Chronic Atrial Fibrillation Patients with Left Atrial Spontaneous Echo Contrast. *Journal of Cardiovascular Electrophysiology*, **23**, 239-246. <https://doi.org/10.1111/j.1540-8167.2011.02170.x>
 - [7] Sohns, C. and Marrouche, N.F. (2020) Atrial Fibrillation and Cardiac Fibrosis. *European Heart Journal*, **41**, 1123-1131. <https://doi.org/10.1093/eurheartj/ehz786>
 - [8] Ravassa, S., Ballesteros, G. and Díez, J. (2019) Aging and Atrial Fibrillation: A Matter of Fibrosis. *Aging (Albany NY)*, **11**, 9965-9966. <https://doi.org/10.18632/aging.102501>
 - [9] Dzeshka, M.S., Lip, G.Y., Snezhitskiy, V., *et al.* (2015) Cardiac Fibrosis in Patients with Atrial Fibrillation: Mechanisms and Clinical Implications. *Journal of the American College of Cardiology*, **66**, 943-959. <https://doi.org/10.1016/j.jacc.2015.06.1313>
 - [10] Marrouche, N.F., Wilber, D., Hindricks, G., *et al.* (2014) Association of Atrial Tissue Fibrosis Identified by Delayed Enhancement MRI and Atrial Fibrillation Catheter Ablation. *JAMA*, **311**, 498. <https://doi.org/10.1001/jama.2014.3>
 - [11] Ma, J., Chen, Q. and Ma, S. (2021) Left Atrial Fibrosis in Atrial Fibrillation: Mechanisms, Clinical Evaluation and Management. *Journal of Cellular and Molecular Medicine*, **25**, 2764-2775. <https://doi.org/10.1111/jcmm.16350>
 - [12] Velagapudi, P., Turagam, M.K., Leal, M.A., *et al.* (2013) Atrial Fibrosis: A Risk Stratifier for Atrial Fibrillation. *Expert Review of Cardiovascular Therapy*, **11**, 155-160. <https://doi.org/10.1586/erc.12.174>
 - [13] Kowalewski, C. (2021) Mapping Atrial Fibrillation. *Herz*, **46**, 305-311. <https://doi.org/10.1007/s00059-021-05045-y>
 - [14] Kong, P., Christia, P. and Frangogiannis, N.G. (2014) The Pathogenesis of Cardiac Fibrosis. *Cellular and Molecular Life Sciences*, **71**, 549-574. <https://doi.org/10.1007/s00018-013-1349-6>
 - [15] Chen, Y.J., Chen, S.A., Chen, Y.C., *et al.* (2001) Effects of Rapid Atrial Pacing on the Arrhythmogenic Activity of Single Cardiomyocytes from Pulmonary Veins: Implication in Initiation of Atrial Fibrillation. *Circulation*, **104**, 2849-2854. <https://doi.org/10.1161/hc4801.099736>
 - [16] Pauklin, P., Zilmer, M., Eha, J., *et al.* (2022) Markers of Inflammation, Oxidative Stress, and Fibrosis in Patients with Atrial Fibrillation. *Oxidative Medicine and Cellular Longevity*, **2022**, Article ID: 4556671. <https://doi.org/10.1155/2022/4556671>
 - [17] Schirone, L., Forte, M., Palmerio, S., *et al.* (2017) A Review of the Molecular Mechanisms Underlying the Development and Progression of Cardiac Remodeling. *Oxidative Medicine and Cellular Longevity*, **2017**, Article ID: 3920195. <https://doi.org/10.1155/2017/3920195>
 - [18] Swartz, M.F., Fink, G.W., Sarwar, M.F., *et al.* (2012) Elevated Pre-Operative Serum Peptides for Collagen I and III Synthesis Result in Post-Surgical Atrial Fibrillation. *Journal of the American College of Cardiology*, **60**, 1799-1806. <https://doi.org/10.1016/j.jacc.2012.06.048>
 - [19] Goktekin, O. (2014) Novel Fibro-Inflammation Markers in Assessing Left Atrial Remodeling in Non-Valvular Atrial Fibrillation. *Medical Science Monitor*, **20**, 463-470. <https://doi.org/10.12659/MSM.890635>
 - [20] Begg, G.A., Karim, R., Oesterlein, T., *et al.* (2017) Intra-Cardiac and Peripheral Levels of Biochemical Markers of Fibrosis in Patients Undergoing Catheter Ablation for Atrial Fibrillation. *EP Europace*, **19**, 1944-1950. <https://doi.org/10.1093/europace/euw315>
 - [21] Begg, G.A., Karim, R., Oesterlein, T., *et al.* (2018) Left Atrial Voltage, Circulating Biomarkers of Fibrosis, and Atrial Fibrillation Ablation. A Prospective Cohort Study. *PLOS ONE*, **13**, e189936. <https://doi.org/10.1371/journal.pone.0189936>
 - [22] Duprez, D.A., Heckbert, S.R., Alonso, A., *et al.* (2018) Collagen Biomarkers and Incidence of New Onset of Atrial Fibrillation in Subjects with No Overt Cardiovascular Disease at Baseline. *Circulation: Arrhythmia and Electrophysiology*, **11**, e006557. <https://doi.org/10.1161/CIRCEP.118.006557>
 - [23] Ionin, V.A., Baranova, E.I., Zaslavskaya, E.L., *et al.* (2020) Galectin-3, N-Terminal Propeptides of Type I and III Procollagen in Patients with Atrial Fibrillation and Metabolic Syndrome. *International Journal of Molecular Sciences*, **21**, 5689. <https://doi.org/10.3390/ijms21165689>
 - [24] Ravassa, S., Ballesteros, G., Lopez, B., *et al.* (2019) Combination of Circulating Type I Collagen-Related Biomarkers

- Is Associated with Atrial Fibrillation. *Journal of the American College of Cardiology*, **73**, 1398-1410. <https://doi.org/10.1016/j.jacc.2018.12.074>
- [25] Bi, X., Yang, C., Song, Y., *et al.* (2021) Matrix Metalloproteinases Increase Because of Hypoperfusion in Obstructive Hypertrophic Cardiomyopathy. *The Annals of Thoracic Surgery*, **111**, 915-922. <https://doi.org/10.1016/j.athoracsur.2020.05.156>
- [26] Su, F., Zhang, W., Chen, Y., *et al.* (2014) Significance of Hypoxia-Inducible Factor-1 α Expression with Atrial Fibrosis in Rats Induced with Isoproterenol. *Experimental and Therapeutic Medicine*, **8**, 1677-1682. <https://doi.org/10.3892/etm.2014.1989>
- [27] Xiao, H., Lei, H., Qin, S., *et al.* (2010) TGF- β 1 Expression and Atrial Myocardium Fibrosis Increase in Atrial Fibrillation Secondary to Rheumatic Heart Disease. *Clinical Cardiology*, **33**, 149-156. <https://doi.org/10.1002/clc.20713>
- [28] Tian, Y., Wang, Y., Chen, W., *et al.* (2017) Role of serum TGF- β 1 Level in Atrial Fibrosis and Outcome after Catheter Ablation for Paroxysmal Atrial Fibrillation. *Medicine*, **96**, e9210. <https://doi.org/10.1097/MD.00000000000009210>
- [29] Ho, J.E., Yin, X., Levy, D., *et al.* (2014) Galectin 3 and Incident Atrial Fibrillation in the Community. *American Heart Journal*, **167**, 729-734. <https://doi.org/10.1016/j.ahj.2014.02.009>
- [30] Gong, M., Cheung, A., Wang, Q.S., *et al.* (2020) Galectin-3 and Risk of Atrial Fibrillation: A Systematic Review and Meta-Analysis. *Journal of Clinical Laboratory Analysis*, **34**, e23104. <https://doi.org/10.1002/jcla.23104>
- [31] Dong, Q., Li, S., Wang, W., *et al.* (2019) FGF23 Regulates Atrial Fibrosis in Atrial Fibrillation by Mediating the STAT3 and SMAD3 Pathways. *Journal of Cellular Physiology*, **234**, 19502-19510. <https://doi.org/10.1002/jcp.28548>
- [32] Mizia-Stec, K., Wieczorek, J., Polak, M., *et al.* (2018) Lower Soluble Klotho and Higher Fibroblast Growth Factor 23 Serum Levels Are Associated with Episodes of Atrial Fibrillation. *Cytokine*, **111**, 106-111. <https://doi.org/10.1016/j.cyto.2018.08.005>
- [33] Chen, C., Ponnusamy, M., Liu, C., *et al.* (2017) MicroRNA as a Therapeutic Target in Cardiac Remodeling. *BioMed Research International*, **2017**, Article ID: 1278436. <https://doi.org/10.1155/2017/1278436>
- [34] Nattel, S. and Harada, M. (2014) Atrial Remodeling and Atrial Fibrillation: Recent Advances and Translational Perspectives. *Journal of the American College of Cardiology*, **63**, 2335-2345. <https://doi.org/10.1016/j.jacc.2014.02.555>
- [35] Da Silva, A.M.G., de Araújo, J.N.G., de Oliveira, K.M., *et al.* (2018) Circulating miRNAs in Acute New-Onset Atrial Fibrillation and Their Target mRNA Network. *Journal of Cardiovascular Electrophysiology*, **29**, 1159-1166. <https://doi.org/10.1111/jce.13612>
- [36] Lu, Y., Zhang, Y., Wang, N., *et al.* (2010) MicroRNA-328 Contributes to Adverse Electrical Remodeling in Atrial Fibrillation. *Circulation*, **122**, 2378-2387. <https://doi.org/10.1161/CIRCULATIONAHA.110.958967>
- [37] Rizvi, F., Mirza, M., Olet, S., *et al.* (2020) Noninvasive Biomarker-Based Risk Stratification for Development of New Onset Atrial Fibrillation after Coronary Artery Bypass Surgery. *International Journal of Cardiology*, **307**, 55-62. <https://doi.org/10.1016/j.ijcard.2019.12.067>
- [38] Qiao, G., Xia, D., Cheng, Z., *et al.* (2017) miR132 in Atrial Fibrillation Directly Targets Connective Tissue Growth Factor. *Molecular Medicine Reports*, **16**, 4143-4150. <https://doi.org/10.3892/mmr.2017.7045>
- [39] Chung, M.K., Martin, D.O., Sprecher, D., *et al.* (2001) C-Reactive Protein Elevation in Patients with Atrial Arrhythmias: Inflammatory Mechanisms and Persistence of Atrial Fibrillation. *Circulation*, **104**, 2886-2891. <https://doi.org/10.1161/hc4901.101760>
- [40] Aviles, R.J., Martin, D.O. and Apperson-Hansen, C. (2004) Inflammation as a Risk Factor for Atrial Fibrillation. *ACC Current Journal Review*, **13**, 64. <https://doi.org/10.1016/j.accreview.2004.02.062>
- [41] Marott, S.C.W., Nordestgaard, B.G., Zacho, J., *et al.* (2010) Does Elevated C-Reactive Protein Increase Atrial Fibrillation Risk? *Journal of the American College of Cardiology*, **56**, 789-795. <https://doi.org/10.1016/j.jacc.2010.02.066>
- [42] Pellegrino, P.L., Brunetti, N., De Gennaro, L., *et al.* (2013) Inflammatory Activation in an Unselected Population of Subjects with Atrial Fibrillation: Links with Structural Heart Disease, Atrial Remodeling and Recent Onset. *Internal and Emergency Medicine*, **8**, 123-128. <https://doi.org/10.1007/s11739-011-0557-z>
- [43] Marcus, G.M., Smith, L.M., Ordovas, K., *et al.* (2010) Intracardiac and Extracardiac Markers of Inflammation during Atrial Fibrillation. *Heart Rhythm*, **7**, 149-154. <https://doi.org/10.1016/j.hrthm.2009.10.004>
- [44] Kimura, T., Takatsuki, S., Inagawa, K., *et al.* (2014) Serum Inflammation Markers Predicting Successful Initial Catheter Ablation for Atrial Fibrillation. *Heart, Lung and Circulation*, **23**, 636-643. <https://doi.org/10.1016/j.hlc.2014.02.003>
- [45] Carballo, D., Noble, S., Carballo, S., *et al.* (2018) Biomarkers and Arrhythmia Recurrence Following Radiofrequency Ablation of Atrial Fibrillation. *Journal of International Medical Research*, **46**, 5183-5194. <https://doi.org/10.1177/0300060518793807>
- [46] Ren, M., Li, X., Hao, L., *et al.* (2015) Role of Tumor Necrosis Factor Alpha in the Pathogenesis of Atrial Fibrillation: A Novel Potential Therapeutic Target? *Annals of Medicine*, **47**, 316-324.

- <https://doi.org/10.3109/07853890.2015.1042030>
- [47] Abe, I., Teshima, Y., Kondo, H., *et al.* (2018) Association of Fibrotic Remodeling and Cytokines/Chemokines Content in Epicardial Adipose Tissue with Atrial Myocardial Fibrosis in Patients with Atrial Fibrillation. *Heart Rhythm*, **15**, 1717-1727. <https://doi.org/10.1016/j.hrthm.2018.06.025>
- [48] Zhou, P., Waresi, M., Zhao, Y., *et al.* (2020) Increased Serum Interleukin-6 Level as a Predictive Biomarker for Atrial Fibrillation: A Systematic Review and Meta-Analysis. *Revista Portuguesa de Cardiologia (English Edition)*, **39**, 723-728. <https://doi.org/10.1016/j.repc.2020.07.009>
- [49] Hak, A., Myśliwska, J., Wickiewicz, J., *et al.* (2009) Interleukin-2 as a Predictor of Early Postoperative Atrial Fibrillation after Cardiopulmonary Bypass Graft (CABG). *Journal of Interferon & Cytokine Research*, **29**, 327-332. <https://doi.org/10.1089/jir.2008.0082.2906>
- [50] Marcus, G.M., Whooley, M.A., Glidden, D.V., *et al.* (2008) Interleukin-6 and Atrial Fibrillation in Patients with Coronary Artery Disease: Data from the Heart and Soul Study. *American Heart Journal*, **155**, 303-309. <https://doi.org/10.1016/j.ahj.2007.09.006>
- [51] Kaireviciute, D., Blann, A.D., Balakrishnan, B., *et al.* (2010) Characterisation and Validity of Inflammatory Biomarkers in the Prediction of Post-Operative Atrial Fibrillation in Coronary Artery Disease Patients. *Thrombosis and Haemostasis*, **104**, 122-127. <https://doi.org/10.1160/TH09-12-0837>
- [52] Liuba, I., Ahlmroth, H., Jonasson, L., *et al.* (2008) Source of Inflammatory Markers in Patients with Atrial Fibrillation. *Europace*, **10**, 848-853. <https://doi.org/10.1093/europace/eun111>
- [53] De Gennaro, L., Brunetti, N.D., Montrone, D., *et al.* (2012) Inflammatory Activation and Carbohydrate Antigen-125 Levels in Subjects with Atrial Fibrillation. *European Journal of Clinical Investigation*, **42**, 371-375. <https://doi.org/10.1111/j.1365-2362.2011.02592.x>