

Role of Inflammation and Epicardial Adipose Tissue in Atrial Fibrillation

Runxia Xu¹, Hua Xiao^{1*}

¹ The First Affiliated Hospital of Chongqing Medical University, Chongqing, China

Email Address

xiaohua197408@163.com (Hua Xiao)

*Correspondence: xiaohua197408@163.com

Received: 24 January 2024; **Accepted:** 14 February 2024; **Published:** 20 February 2024

Abstract:

Atrial fibrillation(AF) is the most prevalent arrhythmia in clinical practice. The associated comorbidities and complications of AF severely impact a patient's standard of living, increasing the burden of health care system. Inflammation is closely related to cardiovascular disease, and plays a crucial role in the development of AF. Furthermore, obesity increases the risk of AF. Epicardial adipose tissue(EAT) is thought to be a separate risk factor for AF. Inflammatory factors derived from EAT may lead to both structural and electrical remodeling of the atria, contributing to the development and progression of AF. Inflammation and EAT are progressively emerging as potential therapeutic targets for AF. This study mostly addresses EAT and inflammation's roles in AF.

Keywords:

Atrial Fibrillation, Inflammation, Inflammatory Factors, Epicardial Adipose Tissue

1. Introduction

One of the most prevalent clinical arrhythmias, atrial fibrillation (AF), is more common in older adults. It is estimated that 3.1 million women and 5.2 million men over 60 in China will have AF by the year 2050, which is expected to be approximately 2.3 times greater than the predicted prevalence for the US [1]. The comorbidities and complications associated with AF, such as heart failure, myocardial infarction, stroke and thromboembolism significantly reduce patients' quality of life, increase mortality rates, and impose a heavy burden on the healthcare system. At present, the treatment for AF includes restoring sinus rhythm, controlling ventricular rate, and anticoagulation. Restoring sinus rhythm involves antiarrhythmic drugs, electrical cardioversion, and catheter ablation. The treatment including rhythm and rate control can alleviate AF-related symptoms, while anticoagulation treatment can prevent adverse events such as stroke [2]. Despite significant progress in the treatment of AF, current limitations persist. A deeper comprehension of the processes of AF pathophysiology is needed to identify new treatment targets and develop novel therapeutic approaches.

The development of AF involves a complex pathogenesis, with inflammation playing a pivotal role in its progression. As we know, pre-existing inflammation may

promote AF. Furthermore, AF can induce inflammation, creating a cycle that perpetuates the arrhythmia, known as the 'AF begets AF' phenomenon [3]. It is believed that obesity is a long-term, low-grade inflammatory condition. Substantial evidence exists linking obesity to a heightened risk of AF. Compared to subcutaneous adipose tissue, visceral adipose tissue is thought to have a more significant function in the pathophysiology of AF [4]. Epicardial adipose tissue (EAT) is located between epicardium and visceral pericardium. It is closely adjacent to myocardium and shares the same microcirculation, which is closely related to cardiovascular disease. In recent years, There is mounting evidence linking EAT to the incidence, severity, and unfavorable consequences following AF ablation [5,6]. Inflammatory factors derived from epicardial adipose tissue may play a role in the occurrence and maintenance of AF through related molecular mechanisms. Inflammation and EAT may also be potential therapeutic targets for AF. This article summarizes the development of EAT and inflammatory research in AF.

2. Inflammation and AF

2.1. Inflammation Promotes AF

Research on atrial tissue biopsies of patients with lone AF has discovered lymphomononuclear infiltrates with necrosis of the surrounding myocytes [7]. The count of inflammatory CD3-positive T cells demonstrated a significant increase from patients with sinus rhythm to those with paroxysmal AF and persistent AF, respectively [8].

Many inflammatory cytokines, including interleukin(IL)-6, IL-8, IL-10, tumor necrosis factor (TNF)- α and C-reactive protein (CRP), are known to be biomarkers that can predict the occurrence and prognosis of AF. CRP is a non-specific inflammatory marker primarily produced by liver cells. An connection has been found in a Mendelian randomization study between increased CRP levels and incident AF [9]. Additionally, Yang et al. [10] discovered that, after fully adjusting for covariates, there was an evident linear positive correlation between CRP levels and the risk of various arrhythmias, including AF. TNF- α is a multifunctional pro-inflammatory molecule synthesized by monocytes and macrophages. In a case-control study, TNF- α levels were found to progressively increase in sinus rhythm, paroxysmal AF, and persistent AF [11]. IL-6 is synthesized by macrophages, T lymphocytes, and endothelial cells. It has the ability to stimulate the synthesis of CRP and mediate inflammatory responses. A meta-analysis report suggests a notable link between increased levels of CRP, TNF- α , IL-6, and the risk of AF. Increased levels of IL-6 and CRP are also linked with the development of new-onset AF after coronary artery bypass grafting and an increased risk of AF recurrence after ablation [12]. IL-8 is expressed by various cells and serves as a chemotactic factor for lymphocytes and neutrophils. Studies indicate increased levels of IL-8 in the serum of patients with various heart diseases. The serum levels of IL-8 in patients who experience AF following coronary artery bypass grafting show a significant elevation at 2 hours, 1 day, and 2 days after the surgery [13]. Initially identified as a pleiotropic anti-inflammatory cytokine across the body, IL-10 now seems to play two roles in heart disease [14]. Kondo et al. [15] found that systemic IL-10 administration markedly slows the course of obesity-induced AF caused by a high-fat diet. In contrast, Bai et al. [16] discovered that the blood concentrations of IL-10 are linked with development from paroxysmal or chronic AF. The studies mentioned above suggest a strong

correlation between inflammation and the beginning and progression of AF. Pre-existing inflammation could aid in the creation of AF substrates, thereby elevating the risk of experiencing AF.

2.2. AF Promotes Inflammation

Inflammation promotes the onset and progression of AF, and AF further triggers an inflammatory response, leading to its sustained presence. Studies reveal that individuals experiencing recurrence of AF following cardioversion exhibit markedly elevated concentrations of high-sensitivity C-reactive protein (hs-CRP) in comparison to those who do not experience recurrence [17]. In contrast, patients who successfully maintain sinus rhythm after these procedures show a progressive reduction in circulating CRP levels [18]. In a canine model undergoing rapid atrial pacing, one week of such pacing leads to an elevation in serum CRP levels, a shorter atrial effective refractory period, and a higher risk of atrial fibrillation [19].

3. Epicardial Adipose Tissue(EAT)

3.1. Anatomy

EAT is situated between the myocardium and the visceral layer of the pericardium, without a fascial interval between the EAT and myocardium. It is mainly distributed on the surface of the right ventricle, anterior wall of the left ventricle, atrioventricular grooves, interventricular grooves, and alongside major branches of the coronary arteries, supplied by the coronary arterial network [20,21]. Paracardial adipose tissue is located outside the parietal layer of the pericardium and is supplied by branches of the internal mammary artery [22]. EAT and paracardial adipose tissue together form the collective term known as pericardial adipose tissue. Nevertheless, in certain literature, there might be confusion in terminologies between EAT and pericardial adipose tissue, emphasizing the significance of distinguishing between these concepts.

3.2. Physiology

In a state of health, EAT frequently serves various protective functions. EAT provides mechanical protection to the heart and coronary arteries. EAT is similar to brown adipose tissue, expressing elevated levels of uncoupling protein-1 (UCP-1) and exhibiting thermol functions. This characteristic provides protection to the myocardium and coronary arteries against cold-induced damage [23]. EAT which is next to the myocardium, releases free fatty acids that can rapidly provide energy to the myocardium. Furthermore, EAT has the ability to sequester circulating free fatty acids, thereby shielding the myocardium from lipotoxic damage [24]. EAT functions as an active endocrine organ capable of secreting various hormones and bioactive substances. It actively participates in the regulation of cardiovascular system function. Nevertheless, in aging and under pathological situations, EAT changes to a pro-inflammatory phenotype and releases a large amount of inflammatory mediators. This participation contributes to the initiation and development of cardiovascular diseases.

3.3. Assessment of EAT

Measurements of EAT can be conducted using echocardiography, CT, CMR and PET. Iacobellis et al. suggested employing transthoracic echocardiography to measure the echolucent gap between the outer wall of the myocardium and the visceral layer of the pericardium as a means to evaluate the thickness of EAT [25]. Transthoracic

echocardiography is cost-effective and straightforward for measuring EAT thickness but has limitations in volumetric quantification. It also has low spatial resolution and depends on the operator's technical proficiency. CT and CMR are capable of volumetric quantification of epicardial adipose tissue, providing high spatial resolution. CT can further evaluate the perivascular adipose tissue attenuation index. Moreover, the combination of PET with CT or MRI enables the evaluation of the metabolic activity of adipose tissue.

4. EAT and AF

There is increasing evidence that EAT and AF are strongly correlated. The Framingham Heart Study, analyzing CT scans of 3217 participants, identified a correlation between EAT and AF. Even after controlling for AF risk variables, such as BMI, this association remained [26]. According to Wong et al. [6] pericardial fat volume was considerably higher in AF patients than in non-AF patients. It has been found that pericardial fat is an independent predictor of AF. Furthermore, the study revealed a correlation between pericardial fat and the severity of AF, as well as AF recurrence after ablation. Researchers have also explored the link between AF and the regional distribution of EAT. They observed a notable rise in EAT volume and thickness near the atria in atrial fibrillation patients, with no evident difference in EAT thickness around the ventricles between the AF and control groups [27]. EAT and postoperative AF are tightly related. In postoperative monitoring of patients undergoing elective cardiac surgery who have never had AF before, it was found that the thickness of EAT was greater in patients who experienced AF after the surgery than to those who did not [28].

The intricate interaction between EAT and the nearby atrial myocardium is responsible for the association between EAT and the onset, severity, and recurrence of AF [29]. EAT may contribute to the onset and progression of AF through various mechanisms. Inflammation has been suggested as the primary pathogenetic processes that links EAT to AF. Mazurek et al. [30] used 18-fluorodeoxyglucose (FDG)-positron emission tomography (PET)/ computerized tomography(CT) to investigate the inflammatory activity of EAT. it was found that AF patients show a notable rise in the uptake of 18F-FDG in EAT, indicating an elevation in inflammatory activity in EAT of AF patients. The IL-1 β mRNA expression in EAT is markedly heightened in individuals with AF, and IL-1 β derived from EAT is recognized as an separate risk factor for persistent AF [31]. Moreover, there is evidence indicating that the inflammatory status of EAT is linked to postoperative AF. In patients who develop AF after cardiac surgery, the inflammatory factors originating from EAT, such as IL-1 β , IL-6, and monocyte chemoattractant protein (MCP)-1, is markedly higher compared to patients without AF [28,32].

5. EAT and Inflammatory Role in AF

The inflammatory factors released by EAT have the potential to modify potassium, calcium currents, and gap junctions, thereby affecting atrial electrical remodeling and contributing to the development of arrhythmias. An essential component of the action potential is the transient outward potassium current (I_{to}), which serve as the major transmembrane current for phase 1 rapid repolarization of myocardial cells. TNF- α and IL-1 β can decrease I_{to}, prolonging the action potential duration and leading to electrical remodeling of myocardial cells [33,34]. Inflammatory factors can also regulate the intracellular calcium current in myocardial cells. IL-6 can directly

modulate L-type calcium channels, downregulate the activity and expression of Sarcoplasmic reticulum calcium ATPase 2 (SERCA2), potentially affecting action potentials and calcium-induced triggered activities [35]. TNF can induce abnormal calcium handling in pulmonary vein myocardial cells and lead to arrhythmias [36]. Duncan et al. [37] found that incubating myocardial cells with TNF- α and IL-1 β increases sarcoplasmic reticulum Ca²⁺ leakage, results in a decrease in calcium transient amplitude and contractile function. This may potentially increase susceptibility to arrhythmias. Gap junctions exist between most cells and mediate the exchange of ions, signaling molecules, and metabolites between adjacent cells. Gap junction channels are composed of connexin proteins (Cx), such as Cx43 [38]. In a canine sterile pericarditis model, abnormalities in atrial conduction and heightened vulnerability to AF are linked to decreased expression of Cx40 and Cx43 [39]. Specific inflammatory factors, including IL-6, IL-1 β , and TNF- α , have the potential to decrease the expression of connexin proteins, resulting in a deceleration of cardiac conduction velocity [24].

Myocardial fibrosis is a potential substrate for arrhythmias. There are a lot of inflammatory cytokines in the EAT secretome that can induce atrial fibrosis, mediate atrial remodeling, and are essential to the development of AF. Fibrosis refers to the excessive proliferation of fibroblasts under pathological conditions, leading to an increase in the amount of extracellular matrix (ECM) deposited in the interstitial tissue of heart. This process can reduce cardiac conduction velocity and contribute to arrhythmias [40]. The matrix metalloproteinase (MMP) family consists of various proteins that could be engaged in the remodeling of the ECM in the heart [24]. TNF can activate the Transforming Growth Factor-beta (TGF- β) signaling pathway and myofibroblasts, promoting the secretion of MMP-2 and MMP-9, thereby mediating atrial remodeling [41]. IL-6 is also involved in the progression of cardiac fibrosis. Animal experiments have shown that intravenous infusion of IL-6 in rats leads to a significant increase in collagen volume fraction. Additionally, IL-6 can induce the transformation of fibroblasts into myofibroblasts, promoting the expression of collagen [42].

6. Potential Therapeutic Targets

EAT and inflammation may be potential therapeutic targets for AF. Research suggests that lifestyle changes, including exercise and dietary control, as well as weight loss surgery, can reduce the volume of EAT [43, 44]. Furthermore, Jamaly et al. [45] found that severely obese patients experienced a significant reduction in the risk of AF after shedding pounds through bariatric surgery. The beneficial effects of weight loss surgery on the development of AF seem to be associated with attenuating various hemodynamic, metabolic, and inflammatory stimuli. However, further research is needed to confirm whether the reduction in AF risk is achieved through the reduction or modulation of EAT [4]. Anti-inflammatory treatment is also a potential therapeutic strategy for AF. In a rat model of sterile pericarditis, treatment with colchicine lessened neutrophil infiltration, expression of IL-6, and atrial fibrosis, leading to a decreased incidence and duration of AF [46]. In a randomized controlled trial, AF patients undergoing radiofrequency ablation who received colchicine treatment indicated a decrease in the early recurrence of AF. This could be linked to a notable reduction in inflammatory mediators such as CRP and IL-6 [47]. Corticosteroids have anti-inflammatory effects. Low-dose corticosteroid therapy has been demonstrated to lower the risk of postoperative AF in individuals undergoing heart surgery. This

approach also minimizes potential side effects such as gastrointestinal bleeding, infection, and hyperglycemia [48].

7. Conclusions

The onset and maintenance of AF are greatly impacted by inflammation, and EAT stands alone as a risk factor for AF. The various inflammatory factors originating from EAT result in structural and electrical modification of the atrium through different molecular mechanisms, ultimately causing the onset and progression of AF. Over the past few years, there is a increasing body of research on novel treatment strategies targeting EAT and inflammatory factors, including weight reduction and anti-inflammatory approaches. Interventions targeting EAT and anti-inflammatory treatments show promise in the treatment of AF, and further exploration of their complex mechanisms is warranted.

Conflicts of Interest

The authors declare that there is no conflict of interest regarding the publication of this article.

Funding

This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

References

- [1] Brundel, B.; Ai, X.; Hills, M.T., et al. "Atrial fibrillation". *Nat Rev Dis Primers*, 2022, 8(1), 21.
- [2] Hindricks, G.; Potpara, T.; Dagres, N., et al. 2020 ESC Guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS): The Task Force for the diagnosis and management of atrial fibrillation of the European Society of Cardiology (ESC) Developed with the special contribution of the European Heart Rhythm Association (EHRA) of the ESC. *Eur Heart J*, 2021, 42(5), 373-498.
- [3] Hu, Y.F.; Chen, Y.J.; Lin, Y.J., et al. Inflammation and the pathogenesis of atrial fibrillation. *Nat Rev Cardiol*, 2015, 12(4), 230-43.
- [4] Conte, M.; Petraglia, L.; Cabaro, S., et al. Epicardial Adipose Tissue and Cardiac Arrhythmias: Focus on Atrial Fibrillation. *Front Cardiovasc Med*, 2022, 9, 932262.
- [5] Huber, A.T.; Fankhauser, S.; Chollet, L., et al. The Relationship between Enhancing Left Atrial Adipose Tissue at CT and Recurrent Atrial Fibrillation. *Radiology*, 2022, 305(1), 56-65.
- [6] Wong, C.X.; Abed, H.S.; Molaei, P., et al. Pericardial Fat Is Associated With Atrial Fibrillation Severity and Ablation Outcome. *Journal of the American College of Cardiology*, 2011, 57(17), 1745-51.
- [7] Frustaci, A.; Chimenti, C.; Bellocci, F., et al. Histological substrate of atrial biopsies in patients with lone atrial fibrillation. *Circulation*, 1997, 96(4), 1180-4.

- [8] Hohmann, C.; Pfister, R.; Mollenhauer, M., et al. Inflammatory cell infiltration in left atrial appendageal tissues of patients with atrial fibrillation and sinus rhythm. *Sci Rep*, 2020, 10(1), 1685.
- [9] Li, X.; Peng, S.; Wu, X., et al. C-reactive protein and atrial fibrillation: Insights from epidemiological and Mendelian randomization studies. *Nutr Metab Cardiovasc Dis*, 2022, 32(6), 1519-27.
- [10] Yang, X.; Zhao, S.; Wang, S., et al. Systemic inflammation indicators and risk of incident arrhythmias in 478,524 individuals: evidence from the UK Biobank cohort. *BMC Med*, 2023, 21(1), 76.
- [11] Li, J.; Solus, J.; Chen, Q., et al. Role of inflammation and oxidative stress in atrial fibrillation. *Heart Rhythm*, 2010, 7(4), 438-44.
- [12] Wu, N.; Xu, B.; Xiang, Y., et al. Association of inflammatory factors with occurrence and recurrence of atrial fibrillation: a meta-analysis. *Int J Cardiol*, 2013, 169(1), 62-72.
- [13] Wu, Z.K.; Laurikka, J.; Vikman, S., et al. High postoperative interleukin-8 levels related to atrial fibrillation in patients undergoing coronary artery bypass surgery. *World J Surg*, 2008, 32(12), 2643-9.
- [14] Bartekova, M.; Radosinska, J.; Jelemensky, M., et al. Role of cytokines and inflammation in heart function during health and disease. *Heart Fail Rev*, 2018, 23(5), 733-58.
- [15] Kondo, H.; Abe, I.; Gotoh, K., et al. Interleukin 10 Treatment Ameliorates High-Fat Diet-Induced Inflammatory Atrial Remodeling and Fibrillation. *Circ Arrhythm Electrophysiol*, 2018, 11(5), e006040.
- [16] Bai, W.; Liu, Z.Q.; He, P.Y.; et al. The role of IL-6, IL-10, TNF- α and PD-1 expression on CD4 T cells in atrial fibrillation. *Heliyon*, 2023, 9(8), e18818.
- [17] Kallergis, E.M.; Manios, E.G.; Kanoupakis, E.M., et al. The role of the post-cardioversion time course of hs-CRP levels in clarifying the relationship between inflammation and persistence of atrial fibrillation. *Heart*, 2008, 94(2), 200-4.
- [18] Rotter, M.; Jais, P.; Vergnes, M.C., et al. Decline in C-reactive protein after successful ablation of long-lasting persistent atrial fibrillation. *J Am Coll Cardiol*, 2006, 47(6), 1231-3, .
- [19] Shiroshita-Takeshita, A.; Brundel, B.J.; Lavoie, J., et al. Prednisone prevents atrial fibrillation promotion by atrial tachycardia remodeling in dogs. *Cardiovasc* 2006, 69(4), 865-75.
- [20] Le Jemtel, T.H.; Samson, R.; Ayinapudi, K., et al. Epicardial Adipose Tissue and Cardiovascular Disease. *Curr Hypertens Rep*, 2019, 21(5), 36.
- [21] Ansaldo, A.M.; Montecucco, F.; Sahebkar, A., et al. Epicardial adipose tissue and cardiovascular diseases. *Int J Cardiol*, 2019, 278, 254-60.
- [22] Wong, C.X.; Ganesan, A.N.; Selvanayagam, J.B. Epicardial fat and atrial fibrillation: current evidence, potential mechanisms, clinical implications, and future directions. *Eur Heart J*, 2017, 38(17), 1294-302.
- [23] Piché, M.E.; Poirier, P. Obesity, ectopic fat and cardiac metabolism. *Expert Rev Endocrinol Metab*, 2018, 13(4), 213-21.

- [24]Ernault, A.C.; Meijborg, V.M.F.; Coronel, R. Modulation of Cardiac Arrhythmogenesis by Epicardial Adipose Tissue: JACC State-of-the-Art Review. *J Am Coll Cardiol*, 2021, 78(17), 1730-45.
- [25]Iacobellis, G.; Assael, F.; Ribaudo, M.C., et al. Epicardial fat from echocardiography: a new method for visceral adipose tissue prediction. *Obes Res*, 2003, 11(2), 304-10.
- [26]Thanassoulis, G.; Massaro, J.M.; O'Donnell, C.J., et al. Pericardial fat is associated with prevalent atrial fibrillation: the Framingham Heart Study. *Circ Arrhythm Electrophysiol*, 2010, 3(4), 345-50.
- [27]Shin, S.Y.; Yong, H.S.; Lim, H.E., et al. Total and interatrial epicardial adipose tissues are independently associated with left atrial remodeling in patients with atrial fibrillation. *J Cardiovasc Electrophysiol*, 2011, 22(6), 647-55.
- [28]Petraglia, L.; Conte, M.; Comentale, G., et al. Epicardial Adipose Tissue and Postoperative Atrial Fibrillation. *Front Cardiovasc Med*, 2022, 9, 810334.
- [29]Hatem, S.N.; Redheuil, A.; Gandjbakhch, E. Cardiac adipose tissue and atrial fibrillation: the perils of adiposity. *Cardiovasc Res*, 2016, 109(4), 502-9.
- [30]Mazurek, T.; Kiliszek, M.; Kobylecka, M., et al. Relation of proinflammatory activity of epicardial adipose tissue to the occurrence of atrial fibrillation. *Am J Cardiol*, 2014, 113(9), 1505-8.
- [31]Liu, Q.; Zhang, F.; Yang, M., et al. Increasing Level of Interleukin-1 β in Epicardial Adipose Tissue Is Associated with Persistent Atrial Fibrillation. *J Interferon Cytokine Res*, 2020, 40(1), 64-9.
- [32]Cabaro, S.; Conte, M.; Moschetta, D., et al. Epicardial Adipose Tissue-Derived IL-1 β Triggers Postoperative Atrial Fibrillation. *Front Cell Dev Biol*, 2022, 10, 893729.
- [33]Fernández-Velasco, M.; Ruiz-Hurtado, G.; Hurtado, O., et al. TNF-alpha downregulates transient outward potassium current in rat ventricular myocytes through iNOS overexpression and oxidant species generation. *Am J Physiol Heart Circ Physiol*, 2007, 293(1), H238-45.
- [34]Monnerat, G.; Alarcón, M.L.; Vasconcellos, L.R., et al. Macrophage-dependent IL-1 β production induces cardiac arrhythmias in diabetic mice. *Nat Commun*, 2016, 7, 13344.
- [35]Alí, A.; Boutjdir, M.; Aromolaran, A.S. Cardiolipotoxicity, Inflammation, and Arrhythmias: Role for Interleukin-6 Molecular Mechanisms. *Front Physiol*, 2018, 9, 1866.
- [36]Lee, S.H.; Chen, Y.C.; Chen, Y.J., et al. Tumor necrosis factor-alpha alters calcium handling and increases arrhythmogenesis of pulmonary vein cardiomyocytes. *Life Sci*, 2007, 80(19), 1806-15.
- [37]Duncan, D.J.; Yang, Z.; Hopkins, P.M., et al. TNF-alpha and IL-1beta increase Ca²⁺ leak from the sarcoplasmic reticulum and susceptibility to arrhythmia in rat ventricular myocytes. *Cell Calcium*, 2010, 47(4), 378-86.
- [38]Burke, S.; Nagajyothi, F.; Thi, M.M., et al. Adipocytes in both brown and white adipose tissue of adult mice are functionally connected via gap junctions: implications for Chagas disease. *Microbes Infect*, 2014, 16(11), 893-901.

- [39]Ryu, K.; Li, L.; Khrestian, C.M., et al. Effects of sterile pericarditis on connexins 40 and 43 in the atria: correlation with abnormal conduction and atrial arrhythmias. *Am J Physiol Heart Circ Physiol*, 2007, 293(2), H1231-41.
- [40]Sagris, M.; Vardas, E.P.; Theofilis, P., et al. Atrial Fibrillation: Pathogenesis, Predisposing Factors, and Genetics. *Int J Mol Sci*, 2021, 23(1), 6.
- [41]Liew, R.; Khairunnisa, K.; Gu, Y., et al. Role of tumor necrosis factor- α in the pathogenesis of atrial fibrosis and development of an arrhythmogenic substrate. *Circ J*, 2013, 77(5), 1171-9.
- [42]Meléndez, G.C.; McLarty, J.L.; Levick, S.P., et al. Interleukin 6 mediates myocardial fibrosis, concentric hypertrophy, and diastolic dysfunction in rats. *Hypertension*, 2010, 56(2), 225-31.
- [43]Christensen, R.H.; Wedell-Neergaard, A.S.; Lehrskov, L.L., et al. Effect of Aerobic and Resistance Exercise on Cardiac Adipose Tissues: Secondary Analyses From a Randomized Clinical Trial. *JAMA Cardiol*, 2019, 4(8), 778-87.
- [44]Willens, H.J.; Byers, P.; Chirinos, J.A., et al. Effects of weight loss after bariatric surgery on epicardial fat measured using echocardiography. *Am J Cardiol*, 2007, 99(9), 1242-5.
- [45]Jamaly, S.; Carlsson, L.; Peltonen, M., et al. Bariatric Surgery and the Risk of New-Onset Atrial Fibrillation in Swedish Obese Subjects. *J Am Coll Cardiol*, 2016, 68(23), 2497-504.
- [46]Wu, Q.; Liu, H.; Liao, J., et al. Colchicine prevents atrial fibrillation promotion by inhibiting IL-1 β -induced IL-6 release and atrial fibrosis in the rat sterile pericarditis model. *Biomed Pharmacother*, 2020, 129, 110384.
- [47]Deftereos, S.; Giannopoulos, G.; Kossyvakis, C., et al. Colchicine for prevention of early atrial fibrillation recurrence after pulmonary vein isolation: a randomized controlled study. *J Am Coll Cardiol*, 2012, 60(18), 1790-6.
- [48]Ho, K.M.; Tan, J.A. Benefits and risks of corticosteroid prophylaxis in adult cardiac surgery: a dose-response meta-analysis. *Circulation*, 2009, 119(14), 1853-66.



© 2024 by the author(s); licensee International Technology and Science Publications (ITS), this work for open access publication is under the Creative Commons Attribution International License (CC BY 4.0). (<http://creativecommons.org/licenses/by/4.0/>)