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Atrial Fibrillation and Gastro-Oesophageal Reflux Disease - Controversies and Challenges

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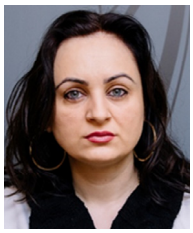

Oana Barboi

Abstract: Atrial fibrillation and gastro-oesophageal reflux are common manifestations in daily practice. The atria and the oesophagus are closely located and have similar nerve innervations. Over the last years, it has been observed that atrial fibrillation development and reflux disease could be related. Atrial fibrillation occurrence could be due to vagal nerve overstimulation. This, in association with vagal nerve-mediated parasympathetic stimulation, has also been observed in patients with gastro-oesophageal reflux. These mechanisms, in addition to inflammation, seem to be implicated in the pathophysiology of both diseases. Despite these associations supported by clinical and experimental studies, this relationship is still considered controversial. This review summarizes critical data regarding the association of gastro-oesophageal reflux and atrial fibrillation as well as their clinical implications.

Keywords: Atrial fibrillation, gastro-oesophageal reflux disease, inflammation, vagal stimulation.

INTRODUCTION

Atrial fibrillation (AF), the most frequent arrhythmia in clinical practice, has an incidence that increases with aging and a prevalence of approximately 1–2% [1]. According to the current guidelines, this particular arrhythmia determined an increased risk of stroke and congestive heart failure (five-fold and three-fold, respectively). Subsequently, AF increases hospitalization and the mortality rate [1]. Atrial fibrillation is due to structural and/or electrical atrial remodeling, thereby promoting abnormal mechanisms of atrial depolarization. These changes may induce diverse pathophysiologic mechanisms and AF may represent a phenotype for multiple disease pathways. However, the potential mechanisms leading to AF are still not entirely understood.

Gastro-oesophageal reflux disease (GORD), one of the most frequent benign disorders of the upper gastrointestinal tract has an increasing prevalence (varying between 0.8-40%). It is defined as symptoms or complications related to the reflux of gastric content [2-8]. The pathophysiology of GORD is multifactorial. An abnormal oesophagogastric junction (EJ) function (pathologic transient low oesophagus sphincter (LOS) relaxation, hypotensive LOS or impaired clearance) and/or anatomy (hiatus herniation) are the main pathophysiological factors [9]. Abnormal gastric secretion and impaired gastric emptying may also contribute to GORD. Age related-changes and abdominal obesity appear to be important components that contribute to alterations of the EJ [9]. According to the Montreal classification, GORD is classically grouped in oesophageal syndrome and extraoesophageal syndrome (Fig. **1**) [2]. Chest pain syndromes together with typical reflux syndromes are considered part of the oesophageal syndrome. According to this classification, the established extraoesophageal manifestations are chronic cough or laryngitis, bronchial asthma and dental erosions, while the proposed manifestations are sinusitis, pulmonary fibrosis, pharyngitis and recurrent otitis [2].

The relationship between GORD and AF was observed for the first time in 1952 [10]. At that time the induction of chest pain and/or cardiac dysrhythmias by an irritant oesophago-gastric syndrome was called Roemheld gastrocardiac syndrome. Due to the fact that the esophagus and atria are adjacent and have identical nerve innervations, it has been emphasized that AF appearance could be related to the development of GORD [11-17]. However, GORD also seems to be independently correlated with AF initiation. We used the keywords as AF and GORD to find and analyze the evidences of this potential association, published after 1952. Despite the experimental and clinical data supporting this association, as detailed in this review, AF is not included as a possible extraoesophageal manifestation of GERD according to the Montreal classification [2].

POSSIBLE MECHANISMS OF ATRIAL FIBRILLATION ASSOCIATED WITH GASTRO-OESOPHAGEAL REFLUX DISEASE

Sympatho-vagal imbalance is one of the principal mechanisms suspected to be involved in the association of AF with GORD. Both components of autonomic nervous system play a role in AF pathophysiology. However, the cholinergic component seems to be critical for AF appearance [18]. Electrical activation of the ganglionic plexi situated on left atrial posterior wall (near the oesophagus) induces AF initiation [18, 19]. The majority of AF patients with GORD have triggered AF, and these patients have a positive vagal response during radiofrequency ablation [20]. Gastro-oesophageal reflux disease could induce vagal nerve stimulation [21-23]. It seems that AF initiation is related to vagal nerve overstimulation and vagal nerve-mediated parasympathetic stimulation [24-26]. In effect, the vagal nerve overstimulation involved in GORD development is also responsible for AF promoting in patients with GORD.

The second mechanism that seems to be implicated in the association of GORD with AF is *hiatal hernia*. Mechanical function alteration of the EJ may result in symptomatic or asymptomatic reflux disease. Obesity, neuromuscular dysfunction and oesophageal fibrosis may exacerbate and perpetuate progression of the disease through an overt hiatal hernia. The latter has an important role in gastro-oesophageal reflux, as it has an impact on most of the underlying pathways involved. By modifying the LOS pressure or relaxation, oesophageal clearance and acid pocket position, hiatal hernia is associated with a more severe GORD [18]. Nearly all

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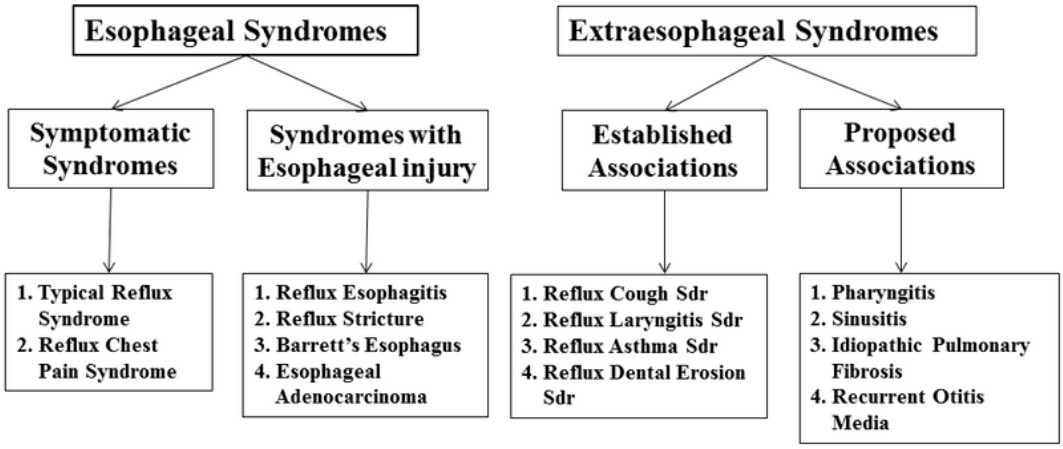

Fig. (1). The Montreal classification of gastro-oesophageal reflux disease [2].

patients with severe reflux disease have hiatal hernia [27]. Obesity, particularly central obesity, is an important factor in the etiology of reflux, as well as in AF. Obesity could increase the abdominothoracic pressure gradient inducing hiatal hernia thereby increasing the rate of flow of reflux when sphincter opens. Dysrhythmias are common in upper gastrointestinal endoscopy due to the manipulation of the upper gastrointestinal tract. The possible mechanisms that could create this association between hiatal hernia, acid reflux and atrial arrhythmias are mechanical effects on the left atrial posterior wall that are either related to the mechanical effect of the food passage or left atrium compression by the hernia [26]. However, these purely mechanical effects are hypothetical and have not yet been confirmed by scientific data.

Another possible mechanism that should be considered a participating factor in arrhythmias is *inflammation* [28, 29]. Inflammation via cytokines is known to provoke calcium channel dysfunction, which is a cornerstone of AF and is known to be highly sensitive to reactive oxygen species [29]. Mediators of inflammation have been implicated in the alteration of connexin integrity that plays a crucial role in gap junctions, which are inherent to electrical conduction [30]. Finally, inflammatory pathways regulate extracellular homogeneity and are strongly linked to fibrosis, through the production of reactive oxygen species, cytokines, matrix metalloproteinases and growth factors [30]. All of these modifications could contribute to left atrial electrical and structural remodeling witch mean initiation and persistence of AF.The inflammation could be a cause or a consequence of AF [30-35]. The patients with AF had increased inflammatory cell infiltration in the atrial myocardium [31, 32]. Proliferation and activation of epicardial fibroblasts could induce the loss of cardiomyocytes and alter gap junctions that favor the occurrence of AF through a non-uniform decrease in conduction velocities [36].

Local inflammation seems to be involved in the pathophysiology of both AF [37] and GORD [36]. The high sensitivity C-reactive protein level is correlated with the incidence, defibrillation efficacy [38], recurrence [39] and prognosis of AF [40]. Recurrent acid reflux also induces persistent low-grade inflammation and the secretion of inflammatory cytokines [41-43]. It is speculated that local inflammation of the oesophagus may increase the risk of triggered atrial activity due to the close position of the oesophagus with the left atrium posterior wall (where are localized pulmonary veins) [44]. Because inflammation seems to play a role in both AF and GORD, this pathophysiological mechanism may be a common link between these diseases.

While sympathovagal imbalance, hiatal hernia and chronic inflammation seems to be the cornerstones in the etiopathogenesis of this association [20, 44], there may be other mechanisms involved.

In patients with ischemic heart disease the stimulation of lower oesophagus by gastric acid reflux may determine a significant reduction in coronary blood flow. This condition is called cardio-oesophageal reflex [45]. Another proposed mechanism is chronic atrial ischemia [46]. It is well known that GORD is common in patients with coronary artery disease [47]. It was observed that short-term treatment with proton pump inhibitor may reduce myocardial ischemia. A phenomenon known as "linked angina" could be due to the coronary perfusion decreasing by acid-derived cardio-oesophageal reflex [45]. However, 51% of patients with non-cardiac chest pain have GORD [2.] Notably, chest pain identical with ischemic cardiac pain can be induced by GORD. As such, GORD can determine chest pain that resembles ischemic cardiac pain, without accompanying heartburn or regurgitation [2]. However, it is important to note that oesophageal motor disorders can also induce pain similarly to ischemic heart disease through a mechanism that is distinct from GORD [2].

Non-valvular AF alone may be significantly correlated with symptomatic GORD and it is significantly more prevalent among patients with permanent AF than those with paroxysmal AF and sinus rhythm [48].

It seems that AF severity may decrease after GORD treatment [12-14]. The successful treatment of hiatal hernia with a Nissen fundoplication may convert paroxysmal AF to a normal sinus rhythm [14]. Epigastric pain, inflammation and the AF attacks either decreased in frequency or was completely eliminated after treatment with proton pump inhibitors [13]. Treatment with proton pump inhibitors is successful in decreasing AF symptoms in 78% of cases with AF and GORD [13]. In addition anti-arrhythmic treatment was discontinued in 28% of the patients. The therapy with proton pump inhibitors may decrease arrhythmia symptoms (confirmed by Holter monitoring) due to the gastric acid suppression [13]. Patients with symptoms of GORD requiring proton pump inhibitors seem to have a higher arrhythmogenic risk of AF [12]. On the other hand, some reports have indicated that proton pump inhibitors may be proarrhythmic[49]. However, this proarrhythmic effect attributed to proton pump inhibitors remains controversial [13-17, 49].

In conclusion, there are several mechanisms underlying the development of GORD related-AF. Autonomic and anatomical mechanisms have been postulated with regards to the role of AF as

a risk factor for symptomatic GORD. Prandial paroxysm of AF is mediated by augmented efferent vagal nerve activity, which induces gastric juice secretion and relaxation of the oesophageal sphincter thereby leading to acid reflux [50]. An enlarged and fibrillating left atrium may compress or irritate the neighboring lower oesophagus [51]. Paroxysmal prandial AF could be triggered by hiatal hernia [14]. Oesophageal stimulation decreases the ventricular rate, increases the high-frequency spectral component and reduces the low frequency power. These results suggest that oesophageal stimulation potentiates efferent vagal nerve activity [52]. The same autonomic trends were observed prior to the initiation of paroxysmal AF [53] and the early recurrence of persistent AF following electrical cardioversion [54]. Therefore, whether this link is causative or correlative, GORD and AF may have common pathways. However, GORD and AF also share the same predisposing factors including metabolic syndrome [55, 56], sleep apnea [57, 58] and increased age [59], alcohol or drug use.

STUDIES REGARDING ASSOCIATION BETWEEN ATRIAL FIBRILLATION AND GASTRO-OESOPHAGEAL REFLUX DISEASE

There is evidence from case reports with small sample sizes, [14, 27, 60], case series [12], large retrospective [17, 62, 63] and prospective [7, 16, 48, 52, 61] studies that GORD, and more specifically oesophagitis, is associated with AF (Table **1**). Despite this, the supporting literature is still relatively few. A recent published review identified only 8 original articles with more than 10 subjects examining the relationship between GORD and AF in English and French from five electronic databases [64].

In the oldest study on 14 healthy volunteers was shown that oesophageal stimulation could modulate autonomous nervous system by amplifying vagal activity and decreasing sympathetic activity [52]. In some patients with idiopathic supraventricular arrhythmias and GORD, neutralization of the gastric acid seems to improve reflux disease and related symptoms [61]. In addition patients with lone AF, proton pump inhibitors seem to reduce not only GORD-related but also paroxysmal AF-related symptoms [62].

In a large retrospective study of more than 160,000 patients the relative risk of a diagnosis of AF was increased with 39% by the presence of GORD. This relationship remained even after correction of risk factors for AF [17]. The authors of this study have used a database containing all health care encounters for patients who received ambulatory care. In a multicenter survey with 188 consecutive subjects designed for GORD screening using a scale for GORD symptoms, AF alone was showed significant correlation with GORD [63].

GORD was independently correlated with a high risk of AF in the largest prospective epidemiological study of 1,000,000 people [7]. The diagnosis of GORD was made using the ICD-9 codes from a database. Therefore GORD or AF prevalence could be underestimated (due to asymptomatic patients).

Only one study, which was based on a self-report questionnaire and included more than 5,000 patients, concluded that GORD did not involve higher risk for AF after exclusion of other risk factors. However, this study did find that patients with more frequent GORD had a slightly higher AF risk [16]. In this study, oesophagitis increased the risk of AF, but this relation was not maintained when controlling for other risk factors. The authors concluded that no association was found between GORD and AF and also that this association requires further studies. Unfortunately, this study did not use an objective method like endoscopy to diagnose GORD. It is well known that GORD could be asymptomatic.

ATRIAL FIBRILLATION AND GASTRO-OESOPHAGEAL REFLUX DISEASE: THE CARDIOLOGIST PERSPECTIVE

Atrial fibrillation is associated with an increasing morbidity and mortality that continue to remain unacceptably high despite all efforts aimed at improving its management. Therefore the etiology of AF was placed in the foreground for the first time by the Third Consensus Conference of the Atrial Fibrillation Competence Network/European Heart Rhythm Association [65].

In a large majority of patients with AF we can find pathologies like hypertension, obesity or diabetes mellitus as substrate for left atrial remodeling. Most common substrates for both AF and GERD are obesity and aging. In addition, both AF and GERD are associated with other pathologies like sleep apnea or diabetes mellitus. It seems that among traditional cardiovascular risk factors, GORD could be an independent risk factor for AF. Also, we think that AF should be considered as possible extraoesophageal syndrome in the GORD classification [2].

Sympatho-vagal imbalance is one of the principal mechanisms of AF associated with GORD [20]. Although both autonomic nervous system components play a role in AF, the cholinergic component seems to be more important for spontaneous initiation of AF. Electrical stimulation of the left atrial ganglionic plexi (situated on

Table 1. Studies to date on atrial fibrillation and gastro-oesophageal reflux disease. [7, 16, 17, 48, 52, 61, 62, 63].

AUTHORS	STUDY TYPE	NO. OF PATIENTS	CONCLUSION
Tougas *et al*. [52] (1997)	Prospective	14 volunteers	Pros
Cuomo *et al*. [61] (2006)	Prospective	32 patients with GORD and idiopathic supraventricular dysrhythmias, and 9 with GORD only	Pros
Huang *et al*. [7] (2012)	Prospective	1,000,000-person cohort dataset sampled from the Taiwan National Health Insurance database	Pros
Kubota *et al*. [48] (2013)	Prospective	479 consecutive subjects	Pros
Bunch *et al*. [16] [2008]	Prospective	5288 patients	Cons
Weigl *et al*. [62] (2003)	Retrospective	89 patients with reflux oesophagitis, 18 out of those with lone paroxysmal AF	Pros
Kunz *et al*. [17] (2009)	Retrospective	163 627 patients	Pros
Shimazu *et al*. [63] (2011)	Retrospective	188 consecutive subjects	Pros

AF=atrial fibrillation, GORD=gastro-oesophageal reflux disease, PPI=proton pump inhibitors, Pros=the conclusion was in favor for this association, Cons=the conclusion was not in favor for this association.

left atrial posterior wall, close to the esophagus) induces spontaneous ectopic beats (foci) from pulmonary veins promoting AF [20]. Majority of AF patients with GORD have triggered AF [36]. During radiofrequency ablation, these patients may have positive vagal response [36]. Gastro-oesophageal reflux could be only a trigger for AF in paroxysmal AF. Probably in these patients the therapy with proton pump inhibitors decreases arrhythmia symptoms (proved by Holter monitoring). Less known, not only GORD may trigger AF, but also AF may determine the occurrence of GORD

For cardiologists and especially electrophysiologists the relationship between esophagus and left atrium have a different significance because it seems that GORD is more frequent after AF ablation. This complication of radiofrequency ablation was first described in 2001 [66]. After that more and more oesophageal injury has been reported with delivery of radio-frequency lesions at the left atrium posterior wall in catheter ablation procedures for AF[67-71]. Erythema of the oesophagus seems to be a common finding in patients undergoing pulmonary vein antrum isolation procedures, with important clinical relevance. In addition it seems to be a correlation between reflux-like symptoms and oesophageal lesions [72]. A significant number of patients undergoing radiofrequency catheter ablation of AF develop pathologic acid reflux after ablation (19.2%) [67]. Using endosonography peri-oesophageal injury was detected in 27% of patients undergoing pulmonary vein isolation [73]. Oesophageal ulceration may evolve to left atrial-oesophageal fistula, a very severe complication. Oesophageal thermal lession during catheter ablation for AF could be minimized by oesophageal temperature monitoring; multiple factors such as patient characteristics and specific strategies for radiofrequency energy delivery also merit consideration [72]. Initiating proton pomp inhibitors in these patients might facilitate recovery of oesophageal wall injuries produced during radiofrequency catheter ablation [74]. However, this complication of AF ablation *has another type of pathogenic mechanism*. Most important in this relationship is the proximity of oesophagus with posterior wall of the left atrium.

In conclusion, cardiovascular involvement in GORD is less assessed. It is mandatory to extend the research in this field for better understanding the relationship of AF with GORD.

CONCLUSION

Gastro-oesophageal reflux disease seems to be independently associated with increased risk of developing atrial fibrillation. Even this relationship is still controversial the clinicians should be aware of this possible association. Identification and appropriate treatment of gastro-oesophageal reflux in patients, particularly in those with lone AF, may decrease the use of anti-arrhythmic agents, which often have complex side effects and the potential for producing pro-arrhythmic effects.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflicts of interest.

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