ISSN: 0250-6882

Volume 5

EMA
جمعية الإمارات الطبية
EMIRATES MEDICAL ASSOCIATION

NEW EMIRATES MEDICAL JOURNAL

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Emirates Med J 2024; 5: e02506882332720

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REVIEW ARTICLE

Exploring the Gut-Atrial Fibrillation Link: A Comprehensive Review

Mohammad Abdallah[1], Rima Othman[1], Gaelle Antar[2,#], Maya Atwi[2,#], Tony Butrus[2,#], Elias Hajjar[2,#], Osamah Jaafar[2,#], Marita Machrekeki[2,#], Eddy Mikhael[2,#], Tatiana Rbeiz[2,#], Jessica Swesa[2,#], Firas Alani[3] and Muriel Tahtouh Zaatar[2,*]

[1]*Faculty of Medicine, University of Balamand, Beirut, Lebanon*
[2]*Department of Biological and Physical Sciences, American University in Dubai, Dubai, United Arab Emirates*
[3]*Interventional Cardiology, American Hospital Dubai, Dubai, United Arab Emirates*

Abstract:

This literature review explores the correlation between atrial fibrillation (AF) and the gut microbiome by elucidating its significance in cardiovascular health. AF stands as a prevalent cardiac arrhythmia associated with increased morbidity and mortality rates worldwide. The gut microbiome, a complex ecosystem of microorganisms inhabiting the gastrointestinal tract, plays a crucial role in systemic health through its influence on immune modulation, metabolic processes, and host-microbe interactions. Emerging evidence suggests a potential link between AF and alterations in gut microbial composition, raising intriguing questions about underlying mechanisms and clinical implications.

Recent investigations have shed light on the potential interplay between AF and gut microbial composition. Alterations in gut microbiota diversity and abundance have been observed in AF patients compared to healthy controls, suggesting a possible link between gut dysbiosis and arrhythmia susceptibility. Mechanistic studies propose several pathways through which gut microbial metabolites and immune modulation may influence atrial electrophysiology and arrhythmogenesis.

The clinical implications of the AF-gut microbiome connection are profound. Microbiome-based biomarkers hold promise for risk stratification, enabling early identification of individuals at elevated risk of AF development or recurrence. Furthermore, interventions targeting the gut microbiome, such as probiotics, prebiotics, and dietary modifications, offer innovative therapeutic avenues for AF management, potentially augmenting traditional treatment modalities.

Despite significant progress, challenges such as methodological limitations and the need for further validation in diverse patient cohorts remain present. Longitudinal studies are warranted to elucidate the temporal relationship between gut microbiome alterations and AF onset or progression. Nevertheless, understanding the AF-gut microbiome connection provides a foundation for personalized medicine approaches, optimizing AF management and improving cardiovascular health outcomes.

Keywords: Gut-atrial, Fibrillation link, Gut microbiota, AF-gut microbiome, Gastrointestinal tract, Atrial fibrillation (AF).

Article History	Received: June 16, 2024	Revised: August 27, 2024	Accepted: August 30, 2024

1. INTRODUCTION

Atrial fibrillation (AF), characterized by irregular and rapid heartbeats, is one of the most prevalent cardiac arrhythmias worldwide [1, 2]. Its growing prevalence and associated health have spurred extensive research into understanding its multi-factorial etiology. While factors such as age, hypertension, and heart disease have long been recognized as contributors, recent studies have suggested a potential link between the gut microbiome and cardiac health [2, 3]. This emerging concept of the gut-heart axis involves the intricate relationship between the gut microbial community and various aspects of cardiovascular function, including atrial function.

Atrial fibrillation presents a significant global health burden, affecting millions of individuals and contributing to increased mortality and morbidity rates [1]. As traditional risk factors alone do not account for all instances of AF, researchers have turned their attention to the gut microbiome, a dynamic ecosystem residing within the gastrointestinal tract that is comprised of an array of microorganisms, including bacteria, viruses, and fungi [1]. The gut microbiome is known to play a vital role in metabolic processes, immune modulation, and inflammation regulation, all of which are factors implicated in cardiac health.

Emerging evidence suggests that the composition and diversity of gut microbiome might influence both local gut health and systematic conditions, including those affecting the cardiovascular system [4,3]. This has led to a growing curiosity about whether an altered gut microbiome composition could

* Address correspondence to this author at the Department of Biological and Physical Sciences, American University in Dubai, Dubai,United Arab Emirates; E-mail: mzaatar@aud.edu
#*These authors contributed equally to this work.*

contribute to the pathogenesis of atrial fibrillation or its exacerbation.

While research on the gut-heart axis is still in its infancy, preliminary studies have offered intriguing insights into the potential relationship between gut microbiota and cardiac arrhythmias [5]. However, a comprehensive understanding of the mechanisms underpinning this connection and the clinical implications it holds for individuals with atrial fibrillation remains unclear [5]. This literature review aims to explore the existing body of research on the correlation between atrial fibrillation and the gut microbiome, shedding light on the current state of knowledge, identifying knowledge gaps, pointing towards avenues for future investigations, and our endeavor to gain a deeper understanding of whether the gut-heart axis holds the potential to offer novel insights and therapeutic approaches for managing atrial fibrillation.

2. ATRIAL FIBRILLATION (AF)

2.1. Definition, Types, Prevalence, and Significance

Atrial fibrillation (AF) is a common cardiac arrhythmia characterized by irregular and rapid electrical activity in the atria. It can be classified into several types, including paroxysmal AF, persistent AF, and permanent AF [3, 4, 6]. Atrial fibrillation presents a significant global health burden due to the costs associated with hospitalizations, outpatient visits, and management of associated complications, affecting millions of individuals and contributing to increased mortality and morbidity rates [3, 4]. Its prevalence increases with age, particularly in individuals over 60 years old [4, 6]. AF significantly impacts cardiovascular health due to its association with an increased risk of stroke, heart failure, myocardial infarction, and mortality [5, 6].

2.2. Risk Factors and Pathophysiology of AF

Numerous risk factors contribute to the development of AF, including advancing age, hypertension, diabetes mellitus, obesity, coronary artery disease, valvular heart disease, and structural heart abnormalities [6 - 8]. Modifiable risk factors, such as alcohol consumption, smoking, and obstructive sleep apnea, also play significant roles in AF pathogenesis [9 - 11].

The pathophysiology of AF involves complex interactions between structural, electrical, and autonomic factors within the atria [6, 12]. Structural remodeling, characterized by atrial fibrosis, dilation, and hypertrophy, disrupts normal atrial architecture and creates a substrate for arrhythmia initiation and perpetuation [6, 12]. Electrical remodeling, including alterations in ion channel function and conduction properties, contributes to conduction abnormalities and reentrant circuits and further promotes atrial arrhythmogenesis [6, 12].

2.3. Impact of AF on Cardiovascular Health and Quality of Life

AF exerts significant effects on cardiovascular health, leading to adverse outcomes, compromising quality of life, and increasing the risk of thromboembolic events, particularly ischemic stroke [5, 7]. The irregular rhythm predisposes individuals to blood stasis within the atria, leading to thrombus formation and embolization [13].

Furthermore, AF contributes to hemodynamic instability, leading to symptoms such as palpitations, dyspnea, fatigue, and exercise intolerance [9]. It exacerbates underlying cardiovascular conditions, including heart failure and coronary artery disease, leading to worse outcomes and increasing mortality [5, 7]. Additionally, the unpredictable nature of AF episodes and the need for chronic management impose psychological distress and reduce patients' quality of life [9, 14].

In conclusion, understanding its risk factors, pathophysiology, and impact on cardiovascular health is essential for effective management and improving patient outcomes. Multidisciplinary approaches focusing on risk factor modification, rhythm and rate control, stroke prevention, and patient-centered care are crucial in optimizing AF management and enhancing patients' quality of life.

3. GUT MICROBIOME

3.1. Gut Microbiome Composition and Functions

Gut microbiota is composed of different types of organisms, such as bacteria, viruses, fungi, protozoans, and archaea. It is mostly comprised of bacteria, which have a significant influence on intestinal function. The human gut harbors around 100 trillion bacterial cells [8, 15, 16]. The major phyla found in the human gut are *Bacteroidetes*, which is associated with the breakdown of complex carbohydrates, and *Firmicutes*, which metabolizes dietary fibers [9, 17]. *Actinobacteria* and *Proteobacteria* are also present, but they are significantly fewer.

Every individual has a unique gut microbiome composition, like a fingerprint. Specifically, the gut microbiome is influenced by determinants and attributes such as gestation period, mode of birth delivery, feeding, enterotypes, body mass index (BMI), exercise, lifestyle, and dietary habits [18]. The gut microbiota is established at the time of birth and is greatly influenced as it progresses in response to diet, medication, and diseases. The type of nourishment given to a newborn determines its microbiome composition. *Actinobacteria* grow in abundance, while there is little growth or none at all of *Firmicutes* and *Proteobacteria* when a newborn is breastfed [10, 15, 17]. There is a predominance of *Firmicutes* and *Bacteroidetes* in vegetarians. Diets with high protein and fats are known to be associated with high levels of *Bacteroides*, *Bilophila*, and *Alistipes*, as well as low levels of *Firmicutes*. Age is also a significant factor that impacts microbiota composition [18]. Age is also a significant factor that impacts microbiota composition [10, 18]. The first year of life is an essential stage for the establishment of the gut microbiome. Increased microbial diversity is a result of exercise through internal and external mechanisms, including overall healthy living practices, lower levels of inflammation, lower disease incidence, and favorable biochemical parameters, such as blood sugar level and lipid profile [10, 18]. Increased microbial diversity is a result of exercise through internal and external mechanisms, including overall healthy living practices, training-related intrinsic adaptations, lower levels of inflammation, lower disease incidence, and favorable biochemical parameters, such as

blood sugar level and lipid profile. Athletes' gut microbiomes have shown higher quantities of *Firmicutes* and a lower amount of *Bacteroidetes* relative to the gut microbiota of non-athletes [18].

There are many roles played by the gut microbiome, which substantially affect food digestion, support of immunity, regulation of intestinal functions and neural signals, body detoxification, metabolism, and production of compounds that affect host physiology. When its composition is balanced, the gut microbiome interacts with its host in a symbiotic manner, effectively maintaining intestinal homeostasis [19]. The gut microbiome is important in carbohydrate metabolism, vitamin production (*e.g.*, B vitamins and vitamin K), and the breakdown of indigestible nutrients. The gut microbiome keeps the gut mucosal barrier intact, which helps to stop the passage of harmful materials to the bloodstream and contributes to the regulation of the immune system. It enables the immune system to differentiate between pathogens and beneficial microorganisms [16].

Furthermore, it serves as a protective barrier against pathogenic bacterial colonization through various mechanisms, such as competition for available substrates and nutrients, secretion of antibacterial peptides, and maintenance of the epithelial barrier integrity. Digestive bacteria assist in extracting, synthesizing, and absorbing nutrients and metabolites. The gut microbiota is also important for the fermentation of dietary fibers to produce SCFAs. The SCFAs acetic acid, butyric acid, and propionic acid are major products of bacterial fermentation of fibers in the colon. These SCFAs enter the body through the intestinal epithelium and interact with host cells, which affects immune responses and risk of disease. SCFAs are not only crucial energy sources for the gut microbiota, but they also have various regulatory functions in host physiology and immunology, and they are generally viewed as beneficial metabolites with anti-inflammatory effects [14, 20]. They also act as substrates for catabolism, which contributes to a healthy gut [16, 20].

3.2. Factors Influencing the Gut Microbiome, Such as Diet, Antibiotics, and Lifestyle

Personal lifestyle choices, including exercise and antibiotic use, are major factors that determine the balance of the gut microbiome [21, 22]. Studies have shown that exercise levels, especially in younger populations and athletes, can significantly affect gut microbiota composition [14, 23], highlighting the impact of controllable lifestyle factors on gut health [24, 25].

Diet is another factor that plays a crucial role in shaping the gut microbiota composition [24]. Studies using animal models have shown that high protein intake is linked to microbiota dysbiosis. Human athletes have been shown to exhibit dysbiosis following high-protein diets (above 1–1.2 g/kg body weight/day) [21, 26]. Dietary fiber is important for promoting diversity in gut microbiota but also helps increase the presence of *Bifidobacteria* and bacterial species that produce SCFAs [21]. The main sources of fiber are fruits and vegetables, which are also sources of polyphenols that regulate oxidative stress and prevent gut microbiota dysbiosis related to aging when metabolized in the gut by microbial species [21]. In addition, individuals who follow a plant-based diet, such as a vegan diet, tend to show higher populations of *Prevotella* species [24]. A high-fat diet has also been linked to reduced SCFA release in contrast with a low-fat diet [25].

Furthermore, a high-fat diet increases the release of bile acids (BAs), 5% to 10% of which are converted to secondary BAs by microbes in the colon, leading to colon carcinogenesis [25]. Vitamins are also able to affect the affluence and diversity of the gut microbiota [25]. Further, it has been revealed that dietary patterns may show more noticeable effects on gut microbiota compared to individual nutrients [25]. A Western diet, for example, is marked by heavy consumption of red meat, sugars, saturated fats, and processed food, as well as low fiber intake, which decreases species associated with anti-inflammatory environments [24]. The Mediterranean diet consists of a balanced number of proteins with high biological value and a high intake of complex carbohydrates, fibers, and polyphenols [21]. This diet increases the populations of *Oscillospira*, *Roseburia*, and *Parabacteroides distasonis*, which can inhibit colon tumor formation in mice and *Bacteroides*, thereby reducing the risk of illness [24]. In addition, increased levels of SCFAs are associated with the Mediterranean diet, which can increase levels of *Firmicutes* and *Bacteroidetes*. Therefore, the Mediterranean diet may be beneficial to a healthy gut microbiota [24].

Efficiency of sleep has been found to be an essential contributor to the composition and diversity of the gut microbiota regardless of age. In younger adults, better sleep quality was correlated with an increase in the *Firmicutes/Bacteroidetes* ratio [27]. Likewise, sleep efficiency was associated with an increase in both *Firmicutes* and *Bacteroidetes* phyla, as demonstrated by gene sequencing analysis in young adults [27]. However, the effect of sleep disruption on the composition of the gut microbiome, especially the ratio of beneficial *Firmicutes* over *Bacteroidetes* phyla, is still controversial and not clearly understood in young adults, warranting further research [27]. Further, a shorter duration of sleep in older adults has been shown to increase pro-inflammatory bacteria, while increasing sleep quality is positively correlated with increased populations of beneficial Verrucomicrobia and Lentisphaerae phyla [27].

Using mouse models, it has been found that using four commonly used antibiotics: ampicillin, vancomycin, metronidazole, and neomycin, and a combination of the four as a treatment can decrease the diversity of gut microbiota [27]. Combination treatment using the four antibiotics led to reduced populations of potentially beneficial bacteria, namely *Coprococcus* and *Lactobacillus*, as well as an increase in the populations of potentially pathogenic bacteria, namely *Enterococcus* [27]. In addition, oral antibiotics were found to cause long-term adverse effects on the gut microbiota while also promoting drug-resistant bacteria, such as *Bacteroides* and *Escherichia* [27].

Psychological factors, such as stress, may contribute to gut microbiota dysbiosis. The hypothalamic-pituitary-adrenal system plays an important role in the stress response, and its activation is triggered by stress. This axis regulates stress

hormones, such as cortisol, which may have an impact on the gut itself or the colonizing microbes within. In this regard, stress can lead to changes in gut motility and secretion that may, in turn, modify the environment surrounding gut bacteria. Changes in peristalsis and intestinal secretions may affect the distribution or number of certain bacteria [28]. Stress can also influence immune activity against bacteria within the gut, altering the normal patterns of immune response in general. Such a modulation may contribute to dysbiosis by disturbing the equilibrium between beneficial and harmful microorganisms. Research has revealed that chronic stress can lead to disruption of the normal function of the intestinal barrier [28]. Increased permeability of the intestinal membrane may lead to bacterial and microbial product translocation, thus affecting the composition of the gut microbiota and consequently resulting in dysbiosis. For example, stress can release neurotransmitters, such as norepinephrine and serotonin, which have implications for gut-brain communication. Directly, these neurotransmitters can affect the development and functioning of certain gut microorganisms [28]. The gut microbiota communicates with the CNS, which influences brain function [28]. Microbiota release neuroactive compounds, such as GABA, serotonin, dopamine, and acetylcholine, which act on the enteric nervous system [16, 29, 30]. Numerous neuroactive substances reach the brain through the blood and the circumventricular organs or through the vagus nerve [28].

3.3. Gut Microbiome Dysbiosis and Inflammation

3.3.1. Relationship Between Gut Microbiota and Systemic Inflammation

Microbes play a crucial role in human health by influencing nutrient metabolism, immune function, and drug metabolism. They possess a variety of enzymes that enable them to break down and utilize nutrients, including indigestible carbohydrates, which are then converted into absorbable forms, and beneficial short-chain fatty acids (SCFAs), which exert anti-inflammatory and immunomodulatory effects [31 - 33]. In addition to producing enzymes and metabolites, microbes release components, such as lipopolysaccharides, cell capsule carbohydrates, and other endotoxins, that can have secondary effects on the host. These effects include maintaining gut epithelium integrity, producing vitamins, and interacting with immune system signaling molecules and cells, both activating and inhibiting specific responses. Gut microorganisms also influence pharmacokinetics by carrying out drug metabolism and providing a natural defense against pathogenic species through competition and maintenance of the mucosa [31, 32]. The interplay between gut microbes and the immune system can lead to either anti-inflammatory or pro-inflammatory responses. Anti-inflammatory mechanisms involve the stimulation of regulatory cells of the immune system to suppress inflammation. Conversely, certain microbes can promote a “leaky gut,” allowing metabolites to enter the bloodstream and trigger an inflammatory response. This persistent inflammation may contribute to the development of chronic diseases such as inflammatory bowel disease, diabetes, or cardiovascular disease [31, 33].

Lipopolysaccharides (LPS), also known as endotoxins, are essential components of the cell walls of Gram-negative bacteria. Elevated levels of LPS have been linked to obesity and other metabolic disorders, as well as adipose tissue inflammation and pancreatic beta-cell dysfunction in gnotobiotic mice [34, 35]. Under normal circumstances, the gut barrier, composed of intestinal epithelial and mucosal layers, effectively restricts the movement of LPS from the intestines into the bloodstream. However, disruption of this barrier by factors, such as diet or pathogenic bacteria can lead to LPS translocation, allowing it to leak into the circulation [36, 32]. This increased gut permeability and LPS leakage can trigger local inflammation by attracting macrophages, which produce and activate inflammatory cytokines. Moreover, LPS can bind to toll-like receptor 4 (TLR-4) on immune cells, activating pro-inflammatory signaling pathways both locally in the intestine and at distant sites [36].

Investigations in both animals and humans have identified circulating levels of LPS as a critical link between the gut microbiota and inflammation in metabolic syndrome. Translocated LPS, originating from the gut, can trigger pro-inflammatory pathways by activating toll-like receptor 4 (TLR4) on adipocytes and upregulating NF-κB, ultimately contributing to insulin resistance [37, 38]. Individuals with type 2 diabetes (T2DM), obesity, and glucose intolerance exhibit elevated circulating LPS levels compared to those unaffected by these conditions [37, 38]. Moreover, increased serum LPS levels are associated with pro-inflammatory cytokines, such as tumor necrosis factor-α (TNF-α) and interleukin-6 (IL-6) [37]. These circulating pro-inflammatory cytokines can impede insulin signaling, further promoting insulin resistance. The ability of LPS to activate inflammatory cascades varies among microbial species because of structural differences in their LPS molecules. Notably, members of the Gram-negative phylum *Proteobacteria*, particularly the family *Enterobacteriaceae*, are known to possess highly immune-stimulatory LPS [37].

SCFAs play a crucial role in the complex interplay between diet, the gut microbiota, and inflammation. They also contribute to the regulation of energy homeostasis and appetite through their effects on metabolic pathways. The specific effects of SCFAs on inflammation vary depending on the type and concentration of SCFA, which may differ between obese and lean individuals [39]. Butyrate, a specific type of SCFA, has been extensively studied in animal models and has been shown to play a variety of roles in preventing metabolic disorders. Through epigenetic interactions, butyrate promotes lipolysis and mitochondrial functioning in adipocytes, leading to increased energy expenditure and potentially preventing or reversing obesity. Additionally, butyrate is a potent anti-inflammatory metabolite that inhibits the production of pro-inflammatory cytokines. The effects of SCFAs on energy metabolism, appetite regulation, and inflammatory processes make them promising targets for developing therapeutic strategies to combat obesity and other metabolic disorders [39].

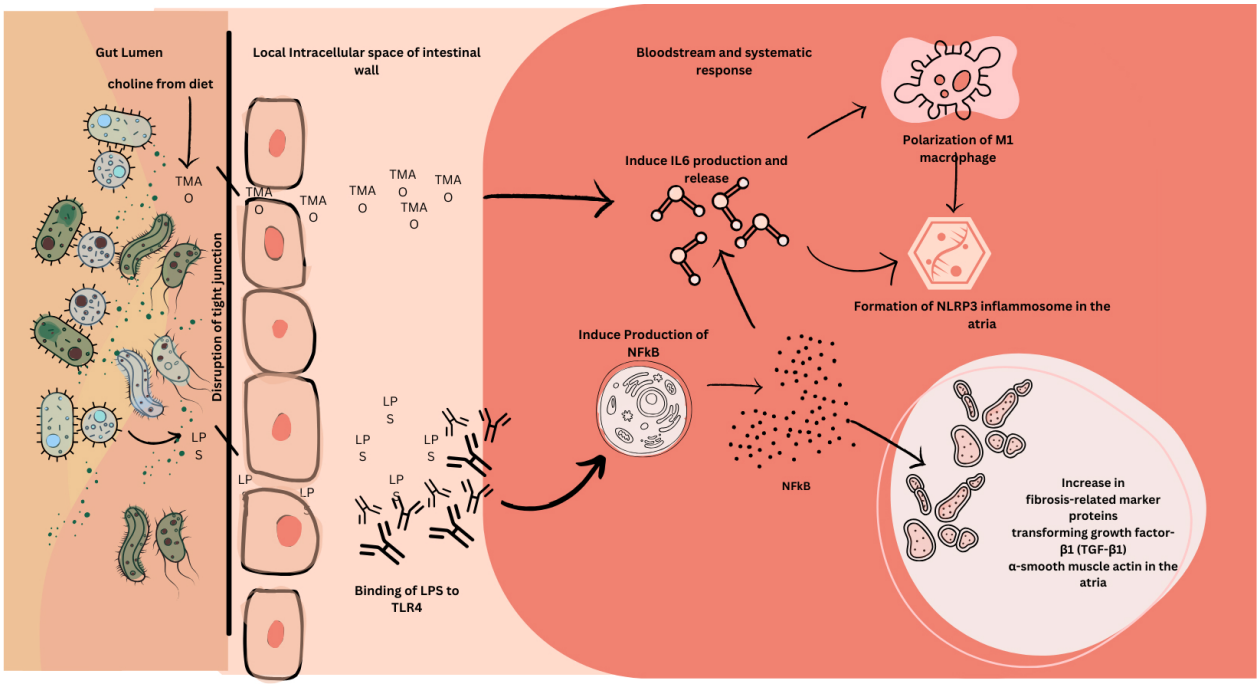

Fig. (1). Graphical abstract reviewing chain of events leading to pro-inflammatory cytokine release and subsequent changes in atria. Endo-luminal bacteria release LPS through an already existing disruption of endothelial tight junctions. LPS translocates into the intercellular space of the intestinal wall, which later binds to TLR4, leading to the production of NFkB. The latter induces the release of IL6 as well as other pro-inflammatory and prosclerotic factors in the atria. Endoluminal intestinal bacteria also break down Choline present in the diet into TMAO, which translocates through tight junction disruptions and leads directly to the release of IL6. IL6 subsequently induces M1 polarization and the formation of NLRP3 inflammasomes in the atrial cells leading to sclerosis.

3.3.2. Role of Inflammation in AF Development and Progression

It has been found in many studies that inflammation aids in the development and progression of atrial fibrillation (AF) [40, 41]. A study states, "Inflammation has been implicated in various AF-related pathological processes, including oxidative stress, fibrosis, and thrombogenesis" [40, 42]. Inflammation causes increased activity of platelets, which results in increased thrombogenesis and fibrosis. Others observed that an inflammatory marker, IL-6, induces the expression of tissue factor (TF), fibrinogen, and other factors that contribute to blood coagulation, fibrosis, and thrombogenesis [34] (Fig. **1**). These factors can mediate the narrowing and thickening of blood vessels, which can elevate blood pressure and decrease blood flow to organs. Increased blood pressure and thickening of the vessel walls contribute to multiple heart conditions, including AF. It was further proved that inflammation factors, such as IL-6 and tumor necrosis factor (TNF), cause the release of C-reactive protein (CRP) [41, 43]. CRP in high concentrations has been proven by many studies to cause AF [42, 43] (Fig. **1**). Collectively, these works have established the effect of inflammation on the development of AF.

3.3.3. Connecting Gut Microbiota Composition and Inflammatory Markers in AF Patients

Many studies have been conducted on inflammatory markers linking the health of the gut microbiota to the development of AF [29, 43, 44]. Others found that AF patients have less variability of gut microbiota than non-AF patients [45].These studies have previously shown that deficiency in the diversity of gut microbiota causes inflammation [45, 46]. Inflammation, in turn, can cause an imbalance in the composition of gut microbiota. It was concluded that intestinal dysbiosis is a significant factor affecting atrial fibrillation. They found that bacterial endotoxin (LPS), which is produced by Gram-negative bacteria, increases the secretion of pro-inflammatory cytokines [47, 48] (Fig. **1**). These points correlate to the findings of previous studies showing that an "imbalance in the gut flora… would promote increased LPS translocation from the intestinal lumen into host circulation (*via* transcellular and/or paracellular mechanisms)" [48,49]. This means that some bacterial components can cause inflammation. Therefore, differences in the gut microbiota can contribute to inflammation and, in turn, cause AF. It was further discussed that trimethylamine N-oxide (TMAO), a metabolite derived from gut microbiota, is linked to the pathogenesis of AF [44, 50]. TMAO was proven to increase the production of pro-inflammatory cytokines, including IL-6, adding to the body of evidence indicating a role of gut-flora-modulated inflammation in AF [49] (Fig. **1**).

3.4. AF and Gut Microbiome

3.4.1. Gut Microbiome Composition in AF Patients

In the past, the correlation between gut microbiota and AF was not thoroughly studied. However, with advancements in

technology, there has been a revolutionary shift in gut microbiome research. This has opened opportunities to explore how the gut microbiota influences the heart. One study of 34 hospitalized patients with AF and 66 control subjects with no AF history was conducted to show the differences between the gut microbiome of patients with AF and unaffected control patients [29, 45, 51]. Most confounding factors, such as age, sex, and comorbidity, were accounted for, while dietary habits were assessed using a self-administered diet history questionnaire. It was found that there were no differences in Gram-negative and Gram-positive ratios between the AF patients and control subjects, and the diversity of the gut microbiota was comparable between the two. However, the richness of the microbiota was lower in the AF patients than in the control subjects. Lower bacterial richness has been linked to insulin resistance, dyslipidemia, and inflammation, which are risk factors for AF [29, 45, 52].

On the contrary, other studies found that microbial richness and diversity were higher in AF patients compared to the control group [53]. These high indices indicate the growth of various types of harmful bacteria in AF patients. Moreover, *E. coli* was the most abundant species of harmful bacteria, which may be linked to the progression of AF [53]. Other differences that were observed included higher numbers of mainly *Streptococcus and Enterococcus* [53]. Another study found an abundant growth of *Ruminococcus*, *Streptococcus,* and *Enterococcus* and a reduction of *Faecalibacterium*, *Alistipes*, *Oscillibacter,* and *Bilophila* in patients with AF [50].

Differences in gut microbiota were also studied in patients who underwent coronary artery bypass surgery and later developed postoperative atrial fibrillation (POAF) [54]. This study selected 45 patients who developed POAF and 90 who did not develop POAF as control subjects. Diversity was shown to be higher in POAF patients than in the control group. The microbiota was comprised of 3578 operational taxonomic units (OTUs) that were unique to the POAF group and 7191 OTUs that were specific to the control group [54]. These collective results show that there are some differences between the gut microbiome of patients with AF compared to non-AF patients. In addition, POAF patients had the highest abundance of *Lachnospira*, while the abundance of *Escherichia, Shigella,* and *Streptococcus* was significantly lower. *Lachnospira* has been shown to have a negative correlation with vitamin D [55], a deficiency that may promote the initiation and development of AF [54].

Patients with AF exhibit overgrowth of*Streptococcus* and *Enterococcus*, along with a decrease in *Faecalibacterium,* among others [50]. According to comparable studies, there were variations in the enrichment of specific bacteria at different durations of AF, including a decrease in the abundance of *Butyricicoccus* and *Paraprevotella*, and an increase in the abundance of *Blautia*, *Dorea*, and *Coprococcus* among patients with persistent AF [50]. Additionally, *Lachnoclostridium*, *Parabacteroides*, and *Dorea*, which were present at elevated levels in patients with AF, are known to produce significant amounts of TMAO in the human gut. Conversely, *Enterobacter*, which was found to be reduced in AF patients, has the capability to consume TMAO [3, 35]. Differences in specific bacterial taxa between AF and non-AF patients are highlighted in Table **1**. Changes in the composition of these gut microbiota may influence the production of gut microbial metabolites, potentially impacting the development of AF [56].

Table 1. Gut composition comparison between AF and non-AF patients.

Gut Composition	AF Patients	Control Group
Streptococcus	High	Low
Enterococcus	High	Low
Blautia	High	Low
Dorea	High	Low
Veillonella	High	Low
Coprobacillus	High	Low
Ruminococcus	High	Low
Faecalibacterium	Low	High
Alistipes	Low	High
Oscillibacter	Low	High
Bilophila	Low	High

Recent research has shed light on how metabolites from gut bacteria can influence the development of AF at cellular and molecular levels. In AF, the persistence of irregular heart rhythms relies on a “substrate”, which includes the mechanical, electrical, and anatomical features of the atria. This substrate is shaped by both structural and electrical remodeling processes, and these remodeling events occur when the gut microbiota is disturbed. An overgrowth of Gram-negative pathogenic bacteria may contribute to the development of AF through an inflammatory response to LPS. Dysbiosis may contribute to remodeling in both the electrical and structural aspects of the atria, ultimately playing a role in the initiation and progression of AF. One study identified a distinction in microbial diversity between individuals with persistent AF and the control group. However, the diversity of the gut microbiome did not significantly differentiate individuals with existing or newly developed AF [47]. Finally, introducing *Bacteroides dorei* and *Bacteroides vulgatus* through transplantation or adding *Lactobacillus plantarum* ATCC 14917 to the diet has been found to prevent the buildup of arterial plaques by reducing substances in the bloodstream. These discoveries may help uncover the underlying biology of AF and how novel treatments might affect metabolic processes [1].

3.4.2. Mechanisms of Gut Microbiome-AF Interactions

The gut microbiota may indirectly contribute to the development of AF by influencing the immune system to regulate risk factors associated with AF through the gut-immune-heart axis [1]. When the tight junctions between cells in the colon are disrupted, LPS can enter the bloodstream, triggering a strong inflammatory response [57, 58] (Fig. **1**). Once in the bloodstream, LPS is primarily detected by Toll-like receptors (TLRs) on the surface of immune cells [59]. Activation of TLR signaling, prompted by the binding of bacterial ligands, leads to the release of pro-inflammatory cytokines. This sequence of events contributes to the regulation of the host's pro-inflammatory condition [59] (Fig. **1**).

Dysbiosis acts as an upstream factor in AF by inducing the activation of the NACHT, LRR, and PYD domains-containing protein-3 (NLRP3) inflammasome through LPS stimulation. A novel etiological role of abnormal gut microbiota in age-related AF pathogenesis was recently revealed using fecal microbiota transplantation (FMT) rat models. Young rats subjected to a 6-week FMT with fecal samples from aged AF rats showed a significant rise in the expression levels of fibrosis-related marker proteins, transforming growth factor-β1 (TGF-β1), and α-smooth muscle actin in the atria [60, 61]. This response was attributed to the "priming" and "triggering" of the atrial NLRP3 inflammasome *via* the toll-like receptor (TLR) 4/MyD88/nuclear factor-κB (NF-κB) pathway and an enhanced nuclear translocation of phosphorylated NF-κB in response to LPS stimulation [1, 61]. (Fig. **1**)

Several group and systematic review studies have linked TMAO with hypertension, obesity, heart failure, and coronary artery disease. As atrial fibrillation shares common risk factors with coronary artery disease, the role of TMAO in AF is currently uncertain [50]. However, several studies implicate TMAO in AF. The direct influence of gut microbiota on blood pressure was illustrated by transplanting fecal content from hypertensive human donors into germ-free mice [57]. TMAO was shown to significantly extend the blood pressure-elevating impact of angiotensin II in rats [57]. Furthermore, in studies using canine models, the injection of TMAO locally activated the atrial autonomic ganglion plexus, leading to the promotion of arrhythmia. This effect is potentially mediated through the activation of p65 NF-κB signaling and an increase in the expression of inflammatory cytokines. Administration of TMAO exacerbates doxorubicin-induced cardiac fibrosis by activating the NLRP3 inflammasome, a known contributor to the development of AF [47, 62]. TMAO has been demonstrated to induce cardiac hypertrophy and the expression of hypertrophic markers, including atrial natriuretic peptide, both *in vivo* in Sprague–Dawley rats and *in vitro* in neonatal ventricular cardiomyocytes [45, 62].

Several studies have outlined various potential mechanisms linking TMAO with AF [50]. These mechanisms involve activation of the cardiac autonomic nervous system, inflammation, oxidative stress, endothelial dysfunction, and myocardial fibrosis. Synthesis of TMAO by intestinal flora promotes the polarization of M1 macrophages, exacerbating structural remodeling in the atria and ultimately leading to AF. The inflammatory markers induced by the TMAO-activated thioredoxin-interacting protein-NLRP3 inflammasome could contribute to plaque formation by generating cholesterol-packed foamy macrophages in arteries. TMAO also enhances protein kinase C/NF-κB activation, leading to increased expression of monocyte adhesion and vascular cell adhesion molecules [1]. These vascular pathological changes may evolve into risk factors for AF [1]. While these mechanisms are implicated in AF pathophysiology in various contexts, their specific role in mediating TMAO's effects on AF requires further assessment in animal models and AF patients.

To further enhance said pathways, multiple reviews have elucidated how TMAO, and other active metabolites are pro-arrhythmogenic [60, 63]. Systemic reviews have pinpointed SCFA and TMAO as cornerstones in the pathway [60]. The pathway starts with gut dysbiosis, triggered by diet change, and dysbiosis leads to an increase in LPS and TMAO while decreasing SCFA, which is usually produced from fiber breakdown. These active metabolites are homogenously transported through enteric circulation and, later, systemic circulation [60]. Research poses that these active metabolites are pro-arrhythmogenic by unknown intracellular mechanisms but seem to accelerate atrial architecture and predispose patients to atrial fibrillation and other reentrant cycles [60, 64].

Overall, the cumulative evidence suggests that the gut-heart axis is affected by a complex interplay of factors, and further research is needed to fully understand the role of the gut microbiota and associated metabolites in atrial fibrillation [63].

3.4.3. Clinical Correlations

A recent study demonstrated that aging-associated gut dysbiosis promotes AF partly through increased levels of circulating LPS and glucose, along with enhanced activity of the atrial NLRP3 inflammasome, which leads to atrial fibrosis [60, 65]. This provides powerful evidence for the link between the gut microbiome and cardiac electrophysiology. Many approaches can be taken to decrease the risk of atrial fibrillation through the modification of our microbiome. A recent study revealed a novel etiological role of abnormal gut microbiota in age-related AF pathogenesis by using FMT rat models to show a significant rise in the expression levels of fibrosis-related marker proteins and decrease systematic inflammation [47]. As a result, FMT could represent novel therapeutic avenues for AF management as standalone therapies, adjuncts to existing treatments, or by regular consumption of probiotics, prebiotics, and synbiotics. These components not only enhance the growth of local beneficial bacteria but also might introduce some species that the gut is deficient in because of a poor diet. Affected Species can provide endocrine neurohormones that will affect distant organs such as the heart [47]. Several systematic review studies have linked TMAO with hypertension, obesity, heart failure, and coronary artery disease. As atrial fibrillation shares common risk factors with coronary artery disease, the role of TMAO in AF is currently uncertain [50, 66]. However, several studies implicate TMAO in AF. Several studies have outlined various potential mechanisms linking TMAO with AF [50]. These mechanisms involve activation of the cardiac autonomic nervous system, inflammation, oxidative stress, endothelial dysfunction, and myocardial fibrosis. Synthesis of TMAO by intestinal flora promotes the polarization of M1 macrophages, exacerbating structural remodeling in the atria and ultimately leading to AF [50, 65]. Gut microbiome-based biomarkers may serve as predictive tools for identifying individuals at heightened risk of developing AF, facilitating early intervention and risk stratification. Changes in the composition of the gut microbiota may influence the production of gut microbial metabolites, promoting obesity, insulin resistance, and other metabolic disorders, potentially impacting the development of AF [67, 68]. Incorporating information about an individual's gut microbiome profile into clinical decision-making could enable tailored treatment approaches, optimizing therapeutic outcomes and minimizing adverse effects [57, 67].

Another approach is through thorough monitoring antibiotic administration. As these medications are generally given orally, they have a significant effect on the gut microbiome. Some may play key roles in the eradication of beneficial species and subsequent dysbiosis.

Overall, the cumulative evidence suggests that the gut-heart axis is affected by a complex interplay of factors, and further research is needed to fully understand the role of gut microbiota and associated metabolites in atrial fibrillation. Further elucidation of the underlying mechanisms, validation of gut microbiome-based biomarkers, and exploration of microbiome-targeted therapies are warranted to harness the full potential of this relationship in improving outcomes for patients with AF [69, 70].

CONCLUSION

In conclusion, the correlation between atrial fibrillation (AF) and the gut microbiome represents a burgeoning area of research with profound implications for cardiovascular health. This literature review outlines existing evidence, highlighting the significance of understanding the interplay between AF and gut microbial composition.

Through an exploration of microbial diversity, alterations in gut microbiota, and potential mechanisms linking gut dysbiosis to AF pathogenesis, this review has underscored the complex interrelationships between the gastrointestinal tract and cardiac function. Emerging findings suggest that microbial metabolites, inflammatory pathways, and neurohormonal signaling play pivotal roles in modulating atrial electrophysiology and the arrhythmogenic substrate.

Moreover, the clinical implications of the AF-gut microbiome connection are far-reaching. By identifying microbial signatures associated with AF susceptibility and progression, clinicians can develop microbiome-based biomarkers for risk stratification and personalized treatment strategies. Interventions targeting the gut microbiome, such as probiotics, prebiotics, and dietary modifications, hold promise as adjunctive therapies for AF management, potentially complementing existing pharmacological and procedural approaches.

Furthermore, understanding the AF-gut microbiome connection extends beyond arrhythmia management to encompass broader cardiovascular health. By addressing gut dysbiosis and associated comorbidities, clinicians may mitigate overall cardiovascular risk and improve long-term outcomes for patients with AF and related conditions.

However, several challenges and unanswered questions remain. Methodological limitations, variability in microbial profiling techniques, and confounding factors necessitate further validation and replication of findings in diverse patient cohorts [42, 68]. Longitudinal studies are needed to elucidate the temporal relationship between gut microbiome alterations and AF onset or progression. Unfortunately, no further intracellular research has been proven to explain how the presumed active metabolites alter the atrial architecture. These hypotheses are still in the infancy regarding large animal trials and clinical trials that might give us solid ground to develop novel treatments for AF based on gut dysbiosis theories [70]. The mentioned research shares a profile of small sample sizes and short-term analysis as limitations to its results, and we must keep that in mind while approaching further research regarding the gut microbiome.

In light of these considerations, continued research efforts are warranted to unravel the mechanistic underpinnings of the AF-gut microbiome connection and translate these insights into clinical practice. By leveraging microbiome data and advancing personalized medicine approaches, clinicians can optimize AF management, improve patient outcomes, and ultimately enhance cardiovascular health for individuals worldwide.

AUTHORS' CONTRIBUTIONS

The authors confirm their contribution to the paper as follows: study conception and design were contributed by MTZ; data analysis and interpretation of results were performed by FA; the manuscript was drafted by MA, RO, GA, MA, TB, EH, OJ, MM, EM, TR, and JS. All authors reviewed the results and approved the final version of the manuscript.

LIST OF ABBREVIATIONS

AF	=	Atrial Fibrillation
BMI	=	Body Mass Index
BAs	=	bile acids
SCFAs	=	Short-Chain Fatty Acids
LPS	=	Lipopolysaccharides
TLR4	=	Toll-Like Receptor 4

CONSENT FOR PUBLICATION

Not applicable.

FUNDING

None.

CONFLICT OF INTEREST

The authors declared no conflict of interest, financial or otherwise.

ACKNOWLEDGEMENTS

Declared none.

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