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CLINICAL REVIEW

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Association of atrial fibrillation and gastroesophageal reflux disease: Natural and therapeutic linkage of the two common diseases

Toru Maruyama MD | Mitsuhiro Fukata MD | Koichi Akashi MD

Department of Medicine and Biosystemic Science, Kyushu University Graduate School of Medical Sciences, Fukuoka, Japan

Correspondence
Toru Maruyama, MD, PhD, Department of Medicine and Biosystemic Science, Kyushu University Graduate School of Medical Sciences, Fukuoka, Japan.
Email: maruyama@artsci.kyushu-u.ac.jp

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Abstract

Atrial fibrillation (AF) is a common arrhythmia and gastroesophageal reflux disease (GERD) is popular in Japan. The two common diseases share several predisposing factors such as lifestyle and senescence, and inflammation and oxidative stress play an important role in their development and progression. Incidental cases of AF treated successfully by proton pump inhibitor (PPI) applied for coexisting GERD have been sporadically reported. An increasing evidence indicates that GERD induces the initiation and the perpetuation of AF. This is caused by the autonomic nerve influence, mechanical compression, and propagation of local inflammation due to proximity of left atrium (LA) and lower esophagus. Meanwhile, AF also develops GERD by mechanical and inflammatory actions of LA characterized by remodeling and inflammation. The robust association of AF with GERD is not limited to their natural interaction, i.e., pharmacological or nonpharmacological treatment of AF is reported to aggravate GERD. Many cardiac drugs (anticoagulants, calcium antagonists, and nitrates) induce esophageal mucosal damage and lower esophageal sphincter relaxation promoting acid reflux. These drugs are frequently prescribed in patients with AF for stroke prevention, rate control, and for coexisting coronary heart disease. Catheter ablation also yields both GERD and esophageal thermal injury, which is a precursor lesion of atrioesophageal fistula. The notion that AF and GERD are mutually interdependent is widely and empirically recognized. However, mechanistic link of the two common diseases and objective evaluation of PPI as an adjunctive AF treatment warrant future large-scale prospective trials.

KEYWORDS
atrial fibrillation, catheter ablation, gastroesophageal reflux disease, inflammation, proton pump inhibitor

1 | INTRODUCTION

Atrial fibrillation (AF) is the most common arrhythmia encountered in cardiac practice. AF occurs in 1%-2% of general population, and the prevalence doubles or triples in the following two or three decades.[1,2] This trend of increasing prevalence of AF is considered as multiple conditions such as aging of the population, changing lifestyle, and incomplete control of cardiovascular risk factors. Actually, strict control of hypertension, diabetes, sleep apnea, and obesity prevents progression and recurrence of AF.[3,4] AF is associated with

impaired quality of life and various comorbidities including cardiogenic stroke and heart failure. Therefore, primary AF prevention in the elderly is drawing an increasing attention in the super-aged society of Japan from the viewpoint of health care and economic burden.

Gastroesophageal reflux disease (GERD) is the most common gastroesophageal disorder and increasing in developed countries including Japan. This is due to the inappropriate lifestyle in the middle ages such as excess food consumption,[5] obesity,[6] sleep apnea[7] and hiatus hernia in the elderly.[8] Because susceptible age for AF overlaps that for GERD, causal relationship between AF and GERD has been suggested. Since we encountered a case of paroxysmal AF treated successfully by proton pump inhibitor (PPI) administered for coexisting GERD,[9] the relationship between AF and GERD has been investigated in our laboratory.[10-13] In this article, we review the potential linkage of these two common diseases including our investigations and highlight that this association is not coincidental, i.e., the two common diseases show natural linkage and the treatments of AF affects GERD and vice versa irrespective of whether the treatment is pharmacological or non-pharmacological. Herein, AF means non-valvular AF, unless otherwise mentioned in this article.

2 | GERD AS A CAUSE OF AF

Several epidemiological studies have clarified GERD playing a pivotal role triggering and promoting AF. Huang et al[14] conducted a population-based study and demonstrated the higher incidence of future AF development in patients with GERD than in controls (HR of 1.31, 95% confidence of interval [CI] of 1.06-1.61, $P = 0.013$) as a nationwide cohort in Taiwan (Figure 1). Kunz et al[15] also reported the relative risk for developing AF in patients with GERD as compared with controls in health care encounters in the USA (HR of 1.39, 95% CI of 1.33-1.45). Bunch et al[16] reported similar temporary findings in the association of acid reflux and future AF (HR of 1.94, 95% CI of 1.35-2.78, $P < 0.001$) only in the presence of esophagitis. However, they showed opposing results with respect to the link of GERD and AF (HR of 0.81, 95% CI of 0.68-0.96, $P = 0.014$) after adjusting other risk factors in a population study held in Olmsted County, Minnesota. One possible reason for discrepancy is that subclinical, asymptomatic AF is not detected in these large-sample studies using cohort datasets. The other reason is the diagnosis and screening of esophagitis and GERD.

Causal relationship between AF and GERD is based potentially on the three main factors, such as (a) autonomic nerve activation, (b) mechanical irritation of esophagus to the left atrium (LA) due to anatomical proximity, and (c) esophageal inflammation inducing the development of local pericarditis or atrial myocarditis.[17-19]

2.1 | Autonomic influence

The episodes of atrial arrhythmia are sometimes induced by swallowing and food passage through esophagus.[20-22] Paroxysmal AF is also triggered by gastrointestinal movements such as defecation, abdominal bloating, swallowing, and eating. Neurocardiac responses to esophageal stimulation have been reported since 1990s. Tougas et al[23] investigated the effects of distal esophageal stimulation on the human heart rate variability using power spectrum of frequency domain analyses. They found that esophageal stimuli, whether electrical or mechanical, increased high frequency component (HF) and decreased low frequency component (LF) and basic heart rate. These autonomic nervous conditions are prerequisite of vagally mediated AF development.

Chemical esophageal stimulation due to acid exposure also modulates human autonomic nervous activity. Cuomo et al[24] demonstrated clear positive relationship (n = 12) and negative relationship (n = 6) between esophageal pH and LF/HF in arrhythmic patients with GERD (n = 18) but no relationship in patients with GERD alone (n = 9) by esophageal acid perfusion under simultaneous Holter and pH monitoring (Figure 2). These indicate that acid reflux potentiates afferent vagal nerve activity in the majority of patients with GERD and concomitant arrhythmia. Elevated vagal tone abbreviates effective atrial refractoriness inhomogeneously leading to the development of AF. Esophageal acid exposure also has potential impact on the coronary blood flow. In 1990s, Chauhan et al[25] demonstrated the coronary flow reduction induced by acid instillation into human esophagus. They demonstrated that this phenomenon is mediated by autonomic reflex and postulated that this is one of the main causes of syndrome X, which is characterized by typical angina chest pain in spite of normal coronary arteries.[26]

2.2 | Mechanical influence

The posterior wall of LA is separated from esophageal adventitia by thin connective tissue layer showing 1-4 mm in thickness.[27,28] LA mechanical activity during cardiac cycle is reflected by lower esophageal wall motion observed by endoscopy. Hiatus hernia, one of the

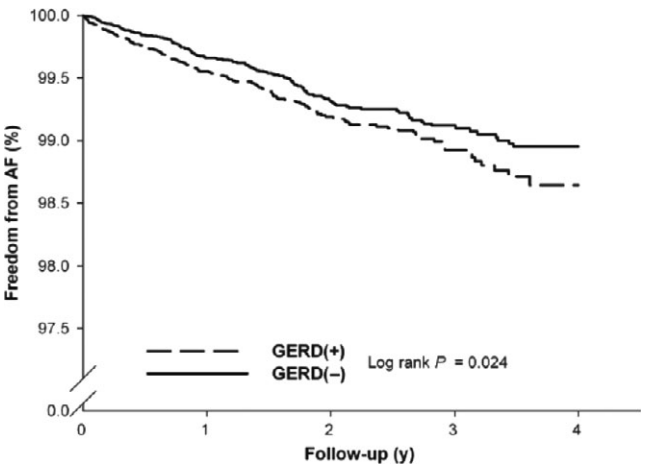

FIGURE 1 Kaplan-Meier curves of the freedom from atrial fibrillation (AF) in patients with or without gastroesophageal reflux disease (GERD). There is a significant difference between the two curves ($P = 0.024$ in log-rank test)[14]

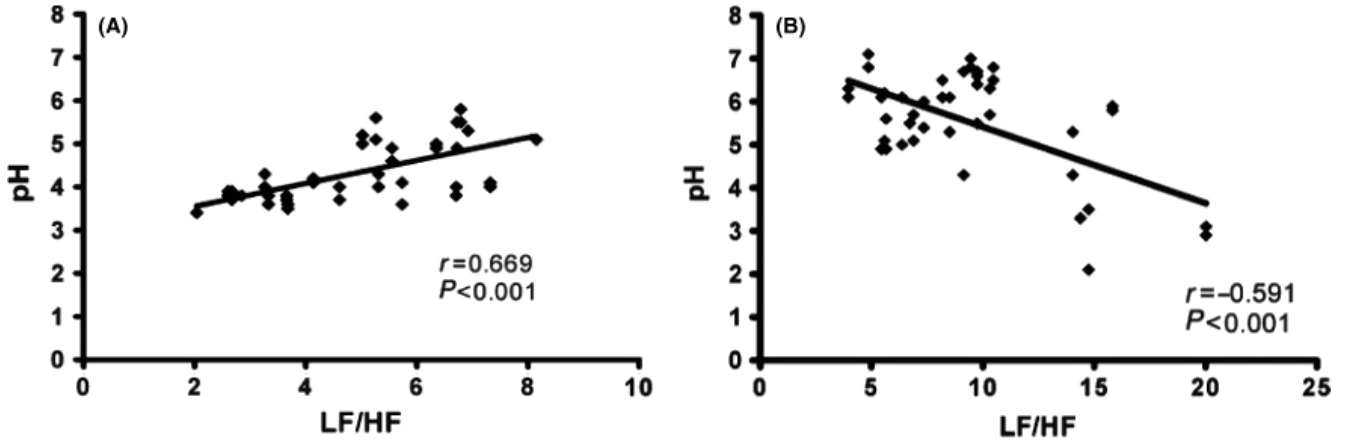

FIGURE 2 Correlation between lower esophageal pH and low/high frequency component ratio (LF/HF) obtained by pH monitoring and power spectrum analysis of heart rate variability in patients with arrhythmia and gastroesophageal reflux disease (n = 18). Two thirds of these patients showed positive correlation indicating that acid reflux elevates vagal nerve activity (A), whereas one third of patients demonstrated negative correlation meaning acid-induced sympathetic activation (B)[24]

underlying etiologies of GERD, is increasing in Japan due to kyphosis in the elderly and lack of physical exercise or excess food consumption in the middle ages. Intrathoracic gastric part acts as an acid pocket and compresses LA. Mechanical contact and irritation by hernia on the LA or pulmonary veins (PV) potentially contributes to the ectopic firing leading to the AF burden in patients with hiatus hernia. Actually, some cases of paroxysmal AF treated successfully by repair of associated hernia were reported.[29,30] Further, Roy et al[31] investigated the prevalence of AF in patients with hernia in comparison with general population from 1976 to 2006 at Mayo Clinic in Rochester, Minnesota. They concluded that the development of AF is frequent in patients with hernia especially in young patients, indicating that chronic mechanical LA compression underlies future AF.

2.3 | Inflammatory process

In recent years, it is acceptable that local or systemic inflammation is a risk factor for AF. Inflammatory process is known to trigger new-onset of AF, sustain AF and allow postablative AF recurrence.[32-35] AF without any structural heart diseases is termed lone AF. However, atrial myocarditis is confirmed in 66% of atrial biopsy specimens in patients with lone AF.[36] As compared with conventional risk factors for AF (hypertension, valvular disease, cardiomyopathy, pulmonary, and thyroid diseases), new risk factors (metabolic syndrome and its individual components) are characterized commonly by low-grade persistent inflammation. GERD is also induced by chemical inflammation of esophageal mucosal acid exposure. Propagation of regional inflammation into the LA across thin layer causes local pericarditis or atrial myocarditis. Acid reflux may also release inflammatory mediators such as interleukin (IL)-1β and IL-6.[37] These proinflammatory cytokines are also involved in the pathogenesis of AF. Actually, C-reactive protein (CRP) as an index of chronic inflammation correlates with the incidence,[38,39] defibrillation efficacy,[40] recurrence[41,42], and prognosis of AF.[43] AF and GERD may be complementary partners sharing common inflammatory mediators, which maintain and progress these two diseases.

2.4 | Effects of PPI on AF

Proton pump inhibitors are the first line therapy for GERD, although the efficacy of PPI depends substantially on the CYP2C19 polymorphisms. Considering the prevalence of GERD and the Japanese CYP2C19 polymorphisms, GERD may be undertreated in Japan. Sporadic case reports and case series studies indicate that PPI therapy may help to ameliorate symptomatic AF, allow to interrupt the ongoing antiarrhythmic drugs or facilitate conversion of AF to sinus rhythm in a subset of patients with concomitant GERD.[9,44] Weigl et al[45] found 18 patients with lone AF among 89 patients with GERD (20%) and concluded that PPI was effective for coexisting AF in 14 of 18 patients with GERD (78%). Gerson et al[46] demonstrated more directly the temporal correlation between GERD and arrhythmia. They reported in three patients that the episodes of acid reflux coincided well with paroxysms of AF by simultaneous Holter and esophageal pH monitoring and arrhythmic symptoms were improved by the administration of PPI.

These observational studies indicate that the therapeutic effects of PPI on the paroxysmal AF are mediated by cardiogastric interaction triggered by acid reflux. In addition, PPI has multimodal effects beyond acid suppression mediated by inhibiting proton pump (K^+-H^+ ATP_{ase}) in gastric mucosa.[47] Emerging evidence suggests that PPI shows antioxidant and anti-inflammatory effects that also potentiate acid inhibition. PPI is reported to suppress stress-induced production of hydroxyradical ($^-$OH) in vitro.[48,49] Further, there have been several reports concerning anti-inflammatory actions of PPI against leukocytes, epithelial, and endothelial cells, which are mediated in part by modulating tissue and intracellular pH homeostasis.[47]

The oxidative and inflammatory process is considered to play an important role in the initiation and progression of AF.[32-35] Gastric

K^+-H^+ ATP_{ase} isoform is expressed in mammalian hearts in transcript and protein levels,[50] and the involvement of K^+-H^+ ATP_{ase} in regulating cardiac function has been suggested in our and other laboratories.[50,51] These indicate specific binding site(s) of PPI on mammalian cardiac muscle. Scanning electron microscopy revealed leukocytes infiltration into the left atrial endothelium in patients with valvular AF undergoing open-heart surgery for valve replacement.[52] PPI may act as a novel antiarrhythmic and cardioprotective agent beyond antacid action for a subset of patients with paroxysmal symptomatic AF triggered by cardiogastric reflex.[53]

3 | AF AS A CAUSE OF GERD

Several clinical studies have documented AF as a potential cause of GERD. Shimazu et al[11] investigated the relationship between the symptomatic GERD and baseline characteristics of outpatients and concluded that AF alone contributed to the development of GERD. They enrolled patients with valvular and nonvalvular AF into their case-control study. Likewise, Kubota et al[12] focused on the nonvalvular AF and reported that symptomatic GERD was prevalent in the order of patients with permanent AF, paroxysmal AF, and then sinus rhythm. Although these studies are multicenter studies, they screened GERD by self-administered questionnaire showing sensitivity of 62%, specificity of 59%, and diagnostic accuracy of 60% as compared with endoscopy.[54] Thereafter, Hwang et al[55] conducted a longitudinal case-control study, classified patients into two groups showing AF vs. sinus rhythm and followed them up to 3 years. The diagnosis of AF was based on standard or ambulatory electrocardiogram (ECG), and that of GERD was on the questionnaire, endoscopy or pH monitoring. They observed higher incidence of GERD in the AF group than in the control group showing persistent sinus rhythm (HR of 1.37, 95% CI of 1.16-1.57, $P = 0.009$) and indicated AF as a potential cause of GERD (Figure 3).

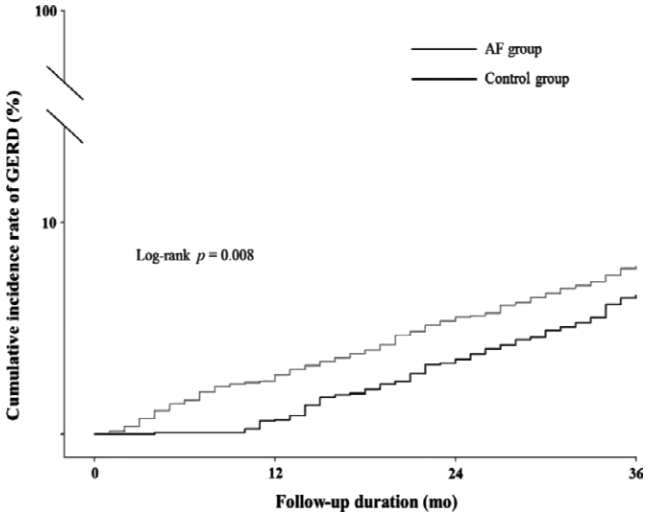

FIGURE 3 Kaplan-Meier curves of the cumulative incidence of gastroesophageal reflux disease (GERD) in patients with and without atrial fibrillation (AF). There is a significant difference between the two curves ($P = 0.008$ in log-rank test)[55]

To date, the exact mechanisms of AF as a potential cause of GERD remain inconclusive. However, some possibilities are postulated including mechanical interaction and inflammatory process. The progression of AF is characterized by the electrical and structural remodeling of atria and inflammatory mediators are involved in the development, recurrence, and prognosis of AF.[32-35] Enlarged LA is characterized by inflammatory cell infiltration and in firm contact with lower esophagus,[52,56] where LA inflammation may propagate to esophageal adventitia leading to the esophageal mucosal inflammation.[17-19,37] The potentially involved mechanisms for natural linkage of AF and GERD are illustrated in Figure 4.[19] However, conventional treatment of AF per se may have a potential risk for GERD. Therapeutic strategy of AF includes pharmacological and nonpharmacological treatment. AF treatment tends ironically to develop and aggravate GERD, and therapeutic linkage of AF and GERD may be stronger than the natural linkage of the two common diseases.

3.1 | Pharmacological treatment

Many cardiac and noncardiac drugs are involved in the development of GERD. Although noncardiac drugs such as nonsteroidal anti-inflammatory drugs, anticholinergic drugs, and β agonistic drugs are reported to cause GERD,[57] we would like to focus on common cardiac drugs likely causing GERD. Because GERD is a representative disease inducing noncardiac chest pain (NCCP) and cardiac drugs may be prescribed frequently to the patients complaining NCCP in general practice. Nakaji et al[10] investigated the influence of the common cardiac drugs on the development of GERD by multicenter questionnaire survey. They concluded that both calcium channel blockers and warfarin are independent risk factors for symptomatic GERD. Although calcium channel blockers and nitrates may be effective to NCCP underlying spastic esophageal motility,[58] these drugs cause lower esophageal sphincter relaxation, impair the esophageal clearance, and allow acid reflux.[57] Calcium channel blockers are used widely for rate control in patients with AF, and so are nitrates for coexisting coronary heart disease.

Current problem with this concern is the worldwide use of direct oral anticoagulants (DOAC) for stroke prevention in patients with AF. Dabigatran, a direct thrombin inhibitor, is the first DOAC commercialized in the world. This DOAC is known to cause dyspepsia in the RE-LY study, an international phase III trial demonstrating the noninferiority for efficacy (i.e., stroke prevention) and the superiority for safety (i.e., major bleeding) of dabigatran compared with conventional vitamin K antagonist (VKA: warfarin) under keeping steady time in therapeutic range. In this trial, dabigatran-induced upper gastrointestinal nonbleeding adverse effect was 16.9% compared with 9.4% in controls (warfarin group) showing relative risk of 1.81 (1.66-1.97 in 95% CI, $P < 0.001$).[59] The most frequent adverse event was GERD compared with simple dyspepsia or dysmotility, and the symptoms were dose-independent and mostly mild to moderate in severity. Dabigatran-induced esophagitis was found to be about 20% of

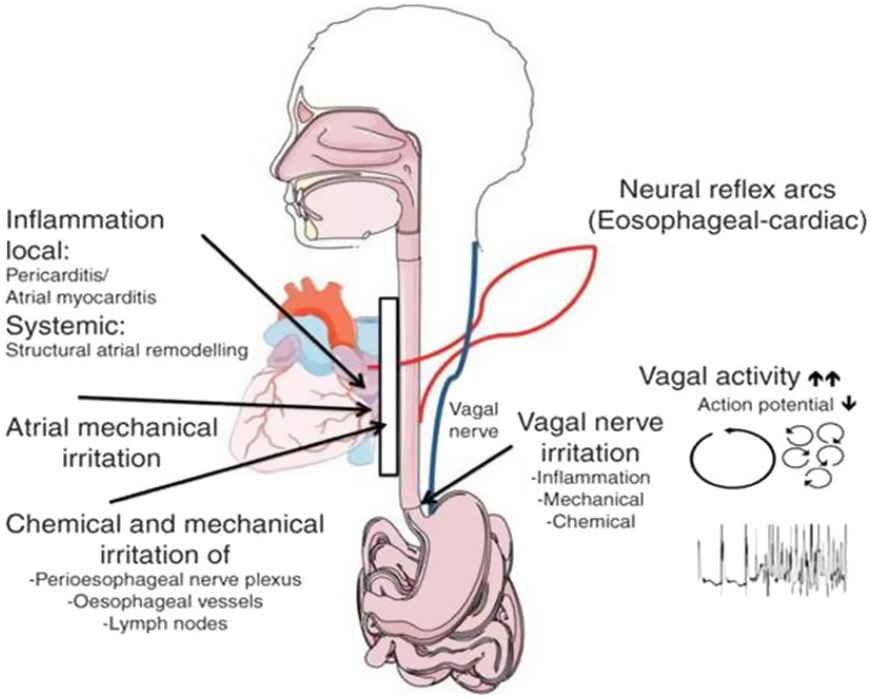

FIGURE 4 Potential but unproved mechanisms involved in the association of atrial fibrillation with gastroesophageal reflux disease[19]

dabigatran use in Japanese endoscopic study.[60] Because patients with AF are managed with long-term anticoagulants either DOAC or VKA, these gastroesophageal findings should guide management of AF patients.

3.2 | Nonpharmacological treatment

Pulmonary vein isolation (PVI) is a standard ablation technique for symptomatic and drug-refractory AF. To date, many kinds of power energy are available such as irrigating radiofrequency (RF) energy, hot balloon, cryo-balloon, laser balloon, and so on. Whatever power modality used, ablation technique is associated sometimes with the complication of esophageal lesions leading to the lethal atrioesophageal fistula (AEF).[61] The esophageal lesion is considered as thermal injury induced by ablation procedure and ranging in severity from erythema, esophagitis, ulceration, necrosis, and finally to fistula formation.[62] In parallel to such thermal injury, significant acid reflux is documented after the RF catheter ablation targeting AF. Martinek et al[63] demonstrated significant acid reflux in nearly 20% of patients with AF after RF ablation by using leadless lower esophageal pH monitoring. Because acid reflux did not correlate to the baseline characteristics, sedation, ablation approach, and total ablating energy, they speculated that the reflux might be caused simply by the prolonged supine position of the patients during procedure.

Atrioesophageal fistula is a catastrophic complication of ablation for AF with an incidence of 0.03%-1.5% per year.[64] Although conflicting results with respect to the genesis of AEF were reported,[65] esophageal ulcer caused by thermal injury is considered as a precursor lesion of AEF, and acid reflux is thought to aggravate ulceration to the fistula.[63] This "two hit theory" for the development of AEF is supported by the following results, i.e., (a) thermal esophageal lesion is associated with acid reflux as a consequence of periesophageal vagal nerve injury,[66] (b) prophylactic use of PPI is highly recommended for prevention of the development of AEF,[64,67] and (c) AEF formation is a delayed complication of ablation procedure.[64,68] Actually, acute gastric expansion and hypomotility are sometimes reported in AF patients undergoing ablation. This kind of postabative gastroparesis is considered as an adverse event of ablation procedure causing periesophageal vagal nerve injury. Contrary to the possible harmful effects of AF ablation on esophageal lesions, nonpharmacological treatment of GERD may have an adjunctive chance of PVI as an AF treatment. Gillinov et al[69] reported a patient with GERD and AF, who underwent off-pump PVI for prandial AF at an occasion of Nissen fundoplication for PPI-resistant GERD.

4 | STRENGTH AND LIMITATIONS

So far, several studies indicated direct temporal correlation of AF and GERD under the objective monitoring. As aforementioned, Weigl et al[45] reported the efficacy of PPI on both ECG-documented AF and endoscopic findings of GERD. Standard dose of PPI for 2 months administration improved both gastroesophageal and cardiac symptoms in 78% of enrolled patients, and antiarrhythmic drugs were not changed or interrupted in these patients. Gerson et al[46] demonstrated coincidence of acid reflux with paroxysms of AF and suppression of both phenomena by the administration of PPI under the simultaneous Holter and esophageal pH monitoring. Although these are small-sample studies without control group to exclude placebo effects, these two studies indicate PPI as an adjunctive treatment for a certain subset of AF patients showing vagally mediated prandial AF paroxysms.

The potential association of AF with GERD is supported by several predisposing factors shared by these two common diseases. Anatomical vicinity, mechanical contact, autonomic reflex, and inflammatory biomarkers are involved in this association. However, many large-sample investigations are retrospective observational studies or case-control studies using health insurance dataset.[14-16,55] The diagnosis of AF is based on the International Disease Classification, and asymptomatic, paroxysmal AF may have been underestimated in epidemiological studies. Many paroxysms of AF are usually asymptomatic, and hence accurate diagnosis of AF should be based on the insertable loop recorder or the implantable device interrogation.[70] In this sense, Odashiro et al[13] investigated the prevalence of GERD in arrhythmic patients and the effects of adjunctive PPI administration on the comorbid AF. They showed (a) that AF was most prevalent in arrhythmic patients associated with GERD and (b) that temporal correlation between AF and GERD symptoms was improved simultaneously by the oral administration of PPI. However, they failed to demonstrate the therapeutic effects of PPI on the number, the maximum duration, and the total duration of paroxysms of AF by the interrogation of permanent pacemaker implanted for sick sinus syndrome.

5 | CORRELATION OF AF AND SYSTEMIC DISEASES

Many clinical and epidemiological studies clarified a significant percentage of AF patients have a coexisting systemic diseases such as metabolic syndrome,[71] nonalcoholic fatty liver disease,[72] obesity,[73] and sleep apnea.[74] These common diseases are associated also with GERD, relating to inappropriate lifestyle, and become a public health burden in Japan. Such lifestyle related diseases have a robust association with AF, which is mediated partly by left ventricular hypertrophy and LA enlargement. Meanwhile, these lifestyle related diseases are accelerated by proinflammatory, procoagulant, and profibrotic mediators such as IL-1β and IL-6 as is AF.[75,76] These mediators can alter the atrial electrophysiology and microstructure thereby leading to the increased vulnerability to AF. This is based on the inflammatory modulation of intracellular Ca^{2+} handling and intercellular connexin underlying electrical remodeling such as dispersed refractoriness and inhomogeneous atrial conduction slowing. Moreover, inflammatory response activates transforming growth factor-β and matrix metalloprotease leading to the loss of cardiomyocytes and increased fibroblasts contributing to atrial structural remodeling.

In addition to the lifestyle related diseases, AF is associated closely with chronic inflammation caused by active rheumatoid arthritis,[77] systemic lupus erythematosus,[78] and inflammatory bowel diseases.[79] AF is also encountered in critically ill patients. Makrygiannis et al[80] investigated the prevalence of AF in patients admitted to the intensive care unit (ICU). They reported that the risk factors for developing new-onset AF in ICU patents included aging (>65 years old) and systemic inflammation such as sepsis, and that hypovolemia, electrolyte disorders, and elevated or rising serum CRP were contributory to the development of AF. A whole body of above evidence indicates that AF per se reflects local or systemic inflammation by infiltrating inflammatory cells into atrial tissue and releasing inflammatory mediators,[33-35] and GERD may be the nearest and persistent inflammatory locus for AF.

6 | CONCLUSION

Gastroesophageal reflux disease and AF share many risk factors including senescence and many lifestyle related diseases, which are characterized commonly by persistent inflammation. In addition to this natural linkage between GERD and AF, therapeutic intervention to AF, whether pharmacological or nonpharmacological, has a potential risk for development of GERD. Many cardiac drugs available for rate control and stroke prevention in AF aggravate GERD. AF ablation is also associated with thermal esophageal injury and acid reflux. These findings should guide the long-term management of AF patients. Considering that esophageal ulcer is a prerequisite of AEF, and that acid reflux may act as a quietus converting esophageal ulcer to fistula, PPI is essential for prevention of AEF. However, possible antiarrhythmic effects of PPI on AF derives from small-sample observational investigations. The objective evaluation of PPI in AF patients requires further validation by large-scale prospective trials, and the indication of PPI administration to a certain subset of AF patients should be established to clarify the cardiogastric interaction in more detail and to manage this subset of AF patients more appropriately.

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CONFLICT OF INTERESTS

The first author received speaker honoraria from Daiichi-Sankyo Co. Ltd. (Tokyo, Japan), Eisai Co., Ltd. (Tokyo, Japan), and Boehringer Ingelheim Japan Co., Ltd. (Tokyo, Japan) with respect to this article content. The other authors declare that they have no conflicts of interest.

ETHICAL APPROVAL

A part of this review was based on our original studies approved by the internal ethics committee (18038 and 24064, UMIN000009151).

ORCID

Toru Maruyama http://orcid.org/0000-0001-6543-4377

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