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Atrial fibrillation and gastroesophageal reflux disease: association mechanisms, treatment approaches

Antropova O. N., Pyrikova N. V., Osipova I. V.

The article is devoted to assessing the relationship of atrial fibrillation (AF) and gastroesophageal reflux disease (GERD). We studied possible anatomical correlations, common risk factors and mechanisms of AF development in patients with gastroesophageal reflux. We demonstrated the problems of the treatment of such patients, since a number of studies have proved the possibility of using proton pump inhibitors in the treatment of AF. In other cases the arrhythmogenic effect of these drugs was obtained. Treatment of AF by catheter ablation most commonly worsens the course of GORD and can lead to the development of fatal complications. Large-scale prospective researches are needed for further detailed study of AF and GERD associations, as well as tactics for management of these patients.

Key words: gastroesophageal reflux disease, proton pump inhibitors, radiofrequency ablation, atrial fibrillation.

Conflicts of Interest: nothing to declare.
Altai State Medical University, Barnaul, Russia.

Antropova O. N.* ORCID: 0000-0002-6233-7202, Pyrikova N. V. ORCID: 0000-0003-4387-7737, Osipova I. V. ORCID: 0000-0002-6845-6173.

***Corresponding author:** antropovaon@mail.ru

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Atrial fibrillation (AF) is a common rhythm disorder with a 3% approximate frequency in adults aged 20 years and older [1, 2]. By 2030, in the countries of the European Union, AF prevalence can reach 14-17 million patients [3]. AF is independently associated with a twofold increase in the risk of all-cause mortality in women and 1,5-fold — in men [4].

Concomitant cardiovascular disease and many other comorbidities are often predisposing factors for AF. It increases the risk of recurrent arrhythmias and the incidence of complications. Identification of such factors, its prevention and timely modification are necessary for choosing the optimal strategy of successful AF control and complications' preventing [5].

In the last decade, interest in functional relationship between the gastrointestinal (GI) tract, in particular the esophagus, and the cardiovascular system has renewed. In the past, supposed association between upper GI and cardiovascular diseases was defined as Roemheld syndrome, where irritant esophagogastric stimulus cause not only chest pain, but also arrhythmias and increased blood pressure. Currently, researchers pay more and more attention to the mechanisms of arrhythmias associated with pathological gastroesophageal reflux, as well as its pharmacotherapy [6].

Several studies have reported a correlation between gastroesophageal reflux disease (GERD) and AF. The coincidence of acid reflux and AF paroxysm was shown with simultaneous pH meter using and 24-hour Holter monitoring [7]. It was found that in a number of arrhythmias, vegetative imbalance was caused by gastroesophageal reflux [8]. After modification of other risk factors, a strong correlation between GERD and AF was demonstrated [9, 10]. At the same time, in a retrospective study involving 5288 residents of Olmstead County, Minnesota, there was no correlation between GERD and AF [11].

Thus, the relationship between AF and GERD cannot be considered as completely studied due to the limited number of studies and sample sizes, but it is of scientific and practical interest.

Potential common mechanisms between GERD and AF

Anatomical interactions. Inflammatory and infiltrative changes in the left atrium (LA) can be associated with the pathogenesis of GERD or AF, especially when the LA contact with the lower esophagus. Atrial inflammatory response associated with chronic AF, theoretically determines the GERD mechanisms by anatomical connection between the esophagus and the LA. The LA posterior wall and the esophagus are separated by a layer of tissue about 5 mm thick. Anatomical interactions between the esophagus and the LA are not well understood. Computed tomography data before and during the contrast esophagiogram showed that esophageal location may differ. In some patients, the esophagus is closer to the left pulmonary vein, while in others to the right pulmonary vein. The periesophageal plexus, which regulates the gastric motility, can branch above or below the LA [12].

When studying the AF prevalence in patients with hiatal hernia from 1976 to 2006 at the Mayo Clinic in Rochester, the authors concluded that the AF development often, especially in young patients, is associated with chronic mechanical LA compression that underlies future AF [13]. In patients with a hiatal hernia, arrhythmias may be a result of mechanical compression of the LA anterior wall by food passing through the esophagus. If this happens regularly and lasts for a long time, over many years, it can lead to chronic ischemia of this zone and development of reentry arrhythmia [14].

Autonomic activation. The occurrence of arrhythmias in patients with GERD is associated with an imbalance of cardiac autonomic effects. The process can be started by the action of a refluctant on the reflexogenic zones of the distal esophagus and the development of viscero-visceral reflexes mediated by the vagus.

Chemical, electrical and mechanical stimulation of the esophagus alters the sympathovagal balance. Several observations confirm the important role of the autonomic nervous system in AF initiating and maintaining. The effect of vagal stimulation on atrial refractoriness is heterogeneous, since the distribution of parasympathetic nerve endings and/or muscarinic receptors is different. The increased vagus activation in GERD patients creates an arrhythmogenic substrate for the reentry mechanism, and thereby increases the AF risk.

Stimulation with hydrochloric acid is associated with an increase in vagus activity [15]. Gastroesophageal reflux causes a local inflammatory process that can directly change the autonomic innervation of the esophageal mucosa and stimulate contiguous vagus. Such excessive vagus stimulation creates the basis for the AF development [16, 17].

Although both sympathetic and parasympathetic components may play a role in the AF development, the cholinergic component is probably the most important. Electrical stimulation of LA ganglion plexuses (located on the LA posterior wall, close to the esophagus) or autonomic nerve endings cause spontaneous stimulation of the pulmonary veins and subsequent AF development [18]. Gastroesophageal reflux may be a trigger for AF in paroxysmal AF.

Table 1

Studies on the PPIs use in patients with GERD and AF

Year of publication	Authors	Study design	Main results
Studies where the positive PPIs effect has been proven			
2006	Cuomo R, De Giorgi F, Adinolfi L, et al.	Observational prospective control study. 32 patients with GERD and arrhythmia and 9 patients with GERD only. Valid questionnaires and endoscopy were used to establish GERD. Holter ECG monitoring, esophageal manometry, acid perfusion test and 24-hour pH monitoring were performed. Within 3 months the PPIs maximum dose was prescribed.	PPI therapy was effective in 56% of patients; significant cardiac symptom improvement was recorded.
2006	Gerson LB, Friday K, Triadafilopoulos G.	Observational prospective study. Three patients had an association of heartburn, acid regurgitation and tachycardia. Patients underwent both an ambulatory 24-hour esophageal pH monitoring and Holter monitoring. Antireflux therapy lased at least 7 days.	Symptoms of GERD and AF decreased with omeprazole therapy.
2015	Chen KP, Lee J, Mark RG, et al.	Multiparameter Intelligent Monitoring in Intensive Care II (MIMIC-II) of 8457 patients taking PPIs or H2 receptor blockers.	The use of PPIs and H2 receptor blockers was not associated with an increased risk of arrhythmia (OR 0,85; 95% CI 0,72-1,01, p=0,07; OR 0,88; 95% CI 0,66-1,18, p=0,40, respectively).
Studies where the positive PPIs effect has not been proven			
2010	Marcus GM, Smith MM, Scheinman MM, et al.	"Case-control" study, the use of PPIs in 80 patients with focal tachycardia, the control group consisted of patients with recurrent rhythm disturbances due to anatomical abnormalities. 12-lead ECG in and electrophysiological test was conducted.	The proportion of patients with focal atrial tachycardia and PPIs use was significantly higher than in the control group (p=0,009). After adjustment, the use of PPIs was associated with a greater risk of focal arrhythmia (OR 3,6; 95% CI 1,2-11,1, p=0,025) and focal atrial arrhythmia (OR 4,5; 95% CI 1,3-15,7, p=0,018).
2012	Huang CC, Chan WL, Luo JC, et al.	Prospective study. 29688 patients with GERD from the Taiwan National Health Insurance Database. Control group included 29597 people without GERD or history of arrhythmias. GERD was diagnosed with ICD-9 codes; AF — with ICD-9, ECG and Holter monitoring. Participants took PPIs; follow-up lasted three years.	Those receiving PPI therapy had an increased risk of AF (RR=1,46; 95% CI 1,15-1,86, p=0,002). Patients with GERD who did not receive PPIs did not have an increased risk of AF.
2015	Odashiro K, Yasuda S, Yokoyama T, et al.	Single-center study. Patients with AF and GERD (n=27). Questionnaires on the symptoms of GERD and AF before and after PPI therapy for 3 months was used. From this group, 5 patients with pacemakers were selected with ongoing PPI therapy for 6 months.	Common symptoms of GERD (p<0,001), reflux (p<0,001) and regurgitation (p=0,013) were significantly improved with PPI. The frequency and duration (p=0,001), severity (p<0,001) of AF symptoms were decreased. Analysis of the device data did not confirm significant changes regarding the number (p=0,138) and the maximum duration (p=0,345) of AF paroxysms.

Muscarinic acetylcholine receptors are the primary neurotransmitters of parasympathetic cardiac control. Stimulation of the muscarinic receptor with acetylcholine activates G-protein-linked potassium currents, leading to a reduction in the duration and effectiveness of the atrial refractory period [16].

It is less known that AF can also cause GERD, since an enlarged LA can compress or irritate the contiguous lower esophagus [19].

Inflammation. Another assumption is that as a result of reflux esophagitis, an inflammatory process develops in the esophageal wall and then can

Table 2

Outcomes and complications of RFA use in AF patients

Year of publication	Authors	Study design	Main results
2013	Reddy YM, Singh D, Nagarajan D, et al.	A prospective case-control study. 30 patients with AF, GERD and/or IBS (group 1), 30 patients with AF without GERD or IBS (group 2).	During RFA, more patients in group 1 had a "vagal response" (60 vs.13%; p<0.001). After 1 year, 93% of patients showed no signs of AF without differences between the two groups.
2014	Knopp H, Halm U, Lamberts R.	Cohort study. 425 patients with symptomatic AF who underwent RFA of the LA. EGD was performed by everyone 1-3 days after the procedure. Patients did not have GI tract symptoms.	Pathological symptoms were observed in 77% of patients and included gastric erosion (22%), esophageal erythema (21%), gastroparesis (17%), esophageal hernia (16%), reflux esophagitis (12%), thermal esophageal lesion (11%) and suspected Barrett's esophagus (5%).
2015	Tolone S, Savarino E, Docimo L.	Clinical case. 65-year-old man with drug-resistant paroxysmal AF. Before the RFA, patient underwent high resolution manometry and pH-impedance monitoring. Pathology is not revealed.	After 8 weeks, manometry showed spastic hypercontraction, while pH-impedance monitoring did not show GERD signs.
2015	Chavez P, Messerli FH, Dominguez AC, et al.	A systematic review of observational cases of AEF after ablation procedures in accordance with the PRISMA protocol, 53 cases.	The average interval between the procedure and the complication was 20±12 days. AEF was observed in 12 patients who underwent surgical RFA, and in 41 patients with percutaneous RFA. Fever (n=44), neurological disorders (n=27) and hematoma (n=19). Computed tomography of the chest (n=27) was the preferred diagnostic test. Patients who did not perform the operation were more likely to die (34% vs. 83%; p<0,05).
2017	Han HC, Ha FJ, Sanders P, et al.	Review of PubMed and Embase sources. Of 628 references, 120 AF cases with catheter ablation were identified.	The clinical performance of AEF manifested on day 21: fever (73%), neurological (72%), GI (41%) and cardiac (40%) symptoms.
2017	Orosey M, Garg L, Agrawal S, et al.	Two clinical cases. 1) A 46-year-old man with persistent AF and multiple cardioversion underwent catheter ablation. 2) A 63-year-old woman with paroxysmal AF underwent ablation with pulmonary vein isolation.	1) Post-ablation EGD revealed an esophageal ulcer (1,3 cm). 21 days later, neurological symptoms manifested, EGD confirmed the presence of AEF. 2) After 1 month, EGD revealed an esophageal ulcer; during an emergency surgery — LA defect.

Abbreviations: AEF — atrioesophageal fistula, GI — gastrointestinal, IBS — irritable bowel syndrome, EGD — esophagogastroduodenoscopy.

involve closely located LA wall with subsequent AF development. Observational studies also suggest that it is not the symptoms of GERD in general, but specifically the endoscopic signs of esophagitis that are associated with an increased AF risk [15]. The spread of the local inflammatory process through the esophageal wall can also cause local pericarditis or atrial myocarditis due to the esophagus and LA closeness.

In patients with AF without structural heart disease, myocarditis can be detected in 66% of patients. Cytokines have been shown to play an important role in the AF pathophysiology [16, 20]. Esophageal mucosa inflammation affects local receptors, which can cause afferent and efferent reflexes. Inflammatory factors, including oxidative stress, leukocytes and cytokines, such as interleukin (IL) -6, IL-8, are known to cause GERD [21].

Thus, AF and GERD can be considered as complementary partners with common inflammatory mediators that support and lead to the progression of these diseases.

Common risk factors

Many clinical and epidemiological studies have found that a significant percentage of patients with AF have coexisting diseases, such as metabolic syndrome, non-alcoholic fatty liver disease, obesity, sleep apnea [5].

The development of GERD correlates with these same common diseases: obesity [22], metabolic syndrome [23], sleep apnea [24]; obesity increases the gastroesophageal pressure gradients [25].

These lifestyle-related diseases are accelerated by proinflammatory, procoagulant and profibrotic mediators, which also alter atrial electrophysiology and microstructure, which contribute to structural remodeling in AF.

Management of patients with GERD and AF

The management of patients with GERD and AF is an important problem that has not been completely resolved [15]. It has been proven that modification of cardiovascular risk factors, especially obesity, prevents the recurrence and progression of AF and improves the ablation outcome [26, 27]. Along with this, lifestyle changes and weight loss should be considered prerequisites for effective antireflux therapy [28].

The effect of antisecretory therapy on AF. A number of authors consider that acid-suppressive therapy used to treat GERD has positive effects on AF [29]. Proton pump inhibitors (PPIs) can be an addition to standard antiarrhythmic treatment by improving AF symptoms [7, 8, 30] (Table 1) and facilitating the restoration of sinus rhythm, with the advantage that it are less expensive and have fewer side effects [31].

These studies show that the therapeutic effects of PPIs in AF are mediated by the elimination of the trigger for the cardiogastric reflex caused by acid reflux. In addition to acid suppression by blocking the proton pump (hydrogen potassium ATPase) in the gastric mucosa, PPIs have an antioxidant and anti-inflammatory effect [32] — it blocks the production of nitric oxide *in vitro* and decreases the secretion of pro-inflammatory cytokines [33]. Scanning electron microscopy revealed leukocyte infiltration in the LA endothelium in patients with valvular AF after valve replacement open heart surgery [34]. PPIs are able to suppress the activity of leukocytes, epithelial and endothelial cells, which are indirectly activated by changes in intracellular pH and homeostasis [29]. The role of hydrogen potassium ATPase in the heart function regulation was confirmed in laboratory conditions: gastric isoforms of hydrogen potassium ATPase and receptors for PPIs binding are present in mammalian heart cells. Scientists have concluded that PPIs can have antiarrhythmic and cardioprotective effects [35].

However, not all studies clearly demonstrated the positive effect of PPIs in patients with GERD and AF [36, 37] (Table 1), since there are data regarding the potential proarrhythmic effect of PPIs [38]. A possible mechanism is associated with the fact that it can cause hypomagnesemia and concomitant electrolyte disturbances, including hypocalcemia and hyperpotassemia, provoking life-threatening arrhythmias [39, 40].

The pathogenesis of hypomagnesemia is still not completely clear; several studies have suggested PPI-induced impaired magnesium absorption in the GI tract. Although most oral magnesium is absorbed passively through the paracellular pathways between enterocytes, PPIs affect the functioning of the second transport system of magnesium — transcellular cation channels. It allows adaptation to low magnesium intake by increasing of its fractional absorption. Chronic use of PPIs is believed to impair this adaptive intestinal response to low dietary magnesium intake [41-44]. Hypocalcemia, secondary to hypomagnesemia, develops due to functional hypoparathyroidism [45], as well as due to a decrease of calcium bioavailability as a result of achlorhydria [46].

The effect of AF therapy on GERD. Non-pharmacological AF treatment includes radiofrequency ablation (RFA). Three main mechanisms of the RFA negative effect on the GERD are distinguished: 1) periesophageal vagal injury 2) direct thermal damage to esophageal mucosa and 3) atrioesophageal fistula formation [18, 47] (Table 2). The RFA itself can lead to an increase in the number of new GERD cases by 19%, since the appearance of reflux is associated with direct vagal stimulation and a decrease of esophageal sphincter tone, as well as with a long lying position of patients during the procedure. Moreover, the "vagal response" can be caused both by a direct stimulus to the vagus nerve, which is adjacent to the heart, and by thermal damage to the esophageal vagal fibers. It causes an imbalance in favor of excitatory innervation with characteristic changes in the esophageal motility [48].

Another esophageal lesion caused by the ablation is thermal trauma. It varies in severity from erythema, esophagitis and ulceration to necrosis and depends on the RFA technique, as well as on the maximum energy arrived at the posterior wall. Some authors consider that esophageal ulceration may be a potential precursor to a life-threatening condition — atrioesophageal fistula [49, 50] with a complication rate of 0,03-1,5% per year [51, 52]. Death is usually inevitable, although survival is possible with timely diagnosis and emergency surgery.

The clinical manifestation of GERD is chest pain, in connection with which general practitioners may mistakenly prescribe cardiac drugs to these patients. Although calcium channel blockers and nitrates can be effective for chest pain by eliminating the spastic motility of the esophagus [53], these drugs cause relaxation of the lower esophageal sphincter and increase acid reflux [54].

A number of authors have shown that anticoagulants' taking, in particular warfarin, is an independent risk factor for symptomatic GERD [54]. The RELY study demonstrated that, against the background of dabigatran administration, an increase in the incidence of gastroenterological symptoms such as dyspepsia, gastroesophageal reflux, impaired motility of the upper GI tract, and damage to the gastroduodenal mucosa was noted [55]. These pathologies occurred in 16,9% of patients, and 4% had to stop dabigatran therapy. Similar results were obtained by Japanese doctors: dabigatran-induced esophagitis was detected in 20% of endoscopic studies [56].

Mechanisms of gastroenterological side effects of dabigatran are not fully understood. It was assumed that this is due to the release of tartaric acid from the capsule and irritation of the mucosa. It is believed that if dabigatran is taken in accordance with the recommendations (in an upright position, with food and washed down with water), then adverse effects can be significantly minimized. Also, PPIs should be added to therapy, although their effect on the improvement of side effects has not been proven [57].

Conclusion

Clinicians should be aware of a possible cardiogastric interaction between GERD and AF. There is a need for further studies to determine whether there are true causal relationships (independent of concomitant diseases), whether the identification and treatment of GERD, especially esophagitis, can help to restore and maintain sinus rhythm. It is important to determine whether the pharmacological or non-pharmacological potential of GERD treatment plays a role in the long-term management of AF patients. Large-scale prospective studies are required to determine the indications for the PPIs use for a specific group of patients with AF.

Conflicts of Interest: nothing to declare.

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