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Association of Gut Dysbiosis with Potential Mechanisms Leading to Atrial Fibrillation: A Narrative Review

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Abstract:- Atrial fibrillation stands as one of the deadliest forms of arrhythmia known to mankind due to its severe complication and co-morbidities. Its association with gut dysbiosis is profound. The gut microbiota hosts a diverse variety of microbes crucial for immune function and protection against cardiovascular and metabolic diseases. Poor lifestyle habits such as diet, decreased physical activity, and drug disrupt this gut homeostasis. Multiple studies have provided compelling evidence linking alterations in gut microbiota to the risk and progression of atrial fibrillation. Some proposed mechanisms involve key metabolites such as trimethylamine N-oxide (TMAO), lipopolysaccharides, short-chain fatty acids (SCFAs), bile acids, and tryptophan. These mechanisms encompass inflammation, oxidative stress, autonomic dysfunction, atrial remodeling, altered electrical activity, and calcium homeostasis. This review meticulously examines gut dysbiosis and its pivotal role in the progression of atrial fibrillation through diverse potential mechanisms, emphasizing the significance of dietary factors and potential interventions.

Keywords:- *Atrial Fibrillation, Gut Dysbiosis, Cardiovascular Diseases, Arrythmia, Lifestyle, Gut Health.*

I. INTRODUCTION

➢ *Defining Gut Microbiota*

The gut microbiota is a term used for a wide ecosystem of microorganisms that has a pathogenic and symbiotic relationship with the human gut. The human gut microbiota is an ecosystem of trillions of symbiotic microbial cells which are primarily bacterial [1]. Phyla Bacteroidetes and Firmicute are seen to be mainly present in an adult gut [2]. A human acquires it at birth and over time, it evolves with one's lifestyle habits like diet, physical activity, and medications that they take[2],[3]. The human microbiota contains the genetic material of these microbial cells[4]. Over the years, there have been several studies that were conducted to understand the microbiota, its existence, and its relation with human physiology [5]. The gut microbiota is a topic that has received immense attention from researchers and is something that has been studied to a greater extent in the past few decades. Joshua Lederberg was the first person to coin this term in the year 2001 and since then it has raised many questions that are clinically very significant [2]. The terms microbiota and microbiome are often used interchangeably with the previous one referring to the microbial taxa linked to humans and the latter referring to the catalog of microbes with their genetic information [1]. In 1680, Antonue ven Leewenhoek compared the microbiota of his oral and fecal material which led to his understanding of the difference in the microbiota in these two regions and their nature as well as from people who had associated pathologies in these areas [6]. With modern medical science and the advances in the healthcare sector, we have a deeper understanding of various pathologies and their association with the gut microbiota. One of which is Atrial Fibrillation, which is discussed in this review.

➢ *Understanding Gut Dysbiosis*

The interaction of the food with these metabolites is termed a metabolome. Our immune system is greatly regulated by this interaction [2], [7]. Gut dysbiosis refers to the the disturbance or disruption of the gut microbiota and is strongly linked with some severe pathologies particularly cardiovascular pathologies [2]. Over the past few decades of in-depth research about the gut microbiota, researchers have found some direct association of gut dysbiosis with fatal arrhythmias like atrial fibrillation.

II. THE EFFECT OF EXTERNAL AND LIFESTYLE FACTORS ON GUT MICROBIOTA

Gut homeostasis is crucial for health. However, many factors can affect this homeostasis which leads to a state of dysbiosis[3]. Some are modifiable like lifestyle.

Gut dysbiosis is characterized by the increased ratio of Firmicutes and Bacteroidetes (F/B ratio) which is associated with an increased production of metabolites. Some of these include Lipopolysaccharide (LPS), bile acids, trimethylamine N-oxide (TMAO), and significant reduction in short-chain fatty acids (SCFA) [2]. The association of these changes with the cardiovascular system is illustrated in Fig 1.

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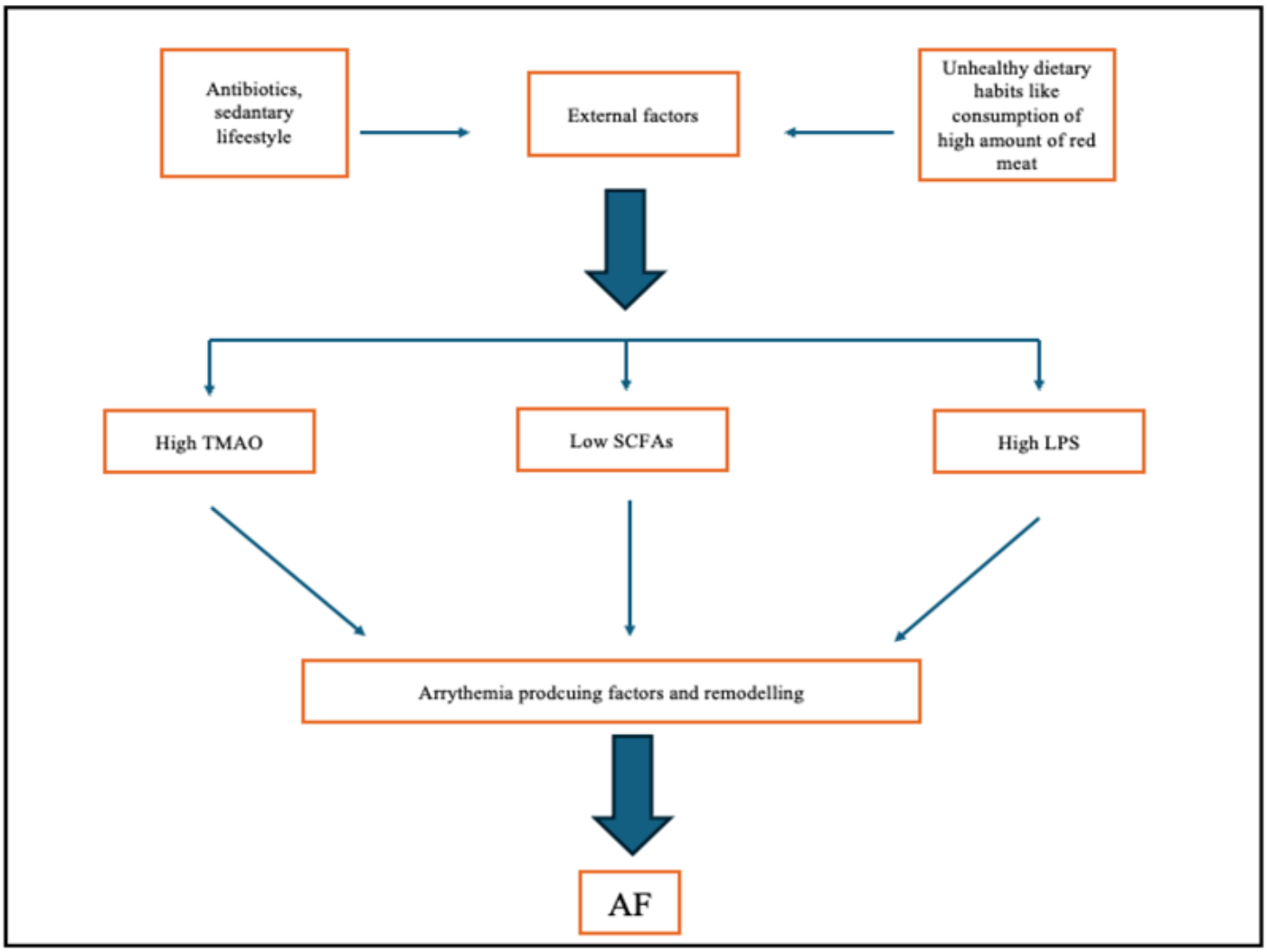

Fig 1: Association of External Factors with Atrial Fibrillation Promoting Factors
[TMAO= Trimethylamine N-oxide; SCFAs = short chain fatty acids; LPS = Lipopolysaccharides; AF = atrial fibrillation]

Studies have found that the ratio of Firmicutes and Bacteroidetes in people from the same population changes a lot, because of lifestyle things like diet, physical activity, antibiotics consumption with variable dosage, and more. However, it is seen that this ratio is higher in obese people making it a potential biomarker. And obesity in turn is linked to many co-morbid conditions[8].

III. ASSESSMENT OF GUT MICROBIOTA

In traditional setting, microbiologists use selective in vitro culture methods to study bacterial compositions by adjusting nutrients and conditions like aerobic/anaerobic environments and temperature. However, these methods only culture a small portion of gut flora, mostly obligate anaerobes not viable from stool samples[9]. Molecular techniques, not requiring cultured cells, offer a more detailed view of the gut microbiota. Polymerase chain reaction (PCR) amplification with species-specific DNA primers can detect clinically important species. Bacterial 16S sequencing, made possible by newer generation DNA sequencing, reads hypervariable regions of the 16S rRNA gene, distinguishing bacterial species. Typically targeting variable regions like V3-V4, 16S sequencing classifies bacteria reliably to order or genus levels; full sequencing enhances species-level classification[10], [11].

Similar methods exist for fungi, targeting internal transcribed spacer sequences. Shotgun metagenomics, fragmenting and aligning microbial DNA to genomic databases, provides comprehensive insights into microbial composition, including bacteria, fungi, viruses, and protists as well s information about gene grouping, encodings for specific substrates [12], [13], [14].

The circulating metabolome includes these bacterial metabolites as mentioned above. Biochemical profiling from plasma or serum can be helpful in its investigations. Gas chromatography-coupled mass spectrometry (GC-MS) involves chemically modifying samples to make them volatile, and then separating them in a gas phase with a temperature ramp. Mass spectrometry identifies compounds by matching the precise molecular masses of their fragments [2]. Liquid chromatography MS (LC-MS) is similar but detects more metabolites. Nuclear magnetic resonance spectroscopy is advantageous for measuring certain metabolite classes like lipoproteins and inorganic metabolites or ions [15].

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IV. ATRIAL FIBRILLATION

Atrial fibrillation (AF) is one of the most common types of arrhythmias. With an overall prevalence of approximately 1% of the total population and over 9% of individuals above 70 years of age, it is associated with a two-fold increase in mortality with significant morbidity [16, pp. 470–475]. It is characterized by tachyarrhythmias. There is a higher chance for the thrombus to be formed because of the turbulent flow because of the irregularity in the rhythm. Atrial fibrillation is the leading cause of stroke. It is seen that the prevalence of atrial fibrillation is rising constantly even with adjustments of co-morbidities [17], [18].

Any condition that leads to inflammation, stress, damage, and ischemia to the heart can eventually develop into AF [19]. Some of the common causes include congenital heart disease, increased alcohol consumption, coronary artery disease, hypertension, diabetes, hyperthyroidism, subarachnoid hemorrhage or stroke, mitral valve pathologies, and obstructive sleep apnea to name some. It can also be idiopathic as seen in lone atrial fibrillation [16], [19]. It can be of mainly three patterns based on the episodes and recurrence. These are Paroxysmal (terminates within 7 days), persistent (lasts more than 7 days), and long-standing AF (lasting more than 12 months). AF can be detected from ECG efficiently where it presents with a narrower complex with non-distinguishable p-waves as seen in the ECG in Fig 2. Laboratory tests are also important to take under consideration for the detection of certain co-morbid conditions. Cardiac biomarkers like troponin t, B type natriuretic peptide (BNP) can also tell about underlying conditions causing AF [19].

AF is characterized by both abnormal autonomic firing and the presence of multiple interacting receptors circuiting impulses around the atrium. Initiated by rapid bursts or ectopic beats arising from conducting tissues in the pathological tissue. The mechanism of this initiation can be understood from the beats arising from the pulmonary veins triggering AF and then re-entering within the atria with many interacting re-entering circuits running parallelly. This sustains the AF to continue. Due to these reasons, during AF, the atria beat very fast and in irregular manner and uncoordinated manner resulting in ventricles activating irregularly as well. Because of this, it is often referred to as an ‘irregularly irregular’ pulse [16]. There are many pathophysiological mechanisms due to which AF develops. However, the best understood is cardiac remodeling. Particularly atrial remodeling results in these structural and electrical changes which in turn becomes a cause of this irregularity in rhythm. These remodeling are caused by changes in myocytes and extracellular matrix (ECM) as well as deposition of the fibrous tissue [19]. Studies have also shown an association with genetics. Mutation in the alpha subunit of cardiac Ik5 in chromosome 10 can cause AF[17], [19]. More recent studies have found an association between the diet interacting with gut metabolites giving rise to certain AF-producing mechanisms [2], [20] . In this review, we will be discussing more about these metabolites and their related mechanisms.

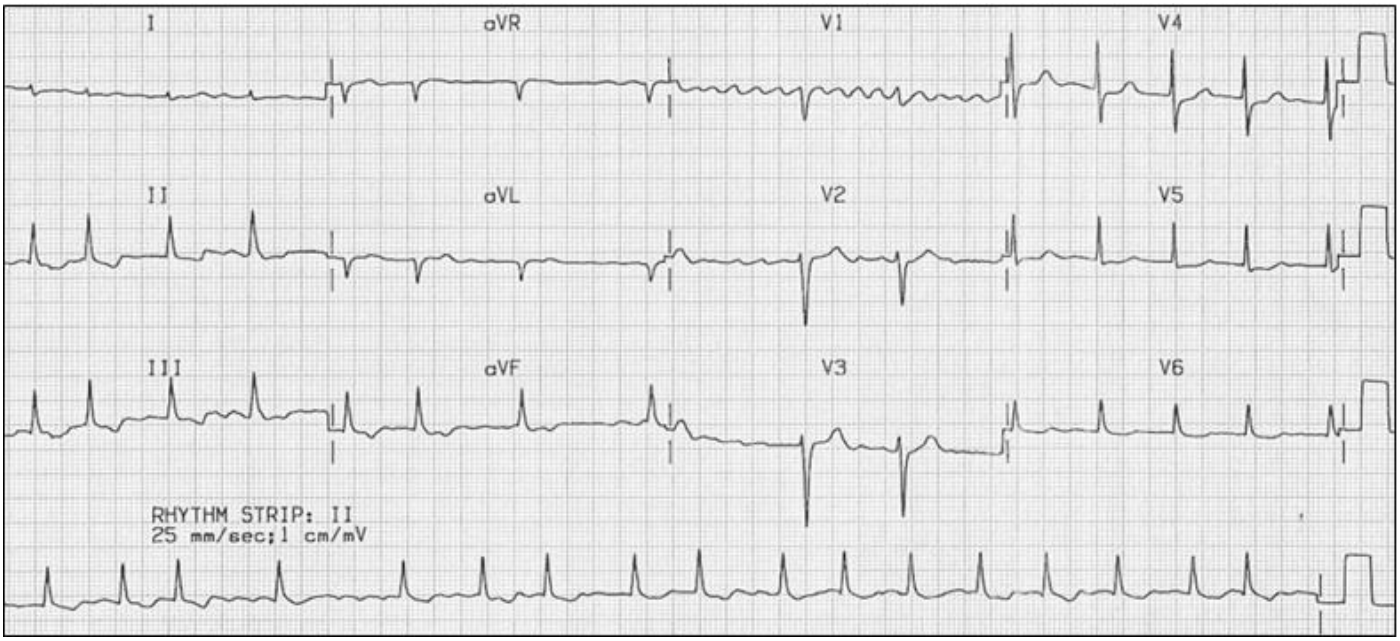

Fig 2 ECG Showing Atrial Fibrillation. Absence of p-waves can be Observed
Derived from https://litfl.com/atrial-fibrillation-ecg-library/

Stroke is the major complication of atrial fibrillation along with other cerebral vascular accidents. These account for severe morbidity and mortality rates globally. Other complications can include heart failure and other life-threatening pathologies. It can also be linked to an increased risk of sudden cardiac death [21]. Atrial fibrillation in the elderly age increases the risk of mortality by a significantly higher percentage.

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Untreated AF can have a severe effect on one's life expectancy due to elevated risks of heart attacks, strokes, etc. With treatment, it can be controlled but the patient can have anticoagulation-related complications for a lifetime [19]. It is often seen as a costly heart issue due to its expensive treatment options costing billions of dollars in national cost in the United States [22] . Lone AF is seen to have a poor prognosis and is often associated with severe cardiovascular events[23].

V. GUT MICROBIOTA AND ITS EFFECT ON ATRIAL FIBRILLATION: UNDERSTANDING IT AS AN INFLAMMATORY PROCESS

Inflammation, seen to be mediated by the NLRP3 inflammasome, is proposed as a key player in atrial fibrillation [19], [24]. This complex activates caspase 1, triggering the release of inflammatory cytokines [25]. The inflammasome, a cellular complex, activates caspase 1 to produce inflammatory cytokines like IL-1β and IL-18. NLRP3, a key inflammasome in cardiovascular diseases, shows increased activity in atrial cardiomyocytes of AF patients, implicating it in AF progression[26]. Elevated NLRP3 activity in AF patients correlates with atrial remodeling, shorter refractory periods, and increased AF susceptibility. Modifiable risk factors like obesity, hypertension, and diabetes contribute to AF progression[2], [25], [26].

VI. ALTERATION IN GUT MICROBIOTA IN PATIENTS WITH ATRIAL FIBRILLATION

It is very much evident that gut dysbiosis is strongly linked to many cardiovascular disorders. Many studies have been conducted finding the variation of gut microbiota in these patients comparing them with normal or control groups [2]. These studies have revealed some interesting alterations that are very crucial for understanding its pathogenesis and progression to AF. One such alteration which happens to be the most important one is the growth of certain microbes. These microbes are seen to be growing abnormally which becomes harmful for the human body. There is strong evidence supporting the overgrowth of these bacteria in patients with AF. These are *Streptococcus, Ruminococcus, Enterococcus, Veillonella, Eubacterium, Bifidobacterium along with E.Coli* which were commonly found in an increased state [27]. On the other hand, there was a significant reduction in *Faecalibacterium, Oscillibacter, Bilophila, Alistipes, Prevotella, and Sutterella* that was observed in patients with AF [27], [28]. A similar pattern was observed in patients with persistent AF form which suggested the correlation with its progression. This variation is known to be linked to an increase of *Blautia, Coprococcus, and Dorea* with a relative decrease in species like *Butyricicoccus* [28]. This form of dysbiosis suggests a potential relation between the progression of persistent AF and its expression clinically. Serum and stool samples revealed imbalances in certain metabolites like cholic acid, oleic acid, and linoleic acid in patients with atrial fibrillation [28]. Following an ablation of AF, these metabolites were seen to be changed positively. With an increase in beneficial bacteria and a reduction of the harmful ones and a similar relation with their respective metabolites, ablation was seen to alter the dysbiosis in such patients [30]. Overall this indicates a higher F/B ratio in patients with all forms of Atrial fibrillation which are independent of other co-morbid conditions and associated factors [27].

VII. PROPOSED MECHANISMS LEADING TO ATRIAL FIBRILLATION

In this review, we analyzed the current evidence that supports gut dysbiosis and its effect on the expression and progression of AF. Among several studies mechanisms, the important mechanisms are in major association with TMAO, lipopolysaccharides, and short chain fatty acids. A summary of these mechanisms is mentioned in Table 1.

A. Trimethylamine N-oxide(TMAO)

Derived from the gut microbiota, TMAO is a biologically active metabolite [2]. The gut microbiota processes our diet and as a result, TMAO is produced. L-carnitine or choline derived from our daily diet is transformed by the microbiota in this process. Choline is converted into trimethylamine which is a gas. Trimethylamine is further connected to TMAO. Flavin containing monooxygenases in the liver is involved in this conversion [31]. A diet rich in red meat, fish, eggs, and poultry is high in choline [32]. Consumption of L carnitine orally as supplementation for fat loss among fitness enthusiasts can also lead to the resultant accumulation of TMAO.

TMAO is seen to play an important role in the progression of many cardiovascular pathologies [27]. Many factors that support the development of atherosclerosis are associated too increased TMAO levels [33]. Further research establishing a direct link between TMAO levels and atrial fibrillation is the need of the hour. However, given the similarity in risk factors of atherosclerosis and other coronary artery disease, it can indicate the effect of TMAO on AF [27].In animal models, TMAO is seen to release inflammatory molecules that in turn affect the autonomic nervous system activity and are also linked to oxidative stress [20]. These studies tell us that an increased TMAO level results in electrical remodeling, hypertrophic conditions, a significant increase in proinflammatory factors like IL-1ß, IL-6 as well as Tumor necrosis factor (TNF), an evident proliferation of atrial fibroblasts by activation of certain pathways [20], [34], [35]. TMAO is also associated with age with its level increasing with age but the lifestyle factors leading to its increase in younger ages leads to increased cardiovascular disease prevalence in a population.

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B. Lipopolysaccharides and Short-Chain Fatty Acids

Table 1 Summary of Association of Metabolites and Respective Potential Mechanisms with Atrial Fibrillation

Sl n.o.	Metabolite	Mechanism
1	Trimethylamine *N*-oxide (TMAO)	Higher TMAO levels are associated with increased risk and incidence of CVDs. This increase in TMAO results in the release of inflammatory molecules and oxidative stress, impacting the autonomic nervous system and promoting arrhythmia-generating factors. Moreover, TMAO contributes to cardiac changes such as electrical remodeling, hypertrophy, and the proliferation of atrial fibroblasts, accompanied by heightened levels of proinflammatory factors. These effects suggest a potential association between elevated TMAO levels and the development of atrial fibrillation.
2	Lipopolysaccharides	Increased gut permeability allows LPS into circulation, elevating LPS levels. LPS is linked to hypertension and gene expressions affecting the atrial refractory period, promoting atrial fibrillation (AF). AF patients exhibit higher levels of gut microbes involved in LPS synthesis, correlating with cardiovascular events and platelet activation.
3	SCFAs	The gut microbiota generates SCFAs from dietary fibers which have immune-supporting properties. AF patients show diminished SCFA-producing bacteria. Though SCFAs aren't directly linked to AF, their reduction correlates with AF risk factors such as hypertension, obesity, and coronary artery disease, due to fiber-deficient diets.
4	Other factors	Tryptophan metabolized by the gut microbiota into indole converts to indoxyl sulfate in the liver, linked with cardiovascular complications in conditions like CKD. Indoxyl sulfate elevation is associated with arrhythmia development, cardiac fibroblast hypertrophy, and increased proinflammatory factors. Higher chenodeoxycholic acid levels, a primary bile acid, in AF patients correlate with atrial anatomy alterations. Bile acids' direct role in AF remains unclear, it could involve myocardial fibrosis, autonomic dysfunction, and atrial refractory period changes.

CVDs = cardiovascular diseases; AF = Atrial fibrillation; LPS = lipopolysaccharides; SCFAs = short chain faatty acids, CKD = chronic kidney disease

Lipopolysaccharide is an endotoxin that is present on the outer layer of gram-negative bacteria [36]. With increased permeability of the gut, LPS can get into systemic circulation thus increasing in level. This can be seen to be associated with hypertension and the generation of factors that promote arrhythmia like AF. Animal models have shown us the association of increased levels of LPS with some gene expressions that affect the atrial refractory period to make it short. It is also seen to increase the concentrations of some pro-inflammatory factors that induce AF. Patients with AF were found to have gut microbes that are involved in LPS synthesis and such patients do experience other cardiovascular events and platelet activation as well [37], [38].

On the other hand, gut microbiota derives a metabolite from the dietary fibers. This metabolite is called Short-chain fatty acid or SCFA [39]. There are many types of SCFAs but the important ones that are present in the majority are Propionate, acetate, and butyrate. These are biologically active SFCAs that are produced by the gut microbiota and are beneficial for the immune system. People with AF are seen to have reduced microbes that produce SCFA. SCFA does not have a direct relation with AF. However, it is associated with risk factors of AF. These include hypertension, obesity, and coronary artery disease. Dietary habits that are not rich in fiber are linked to conditions like hypertension and other comorbid conditions[40], [41], [42], [43].

C. Other Potential Mechanisms Associated with AF

Tryptophan when metabolized in indole by gut microbiota then gets converted into indoxyl sulfate in the liver which is a toxin associated with cardiovascular complications in diseases like chronic kidney disease (CKD) [44]. Animal model studies have shown an increase in the development of arrhythmias and a reduction in nodal pacemaker activity eventually causing oxidative stress and other factors that may promote AF [45]. It has also been shown to cause hypertrophic effects on cardiac fibroblasts and myocytes and increase proinflammatory factors [46]. Elevated indoxyl sulfate following ablation is linked to an increased incidence of recurrence of AF[47], [48].

Bile acids are important molecules regulating metabolism in extrahepatic organs. Gut microbiota metabolizes primary bile acids into secondary[49]. Higher serum levels of chenodeoxycholic acid, a primary bile acid is often found in patients with AF. This is positively linked with atrial anatomy and voltage activity. It is found that secondary

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bile acids are associated with risk factors of atrial fibrillation [50], [51]. The direct association of bile acids with AF is not very well understood. However potential mechanisms linking it include myocardial fibrosis dysfunction in autonomic activity, atrial refractory period shortening, and alteration in Ca^{2+} homeostasis [52].

VIII. CONCLUSION

This review discusses the relationship between gut dysbiosis and atrial fibrillation (AF), emphasizing its development and progression. Dysbiosis in general is a shift in microbial composition and its associated metabolite production. These alterations correspond with changes in the metabolites circulating in systemic circulation and are eventually associated with an increased risk of AF. This review also discusses certain metabolites that are associated with increased incidence of AF. These metabolites are trimethylamine N-oxide (TMAO), lipopolysaccharides, and short-chain fatty acids (SCFAs) along with others like bile acids and tryptophan. The potential proposed mechanism includes inflammatory processes, oxidative stress, autonomic dysfunction, atrial remodeling, alteration in electrical activity, and calcium homeostasis along with some potential endothelial alterations that are associated with arrhythmia-causing factors. Lifestyle factors like diet are seen to be one of the major factors that are responsible for gut dysbiosis eventually leading to AF. Fortunately, it is a modifiable factor and with proper intervention, the risk and incidence of AF can be reduced. Finally, understanding the influence of the gut microbiota and resultant dysbiosis on AF presents hopeful strategies for therapeutic approaches, yet additional research is needed to understand the direct connections of different pathways and metabolites to propose effective strategies that can be helpful in managing and reducing the risk of AF in human.

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